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Disparities in Kidney Transplantation in the Immigrant Patient Population in Italy: Towards an Intervention to Improve Equity

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To the attention of:
The PhD Thesis Committee
Degree in Experimental and Clinical Medicine
and Medical Humanities
University of Insubria
Varese – Italy

Padova, January 3rd, 2021

Assessment of the PhD thesis submitted by Miss Alessandra Agnese Grossi and entitled: "Disparities in Kidney Transplantation in the Immigrant Patient Population in Italy: Towards an Intervention to Improve Equity»

I have read with great interest the thesis prepared by the PhD candidate.

The aim of the research was to provide insight into the disparities possibly existing in kidney transplantation in the immigrant patient population in Italy, with the ultimate goal to identify targets of intervention to improve equity.

Unquestionably, the topic selected by the candidate is rather novel and extremely complex. In this light, to enable an appropriate understanding and evaluation of the work performed and the interpretation of the results, in the first chapter the candidate clearly and exhaustively sets the scene of the study. In particular, the candidate provides the necessary background information, the key definitions and clearly outlines the main objectives of the thesis.

Specifically, the study addresses three fundamental issues. First, it assesses whether disparities exist in kidney transplantation (KT) outcomes in the non-EU-born immigrant patient population in Italy. Second, it tries to determine the ethical relevance of detecting and understanding determinants of disparities in KT and discusses the inherent ethical dimensions. Finally, in an attempt to identify potential targets of intervention to prevent or eliminate possible disparities in KT in this vulnerable group of patients, the study explores the mechanisms linking immigration background with KT outcomes.

In this thesis, the candidate undertakes a very detailed and updated analysis of the immigration phenomenon in Italy and introduces the reader to the concept of immigration as a major social determinant of health (SDH) disparities. Subsequently, the candidate provides an overview of disparities in end-stage kidney diseases and KT in the immigrant patient population in Italy and compares the situation with that in other EU countries. In this context, the applicant identifies research gaps that will need to be tackled in the near future. Next, the candidate undertakes an in-depth analysis to assess the possible association of the non-EU immigration background with kidney graft function and transplant survival in Italy. Then, the thesis illustrates three emblematic clinical cases that describe the various challenges that may account for disparities in access and outcomes of KT in the non-EU immigrant patient population. A discussion of the ethical relevance to consider the SDH when performing pre-transplant multidisciplinary assessments in this vulnerable group of patients is also presented. Subsequently, the candidate proposes a very

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elegant conceptual model of the causal mechanisms linking immigration background with disparities in kidney transplantation. Finally, the thesis ends up with a critical discussion of the results with future research directions.

Unquestionably, the topic selected by the candidate is extremely complex and this thesis provides a clear demonstration that the candidate has done a tremendous effort to become acquainted with the latest literature and documents on the subject. Indeed, the fundamental references appear to have been included and for each of the citations used the candidate clearly provides evidence that she has become familiar with the crucial content of such corner-stone articles.

Altogether, the research conducted and the data generated are of very high quality. Likewise, their analysis and interpretation are very meticulous and fact-based. The quality of the data generated and the accuracy of the analysis and interpretation are additionally endorsed by the publication of 4 manuscripts in peered-reviewed journals, including 1 article as first author this year in Transplant International. Furthermore, at least 5 additional manuscripts are in preparation (one of which has already been submitted).

The general discussion is sound and nicely integrates the different aspects of the research conducted showing complementarity between the different phases of the studies undertaken.

The text of the thesis is very accurately written and very clear. It is easily accessible also to non-expert scientists. Likewise, the figures provided are of high clarity and nicely illustrate the key concepts underlying this research initiative and its achievements.

After a careful assessment of the document, I have come to the conclusion that the work achieved by the candidate in the 3 years duration of the course is really outstanding, both from a qualitative and a quantitative standpoint.

In summary, the thesis submitted demonstrates the tremendous level of knowledge acquired by the candidate on the disparities in kidney transplantation in the immigrant patient population in Italy. Furthermore, the novel scientific acquisitions generated by the candidate and the important findings of the research undertaken represent a unique step forward for the development of possible areas of intervention to prevent such a form of health inequity.

In this light, I unreservedly support the promotion of the candidate to the title of Doctor in Philosophy.

Accordingly, the thesis can be admitted to the oral defense in front of the Committee which will award the PhD title.

Yours sincerely,

Prof. Emanuele Cozzi

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Barcelona, December 12th, 2020.

The PhD thesis "**Disparities in Kidney Transplantation in the Immigrant Patient Population in Italy: Towards an Intervention to Improve Equity"** by *Alessandra Agnese Grossi* addresses immigration as a social determinant of health related to kidney transplantation, which is the best therapeutic intervention in the treatment of end-stage renal disease (ESRD). The pertinence of this work is supported by the fact that the growing immigration in EU countries has resulted in gradual increments of immigrant patients with ESRD which may account for more than 20% in dialysis units or in kidney transplant programs.

In this dissertation, Grossi reviews the factors of vulnerability of the immigrant population, the epidemiology of ESRD and the access to and performance of transplantation in Italy. Importantly, Grossi describes that there was a significant decline in estimated glomerular filtration rate (eGFR) in non-EU-born kidney transplant recipients (KTRs) (- 5 ml/min/1.73 m^2) at 5 years, despite that the mean baseline 1-year eGFR values were similar with native Italians. Importantly, even though that poor renal function may be considered as a surrogate marker for late graft loss, at 5 years these differences in eGFR did not result in inferior transplant survivals, although there was a trend for worse outcomes in non-EU born KTRs with an increased hazard ratio for transplant failure. The relevance of Grossi's study derives from the identification of poorer functional kidney allograft performance after transplantation among non-EU born, without an apparent negative impact on transplant survivals in the mid-term, but which might herald reduced survivals in the long-term.
These data raise the need to establish specific programs in immigrant transplant candidates and recipients to improve renal transplant outcomes.
By using the Four Boxes Method, Grossi analyses 3 clinical cases of immigrant transplant candidates to kidney transplant which illustrate the value of using a standardised scoring system for the pre-transplant patient's psychosocial evaluation to make an objective risk assessment and to prevent preconceived biases on the indication of transplantation and the inclusion in the waiting list.

Additionally, this PhD thesis also identifies the causal mechanisms linking immigration and disparities related to transplantation.

Such contributions may allow to design prospective protocols to ameliorate detrimental modifiable factors to implement effective interventions in order to ultimately improve transplant outcomes.
This integrated project including distinct studies has generated publications in peer reviewed journals and scientific communications, which support the value of this dissertation.

Because of these considerations, the thesis can be admitted to the oral defense in front of the Committee which will award the PhD title.

Signed: Josep M. Grinyó.

To my parents:
for being there all along,
for your never-ending trust,
support,
encouragement,
patience
and love.

Abstract

Background and Objectives: In Italy, many adult patients with end-stage kidney disease (ESKD) are of non-European Union (EU) origin. These patients account for as high as 35% of the prevalent population on chronic dialysis treatment in some centers in Northern areas. Kidney transplantation (KT) is the gold standard for treatment of ESKD. Italy guarantees universal access to KT and post-transplant medical regimens for all clinically eligible migrants registered in the National Health System under the same conditions as nationals. Yet, immigration is an important social determinant of health, with the potential for disparities in accessibility, quality, and outcomes of care. Prior research has shown that non-EU-born individuals in Italy are more likely to experience unequal access to and quality of care because of potential barriers associated with immigration. While disparities in KT for ethnic minority patients are well-known, especially in the United States, studies on disparities associated with immigration background remain scarce in the EU and none have ever been performed in Italy. This study pursues three main objectives: (1) to assess whether disparities exist in KT outcomes in the immigrant patient population in Italy, (2) to discuss the ethical dimensions with the potential for disparities in this vulnerable group of patients, and (3) to explore the causal mechanisms linking immigration with disparities in KT and identify areas for intervention to prevent, mitigate and/or eliminate them. **Methods:** Three research phases were outlined to pursue the three objectives: (A) A study to assess disparities in KT outcomes in the immigrant patient population was retrospectively performed based on national-level data extracted from the Transplant Information System registry of the Italian National Transplantation Center. (B) three clinical cases describing the challenges that might account for disparities in KT in this group of patients were analyzed by the Stanford Integrated Psychosocial Assessment for Transplantation and by the Four-Boxes Method for ethical decisions in clinical medicine. (C) a conceptual model of the causal mechanisms of disparities was developed and the potential for intervention to reduce them was discussed. **Results:** (A) The study revealed that non-European immigration background is associated with long-term kidney graft function decline. (B) The Four-Boxes Method is a useful tool to gain a more comprehensive picture of the ethical dimensions of single clinical cases and to fulfill the ethical obligation to provide whole-person care (C) Multiple modifiable factors may explain disparities in KT. **Conclusion:** While it would be necessary to act directly upon the structural causes of disparities, it is more realistic to foster action on modifiable risk factors by development of targeted interventions with the potential to enable the prevention/mitigation/elimination of disparities in KT in this vulnerable group of patients. Prospective studies are needed to further elucidate the causal mechanisms linking immigration with disparities in KT more rigorously. Further, research is necessary to develop interventions and to assess their effectiveness in immigrant patients pursuing KT.

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List of Abbreviations

CKD: Chronic Kidney Disease
CNT: Italian National Transplantation Center
CVD: Cardiovascular Disease
DDKT: Deceased Donor Kidney Transplant
ED: Emergency Department
eGFR: Estimated Glomerular Filtration Rate
ESKD: End Stage Kidney Disease
EU: European Union
GFR: Glomerular Filtration Rate
HL: Health Literacy
HCP: Health Care Professionals
HDC: Highly Developed Countries
HLA: Human Leucocyte Antigen
HMPC: High Migratory Pressure Countries
HR: Hazard Ratios
LLP: Limited Language Proficiency
KT: Kidney Transplant
KTR: Kidney Transplant Recipient
NHS: Italian National Health System
SDH: Social Determinants of Health
LDKT: Living Donor Kidney Transplant
RRT: Renal Replacement Therapy
WL: Waiting List
WHO: World Health Organization

Chapter 1. Introduction to the study

1.1. Context and motivation for the study

Equity is a major principle in the general field of solid organ transplantation (EDQM 2018), and disparities in the process of kidney transplant (KT) are an emergent issue in the transplant literature. It is well known that socio-economically disadvantaged subjects, individuals who have migrated from other countries or are from ethnic minorities/non-native speakers, patients with limited HL, elderly persons, and other vulnerable social categories are more likely exposed to disparities when compared to their referents (Davison and Holley 2008; Segall et al. 2016; Halpern and Goldberg 2017; Zhang et al. 2018; Van Biesen et al. 2018). Many studies from the United States (US) document extensive racial/ethnic disparities at different stages of the KT process, from the prevalence of chronic kidney disease (CKD), to the progression towards end stage kidney disease (ESKD), receiving KT, through to KT outcomes (Ladin, Rodrigue and Hanto 2009; Malek et al. 2011). However, it is difficult to transfer these findings to the context of the European Union (EU) where immigration is a more recent phenomenon and where, as opposed to the US, health systems generally guarantee universal coverage of nephrological care, from the point of access through to accessibility of post-transplant regimens (Bello et al. 2017). Immigration is considered as a major social determinant of health (SDH) disparities (Castañeda et al. 2015). Immigrant patients encounter major barriers to effective care in their host countries. The nephrology community in the EU and in Italy alike has highlighted that immigrant populations pose multiple challenges raising moral-ethical questions as to the management of ESKD, including KT. These individuals present a variety of relational, cultural, social, economic, and biological factors that may be relevant to accessibility and outcomes of KT. These include language and cultural barriers challenging knowledge and understanding of the transplant process, medication adherence, different dietary habits, lifestyles, cultural beliefs about illness and treatment, lack of family and/or social support network, unstable living and housing conditions, socio-economic deprivation, lower health literacy (HL), different expectations and approaches to care possibly compromising mutual trust between patients and physicians, periodic visits to home countries where they have the potential to have limited access to care, and biological factors which vary among ethnic groups (Poulakou, Len and Akova 2019; Van Biesen et al. 2018; Forneris et al. 2011; Maloney, Clay and Robinson 2005). It is well established that health disparities are frequently associated with a variety of disadvantages such as lack of access to services (including transportation to access these services), information, limited HL, poor educational level, poor living conditions (including neighborhood characteristics: i.e. availability of recreational services, parks and other leisure facilities that may promote a healthy lifestyle), higher levels of stress derived from low socio-economic condition or social discrimination, cultural bias, lack of social support, and inappropriate policies (Schiavo 2014).

The Italian National Health System (NHS) is a regionally based healthcare system providing free-of-charge universal coverage to all individuals, regardless of ability to pay. Regular migrants are required to register within the NHS so as to enjoy medical rights under the same conditions as nationals including primary, secondary and emergency care. Migrants who do not hold a valid residency permit, whose permit has expired for more than 60 days, or are pending regularization are required to be assigned a special code (the so-called *Straniero Temporaneamente Presente*; Temporarily Present Foreigner) (STP) to access essential and emergency care, including KT (INMP 2010; Li Cavoli et al. 2019). However, inability to assess the needs and to develop appropriate care plans for migrant and ethnic minority patients is widespread across EU countries (Rafnsson and Bhopal 2009). For instance, while accessibility rights are legally guaranteed, studies report that migrants experience more barriers to care, receive inferior healthcare quality, and are more likely to report diminished health outcomes.

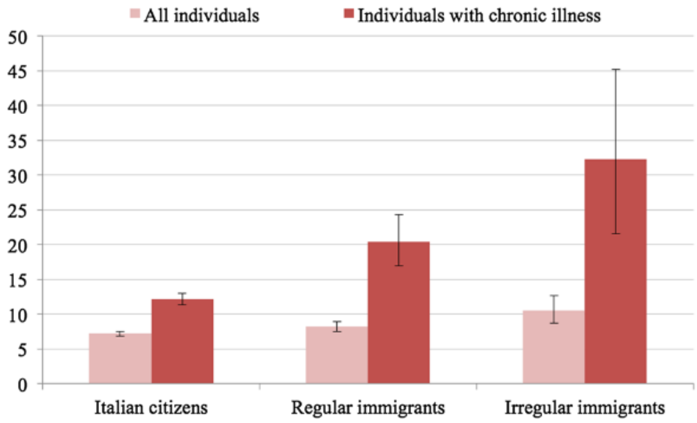
A study in Tuscany (one of the Italian regions with the highest standards of care for immigrant populations) reveals that migrants are more likely than their native-born counterparts to be hospitalized inappropriately, to make use of emergency departments (ED), to be hospitalized for reasons associated with the SDH and preventable care (especially living and working conditions) and, for women, to experience inequities regarding promptness and access to visits throughout the maternal pathway. Also, studies report higher rate of drug and alcohol abuse-, and mental health-related hospitalizations among the most vulnerable subgroups of immigrant populations (i.e. those without a residency permit and, although less frequently, among migrants from least developed countries) when compared to less vulnerable groups of migrants and to their native-born referents (Barsanti 2018).

Similarly, a national level study reports disparities in access to healthcare services especially among non-EU migrants even after controlling for multiple confounders (i.e. demographic and socioeconomic characteristics, lifestyle habits and healthcare needs), consistent with prior research (De Luca, Ponzo, Andrés 2013). These subjects are more likely to access EDs, and less likely to visit specialist physicians and to use preventive services relative to their native- and EU-born counterparts. In line with earlier studies (Geraci, El Hamad 2011), the authors contend that non-EU-born individuals lack information because of linguistic, administrative, and bureaucratic barriers. Informative barriers may reflect the complexity of the procedures to access specialist medicine in the NHS when compared to accessibility of general practitioners and hospital services, especially EDs (Devillanova and Frattini 2016). Overuse of EDs suggests that individuals with an immigration background are more likely to be treated during acute events rather than being taken in charge as recommended in certain healthcare settings.

The lower uptake of preventive services such as cervical and breast cancer screening among women with an immigration background is consistent across multiple studies (Campostrini et al. 2015; Francovich et al. 2017; Bianco et al. 2017). The joint WHO, Istituto Superiore di Sanità (ISS) and Cà Foscari University report on risk behaviors, prevention and health disparities in immigrant populations in Italy provides useful insights into this phenomenon. The report suggests that women from Asia, Northern and Sub-Saharan Africa (i.e. so-called high migratory pressure countries; HMPC) have significantly lower screening uptake, especially within the first five years after migration and in Southern Italian regions. The report stresses that this finding is similar among other socioeconomically disadvantaged native women. However, uptake was found similar to that of Italian women's over time after migration (i.e. after 10 years since immigration) (Campostrini et al. 2015).

A study based on data derived from the 2009 standard Italian SILC (Survey on Income and Living Conditions) and the 2009 special Italian SILC of households with foreign-born subjects revealed that both regular and irregular migrants are more likely to experience unmet need for medical care when compared to their native-born referents. Particularly, disparities are more prominent among individuals with chronic illnesses even after controlling for multiple confounding factors (i.e. sex, age, education, labor force participation, self-assessed health, self-rated poverty, and geographical area) (Busetta, Cetorelli and Wilson 2018) (**Figure 1**).

Figure 1. Percentage of individuals who have experienced unmet need for medical care during the last 12 months



Source: Busetta, Cetorelli and Wilson 2018

Studies have noted also that immigrants from HMPCs are more likely to experience disparities in diabetes management and glycemic control because of inferior quality care and nonadherence when compared to migrants from highly developed countries (HDC) and their native-born referents (Ballotari et al. 2015). Similarly, a study of various chronic diseases such as diabetes, congestive heart failure, and coronary heart disease revealed that migrants from HMPCs are significantly less likely to score well across various indicators of quality of disease management – including adherence to disease management plans – relative to migrants from HDCs and to their native counterparts (Buja et al. 2013).

The co-existing presence of multiple aspects of vulnerability (i.e. poverty, racial/ethnic minority status, chronic physical or mental illness, lack of insurance, old age, incarceration, immigrant status, low level of education, residence in underserved areas, unemployment, widowed status, and homelessness) is reported to be associated with lower accessibility and quality of care (Grabovschi et al. 2013). Based on the evidence-based phenomenon of the Inverse Care Law[1] (Hart 1971), Grabovschi and colleagues (2013) have developed a conceptual model of multi-vulnerability illustrating the dynamic relationship between the health care services

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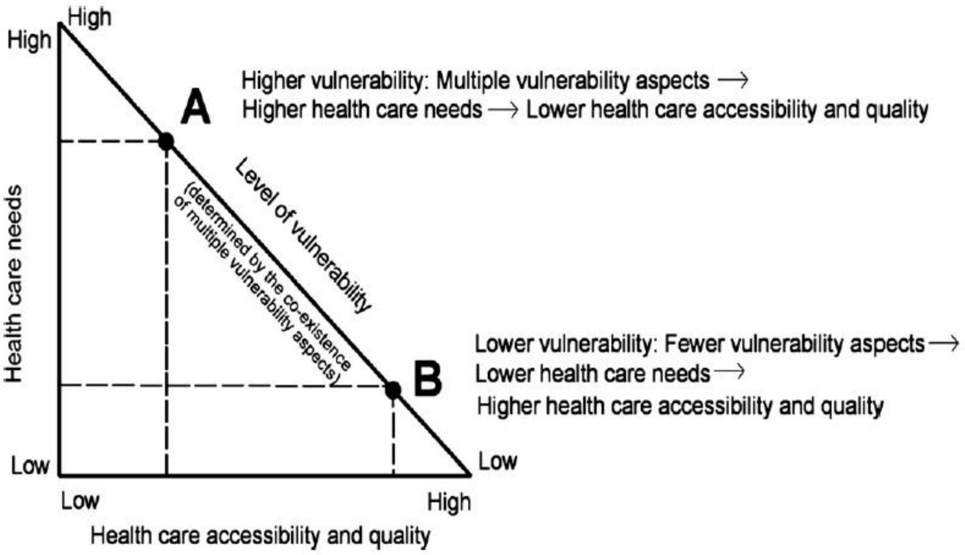
[1] The *Inverse Care Law* states that the people with the greatest health care needs receive the least health care services.

that patients receive, their needs, and the level of vulnerability (**Figure 2**). The model is a right-angled triangle whose horizontal axis stands for the continuum of accessibility and quality of care, whereas the vertical axis represents the continuum of health care needs with varying degrees from low to high depending on the number of vulnerability aspects that co-exist in a given subject at a given point in time. The oblique axis stands for the level of vulnerability that tends to vary depending on health care needs and inversely with accessibility and quality of care.

Figure 2. The dynamic multi-vulnerability model of health care disparities



Source: Grabovschi et al. 2013

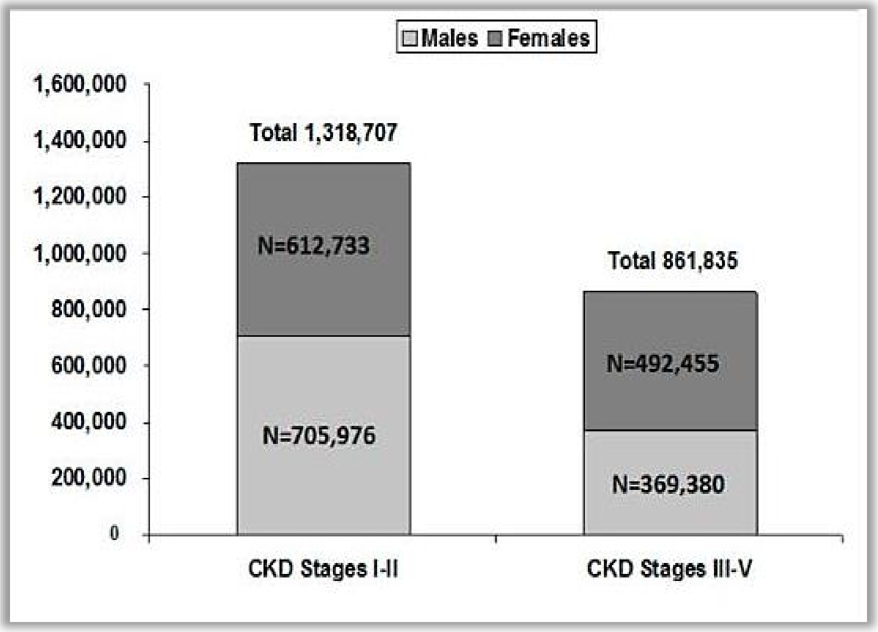
Although vulnerability is recognized as a universal, ontological component of human condition, a variety of vulnerabilities are context-specific and require ethical responses because of their consequences in particular settings (Rendtorff 2002). Beyond being a major principle in organ transplantation (EDQM 2018:31) and migrant health (WHO 2018), equity in healthcare is broadly considered as an ethical imperative. Article 8 of the Universal Declaration on Bioethics and Human Rights (UNESCO 2005:77) states that “in applying and advancing scientific knowledge, medical practice and associated technologies, human vulnerability should be taken into account. Individuals and groups of special vulnerability should be protected, and the personal integrity of such individuals respected”. Consistent, Braveman (2003:185) contends that “it is an ethical responsibility and consonant with principles of human rights to give special priority to action on important public-health problems that differentially affect those with fewer resources and/or greater obstacles to addressing problems”. Similarly, Marmot and Allen (2014: S519) argue that “the case is moral—reducing health inequities and improving health is a duty and should be a priority for governments and those with influence to improve health”.

While many studies consider ethnic minority status as a prominent vulnerability factor, healthcare disparities associated with immigrant status involve more complex, interrelated aspects because of additional vulnerability when compared to ethnicity alone (Grabovschi et al. 2013). For instance, the relevance of addressing the potential barriers to transplant services associated with immigration has been put forward in a recent document endorsed by multiple European transplant organizations, scientific societies and academic institutions (Joint Statement of the Thematic Network on Organ Donation and Transplantation submitted to the European Commission 2019) as well as by other scholars in the European context (Poulakou, Len and Akova 2019; Van Biesen et al. 2018; Forneris et al. 2011).

1.2. Framing disparities in kidney transplantation

According to the Italian Association of Hospital Cardiologists (ANMCO) and the Italian Society of Nephrology (SIN), it is estimated that, in Italy, there are more than 2 million adult subjects (age range 35-79) with CKD (1,075,354 men and 1,105,187 women) (**Figure 3**), the majority of whom with early disease (60.4%) and older age (69.8%) (De Nicola et al. 2015; Conte et al. 2014).

Figure 3. Estimate number of subjects with CKD in the Italian resident population

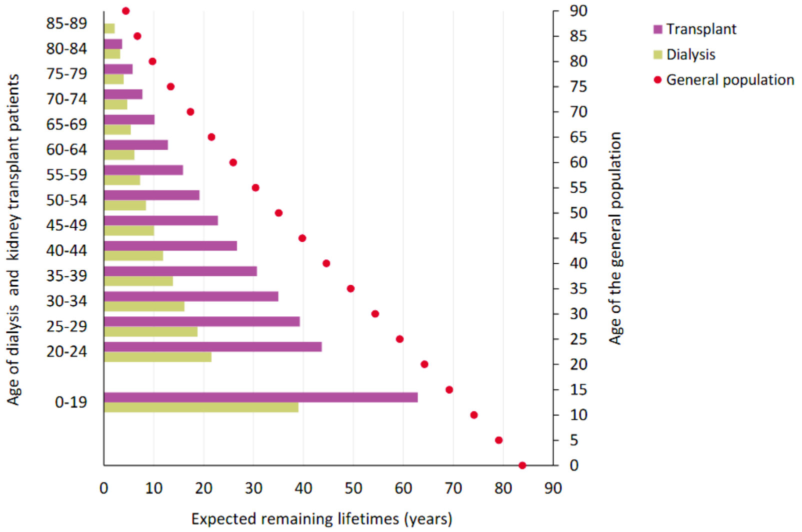


Source: Conte et al. 2014

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health (KDIGO 2013). While the prevalence of CKD is relatively lower when compared to other countries (Provenzano et al. 2019), CKD remains a life-threatening condition associated with progression toward kidney failure, complications of decreased kidney function, and cardiovascular disease (CVD) (De Nicola et al. 2015; Levey et al. 2003). CKD in Italy is associated with a higher prevalence of hypertension, diabetes, obesity, anemia, CVD and low educational level (De Nicola et al. 2015). Patients with Glomerular Filtration Rate (GFR) <15 (i.e. ESKD) require renal replacement therapy (RRT) by dialysis or KT.

In Italy, the yearly incidence of patients on RRT is around 160 per million population, and projections estimate a substantially stable trend up to 2025 (Nordio et al. 2020). KT is the gold standard RRT for ESKD, resulting in better quality of life, improved life-expectancy, and higher cost-effectiveness relative to dialysis (**Figure 4**) (Nordio et al. 2020; Axelrod et al. 2018; Tonelli et al. 2011).

Figure 4. Expected remaining lifetime (years) of the general population (cohort 2013-2017) and of prevalent dialysis and kidney transplant patients (cohort 2013-2017) – by age and sex

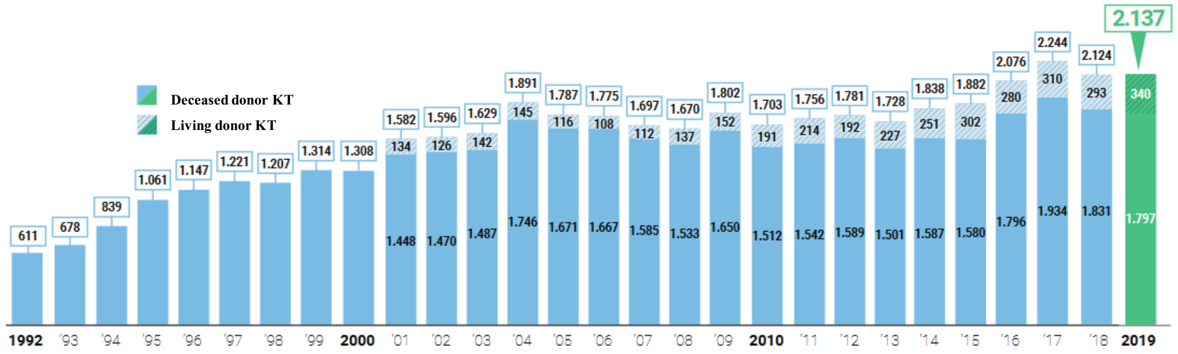


Source: ERA-EDTA 2019

Patients eligible for KT are a selected group of individuals with ESKD. They are selected based on clinical criteria, and on their "capacity to benefit" from treatment. The *KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation* (KDIGO 2020) strongly recommends considering all ESKD patients without absolute contraindication for KT. While, ideally, all patients with ESKD should receive KT provided that their clinical condition allows this, clinical and nonclinical factors (beyond ability to pay) existing in the early stages of the pathway of CKD may have downstream effects on all the subsequent phases of the process, including progression towards ESKD, enrollment on the waiting list (WL), receiving KT, and KT outcomes (Ladin, Rodrigue and Hanto 2009; Maloney, Clay and Robinson 2005) (see below). However, not all patients decide to initiate and/or remain on dialysis or pursue transplantation (Neri et al. 2013; Morton et al. 2010), whereas others present one or more contraindications to KT. Over the years, eligibility criteria for KT have undergone multiple changes. In the early era of transplantation, age older than 40 years was deemed an absolute contraindication, whereas older age *per se* is currently judged a relative contraindication to be considered in the context of other comorbidities that may affect the outcome of transplant (KDIGO 2020:S35). Absolute contraindications to KT include metastatic cancer or active malignancy, active or recurrent infections that are not effectively treated, serious cardiac or peripheral vascular disease, liver insufficiency (unless candidates are suitable for combined liver-kidney transplantation), progressive central neurodegenerative disease, unstable psychiatric and/or substance use disorders affecting decision-making or putting the candidate at an unacceptable risk of post-transplant risk, and other serious conditions that are unlikely to improve after KT (KDIGO 2020; Collins 2019). Yet, because variability exists across guidelines on waitlisting for KT (Batabyal et al. 2012), studies suggest that patients with relative contraindications such as inadequate social support, limited understanding of the transplant process, and age over 65 years are all less likely to be referred for KT (Bartolomeo et al. 2019). Whether these patients should not be eligible for transplantation is debatable. Many relative nonclinical contraindications (i.e. social support, adherence, understanding of the transplant process, etc.) are related to modifiable factors that have the potential to be eliminated by implementation of targeted interventions. In the second place, whether these factors do affect the outcome of KT is uncertain, since studies have led to various outcomes.

When candidates have proven eligible for transplantation, the following challenge is to find a kidney to achieve a successful outcome of KT. While preemptive living donor kidney transplant (LDKT) has advantages over deceased donor kidney transplant (DDKT) in terms of superior patient and graft survival and for expanding the donor pool (Baid-Agrawal and Frei 2007), LDKTs remain limited in Italy when compared with DDKTs (**Figure 5**).

Figure 5. Kidney transplants in Italy (1992-2019)



Source: CNT 2020

Those who do not manage to find a suitable living donor (LD) are registered on the deceased donor WL. Yet, disparities in accessibility and outcomes of DDKT may be associated with a variety of factors of a both clinical and nonclinical nature, which may affect the stages of the process of KT and which are illustrated throughout the following sections.

1.2.1. Factors affecting access to deceased donor kidney transplant

1.2.1.1. Waitlisting

Clinical factors negatively affecting access to the WL include older age, the presence of comorbidities (i.e. CVD, diabetes, past history of malignancy, respiratory disease, cognitive and/or physical impairment, and psychiatric disorders), higher Body Mass Index (BMI), lower serum albumin and hemoglobin levels, and primary cause of kidney failure (i.e. particularly diabetic ESKD) (Chu et al. 2020; Neri et al. 2013; Dudley et al. 2009; Bayat et al. 2006; Kiberd et al. 2006; Winkelmayer et al. 2001). However, other nonclinical factors have been reported to impact WL registration. These include social deprivation, marital status, income, educational level, HL, linguistic isolation, area of residency (i.e. urban vs. rural and socially deprived neighborhoods), distance from transplant center, size of kidney unit, and ethnicity (Taylor et al. 2019; Warsame et al. 2019; Zhang et al. 2018; Schold et al. 2018; Talamantes et al. 2017; Reese et al. 2014; Sandhu et al. 2011; Khattak et al. 2010; Dudley et al. 2009; Axelrod et al. 2008; Hall et al. 2008; Winkelmayer et al. 2001). Particularly, research reveals that ethnic minority status may affect waitlisting regardless of the lower prevalence of medical barriers to transplantation (Ku et al. 2019), consistent with prior studies of immigrant patients in Italy (Forneris et al. 2011). US studies have shown that medical mistrust, experienced discrimination, and perceived racism are equally associated with lower evaluation initiation (Hamoda et al. 2020). Nephrologists' opinions and preferences concerning medical, psychosocial, and behavioral considerations, as well as the potential candidate's sociodemographic and educational status may equally explain disparities in access to KT (Tong et al. 2014).

In other cases, sometimes patients are considered eligible for KT but are not willing to receive one. In Italy, these patients are more likely to be younger, with longer dialysis vintage, less comorbid conditions, poorer expectations towards transplant, lower illness intrusiveness[2], and higher social support from health care providers (HCP) (Neri et al. 2013). These factors are summarized in **Table 1**.

Table 1. Factors influencing access to kidney transplantation

	Clinical factors	*Nonclinical factors (patient)*	*Nonclinical factors (provider/healthcare system))*
Wait-list enrollment	· Older age · Comorbidities (CVD, diabetes, past history of malignancy, respiratory disease, cognitive and/or physical impairment, psychiatric disorders) · Higher BMI · Lower serum albumin · Lower hemoglobin levels · Primary cause of kidney failure (i.e. diabetic kidney disease)	· Social deprivation · Marital status · Income · Educational level · Health literacy · Linguistic isolation · Area of residency (rural vs. urban and/or socially deprived neighborhoods) · Distance from transplant center · Ethnicity/Immigration background · Patient's willingness to receive KT (i.e. preferences)	· Prioritizing individual benefit and safety · Maximizing efficiency · Patient accountability · Justifying gains · Protecting unit outcomes · Reluctance to raise patients' expectations · Physician bias · Size of kidney unit

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[2] "Illness intrusiveness results from illness-induced interference with valued activities and interests. It … derives from diverse sources, such as disease-related anatomical changes, functional losses, treatment side effects, and disease- and/or treatment-related lifestyle disruptions (of course, the reduction of these by effective treatment also reduces illness intrusiveness). Illness intrusiveness compromises psychological well-being and contributes to emotional distress by reducing (a) positively reinforcing (i.e. gratifying) outcomes derived from valued activities and (b) personal control by limiting the ability to obtain positive outcomes and/or to avoid negative ones" (Devins 2010)
Devins GM. Using the illness intrusiveness ratings scale to understand health-related quality of life in chronic disease. J Psychosom Res. 2010;68(6):591-602. doi:10.1016/j.jpsychores.2009.05.006

1.2.1.2. Receiving transplant

Disparities in receiving KT result from a variety of medical and nonmedical factors. In Italy, the time the transplant candidate remains waiting for a suitable organ varies based on various factors: ABO blood type, Panel Reactive Antibody (PRA) value, donor/recipient age Δ, Human Leucocyte Antigen (HLA) mismatches, dialysis vintage, time on the WL, donor HLA typing (homozygosis), and list of prohibited antigens (CNT 2019). Programs and strategies have been developed to supplement the persistent discrepancy between demand and supply of organs for transplantation, as well as to overcome the difficulty in finding a suitable LD or to fill gaps for highly sensitized patients (i.e. patients who develop antibodies against a broad variety of HLA antigens, particularly following pregnancy, blood transfusions and/or previous transplants) (Maggiore et al. 2015). These include strategies to expand the LD pool such as KT from ABO- and/or HLA-incompatible LDs, national and international kidney exchange programs (KEP) including, more recently, kidney exchange programs using deceased donors to initiate kidney exchange chains (DEC-K program) (Maggiore et al. 2015; EKHA 2018; Furian et al. 2019). Other strategies for highly sensitized patients (CDC-PRA ≥85%) with no LD available include the so-called Eurotransplant Acceptable Mismatch Programme (Claas et al. 2009) and, in Italy, a national priority allocation program (PNI) for highly sensitized patients (Maggiore et al. 2015). The procurement of organs from non-standard risk donors (NSRD), donors after circulatory death (DCD), and expanded criteria donors[3] (ECD) have equally been developed to expand the deceased donor pool.

Yet, other reasons why KT candidates do not make it to KT include various reasons for withdrawal from the WL such as death, LDKT, and clinical deterioration (i.e. too sick for transplant) (Schold et al. 2016). Studies have shown that risk factors for WL withdrawal include older age, diabetes, Caucasian ethnicity, longer time on dialysis prior to wait-listing, public health insurance, lower educational level, initial inactive wait-list status, peripheral and cerebrovascular disease and non-paid jobs. Rates of WL removal have been noted to be disproportionately high in certain groups, suggesting that they likely reflect the combination of medical and social risk factors (Poggio et al. 2016).

1.2.2. Factors affecting patient and graft survival and kidney graft function

Advances in surgical techniques, immunosuppressive medication (ISM), assessments of donor-related risks, and perioperative and postoperative management of transplant recipients have made KT a safe and effective treatment for ESKD. However, a variety of donor, recipient, donor-recipient, transplant-related factors, and other non-immunological mechanisms influence the short- and/or long-term outcomes of KT (i.e. patient and graft survival and kidney graft function) (EDQM 2018:385 ; Legendre et al. 2014 ; Gordon et al. 2010), which are briefly summarized in **Table 2**.

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[3] Popular criteria to define ECDs include: age ≥60 years or between 50-59 years and the presence of 2 of the following 3 factors: cerebrovascular death, a past history of hypertension, or terminal serum creatinine levels >1.5 mg/dl (Port et al. 2002) (Port FK, Bragg-Gresham JL, Metzger RA, et al. Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. *Transplantation* 2002; 74: 1281.)

1.2.2.1. Donor Factors

Donor factors affecting the quality of the kidney graft are considered the most significant. Donors are defined based on broad categories such as living versus deceased, and deceased donors' subcategories including ECDs and DCDs. As stated previously, LD kidneys present multiple non-immunological advantages over deceased donor kidneys. These include a more thorough evaluation of LD kidney function, lower detrimental effects of pre-agonal and agonal phases, shorter cold ischemia time[4], and the more frequent involvement of more experienced surgeons.

In the second place, because of their inherent characteristics, *ECDs* have the potential to influence kidney graft function (eGFR) and graft survival. Yet, more thorough scoring systems inclusive of multiple additional variables have led to a broader variety of ECD subgroups that can lead to better outcomes.

The *DCD* donor category can be associated with inferior short-term outcomes because of a higher incidence of primary non-function and delayed graft function (DGF), although long-term data have shown similar results when compared to SCDs.

Pre-implantation histological biopsy data combined with demographic variables and other donor data (i.e. serum creatinine level >150 µm, hypertension, and percentage of sclerotic glomeruli >10) may equally prove useful to determine the quality of the transplanted kidney and predict long-term KT outcomes (Legendre et al. 2014).

1.2.2.2. Recipient factors at the time of transplantation

Recipient *age* (i.e. > 65 years) comes along with multiple problems that are less common in younger age groups. These include cognitive impairment, frailty, and a variety of comorbidities that have been associated with increased morbidity and mortality following transplantation (McAdams-Demarco et al. 2017; Karim et al. 2014; Garonzik-Wang et al. 2012; McAdams-Demarco et al. 2012). The potentially negative effect of age on KT outcomes in older recipients is further exacerbated by allocation policies preferentially assigning older donor kidneys to older recipients because of the donor-recipient age-matching algorithm. However, while KT from ECDs has survival advantages over dialysis, KT from SCDs has been shown to lead to better results when compared to ECD kidneys.

Regarding long-term outcomes, the negative influence of the *recurrence of native kidney failure* is the third cause of kidney graft loss 10 years following transplantation. The risk of recurrence chiefly observed in metabolic diseases and glomerulonephritis varies greatly among diseases. In other cases, the risk of recurrence is correlated with the presence of circulating antibodies or with the activity of the underlying disease. In addition to the relapse of glomerulonephritis, other diseases such as antiphospholipid nephropathy (APSN)

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[4] "In surgery, the time between the chilling of a tissue, organ, or body part after its blood supply has been reduced or cut off and the time it is warmed by having its blood supply restored. This can occur while the organ is still in the body or after it is removed from the body if the organ is to be used for transplantation" (NCI). NCI Dictionary of Cancer Terms, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/cold-ischemia-time.

may recur. In the case of APSN recurrence, vascular changes may result in fibrotic lesions that progressively lead to ESKD.

Good *HLA matching* has always had a favorable long-term effect on KT outcomes including graft survival, diminished patient mortality from infectious complications, the need for lower doses of ISMs along with lower incidence of their side effects, and lower grade of sensitization. Anti-HLA immunization equally has a major negative impact on antibody-mediated rejection and poor outcomes of KT.

Other factors that may account for KT performance include *dialysis vintage* (i.e. time on dialysis) and *cardiovascular comorbidities*, which is correlated with the time the patient remains on dialysis.

1.2.2.3. Graft function in the course of transplantation

In about half of cases in DDKTs and 10% of LDKTs, the immediate post-transplant course may be complicated by *early graft dysfunction*, which is a consequence of multiple intricate factors. This early dysfunction may lead to slow or DGF, increased morbidity, prolonged post-transplant hospitalization along with higher health care costs, and acute kidney injury and dialysis predisposing the graft to acute and chronic rejection, chronic allograft nephropathy (CAN) and premature graft loss (Yarlagadda et al. 2008).

Kidney graft function (eGFR) results from a variety of factors associated with donor, recipient, post-transplant course, and immunosuppressive regimens. The decrease in eGFR between 3 months and 1-year post-transplant is strongly predictive of graft failure, death-censored graft failure and death with a functioning graft because of its independent association with CVD. An additional biomarker with a high potential of long-term kidney graft damage is *proteinuria*[5].

Regarding anti-rejection drugs, while ISMs have lowered the incidence of rejection, they still expose the recipient to specific side effects such as higher risk of developing new onset diabetes along with CVDs but also nonspecific side effects including infections and cancer.

Finally, the risk of *nonadherence* is a very significant risk factor for allograft loss.

1.2.2.4. Other non-immunological risk factors

Beyond the factors mentioned earlier in this chapter, the KT literature documents extensive socioeconomic, sociocultural, and geographic disparities in KT outcomes.

Because of immunological and non-immunological reasons, ethnicity has for long been considered a major risk factor for poor kidney graft outcomes. Multiple mechanisms which have not yet been fully elucidated may explain the inferior graft outcomes in Black minority patients when compared to their White and other ethnic minority counterparts. Among these, a higher incidence of acute rejections, DGF, higher rates of and shorter mean time to CAN, immunological and pharmacokinetic biomarkers of anti-rejection drug metabolism, and increased alloreactivity have been suggested as possible explanations of the inferior outcomes in this group of

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[5] Proteinuria is defined as “a protein concentration of more than 500mg/l in a random specimen of urine or a protein excretion of more than 300mg per 24h” (International Encyclopedia of Public Health 2008)

patients. Also, research reveals that non-white ethnicity, along with poor social support and poor perceived health increase patients' risk for nonadherence to ISM (Dew et al. 2007). However, most of the literature concerning this issue comes from the US, where access to post-transplant ISM is guaranteed to patients with health insurance coverage, whereas it can be accessed by patients with Medicare/Medicaid coverage only over the first 36 months after transplant. Yet, studies have shown that ethnicity affects kidney graft outcomes even after controlling for socioeconomic status (SES) (Gordon et al. 2010).

In contrast, studies from Europe where post-transplant medical regimens are free at the point of access have reported similar outcomes for Black kidney transplant recipients (KTRs) relative to their White referents (Pallet et al. 2005; Mérida et al. 2009), albeit with some inconsistency (Roodnat et al. 1999).

A study from the United Kingdom (UK) suggests that worse kidney graft outcomes are not directly associated with ethnicity but rather with their multiple high-risk baseline variables (higher mean listing time, matching difficulty, socio-economic deprivation, HLA mismatches, donor type - more frequently deceased donor -, recipient CMV positivity, and cold ischemia time) (Williams et al. 2018). Some studies also speculated that worse outcomes could be associated with the lower rates of organ donation among migrant and ethnic minority individuals and the consequent more difficult ethnicity matching. However, recent research refuted this hypothesis (Pisavadia et al. 2018).

Compared to research on ethnicity, less studies have examined the impact of other sociodemographic and socioeconomic variables on KT outcomes. Graft survival has been associated with gender, marital status, educational level, immigration background varying among ethnic groups, area of residency and employment status (Schold et al. 2018; Mistretta et al. 2009; Schaeffner et al. 2008; Naiman et al. 2007; Goldfarb-Rumyantzev et al. 2006; Roodnat et al. 1999).

Table 2. Factors influencing long-term outcomes following kidney transplantation

Donor factors	· Quality of the kidney · Living donor vs. deceased donor · Standard Criteria Donors (SCD) vs. Expanded Criteria Donors (ECD) vs. Donors after Circulatory Death (DCD) · Preimplantation biopsy data
Recipient factors at the time of transplantation	· Age · Native kidney disease · HLA matching · Anti-HLA immunization · Ethnic background · Time on dialysis · Cardiovascular comorbidities
Graft function in the course of transplantation	· Delayed graft function (DGF) · Graft function in a stable condition · Chronic allograft dysfunction · Immunosuppression effects · Prevention of rejection and compliance · Specific side effects · Nonspecific side effects: infections and cancer
Other non-immunological risk factors	· Ethnicity · Area of residency · Gender

- Marital status
- Educational level
- Employment status
- Income
- Insurance coverage (i.e. access to care and to post-transplant regimens)
- Immigrant status

Source: adapted from Legendre et al. 2014

1.3. Definition of the key terms

1.3.1. Health disparities

Lack of consensus exists regarding the meaning of "health disparities," "health inequalities," or "health equity" (Braveman 2006). For the purposes of this dissertation, we define *health disparities* as "potentially avoidable differences in health (or in health risks that policy can influence) between groups of people who are more or less advantaged socially; these differences systematically place socially disadvantaged groups at further disadvantage on health" (Braveman 2006). It follows that differences and disparities are not synonymous. The above definition, grounded in ethical and human rights principles, emphasizes on the subcategory of health differences indicative of social injustice, which distinguishes health disparities from other health differences. In terms of assessment of health disparities, we additionally define them as "observed clinically and statistically significant differences in health outcomes or health care use between socially distinct vulnerable and less vulnerable populations" (Kilbourne et al. 2006), where vulnerable populations are defined as "social groups who have an increased relative risk or susceptibility to adverse health outcomes" (Flaskerud and Winslow 1998). Further, we here intend vulnerability as "an increased susceptibility to health and health care disparities due to a combination of individual[6] and environmental factors[7]" (Grabovschi et al. 2013). This applies equally to the pathway to and following KT in which, as noted earlier, a variety of clinical and nonclinical factors may contribute to disparities along the continuum of care (Ladin, Rodrigue and Hanto 2009) **(Figure 6)**.

1.3.2. Health equity

Health equity is here defined as "the principle underlying a commitment to reduce – and, ultimately, eliminate – disparities in health and in its determinants, including social determinants. Pursuing health equity means striving for the highest possible standard of health for all people and giving special attention to the needs of those at greatest risk of poor health, based on social conditions" (Braveman 2014). Some scholars put forward a process view of health equity, whereas others focus on equity in health outcomes (Cohen, Grogan

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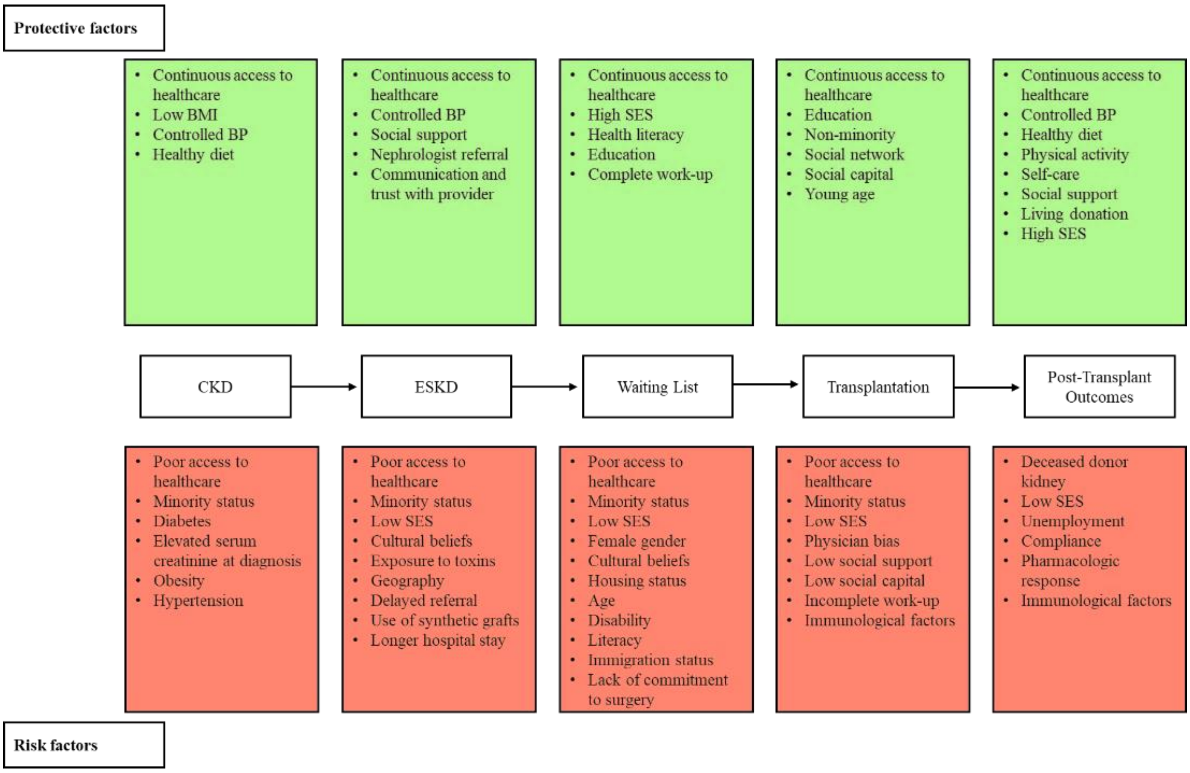
[6] *Individual features* may be either inborn (i.e. gender, ethnicity, genetic predispositions to disease) or acquired (i.e. trauma, diseases, lifestyle)

[7] *Environmental factors* either refer to the immediate physical environment (i.e. temperature, pollution, housing, community and neighborhood characteristics) or to the broader socioeconomic environment (i.e. social networks, historical, political, and cultural context)

and Horwitt 2017). However, as noted earlier, because some vulnerabilities are context-specific and require ethical answers because of their consequences in particular settings (Rendtorff 2002), we contend that promoting health equity in the context of this study requires consideration of both a process view of equity (rather than equality) so as to achieve equity in KT accessibility and outcomes accordingly.

Figure 6. Framework for Disparities in Kidney Transplantation



Source: Ladin, Rodrigue and Hanto 2009

1.3.3. Ethnicity and race

Ethnicity is generally defined as “the social group a person belongs to, and either identifies with or is identified with by others, as a result of a mix of cultural and other factors including language, diet, religion, ancestry, and physical features traditionally associated with race” (Bhopal 2004). From this perspective, the concept of ethnicity is frequently overlapping with the concept of “race” and they are often considered synonymous. Race is defined as “the group […] a person belongs to as a result of a mix of physical features such as skin colour and hair texture, which reflect ancestry and geographical origins, as identified by others or, increasingly, as self-identified” (Bhopal 2004). However, there is general agreement that both ethnicity and race are social constructs that have no genetic bases (Senior and Bhopal 1994; Gordon 2002). A medical encyclopedia provides a clear and strong statement relative to the scientific inappropriateness of the term race, defining it as “a vague, unscientific term for a group of genetically related people who share some physical traits" (Glanze, Anderson and Anderson 1994). Yet, as opposed to race, some authors contend that an individual's ethnicity can provide clinical clues that may be of value for medical purposes and for studying differences in populations that may be important to health. These include geographic origin and immigrant status, housing conditions and employment patterns, dietary habits, cultural and environmental factors, and genetic ancestry (Witzig 1996). These features can be present at various intensities across the composition of different ethnic minority groups. However, lack of consensus is widespread regarding the assessment of ethnicity and race in genetic or epidemiologic studies. Different classifications exist among EU countries and, given the different history of immigration, between EU countries and the United States (US). While ethnicity in the US is mostly self-perceived, ethnicity across the EU is broadly defined by surrogate variables (European Commission 2017). Similarly, in Italy, neither racial and/or ethnic statistics are permitted and, in the Italian Census, they are identified with proxies like citizenship, place of birth, former citizenship for Italians, and, since the 2011 Census, citizenship of parents (Ambrosetti and Cela 2015). However, since Italy was first among the EU-28 countries for number of acquisitions of citizenship in 2016 (201,591, corresponding to 20.3% of the total in the EU) (Caritas Italiana 2018), the use of citizenship as a proxy for ethnicity has several limitations, whereas former citizenship is often difficult to derive from registry data. Therefore, for the purposes of this study, country of birth was considered as the most suitable surrogate to identify ethnic minority individuals.

1.3.4. Immigrant status

Immigrant status diverges from ethnicity and race, but simultaneously includes elements of both. The International Organization for Migration (IOM) broadly defines 'international migrant' as "any person who is outside a State of which he or she is a citizen or national, or, in the case of a stateless person, his or her State of birth or habitual residence. The term includes migrants who intend to move permanently or temporarily, and those who move in a regular or documented manner as well as migrants in irregular situations" (IOM 2019). Therefore, migrants are a heterogeneous group including regular and irregular migrants, economic migrants, asylum seekers, refugees, displaced persons, and others. More vulnerable immigrant categories (i.e. refugees, asylum seekers, and undocumented migrants) are more likely to experience more significant disparities. However, these individuals represent a minority of the total dialysis population in Europe (1.5%), and most dialysis centers in the EU have no refugees at all (Van Biesen et al. 2018; Van Biesen et al. 2016). Therefore, we define migrants as those individuals who "choose to move not because of a direct threat of persecution or death, but mainly to improve their lives by finding work, or in some cases for education, family reunion, or other reasons" (UNHCR 2016). At the European level, the European Commission (EC) stresses that the immigrant category "does not include intra-EU mobility of citizens or residents" (European Commission). Therefore, for the aims of this study, we consider individuals who were born in a country outside the EU as first-generation immigrants (as opposed to second-generation immigrants, namely subjects who were born of immigrant parents originating from non-EU member states). Because individuals who have migrated from other countries or are from ethnic minorities in Europe are likely to experience similar health care disparities (EUPHA 2018; Bhopal 2014), because some biological features vary among ethnic groups (Gordon et al.), and because individuals belonging to "visible" ethnic minorities may experience more significant inequities (Llácer et al. 2007), both immigration background and ethnicity will be considered for the purposes of this study. Therefore, we will focus on regular migrants, acknowledging that migrants' legal status may contribute to diminished accessibility and quality of care. Since immigration from non-EU countries is a recent, extensive, and growing phenomenon in Italy and other European countries, this study will focus on first-generation (i.e. foreign-born) non-EU-born immigrants relative to natives and natives of the other EU-28 member states in Italy.

1.4. Objectives and outline of the dissertation

The structure of this dissertation follows the three steps prescribed by the disparities research agenda by Kilbourne et al. (2006). The framework they propose originates in epidemiology, defined as "the study of the distribution [detection] and determinants [understanding] of health-related states or events in defined populations, and the application of this study to the control of health problems [reduction/elimination]". Based on this definition, the framework organizes the process of disparities research into three distinct phases, namely (1) detection, (2) understanding, and (3) mitigation or elimination (**Figure 7**). The first phase is devoted to the definition of health disparities, identification of vulnerable subjects and development of measures for studying them. The second phase of the research agenda entails identification of factors explaining gaps in health and healthcare between vulnerable and less vulnerable groups. The third phase encompasses the development, enactment, and evaluation of interventions aimed at reducing or eliminating health care disparities (Kilbourne et al. 2006).

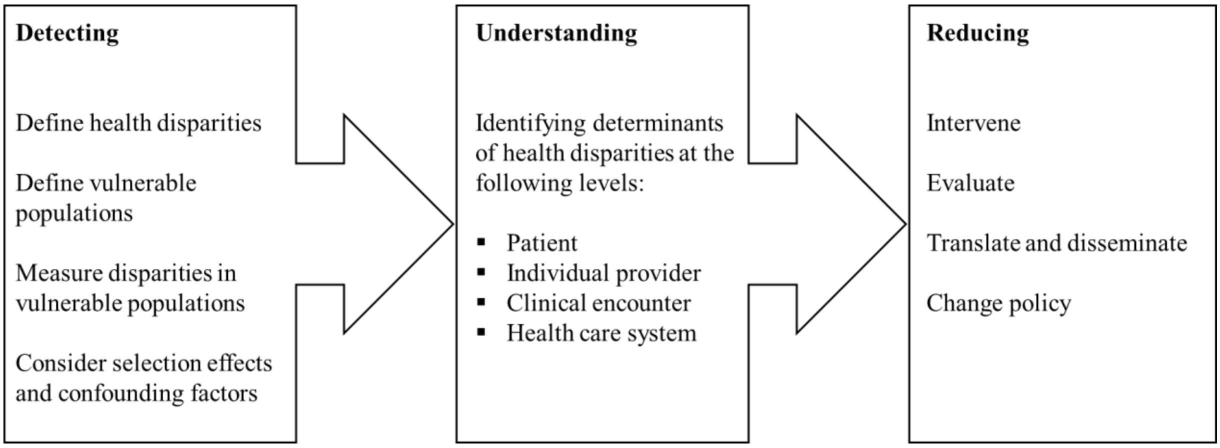
Following from this perspective, three research phases were outlined to pursue three main objectives:

1) To assess whether disparities exist in KT outcomes in the non-EU-born immigrant patient population in Italy.

2) To determine the ethical relevance of detecting and understanding determinants of disparities in accessibility and outcomes of KT and to discuss inherent ethical dimensions.

3) To explore the causal mechanisms linking immigration background with KT outcomes and identify the potential for interventions to prevent, mitigate or eliminate disparities in accessibility and outcomes of KT in this vulnerable group of patients.

Figure 7. The Three Phases of the Disparities Research Agenda



Source: Kilbourne et al. 2006

The definition of health disparities, vulnerable populations, along with potentially confounding factors regarding disparities in accessibility and outcomes of KT are provided earlier in this Chapter. In Chapter 2 the immigration phenomenon in Italy, and the multiple general challenges and aspects of vulnerability experienced by the immigrant patient population are described along with the potential barriers in access to and outcomes of care. Further, it presents the theoretical underpinnings regarding the SDH and immigration as an SDH. Chapter 3 provides an overview of disparities in ESKD and KT in the immigrant patient population in Italy along with comparisons with other countries in the EU. In the process, it identifies research gaps so as to inform the agenda for future research. In Chapter 4 we assess the association of non-EU immigration background with kidney graft function (eGFR) and transplant survival in Italy. In Chapter 5, three emblematic clinical cases describing the various challenges that might account for disparities in accessibility and outcomes of KT in the non-European immigrant patient population are reported along with a discussion of the ethical relevance to consider the SDH when performing pre-transplant multidisciplinary assessments in this vulnerable group of patients. Chapter 6 proposes a conceptual model of the major mechanisms at the level of patient/donor, individual provider, clinical encounter and healthcare system which are likely to contribute to disparities in KT accessibility and outcomes in immigrant patient populations in the EU. In the process, we identify potential areas for intervention along with the gaps in our understanding of the determinants linking non-European immigration background with disparities in KT. Finally, in Chapter 7, a general discussion of the results of the dissertation is presented along with future research directions.

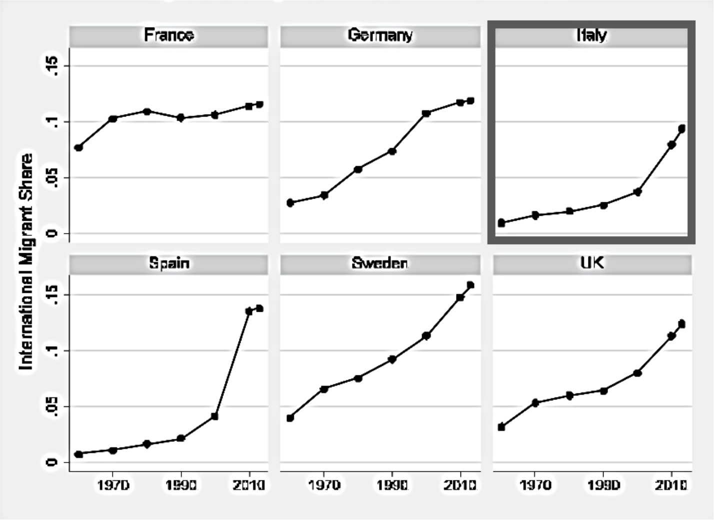
Chapter 2. The immigration phenomenon in Italy and the social determinants of health

> *"Health is about more than health care, and the same is true for health equity.*
> *Health equity is achieved not only by treating illnesses but also by addressing the physical and social*
> *environments that shape health behavior and produce disease*
> *and by creating the opportunity for vulnerable populations*
> *to build social and economic resources"*
> (Woolf 2017)

2.1. The immigration phenomenon in Italy

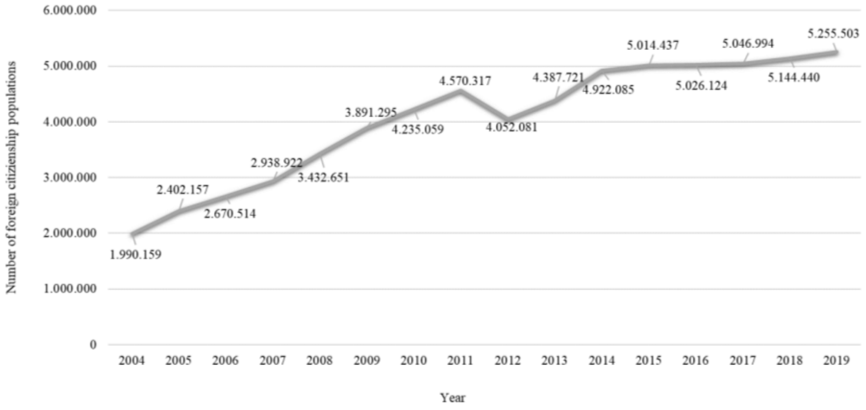
Over the past few decades, the European Union (EU) has experienced major demographic changes, shifting from being an emigration area to a net immigration destination (European Commission 2006). In 2018, 39.9 million non-citizens were found to reside in EU member states and primarily in Germany (9.7 million individuals), the United Kingdom (UK) (6.3 million), Italy (5.1 million), France (4.7 million) and Spain (4.6 million). Of these, the majority were first-generation immigrants from non-EU countries (22.3 million) with variations in countries of origin across the EU-28 member states (Eurostat 2018). While immigration in former European colonial powers (especially the UK and France, but also Belgium, the Netherlands, and Portugal) dates back to the 1950s, the immigration phenomenon in Southern European countries like Italy, Greece, and Spain is more recent and began in the 1990s, with a fast growth rate since the year 2000 (**Figure 8**; **Figure 9**).

Figure 8. Immigrant Stock in Selected Countries



Source: De La Rica, Glitz and Ortega 2013 : 13

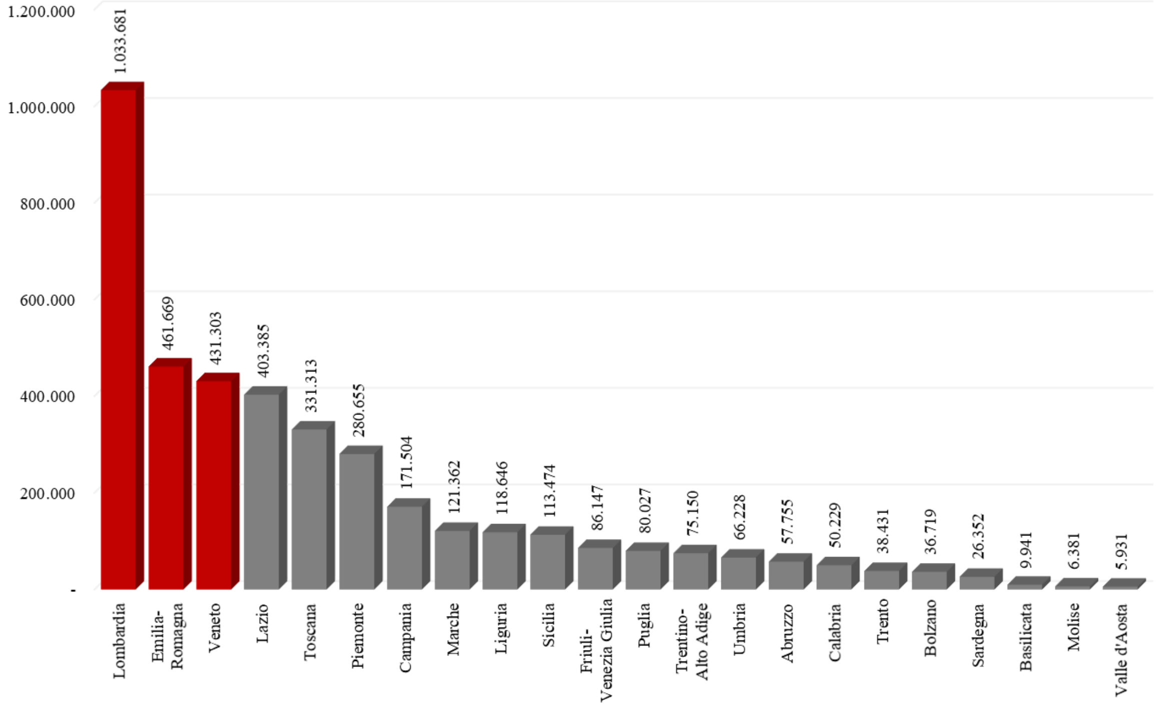
Figure 9. Trend of populations with foreign citizenship in Italy (2004 – 2019)



Source: Italian National Institute of Statistics (ISTAT) 2019

Between the 1990s and 2000s, immigrants in Italy originated primarily from Romania, Albania, and the former Yugoslavia, and settled chiefly in the economically wealthier areas in the Northern part of the country. The higher presence of immigrants across Northern areas has remained substantially unaltered throughout the years, and recent data of the Italian National Institutes of Statistics (ISTAT) show this (**Figure 10**).

Figure 10. Distribution of regularly present foreign citizens by Region in Italy (2019)



Source: Italian National Institute of Statistics (ISTAT) 2019

Particularly, the geographical and linguistic proximity of Romania made Italy an appealing place for the settlement of individuals of Romanian origin, mostly for economic reasons. In May 2004 and January 2007, respectively, the most substantial enlargements of the EU occurred and came to include Central and Eastern European countries (Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia and Slovenia first and Romania and Bulgaria afterwards). Many Poles settled in Ireland and the UK, whereas Bulgarians and Romanians moved primarily to Italy and Spain (De La Rica, Glitz and Ortega 2013). While the vast majority of the immigrant share in Italy was composed initially of individuals from Albania, Romania, and Morocco, starting from 2014, the crises that have been affecting numerous countries in Africa and the Middle-East have led to a massive flow of immigrant populations seeking protection throughout the Mediterranean areas of Europe, including Italy. A significant increase in migrant flows from these areas was registered in the period between 2014-2017, when the phenomenon of mass immigration on the Italian shores was the greatest reported ever. Until 2018, a change in the countries of origin relative to the pre-2014 period could equally be observed, with most subjects originating from Sub-Saharan Africa, the Middle East and the Indian Subcontinent (**Table 3**), driven mostly by economic motivations towards the Italian coasts. Therefore, ethnic minority individuals in Italy are composed largely by first-generation immigrants originating from countries outside the EU beyond the Eastern European area.

Table 3. National origin of foreigners registered as residents in Italy by macro region. On January 1st in 2014 and 2018 (values in thousands)

Macro regions	*2014*	*2018*	*Variations % (*)*	*Most represented countries*
EU 28	1.442	1.562	8,4	Romania, Poland, Bulgaria
Central Eastern Europe	1.131	1.048	-7,4	Albania, Ukraine, Moldavia
Other Europe	11	10	-4,3	Switzerland, San Marino, Norway
North Africa	675	655	-3,0	Morocco, Egypt, Tunisia
Western Africa	**279**	**377**	**34,9**	**Nigeria, Senegal, Ghana**
Eastern Africa	41	40	-2,9	Eritrea, Somalia, Ethiopia
Central Southern Africa	**22**	**25**	**10,5**	**Cameroon, Congo DR, Congo**
Western Asia	**39**	**48**	**24,4**	**Georgia, Iran, Syria**
Central Southern Asia	**451**	**524**	**16,1**	**India, Bangladesh, Pakistan**
East Asia	442	482	9,1	China RP, the Philippines, Japan
North America	17	17	0,5	USA, Canada
Center and South America	369	354	-3,9	Peru, Ecuador, Brazil
Oceania	2	2	-2,3	Australia, New Zealand, Papua NG
Total	**4.922**	**5.144**	**4,5**	

(*) Values have been calculated on data not rounded to thousands.
Source: Fondazione ISMU 2019:23

However, in 2018, there was an 80% decrease in migration flows relative to 2017 (the number of migrants landed by sea dropped from 107,000 to 21,000) (Fondazione ISMU 2019). In 2017, the maximum number of asylum applications since 1997 was reported (130,000), while it diminished significantly in 2018 (44,000). Yet, out of 71,000 applications presented over the first nine months of 2018, the majority were denied. Five-thousand individuals obtained the refugee status, humanitarian protection was granted to over 18,000 people, and subsidiary protection to approximately 3,000.

In Italy, at the general national elections in 2018, it is well-known that none of the main political groups (center-left coalition, center-right coalition, and the Five Stars Movement) achieved parliamentary majority, and only 24.7% of citizens voted for parties with pro-immigration attitudes. Over the past few years, immigration has gained increasing importance on the political agenda of many EU countries as a public-, economic-, and public health-safety issue. The anxiety about a possible "invasion" by asylum seekers, refugees, undocumented migrants and, more generally speaking, outsiders, remains one of the most politically debated topics across Western European countries (Van Dijk 2000 ; Huysmans 2006). The fear that asylum seekers may impact negatively on the host countries' economies due to the need to invest public money to support them, along with the concern that newcomers may be worsening unemployment rates (especially among low- and medium-skilled workforces), may be listed among the reasons underlying the generally negative attitude towards outsiders (Semyonov et al. 2006; Hiscox 2007; Dustmann and Preston 2007; Montserrat 2010). Economic uncertainty and instability in people's everyday lives can be grounds for the widespread anti-immigrant sentiment in the EU context (Montserrat 2010). Among unemployed low and medium-skilled workers, "the perception that immigrants come to their countries to "steal" their jobs as well as the view […] that asylum seekers and refugees receive greater social benefits than nationals, is contributing to a process of increasing resentment towards the state and towards society as a whole". In contrast, individuals in higher social strata and often supporting new radical right parties "are not so much driven by economic motivations, but regard the impact of migration as a deadly threat to national identity" as they "are concerned about the "leveling down" of their own cultures as a result of 'hybridization' " (Montserrat 2010). Within this context, the so-called "Italians first" political rhetoric regarding access to welfare state benefits for immigrant populations is widespread, and has the potential to affect welfare polices with negative implications for migrants' health (Stronks and Agyemang 2020). In 2018, various regional governments across the country set out stringent criteria for immigrants' access to public nursery schools (15 years of prior residency in the Region) and public housing (10 years of residency in Italy were required), with clear indirect discrimination towards these subjects. In all cases, provided that foreign-born individuals are entitled to receive benefits under the same conditions as nationals, the Constitutional Court concluded that such criteria are constitutionally inapplicable given the inherent violation of the equality principle ascribed in the Italian Constitutional Charter.

However, since 2018, Italian policies on immigration have undergone multiple changes which negatively affected the chance for more vulnerable immigrant categories to obtain humanitarian protection permits, which were actually abolished. While this measure automatically turned thousands of immigrants with humanitarian protection status into undocumented migrants, data reveal that most foreign-born individuals in Italy are regular residents as opposed to regular non-residents (i.e. those whose regularization is pending prior to immigration) and irregular migrants (i.e. those without a valid residency permit) (**Table 4**).

Table 4. Foreigners in Italy on 1st January 2016-2018 by type of presence (in thousands)

Type of presence	*1.1.2016*	*1.1.2017*	*1.1.2018*
Residents	**5,026**	**5,047**	**5,144**
Non-residents, legal	410	420	431
Undocumented	435	491	533
Total presences	**5,871**	**5,958**	**6,108**

Source: Fondazione ISMU 2019:21

Yet, the number of undocumented migrants has grown significantly with the rise of unauthorized arrivals by sea since 2014 along with the many cases of rejected applications (**Table 5**). However, despite the thousands of expulsion and/or repatriation decrees released, only a minority (i.e. less than 20%) were actually repatriated and/or expulsed (Fondazione ISMU 2019).

Table 5. Asylum application results in Italy. 2016 and 2017

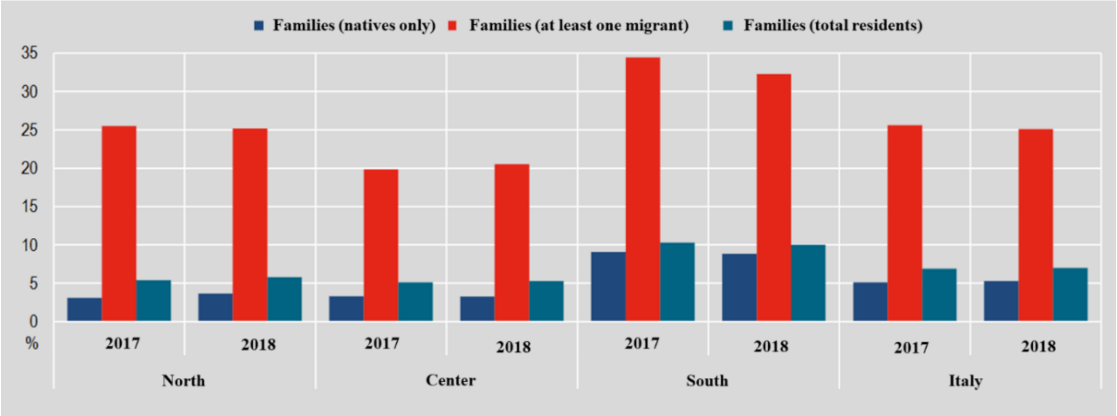
Result (*)	*2016*	*%*	*2017*	*%*	*Variation %*
Refugee status	4,940	5.5	6,854	8.5	38.7
Subsidiary protection	11,200	12.4	5,796	7.2	-48.3
Humanitarian protection	18,801	20.8	19,541	24.4	3.9
Rejection (**)	**55,425**	**61.3**	**47,839**	**59.6**	**-13.7**
Other results (***)	107	0.1	173	0.2	61.7
Total	**90,473**	**100**	**80,203**	**100**	**-11.4**

(*) Applications examined in the given year independently from the application date; (**) Unrecognized + untraceable; (***) Includes renunciations.

Source: Fondazione ISMU 2019:24

Immigrants in Italy are more likely to be *socioeconomically disadvantaged* (**Figure 11**). More than 1.5 million foreign-born individuals are in a state of absolute poverty. The incidence is highest in families composed exclusively by migrants (27.8%) or with at least one foreign-born subject (25.1%) as opposed to families with native-born members only (5.3%). The uppermost incidence is reported in bigger urban areas (it is 26.2% for families with at least one foreign-born subject and 28.8% for those with foreign-born members only), and in Southern regions. In Southern areas, consistent with the historical North-South gap, immigrant families are four times more likely to be in a state of absolute poverty when compared to natives (32.3% vs. 8.9%), especially in families with at least one child below the age of 18 (40.5% vs. 12.4%). Foreign-born families whose head of household is in search of a job is in a condition of absolute poverty in more than half of cases (51.5%); this occurs less frequently when he/she is occupied (25.5%) (ISTAT 2019). According to the 27th Caritas Report on immigrant populations, out of 205,090 persons referring to Caritas services, 16,000 were refugees and, overall, more than half were migrants (56.2%) (Caritas Italiana 2018).

Figure 11. Incidence of absolute poverty by citizenship of family members and geographic area, 2017-2018 (%)



Source: Italian National Institute of Statistics (ISTAT) 2019

Immigrant populations in Italy are also more likely to experience language difficulties (ISTAT 2014) and to have lower *educational levels* when compared to native Italians. More than half of migrants aged 15-64 have at most achieved lower secondary (vs. 38.4%) or upper secondary education (34.4% vs. 43.4%), whereas only a minority holds a university degree (10.7% vs. 18.2%) (ISTAT 2019). Also, they report lower educational attainment levels when compared to individuals who have migrated to other EU countries (**Figure 12**). Overall, despite *employment*[8] rates among migrant subjects aged 15-64 being slightly higher (64.4% vs. 63.4%), and inactivity[9] ones lower (29.1% vs. 34.9%) relative to their native-born counterparts', unemployment[10] rates are higher among immigrant populations (13.8% vs. 9.5%), and the gap has remained substantially unaltered over the past 14 years (ISTAT 2019; Fondazione ISMU 2019). Immigrant labor is concentrated chiefly in blue collar (76.3%) and low-skilled jobs (i.e. house assistants and caregivers), which is sometimes indicative of uprising segregation phenomena. Particularly, one in two migrants of non-EU origin is occupied in a low-skilled position. The rate of independent workers, entrepreneurs, and freelance professionals is markedly lower among immigrant populations when compared to natives (13.1% vs. 24.4%; 0.4% vs. 1.3%; and 1.1% vs. 6.7%, respectively).

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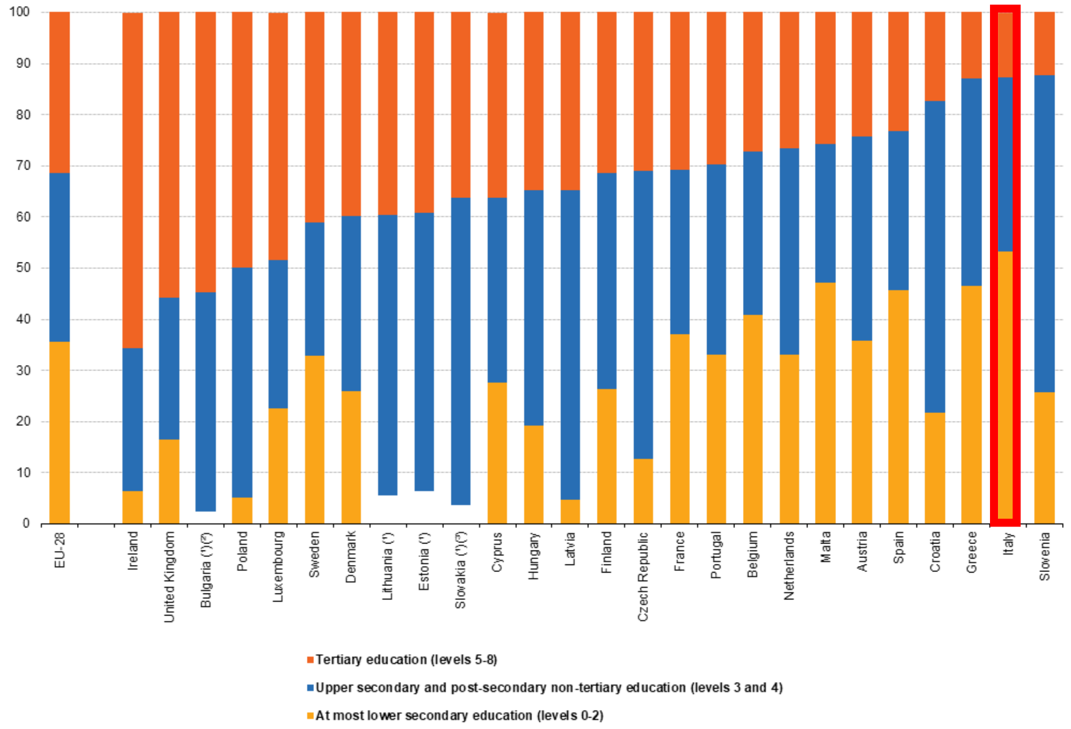
[8] *Employment rate*: percentage ratio between unemployed subjects in a given age-group (usually 15-64 years) and the whole of employed and unemployed (work forces) within the same age-group

[9] *Inactivity rate*: percentage ratio between subjects who do not belong to any work force (inactive) in a given age-group (usually 15-64 years) and the corresponding total resident population within the same age-group

[10] *Unemployment rate*: percentage ratio among unemployed subjects in a given age-group (usually 15-64 years) and the whole of employed and unemployed (work forces) within the same age-group

Figure 12. Analysis of the population born outside the EU and aged 25-54, by educational attainment level, 2016 (%)



Source: Eurostat 2016

Further, some ethnic communities appear to have sectoral specialization, with a so-called phenomenon of 'ethnicization' of certain sectors (a prominent example is that of the Filipino community who is mostly - nearly 80% - employed in domestic work). 'Ethnicization' equally applies to other vulnerable groups of migrants experiencing phenomena of working marginality. These subjects are more likely to end up in less beneficial occupational sectors and, in the worst cases, in the so-called 'hidden economy'. In 2017, migrants were employed chiefly as agricultural workers, personal assistance staff, waiters, house-assistants/caregivers, unqualified personnel in catering services, doorkeepers, cooks, unskilled workers, and cleaning employees. This has the potential for exposure of these populations to higher occupational insecurity and, given their overall lower educational attainment level and low-skilled jobs, also to higher likelihood of being unemployed in a 4.0 economy increasingly requiring more highly-skilled persons. The combination of these factors contributes to the multiple vulnerabilities experienced by individuals with an immigration background. These include income penalization (the average income of migrant workers is 35% lower than that of native-born subjects), the potential for intergenerational transmission of disadvantage from parents to children, the lower chance to participate in the Gross National Product (GNP) and contribute to the welfare system (with possible consequences on future retirement funds for these populations), and, for immigrants with higher qualifications, the lower chance to have job opportunities that are consistent with their educational backgrounds when compared to natives (26% vs. 90%) (Fondazione ISMU 2019). While the employment rate of immigrant women slightly exceeds that of native Italian ones, both inactivity and employment rates remain strikingly above average for some ethnic groups, particularly in association with the type of migration pattern (i.e. family reasons) (**Table 6**).

Table 6. Entries for family reasons (%), inactivity rates, NEET (%) and unemployment rates among the women of given non-EU citizenships

	Entries for family reasons (%)	*Inactivity rate*	*Neither in Employment nor in Education and Training (NEETt) (%)*	*Unemployment rate*
Albania	76.6	54.3	52.9	24.0
Bangladesh	97.7	80.2	80.7	46.6
China	49.4	32.0	18.1	3.4
Ecuador	--	34.0	29.8	18.4
Egypt	95.7	88.9	59.5	44.5
Philippines	82.9	18.8	28.4	5.3
Ghana	79.2	53.8	53.8	50.9
India	84.9	76.4	63.2	19.0
Morocco	93.1	68.8	58.9	29.4
Moldavia	--	24.3	21.5	14.2
Pakistan	92.2	86.7	64.5	42.8
Peru	--	23.0	19.7	11.2
Sri Lanka	91.8	53.0	58.2	23.2
Tunisia	90.4	70.2	69.1	51.2
Ukraine	58.1	26.3	37.3	10.9
Total	**66.1**	**44.1**	**46.3**	**12.8**

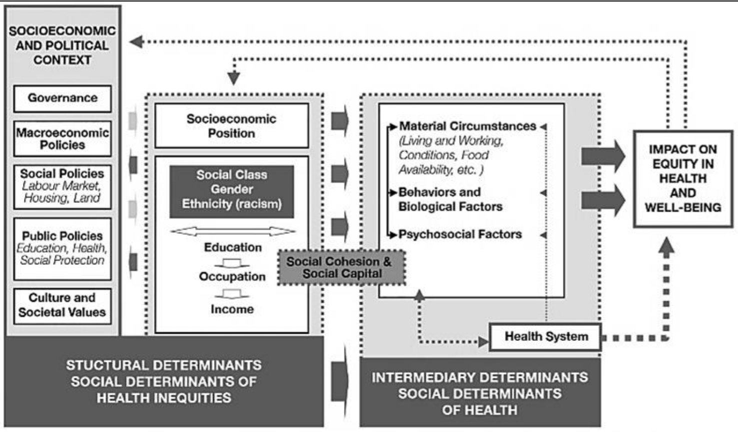
Source: Fondazione ISMU 2019:40

2.2. The Social Determinants of Health

The World Health Organization (WHO) defines the social determinants of health (SDH) as the "conditions in which people are born, grow, live, work, and age" (WHO 2015). According to the conceptual framework by Solar and Irwin (2010), the key components of the SDH include 1) the socio-political context, 2) structural determinants and socioeconomic position, and 3) intermediary determinants (**Figure 13**).

Given the terminological ambiguity of the concepts addressed in their model, the authors distinguish between "structural determinants" – i.e. the "interplay between the socioeconomic-political context, structural mechanisms generating social stratification and the resulting socioeconomic position of individuals"; "social determinants of health inequities" – i.e. "the social processes shaping the distribution of downstream social determinants" and "intermediary determinants of health" – i.e. the more downstream factors affecting equity in health and well-being.

Figure 13. Conceptual Framework for Action on the Social Determinants of Health



Source: Solar and Irwin 2010

The *socioeconomic-political context* includes a variety of structural, cultural, and functional aspects of a social system whose impact on individuals is difficult to quantitatively measure but which play the greatest role in the formation of social stratification patterns and, as a consequence, to the health opportunities of individuals. It is within this context that political and social mechanisms produce, shape, and maintain social hierarchies (i.e. the labor market, the educational and social protection system, along with political institutions including the welfare state). Political movements/parties and the policies they implement influence the organization of healthcare as well as social and health disparities by means of unequal distribution of the SDH across social groups in society. Generally speaking, this broader context (which may vary greatly from one country to another) should include: 1) governance - defined as "[the] system of values, policies and institutions by which society manages economic, political and social affairs through interactions within and among the state, civil society and private sector. It is the way a society organizes itself to make and implement decisions" (UNDP 2011) - and its inherent processes (i.e. definition of needs, forms of discrimination, participation to civil society, and accountability of public administration; 2) macroeconomic policies such as fiscal, financial, balance of payments and commercial policies and labor market structures and policies[11]; 3) social policies having an impact on factors such as labor, social welfare, housing and land distribution. 4) public policies in important areas including education, health care, and social protection. Particularly, the "welfare state" plays a critical role in the protection and promotion of the economic and social well-being of the citizens of a given country and includes primarily income redistribution and features such as the public provision of social insurance, basic education, health care services, housing, and anti-poverty programs, to name a few; 5) culture and societal values with special attention on the value attributed to health as a collective social matter and to the health policies it develops; and 6) epidemiological conditions, with a focus on major epidemics with the potential for significant influence on social structures (i.e. HIV).

Structural determinants generate and/or strengthen social stratification and shape the socioeconomic position of individuals. These processes define the health opportunities of the various social groups in society within hierarchical position(s) of power, prestige, and access to resources. It is the processes of structural social stratification, together with and influenced by institutions and mechanisms ingrained in the socio-economic and political context that can, together, be considered as the social determinants of health disparities. Some of the major variables used to operationalize socioeconomic position include income, education, occupation, social class, gender, and race/ethnicity that are affected by the socio-economic and political context. Structural determinants function through so-called intermediary social factors or social determinants of health. Structural determinants of health disparities causally precede intermediary determinants which are connected with influences at the individual level, including health-related behaviors and biological factors. The main intermediary determinants include material conditions (i.e. working and neighborhood environment, living and housing circumstances, financial means to buy healthy food and climate-appropriate clothes, and others),

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[11] Labor market policies can be either active – i.e. professional training and job creation usually targeting groups with special difficulties including older and younger subjects, women, and other vulnerable individuals like the disabled - or passive – i.e. unemployment insurance, assistance and/or early retirement.

psychosocial circumstances, behavioral and biological factors. It is the unequal distribution of these intermediary factors that represents the principal means by which socioeconomic position determines health disparities. Further, given its ability to influence the process by acting upon differences in exposures, vulnerability, and in the consequences of illness for people's health and their social and economic circumstances, the health system itself - along with healthcare organizations and healthcare providers - is intended as a social determinant of health.

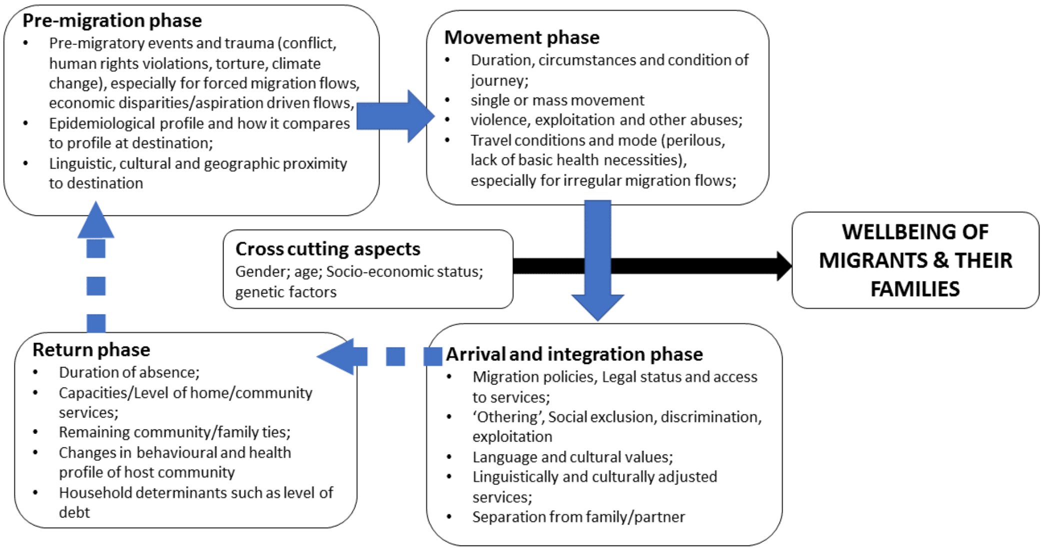
2.3. Immigration as a social determinant of health

It is well established that being a migrant does not represent itself a risk to poor health. Rather, it is the combination of the multiple conditions and vulnerabilities that can be associated with immigrant status and to the entire migration process that have the potential to lead to inferior health, accessibility, quality, and outcomes of care (Grabovschi et al. 2013). Research on immigrant health has been disconnected for long from an SDH perspective in the past. However, in more recent years, immigration is increasingly considered not only as a result of the SDH but also as an important SDH in its own right (National Academies of Sciences, Engineering, and Medicine 2018; IOM). Castañeda and colleagues (2015) highlight that the vast majority of studies of immigration and health have been focusing chiefly on behavioral (i.e. individual-level) and cultural (i.e. group-level) factors. While these approaches are useful to gain insights and to develop targeted interventions to improve the health of these vulnerable subjects, they both present several limitations. On the one hand, health behavior frameworks *per se* tend to individualize responsibility and risks and to overlook upstream structural factors that may affect health outcomes. On the other hand, similar to behavioral frameworks, cultural frameworks assume group traits, shared beliefs, values, norms, habitual practices, or traditions which influence individual choices, behaviors and perception of health-related risks. Beyond individualizing responsibility, the cultural framework – which is frequently associated explicitly with ethnicity, race, or country of origin – promotes an ethnocentric view of a host country's mainstream culture (often unclearly and/or implicitly defined) against minority cultures having the potential to affect health negatively. In combination with these approaches, the structural framework acknowledges also the social forces which affect health. Studies adopting this framework focus primarily on either (a) *access* to care or, although less frequently, on (b) specific *health outcomes* associated with immigrant status. For a variety of factors, individuals with immigration experience or background face barriers and challenges similar to those of other socioeconomically disadvantaged ethnic minority groups in society (i.e. poor living, working, and housing conditions, neighborhood safety, and others). However, relative to ethnic minority individuals, immigrant subjects face additional challenges that are specifically associated with immigrant status.

The relationship between immigrant status and health is complex, and its influence varies substantially across different groups of migrants and from one individual to another. The health of migrants is influenced by a variety of factors and events that can be attributed to the different phases of the migration process, namely pre-departure, travel and transit, destination and integration, and return (Wickramage et al. 2018; Epicentro

2013; IOM 2009) (**Figure 14**). The material, microbiological, cultural, and socioeconomic environment in the country of origin shape many of the pre-conditions of immigrant individuals (*pre-migration phase*). These subjects may have experienced difficulties in preventive care and access to healthcare services with a consequently higher difficulty in treating their illnesses in destination countries because of advanced disease conditions. Also, they may have fled from wars, persecution, and/or other traumatic circumstances that may have impacted their physical and mental health significantly. Similarly, the migration journey (*movement phase*) is influenced by the travel modality and the migrant's legal status. Individuals who migrate in an irregular situation and, likewise, refugees and displaced persons are more likely to have their health affected because of the characteristics of the journey when compared to those who migrate through legally regulated channels. Irregular migrants often travel in life-threatening conditions which may affect both their physical and mental health over the short and long term.

Figure 14. Factors influencing the health and well-being of migrants and their families along the phases of migration



Source: Wickramage et al. 2018

Regarding the arrival phase in destination countries (*arrival and integration phase*), variation exists in the approaches adopted for integrating the needs of migrants (especially from non-EU areas) into national health and welfare systems in the EU. These variations depend largely on the specific patterns of migration and type of migrants entering a given country, along with the type of welfare state and legal organization. Policies addressing the health needs of migrants are more developed in some countries compared to others and, in many countries, undocumented immigrants are not entitled to receive health care (IOM 2006). According to the epidemiological paradox of the so called "healthy immigrant effect"[12], the majority of migrants arrive in the destination country in relatively good health. This is due to younger and healthier migrants being more likely to migrate and to survive long, difficult journeys under life-threatening circumstances (Vissandjee et al. 2004). However, research has shown that immigrants' health tends to decline over time after migration. The host

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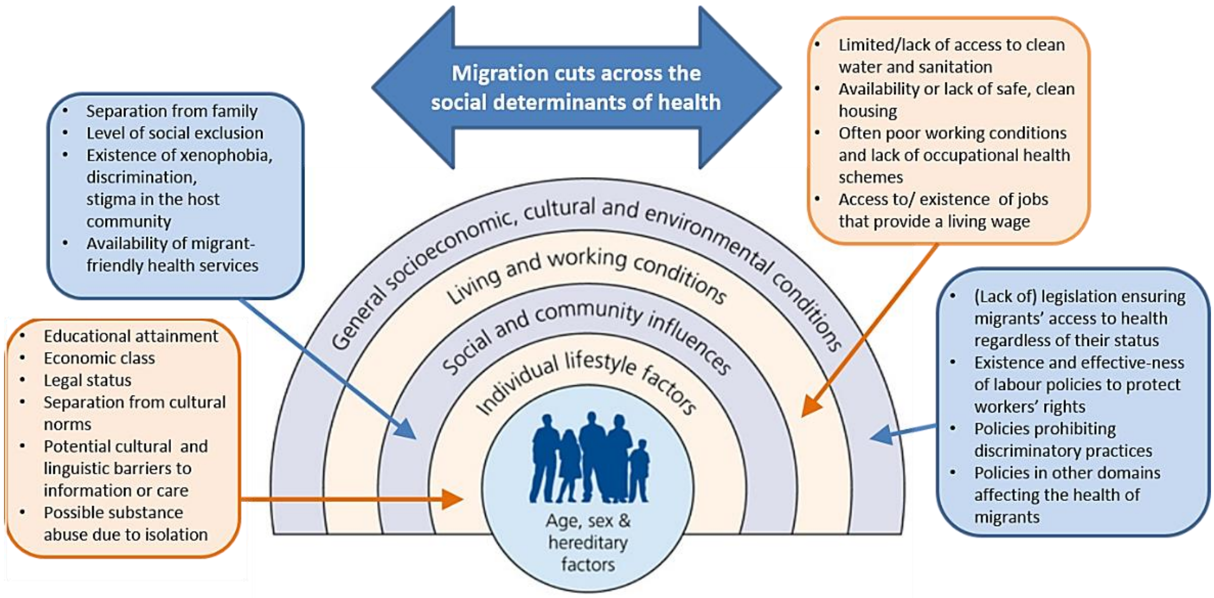
[12] The generally healthier condition of recently immigrated individuals compared to native-born subjects

country's immigration policies and immigrants' legal status may affect access to services (i.e. they are less likely to interact with state and/or government services that could alleviate their difficulties on account of fear of deportation or family separation); discrimination experience or lack of labor rights and exploitation in their workplace; discrimination, "othering", and social exclusion in their personal life and exposure to family separation along with the associated consequences on mental health; language difficulties and different cultural values affecting interaction with the healthcare system; lack of linguistically and culturally appropriate services; and lack of social support out of separation from family and/or partner (Wickramage et al. 2018; IOM 2009). Also, the socioeconomic position, including the type of occupation is strongly influenced by educational level and by the difficulties in the process of integration (Stronks and Kunst 2009). In Italy, research has noted that integration policies remain limited and may challenge overall health status over time after migration (Giannoni et al. 2016). Further, studies suggest that, throughout the "arrival and integration phase", migrants encounter multiple barriers of a (a) juridical-legal, (b) economic, (c) administrative, and (d) organizational nature in healthcare services accessibility (Geraci and El Hamad 2011). Juridical-legal barriers include the obstacles and uncertainties regarding the rights to healthcare associated with the legal status of these populations. Economic barriers remain an obstacle with the potential for disparities in accessibility of care for individuals with an immigration background. Although health policies in Italy guarantee healthcare under the same conditions as nationals, along with registration in the NHS or the exemption from healthcare payment for asylum seekers, things have changed in more recent years. Studies have shown that immigrants in Italy report a better self-perceived health when compared to natives. However, a decline in mental health is observed over time after migration. Administrative barriers are those which, even more than legal ones, have mostly influenced access to healthcare services. Hospital requests for reimbursements from Prefectures for the hospitalization of irregular and socioeconomically disadvantaged migrants frequently end up with the nominal, formal reporting of the foreign-born patient to Italian authorities. Regarding organizational barriers, some examples include physical obstacles (i.e. lack of healthcare services flexibility such as work-incompatible opening hours) and usability ones (i.e. physician gender as for the availability of female doctors in gynecology services). Also, usability barriers include a) linguistic, b) communicative, c) interpretive, and d) behavioral barriers in access to services. On the one hand, it should be kept in mind that, regardless of the patient's background, the therapeutic relationship is complex in its own right; on the other, it should be noted that culture – along with its symbolic values – strongly influences the concepts of health, illness and care (Institute of Medicine Committee on Health Literacy 2004). While it would be virtually impossible for healthcare professionals to become experts in anthropology and be knowledgeable of all cultures, acquiring the ability to listen carefully to the patient's individual perspective and to adopt a holistic approach would be desirable so as to overcome patients' behavioral barriers and physicians' bias at the same time (Geraci and El Hamad 2011).

Likewise, the features of immigrant populations' return to home countries (*return phase*) have the potential to affect their health significantly depending on a variety of factors. These include the duration of absence from the host country, the availability of community services, the remaining presence of family ties and/or significant others, the changes in the behavioral and health profile of the host community, and other household determinants such as level of debt.

The International Organization for Migration (IOM) contends that immigrant status cuts across the SDH and has the potential to exacerbate them at multiple levels which influence a person's health (**Figure 15**). These include biological factors (i.e. age, sex, constitutional factors); individual lifestyle factors; social and community influences; living and working conditions; and the general socioeconomic, cultural, and environmental conditions.

Figure 15. Social Determinants of Migrant Health



Source: IOM

Studies suggest that the decline in migrants' health can be related to the socioeconomic disadvantage which they often experience in the host country. This occurs in European countries where, because of widespread social inequalities, the chance to satisfy basic needs is less frequent for immigrant populations when compared to their native referents. Migrants often lack the autonomy, freedom and empowerment to lead their life according to their cultural and social values and norms, thus limiting the opportunity for them to make healthy life choices. Also, households with lower income are more likely to have more limited living space (i.e. with less than one room available for each person in the household), more noise disturbance, lower indoor air quality, and lack of privacy which may affect both physical and mental health.

Chapter 3. Kidney transplantation in the immigrant patient population in Italy

> *"Of all the forms of inequality, injustice in healthcare*
> *is the most shocking and inhumane"*
> (Martin Luther King 1966)

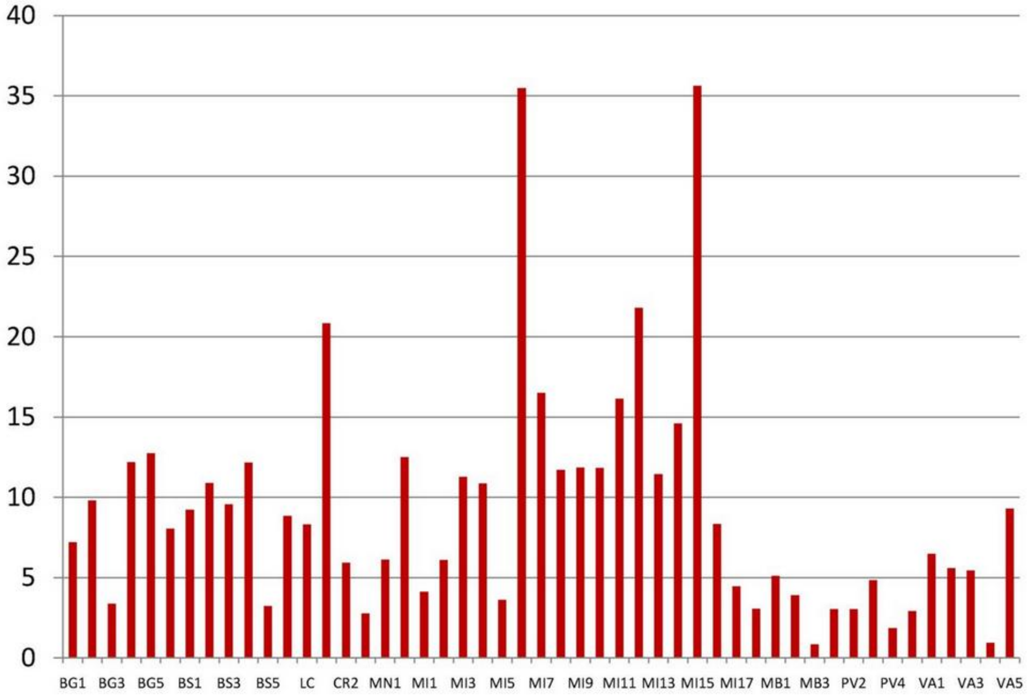
3.1. Introduction

Many studies from the US document extensive racial/ethnic disparities at different stages of the KT process, from the prevalence of CKD, progression towards ESKD through to KT outcomes (Ladin, Rodrigue and Hanto 2009; Malek et al. 2011). However, it is difficult to transfer these findings to the context of the EU and particularly to Italy where immigration is a more recent phenomenon and where, as opposed to the US, health systems generally guarantee universal coverage of nephrological care, from the point of access through to the provision of post-transplant medical regimens (Li Cavoli et al. 2019; Bello et al. 2017). This chapter summarizes existing studies on disparities at different stages of the KT process among immigrant individuals in Italy, with a focus on variations in the prevalence of ESKD, treatment, access to and outcomes of KT.

3.2. Prevalence of end stage kidney disease

In Italy, according to data from high migratory pressure areas (i.e. Piedmont, Lombardy and Lazio) (**Figure 10**), a considerable proportion of first-generation immigrants is on chronic RRT. Consistent with the growth of the immigration phenomenon in Italy, a registry study from Lazio (Di Napoli et al. 2015) and a multi-center survey study from Piedmont (Forneris et al. 2011) reported an increase of the prevalent immigrant patient population on chronic dialysis treatment in the periods 2004-2012 (from 4.4% to 7.6%) and 2002-2008 (from 2% to 10% in some larger urban dialysis facilities), respectively. A multi-center survey study of dialysis centers in Lombardy revealed that the prevalence of non-EU-born patients ranges from 0.8 to as high as 35% in some centers in the Milan area (Corghi et al. 2016) (**Figure 16**).

Figure 16. Prevalence (%) of non-EU-born patients in dialysis centers in Lombardy



Source: Corghi et al. 2016

These studies report comparable findings regarding the primary causes of ESKD among patients with an immigration background compared to their native referents. According to the study from Lazio, glomerulonephritis is more frequently the cause of ESKD among foreign-born individuals relative to nationals (18.1 vs. 13.9, p=0.03) whereas it is comparatively more prevalent and less differences are reported between non-natives and natives in Lombardy (27.03 vs. 30.5%) and Piedmont (33% vs. not shown) (Forneris et al. 2011; Di Napoli et al. 2015; Corghi et al. 2016). Rates of ESKD of an unknown origin/undiagnosed are similar in Lombardy (31.8%) and Piedmont (31%). Rates of diabetes (D) and vascular nephropathies (VN) are comparable between individuals with an immigration background and their native referents and more prevalent in Lazio ([D] 24.9 vs. 27.8%; [VN] 23.6 vs. 24.2%) as opposed to Lombardy ([D] 18.4 vs. 15.8%; [VN] 12.8 vs. 19.6%). Diabetic nephropathies in the immigrant group compared to the native group are lower in Piedmont (12% vs. not shown). These findings are consistent with prior research from the UK showing no difference in comorbidity scores or diabetes between White, Black and South Asian patients (Jain et al. 2009). Yet, other European figures report significantly higher rates of diabetes in immigrant and/or ethnic minority groups with ESKD compared to their native/non-ethnic minority counterparts (van den Beukel et al. 2010; van den Beukel et al. 2012; Udayaraj et al. 2013). Also, ethnic minority individuals of a Sub-Saharan African origin living in Europe are more likely to have higher BP levels relative to individuals of a South Asian and European origin (Modesti et al. 2016). A recent nationwide cohort study in Sweden of more than six million patients found higher incidence rates and hazard ratios (HR) of ESKD in first-generations immigrants from Eastern European and other non-European countries when compared to native-born individuals (including second generation immigrants). The authors found a higher risk of ESKD in first-generation immigrants from Eastern European countries, Africa and Asia (particularly Middle-Eastern countries), and higher risk of hypertension and diabetes in both first- and second-generation immigrant groups (Wändell et al. 2019). While Italian data on the primary causes of ESKD differ from most data from across countries in Europe, these figures parallel those on the prevalence of diabetes in immigrant populations in Italy. Studies reveal that these subjects present significantly higher rates of diabetes (especially among populations from South Asia and Northern Africa) (Buja et al. 2013; Ballotari et al. 2015) and other risk factors for progression towards ESKD such as hypertension (at least 10% higher than their native-born counterparts) (Esposito et al. 2016; Buja et al. 2013; Ballotari et al. 2015) which, combined with lower quality management, may have the potential to expose immigrant subjects to more rapid progression towards ESKD..

3.3. Treatment of end stage kidney disease

In Italy, consistent with prior data of non-Caucasian groups on chronic RRT in the European area (i.e. Netherlands, Italy, Spain, Germany, UK, Greece, France) (van den Beukel et al. 2010), first-generation immigrants are generally younger when compared to their native-born counterparts and they are mostly represented in the 41-60 age range (Forneris et al. 2011; Di Napoli et al. 2015; Corghi et al. 2016). Yet, late referral to nephrological care is common in patients with an immigration background (Forneris et al. 2011; Di Napoli et al. 2015; Corghi et al. 2016). These patients are also more likely to be treated with hemodialysis (HD) as opposed to peritoneal dialysis (PD) relative to their native-born referents (Forneris et al. 2011; Di Napoli et al. 2015; Corghi et al. 2016), reflecting the same figures reported by studies from other countries in the EU (Schoenmaker et al. 2012; Tromp et al. 2012).

As for RRT survival, only one registry study from the Italian region of Lazio revealed that foreign-born patients have higher survival probability at 1 (91.9% vs. 84.7%) and 5 years (74.6% vs. 51.5%) and lower mortality risk (hazard ratio [HR]=0.71; CI 95%: 0.58-0.87) after chronic dialysis initiation relative to nationals (Di Napoli et al. 2016). Lower mortality rates on dialysis in migrant and ethnic minority populations are frequent in Europe (Rhee et al. 2016). However, ethnic minority patients report significantly higher levels of distress and need for support when compared to their native referents (Damery et al. 2019[a]; Damery et al. 2019[b]). To date, no study has ever been performed at the national level in Italy to investigate 1) RRT survival, 2) rates of preemptive and 3) LDKT, and 4) quality of life on RRT among first-generation immigrants when compared to their native-born counterparts.

3.4. Access to Kidney Transplantation

3.4.1. Waitlisting

In Italy, studies on waitlisting for patients with an immigration background remain scarce and of limited size and quality. A survey study in Piedmont (Forneris et al. 2011) found that these patients had an active status on the waiting list (WL) (27%), were in the process of being evaluated for enrollment (23%) or were inactive (2%). Irrespective of the younger age and better clinical conditions of these subjects compared to natives, a large proportion was not yet considered for KT (46%). The authors reported that language barriers compromise patient-provider communication in at least 40% of cases. This leads to impairment of the informed consent process and challenges adherence to prescribed medical and dietary regimens. Pending regularization status and other socioeconomic factors (i.e. poverty and poor housing quality) may equally counter the chance for these patients to be registered on the WL. Further, periodic visits to home countries have the potential for exposure of these patients to endemic infections and/or undertreatment of ESKD (Forneris et al. 2011). It is also possible that the generally lower educational level of these patients (Eurostat 2016) may have an impact on the lower rates of WL registration in this group of patients (Neri et al. 2013). Regardless of these factors, KT eligibility (31.2% vs 29.5%, p=0.57) and WL registration (93.9% vs 91.6%, p=0.43) rates are comparable between immigrants and natives in the region of Lazio (Di Napoli et al. 2015), and significantly higher among non-EU-born patients relative to their EU-born referents in Lombardy (34.8% vs 18%, p<0.01) (Corghi et al. 2016).

Although studies addressing this issue remain limited in Europe, regional figures from Italy parallel those from other countries in the EU. Contrary to evidence from the US (Patzer et al. 2009), studies from the UK report comparable rates of waitlisting between MEM and native-born populations (Caskey 2013; Pruthi et al. 2013; Udayaraj et al. 2013; Udayaraj et al. 2010). However, a national registry study in the UK contradicts this positive trend. Pruthi et al. (2015) found significant cross-center (transplanting vs. non-transplanting centers) differences showing a negative association with increasing age, non-White ethnicity and diabetes in terms of accessing the transplant WL. Shorter length of stay in the host country, limited language proficiency impairing communication, pending regularization of immigration status and lack of familiarity with the administrative complexities of the Italian health care system may contribute to challenge accessibility of transplantation in Italy (Forneris et al. 2011; Devillanova and Frattini 2016). Also, perceived discrimination, medical mistrust and different representation and expectations of health care between physicians and patients may prove further barriers to care (Van Biesen et al. 2018). Studies found that some of these sociocultural factors are significantly associated with not starting the KT evaluation process (Hamoda et al. 2019).

3.4.2. Receiving Transplant

In Italy, only one regional registry study from Lazio analyzed the prevalence of KT in the foreign-born patient population under 65 years of age and found that these subjects were more likely to receive KT when compared to their native-born referents (8.6% vs. 7.4%) (Di Napoli et al. 2015). Yet, the study did not comparatively assess the time elapsed from first dialysis to KT (i.e. dialysis vintage), from waitlisting to KT, and the survival advantage of KT over dialysis in this vulnerable group of patients.

Studies have shown that immigrant and/or ethnic minority status may be associated with longer waiting time for KT even after waitlisting (Laging et al. 2014; Tromp et al. 2012) and lower likelihood to receive preemptive and LDKT. In the US, disparities in access to LDKT for individuals who are from ethnic minorities are well-known (Purnell et al. 2018). As opposed to the US and other Northern European countries, immigration from non-EU countries beyond Eastern Europe is a recent and extensive phenomenon in Southern Europe, including Italy, and ethnic minorities consist basically of non-European migrants (De La Rica, Glitz and Ortega 2013). The majority of health systems in the EU guarantee equal access to KT, regardless of ability to pay (Bello et al. 2017). However, the results of EU studies parallel those performed in the US (Wu et al. 2017; Tjaden et al. 2016; Tromp et al. 2012; Udayaraj et al. 2012; Roodnat et al. 2010). Although immigration is a growing phenomenon in Europe, studies on the association between non-European immigration background and access to preemptive DDKT and LDKT are lacking for most countries in the EU and none have ever been performed in Italy.

A multicenter prospective observational cohort study across four university hospital renal units in the UK revealed no statistically significant difference in the median waiting time for KT between White, Black and South Asian patients (P=0.099). However, it did report a significantly lower likelihood of receiving KT and longer dialysis vintage among subjects of Black and South Asian ethnicity (Jain et al. 2009).

Other studies in both adult and pediatric settings across various countries in the EU report significantly longer time from initiation of dialysis until the first KT and lower likelihood of receiving deceased and/or LDKT in immigrant and/or ethnic minority patient populations compared to their native/non-ethnic minority counterparts (Williams et al. 2018; Tjaden et al. 2016; Laging et al. 2014; Udayaraj et al. 2013; Rudge et al. 2007; Tromp et al. 2012).

Only one study of pediatric patients from Austria documented significantly higher rates of non-preemptive LDKTs (57% vs. 27%; p = 0.03) in immigrant families compared to their non-immigrant counterparts (Oztek-Celebi et al. 2019).

Studies suggest that the longer time migrant and ethnic minority patients remain on the WL and the longer dialysis vintage may be due to underrepresentation of ethnic minority subjects within the donor pool, making HLA matching more difficult to achieve (Rudge et al. 2007; Morgan et al. 2015). The higher HLA A/B/DR mismatches may equally be explained by the lower availability of ethnicity-matched organs. Other factors that carry potential for disparities in the time migrant and ethnic minority patients remain on the WL is the ABO blood type. Studies from Europe found a higher prevalence of B (Roodnat 1999) and O blood group (Give Blood) among patients of a non-European origin.

Given the overall consistency of the finding of longer dialysis vintage in migrant and ethnic minority individuals across multiple studies, research is needed to further investigate (1) the factors that contribute to delay KT, (2) the factors affecting lower uptake of LDKT, (3) the time elapsed from first dialysis to WL, from dialysis start to KT, and from WL to KT, as well as (4) the rates of deceased organ donation among patients with an immigration background in Italy.

3.5. Follow-up and Kidney Transplant Outcomes

To date, no studies have ever assessed the outcomes of KT in the immigrant patient population in Italy. Data from other countries across the EU remain limited and have led to various outcomes, as illustrated throughout the following paragraphs.

In a single-center research of 1,338 kidney transplant recipients (KTRs) in the Netherlands, 361 of whom were of non-European origin (i.e. Arabian, Asian and Turkish), no significant influence of non-EU origin was detected on either patient or graft survival, even after controlling for socioeconomic indicators (Laging et al. 2014). As opposed to the US, where socioeconomic status (SES) challenges access to post-transplant regimens, the authors stress that the Dutch health system guarantees equal provision of immunosuppressive medication thus contributing to prevent graft failure.

Likewise, a previous study carried out at the same center equally found no statistically significant difference in graft survival between European and non-European KTRs. Causes of death and transplant loss were equally comparable between the two groups. However, the study reported a higher relative risk of death or transplant failure in KTRs of Arab and African origin as opposed to European and Asian KTRs (Roodnat et al. 1999).

In the more recent research, the authors argue that the larger proportion of second and third generation immigrants included in the study, their higher employment rates, educational levels, and better integration in the host country may be possible explanations to the improved outcomes when compared to their prior findings (Laging et al. 2014).

Similarly, Oztek et al. found equal KT outcomes between immigrant and native Austrian pediatric KTRs, where immigrant KTRs were mainly from the Balkan area (Oztek et al. 2011).

Prior research by the same authors led to parallel findings and no differences were detected across multiple outcomes: patient and graft survival, long-term graft function (eGFR), rates of acute rejection, 24-hour blood pressure, and growth velocity (Oztek et al. 2009).

In contrast, in a multicenter prospective cohort study in the Netherlands and Belgium, Tromp et al. found more rejection in immigrant children of Turkish, North African, and Caribbean origin when compared to native Dutch and Belgian children without affecting estimated Glomerular Filtration Rate (eGFR) (i.e. kidney graft function) at 3- and 12- months post-transplant (Tromp et al. 2012).

A study from the United Kingdom reported poorer graft survival in Black and South Asian recipients (Medcalf et al. 2011).

Similarly, a single center retrospective cohort study in the UK found that Black KTRs have diminished renal graft-related outcomes compared to Whites (23.8% vs 11.1%; P=.002). These include higher risk for delayed graft function (34.3% vs. 10.2%; P<.001), increased 1-year rejection (16.7% vs. 7.3%; P=.012), higher 1-year creatinine levels (166 vs. 138 mmol/L; P=.003), and longer posttransplant length of stay (14.5 vs 9.5 days; P=.020). However, the adjusted Cox-regression model revealed that worse kidney graft outcomes were not directly associated with ethnicity but rather with their multiple high-risk baseline variables (higher mean listing time, matching difficulty, socio-economic deprivation, HLA mismatches, donor type – more frequently deceased donor -, recipient CMV positivity, and cold ischemia time) (Williams et al. 2018).

In a single-center study, Ng and colleagues suggested that Black KTRs have inferior long-term graft survival than other CYP3A5 expressers. Yet, in a multivariate analysis which was however not adjusted for socio-economic factors, this finding was no longer significant (Ng et al. 2010).

In multivariate Cox regression analyses (with and without death as a competing risk event), Udayaraj et al. (2013) found that Black patients had lower graft survival relative to South Asian and White patients. However, they reported significantly better median eGFR for Black and South Asian patients when compared to their White counterparts (Udayaraj et al. 2013).

3.6. Discussion

Disparities along the continuum of the KT process in individuals with an immigration background remain largely unexplored in Italy. Research on the differences and disparities in the diseases and care of patients with CKD and ESKD remain sparse in Europe and has led to heterogenous findings. Within the EU, studies of the association of migrant and ethnic minority status with inequities in the KT process are equally limited and mostly originate from the UK and the Netherlands, which have a longer standing history of immigration. In Italy, only three studies investigated ESKD- and KT-related issues in this sub-group of patients (Forneris et al. 2011; Di Napoli et al. 2015; Corghi et al. 2016). However, categories for analyses were inconsistent both among the three Italian studies and among studies in the EU. This is possibly due to a variety of factors: the different ethnic composition of the populations under scrutiny, the generally limited sizes of study samples leading to inconsistent categories for analyses, the different legal frameworks regulating accessibility of health care, health system characteristics, status of immigration (i.e. refugee, temporarily present foreigner, economic migrant, etc.), degree of immigrants' integration in host countries, availability of migrant-sensitive, culturally competent health care services, as well as patients' socioeconomic, sociocultural, educational and behavioral features. Much remains to be explored as to whether disparities exist in accessibility and outcomes of KT in the non-EU-born patient population in Italy. Studies using the ethnic minority status category alone does not specify whether patients have a direct immigration experience, or they have a history of immigration in prior generations. While it is possible that some gaps in accessibility and outcomes of KT may persist because of biological variations in some ethnic groups, addressing the portion of health disparities engrained in modifiable factors is a compelling duty.

Chapter 4. Measuring disparities in kidney transplant outcomes in the Non-European immigrant patient population in Italy

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Abstract

The impact of immigration background on kidney graft function (eGFR) is unknown. Italy has a publicly funded health system with universal coverage. Since immigration from non-EU countries beyond Eastern Europe is a recent and extensive phenomenon, Italy is a rather unique setting for studying the effect of immigration status as a socioeconomic and cultural condition. We retrospectively identified all adult deceased donor kidney transplant recipients (KTRs) in Italy (2010-2015) and followed them until death, dialysis or 5-years post-transplantation; 6,346 were EU-born, 161 Eastern European-born, and 490 non-European-born. We examined changes in eGFR after 1-year post-transplant using multivariable-adjusted joint longitudinal survival random-intercept Cox-regression. Compared to EU-born KTRs, in non-European-born KTRs the adjusted average yearly eGFR decline was -0.96 mL/min/year (95% confidence interval: -1.48 to -0.45; P<0.001), whereas it was similar in Eastern European-born KTRs (+0.02 mL/min/year [-0.77 to +0.81; P =0.96]). Adjusted five-year transplant survival did not statistically differ between non-European-born, Eastern European-born and EU-born. In those surviving beyond 1-year, it was 91.8% in EU-born (87.1 to 96.8), 92.5% in Eastern European-born (86.1 to 99.4), and 89.3% in non-European-born KTRs (83.0 to 96.0). This study provides evidence that among EU KTRs, non-European immigration background is associated with eGFR decline.

"Health inequalities that are preventable
by reasonable means are unfair"
(Marmot 2019 [13])

4.1. Introduction

In Italy, many adult patients with end-stage kidney disease (ESKD) are of non-European origin (Corghi et al. 2016; Di Napoli et al. 2015; Forneris et al. 2011). These patients account for 35% of the prevalent population on chronic dialysis treatment in some centers in Northern areas (Corghi et al. 2016). Immigration from non-European Union (EU) countries beyond Eastern Europe is a recent phenomenon in Italy when compared to other Central and Northern European countries (De La Rica et al. 2013). The number of foreign-born individuals (i.e. first-generation immigrants) has grown from 1.9 to over 5 million between 2004-2017, the majority of whom were born outside the EU (3.5 million) (ISTAT). Immigration is an important social determinant of health, carrying the potential for disparities in accessibility, quality and outcomes of care (Castañeda et al. 2015; Grabovschi et al. 2013). The health of migrants and prevention of inequities for these populations is a priority of the World Health Organization (WHO 2018). Italy guarantees universal access to primary, secondary and emergency care to regular and undocumented immigrants registered within the Italian National Health System. Kidney transplantation (KT) is the gold standard for treatment of ESKD; KT, post-transplant immunosuppressive medication and medical regimens are available for clinically eligible migrants with regular immigration status, regardless of ability to pay (Li Cavoli et al. 2019).

The immigrant patient population presents a variety of relational, cultural, social, economic, and biological factors that may be relevant to treatment outcomes (Forneris et al. 2011; Maloney et al. 2005; Van Biesen et al. 2018; Poulakou et al. 2019). In Italy, non-European-born individuals are more likely to be socioeconomically disadvantaged, with lower levels of education when compared to other EU countries, and with difficulties in oral and written communication (Forneris et al. 2011; Fondazione ISMU 2019; Eurostat 2016; ISTAT 2014). Immigrants in Italy receive lower quality management of chronic conditions such as diabetes and are less likely to adhere to prescribed medical regimens, resulting in a higher risk of diminished treatment outcomes (Ballotari et al. 2015; Buja et al. 2013). Also, limitations in integration policies may challenge overall health status over time after migration (Giannoni et al. 2016). It is possible that the multiple aspects of vulnerability associated with immigrant status may affect long-term care and the clinical course of KT when comparing EU and non-European-born kidney transplant recipients (KTRs) (Grabovschi et al. 2013). European data suggest that immigration may be associated with inferior KT outcomes in some (Roodnat et al. 1999; Tromp et al. 2012) but not all situations (Pallet et al. 2005; Mérida et al. 2009; Laging et al. 2014; Oztek et al. 2009; Oztek et al. 2011). Studies on the association between immigration background and KT outcomes

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[13] Marmot M. Fair Society, Healthy Lives. The Marmot review. Strategic Review of Health Inequalities in England post-2010. 2019. www.ucl.ac.uk/marmotreview

remain limited in Europe, and only few if any have assessed long-term kidney graft function decline rate (i.e., change over time in estimated Glomerular Filtration Rate, eGFR) beyond 1-year post-transplant. Previous studies have shown that eGFR decline at 1-year post-transplant does not differ significantly between KTRs with a non-European immigration background and natives (Tromp et al. 2012; Pallet et al. 2005; Oztek et al. 2011). Most registries lack long-term longitudinal data on eGFR. To fill this gap, we carried out a retrospective cohort study of adult KTRs in Italy, comparing long-term eGFR and transplant survival between Eastern European-born, non-European-born, and EU-born recipients. To our knowledge this is the first Italian study examining whether non-European individuals experience altered KT clinical outcomes compared to EU-born patients, and the first registry study that examines the relationship between immigration background and long-term kidney graft function.

4.2. Materials and methods

We performed a retrospective cohort study of adult patients (≥ 18 years of age) who received KT from deceased donor (DD) from January 1, 2010, through December 31, 2015 in Italy. Non-European recipients were first-generation immigrants with migration experience (European Commission 2017; SISTAN 2014) and with a regular immigration status (Li Cavoli et al. 2019). We distinguished individuals born outside the EU between Eastern European-born and non-European-born. Non-European-born KTRs included patients from four geographic areas: Asia, Latin America, North Africa and Middle East, and Sub-Saharan Africa. Because they may not be regarded as exposed to social disadvantage and we should have analyzed them as a separate group, recipients born in North America or Oceania were excluded (n=10). Eastern European-born patients included individuals from Albania, Moldavia, Former Yugoslavia, Ukraine and other countries of the Eastern European and Balkans area. EU-born KTRs included all patients from the EU-28 member states including Switzerland. We did not further subdivide the Eastern European-born, non-European-born, and EU-born area-of-birth categories given limitations in the numbers in each category for statistical analyses. However, in order to verify whether specific ethnic subgroups might explain any relationship between immigration status and eGFR decline, we additionally classified non-European-born KTRs according to the four ethnic subgroups, namely Asian (South-East and North-East Asia), Hispanic (Latin America), African (Sub-Saharan Africa), and Other (North-African and Middle-East) (Bhopal 2004).

Data were collected from the Italian National Transplant Center's (CNT) Transplant Information System (SIT), a national-level mandatory registry (established by Law: 1 April 1999, n° 91) collecting data relative to the entire transplant process (donation-procurement-transplant) drawn from the whole Italian National Transplantation Network (RNT). Data were available concerning recipients' demographics, primary kidney disease, dialysis vintage, time to wait-listing (WL), dialysis modality, donors' age, ethnic origin, HLA A/B/DR mismatches, re-transplantation, maximum Panel Reactive Antibody (PRA) value, transplant center, date of censoring, death, or dialysis. Data were also available on yearly post-transplant eGFR, according to the CKD-EPI equation, starting from the first post-transplant year.

This retrospective study was approved by the Italian CNT and included patients' data that were anonymized and de-identified directly in the Italian SIT database before extraction for the analysis. The study was carried out in accordance with the ethical principles of the Declaration of Helsinki (with amendments).

Statistical Analyses

All analyses were performed using the Stata Statistical Software package, Release 16.0. (StataCorp. 2019, College Station, TX, US). A two-tailed p-value less than 0.05 was regarded as statistically significant, unless otherwise stated. Differences between groups in continuous variables were examined by Kruskal-Wallis and by Mann-Whitney two-sample test, in categorical variables by Fisher's exact test. The primary exposure was recipients' country of birth compared to EU-born patients. In all the analyses we included only patients who had available data on HLA mismatch, dialysis vintage, and follow-up. Follow-up was continued until death or dialysis, whichever came first, otherwise it was censored 5-year post-transplantation. Because we believed that systematic differences between the observed and missing data could not be explained by associations with the observed data (i.e. we believed that the covariate patterns and outcomes were not Missing at Random) we did not make any attempt to perform multiple imputation as it would have caused biased estimates compared to complete case analysis (Hughes 2019). We reported Kaplan-Meier plots as summary statistics of the survival of the study population and of the number of patients at risk at each time point in the period from year 1 to year 5. We fitted a joint longitudinal survival model (Wulfoshn and Tsiatis 1997; Tsiatis and Davidian 2004), in which yearly eGFR and transplant survival time were analyzed jointly under the assumption that the longitudinal and survival processes are underpinned by shared latent patient random effects. The joint longitudinal survival model consists of two sub-models; a longitudinal sub-model (i.e. a linear mixed effects model for eGFR) and a time-to-event sub-model (i.e. a Cox proportional hazards model for transplant failure) which are linked using an association structure. Because the two outcomes of transplant survival time and graft function might be highly correlated, joint analysis can reduce bias and improve precision of estimated parameters from both survival and longitudinal models over simpler approaches. Additionally, major results available from joint analyses, as opposed to time-dependent Cox regression analysis, is that they naturally deal with eGFR measurement error, interval missing data, and whenever it happens, lack of consistency among subjects in timing of the eGFR assessment; they provide an optimal "adjustment" for the pre-transplant failure longitudinal eGFR, and provide a precise estimate of the impact of the eGFR on the hazard of graft failure (reported as the "association parameter.") (Tsiatis and Davidian 2004; Gould et al. 2015; Rizopouolos 2012) [31-33]. We fitted a joint longitudinal survival random-intercept model using the Stata user-written command *jmxtstcox* (StataCorp LLC) which allows to model the survival outcome semi-parametrically using Cox proportional hazard regression.

All multivariable-adjusted regression models included the following characteristics: year of transplantation (continuous variate), donor and recipient age, recipient gender, dialysis vintage (log-transformed), number of HLA A/B/DR mismatch (continuous variate), sensitization status (maximum CDC-PRA > 10%), and re-transplantation. There were 33 patients with missing CDC-PRA values, which were evenly distributed between immigrant groups. In fact, the multiple regression models that included CDC-PRA yielded virtually identical results. Anyhow, we reported the results of regression models including CDC-PRA throughout.

For the longitudinal component of the model (eGFR), time was modeled both as a categorical variate (yearly change in eGFR from the baseline value 1-year post-transplantation) and as a continuous variate (and average linear decline of eGFR from year 1 to year 5). The main analyses consisted in the comparison between eGFR changes in the two immigrant groups, namely Eastern European- and non-European-born, with eGFR change in EU-born KTRs. However, in additional models, we split the non-European-born KTRs into four ethnic groups and compared each of them with EU-born KTRs. We also performed statistical tests of every pairwise comparison between ethnic groups, for which a two-tailed p-value of less than 0.01 was regarded as statistically significant to allow for multiple testing.

4.3. Results

Baseline characteristics

Between January 1, 2010, through December 31, 2015, 6,997 DD KTRs were eligible for the present study: 163 patients with missing follow-up, and 1,480 patients with missing covariate status were excluded. The summary of baseline patient demographics and risk factors is reported in **Table 7**, and crude transplant survival since time of transplantation is reported in **Figure 17**. EU-born (6,346), Eastern European-born (161), and non-European-born (490) recipients were identified. Eastern European-born and non-European-born recipients were younger compared to EU-born recipients. Because of the donor-recipient age-matching algorithm, Eastern European-born, and non-European-born recipients had also younger donor ages. However, dialysis vintage, time to WL, and number of HLA mismatches tended to be slightly higher in Eastern European-born, and non-European-born compared to EU-born recipients.

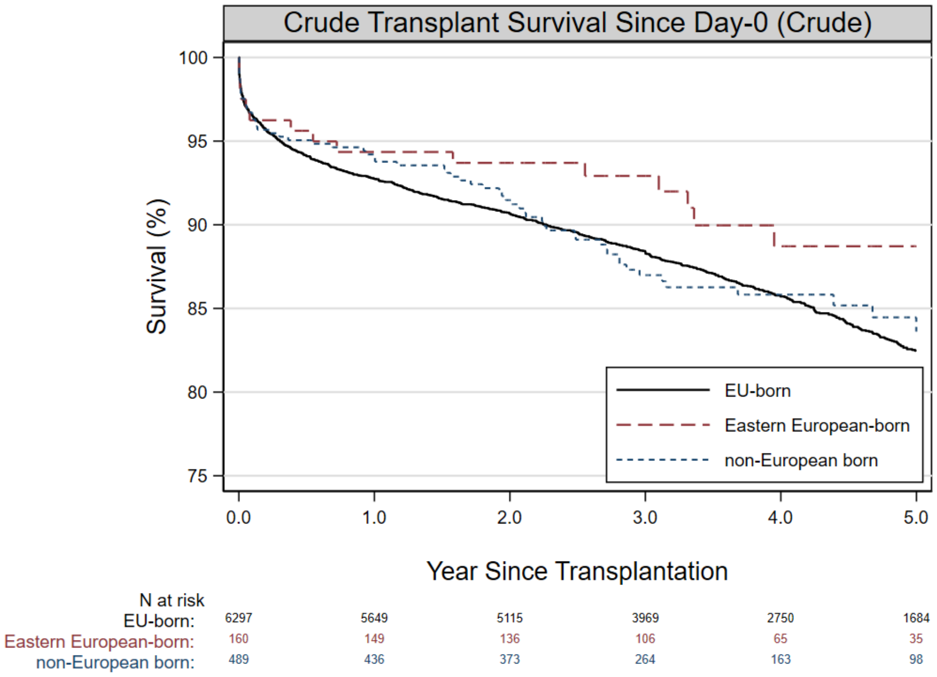

Figure 17. Crude survival probability and number at risk of EU-born, Eastern European-born, and non-European-born kidney transplant recipients. Joint longitudinal survival analyses include patients surviving beyond 1-year post-transplantation, the time of *the first eGFR measurement.*

Table 7. Baseline characteristics of adult patients who received deceased donor kidney transplant

	Total	EU-born	Eastern European-born	non-European-born	P value
Origin		Italy: 6202 Germany: 20 Romania: 67 Switzerland: 21 Other: 36	Albania: 76 Moldavia: 17 Rep. of Yugoslavia: 18 Ukraine: 23 Other: 27	Argentina: 8; Bangladesh:9; Burkina Faso: 7; Brazil: 7; China: 34; Colombia: 6; Dominican Republic: 6; Ecuador: 7; Egypt: 22; Ghana: 27; India: 17; Ivory Coast: 12; Lybia: 6; Morocco: 85; Nigeria: 30; Pakistan: 19; Peru: 9 Philippines: 51; Other Latin American: 19; Other North-African and Middle-Eastern: 15; Other North-East and South-East Asian: 12; Other Sub-Saharan African: 32; Senegal: 28; Tunisia: 16; Venezuela: 6	
N	6997	6346	161	490	-
Recipent's Age -yrs	52.4 (12.2)	53.2 (11.9)	44.4 (12.5)	44.9 (11.4)	<0.001[a,b]
Recipient's ethnic origin					
European	6457 (93.0)	6297 (100)	160 (100)		<0.001[a,b]
Asian	142 (2.0)	23 (0.4)		142 (29.0)	
Hispanic	68 (1.0)			68 (13.9)	
African	135 (1.9)			135 (27.6)	
Other	144 (2.1)			144 (29.4)	
Donor's Age -yrs	54.6 (16.3)	55.3 (16.2)	47.9 (16.1)	48.8 (16.1)	<0.001[a,b]
Donor's ethnic origin					< 0.001[a,b]
European	6796 (97.8)	6173 (98.1)	151 (94.4)	472 (96.5)	
Asian	30 (0.4)	23 (0.4)	3 (1.9)	4 (0.8)	
Hispanic	77 (1.1)	66 (1.0)	6 (3.7)	5 (1.0)	
African	19 (0.3)	15 (0.2)	0 (0.0)	4 (0.8)	
Other	24 (0.3)	20 (0.3)	0 (0.0)	4 (0.8)	
Male gender - %	5535 (65%)	5067 (65%)	108 (57%)	360 (65%)	0.076
Primary kidney disease					< 0.001[a,b,c]
Glomerulonephritis	2700 (38.9)	2400 (38.1)	74 (46.5)	226 (46.2)	
ADKPD	1265 (18.2)	1222 (19.4)	17 (10.6)	26 (5.3)	
Hypertension/Vascular	748 (10.8)	657 (10.4)	12 (7.5)	79 (16.2)	
Diabetes	271 (3.9)	246 (3.9)	3 (1.9)	22 (4.5)	
Pyelonephritis/tubule-interstitial disease	469 (6.7)	426 (6.8)	19 (11.9)	24 (4.9)	
Congenital	150 (2.2)	140 (2.2)	6 (3.7)	4 (0.8)	
Other or unknown	1343 (19.3)	1206 (19.1)	29 (18.1)	108 (22.1)	
Dialysis vintage -yrs	3.6 (2.1-5.8)	3.5 (2.1-5.8)	4.0 (2.3-5.9)	4.3 (2.6-6.4)	<0.001[b]
Time to wait-listing -yrs	1.3 (0.7-2.4)	1.3 (0.7-2.3)	1.6 (0.8-2.8)	1.6 (0.8-2.9)	<0.001[a,b]
Dialysis modality					<0.001[b]
Preemptive	85 (1.2)	83 (1.3)	1 (0.7)	1 (0.2)	
HD	5583 (78.6)	5069 (77.9)	120 (81.8)	394 (88.5)	
PD	1431 (20.2)	1354 (20.8)	27 (18.2)	50 (11.2)	
CDC-PRA >10%	1316 (19.0)	1187 (18.8)	32 (20.0)	97 (19.8)	0.78
CDC-PRA - %	0 (0-2)	0 (0-2)	0 (0-2)	0 (0-4)	0.96
HLA A/B/DR mm -number	3.2 (1.2)	3.2 (1.2)	3.3 (1.2)	3.6 (1.1)	<0.001[b,c]
HLA DR mm					<0.001[b]
zero mm	2334 (31)	2177 (32)	46 (27)	111 (22)	
one mm	5163 (69)	4654 (68)	123 (73)	386 (78)	

Continuous variates are reported as mean (standard deviation) or median (interquartile range). Categorical variates as number (percentage)
Superscripts indicate statistical significance (P<0.05), as follows:

[a] *EU-born vs Eastern European-born*

[b] *EU-born vs non-European-born*

[c] *Eastern European-born vs non-European-born*

EU, European Union; Eastern European-born, born in Eastern Europe or Balkans; HD, hemodialysis; PD, peritoneal dialysis; mm, mismatch; PRA, Panel reactive antibody; CDC-PRA, Complement-dependent cytotoxicity Panel Reactive Antibody; ADPKD, Autosomal Dominant Polycystic Kidney Disease

Joint analysis of transplant survival and graft function (eGFR)

Among the 6,281 DD KTRs recipients who were followed beyond one-year post-transplantation, 594 had transplant failure (301 of them because of death with a functioning graft) after a mean follow-up of 3.4 years since transplantation. Overall, in the period from year 1 to year 5, DD KTRs recipients provided 17,047 eGFR data and 23,294 person-years of time at risk to the joint longitudinal survival analysis. After adjusting for confounders, mean 1-year (baseline) eGFR was similar between groups (52.4. mL/min/1.73m^2 in the EU-born KTRs, 54.4 mL/min/1.73m^2 in Eastern European-born [P=0.24 vs EU-born], and 53.7 mL/min/1.73m^2 in non-European-born KTRs [P=0.20 vs EU-born]). In EU-born KTRs the average yearly change in eGFR was +0.19 mL/min/1.73m^2/year (95%CI. +0.06 to +0.31). It was similar in Eastern European-born KTRs (difference with EU-born: +0.02 mL/min/1.73m^2/year [-0.77 to +0.81; P =0.96]). In contrast, compared to EU-born KTRs, non-European-born KTRs, had a significant decline in eGFR (difference with EU-born: -0.96 mL/min/1.73m^2/year [-1.48 to -0.45; P<0.001]). Compared to EU-born KTRs, in non-European-born KTRs the adjusted difference at 4 years in the change from 1-yr eGFR was -3.1 mL/min/1.73m^2 (95% CI: -5.2 to -1.1; P=0.003); at 5 years, it was -4.7 mL/min/1.73m^2 (-7.3 to -2.2; P<0.001), whereas EU and Eastern European-born KTRs had similar eGFR decline throughout (**Table 8**).

After stratifying non-European-born KTRs according to ethnicity, each ethnic group had similar eGFR decline at 5 years (P value >0.01 for every multiple pairwise comparison between ethnic groups). In fact, compared to non-European-born KTRs, the average yearly change in eGFR was -0.58 mL/min/1.73m^2/year (95%CI: -1.52 to + 0.35; P=0.22) in Asians, -2.24 mL/min/1.73m^2/ year (-3.50 to -0.98; P < 0.001) in Hispanics, -0.59 mL/min/1.73m^2/year (-1.64 to +0.47; P=0.28) in Africans, and -1.00 mL/min/1.73m^2/year (-1.90 to -0.11; P= 0.028) in Others; GFR decline at 5 years was -3.3 mL/min/1.73m^2 (-8.0 to +1.3; P =0.16) in Asians, -7.0 mL/min/1.73m^2 (-13.4 to -0.7; P =0.030) in Hispanics, -4.2 mL/min/1.73m^2 (-9.6 to +1.1; P =0.12) in Africans, and -5.5 mL/min/1.73m^2 (-9.9 to -1.0; P= 0.016) in "Other" ethnic groups.

Compared to EU-born KTRs, non-European-born KTRs had a hazard ratio of transplant failure of 1.36 (95%CI: 0.95 to 1.95; P=0.090), and Eastern European-born KTRs of 0.91 (0.44 to 1.88; P=0.79) (**Table 8**). In those surviving 1-year post-transplantation, adjusted 5-year transplant survival was 91.8% in EU-born (95%CI: 87.1 to 96.8), 92.5% in Eastern European-born (86.1 to 99.4), and 89.3% in non-European-born KTRs (83.0 to 96.0). After stratifying non-European-born patients according to ethnicity, African was the only group showing significantly increased mortality compared to EU-born KTRs (hazard ratio of transplant failure being 0.84 [95%CI: 0.38 to 1.80] for Asians, 1.14 [0.41 to 0.38] for Hispanics, 3.84 [2.28 to 6.45] for Africans, 0.69 [0.32 to 1.50] for Other).

Table 8. Adjusted difference in change from 1-yr eGFR and adjusted hazard ratio from joint longitudinal survival analysis based on Cox regression for the analysis of survival time.

	Eastern European-born vs EU-born ΔeGFR, mL/min/1.73m^2 Difference between groups (95% CI) P value	Non-European-born vs EU-born ΔeGFR, mL/min/1.73m^2 Difference between groups (95% CI) P value
Year since transplantation		
2-yr	+1.1 (-1.3 to +3.6) P=0.36	-2.6 (-4.2 to -1.1) P=0.001
3-yr	-0.5 (-3.0 to +2.1) P=0.73	-1.9 (-3.6 to -0.2) P=0.029
4-yr	+0.8 (-2.3 to +4.0) P=0.60	-3.1 (-5.2 to -1.1) P=0.003
5-yr	-0.4 (-4.4 to +3.6) P=0.84	-4.7 (-7.3 to -2.2) P<0.001
	Eastern European-born vs EU-born HR (95% CI) P value	Non-European-born vs EU-born HR (95% CI) P value
	0.91 (0.44 to 1.88) P=0.79	1.36 (0.95 to 1.95) P=0.090
Association parameter γ (logarithm of HR of graft failure per 1mL/min/1.73m^2 increase in eGFR)	-0.31 (95%CI: -0.28 to -0.35)	
Association parameter γ expressed as HR of graft failure per1mL/min/1.73m^2 decrease in eGFR	1.37 (95%CI: 1.33 to 1.41)	

Results from joint longitudinal survival analysis (fitted via Cox regression). eGFR differences represent adjusted differences between groups in the change from baseline eGFR (1-yr post-transplantation) estimated by linear mixed models with time modeled as categorical variate (differences in eGFR by year are estimated from the interaction term between group and categorical time, and may be affected by random differences in baseline 1-yr eGFR). Adjusted 1-yr eGFR did not differ between groups (see text). The analysis was performed in transplant recipients survived beyond 1-year post-transplantation.

The joint longitudinal survival analysis was adjusted for donor and recipient age, recipient gender, dialysis vintage, number of HLA mismatches and re-transplantation. The association parameter γ between longitudinal and survival patient latent random-effects had a negative estimate, which implies a negative association between eGFR and transplant survival: the higher the eGFR, the lower the chance of transplant failure. The association parameter is reported as log (hazard ratio) of graft failure per 5mL/min/1.73m^2 *increase* in eGFR, and as hazard ratio per 5mL/min/1.73m^2 *decrease* in eGFR. the likelihood ratio test of no latent association between longitudinal and survival random effect (H0: γ = 0) yielded χ^2 (1) = 362 (P<0.001).

ΔeGFR, difference in eGFR change from baseline eGFR (1-yr post-transplantation)

HR, hazard ratio

95% CI, 95 percent confidence interval.

4.4. Discussion

To the best of our knowledge, this is the first study examining the relationship between long-term eGFR decline and immigration status in adult KTRs in Europe (**Table 9**). This study provides the first evidence that non-European immigration background is associated with long-term eGFR decline. This study was performed in Italy which is a rather unique setting for studying the effect of immigration status as a socioeconomic and cultural condition. Since immigration from non-EU countries beyond Eastern Europe is a relatively recent and extensive phenomenon, ethnic minorities among adult subjects are largely composed by first-generation immigrants as opposed to native-Italians and natives of the other EU-28 member States.

Table 9. Studies of kidney transplant outcomes in non-European-born recipients with an immigration background

Study ID	Study location	Study type	Study period	Number of patients	Patient population	Length of follow-up	Assessment of immigration background	Access to post-Tx care	Non-EU-born KTRs' origin	Assessment of Post-Tx eGFR	Timing of eGFR measurement post-Tx	Effect of eGFR decline
1) Roodnat et al. [19]	Netherlands	SC	1983 - 1997	509	Adult	54 months (mean, Europeans) 44 months (mean, non-Europeans)	Yes	Yes	AF (n=37), AS (n=44), AR (n=13), TR (n=16)	No	-	-
2) Pallet et al. [21]	France	SC	1987 - 2003	1,092	Adult	NS	Yes	Yes	SSA (n=39), CARIB (n=101)	Yes (ClCr CG)	6, 12 months, 5 years	NA
3) Oztek et al. [24]	Austria	SC	1997 - 2005	59	Pediatric	3 years (mean)	Yes	Yes	YU (n=10), TR (n=3), PL, NG, BG, TH (n=1 each)	Yes (Schwartz formula)	NS	NA
4) Mérida et al. [22]	Spain	SC	1996 - 2006	76	Adult	76 months (mean, AF) 68 months (mean, N)	Yes	Yes	MA, GN, NG (n=27)	Yes (MDRD)	1 month, end of follow-up (NS)	NA
5) Oztek et al. [25]	Austria	SC	1978 - 2007	197	Pediatric	6.4 years (mean)	Yes	Yes	YU (n=22), TR (n=9), LY (n=9), other (n=8)	Yes (Schwartz formula)	First outpatient visit (NS), 1 year	NA
6) Tromp et al. [20]	Netherlands/ Belgium	MC	2007 - 2011	119	Pediatric	18 months (median)	Yes	Yes	MA (n=8), TR (n=9) SR (n=7), AS (n=4), CARIB (n=2) Other AF (n=7) Other ME (n=4)	Yes (Schwartz formula)	3, 12 months	NA
7) Laging et al. [23]	Netherlands	SC	2000 - 2010	1,338	Adult	4.5 years (median)	Yes	Yes	AF (n=112), AR (n=48), AS (n=132), TR (n=69)	No	-	-

AF, African; AR, Arab; AS, Asian; BG, Bulgaria; CARIB, Caribbean; ClCr CG, Cockcroft-Gault equation for Creatinine Clearance; EU, European; eGFR, Estimated Glomerular Filtration Rate; GN, Guinea; KTR, Kidney Transplant Recipient; LY, Lybia; MA, Morocco; MC, Multicenter; MDRD, Modification of Diet in Renal Disease equation; ME, Middle East; N, Natives; NG, Nigeria; NA, Not Assessed; NS, Not Specified; PL, Poland; SC, Single Center; SSA, Sub-Saharan Africa; SR, Suriname; TH, Thailand; TR, Turkey; Tx, Transplant; YU, Former Yugoslavia

Moreover, Italy has a publicly funded health system with universal coverage, which may dampen the adverse effect of economic status on health outcomes. Our findings show that, compared to EU-born KTRs, and unlike Eastern European-born KTRs, non-European-born KTRs had an eGFR decline of almost -5mL/min/1.73m^2 at 5-years post-transplantation. It is likely that the observed 5-year differences in eGFR longitudinal changes would have been even sharper had we extended our longitudinal follow-up for ten or more years. The eGFR slope after KT has been put forward as a surrogate for long-term death and death-censored graft failure (Clayton et al. 2016; Maggiore et al. 2020) and as a reliable surrogate endpoint of long-term death and ESKD in chronic kidney disease trials (Inker et al. 2019; Greene et al. 2019). Moreover, eGFR is one of the main mediators of the relation between immigration background and long-term clinical outcomes in KTRs, since immigration background may adversely affect kidney graft function (see below) and graft dysfunction is a cause of ESKD and death. Our analysis started 1-year post-transplantation, at the time when the first eGFR measurement was available. In fact, in agreement with previous studies (Tromp et al. 2012; Pallet et al. 2005; Oztek et al. 2011), we did not find significant differences in adjusted 1-year post-transplant eGFR in KTRs with non-European immigration background compared to their native referents. We contend that, while immigration background may only minimally affect early transplant outcomes given intensive early management, factors such as adherence to medication regimens or clinic visits may have a greater impact over time after the first year post-transplant. Immunological factors appear to be less often the cause of graft loss beyond 1 year after KT (Gordon et al. 2010). In our study, baseline immunological (i.e. HLA, sensitization status) and non-immunological risk variables (i.e. recipient and donor age, dialysis vintage, time to WL) were comparable between Eastern European-born and non-European-born KTRs.

Ethnicity per se did not seem to account for the relation between immigration background and decline in eGFR. In fact, after stratifying non-European-born patients according to the four ethnic groups (i.e. Asian, Hispanic, African, Other), eGFR decline did not present statistically significant differences between groups, apart from numerical differences likely related to the sparse number of subjects within each stratum. African ethnicity was associated with increased hazard of transplant failure within 5 years, despite similar decline in eGFR. Our findings are similar to those of a previous study from the United Kingdom (UK) (Udayaraj et al. 2013) that found comparable 1- and 5-year median eGFR in Black and South Asian KTRs, despite increased hazard of graft failure in Blacks. However, in that study, the analysis on eGFR was based on unadjusted two-sample test between groups and the immigration background of the patients was not assessed (Udayaraj et al. 2013). Yet, given the longer-standing history of immigration in the UK, it is likely that only a minority of Black patients were first-generation immigrants (De La Rica et al. 2013). Another Dutch study, which did assess immigration background but not eGFR, reported equal graft and patient survival in non-European as opposed to European KTRs over a mean follow-up of 54 months. However, after introducing ethnicity in their model, the authors found an increased risk of either death or graft failure in KTRs of Arab and African origin (Roodnat et al. 1999). A monocentric study from France reported 5-year creatinine clearance in African immigrants and their native-born counterparts. However, 5-year creatinine clearance was available in only 37 subjects, and the results were simply based on a summary statistics report (Pallet et al. 2005). A Dutch study with subject ethnicities similar to ours (i.e. African, Arabian, Asian and Turkish) found no significant influence of non-European origin on either patient or graft survival over a median follow-up of 4.5 years. This study included, however, second and third generation immigrants with higher socioeconomic status and better integration compared to the previous Dutch study, and did not examine long-term eGFR (Laging et al. 2014). It is possible that the overall socioeconomic disadvantage and communicative difficulties specific to first-generation immigrants in Italy and other European countries may have impacted the post-transplant course in non-European-born KTRs (Fondazione ISMU 2019; Eurostat 2016; ISTAT 2014). Also, more vulnerable immigrant categories (i.e. refugees, protection status holders, immigrants for family reasons) are all less likely to be well-integrated (Fondazione ISMU 2019).

Interplay among multiple determinants may have played a role in lower eGFR in non-European-born KTRs. Additional factors contributing to reduced kidney graft function among these patients may include reduced utilization of living donor transplantation, undetermined epidemiologic exposures and risk for opportunistic infections, and other immunological and biological factors such as increased alloreactive immune responses, and different pharmacokinetics of immunosuppressive drugs (Tromp et al. 2012; Mérida et al. 2009; Laging et al. 2014; Gordon et al. 2010). Lack of strategies to accommodate the needs of immigrant populations may have equally played a role (Vázquez et al. 2011). Similarly, progressive worsening of kidney graft function over time can also be attributed to non-adherence in KTRs (Vlaminck et al. 2014). The effects of poorer levels of HL, lower educational levels, the complexity of immunosuppressive medications, inadequate patient-provider communication and lack of understanding of patients' cultural influences (i.e. medication beliefs, misconceptions about the post-transplant course, language barriers) on self-management and behaviors cannot be excluded as potential determinants of non-adherence and of consequently reduced kidney graft function among non-European-born KTRs (Poulakou et al. 2019; Demian et al. 2016; McQuaid et al. 2018; Prihodova et al. 2014; Thabit et al. 2009). We were unable to assess the contribution of these factors to lower eGFR in this study, although it seems plausible that access to care alone is unlikely to be an independent determinant of successful KT outcomes.

Our study has several limitations. First, the retrospective nature of the research relies on data included within a national database which, while accurate, cannot identify all the potential confounding variables. No data relative to time elapsed since immigration, post-transplant migration routes, language proficiency, socioeconomic and educational status, rejection episodes, delayed graft function, chronic allograft nephropathy, type of immunosuppressive treatment, immunological and pharmacokinetic biomarkers, and other psychosocial variables including treatment adherence can be retrieved. No data regarding ancestries of EU-born recipients can be obtained. However, because immigration from non-EU countries beyond Eastern Europe is a recent phenomenon in Italy, we basically did not have adult EU-born individuals with non-European ancestries receiving KT and this mitigates the deficiency. The heterogeneity of the non-European-born categories and the lack of data to further subcategorize these patients based on biomarkers of anti-rejection drug metabolism or increased alloreactivity and immigrant category may conceal disparities in more disadvantaged immigrant groups. Yet, although undocumented immigrants with kidney failure are granted a so-called Temporarily Present Foreigner (STP) permit and are entitled to receive DDKT, KT in this particularly vulnerable group of patients is rather infrequent (i.e. less than 10 cases) and there were none included in our study. Other psychosocial outcomes related to immigration status could not be explored. Finally, we focused on the immigrant patient population; other vulnerable groups might equally merit inclusion into future studies of disparities in KT outcomes. Prospective studies are needed to further elucidate the causal pathways linking immigration and ethnicity with KT outcomes. As immigration worldwide increases, future studies should include psychosocial, sociocultural, and socioeconomic data to generate a more accurate picture of KT patient populations. This will enable to determine the need for targeted strategies to accommodate these vulnerable patients and guarantee provision of high-quality care throughout the transplant process.

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Chapter 5. Detecting determinants of disparities in the process of kidney transplant in the Non-European immigrant patient population: a case series

Case analyses in this chapter were presented following abstract acceptance at:

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Grossi AA, Grossi PA, Picozzi M.
International Conference on Seniors, Foreign Caregivers, Families, Institutions: Linguistic and Multidisciplinary Perspectives (Varese, 9-10 Apr 2019)

Grossi AA, Nicoli F, Ferioli E, et al. European Association of Centers of Medical Ethics (EACME) Conference 2018 (Amsterdam, 6-8 Sep 2018)

One case will be published as a book contribution as follows:
Grossi AA. *Migration projects and challenges to post-transplant follow-up* (case presentation and commentary). In: Picozzi M (ed). Il trapianto di organi. Realtà clinica e questioni etico deontologiche (forthcoming)

In preparation as: **Grossi AA**, Caselli I, Nicoli F, et al. *The Four Boxes Method as a Tool to Detect Determinants of Disparities in the Process of Kidney Transplant in the Immigrant Patient Population: a Case Series*. Journal of Immigrant and Minority Health.

> *“Eliminating disparities requires truly patient-centered care —*
> *that is, individualized care by clinicians who appreciate that*
> *patients’ beliefs, behaviors, social and economic challenges, and environments*
> *influence their health outcomes”*
> (Marshall Chin 2016 [14])

5.1. Introduction

End stage kidney disease (ESKD) is a major cause of morbidity and mortality, with nearly 2 million patients receiving renal replacement therapy (RRT) worldwide (Trillini, Perico and Remuzzi 2017). Kidney transplantation (KT) is the best treatment option for eligible patients with ESKD providing improved quality of life (QoL), longer life-expectancy and higher cost-effectiveness when compared with dialysis (Tonelli et al. 2011; Axelrod et al. 2018). KT is a lifelong process requiring patients’ ability to adhere to complex post-transplant medical regimens including lifelong immunosuppressive medications (ISM), attendance to follow-up outpatient visits, dietary and physical activity prescriptions, avoidance of substance use and non-exposure to infectious risks to preserve patient and graft survival (Dew et al. 2018). Studies have shown that clinical (i.e. diabetes, hypertension, obesity, high serum creatinine at diagnosis) and nonclinical factors (i.e. poor access to healthcare, ethnic minority and/or immigrant status, low socioeconomic status, cultural beliefs) existing in the early stages of chronic kidney disease may have negative downstream effects on the subsequent phases of the process, including enrollment on the waiting list (WL), receiving KT, and KT outcomes (Ladin, Rodrigue and Hanto 2009). Balancing the four ethical principles of patient autonomy (respect for persons), beneficence (to prevent/remove harm and promote good), non-maleficence (to not cause harm) and justice (to treat people fairly) is core to all aspects of decision-making in clinical practice (Beauchamp and Childress 2012). Decision-making regarding the allocation of DD organs is not an exception, and multidisciplinary pre-transplant assessments are the cornerstone for this. Given the scarcity of DD kidneys, the challenge at the time of pre-transplant evaluations is the determination of the prospective «benefit» of transplantation for individual patients (beneficence/non-maleficence) and for KT candidates in general (justice) (EDQM 2017:59; Veatch and Ross 2015; OPTN 2015[a] ; Delmonico 2013). Balance among these principles is frequently challenged throughout pre-transplant recipients’ assessments, especially when vulnerable subjects are involved. These include socio-economically disadvantaged subjects, individuals who have migrated from other countries or are from ethnic minorities/non-native speakers, patients with limited HL, elderly persons, and other vulnerable social categories (Davison and Holley 2008; Segall et al. 2016; Halpern and Goldberg 2017; Zhang et al. 2018; Van Biesen et al. 2018). Ethical issues and disagreements within transplant teams are frequent due to lack of well-defined policies and variability across clinical practice guidelines (Batabyal et al. 2012; OPTN 2015[b]). In their description of how the principle of justice relates to fair/unfair disparities, Beauchamp and Childress

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[14] Chin MH. How to achieve health equity. N Engl J Med 2014; 371(24):2331-2332.

address the following question: “What kind of fair opportunity in life does justice require?” (2009: 248). Regarding disparities associated with immigrant status, this question brings into play the relationship with the concept of equity as a fundamental principle in organ transplantation (EDQM 2018) and migrant health (WHO 2018), and the factors with the potential to affect KT outcomes.

«Capacity to benefit», defined as “the patient’s ability to experience health status improvement” over time is broadly recognized as an ethically appropriate approach to guide pre-transplant multidisciplinary assessments (Bramstedt 2002; Englschalk et al. 2018; EDQM 2018). Yet, given the complexity and multidimensionality of the concept, prediction of KT outcomes regarding patient and graft survival remains a difficult task. «Benefit» is not a monolithic concept. Bramstedt (2002) suggests that evaluation of the expected benefit of medical treatment should include a variety of elements, namely the intensity and duration of the benefit, the probability and amount of time until the benefit occurs, the likelihood of either additional benefits or harmful effects following the initial benefit, and the consequences of the patient’s benefit on others. Further, while considerations regarding patients’ social worth are excluded from evaluations, other social and contextual issues that may affect the patient’s «capacity to benefit» should be included in the formulation. The challenge is therefore to combine a certain degree of standardization with the ethical obligation to provide individualized whole-person care. Consistent with institutional recommendations (KDIGO 2020), this approach promotes individual assessments and prevents discrimination based on stereotypical views that certain vulnerable social categories may not benefit from treatment, with the potential for disparities in accessibility, quality, and outcomes of care. As opposed to the United States, the majority of health systems in the European Union (EU) guarantee equal access to KT and post-transplant medical regimens to all individuals, regardless of ability to pay (Bello et al. 2017). However, EU studies document disparities in accessibility (Tjaden et al. 2016; Tromp et al. 2012;) and outcomes (Grossi et al. 2020; Tromp et al. 2012; Roodnat et al. 2010) of KT among patients with non-European immigration background relative to their European-born counterparts. While many studies consider ethnic minority status as a prominent vulnerability factor associated with inequities in the process of KT (Malek et al. 2011), healthcare disparities associated with immigrant status involve more complex, interrelated aspects because of additional vulnerability factors when compared to ethnicity alone (Grabovschi et al. 2013; Van Biesen et al. 2018; Poulakou, Len and Akova 2019). Migrants are more likely exposed to health risks before, during and following migration, to lack knowledge of national legal and administrative regulations in host countries, to experience cultural (i.e. different health beliefs and health-seeking behaviors) and linguistic difficulties, and to struggle with poor living conditions, social exclusion and/or discrimination (Wickramage et al. 2018; De Luca, Ponzo and Andrés 2013; WHO 2010). Research suggests that adopting an SDH approach in clinical practice allows identification of patients’ social challenges with the potential to prevent implementation of inappropriate care plans and increase chances for improved health care outcomes (Bourgois et al. 2017; Andermann 2016; Metzl and Hansen 2014). While vulnerability is recognized as a universal, ontological component of human condition, a variety of vulnerabilities are context-specific and require ethical responses because of their consequences in particular settings (Rendtorff 2002). Studies contend that comprehensive transplant care considering patients’ and patients' families' cultural beliefs, values and social context can be associated with diminished disparities in KT in patients who have migrated from other countries or who are from ethnic minorities (Gordon et al. 2010). Therefore, multiple studies have emphasized the moral duty to adopt a holistic approach to these vulnerable patients along with the need for targeted interventions to guarantee high quality care throughout the transplant process (Maloney et al. 2005; Forneris et al. 2011; Van Biesen et al. 2018).

Three clinical cases of first-generation non-European immigrant patients on the KT WL were analyzed with the objective to: (1) explore individual patients' preferences and social challenges that might account for disparities in KT clinical practice and (2) to address the ethical dimensions associated with nonclinical factors which may affect accessibility due to the potential for detrimental effects on long-term outcomes of KT.

5.2. Materials and methods

Two main instruments were utilized for the analyses of the three cases. The Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) was used for the psychosocial analysis (Maldonado et al. 2012). In order to integrate the quantitative, standardized psychosocial assessment with the ethics analysis of disparities in this vulnerable group of patients, we used the Four-Boxes Method for ethical decisions in clinical medicine (Jonsen, Siegler and Winslade 2015), allowing also the qualitative exploration of additional nonclinical aspects, with an emphasis on contextual features (see below). The SIPAT, first developed by Maldonado and colleagues (Maldonado et al. 2012) and validated into Italian more recently (Bottesi et al. 2020), is a standardized scoring tool composed of 18 items allowing clinicians to identify the risk factors potentially compromising the clinical and psychosocial outcomes of transplantation. This explores the patient's psychosocial dimensions in terms of: (A) patient's readiness level; (B) social support system; (C) psychological stability and psychopathology; and (D) lifestyle and effect of substance use (**Table 10**). Each item is assigned a specific value (total score range: 0 – 110) and transplant candidates may fall into one of five categories: excellent (0-6), good (7-20), minimally acceptable (21-39), poor (40-69) or high risk (>70).

Table 10. Psychosocial Domains and Factors Measured by the SIPAT

(A) PATIENT'S READINESS LEVEL AND ILLNESS MANAGEMENT (5 ITEMS)	SCORE (min-max)
Item 1: Knowledge and understanding of medical illness process (that caused specific organ failure)	0-4
Item 2: Knowledge and understanding of the process of transplantation	0-4
Item 3: Willingness/desire for treatment (transplant)	0-4
Item 4: History of treatment adherence/compliance (pertinent to medical issues)	0-8
Item 5: Lifestyle factors (including diet, exercise, fluid restrictions, and habits according to organ system)	0-4
(B) SOCIAL SUPPORT SYSTEM LEVEL OF READINESS (3 ITEMS)	
Item 6: Availability of social support system	0-8
Item 7: Functionality of social support system	0-8
Item 8: Appropriateness of physical living space and environment	0-4
(C) PSYCHOLOGICAL STABILITY AND PSYCHOPATHOLOGY (5 ITEMS)	
Item 9: Presence of psychopathology (other than personality disorders and organic psychopathology)	0-8
Item 10: History of organic psychopathology or neurocognitive impairment (i.e., illness or medication-induced psychopathology)	0-5
Item 11: Influence of personality traits vs. disorder	0-4
Item 12: Effect of truthfulness vs. deceptive behavior	0-8

Item 13: Overall risk for psychopathology	0-4
(D) LIFESTYLE AND EFFECT OF SUBSTANCE USE (5 ITEMS)	
Item 14: Alcohol use, abuse, and dependence	0-8
Item 15: Alcohol abuse - risk for recidivism	0-4
Item 16: Illicit substance, abuse and dependence	0-8
Item 17: Illicit substance abuse - risk for recidivism	0-4
Item 18: Nicotine use, abuse, and dependence	0-5

Source: Maldonado et al. 2012

The Four-Boxes Method, developed by Jonsen, Siegler and Winslade (2015), is a tool to identify the ethical problem(s) at stake, to apply the four principles of ethics (beneficence, nonmaleficence, autonomy, and justice) (Beauchamp and Childress 2009) in clinical practice, to gain a more comprehensive picture of the ethical dimensions of clinical scenarios and to fulfill the ethical obligation to provide whole-person care. This method embraces the four topics that the authors regard as constitutive of the essential structure of single clinical cases: (1) Medical Indications; (2) Patient Preferences; (3) Quality of Life; and (4) Contextual Features. Each of these topics considers the specificities of single clinical cases, and answers to a set of questions that serve the function to provide a complete representation of the ethical dimensions of the case and to guarantee that all the necessary information have been gathered (**Table 11**).

(1) *Medical indications* refer to the diagnostic and therapeutic interventions that are being used to evaluate and treat the medical problem in the case;

(2) *Patient preferences* are the declarations regarding treatments expressed by the patients or by those who have received authorization when patients are unable to do so;

(3) *Quality of life* describes the features of the patient's life before and after medical treatment, insofar as these features are pertinent to medical decisions;

(4) *Contextual features* identify the familial, social, institutional, financial, and legal settings within which the particular case takes place, insofar as they influence medical decisions. Further, following from Bramstedt's adapted version of the Method (Bramstedt 2018), this dimension considers additional nonclinical variables with the potential to impact the case such as the patient's religious values, relationship status, occupation, habitation and immigrant status.

Table 11. The Four-Boxes Method for Ethical Decisions in Clinical Medicine

(A) MEDICAL INDICATIONS

The Principles of Beneficence and Non-maleficence

1. What is the patient's medical problem? Is the problem acute? Chronic? Critical? Reversible? Emergent? Terminal?
2. What are the goals of treatment?
3. In what circumstances are medical treatments not indicated?
4. What are the probabilities of success of various treatment options?
5. In sum, how can this patient be benefited by medical and nursing care, and how can harm be avoided?

(B) PATIENT PREFERENCES

The Principle of Respect for Autonomy

1. Has the patient been informed of benefits and risks, understood this information, and given consent?
2. Is the patient mentally capable and legally competent, and is there evidence of incapacity?
3. If mentally capable, what preferences about treatment is the patient stating?
4. If incapacitated, has the patient expressed prior preferences?
5. Who is the appropriate surrogate to make decisions for the incapacitated patient?
6. Is the patient unwilling or unable to cooperate with medical treatment? If so, why?

(C) QUALITY OF LIFE

The Principles of Beneficence, Non-maleficence, and Respect for Autonomy

1. What are the prospects, with or without treatment, for a return to normal life, and what physical, mental, and social deficits might the patient experience even if treatment succeeds?
2. On what grounds can anyone judge that some quality of life would be undesirable for a patient who cannot make or express such a judgment?
3. Are there biases that might prejudice the provider's evaluation of the patient's quality of life?
4. What ethical issues arise concerning improving or enhancing a patient's quality of life?
5. Do quality-of-life assessments raise any questions regarding changes in treatment plans, such as forgoing life-sustaining treatment?
6. What are plans and rationale to forgo life-sustaining treatment?
7. What is the legal and ethical status of suicide?

(D) CONTEXTUAL FEATURES

The Principles of Justice and Fairness

1. Are there professional, inter-professional, or business interests that might create conflicts of interest in the clinical treatment of patients?
2. Are there parties other than clinicians and patients, such as family members, who have an interest in clinical decisions?
3. What are the limits imposed on patient confidentiality by the legitimate interests of third parties?
4. Are there financial factors that create conflicts of interest in clinical decisions?
5. Are there problems of allocation of scarce health resources that might affect clinical decisions?
6. Are there religious issues that might affect clinical decisions?
7. What are the legal issues that might affect clinical decisions?
8. Are there considerations of clinical research and education that might affect clinical decisions?
9. Are there issues of public health and safety that affect clinical decisions?
10. Are there conflicts of interest within institutions or organizations (e.g. hospitals) that may affect clinical decisions and patient welfare?
11. *Are there any nonclinical variables that potentially impact the case such as the patient's religious values, financial status, relationship status, occupation, habitation and immigration status?

Source: Jonsen, Siegler and Winslade 2015 (*Bramstedt 2018)

Clinical data were reported by the patients' attending clinicians. Patients provided a general written informed consent to processing personal data as part of the standard diagnostic procedures; the SIPAT tool was retrospectively applied to the three cases. Data were anonymized and patients' names were altered. Therefore, the subjects of the study may not be identified and, according to the Italian legal regulations (D.L. 196/2003, art. 110-24 July 2008, art. 13), the study did not require authorization from the local Ethical Review Board. The study was carried out in compliance with the ethical principles of the Declaration of Helsinki (with amendments) and *Good Clinical Practice*.

5.3. Results

The analyzed clinical cases are presented in their main characteristics, listed according to the SIPAT tool (**Table 12**); other clinical features, the individual cultural, social, economic and relational factors along with their association with the broader social context and the individual ethical dimensions are presented based on the *Four-Boxes* method (**Table 13**).

Table 12. Presentation of Case Analyses by the “Stanford Integrated Psychosocial Assessment for Transplantation”:

Key component of the SIPAT psychosocial assessment	**Case 1: Stephanie, Nigerian (SN)**		**Case 2: Salma, Moroccan (SM)**		**Case 3: Esther, Nigerian (EN)**	
	SIPAT explanation	*SIPAT Score*	*SIPAT explanation*	*SIPAT Score*	*SIPAT explanation*	*SIPAT Score*
A. Patient’s readiness level						
Knowledge and Understanding of Medical Illness Process (that caused organ failure)	Poor Understanding: Extreme denial or indifference is evident	4	Limited Understanding: Patient has only rudimentary knowledge despite of years of illness and/or extensive teaching by providers	3	Poor Understanding: Extreme denial or indifference is evident	4
Knowledge and Understanding of the Process of Transplantation	Poor Understanding: Extreme denial or indifference evident	4	Limited Understanding: Patient only has rudimentary knowledge despite intensive teaching by providers	3	Poor Understanding: Extreme denial or indifference evident	4
Willingness/Desire for Treatment (Transplant)	Moderate: Patient appears ambivalent; only passively involved in process; actions are only acceptable at best	2	Limited: Patient who has limited involvement in her care. Family member appears more interested in the transplant process than patient	3	Poor: Family member or MD pushing patient to participate in the transplantation evaluation process; the patient is uninterested or mostly unengaged	4
Treatment Compliance/Adherence (Pertinent to medical issues)	Poor: Evidence of significant treatment non-adherence with negative impact to patient’s health (i.e. treatment non-adherence/compliance)	8	Good: Patient is mostly compliant; requires redirection or reeducation; but no significant negative outcomes are documented	2	Moderate: Only partially compliant or excessive self-management; requires multiple efforts and persuasion from the Transplant team and/or family	4
Lifestyle Factors (Including diet, exercise, fluid restrictions; and habits according to organ)	Patient complies with recommended changes only after the development of complications	3	Patient is responsive to recommended changes	1	Patient is reluctant, but compliant with recommended changes, after much prompting and encouragement from support and transplant team	2
B. Social Support System						
Availability of Social Support System	Limited: The patient’s identified support system appears tentative. Identified backup system’s reliability is questionable	6	Good: Various individuals (e.g., minimum of two people) have been identified and are actively engaged in the patient’s care. A back-up system, albeit limited, seems feasible	2	Poor: Patient unable to identify reliable support system. No reasonable back-up support system is in place	8
Functionality of Social Support System	Limited: Member of the identified support system has expressed doubts and hesitation	6	Moderate: Members of the patient’s identified support system may themselves need some psychosocial work before they are ready for transplantation	4	Poor: Patient has suffered due to unreliable support system AND the transplant team has not been able to effectively work with the support team	8
Appropriateness of physical living space and environment	Adequate: Reported arrangement is only temporary and/or tenuous	2	Good: Patient has some stable housing arrangement, albeit not optimal	1	Adequate: Reported arrangement is only temporary and/or tenuous	2
C. Psychological Stability & Psychopathology						
	No Clinical Depression	0	No Clinical Depression	0	No Clinical Depression	0

Presence of Psychopathology (mood, anxiety, psychosis and others)						
History of Organic Psychopathology or Neurocognitive Impairment	No Clinical Anxiety	0	No Clinical Anxiety	0	No Clinical Anxiety	0
Influence of Personality Traits vs. Disorder	None: No history of significant personality disorder or psychopathology/traits	0	None: No history of significant personality disorder or psychopathology/traits	0	None: No history of significant personality disorder or psychopathology/traits	0
Effect of Truthfulness vs. Deceptive Behavior in Presentation	Patient has not been fully forthcoming with negative information. Information obtained only from external sources	6	Patient has not been fully forthcoming with negative information. Information obtained only from external sources	6	There is clear evidence of deceptive behavior as evidence by records, collateral information or testing	8
Overall Risk for Psychopathology	None: No history of personal or familial psychiatric problems; no psychiatric complications in response to illness, medical treatment or psychosocial stressors	0	None: No history of personal or familial psychiatric problems; no psychiatric complications in response to illness, medical treatment or psychosocial stressors	0	None: No history of personal or familial psychiatric problems; no psychiatric complications in response to illness, medical treatment or psychosocial stressors	0
D. Lifestyle and Effect of Substance Use						
Alcohol Use/ Abuse/ Dependence	None: No history of alcohol use	0	None: No history of alcohol use	0	None: No history of alcohol use	0
Alcohol Use/ Abuse/ Dependence - Risk for Recidivism	None: No history of Alcohol use	0	None: No history of Alcohol use	0	None: No history of Alcohol use	0
Substance Use/ Abuse/ Dependence – Including Prescribed and Illicit Substances	None: No history of illicit substance use; or abuse of prescribed substances	0	None: No history of illicit substance use; or abuse of prescribed substances	0	None: No history of illicit substance use; or abuse of prescribed substances	0
Substance Use/ Abuse/ Dependence – Including Prescribed and Illicit Substances - Risk for Recidivism	None: No history of illicit substance Use; or abuse of prescribed substances	0	None: No history of illicit substance Use; or abuse of prescribed substances	0	None: No history of illicit substance Use; or abuse of prescribed substances	0
Nicotine Use/ Abuse/ Dependence	None: Never used tobacco in any form. No history of nicotine use/abuse	0	None: Never used tobacco in any form. No history of Nicotine Use/Abuse	0	None: Never used tobacco in any form. No history of Nicotine Use/Abuse	0
Total SIPAT Score Explanation	**Poor Candidate - Recommend deferral while identified risks are satisfactorily addressed**	**41**	**Minimally Acceptable Candidate - Consider listing. Identified risk factors must be satisfactorily addressed before representing for consideration.**	**25**	**Poor Candidate - Recommend deferral while identified risks are satisfactorily addressed**	**44**

Table 13. Case Analyses by the “Four-Boxes Method” for ethical decisions in clinical medicine

	Case 1 – SN **Age: 20; Sex: F**	**Case 2 – SM** **Age: 65; Sex: F**	**Case 3 – EN** **Age: 36; Sex: F**
Clinical Indications	ESKD (unknown PCKF but likely HIV-associated nephropathy); HIV-HBV co-infection; 3-times weekly HD by AVF; HIV-HBV co-infection treated with cART also effective as HBV treatment; low CD4+ T-cell count (219 uL); fragmented medical records; limited adherence to cART; no clinical contraindication to KT; goal of KT: improve life expectancy and QoL.	ESKD (unknown PCKF); no comorbidities; 3-times weekly HD by AVF; no clinical contraindication to KT; on waiting-list for 9 years; goal of KT: to improve life expectancy and QoL.	ESKD (PCKF: HIV-associated nephropathy); HIV infection; HPV-related condylomata; 3-times weekly HD initially, by AVF and currently by femoral CVC; no clinical contraindication to KT; documented absence of vascular accesses compromised by recurrent infections and thromboses; precariousness of CVC; CVC exposes to infections; CVC limits daily activities; goal of KT: life-saving and QoL improving
Patient Preferences	Acceptance of IRD donor option as part of the pre-tx clinical routine; high motivation to receive KT: desire to free herself from chronic dialysis treatment, leave the host community, initiate pregnancy due to cultural duties toward her partner’s family in Nigeria; return to home country more frequently (failing to initiate childbearing would compromise stability with her partner and partner’s family); interest in knowing in what season deceased donor kidneys become available; mostly uninterested and limitedly involved in her care; mentally capable (no psychopathologies, cognitive impairment, history of substance use/abuse); unwillingness to cooperate with medical treatment; higher trust in traditional healing practices; not fully forthcoming with negative information.	Inability to assess knowledge and understanding of illness process which caused KF and of KT; only able to speak a Moroccan dialect; neither possible to go through KT education nor to offer the IRD option as part of the pre-tx clinical routine; SM very concerned about her health but limitedly involved in her care; information of high motivation to receive KT to free herself from chronic medical care and return to Morocco more frequently obtained from SM’s son; mentally capable; inability to communicate autonomously makes her completely dependent on either her son or nephew for most day-to-day activities.	Limited knowledge and understanding of illness process which caused KF and of KT; extreme denial of HIV positivity and of necessity to urgently receive KT; very concerned about donor’s personal features and life conduct; worried about donor’s character (receiving a kidney from a “bad” person might turn her into a bad person herself); she fears that the kidney of a drug addict or a sex worker might be passing bad luck over to her; uninterested and limitedly involved in her care; mostly reluctant and mistrustful toward physician team and hardly speaks; complains that physician team “does not act as a family; she believes that the IRD reveals physician team’s unwillingness to offer a standard donor kidney (i.e. fear of discrimination); deceptive behavior; mentally capable.
Quality of Life	KT will improve life expectancy and QoL; enable JF to free herself from chronic dialysis treatment, leave host community, initiate pregnancy and return to Nigeria more frequently.	KT will improve life expectancy and QoL; it will enable SM to free herself from chronic dialysis treatment and return to Morocco to visit her family more often.	KT will improve life expectancy and quality of life QoL. EN uninterested in expected post-tx QoL. Fear of inferior QoL depending on donor features. Desire to survive and visit her children in Nigeria.
Contextual Features	SPS permit allows to receive care under the same conditions as nationals; higher trust in traditional healing practices, non-adherence to cART, and representation of KT may have cultural matrixes (extreme denial and indifference toward PCKF and need for KT may be associated to their connection to her HIV-positive status and fear of HIV stigma; donated kidneys viewed as seasonal products); research on adherence among African American women reveals that most participants referred initially to traditional healers for treating chronic illnesses, only seeking Western	Regular family reunification permit allows to receive care equally as nationals; lives with her son, nephew and nephew’s wife in a small village 30 km from tx center; social support system highly committed to SM’s care; very limited knowledge and understanding of tx and of the complexity of post-tx regimens: son willing to undergo tx education but still have not received any oral or written educational package (available at the tx center in 9 different languages including Arabic); translator had no knowledge of the Moroccan dialect and no experience with transplant (post-tx regimens, IRD option); from a	STP permit allows to receive access to all essential and emergency care (including KT) under the same conditions as nationals; lives in a Parish community 150 km from the tx center; unemployed; very limited financial resources; physicians at tx center “passed the hat around” to pay for train transportation and allow EN to travel from and to where she lives; strong faith in God who has been helping her through the many difficulties in her life (including health care problems) appears as a key factor to limit her involvement in her own care and self-

	medical attention when the symptoms progressed; SN lives in a host community (temporary housing) 30 km from tx center (social support limited in availability and functionality); non-adherence to cART and HD during travels to Nigeria (concern for stigmatization for cART and inability to access HD); psycho-educational process enacted for improving cART adherence and potentially improve chances for adherence to post-KT regimens and ISM; nurse concern about SN's insufficient maturity to manage post-tx therapies without supports; immigration status: temporary permit, uncertainty of migration projects, in Nigeria SN may have limited access to ISM regimens and be exposed to endemic diseases. Pressures by social workers to have patient undergo KT fast due to higher costs of HD. No LDKT can be offered given the absence of patient's family members or significant others in Italy. The need to allocate a scarce resource is a major problem and entails great responsibility. The stewardship position that transplant professionals hold towards DD organs is rather unique in the context of healthcare and is often an obstacle to shared DM. Communicative difficulties and cultural influences on representation of KT; negative information obtained from nurse.	cross-cultural perspective, HL's autonomy is questionable, given the overwhelming communicative barrier, the ever son-mediated communication and complete dependency on her son and nephew. A qualitative study on the needs of the Moroccan immigrant female patient population in a municipality in Galicia (Spain) suggests that, among the basic needs of this group of patients, communication is one of the most unmet. Moroccan women often have no knowledge of the Spanish language and depend exclusively on the men in their households. Research has found a significant, positive relationship between social support and adherence to immunosuppressive therapy in adult KT recipients. Yet, studies on the actual impact of the health literacy of caregivers on tx outcomes are still lacking. The patient has been on the WL for 10 years, while the mean waiting time for a DD KT in Italy is currently 26 months (CNT 2020). No family member was willing to pursue LDKT.	management; social support limited in availability and functionality; attends outpatient visits at the transplant center with a female friend, her main reference person is an infectious disease specialist who has been providing clinical assistance since the HIV diagnosis; temporary and unstable housing; temporary permit; uncertain migration projects; mistrust toward medical team and perceived discrimination reported as a leading cause for diminished access to KT; representation of donor influenced by cultural factors. The LDKT option could not be evaluated given the absence of patient's family members or significant others in Italy.

AVF, Arteriovenous Fistula; cART, Combination Antiretroviral Therapy; CVC, Central Venous Catheter; DDKT, Deceased Donor Kidney Transplant; DM, Decision-Making; HD, Hemodialysis; HBV, Hepatitis B Virus; HIV, Human Immunodeficiency Virus; HPV, Human Papilloma Virus; ISM, Immunosuppressive medication; KF, Kidney Failure; KT, Kidney Transplant; LD, Living Donor; LDKT, Living Donor Kidney Transplant; IRD, Increased Infectious Risk Donors; PD, Peritoneal Dialysis; PCKF, Primary Cause of Kidney Failure; QoL, Quality of Life; SPS, Subsidiary Protection Status; STP, Temporarily Present Foreigner; WL, Waiting List.

5.4. Discussion

There is increasing awareness about immigration being an important SDH (Castañeda et al. 2015); acknowledgment of the SDH is critical to detect the social risks and challenges with the potential to foster disparities in health care settings (Andermann 2016).

In the reported cases, all patients have non-European immigration experience and background. Studies document that exposure to potentially traumatic events and post-migration living difficulties are associated frequently with psychopathology (i.e. post-traumatic stress disorder, depression, anxiety and somatization) (Aragona et al. 2013). Further, prior research from Europe has shown that migrant and ethnic minority patients on chronic dialysis treatment are more likely to report higher levels of distress, need for support (Damery et al. 2019), depression, and anxiety when compared to their native-born referents (Loosman et al. 2018). Also, studies document that foreign-born subjects (except Asians) in Italy are more likely than their native-born referents to be diagnosed with alcohol or drug abuse or dependence or induced mental disorders (Migliara et al. 2018). Despite this general trend, in all three cases, analysis by the SIPAT tool revealed no history of psychiatric disease or treatment-induced psychiatric problems, personality disorder, history of alcohol, tobacco or substance use. Cognitive functioning was within normal limits, and no familial or personal psychiatric problems were detected. However, various risk factors in the psychosocial dimensions of (A) patients' readiness level and (B) social support system contributed to patients falling into the poor (SN and EN) and minimally acceptable (SM) candidate categories (**Table 12**).

Qualitative analysis by the Four-Boxes method contributed to adoption of the holistic approach advocated by multiple scholars (Maloney et al. 2005; Forneris et al. 2011; Van Biesen et al. 2018) and guided examination of the ethical dimensions of individual clinical cases. The Four-Boxes method allowed identification of a variety of factors with the potential to contribute to disparities in accessibility of KT and, also, with the potential for detrimental impacts on KT outcomes (**Table 14**).

Table 14. Contextual features with the potential to expose immigrant subjects to increased disadvantage in the process of kidney transplant

SIPAT dimension	**Contextual features (Four-Boxes Method)**
(A) Patient's readiness level	Language barriers Cultural beliefs about health, illness and treatment Limited health literacy Lack of social support and/or presence of family in host country Motivation for transplant Pre- and/or post-transplant migration routes Individual preferences/life goals Differing expectations about communication with physicians/physician role Perceived discrimination Organizational constraints Lack of linguistically and culturally adjusted transplant services
(B) Social support system	Reason for migration Lack of family and/or social support network Temporary residency Poor living and housing conditions Temporary and unstable nature of social support system Caregiver's health literacy Pre- and/or post-transplant migration routes Higher need for support
(C) Psychological Stability & Psychopathology	Cultural backgrounds affecting clinical manifestations of psychiatric symptoms Higher risk of depression, anxiety, and distress Post migration living difficulties
(d) Lifestyle and effect of substance use	Higher risk of alcohol or drug abuse/dependence or induced mental disorders

In order to guarantee homogeneity, we selected only the most relevant questions included in the four topics method to highlight and analyze the common themes between cases so as to focus on the issues pertinent to this study.

5.4.1. Medical Indications

In all cases, KT was prescribed as the gold standard RRT. In two cases (SN and EN), various comorbid conditions were present which, however, were not considered contraindications to KT according to clinical protocols (KDIGO 2020). Further, no psychiatric disorders requiring treatment prior to and following KT were detected (*In what circumstances are medical treatments not indicated?)*. Yet, living donor kidney transplant (LDKT) being the most desirable option for superior KT outcomes could not be pursued given the absence of family members in Italy (SN and EN) or due to family members' unwillingness to pursue living donation (SM), consistent with prior reports (Roodnat et al. 2010; Ismail et al. 2013; Ismail et al. 2010). Two patients (SN and EN) were informed instantly about the increased infectious risk donor (IRD) option as part of the pre-transplant clinical routine, whereas it was not initially proposed to the third patient (SM) given the overwhelming communicative barrier impeding thorough information to allow a valid informed consent process. IRDs are a safe option to increase opportunities to receive KT within a shorter period of time, and to reduce dialysis vintage as a potential cause for clinical complications associated with either WL withdrawal or patient mortality (Grossi et al. 2018; Bowring et al. 2018). This is especially relevant in one patient who has been on chronic dialysis treatment for 10 years (SM) and in another for whom KT is a life-saving treatment given the precariousness of RRT by HD (EN) (*What are the probabilities of success of various treatment options?)*.

5.4.2. Patient Preferences

All three patients received the same type and amount of information regarding the overall risks and benefits of KT in general, about the risks and benefits of different donor options and donor risk profiles (including IRDs), about the need for adherence to lifelong post-transplant medical regimens along with the risks associated with the potential for outbreak of latent infectious diseases or complications under ISMs. In line with prior reports (Forneris et al. 2011; Bennett et al. 1995), willingness to return to home countries to visit families more frequently as the main motivation to pursue KT was common to all cases. However, while being motivated, they were poorly (SN) or limitedly (SM) involved, or uninterested (EN) in their own care. As shown by prior studies, in two cases (SN and SM), the primary reasons to pursue KT and to accept IRDs were the low perceived risk of the option, improved chances to receive KT, trust in clinicians, and willingness to escape the limitations posed by HD and poor quality of life (Gordon et al. 2012), similar to their European referents (Ismail et al. 2010). Consistent with previous research (Bennett et al. 1995), in one case (EN), reasons for refusal of IRDs included concerns regarding donor's personal features (i.e. character) and deviant behaviors with the potential for negative effects on the post-transplant course regarding donor influences on her own personality and lifestyle.

Despite presence of the professional hospital interpreter, communication was mediated by family members in one case (SM), whereas it was entirely mediated by a friend in another (EN). Given the patient's ability to interact with members of the transplant team independently, no professional hospital interpreter was requested in third case (SN). Although interpreters' subjectivity resulting from cognitive mediation is inevitable (Baraldi and Gavioli 2016), research suggests that professional interpreters should be preferred over family members as they provide assurance of quality, accuracy and confidentiality (Rimmer 2020). While studies have shown that, in certain settings, patients find comfort having intimate persons act as interpreters (Kuo and Fagan 1999), interpretation by family members may challenge patient autonomy, right to privacy and patient safety. Lack of familiarity with medical terminology, attitudes and feelings possibly influencing interpretation, and inability or unwillingness to interpret relevant information correctly, all have the potential to compromise the patients' ability to deliberate according to their individual life circumstances and priorities (patient autonomy). At the same time, patients may feel uncomfortable to speak of their own problems and concerns in front of family members (right to privacy). Another challenge to informed consent and KT education is represented by patients' health literacy (HL), defined as "the degree to which an individual has the capacity to obtain, communicate, process, and understand basic health information and services to make appropriate health decisions" (CDC). (*Has the patient been informed of benefits and risks, understood this information, and given consent?*) (see 5.4.4. Contextual Features paragraph below).

Disappointed expectations and lack of trust were reported in one case (EN) regarding the physician team not being sufficiently supportive and due to perceived discrimination because of the IRD option being illustrated repeatedly, regardless of patient's prior persistent refusal. In one case (SN), the preference for traditional healing practices was detected, unless conventional medical practices and medications are strictly necessary. However, multiple contextual factors may explain these attitudes and behaviors (see 5.4.4. Contextual Features paragraph below).

5.4.3. Quality of Life

KT will restore kidney function and the patient's freedom from chronic dialysis treatment in all three cases. However, KT is a lifelong process with the potential for physical, psychological, and social implications which may affect the specific QoL of the patients according to patients' preferences, individual life circumstances and life goals (i.e. enable visits to families in home countries more frequently, initiate pregnancy). The inability to return to a fully normal life given the chronic condition following KT has the potential to influence the features which the patients consider critical to define QoL as subjectively satisfactory. Therefore, it is necessary to place the prospects of a successful KT into the patients' psychosocial reality and individual life circumstances. It is likely that KT will delay initiation of pregnancy with the potential to compromise the patient's individual stability in her own cultural context (SN). Also, while KT enables freedom from HD, post-transplant requirements may affect the circumstances of travels to home countries, where adherence to recommended lifestyle, ISM, and prevention of the potential for epidemiologic exposures to different pathogens which may have a negative impact on the post-transplant course are uncertain (Davies et al. 2011). Further, in one case (SN), inability to benefit from traditional healing practices may compromise the patient's satisfaction with care and, accordingly, subjective QoL (*What are the prospects, with or without treatment, for* *a return to normal life, and what physical, mental, and social deficits might the patient experience even if treatment succeeds?*).

5.4.4. Contextual Features

In our cases, family members and other parties do not have any particular interest in the clinical decisions. Yet, they do have specific roles entailing a challenge which is associated primarily with the interpretation, coherence, and reliability of the transmission of clinicians' explanations of the risks and benefits of KT. In one case (SN), while community nurse is entirely devoted to supporting the patient, major communicative and educational barriers persist. The community nurse reported having started a psycho-educational process for improving cART adherence and to, potentially, improve the chances for adherence to post-transplant regimens and ISMs. However, she was concerned that, in the absence of social supports provided by the host community, the patient would have insufficient maturity to manage the complexity of post-transplant requirements. In the second case (SM), the absence of transplant-experienced, qualified mediation and interpretation services, and the lack of linguistically and culturally-appropriate educational interventions make it mandatory to better understand the role played by the family member regarding listening, comprehension, interpretation, translation and communication of information. Further, the HL level of the caregiver could not be assessed. However, while studies suggest that caregivers' HL may be critical for successful KT outcomes, evidence remains limited (Chisholm-Burns, Spivey and Pickett 2018). While it seems clear that the role of the family mediator (i.e. son, nephew, other external person) is a relevant one, it is not possible to determine the actual contents of communication. In the last case (EN), the role of the patient's friend is limited to translation and there appears to be no particular involvement beyond communicative support. The common theme to all three cases is related to the educational difficulties regarding the meaning, practices, risks, benefits, and responsibilities associated with pursuing KT (*Are there parties other than clinicians and patients, such as family members, who have an interest in clinical decisions?*).

None of the patients presented legal and/or administrative barriers to KT. Italy guarantees universal access to KT, post-transplant ISM and medical regimens for all clinically eligible migrants who are regularly registered in the Italian National Health System (NHS) under the same conditions as nationals (Li Cavoli, Turdo and Li Cavoli 2019). Therefore, no legal issues with the potential to influence clinical decisions were detected (*What are the legal issues that might affect clinical decisions?*).

Multiple nonclinical variables can be detected which may potentially impact the case. It is well known that communication is a critical factor in healthcare; the language barriers that immigrant populations experience in host countries may cause difficulties in medical investigation, diagnosis of mental illness, and patient adherence to recommended medical regimens (Scheppers et al. 2006). Communicative and relational problems may arise also from different cultural representations of illness, medications, health care expectations or cultural needs and taboos (Yilmaz-Aslan et al. 2014; McQuaid and Landier 2018).

Knowledge and understanding of the process of KT is poor in two cases (SN and SN) and limited in one case (SM). Consistent with prior studies in the general immigrant patient population in Europe (Priebe et al. 2011; Suurmond and Seeleman 2006), *language barriers* are a major challenge for transplant professionals to inform and educate patients and to engage into shared decision-making (SDM) (entailing integration of the clinical perspective with the patient's individual circumstances) as the most desirable and ethical model of the patient-physician relationship in KT clinical practice (Gordon et al. 2013). Studies suggest that ESKD patients and kidney transplant recipients (KTRs) who are native speakers have higher HL relative to those who are not (Demian, Shapiro and Thornton 2016; Escobedo and Weismuller 2013). Yet, while multiple tools exist to formally assess HL and comprehension in ESKD and KT settings (Jain and Green 2016), none were available in our cases, accounting as an organizational limitation. However, qualitative analysis of SN and EN's narratives of KT and of available donor options (i.e. IRDs) suggested poor understanding. While studies reveal that patients with limited language proficiency (LLP) are more likely than native speakers to experience adverse events leading to physical harm resulting from communication errors (Divi et al. 2007), whether LLP in the absence of transplant-experienced interpretation services may affect the outcomes of KT through enhanced communication and education is uncertain (Tahir et al. 2017). Prior studies suggest that, because of the limitations posed by LLP, non-native speakers are less likely than their native-born referents to complete pre-transplant assessments in a timely fashion (Forneris et al. 2011; Talamantes et al. 2017), and more likely to have inferior trust in the quality of care received (Manirankunda et al. 2012; Betancourt et al. 2003), to experience diminished likelihood of appropriate follow-up (Anderson et al. 2003), and to challenge understanding of living donation among their potential living donors (Timmerman et al. 2015), similar to our report. Further, because individual beliefs about health and illness are culturally determined and may affect health behaviors (i.e. self-management, type and modality of healthcare seeking behaviors, adherence) both directly and by mediation of psychological processes, cultural factors (particularly health-related beliefs) should be considered when planning care for immigrant patients pursuing KT (Betancourt and Flynn 2009; Liso et al. 2017). In two cases (SN and EN), knowledge and understanding of KT and of available treatment options may be determined by *cultural factors* and low HL, in line with prior reports (Bennett et al. 1995). In one case (SN), KT is viewed as complete remission from illness, deceased donor kidneys are believed to be "seasonal products" which are only available at specific time-points throughout the year, and there is an explicit preference for traditional healing practices unless conventional medical regimens are strictly necessary. The patient's prior limited adherence to cART and the higher trust in traditional healing practices, which have the potential to compromise control of delicate drug-drug interactions balance between complex cARTs and ISMs for preventing allograft rejection should be considered in relation to sociocultural, religious and spiritual values, and dissatisfaction with conventional healthcare (James et al. 2018). Similarly, in another case (EN), the patient's concern about the IRD's personal features having the potential for negative effects on her own personality and lifestyle may, as well, be culturally determined (Bennett et al. 1995) and, possibly, be associated with perceived discrimination and mistrust towards healthcare professionals (Haywood et al. 2014). Longer waiting time for KT may therefore arise from refusal of donor options beyond standard criteria donors

(Bowring et al. 2018). Further, the patients' limited participation in decision-making may be associated with family-centered decision-making, differing from Western, patient-centered models of care (SM) (Ho 2006) or, as in other cases, with acceptance of illness as part of their fate (EN), or expectation to have a doctor tell them what to do (SN, SM and EN) (Liso et al. 2017). Additionally, consistency of deceptive behavior across cases (SN, SM and EN) may be associated with patients' willingness to avoid conflicts with healthcare professionals being viewed as "authority" figures (Chisholm-Burns, Spivey and Pickett 2018). The finding that LDKT could not be pursued given the absence of family members or significant others is in line with prior studies highlighting that immigrant patients are less likely to attend the outpatient clinic with a potential LD (Roodnat et al. 2010). Also, family members' unwillingness to pursue KT was detected in one case (SM) is similar to previous reports (Ismail et al. 2010).

The second emergent aspect is related to *family and/or social support system*. In two cases, social support was limited (SN) or poor (EN) in availability and functionality, out of family separation associated with their migration background (Pavli and Maltezou 2017). In both cases, social support is either tentative given its temporary nature or virtually absent and unreliable. However, evidence of a negative association between social support and KT outcomes primarily by mediation of adherence to medical regimens has led to heterogenous findings and high-quality studies are lacking (Ladin et al. 2018). In contrast, in one case (SM), while efforts were made to enable direct communication with the patient, a family member (i.e. son or nephew) always stood as a mediator, even in the presence of a professional interpreter who, however, was not experienced in transplantation. Differing expectations regarding family involvement in chronic disease care, lack of social support, and patients' and caregivers' HL all have the potential to affect *self-management* and the associated adherence along with the related long-term outcomes (Thabit et al. 2009; Chisholm-Burns, Spivey and Pickett 2018). However, no strategies were in place to assess the actual knowledge and comprehension of the transplant process or the HL of patients and their caregivers rigorously so as to determine the need for further interventions. Additionally, physical *living space* was only adequate, given the temporary nature of the patient's housing conditions in two cases (SN and EN), whereas it was good in one instance (SM). As stated earlier, the motivation to pursue KT is similar between patients. However, the ability to disappear from host communities without notice (SN and EN), and the uncertainty about post-transplant migration routes (SN, SM and EN) pose challenges to follow-up care for successful KT outcomes. These patients may need healthcare treatments and medications that are not available upon return to countries of origin or which they cannot afford (Davies et al. 2011), or may experience inferior entitlements to healthcare accessibility upon migration to other countries (Chiarenza et al. 2019). US research has found that non-citizen non-residents receiving liver transplant are more likely to be lost to follow-up than their citizen residents counterparts, and contend that this phenomenon is likely related to these patients returning to home countries after transplant, where appropriate follow-up is uncertain (Ferrante and Goldberg 2018). Consistent, prior studies in other chronic disease settings such as HIV report that immigrant patients in Italy are more likely to be lost to follow-up relative to their native-born referents (Saracino et al. 2014). Yet, evidence is lacking regarding the impact of return migration or emigration to other countries on KT outcomes.

In all three cases, problems of a communicative, cultural, and organizational nature influenced the varying time elapsed since enrollment on the WL and presentation of a viable option to diminish timing to KT between patients (*Are there any nonclinical variables that potentially impact the case such as the patient's religious values, financial status, relationship status, occupation, habitation and immigration status?*).

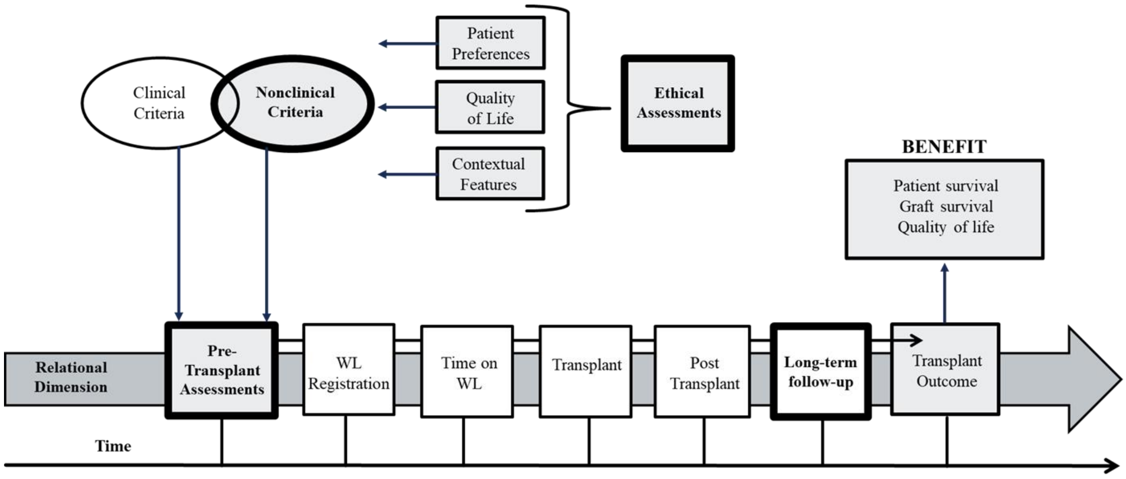
Given the persistent discrepancy between demand and supply of organs for transplantation, the problem of allocation of scarce health resources is inherent to the entire field of solid organ transplantation (Veatch and Ross 2015). Lack of consistency across clinical practice guidelines regarding wait-listing for KT (Batabyal et al. 2012) and the lack of evidence on the effects on KT outcomes of the contextual features detected in the reported cases leaves room for uncertainty and to the potential for physicians' arbitrariness and risk of bias. In the absence of a solid evidence base, decision-making regarding wait-listing may be influenced by the need for transplant teams to maximize efficiency of limited organ resources by guaranteeing a certain life expectancy of the patient and the kidney graft following KT, and by the concern about patient responsibilities regarding negative behaviors such as nonadherence with the potential for detrimental effects on KT outcomes (Tong et al. 2014). Further, given the longer time required to involve professional interpreters, lack of time and resources may explain the lower use of interpretation services that may be perceived by providers as time-consuming (Krupic et al. 2017; Hadziabdic, Lundin and Hjelm 2015) with the potential to affect patient education negatively with downstream detrimental effects on KT accessibility (Waterman et al. 2013) and outcomes. (*Are there problems of allocation of scarce health resources that might affect clinical decisions?*).

5.5. Conclusion

There is growing research interest into the opportunity to address the SDH in clinical practice for prevention of disparities in more vulnerable groups of patients (Andermann 2016; Andermann 2018). Standardized scoring systems for pre-transplant psychosocial evaluations are a valid means to prevent preconceived biases within transplant teams (Lewandowski and Skillings 2016), to identify the risk factors with the potential to reduce harm, mitigate risk, and optimize graft survival, patient's level of functioning and quality of life, and to plan targeted educational and/or psychosocial interventions accordingly (Maldonado 2009). However, these tools are designed for the general transplant population and do not consider that migrants are more likely than their native-born counterparts to present specific cultural, social, economic, relational, and organizational challenges that may affect the overall score of standardized scoring systems negatively, and disproportionately disadvantage immigrant populations accordingly. To date, due to the limited evidence base regarding the actual impact of these factors on clinical (i.e. patient survival, graft survival, kidney graft function) and nonclinical (i.e. quality of life) outcomes of KT, denying KT accessibility on the above listed nonclinical grounds is ethically debatable as regards equity. However, since nonclinical factors are modifiable by implementation of targeted, migrant-sensitive interventions, respect for the principles of beneficence/nonmaleficence and justice requires identification and consideration of these factors early in the process of KT, as highlighted in our case series. The time the patient remains on dialysis and/or on the WL is not neutral. Rather, it may serve the function to identify and employ the best available resources to improve the chances for more timely and comprehensive evaluations as much as successful KT outcomes later in the process. The relational dimension between the health care team and the individual patient is valued as the setting where the patient's vulnerabilities can be detected and guarded against by targeted interventions to achieve successful treatment outcomes (Bramstedt 2002). Multiple tools have been developed to explore the SDH and improve social history-taking in clinical practice (Andermann, 2018). This is especially relevant in chronic disease settings such as KT, in which a variety of nonclinical factors may have detrimental downstream effects on the different phases of the process (Ladin, Rodrigue and Hanto 2009), consistent with our study.

To the best of our knowledge, the Four-Boxes method was used for the first time as a tool to analyze the ethical dimensions of single clinical cases and adopt a holistic approach in KT clinical care involving patients with first-generation immigration background. The Four-Boxes method allowed identification of the specific needs from a clinical ethics perspective. Analyses by the Four-Boxes method revealed that consideration of the SDH is necessary to provide quality care adapted to the patient's individual circumstances (**Figure 18**).

Figure 18. The Four-Boxes Method as a tool to supplement pre-transplant clinical and nonclinical assessments in immigrant populations



Integration of quantitative psychosocial assessments with qualitative evaluations by the Four-Boxes Method allows identification of the multiple social determinants (i.e. nonclinical factors) associated with immigration. Ethical assessments enable reflections on how quantitative assessments in this vulnerable group of patients may unjustly place these individuals at further disadvantage with the potential for disparities in accessibility, quality, and outcomes of kidney transplant.
WL, Waiting List

When evaluating KT candidates with an immigration background, it is possible that physician teams may benefit from linguistically and culturally sensitive assessments. These have the potential to enhance patient-physician-caregiver partnership, to identify areas to perform thorough educational interventions to improve knowledge and understanding of the KT process, to assess comprehension, motivation, views and preferences regarding the multiple risks, benefits, options, and aspects inherent to KT and improve chances for successful clinical and psychosocial outcomes of KT. Further, because different cultural backgrounds may affect clinical manifestations of psychiatric symptoms, standardized mental health assessments in these populations should be integrated with additional tools to acquire qualitative insights into the patient's background and enable more appropriate diagnosis and more effective care plans (Callegari et al. 2020). Much remains to be explored as to the most effective strategies to fulfill these purposes in this vulnerable group of patients pursuing KT. Future studies should generate evidence of the actual association of immigration background with KT outcomes and investigate whether and which targeted interventions considering the multiple specificities of immigrant populations may enable provision of high quality care throughout the lifelong continuum of KT. This may guarantee decision-making based on rigorous scientific evidence rather than on discretionary choices of individual healthcare professionals, as well as the promotion of standardized processes considering also the unique life circumstances of individual patients.

Chapter 6. Conceptual model of the causal mechanisms linking immigration background with disparities in kidney transplant

In preparation as: **Grossi AA**, et al. *Causal Mechanisms Linking Immigration Background with Disparities in Kidney Transplant: a Conceptual Model* (in preparation).

> *"If you always do what you've always done,*
> *you'll always get what you've always got"*
> (Henry Ford)

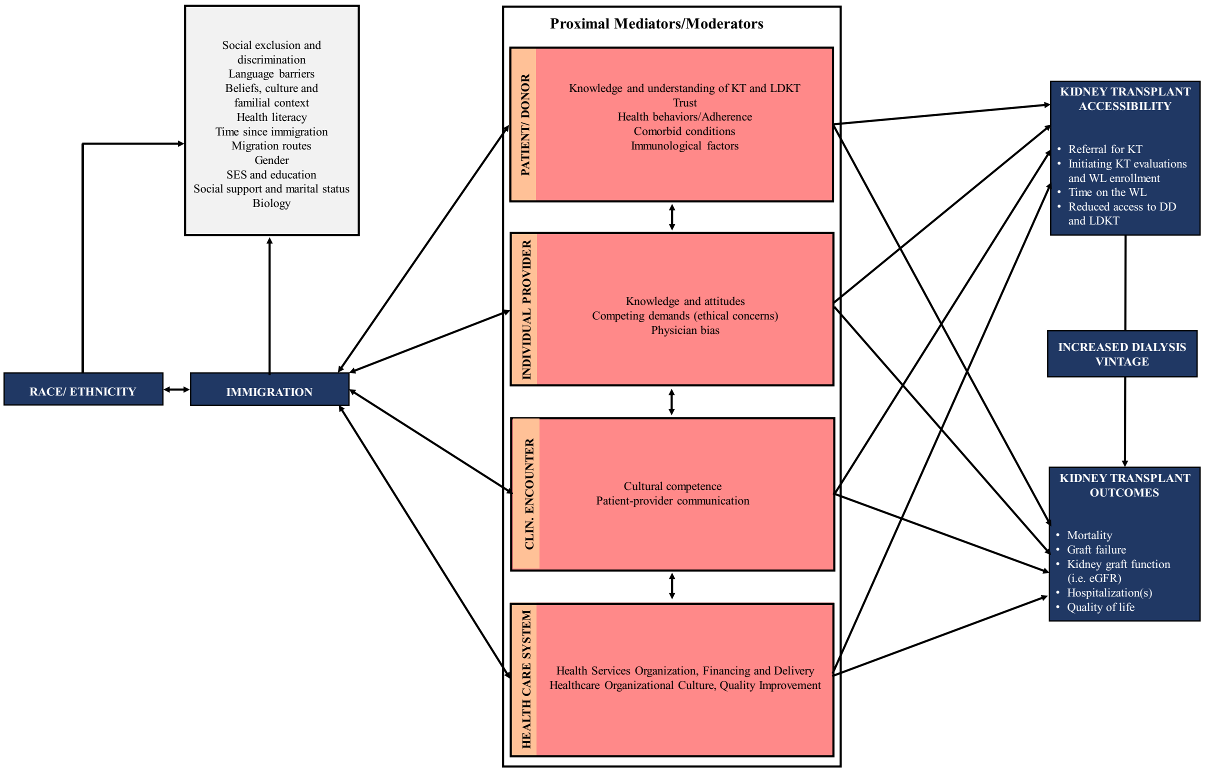
6.1. Introduction

Kidney transplantation (KT) is the gold standard renal replacement treatment (RRT) for patients with end stage kidney disease (ESKD) providing multiple advantages over dialysis such as improved length and quality of life and higher cost-effectiveness (Tonelli et al. 2011; Axelrod et al. 2018). Migrants represent an important minority population in the European Union (EU). On 1st January 2019, there were 21.8 million individuals from outside the EU living in EU countries (Eurostat 2020). The increasing immigration in the EU has resulted in a gradual growth of migrants with ESKD, accounting for more than 20% of patients on RRT by dialysis or in KT programs (Tjaden et al. 2016). While equity is a major principle in solid organ transplantation (EDQM 2018) and a public health priority in migrant health in the EU (WHO 2018), disparities in KT have been reported in non-European patients with an immigration background relative to their EU-born counterparts. Health equity is defined as "the principle underlying a commitment to reduce – and, ultimately, eliminate – disparities in health and in its determinants, including social determinants" (Braveman 2014), whereas health disparities are considered as "potentially avoidable differences in health (or in health risks that policy can influence) between groups of people who are more or less advantaged socially; these differences systematically place socially disadvantaged groups at further disadvantage on health" (Braveman 2006). Prior studies of disparities in KT for immigrant patients in the EU show a heterogeneous relationship between immigration background and KT accessibility and outcomes. Some studies show an association between immigrant status and longer time on the waiting list (WL), lower access to living donor kidney transplant (LDKT), acute rejection episodes or delayed graft function, long-term decline of kidney graft function, graft failure, and mortality (Grossi et al. 2020; Tjaden et al. 2016; Laging et al. 2014; Tromp et al. 2012; Roodnat et al. 1999), whereas others found no association (Laging et al. 2014; Mérida et al. 2009; Pallet et al. 2005) or even an inverse association (Oztek-Celebi et al. 2019; Oztek et al. 2011; Oztek et al. 2009). Recommendations to address the barriers with the potential for disparities in KT in immigrant populations have been put forward as priorities by scholars and institutional actors in the EU and beyond (Poulakou, Len and Akova 2019; Thematic Network on Organ Donation and Transplantation 2019; Rondeau et al. 2019; Van Biesen et al. 2018; Wu et al. 2017; Tong et al. 2017). However, the underlying mechanisms have not yet been fully elucidated. Multiple efforts, especially in the United States (US), have been made to explain the pathways linking racial/ethnic minority status with disparities in KT (Malek et al. 2010; Ladin, Rodrigue and Hanto 2009). Yet, relative to the US, immigration is a more recent phenomenon in the EU and ethnic minorities consist basically of migrants, especially in Southern European countries (De La Rica, Glitz and Ortega 2013).

6.2. Conceptual Framework: Potential Mechanisms Explaining Disparities in Kidney Transplant Outcomes

As in many other disease settings (Bhopal 2016), complex associations make it difficult to determine the direct effect of immigration on KT outcomes. Therefore, understanding of how social, cultural, physical, and biological phenomena interrelate and overlap is necessary. While immigration includes elements of both ethnicity and race (Bhopal 2004), immigration entails more complex, interrelated aspects of vulnerability with the potential for increased disparities in accessibility, quality and outcomes of care when compared to race/ethnicity *per se* (Grabovschi, Loignon and Fortin 2013). Primarily, it should be noted that, although immigration results from demographic and economic determinants like age, poverty, educational and/or employment opportunities, and sometimes family reunification purposes (Simpson 2017), immigration is an important social determinant of health (SDH) in its own right (Castañeda et al. 2015). Being a migrant does not represent itself a risk to poor health. Rather, it is the combination of the multiple conditions and vulnerabilities frequently associated with immigrant status and the entire migration process that have the potential to lead to diminished health outcomes (Wickramage et al. 2018; Grabovschi, Loignon and Fortin 2013). Health outcomes may be affected by individual factors (i.e. age, coping abilities and resources, and genetic composition), factors in the country of origin and the host country, the immigration process and the interaction among these (Sam DL 2006). Disparities in KT outcomes are multifactorial. Studies suggest that immunological (biological, immune, genetic, metabolic and pharmacologic factors) and non-immunological risk factors (comorbidities, time on dialysis, donor characteristics, organ characteristics, socioeconomic status, medication adherence, access to care and health policies) may all contribute to disparities in KT outcomes (Gordon et al. 2010). Based on the model by Kilbourne et al. (2006), this work delivers a review of existing evidence and proposes a conceptual framework named Immigration Background and Disparities in Kidney Transplant (IBDKT) (**Figure 19**) describing some of the major mechanisms at the level of patient/donor, individual provider, clinical encounter and healthcare system which are likely to contribute to disparities in KT outcomes in immigrant patient populations in the EU. We contend that these mechanisms contribute to disparities if they lie along a causal pathway by which immigration background may affect accessibility and outcomes of KT and if they are unjust. In the process, we identify potential areas for intervention along with the gaps in our understanding of the determinants linking non-European immigration background with disparities in KT. Migrants are here intended as those individuals who "choose to move not because of a direct threat of persecution or death, but mainly to improve their lives by finding work, or in some cases for education, family reunion, or other reasons" (UNHCR 2016). Therefore, we will focus on regular migrants, acknowledging that migrants' legal status may contribute to diminished accessibility and quality of care and that more vulnerable immigrant categories (i.e. refugees, asylum seekers, and undocumented migrants) are likely to experience more significant disparities. Yet, these individuals represent a minority of the total dialysis population in Europe (1.5%), and most dialysis centers in the EU have no refugees at all (Van Biesen et al. 2018; Van Biesen et al. 2016). Although it would be necessary to act directly upon the structural causes of disparities so as to improve equity in society, we contend it is more realistic to foster action on the modifiable factors intervening along the pathway to and following KT. Also, while we are aware that migrants are not a homogeneous group (i.e. the features included in the model may vary among individuals) and that the social determinants associated with immigration are often interrelated and do interact with the broader socioeconomic and political context (Solar and Irwin 2010), exploration of these aspects is beyond the scope of this work.

Figure 19. Immigration Background and Disparities in Kidney Transplant (IBDKT) Model



In the IBDKT Model, immigration includes elements of both ethnicity and race (EUPHA 2018). The multiple social determinants associated with immigration may influence various factors at the level of patient/donor, individual provider, clinical encounter, and health care system. The four levels reciprocally influence each other and may contribute to disparities in accessibility of KT including referral, initiating evaluations and wait-list enrollment, the time the candidate remains on the waiting list and inferior access to deceased donor and living donor kidney transplant. The Model highlights that, if these factors are not addressed in a timely manner, they may increase the time the candidate remains on dialysis (i.e. dialysis vintage) and, along with other proximal mediators and/or moderators, they may have downstream effects and contribute to disparities in KT outcomes later in the process.

DD, Deceased Donor; eGFR, estimated Glomerular Filtration Rate; KT, Kidney Transplant; LDKT, Living Donor Kidney Transplant; WL, Waiting List

6.3. Social Determinants of Health Associated with Immigration

6.3.1. Social exclusion and discrimination

Migrants belonging to "visible minorities" (i.e. those who can easily be recognized as belonging to an ethnic origin differing from that of the majority) are more likely exposed to discrimination (Llácer et al. 2007). Discrimination is defined as "the process by which members of a socially defined group are treated differently especially unfairly because of their inclusion in that group" (Solar and Irwin 2010) (group definition being defined based on criteria such as ethnicity/race, gender, age, religion and others). Discrimination impacts health primarily through three main causal mechanisms, namely psychosocial stress, access to health and social resources, and violence and bodily harm (Davis 2020). Among CKD patients, lifetime discrimination is associated with lower likelihood to be willing to pursue KT, suggesting that patients who have experienced significant exposure to discrimination may want to avoid risk in new treatment settings due to diminished expectation of successful outcomes (Klassen et al. 2002). For instance, experiences of discrimination, perceived racism, and medical mistrust are associated with inferior likelihood of KT evaluation initiation (Hamoda et al. 2020). Perceived discrimination is associated also with depression and diminished health outcomes among first generation (i.e. foreign-born) migrants from low-income countries in Europe (Borrell et al. 2015). Perceived discrimination varies among ethnic groups and may lead to feelings of hopelessness and lower self-efficacy (Sanders-Phillips et al. 2009), affecting patients' self-management abilities (Ahmed, Mohammed and Williams 2007) along with the potential for lower medication adherence and delays in medical care through the pathway of patients' trust in healthcare professionals as shown in other chronic disease settings (Haywood et al. 2014 ; Cuffee et al. 2013; Casagrande et al. 2007).

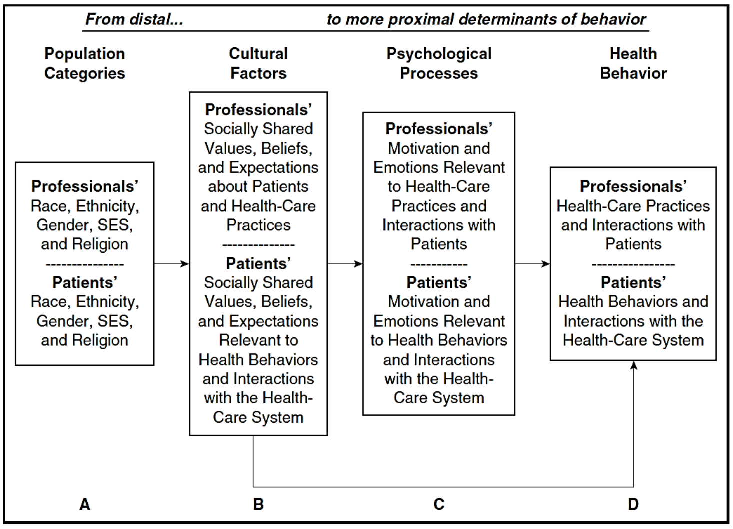
6.3.2. Language barriers

Language barriers are recognized as one of the most significant yet underexplored SDH (Showstack et al. 2019). Inability to communicate with healthcare providers does not only represent a barrier to healthcare accessibility as it may affect knowledge and understanding of KT among ESKD patients and their potential living donors (Forneris et al. 2011; Timmerman et al. 2015), but also challenges trust in the quality of care received (Manirankunda et al. 2012; Betancourt et al. 2003) and decreases the likelihood of appropriate follow-up (Anderson et al. 2003). In the general population, limited language proficiency (LLP) is an independent risk factor for impaired understanding of health condition or recommended treatment (de Moissac and Bowen 2019), medical situations and medications, with the potential to affect self-management and the associated health behaviors negatively (Maneze et al. 2018) and to contribute to undesirable reactions to treatments (Wilson et al. 2005).

6.3.3. Beliefs, culture and familial context

Culture is defined as the "integrated pattern of human behavior that includes thoughts, communications, actions, customs, beliefs, values and institutions of a racial, ethnic, religious or social group" (Georgetown University 1989) which permeates virtually all aspects of an individual's life (O'Sullivan 1994:11-12). Culture relates to social categories that stand as sources of cultural variation which, in turn, influence health behaviors (i.e. adherence) both directly and by mediation of psychological processes (i.e. motivation and emotions relevant to health behaviors), considering that interactions with the healthcare system and healthcare providers also play a role (Betancourt and Flynn 2009) (**Figure 20.**).

Figure 20. Betancourt's model of culture and behavior adapted for the study of health behavior



Source: Betancourt and Flynn 2009

For instance, perceptions of health, illness, attitudes, symptoms or risk vary as a function of belief patterns originating from culture (Betsch et al. 2016; Anderson et al. 2003). For example, religious challenges may account for diminished health outcomes during dialysis treatment. While fasting has no adverse effects on kidney allograft in KTRs (Khedmat and Taheri 2010), higher risk of death and inferior clinical indicators (i.e. increase of serum albumin) may occur in RRT patients throughout the Ramadan period or by the end of it (Sekkarie and Abdel-Rahman 2017). Similar to prior reports from Canada (Vedadi et al. 2019), research of ESKD patients in the Netherlands reveals that non-European individuals are less likely to attend the pre-transplant outpatient clinic with a potential LD and to participate in alternative donation programs (i.e. kidney exchange, domino paired, ABO incompatible) (Roodnat et al. 2010).

6.3.4. Health literacy

Health literacy (HL) is defined by the World Health Organization (WHO) as "the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain good health" (WHO). HL is an important factor in accessibility and outcomes of KT (Kazley et al. 2015; Grubbs et al. 2009) given its impact on health-related behaviors (i.e. adherence to medical regimens) which may, in turn, influence treatment outcomes (i.e. kidney graft function and graft survival) in KTRs (Demian, Shapiro and Thornton 2016) as in other chronic disease settings (Shaw et al. 2009). Research has noted that it is the combination of multiple social determinants associated with immigration (i.e. poverty, low reading level, low level of education, cultural beliefs about health and illness, language barriers and communication) which may have a negative impact on the HL levels of these populations rather than immigration itself (Naus 2016). Further, it should be noted that HL should not only be attributed to patients' individual abilities but also to structural, situational and political conditions (Baumeister et al. 2019).

In a prospective cohort study of 2,274 incident patients on chronic dialysis treatment in the UK, Taylor et al. found that lower HL was associated with lower likelihood of WL enrollment for DDKT, receiving LDKT, or receiving KT from any donor type even after adjusting for multiple factors including age, gender, SES, ethnicity, primary language, primary cause of kidney failure, and comorbidity (Taylor et al. 2019). Lower HL has also been found to be consistently associated with inferior outcomes in solid organ transplant recipients including increased risk of graft failure, mortality, use of emergency services, hospitalization, and inferior clinical indicators (i.e. higher serum creatinine levels in KTRs) (Chisholm-Burns, Spivey and Pickett 2018). Research has shown an association of immigration background with lower HL in other chronic disease settings. An Irish study of diabetic patients found lower HL in immigrants of Southeast Asian, Latin American, Middle Eastern, European and African origin relative to their native-born counterparts, and emphasized the potential for negative effects of low HL on diabetes control and self-management affecting adherence in this group of patients (Thabit, Shah and Nash 2009). However, studies of HL in immigrants remain limited in the EU and none have been performed in immigrant KTRs (Ward, Kristiansen and Sørensen 2018). Further, the levels of HL in the general population differ across countries in Europe and elsewhere, and the effects of different aspects of HL (i.e. numeracy or reading skills) on health may vary between countries and individual patients (Palumbo et al. 2016; Yamashita and Kunkel 2015).

6.3.5. Time elapsed since immigration

Research suggests that the so-called healthy migrant effect tends to decline over time after migration given the social and health care disparities frequently associated with immigrant status (i.e. access to healthcare, unprotected working conditions, lack of integration, discrimination, etc.) (Domnich et al. 2012; Pascoe EA, Smart Richman 2009). However, studies contend that the longer the time elapsed since immigration, the higher the likelihood that migrants will have improved knowledge about health programs in the host country, will experience inferior unmet needs and barriers in access to care (Campostrini et al. 2015 ; Setia et al. 2011), and have increased self-management abilities relative to migrants with a shorter duration of stay (Cramm and Nieboer 2019). In contrast, other studies have shown that acculturation[15] to host country lifestyle and dietary habits may affect the health of migrants negatively by improving chances to develop chronic diseases such as diabetes (O'Brien et al. 2014) and may account for differences in the use of healthcare services among different ethnic minority groups (Anderson et al. 2003).

6.3.6. Migration routes

Return to home countries prior to KT may expose immigrant patients to lack of access to dialysis treatment and, accordingly, to the potential for deterioration of their clinical condition along with physicians' tendency

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[15] The changes produced in an individual's values, beliefs and practices as a result of cultural contact with another (most frequently majority) culture (Berry JW. Acculturation: Living Successfully in Two Cultures. International Journal of Intercultural Relations. 2005;29(6):697–712).

to classify these patients as nonadherent, thus affecting pre-transplant care and progression towards KT (Anderson et al. 2012; Forneris et al. 2011; Bennett et al. 1995). Further, loss to follow-up is common in immigrant populations (Poulakou, Len and Akova 2019; Saracino et al. 2014). Willingness to receive KT in immigrant subjects may be associated with the desire to return to home communities, countries and/or families, with the potential for adverse effects on post-transplant care (Forneris et al. 2011; Bennett et al. 1995). The health of returning migrants may be affected by the cumulative exposure to SDH and risk factors during the migration process, throughout the return movement, and after return. More vulnerable returnees may need healthcare treatments which are not available in countries of origin or which they cannot afford (Davies et al. 2011). Further, migrants who move from one country to another may experience diminished healthcare accessibility under different entitlements to receive care on a free of charge basis (Chiarenza et al. 2019). Because these factors may be relevant to successful care before and after KT, research is needed to assess the impact of pre- and post-transplant migration routes on more proximal mediators/moderators affecting accessibility and outcomes of KT.

6.3.7. Gender

Gender differences occur in all cultures and may vary by ethnicity with the potential to be amplified upon arrival to destination countries depending on the reason for migration. For example, women who migrate for family reunification purposes are more likely to be subject to their husband’s authority because of the dependency of migrant permit release upon the latter’s consent and, for the same reasons, they are more likely exposed to social isolation from society at large, more likely to face additional barriers to adaptation to host culture, and to be exposed to a higher risk of occupational insecurity and victimization in the workplace (ISMU 2019; Llácer et al. 2007). Women may also suffer from triple discrimination for being immigrants, minorities and women at the same time (Llácer et al. 2007). Studies have found also that ethnic minority women are more likely to be living kidney donors than their male counterparts in partner-to-partner settings (Peracha, Hayer and Sharif 2016). Men being more frequently those who lead families financially along with the socioeconomic dependency and lower socioeconomic status of women in some cultures may be one explanation to this phenomenon (Park et al. 2020; Godara and Jeswani 2019; Naghibi, Naghibi and Nazemian 2008). Further, gender may affect preferences for healthcare services delivery such as gender-matched interpretation services for improved understanding of the actual needs of female patients (Lyberg et al. 2012) or unwillingness to receive particular medical tests relevant to KT work-up (i.e. pap smears out of fear to lose their virginity) (Sekkarie and Abdel-Rahman 2017) .

6.3.8. Socioeconomic status

The detrimental effect of lower socioeconomic status (SES) on KT accessibility and outcomes is well known (Zhang et al. 2018). Eurostat data reveal that, in 2018, the majority of individuals who are at risk of poverty or social exclusion are non-EU migrants (Eurostat 2020). A review of migrants’ health and health care in Europe suggests that, while cross-country variations exist, the SES of these populations may affect both accessibility and outcomes of care (Lebano et al. 2020). Access to medical regimens before, during, and after KT is generally guaranteed to regular migrants by all health systems in the EU, regardless of ability to pay (Bello et al. 2017). Studies contend that this is likely to mitigate the adverse effects of lower socioeconomic status on accessibility of healthcare services, including pre- and post-transplant regimens, with the potential for improved adherence and associated outcomes in immigrant populations in Europe (Laging et al. 2014; Mérida et al. 2009; Pallet et al. 2005) relative to ethnic minority patients exposed to similar social disadvantage in the US (Yeates et al. 2009). However, while research from Europe has shown an independent association of socioeconomic deprivation with increased patient mortality following KT, the effect of immigration background was not assessed (Châtelet et al. 2018; Begaj et al. 2013). Also, in a prior nationwide study in Italy, we found long-term decline of kidney graft function among non-European-born KTRs relative to their Eastern European- and EU-born referents, but data were not adjusted for SES (Grossi et al. 2020). Other socioeconomic considerations may equally affect uptake of LDKT. As noted previously, because the spouses of male ESKD patients are more likely to have lower SES and to be financially dependent on their husbands, women may be more likely to be living kidney donors in some ethnic groups when compared to their male referents (Park et al. 2020; Godara and Jeswani 2019; Naghibi, Naghibi and Nazemian 2008). Also, while the educational attainment of migrants varies across different countries in the EU (Eurostat 20), occupational status and educational level have been listed as potential risk factors for post-transplant non-adherence (Chapman 2004). Therefore, while association between SES/education and KT accessibility and outcomes is well documented, migrants in Europe are not a homogeneous group and there may be within-group variations across EU countries and among immigrant individuals living in specific countries. Studies are needed to better determine whether the association of socioeconomic status with KT accessibility and outcomes is consistent among immigrant groups in Europe.

6.3.9. Social support

The positive effects on health derived from social support networks are prominent for immigrant populations who are more likely exposed to social isolation (Llácer et al. 2007). Although evidence of the association of social support with post-transplant outcomes remains limited and has led to heterogeneous findings (Ladin et al. 2018), lack of social support and marital status may affect the completion of pre-transplant assessments and WL enrollments, with a disproportionate effect on more vulnerable subjects, including migrants (Ladin et al. 2018). These individuals are more likely to experience social exclusion and/or separation from family or partners, depending on the reason for migration (Pavli and Maltezou 2017). Studies suggest that instrumental social support (i.e. number of family or friends helping with daily activities) enhances the likelihood of completing pre-transplant evaluations by supporting patients schedule and keep appointments, or help them navigate complex issues in the health system (Clark et al. 2008). Limited social support along with LLP and other cultural issues may also negatively affect self-management and its associated health behaviors (Maneze et al. 2018) with the potential for negative effects on adherence to complex post-transplant medical regimens. US studies have shown that male patients who are unmarried in the pre-transplant period are more likely to report diminished graft survival than their unmarried female counterparts (Naiman et al. 2007). A study of liver transplant patients found that instability of social support, but not low availability of social support was associated with nonadherence (Rodrigue et al. 2013). Therefore, although studies remain inconsistent, social support may play an important role in medication adherence in the specific setting of KT regarding accessibility and outcomes of treatment.

6.3.10. Biology

While sociologists broadly contend that race is a social construct rather than a biological one (Senior and Bhopal 1994; Gordon 2002), multiple scholars have noted that biological factors such as genetic, immune, metabolic and pharmacokinetic factors vary among ethnic groups. Worse outcomes in African American minority groups compared to their Caucasian referents have been ascribed to having more comorbid conditions, higher immunological risk due to greater variation in human leukocyte antigen polymorphisms, diminished control of hypertension, requirement of higher dosages of immunosuppressive drugs, and variability in the pharmacokinetics of immunosuppressive medications (Gordon and Caicedo 2009) (see *6.4.4. Comorbid conditions* and *6.4.5. Immunological factors*).

6.4. Evidence of Patient/Donor-Level Factors

The patient/donor-level variables presented in our model include both modifiable and non-modifiable risk factors associated with immigration. Improved understanding of these determinants may prove useful for nephrologists and transplant professionals to recognize ESKD patients at higher risk of diminished accessibility and/or outcomes of KT. While targeted, migrant-specific interventions are unlikely to have a direct positive impact on non-modifiable risk variables such as biological factors, they may assist healthcare professionals and organizations in implementing actions with the potential to prevent, mitigate or eliminate disparities in KT in this vulnerable group of patients.

6.4.1. Knowledge and understanding of kidney transplant and living donor kidney transplant

It is well known that knowledge and understanding of KT is a critical factor for KT accessibility (McPherson, Hamoda and Patzer 2019). Patients who have access to more transplant educational resources and have greater knowledge of transplant are more likely to complete evaluations and to receive LDKT (Waterman et al. 2013). Yet, factors such as limited language proficiency (LLP) (Forneris et al. 2011; Talamantes et al. 2017; Gordon et al. 2013), culture (Gordon et al. 2013; Ismail et al.) family influences (Ismail et al. 2010; Roodnat et al. 2010), lower socioeconomic status (Gordon et al. 2013), limited HL (Chisholm-Burns, Spivey and Pickett 2018), poor social support networks (Arthur 2002), and shorter time elapsed since immigration (Cramm and

Nieboer 2019) may all pose challenges to patient education and informed consent, leading to diminished likelihood of completing pre-transplant assessments in a timely fashion, to transition from inactive to active status on the WL or to opt for alternative donation programs. In other chronic disease settings such as diabetes, patients' satisfaction with medication information has been shown to be independently associated with improvements in medication adherence (Hofer et al. 2017). Studies have found a significant association between LLP and knowledge of dialysis, transplantation and living donation (LD) among kidney transplant recipients (KTRs) and their potential living donors (LD) (Timmerman et al. 2015), along with lower HL (Demian, Shapiro and Thornton 2016; Escobedo and Weismuller 2013), and difficulty in understanding transplant education (Waterman et al. 2020). Unique barriers to LDKT that non-European patients may experience include lack of knowledge and lack of easily understandable information; fears, anxieties and misunderstandings of the procedure; personal and cultural beliefs preventing discussions with potential LDs; negative influences of social networks when communicating about RRT, and less favorable attitudes towards LDKT, especially among subjects of Northern African and Sub-Saharan African origin (Ismail et al. 2013[a]; Ismail et al. 2010; Oztek-Celebi et al. 2019; Ríos et al. 2018[a]; Ríos et al. 2018[b]; Ríos et al. 2020). As for donor-related factors, while none of the major world religions formally forbids living and/or deceased organ donation (Bruzzone 2008), culture, beliefs, and family influences along with other social factors including the degree of acculturation and integration may explain attitudes towards various factors that have the potential to affect the intent to register for organ donation (Morgan et al. 2015; Salim et al. 2010; Morgan et al. 2010), to accept donor options beyond standard criteria donors (Bowring et al. 2018; Gordon et al. 2012), as well as to delay and/or hinder access to LDKT (Ismail et al. 2010; Roodnat et al. 2010). While religion might not necessarily represent itself a barrier to LDKT, interpretations of Holy Scriptures may vary from one individual to another and among different religious leaders. Also, some patients may believe in the need to preserve the body after death, and others may be uncertain about the attitude of their community towards organ transplantation and LD (Ismail et al. 2012). In a similar fashion, although immigrants represent a significant share of the population on RRT or in KT programs, they are less likely to register for deceased organ donation, affecting the chance to find well-matched deceased donor organs (Rudge et al. 2007; Morgan et al. 2015). Therefore, limited knowledge and/or understanding of additional RRT and KT options, more difficult matching due to inferior rates of deceased donations in subgroups of migrants, sociocultural issues inhibiting discussions of LDKT with family members, the potential for poor understanding of complex post-transplant requirements due to LLP, beliefs about illness and treatment, and limited social supports may affect adherence to pre- and post-transplant regimens. However, further research is needed to address these specific issues in immigrant populations pursuing KT in Europe.

6.4.2. Trust

Patient's trust in healthcare professionals is a relevant concept in healthcare which is associated with multiple benefits such as perception of superior care, higher acceptance and adherence to recommended treatments, facilitated access to healthcare services (Allinson and Chaar 2016), more beneficial health behaviors, less symptoms and improved quality of life (Birkhäuer et al. 2017). Several factors may contribute to diminished trust and to its associated detrimental outcomes. Perceived discrimination (Haywood et al. 2014 ; Cuffee et al. 2013; Casagrande et al. 2007), language and cultural barriers (Betancourt et al. 2003), lack of linguistically and culturally appropriate healthcare delivery (Manirankunda et al. 2012), and miscommunications (Sekkarie and Abdel-Rahman 2017) all have the potential to lead to diminished healthcare quality and outcomes by mediation of patient's mistrust of nephrology team. Yet, the actual impact of trust as a mediator and/or moderator for inferior accessibility and outcomes of KT remains uncertain and needs to be investigated more thoroughly.

6.4.3. Health behaviors/adherence

Adherence, defined as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (WHO 2003), is a key aspect to accessibility, self-management and outcomes of KT. Adherence is multidimensional and includes social and economic factors, therapy-related factors, patient-related factors, condition-related factors, and healthcare team/health care system factors. Patient-related factors include, among others, insufficient knowledge and skills to manage treatment, limited self-perceived need for treatment, lack of perceived effect of treatment, negative beliefs regarding treatment effectiveness, misunderstanding of the disease and treatment instructions, and lack of acceptance of monitoring (WHO 2003). Further, simultaneous use of many immunosuppressive medications, lack of knowledge about their usefulness, and confusion and difficulty in remembering medication taking have all been identified as barriers to adherence (Ganjali et al. 2019). However, other socioeconomic aspects such as fear of job loss may contribute to the inability to adhere to follow-up regimens in this group of patients (Poulakou, Len and Akova 2019). Other social aspects may equally account for diminished adherence. Loss to follow-up and non-adherence to long-term treatments are common in immigrant populations either due to misconceptions about the pre- and post-transplant course (i.e. KT may be perceived as complete remission from illness) or inability to adhere to regimens out of fear to lose their jobs (Poulakou, Len and Akova 2019; Saracino et al. 2014). As in other chronic disease settings (Shahin et al. 2020), religious beliefs, cultural background, and familial context may influence the perception of ESKD, its causes, and the need for medical, dietary, and lifestyle adjustments, with the potential to influence adherence to pre- and post-transplant medical regimens and treatment preferences (Crowley-Matoka 2013; Desseix, Merville and Couzi 2010). The explanatory models of illness that immigrants bring with them from their own countries may differ from those traditionally met in Western biomedical contexts. While variations may exist even within subgroups of the same ethnic group(s), these may drive the preference for traditional, "culture-bound" healing or therapeutic strategies either in isolation or in combination with conventional medication practices (Morrison 2019; Akinlua, Meakin and Freemantle 2017). In some cultures, women may also have a preference for gender-matched providers and may refuse to have pap smears performed during KT work-up out of fear to lose their virginity (Sekkarie and Abdel-Rahman 2017). Prior studies of KTRs reveal that it may be difficult for patients to translate native concepts of health and wellbeing into medication regimens, although they are often reluctant to discuss their beliefs about ESKD in medical consultations (Bennett et al. 1995), consistent with reports in other areas of clinical practice (Rajpura and Nayak 2014; Putsch and Joyce 1990). Use of complementary and alternative medicine is frequent in ESKD patients and KTRs in some cultures, and it is often the result of friends, families and other patients advocating for it. However, despite the potential for detrimental effects on clinical outcomes as well as adherence to conventional medical regimens, utilization is often underreported by patients, possibly out of fear to be judged negatively by physicians (Bahall 2017; Sekkarie and Abdel-Rahman 2017; Luyckx 2012; Osman et al. 2015). Studies of health behaviors and particularly adherence to pre- and post-transplant regimens among immigrant patients in the EU are needed to elucidate this relevant phenomenon in these populations.

6.4.4. Comorbid conditions

While diabetes is generally more prevalent in non-Caucasian groups of migrants in Europe with the potential to affect wait-listing (Oniscu et al. 2003), these individuals tend to be younger, more likely to report higher survival on dialysis, and less likely to have comorbid conditions such as cardiovascular diseases relative to their native-born counterparts (van den Beukel et al. 2010). Other factors associated primarily with the cardiovascular risk profile such as hypertension and diabetes, which may be risk factors for diminished KT outcomes, vary among ethnic groups (Taber et al. 2019) and are more prevalent among non-European migrants in some immigrant subgroups (Wändell et al. 2019; Ballotari et al. 2015; ESRD Incidence Study Group et al. 2006). Patients with LLP have also been shown to be more likely to have pre-transplant CMV reactivity and prolonged post-transplant hospitalization with the potential for negative effects on long-term patient survival following hematopoietic stem cell transplantation (Robles et al. 2020). Also, ethnic minority patients have been found to report significantly higher levels of distress and need for support when compared to their white referents (Damery et al. 2019[a]; Damery et al. 2019[b]). Further, inferior skills for living in the host country may be associated with depressive and anxiety symptoms in immigrant chronic dialysis patients (Haverkamp et al. 2016). Studies are needed to assess whether physical and mental comorbid conditions affect accessibility and outcomes of KT in immigrant populations in the EU.

6.4.5. Immunological factors

Immunological factors contributing to inferior KT outcomes in individuals of non-Caucasian ethnicity are well-known. While some studies from the EU contradict this finding (Williams et al. 2018; Mérida et al. 2009; Pallet et al. 2005), KTRs of African descent in the US are more likely to present immunological risk factors for early graft loss such as superior variability in HLA polymorphisms, stronger immune response requiring higher dosages of immunosuppressive medications, and different absorption of immunosuppressive drugs (Gordon et al. 2010). Further, KTRs of African origin are more frequently expressors of CYP3A5 requiring higher tacrolimus dosages to achieve therapeutic drug levels relative to their Caucasian referents, and these factors may be responsible for a higher risk of acute rejection in KTRs of African ethnicity (Higgins and Fishman 2006). KTRs of Asian origin are equally more likely to present genotype differences with the potential to affect the tacrolimus metabolizing phenotype when compared to their African and Caucasian counterparts (Tang et al. 2016). Additionally, in populations of African descent, the APOL1 gene has been found to be related to an augmented risk of ESKD and has the potential to be a high-risk genotype for inferior graft survival (Newell et al. 2017). However, research is lacking on specific ethnic minority groups across Europe.

6.5. Individual Provider-Related Factors

The effects of individual provider-related factors are an emergent aspect of health disparities research in KT. Nephrologists play a critical role in informing patients about transplantation, about available options for RRT including preemptive KT, LDKT along with its related additional options, DDKT, referring patients for transplant, assessing patients' suitability for WL enrollment and/or LDKT, enabling pre-transplant workup, and educating patients (Tandon et al. 2016; Furth et al. 2003). However, variability and breadth of criteria in recommendations for wait-listing across clinical practice guidelines is widespread, and final decisions are broadly left at the discretion of individual nephrologists and/or transplant surgeons (Batabyal et al. 2012; Tong et al. 2011). Also, whether educational interventions considering the specific needs of immigrant patients are implemented is uncertain. Therefore, it is important to consider the factors which may influence nephrologists' perspectives and educational practices with the potential to contribute to disparities in KT when dealing with immigrant populations.

6.5.1. Knowledge and Attitudes

A review of nephrologists' perspective on patient referral for KT, eligibility, and evaluation suggests that ethnic minority status along with other factors such as comorbidities, non-adherence, unhealthy lifestyle choices, patient quality of life, patient preferences, older age, and socioeconomic status influence referral for transplantation (Tong et al. 2014). Although it is recommended to implement comprehensive transplant care with immigrant and ethnic minority patients so as to consider the multiple social and cultural determinants associated with immigration in individual patients (Maloney et al. 2005; Forneris et al. 2011; Van Biesen et al. 2018; Gordon et al. 2010), studies in the general population suggest that providers are unable to address migrants' illnesses in a holistic fashion and are reluctant to explore patients' details beyond physical illness (Suphanchaimat et al. 2015). Research has shown that providers' self-reported knowledge and competency to work with immigrants is mostly moderate or low, and more negative attitudes may be influenced by physicians' older age and higher frequency of daily contacts with immigrant patients (Dias et al. 2012). Prior studies have shown that the use of complementary and alternative medication practices by ESKD patients is often overlooked by clinicians (Bahall 2017; Sekkarie and Abdel-Rahman 2017; Osman et al. 2015; Luyckx 2012). Providers' inability to understand the influence of illness perceptions, cultural and other beliefs on patients' adherence may negatively affect the opportunity to implement strategies to enhance this critical factor for successful KT outcomes (Shahin, Kennedy and Stupans 2019). When health services cannot be delivered in a linguistically and culturally appropriate manner, providers may also occasionally perceive a lack of trust from their patients with an associated fear of being accused of discrimination (Manirankunda et al. 2012). Research is needed regarding these aspects along with exploration of the association with other factors and with KT outcomes in immigrant populations.

6.5.2. Competing Demands

Research suggests that nephrologists present multiple competing demands at the time of patient assessment for KT. These include (a) the need to prioritize benefit and safety for individual patients so as to enable improvement of survival and quality of life, (b) the need to maximize efficiency of persistently limited organ resources, (c) the concern about patient responsibilities regarding negative behaviors such as smoking, alcohol and drug abuse, and nonadherence with the potential for detrimental effects on surgical and post-transplant outcomes, (d) the necessity to guarantee a certain life expectancy following KT, (e) the need to preserve the reputation of the transplant unit, and (f) unwillingness to initiate discussions about transplantation in the presence of potential contraindications so as to prevent false patient expectations and/or disappointment (Tong et al. 2014). Similarly, providers may be concerned about non-resident donor's medical follow-up following donation along with the risk of donor coercion and the potential risk of organ trafficking (Van Biesen et al. 2018). Fear of higher risk of developing long-term kidney-related conditions and hypertension in certain ethnic minority living donor categories (i.e. young black subjects) may equally play a role (Asgari and Hilton 2020; Massie et al. 2017). It is possible also that financial pressures on providers at for-profit dialysis centers and/or lack of health insurance coverage may limit initiation and quality of transplant information and subsequent access to KT (Waterman et al. 2020; Kucirka et al. 2012; Garg et al. 1999). Additionally, while more time is generally needed to address the needs of immigrant patients before and after KT, providers may be concerned about organizational constraints resulting from demanding workloads along with limited human resources and institutional capacity (Ahmed et al. 2017; Akhavan 2012; Straßmayr et al. 2012; Hultsjö and Hjelm 2005). Time and resource constraints may also explain the lower use of interpretation services that may be perceived by providers as time-consuming (Krupic et al. 2017; Hadziabdic, Lundin and Hjelm 2015). It is possible that these factors, either in isolation and/or as a result of their cumulative effect, may contribute to delays in referral and/or wait-listing for KT with the potential to lengthen the time patients remain on dialysis and possibly affect the outcomes of KT later in the process. Also, lack of available resources and time constraints may hamper the chance to engage into effective communication with immigrant patients by use of professional interpretation and cultural mediation services and compromise effective patient education with potentially negative effects on KT accessibility (Waterman et al. 2013) and, potentially, outcomes. Yet, studies are needed to more thoroughly assess the relationship between physician's competing demands and relevant outcomes in KT in the population under scrutiny in this study.

6.5.3. Physician bias

Physician bias is an additional factor which may concur to health disparities (Blair, Steiner and Havranek 2011; Balsa and McGuire 2003). Implicit bias is defined as "the attitudes or stereotypes that affect our understanding, actions, and decisions in an unconscious manner. These biases, which encompass both favorable and unfavorable assessments, are activated involuntarily and without an individual's awareness or intentional control" (Kirwan Institute for the Study of Race and Ethnicity 2015). Providers may be more likely to withhold information and make decisions for their patients based on the belief that immigrant patients will have limited understanding (Suurmond and Seeleman 2006) or to overestimate the impact of social and cultural factors on patient adherence in KT settings (Anderson et al. 2012). When physicians must make complex judgments with insufficient and deficient information or little time to collect information, they may remedy these shortcomings with beliefs and stereotypes (including statistical evidence) associated with the patients' broader social categories. However, relying exclusively on population statistics and failing to incorporate individual patient characteristics in clinical decision-making may contribute to health inequities in culturally diverse settings (Hajjaj et al. 2010; Burgess, Fu and van Ryn 2004). It follows that nephrologists may be less likely to believe in improved survival for i.e. black patients receiving KT relative to their white referents. Other factors that nephrologists mention to be relevant to explain why black patients are less likely than whites to be evaluated for KT include patients' preferences, availability of LDs, failure to complete assessments, and comorbid conditions (Ayanian et al. 2004). Further, black patients are more frequently deemed unsuitable for KT because they are considered to be "psychologically unfit" (Kucirka et al. 2012), and because they are less likely than their white referents to receive transplant information (Ayanian et al. 2004; Kucirka et al. 2012). Variability and sometimes broadly defined criteria exist for WL recommendations which are generally based on life expectancy, comorbid conditions, lifestyle, and psychosocial factors with the potential for disparities in referral and wait-listing for KT (Batabyal et al. 2012). Regardless of the younger age of immigrant patients with ESKD in Europe (van den Beukel et al. 2010), US studies have shown that ethnic minority status may affect waitlisting regardless of the lower prevalence of medical barriers to transplantation in this group of patients (Ku et al. 2019). Additionally, implicit bias against ethnic minority patients may affect not only treatment decisions but also treatment adherence, patient health outcomes and, mostly, patient-provider interactions (see below) (Hall et al. 2015). However, while studies suggest that physician bias may contribute to inferior accessibility and outcomes of care, this area is poorly understood in KT settings involving immigrant patients in the EU and should be investigated more in-depth.

6.6. Clinical encounter factors

KT is a lifelong process, and appropriate communication should be in place early in the course of pre-transplant assessments and across the entire continuum of care, so as to foster trust and enable shared decision-making (SDM). Enforcing a lifetime relationship is essential because risks may occur during the follow-up period with the potential to compromise successful outcomes of KT. In KT settings, SDM is considered as the most desirable and ethical model of the patient-physician relationship as opposed to earlier paternalistic models of care (Gordon et al. 2013). SDM is defined as “a process of communication in which clinicians and patients work together to make optimal health care decisions that align with what matters most to patients” (Barry, Edgman-Levitan and Sepucha 2018). Research has shown that, in chronic disease settings, SDM repeated throughout multiple sessions over time increases the likelihood of adherence to health behaviors, and engagement in health-promoting or health-maintaining behaviors (Kaplan, Haas and Warsh 2016; Joosten et al. 2008). However, studies suggest that SDM is often impeded in intercultural contexts because of differing linguistic background, values and beliefs about health and illness, role expectations, and prejudices hindering the opportunity for unbiased discussions between physicians and patients (Dobler et al. 2017; Suurmond and Seeleman 2006). A qualitative study of healthcare professionals across 16 countries in Europe revealed that many factors in the care of immigrant patients compromise good clinical practice. These include language barriers, difficulties in arranging care for subjects without health care coverage, social deprivation and traumatic experiences, lack of familiarity with the health care system, cultural differences, different understandings of illness and treatment, negative attitudes among staff and patients, and lack of access to medical history (Priebe et al. 2011). Therefore, it is critical to address the factors that may contribute to clinical encounter-related disparities in KT.

6.6.1. Patient-Provider Communication

Communication is a key aspect of clinical practice which may impact multiple health outcomes by mediation of proximal outcomes of interaction (i.e. satisfaction with care, motivation to adhere, trust in clinicians and the healthcare system, self-efficacy, patient-physician agreement, and mutual understanding) affecting other intermediate outcomes (i.e. adherence) (Street et al. 2009). Prior research has found that communication between providers and patients with an immigration background is less effective than with native-born patients, including more misunderstandings and inferior patient adherence (Van Wieringen, Harmsen and Bruijnzeels 2002). Cultural and language barriers in the clinical encounter may affect communication and trust negatively, with the potential to lead to patient dissatisfaction, poor adherence, and poorer health outcomes (Betancourt et al. 2003). Both clinicians and patients face multiple communication barriers which may contribute to inferior quality of care, trust, and patient health outcomes. Communication with immigrant patients may require longer time to guarantee that the patient has achieved a satisfactory level of understanding of RRT options and, at the same time, it may be challenging for immigrant patients to communicate with physicians who lack knowledge of their culture and practice (Sekkarie and Abdel-Rahman 2017). For many patients with an immigration background, a power differential exists between the physician and the patient, which results in a lack of open and free communication unless stimulated by the physician. The degree of patients’ participation in decision-making may be affected by differing decision-making models (i.e. family-centered vs. patient-centered) varying among cultures (Jazieh, Volker and Taher 2018; Ho 2006), fatalistic attitudes to illness, expectation to have a doctor tell them what to do (Liso et al. 2017), or unwillingness to engage into conflicts with healthcare professionals who may be seen as “authority” figures (Chisholm-Burns, Spivey and Pickett 2018). Healthcare providers in Europe view language barriers as a major problem in providing care to immigrant patients (Priebe et al. 2011). In turn, immigrant patients believe that due to their LLP, physicians will be less likely to understand their concerns. Immigrant patients represent diverse populations with a complex mixture of cultures. Therefore, it is difficult for physicians to be able to understand every culture, which may lead to stereotyping of their immigrant patients (Ahmed et al. 2017). Patients with LLP are also less likely to receive optimal care by having fewer clinical interactions than their proficient referents, and more likely to be given a large amount of information over one single interpreter-mediated session against the multiple sessions provided to their proficient and/or native-speaking counterparts (White et al. 2018). LLP may equally be associated with problems with evaluations, misdiagnosis and/or delayed treatment, limited understanding of health condition or recommended treatment and, in the general population, to experience adverse events leading to physical harm resulting from communication errors (Divi et al. 2007). Further, patients’ cultural perceptions of symptoms may translate into a different expression of needs with the potential to result in missed diagnoses (Smith et al. 2000). Additionally, the interrelation between a variety of patient characteristics and between provider and patient characteristics may influence the clinical encounter significantly. Both providers and patients may both bring their own biases to the clinical encounter, and the bias(es) of one of the two may activate the bias(es) of the other, with the potential to amplify the first’s biased reactions and leading to a magnified effect of individual bias(es), respectively (FitzGerald and Hurst 2017). Different understandings of the patient-physician relationship and unrealistic expectations about the ability of healthcare professionals to address the physical and social problems throughout short medical consultations may equally result in uncertainty and mistrust (Priebe et al. 2011). Research suggests that perceived discrimination, medical mistrust and different representation and expectations of health care between physicians and patients may prove further barriers to care (Van Biesen et al. 2018). These factors, along with lower knowledge of transplant, more religious objection to transplantation, and lower income are significantly associated with either not starting the KT evaluation process or with longer time to be accepted for transplant (Hamoda et al. 2019; Myaskovsky et al. 2012). Providers mention multiple barriers to successful discussions with patients regarding LDKT. These include patients’ cultural background, psychosocial issues, language barriers, belief systems, and age (Sandal et al. 2019). Studies report also diminished perception of providers’ autonomy support among ethnic minority dialysis patients relative to their non-ethnic minority counterparts, with the potential for inferior patient adherence to recommended treatments (Umeukeje et al. 2016). A qualitative study of immigrant patients in the Netherlands reported negative experiences regarding adequate exchange of information with healthcare providers; different expectations between patients and providers about medical procedures, and prejudicial behavior on the part of care providers (Suurmond et al. 2011). These factors may limit the chance for transplant professionals to inform and educate patients about the overall risks and benefits of KT as well as about donor options (i.e. deceased vs. living), alternative living donation programs (kidney exchange, domino paired, ABO incompatible), donor risk profiles (i.e. standard donor vs. non-standard risk donor, expanded criteria donor and donor after circulatory death), about the need for adherence to lifelong post-transplant medical regimens, and about the risks associated with epidemiologic exposure to infectious agents, to the outbreak of latent infectious diseases and/or complications under extensive immunosuppressive protocols (Gordon et al. 2013). Research is needed on these issues in the setting of KT for immigrant populations in the EU.

6.6.2. Cultural Competence

In healthcare, cultural competence entails "understanding the importance of social and cultural influences on patients' health beliefs and behaviors; considering how these factors interact at multiple levels of the health care delivery system (e.g., at the level of structural processes of care or clinical decision-making); and, finally, devising interventions that take these issues into account to assure quality health care delivery to diverse patient populations" (Betancourt et al. 2003). While many models exist to describe cultural competence, the vast majority includes dimensions of knowledge (i.e. understanding what culture means and its relevance to healthcare delivery), attitudes (i.e. being respectful of variations in cultural norms) and skills (i.e. ability to elicit patients' explanatory models of illness) (Saha, Beach and Cooper 2008). In the specific context of care for patients with ESKD, cultural competence also requires consideration of the potential impact of cross-cultural differences in ethical frameworks for decision-making. While Western ethics considers the individual patient as the most suitable subject to make decisions about his/her own health, other cultures (i.e. Asian and Latin American) prioritize family-centered models of decision-making (Davison and Holley 2008). Cultural awareness and sensitivity are of great importance when supporting patients navigate the process of KT and to address issues related to LDKT (Ismail et al. 2013b)). However, providers often lack training in the provision of culturally sensitive transplant education with the potential to fail to address patients' mistrust and concerns regarding LDKT (Waterman et al. 2020). Research found that provision of linguistically and culturally competent education remains sparse across transplant centers in the US (Gordon et al. 2010). However, to the best of our knowledge, no similar studies across different transplant centers have ever been performed at the EU level, and only few if any have assessed the effectiveness of culturally competent provision of KT care among immigrant populations in the EU.

6.7. Healthcare system-level factors

Migrant-sensitive health systems have been identified as one of the key factors to promote equity in health status, health care accessibility, and health outcomes among immigrant subjects. Priorities to ensure the provision of migrant-sensitive services include cultural and linguistic appropriateness, financial sustainability, measures to guarantee continuity and quality of care, and health care delivery by a health and non-health workforce who is aware of the health and social issues associated with immigration (WHO 2010). Yet, while many countries in the EU have implemented migrant-sensitive tools at the national level (i.e. mediation and interpretation services), only few if any have developed comprehensive, targeted migrant health policies to enhance the responsiveness of healthcare systems towards the specific needs of immigrant subjects, making the European scenario heterogeneous (Mikaba 2018). Therefore, it is relevant to consider the factors at the healthcare system level which may contribute to delayed referral for KT, longer time needed for KT evaluations, transplant education about treatment options, and legal regulations about accessibility of LDKT in immigrant patients with non-resident living kidney donors.

6.7.1. Health Services Organization, Financing and Delivery

Healthcare services organization and delivery play a critical role in promoting migrant health by means of multilevel policies, specific programs, measures and cooperation. Yet, great variation is reported across the WHO European Region (WHO 2018). Multiple studies document that legislative, financial, and administrative difficulties may limit the chance for immigrants to benefit from health care services in an easily accessible fashion (Devillanova and Frattini 2016; Chiarenza et al. 2019; Lebano et al. 2020). For instance, lack of integration of care in the host country has the potential to negatively affect the chance to acquire a complete clinical picture of the patient and to arrange integrated care plans involving multidisciplinary teams and considering the patient in a holistic manner (Chiarenza 2019; Pavli and Maltezou 2017). Further, while cultural sensitivity and intercultural competence are increasingly recognized as key factors for equitable and adequate healthcare delivery, education and training of healthcare professionals in KT clinical practice is uncertain. An additional factor at the healthcare system level with the potential to limit the chance for immigrant patients to access LDKT are the legal regulations for non-resident living kidney donors out of uncertainties regarding the financial coverage of living donor work-up, surgical procedure and follow-up (Van Biesen et al. 2018). Research is needed regarding these aspects, along with assessments of the presence of migrant-friendly transplant services across transplant centers in the EU, and rigorous assessments of the association between the latter and disparities in accessibility and outcomes of KT. Further,

6.7.2. Healthcare Organizational Culture, Quality Improvement

There is broad consensus among experts across the EU regarding the right to culturally sensitive healthcare for immigrant populations. A three-round Delphi study in 16 European countries revealed that (1) easy and equal access to health care, (2) empowerment of migrants, (3) culturally sensitive health care services, (4) quality of care, (5) patient/health care provider communication, (6) respect towards migrants, (7) networking in and outside health services, (8) targeted outreach activities, and (9) availability of data about specificities in migrant health care and prevention are broadly recognized as relevant aspects for the provision of accessible and effective healthcare services (Devillé et al. 2011). Standards have been developed in the US and EU contexts to guarantee high quality healthcare provision and equity by culturally and linguistically appropriate services (CLAS) for migrant and ethnic minority populations (U.S. Department of Health and Human Services 2001; Chiarenza 2014). Cultural competence is recognized as an essential and integral component of accessibility and quality of healthcare systems (Anderson et al. 2003). While evidence remains limited, cultural mediation has been shown to positively affect multiple relational outcomes including facilitated communication, enhanced therapeutic relationship by improved intercultural understanding, increased patient participation in health education programs, inferior perceived discrimination, and adaptation of health services to the cultural needs of immigrant populations (Verrept 2019). However, studies suggest that professional cultural mediation and interpretation services are not systematically integrated into existing organizational routines, and they are concentrated primarily in some areas of clinical practice (i.e. mental health, elderly and female care) (Chiarenza et al. 2019; Mikaba 2018). Further, it has been noted that medical schools lack education and training on culturally competent healthcare provision that considers how to handle the SDH in clinical practice (Sorensen et al. 2019). Future studies should investigate these issues along with their association with relevant outcomes along the KT process.

6.8. Potential for interventions and future research directions

Given the multiple relationships between immigration background and KT outcomes noted in the IBDKT, the implementation of this model may (1) inform the agenda for future research where evidence is lacking, and (2) contribute to identification of potential areas for intervention to optimize the process of KT in this vulnerable group of patients. Nephrologists and other transplant professionals in the EU are increasingly confronted with the necessity to effectively respond to the specific needs of immigrant populations pursuing KT to guarantee provision of high quality care as a core principle in transplant clinical practice (EDQM 2018). The patient/donor level factors associated with immigrant status should be considered in relation with factors at the levels of provider, clinical encounter, and healthcare system so as to allow identification of the aspects with the potential for detrimental effects on both accessibility and outcomes of KT. The US National Standards for CLAS recommend provision of "effective, equitable, understandable, and respectful quality care and services that are responsive to diverse cultural health beliefs and practices, preferred languages, health literacy, and other communication needs" (U.S. Department of Health and Human Services 2001). However, whether provision of KT care to immigrant patients in transplant centers in the EU complies with these standards is unknown. LLP, sociocultural factors, socioeconomic factors, and inadequate HL may limit the chance for transplant professionals to educate patients about the complex issues surrounding transplant such as overall risks and benefits of KT, deceased vs. living donor options, alternative living donation programs such as kidney exchange/domino paired/ABO incompatible, donor risk profiles (i.e. standard donor vs. non-standard risk donor, expanded criteria donor and donor after circulatory death), about the need for adherence to lifelong post-transplant medical regimens, and about the risks associated with epidemiologic exposure to infectious agents, and to the outbreak of latent infectious diseases and/or complications under extensive immunosuppressive protocols (Gordon et al. 2013). Therefore, because these factors may contribute to disparities both prior to and following KT, they should be formally assessed and, where appropriate, addressed. While standardization of transplant education may assist in reducing disparities for ethnic minority and socioeconomically disadvantaged individuals (Patzer et al. 2012), KTRs consider "one size fits all" approaches as insufficient to meet their medical, emotional and social support needs (Been-Dahmen 2018). To be effective, education of ESKD patients pursuing KT should be individually tailored, easily understandable for patients with low HL, and culturally competent (Skelton et al. 2015). It is recommended that transplant education should be initiated early in the process of KT and that educational interventions should accommodate the needs of more vulnerable groups of patients (Gordon et al. 2013). However, formal protocols describing the ideal timing, content, modality and frequency of education for immigrant patients pursuing KT in the EU are lacking. Further, evidence is needed regarding KT education practices in these populations. While limited, studies have shown that linguistically and culturally competent KT care is promising. KTRs with LLP who have the opportunity to benefit from interpretation services are less likely to suffer worse KT outcomes and rejection rates relative to other KTRs (Tahir et al. 2017). Further, since the lay explanatory models of ilnness and treatment that many immigrants bring with them from their countries of origin are modifiable factors (Kleinman 1980), linguistically and culturally competent KT may be effective in improving knowledge, understanding and attitudes towards available treatment alternatives (including LDKT), communication, decisional capacity, and self-efficacy (Axelrod et al. 2017; Nathan et al. 2016; Skelton et al. 2015; Gordon et al. 2014; Ismail et al. 2014). These have the potential to improve chances to receive LDKT, to properly evaluate the multiple transplant options and enable more timely KT treatment, to improve self-efficacy and adherence to lifelong medical regimens, and to diminish physicians' ethical concerns regarding KT outcomes. Culturally competent home-based educational interventions (Ismail et al. 2014), culturally competent patient-decision aids (including use of technology such as mobile phone apps) (Axelrod et al. 2017; Nathan et al. 2016), and other culturally tailored educational sessions (Gordon et al. 2014) can be valuable means to achieve these purposes. Medication and transplant learning programs using video technologies available in different languages and responding to patients' cultural needs may also be effective for immigrant patients to facilitate understanding of complex medical information. Additionally, the use of videos in the patients' native language may allow standardization of education preventing the potential for disparities in the provision of information relevant to transplantation among healthcare providers and eliminate the need to coordinate interpretation services (Tsapepas et al. 2018). Further, assessment of HL of immigrant subjects should consider the effects of language barriers and, more importantly, of cultural beliefs about health and illness as critical elements to enable the patient's ability to understand and process information and act according to providers' recommendations (Shaw et al. 2008). While there are signs which may assist providers in predicting which patients may have more limited HL (i.e. incomplete or inaccurate patient registration forms, non-adherence, frequently missed appointments, etc.), a variety of screening tools exist to formally assess patients' HL levels, many of which have been used in ESKD settings (Jain and Green 2016). Best strategies and interventions to improve HL in these populations are currently under scrutiny (Baumeister et al. 2019). Also, because dialysis patients with an immigration background are more likely to present depressive and anxiety symptoms relative to their native-born referents (Loosman et al. 2018), and may have experienced traumatic events and post-migration living difficulties that are associated frequently with psychopathology (i.e. post-traumatic stress disorder, depression, anxiety and somatization) (Aragona et al. 2013), mental health assessments should consider how migration-related experiences and different cultural backgrounds may affect clinical manifestations so as to prevent diagnostic errors and enable effective treatments (Fogel et al. 2020; Callegari et al. 2020; Fatahi and Krupic 2016). Exploration of post-transplant migration routes may also enable the planning and coordination of care upon emigration to other EU countries or in the event of a return to home lands.

At the healthcare system level, use of professional interpreters has proven beneficial to prevent clinical errors, to enhance communication, comprehension, healthcare services utilization, clinical outcomes and patients' satisfaction with care in other areas of clinical practice (Laher et al. 2018 ; Karliner et al. 2007). Similarly, cultural mediation may positively affect various relational outcomes including facilitated communication, enhanced therapeutic relationship by improved intercultural understanding, increased patient participation in health education programs, inferior perceived discrimination, and adaptation of health services to the cultural needs of immigrant populations (Verrept 2019). Further, education and training in cultural competence for nephrologists and other transplant professionals may improve communicative abilities, social history taking, and prevention of preconceived biases with the potential to provide a more effective response to the diverse needs of their immigrant patients (Chiarenza et al. 2019). Improving these critical factors may increase patients' trust, self-management abilities, satisfaction with the potential to positively impact on patients' clinical and psychosocial outcomes, and enable active patient participation so as to promote shared decision-making as the most desirable and ethical model of the patient-physician relationship in clinical practice (Barry and Edgman-Levitan 2012) including KT care (Gordon et al. 2013).

Regarding immunological factors, studies of pharmacokinetics in distinct ethnic minority individuals may support refinement of tacrolimus dosage and exposure to improve patients' management and long-term kidney graft function.

Research suggests that an integrated approach simultaneously considering the specific needs associated with cultural diversity, limited HL and limited LLP may serve as a catalyst to effectively address the special demands of these vulnerable populations at the level of individual providers, clinical encounter and healthcare organizations at the same time (Andrulis and Brach 2007).

6.9. Conclusion

Our conceptual model provides a framework which may supplement understanding of the complex pathways linking immigration background with disparities in the process of KT. The social determinants associated with immigration have the potential to affect multiple patient-level factors (knowledge and understanding of KT and LDKT, trust, adherence to pre- and post-transplant regimens, comorbid conditions, immunological factors), provider-level factors (knowledge and attitudes, competing demands, physician bias), clinical encounter-level factors (provider communication, cultural competence), and healthcare system-level factors (health services organization, financing and delivery; healthcare organizational culture, quality improvement) which may delay and/or hinder KT accessibility, quality of care and, both directly and by mediation of longer dialysis vintage, also KT outcomes. These factors are interrelated and reciprocally influence one another. Therefore, because research surrounding the role of the SDH and of more proximal mediators/moderators in

KT disparities in immigrant populations is sparse, consideration of these factors is required given their potentially negative effects on KT accessibility and outcomes. The elements noted in the IBDKT may inform the design of prospective research protocols to fill in research gaps among immigrant populations pursuing KT in the EU. Further, it may inform the development and implementation of strategies and interventions to address and potentially mitigate and/or eliminate the detrimental effects of immigration background on more proximal mediators/moderators to accessibility and outcomes of KT in this vulnerable group of patients. Studies are needed to determine whether and which interventions on modifiable risk factors may prove effective to improve equity in KT among immigrant populations in the EU.

Chapter 7. General discussion and future research directions

"Health inequalities that are preventable
by reasonable means are unfair"
(Marmot 2019 [16])

7.1. General discussion

Kidney transplantation (KT) has become the gold standard RRT for patients with ESKD. In this dissertation, we investigated the issue of disparities in KT in the immigrant patient population in Italy. Following the disparities research agenda by Kilbourne and colleagues (2006), after framing disparities in KT in general we hypothesized that the multiple conditions and vulnerabilities associated with immigrant status might contribute to inferior KT outcomes in KTRs from non-EU countries relative to their EU-born referents. Overall, we found that disparities along the continuum of the KT process in Italy and in Europe alike are an emergent yet underexplored issue when compared to disparities associated with race/ethnicity *per se* in Europe and beyond. While Italy has a publicly funded health system which guarantees universal healthcare coverage to all individuals, regardless of socioeconomic status and immigration background, the study presented in Chapter 4 revealed that non-European born KTRs had unfavorable long-term eGFR when compared to their EU-born and Eastern European-born counterparts. Our study was the first to assess long-term eGFR decline and immigrant status in adult KTRs in Europe and provided the first evidence that non-European immigration background is associated with long-term eGFR decline. Our findings show that, compared to EU-born KTRs, and unlike Eastern European-born KTRs, non-European-born KTRs had an eGFR decline of almost -5mL/min/1.73m2 at 5-years post-transplantation. However, given the retrospective design of our study, it did present several limitations, since results could not be adjusted for multiple socioeconomic, sociocultural, and psychosocial variables.

From the Italian National Transplant Center's (CNT) Transplant Information System (SIT) registry we also extracted data of 24,958 patients to perform a retrospective cohort study of adult patients (≥ 18 years of age) who received DDKT, LDKT, were permanently withdrawn from or died on the WL, and who received KT in a foreign country from January 1, 2010, through December 31, 2019 in Italy to examine whether non-EU-born individuals experience inferior access to KT and WL outcomes when compared to their EU-born referents. The follow-up time was calculated from time of first wait-listing date to DDKT, LDKT, permanent withdrawal

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[16] Marmot M. Fair Society, Healthy Lives. The Marmot review. Strategic Review of Health Inequalities in England post-2010. 2019. www.ucl.ac.uk/marmotreview

from the WL, death on the WL, KT in a foreign country, to the end of follow-up (December 31st, 2019), whichever came first. Yet, although the study is currently in preparation, we were unable to include it in this dissertation due to COVID-19-related delays. This stands as a study limitation, because we remain unsure of whether immigration background is associated also with disparities in KT accessibility.

In Chapter 5, we determined the ethical relevance of detecting and understanding determinants of disparities in accessibility and outcomes of KT and discussed inherent ethical dimensions. We highlighted the importance of addressing the SDH in clinical practice for prevention of disparities in the immigrant patient population pursuing KT. We stressed the worth of utilizing standardized scoring systems for pre-transplant psychosocial assessments as a valid means to prevent preconceived biases within transplant teams, to identify the risk factors with the potential to reduce risk, to optimize graft survival and patient's level of functioning and quality of life, and to plan individualized educational and/or psychosocial interventions accordingly. We found that, because these tools are designed for the general transplant population, they do not consider that migrants are more likely than their native-born counterparts to present specific cultural, social, economic, relational, and organizational challenges that may affect the overall score of standardized scoring systems negatively. However, due to the limited evidence base regarding the actual impact of these factors on clinical (i.e. patient survival, graft survival, kidney graft function) and nonclinical (i.e. quality of life) outcomes of KT, denying KT accessibility on the above listed nonclinical grounds challenges equity. However, since the nonclinical factors have the potential to be modified by implementation of migrant-sensitive interventions, respect for the principles of beneficence/nonmaleficence and justice requires identification and consideration of these factors early in the process of KT. The relational dimension between individual patients and their physicians is regarded as the setting where the patient's vulnerabilities can be identified and protected against by targeted interventions to achieve successful treatment outcomes. For the first time, the Four-Boxes method was used to explore the SDH in pre-transplant assessments in the setting of KT. This method improves social history-taking and simultaneously allows analysis of the ethical dimensions of single clinical cases along with adoption of a holistic approach in KT clinical care involving patients with an immigration background. Analyses by the Four-Boxes method highlighted also that consideration of the SDH is necessary to provide quality care adapted to the patient's situation. Our findings suggest that, when evaluating KT candidates with an immigration background, it is possible that physician teams may benefit from linguistically and culturally sensitive assessments to enhance patient-physician-caregiver partnership, to identify areas to perform thorough educational interventions to improve knowledge and understanding of the KT process, to assess comprehension, motivation, views and preferences regarding the multiple risks, benefits, options, and aspects inherent to KT and improve chances for successful clinical and psychosocial outcomes of KT. Further, because different cultural backgrounds may affect clinical manifestations of psychiatric symptoms, standardized mental health assessments in these populations should be integrated with additional tools to acquire qualitative insights into the patient's background and enable more appropriate diagnosis and more effective care plans. Much remains to be explored as to the most effective strategies to fulfill these purposes in this vulnerable group of patients pursuing KT in Italy. Future studies should generate evidence of the actual association of immigration background with KT outcomes and investigate whether and which targeted interventions considering the multiple specific considerations in immigrant populations may enable provision of high quality care throughout the lifelong continuum of the KT process. This may guarantee decision-making based on rigorous scientific evidence rather than on discretionary choices of individual healthcare professionals, as well as the development of standardized processes considering also the life circumstances of individual patients.

In Chapter 6, to supplement appreciation of the complex pathways linking immigration background with disparities in KT, we developed a conceptual model to provide a framework to elucidate some of the major mechanisms at the level of patient/donor, individual provider, clinical encounter and healthcare system which are likely to contribute to disparities in immigrant patient populations in the EU. The SDH associated with immigration have the potential to affect multiple patient-level factors (knowledge and understanding of KT and LDKT, trust, adherence to pre- and post-transplant regimens, comorbid conditions, immunological factors), provider-level factors (knowledge and attitudes, competing demands, physician bias), clinical encounter-level factors (provider communication, cultural competence), and healthcare system-level factors (health services organization, financing and delivery; healthcare organizational culture, quality improvement) which may delay and/or hinder KT accessibility, quality of care and, both directly and by mediation of longer dialysis vintage, also KT outcomes. These factors are interrelated and reciprocally influence one another. Therefore, consideration of these factors is required given their potentially negative effects on KT accessibility and downstream outcomes.

7.2. Future research directions

The elements noted in the IBDKT may inform the design of prospective protocols to fill in research gaps among immigrant populations pursuing KT in the EU. Because it is recommended that both immigrant and ethnic minority data should be collected for healthcare disparities research purposes (EUPHA 2018), two aspects should be considered regarding proper definitions of target populations. First, a consistent definition is needed of migrants as distinguished from racial/ethnic minorities, as already done in other chronic disease settings to enable cross-country data comparability in the EU (ECDC 2011). Further, because the various typologies of migrants generally shape the actual experiences that migrants face throughout the four phases of the migration process (**Figure 14**), when exploring the epidemiological profiles along with the associated health outcomes and/or burden of disease, flexible typologies are needed to capture the factors affecting the experience of individuals with an immigration background both at the population level and at the individual one (IOM). Some examples include:

- *Immigrant status*: nationality; documentation status; tourists; business travelers; job seeker; refugees; irregular migrants; asylum seekers; internally displaced persons; migrant workers.
- *Geography*: rural to urban migrants; intra-urban migration; interregional migration; internal migration; transnational migration; return migration.

- *Temporality*: weekly/monthly commuting; seasonal migration; labor-related contractual migration; short-term or protracted migration; time in transit.
- *Socio-demographic status*: age; gender; family structure; economic status; education level; level of professional and occupational skills.
- *Motivations/causal classifications*: job seeking; family reunification; asylum seeking; refugee resettlement; labor migration; student migration.

In the second place, because ethnic minority status may amplify various SDH (i.e. social exclusion/ discrimination, socioeconomic status/education, beliefs/culture/familial context, and biological factors) along with its influence on more proximal mediators and/or moderators of KT accessibility and outcomes, collection of data on ethnicity is recommended so as to clarify associations of both immigrant status and ethnicity on disparities in the process of KT, from the progression towards ESKD through to outcomes relevant in KT (i.e. referral, wait-listing, receiving KT, and clinical and psychosocial outcomes of KT).

Rigorous indicators, proxies and/or measures should be determined for the collection of SDH data as well as for mediators and/or moderators.

Further, we detected some areas with the potential to benefit from the development and implementation of strategies and interventions to mitigate and/or eliminate the detrimental effects of immigration background on more proximal mediators/moderators of accessibility and outcomes of KT.

Prospective studies will be performed to further elucidate the causal mechanisms linking immigration with disparities in KT. Also, as noted earlier, while it would be necessary to act directly upon the structural causes of disparities, it is more realistic to foster action on intervening factors by (1) development of targeted educational interventions for patients, donors and healthcare professionals, and (2) provision of CLAS at the healthcare system level with the potential to enable the prevention/mitigation/elimination of disparities in KT in this vulnerable group of patients. Future research is equally warranted to develop interventions and to assess their effectiveness in KT care.

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Portfolio

Doctoral student: Alessandra Agnese Grossi

Doctoral period: October 2017 – November 2020

Supervisor: Prof. Mario Picozzi

	Date	Workload (hrs)
PhD Courses (University of Insubria, Varese)		
Il vaccino per SARS-COV-2. Questioni etico-giuridiche (Webinar)	25 Jun 2020	2
Bibliographic Databases: (1) Searching PubMed; (2) How to use bibliometric DBs	20 & 24 Jan 2020	8
La nuova Carta dei Principi NITp	24 Jun 2019	9
Etica casistico/narrativa in oncologia e geriatria	4 Jun 2019	4
Neuroetica e neuroscienze	6, 13, 20 Feb & 1 Mar 2019	8
Il significato della donazione nel trapianto d'organi. Una riflessione pluri-prospettica tra gratuità e scambio	23 Jan 2019	2
Psicoanalisi ed etica clinica	10 & 31 Jan 2019	4
La consulenza etica in ambito ospedaliero. Un confronto europeo	3 Dec 2018	4
Norme in materia di consenso informato e di disposizioni anticipate di trattamento. Profili etici, giuridici e ricadute pratiche	21 Nov 2018	4
La legge 180 del 1978: incontro tra etica, diritto e medicina	20 Jun 2018	4
La nascita dell'identità	31 May 2018	4
Research Integrity	10-11 May 2018	4
Genomica e genETICA	11 Apr 2018	4
Disposizioni anticipate di trattamento	14 Feb 2018	

Cosa fare? I medici e gli operatori sanitari di fronte all’incertezza e al dubbio morale	19 Oct 2017	4
Winter schools		
The Quest for Health Equity in the Mediterranean Context: Focusing on Migrants and on the Poor (Istituto Nazionale per la promozione della salute delle popolazioni Migranti ed il contrasto delle malattie della Povertà – INMP)	Rome, 16-20 Dec 2019	34
School on Methodology, Ethics and Integrity in Biomedical Research (University of Insubria)	Varese, 12-16 Nov 2018	40
Attended conferences, courses and seminars		
Uncertainty in offering and accepting an organ - sharing a decision - European Society of Organ Transplantation Transplant Learning Journey (ESOT TLJ) 2.0	Webinar, 5 nov 2020	1
Medicina delle migrazioni: la medicina delle persone fragili - Ospedale Pediatrico Bambino Gesù	Webinar, 14 Oct 2020	7
Giornata scientifica del dottorato in MCSMH	Webinar, 18 Sep 2020	8
Donazione e trapianto di organi al tempo della pandemia. L’esperienza in regione Lombardia: quali domande etiche sono emerse e come sono state affrontate nella filiera del sistema regionale trapianti - Coordinamento Regionale Trapianti (CRT) Lombardia	Webinar, 29 Jun 2020	3.5
Convegno “Come migliorare il programma regionale di donazione a scopo di trapianto” c/o Direzione Generale Welfare, Regione Lombardia	Milano, 27 Jan 2020	4
La donazione di organi a cuore fermo: nuove opportunità terapeutiche	Varese, 27 Nov 2019	7
43° Congresso Nazionale della Società Italiana dei Trapianti d’Organo e Tessuti	Rome, 21-23 Nov 2019	24
Donazioni e trapianti di organo: Etica laica e religiosa - Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico di Milano	Milano, 13 Nov 2019	4
Stati Generali della Rete Trapiantologica Italiana.	Rome, 6-8 Nov 2019	20

2019 European Organ Donation Day (EODD) Session 3: Increasing Donation from Underrepresented Donors with a specific emphasis on Black and Asian Donors	London, 12 Oct 2019	2.5
Giornata scientifica del dottorato in MCSMH	Varese, 27 Sep 2019	8
European Association of Centers of Medical Ethics (EACME) Conference 2019. Rethinking Ethics in 21st Century Europe	Oxford, 12-14 Sep 2019	24
School on Organ Transplantation. Decision-Making in Transplantation: Frontiers of Medicine and Science - Lake Como School of Advanced Studies.	Como, 26-28 Jun 2019	21
Research Visit at Institut Borja de Bioètica – Universitat Ramon Lull	Barcelona, 11-13 Jun 2019	24
International Conference on Clinical Ethics Consultation (ICCEC) 2019	Vienna, 22-25 May 2019	5
7th International Congress - Infections & Transplantation	Varese, 23-25 May 2019	16
International Conference on Seniors, Foreign Caregivers, Families, Institutions: Linguistic and Multidisciplinary Perspectives	Varese, 9-10 Apr 2019	16
Riunione tecnico-scientifica NITp	Trento, 29 Oct 2018	7
Il percorso della donazione e del trapianto in una società che cambia	Milan, 5 Oct 2018	
8th International Meeting on Transplantation from DCD. Midterm Conference of the Italian Society of Organ Transplantation - S.I.T.O.	Milan, 13-14 Sep 2018	8
European Association of Centers of Medical Ethics (EACME) Conference 2018. Ethics in Action	Amsterdam, 6-8 Sep 2018	20
5th European Clinical Ethics Network (ECEN) Forum Day	Amsterdam, 5 Sep 2018	8
4th International Congress Viral Infections in Immunocompromised Patients (VIIP) 2018	Varese, 17-18 May 2018	16

Un confronto internazionale e multidisciplinare sul consenso del paziente alla proposta di organi da donatori con profili di rischio non standard	Varese, 27-28 Oct 2017	12
Accepted conference abstracts (peer reviewed)		
Grossi AA, Nicoli F, Testa J, Picozzi M. Informed Consent for Organ Transplantation in Older Adults: are Patient Decision Aids the Solution for Successful Implementation of Shared Decision-Making in Transplant Clinical Practice? European Association of Centers of Medical Ethics (EACME) Conference 2020.	Cluj Napoca, 10-12 Sep 2020 (postponed to Sep 2021)	
Nicoli F, **Grossi AA**, Testa J, Gasparetto A, Picozzi M. From Acute Events to Chronic Disease Conditions: an Integrated Model for Ethics Consultation along the Continuum of Care. European Association of Centers of Medical Ethics (EACME) Conference 2020.	Cluj Napoca, 10-12 Sep 2020 (postponed to Sep 2021)	
Testa J, Nicoli F, **Grossi AA**, Gasparetto A, Picozzi M. European Association of Centers of Medical Ethics (EACME) Conference 2020.	Cluj Napoca, 10-12 Sep 2020 (postponed to Sep 2021)	
Grossi AA, Picozzi M. Solid Organ Transplantation in the Elderly Patient Population: are Patient Decision Aids the "Cure" for the Challenges of Informed Consent? International Conference Ages2020. Age-Specific Issues. Language, Spaces, Technologies.	Milan, 29-30 Oct 2020	
Grossi AA, Nicoli F, Testa J, De Feo T, Picozzi M. Unintentional Transmission of Cancer in solid organ transplantation: what role for transplant recipients in organ removal and re-transplantation decision-making? European Association of Centers of Medical Ethics (EACME) Conference 2019.	Oxford, 12-14 Sep 2019	
Testa J, **Grossi AA**, Nicoli F, Picozzi M. A migrant clinic: an opportunity for transcultural medicine. European Association of Centers of Medical Ethics (EACME) Conference 2019.	Oxford, 12-14 Sep 2019	
Nicoli F, Decchi B, **Grossi AA**, Testa J, Picozzi M. Treatment decision-making in acquired brain injury in the young patient population: the role of family members' story-telling. European Association of Centers of Medical Ethics (EACME) Conference 2019.	Oxford, 12-14 Sep 2019	

Grossi AA, Nicoli F, Picozzi M. Defining the role of clinical ethics consultation in pre-transplant Recipient Assessment Practices. 15th International Conference on Clinical Ethics Consultation - ICCEC 2019 (forthcoming proceedings on *Journal Hospital Ethics*)	Vienna, 22-25 May 2019
Grossi AA, Grossi PA, Picozzi M. A multidisciplinary perspective on kidney transplantation in an elderly patient with an immigration background. International Conference on Seniors, Foreign Caregivers, Families, Institutions: Linguistic and Multidisciplinary Perspectives	Varese, 9-10 Apr 2019
Grossi AA, Nicoli F, Ferioli E, Roggi S, Testa J, Montaguti E, Piffer Gamberoni I, Picozzi M. Transplant candidates' evaluation: combining clinical and nonclinical criteria with ethical judgment for sound listing decision-making. European Association of Centers of Medical Ethics (EACME) Conference 2018	Amsterdam, 6-8 Sep 2018
Grossi AA, Nicoli F, Picozzi M. Nonclinical criteria and wait-list registration for kidney RE-transplantation. 5th European Clinical Ethics Network (ECEN) Forum Day	Amsterdam, 5 Sep 2018

Publications (peer reviewed journals)

Grossi AA ⌧, et al. Causal Mechanisms Linking Immigration Background with Disparities in Kidney Transplant: a Conceptual Model (in preparation)	-
Grossi AA ⌧, Caselli I, Nicoli F, et al. The Four Boxes Method as a tool to supplement pre-transplant psychosocial assessments in the immigrant patient population pursuing kidney transplant: a case series (in preparation)	-
Nicoli F, Montaguti E, Gasparetto A, Zaninetta G, **Grossi AA**, Mangeri G, Miccinesi G, Petrini C, Picozzi M. The act of consoling helps those who console. A multi-center observational survey study in Hospice Services (submitted to Journal of Palliative Medicine)	2020
Grossi AA ⌧, Nicoli F, Biffa G, *et al*. Ethical Perspectives on Informed Consent to Solid Organ	-

Transplantation from Non-Standard Risk Donors: Position Paper by the *Varese Consensus* Working Group (in preparation).	
Grossi AA ✉, Puoti F, Di Ciaccio P, et al. Is immigration background associated with disparities in access to kidney transplant in a universally accessible health care system? A retrospective cohort study of the Italian National Transplantation Network (in preparation).	-
Grossi AA ✉, Maggiore U, Puoti F, Grossi PA, Picozzi M, Cardillo M. Association of Immigration Background with Kidney Graft Function in a Publicly Funded Health System: A Nationwide Retrospective Cohort Study in Italy. published online ahead of print, 2020 Jul 4]. Transpl Int 2020; 10. doi:10.1111/tri.13688 (https://pubmed.ncbi.nlm.nih.gov/32621764/)	2020
Callegari C, Ielmini M, Caselli I, Mattia M, Gasparini A, **Grossi A**, Ceccon F, Poloni N. The 6-D Model of National Culture as a Tool to Examine Cultural Interpretation of Migration Trauma-Related Dissociative Disorder: A Case Series. J Immigr Minor Health. 2020; 22(3):588-596. doi:10.1007/s10903-019-00904-7 (https://www.ncbi.nlm.nih.gov/pubmed/31165366)	2020
Gulino M, Patuzzo S, Baldelli I, Gazzaniga V, Merlo DF, Maiorana L, Murialdo G, Picozzi M, Armocida G, Cattorini P, Montaguti E, Bonometti S, **Grossi AA** ✉, De Stefano F, Ciliberti R. Bioethics in Italian Medical and Healthcare Education. A pilot study. Acta Biomedica. 2019; 89(4):519-531. (https://www.ncbi.nlm.nih.gov/pubmed/30657121)	2019
Picozzi M, **Grossi AA** ✉, Ferioli E, Nicoli F, Gasparetto A. Donation After Circulatory Death: When Withdrawing Life-Sustaining Treatments Is Ethically Acceptable. Transplantation Proceedings. 2018 Jun 30. (https://www.ncbi.nlm.nih.gov/pubmed/30655134)	2018

Teaching activities and invited speeches

Grossi AA. Patient inclusion initiative joint EPITA/EDTCO/ETAHP Symposium - 11th EPITA Symposium & 40th AIPIT Workshop (Invited Chair)	Online Conference, 25-26 Jan 2021	2
Grossi AA. Communication of Risk to Transplant Recipients - European Donation and Transplant Coordination Organization (EDTCO). Educational Course for Transplant Coordinators (TC) for UEMS Certification Exam (European Society for Organ Transplantation; ESOT - Transplant Live Video Lectures: Donation Module 4 Recipients)	Recorded Video Lecture, Dec 2020	20’
Grossi AA. Organ transplantation and informed consent – Bioethics course for Biomedical Sciences students, Università degli Studi dell’Insubria	Varese, 2 Dec 2020	2
Grossi AA. Communication of Risk to Transplant Recipients - 4th International Congress - Viral Infections in Immunocompromised Patients	Varese, 29-30 Oct 2020	20’
Grossi AA. Disparities in kidney transplantation in the immigrant patient population: towards an intervention to improve equity - Giornata scientifica del dottorato in MCSMH	Webinar, 18 Sep 2020	15’
Grossi AA. Donazione e trapianto di organi al tempo della pandemia - L’esperienza in regione Lombardia: quali domande etiche sono emerse e come sono state affrontate nella filiera del sistema regionale trapianti	Webinar, 30 Jun 2020	20’
Grossi AA. Supervisione in équipe. Trattamento dialitico ed eleggibilità al trapianto di rene in una paziente con alterazioni comportamentali gravi. Corso residenziale c/o ASST Sette Laghi	Varese, 6 Apr 2020	4
Picozzi M, **Grossi AA**. L’etica clinica nel percorso donazione-trapianto - Convegno “Come migliorare il programma regionale di donazione a scopo di trapianto” c/o Direzione Generale Welfare, Regione Lombardia.	Milano, 27 Jan 2020	20’
Grossi AA. Quali elementi decisionali per l’eleggibilità al trapianto di rene? Una nuova vita (im)possibile? Corso residenziale ECM c/o ASST Sette Laghi	Varese, 11 Nov 2019	4

Grossi AA. Organ Transplantation Ethics - Bioethics course for Biomedical Sciences students, Università degli Studi dell’Insubria	Varese, 16 Oct 2019	2
Grossi AA. Towards a holistic approach to kidney transplantation in the immigrant patient population in Italy: Integrating clinical, nonclinical criteria and ethical assessments for improved transplant outcomes – Giornata scientifica del dottorato in MCSMH	Varese, 27 Sep 2019	10’
Grossi AA. Cultural sensitivity, ethics and education - School on Organ Transplantation. Decision-Making in Transplantation: Frontiers of Medicine and Science Lake Como School of Advanced Studies.	Como, 26-28 Jun 2019	1
Grossi AA. Criteri clinici, non-clinici e giudizio etico: quale ruolo nella valutazione del candidato al trapianto di rene con profili multipli di vulnerabilità? Il caso del paziente migrante - Corso residenziale ECM per specialisti in nefrologia dal titolo “Inserimento in lista trapianto del paziente con profili multipli di vulnerabilità e gestione del follow up” c/o Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico.	Milano, 6 Jun 2019	1
Grossi AA. Ethical issues in nonclinical pre-transplant assessments. 7th International Congress - Infections and Organ Transplantation.	Varese, 23-25 May 2019	20’
Grossi AA. La consulenza etica nella pratica clinica dei trapianti - Corso per personale medico Istituto Mediterraneo per i Trapianti e Terapie ad alta specializzazione (ISMETT).	Palermo, 11 Mar 2019	1
Grossi AA. Criteri clinici, non-clinici e giudizio etico: quale ruolo nella valutazione del candidato al trapianto d’organo? - Corso Master di I livello in 'Coordinamento infermieristico e gestione del processo dalla donazione al trapianto di organi e tessuti', in collaboration with Fondazione Trapianti Onlus, Policlinico di Milano.	Milano, 7 Feb 2019	4
Grossi AA. Aspetti legali ed etici dei trapianti d’organo solido - Seminario formativo per studenti dei Corsi di Laurea in Igiene dentale e Tecniche di fisiopatologia cardiocircolatoria e perfusione cardiovascolare dell’Università degli Studi dell’Insubria.	Varese, 25 Jan 2019	2

Picozzi M, **Grossi AA**. Patient Information and Consent to Organ Transplantation from Non-Standard Risk Deceased Donor Organs - 27th European Donation and Transplant Coordination Organization (EDTCO) Congress.	Munich, 8-10 Nov 2018	20’
Grossi AA. Organ Transplantation Ethics - Bioethics course for Biomedical Sciences students, Università degli Studi dell’Insubria.	Busto Arsizio, 8 Nov 2018	2
Grossi AA. Interactive Clinical Case Presentation: Ethnic and Cultural Diversity in Kidney Transplantation: What Role for Clinical Ethics Consultation in Pre-Transplant Assessment Practices - Antimicrobial Therapy in Immunocompromised and Critically Ill Patients: Management and Perspectives (ATCIP) Congress.	Lugano, 4-5 Oct 2018	20’
Picozzi M, **Grossi AA**. Improving the “20 min no touch time” law: Mission Impossible? - 8th International Meeting on Transplantation from DCD. Midterm Conference of the Italian Society of Organ Transplantation - S.I.T.O.	Milan, 13-14 Sep 2018	20’
Grossi AA. Communication and ethics in the process of organ donation and transplantation - 4th International Congress - Viral Infections in Immunocompromised Patients.	Varese, 18-19 May 2018	20’

Thesis Tutoring

Medical School Thesis Tutoring of Dr. Sara Soldarini. Thesis title: Il trapianto di rene: il vissuto del paziente nel periodo post trapianto.	Nov 2017 – Oct 2018

Book contributions

Grossi AA, Mjoen G, Watson C, Oniscu G, Maia P, Braat A, Avsec D, Grossi PA. Communication of risk (Chapter 19). In: European Directorate for the Quality of Medicines and Healthcare (EDQM). Guide to the Quality and Safety of Organs for Transplantation. Strasbourg: Council of Europe.	Forthcoming (2021)
Grossi AA. Comment to a case about Migration projects and challenges to post-transplant follow-up. In: Picozzi M (a cura di). Il trapianto di organi. Realtà clinica e questioni etico deontologiche.	Forthcoming (2021)

Participation in other projects

Ethical aspects of transplantation in vulnerable subjects – Institut Borja de Bioética (Esplugue de Llobregat, Barcelona, Spain)	June 2019
Varese Charter - Ethical Perspectives on Patient Information and Consent to Solid Organ Transplantation from Non-Standard Risk Deceased Donors	Oct 2017 - Aug 2018
Pilot Project Clinical Ethics Consultation – Dep. of Transplantation, ASST Sette Laghi (Varese)	Sep 2017 - Feb 2018

Reviewer activities

Transplantation Reviews	July 2019 - present
Journal of Nephrology	August 2020 - present
Acta Biomedica	September 2020 - present