OPINION ARTICLE

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Measuring kidney transplantation activity

Medindo a atividade de transplantação renal

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ABSTRACT

Kidney allocation from cadaveric donors must balance two main principles: medical utility and justice. The principle of medical benefit is gauged by maximizing efficiency in the use of organs and the principle of justice by its effectiveness, ensuring that all patients have a reasonable opportunity of transplantation. In this paper we present some metrics that, when applied to candidates for kidney transplantation, will help in the best judgment defining kidney allocation systems. Knowing the prevalence and incidence (per year, per million inhabitants) of kidney transplant, candidates demographic factors, such as: sex, age groups, and socioeconomic status; as well as clinical and immunological characteristics: blood group, Panel Reactive Antibody values, Body Mass Index, type of dialysis, cause of renal failure, and comorbidities; allows for an objective comparison of allocation programmes. The waiting time for transplantation should be measured as the median time between the start of dialysis and transplantation of wait-listed patients each year. By using the Cox regression analysis, with time on dialysis for transplantation as a dependent variable and clinical, socio-demographic factors as independent variables, we will shed light on which characteristics affect the access to transplantation.

Key-words: Kidney allocation; kidney transplantation; metrics; waiting time to transplantation.

RESUMO

A distribuição de rins de dador cadáver deve equilibrar dois princípios fundamentais: a utilidade médica e a justiça. O princípio do benefício médico é aferido através da maximização da eficiência no uso dos órgãos, enquanto que o princípio da justiça visa garantir que todos os candidatos tenham uma oportunidade razoável de transplante. Neste artigo, apresentamos algumas métricas que, quando aplicadas a candidatos a transplante de rim, ajudarão na melhor avaliação e definição de sistemas de distribuição de rins. Conhecer a prevalência e incidência (por ano e por milhão de habitantes) dos transplantes de rim, fatores

demográficos dos candidatos, tais como: sexo, faixa etária e nível socioeconómico; bem como as suas características clínicas e imunológicas: grupo sanguíneo, os valores do painel reativo de anticorpos, índice de massa corporal, tipo de diálise, a causa da insuficiência renal e co-morbilidades; permite uma comparação objetiva de programas distribuição. O tempo de espera para o transplante deve ser medido como a mediana do tempo entre o início da diálise e o transplante dos doentes em lista de espera em cada ano. Através da análise de regressão de Cox, com o tempo em diálise para transplante como variável dependente e os fatores clínicos e sócio-demográficos como variáveis independentes, é possível identificar as características que afetam o acesso ao transplante.

Palavras-chave: Alocação do enxerto renal; métricas; tempo de espera para transplante; transplantação renal.

INTRODUCTION

The survival of renal transplanted patients, both at short- and long-term, is better than that of the patients on the waiting-list[1]. This survival benefit of transplanted patients when compared with dialyzed patients is independent of age and the presence of co-morbidities[2] and persists even in patients over 60 years of age.

In the European Union, approximately 360,000 patients currently receive some form of renal replacement therapy and of these, only one third live with a transplanted kidney[3].

The transplanted patient's risk of death compared with patients on the waiting-list varies with time. In the first weeks, the risk is higher (which is expected and is associated with the surgical procedure itself) and it reduces near the end of the first year of transplantation. This risk reduction in the long-term occurs in all subgroups of patients with regard to age, sex, ethnicity and cause of renal failure[4].

Cardiovascular disease is very common among patients waiting for a kidney transplant and the risk of the disease increases during the waiting time[5].

Dialysis favours the development of cardiovascular disease, osteoarthritis, anaemia and other diseases over time. Time on dialysis has proved to have a negative impact on the outcome of the transplant. Furthermore, transplantation is capable of correcting cardiovascular disease attributed to dialysis[6]. The protective effect from cerebrovascular events attributed to the transplant when compared with dialysis is even more evident when compared with return to dialysis after loss of the organ. There is evidence of increased risk of morbidity and mortality after graft loss[7].

In this paper, we sought to identify factors that affect access to kidney transplantation and describe the best metrics that can characterize these factors.

KIDNEY ALLOCATION

Kidney allocation on the basis of human leukocyte antigens (HLA) compatibility is a controversial topic. On one hand, this type of system is less equitable for patients in the access to transplantation but, on the other, it ensures better results for the outcome of the transplant[8].

Human leukocyte antigens compatibility between donor and recipient has a major impact on recipients' sensitization, which can be problematic if they need to be re-transplanted[9].

There are socio-demographic and clinical factors associated with waiting times for deceased donor kidney transplantation, such as age, blood group or sensitization against HLA. The identification of these factors allows us to estimate waiting times for transplant candidates, and so, better advise patients of the merits of living donation, especially those who may have longer waiting times[10].

A kidney allocation programme must take into account factors related to the utility of transplantation: optimal HLA match for patients in whom it is most

relevant (children and youth); prioritization of children; minimization of ischaemia times and correlation of life expectancy of the graft with the recipient's life expectancy (similar ages). Also factors related to justice, such as: reduction of waiting times, greater equity of access for patients regardless of their ethnicity, blood group, HLA homozygosity and geographic location[11].

The United Network of Organ Transplantation (UNOS) is a private non-profit organization in the USA responsible for coordinating and controlling the procedures for organ allocation. This organization considers that the distribution must be made in order to balance the principles of medical utility and justice. The value of medical benefit is guaranteed by maximizing efficiency in the use of organs, and the value of justice is guaranteed by ensuring that all patients have a reasonable opportunity to be transplanted[12]; nevertheless, kidney allocation system by UNOS is mostly based on time on dialysis.

As in the UNOS kidney allocation system, in many other countries, Portugal included[13], distribution of organs is mainly based on the candidates' time on dialysis. Often this method of distribution does not take into account both the expected lifespan of patients (whether transplanted or remaining on dialysis), and the quality of the organs to distribute[14].

A transparent policy based on efficiency criteria means that the organs would be transplanted into patients who would derive a greater benefit from them. Criteria of justice in access to transplantation conflict with the efficiency criteria. In the United Kingdom, in 2006, a revision of the laws governing organ allocation gave higher priority to candidates with longer waiting times and younger candidates, to the detriment of HLA compatibility criteria[15]. The English kidney allocation system is a points-system based on time on dialysis, HLA compatibility, age difference between donor and recipient and geographical proximity in an attempt to allocate organs in a fair way reducing the weight of HLA compatibility and increasing the importance of time on dialysis[16]. Eurotransplant (ET), an international organization located in Leiden, in the Netherlands, and founded in 1967 by Prof. J. von Rood, is the largest organization of sharing in Europe with seven member countries: Austria, Croatia, Germany, Luxembourg, Slovenia, the Netherlands and Belgium[17]. The ET organ allocation system is based on 5 pillars: objectivity, transparency, clinical priority, compatibility and balance between countries. Its scoring system for organ distribution also takes into account the candidate's time on dialysis.

TRANSPLANT OUTCOME

Several factors can influence kidney transplant outcome, for example: HLA compatibility, ischaemia time, duration of dialysis and the ages of donor and recipient[11].

If the candidate with the highest probability of finding a donor with a high number of HLA compatibilities must wait for that donor; those candidates for which the probability of finding a donor with few HLA compatibilities is very low (rare HLA) should be transplanted independently of the number of HLA mismatches[18].

When compared to non-O candidates, ABO blood type O candidates wait longer for transplantation and more often are removed from the waiting list before transplantation. The use of pairs with blood type O donors and non-O recipients in a donor exchange programme, as well as a transplant programme of ABO incompatible patients (organ transplantation of A2 donors with low titers of anti-A recipients) certainly enhance the chances of these blood type O transplant candidates[19].

The advantages of transplant outcome as far as reducing waiting times for transplantation should be actively sought. Programmes, such as the Eurotransplant Senior Program, can be replicated in other countries and eventually extended to any and all candidates of 60 years of age facilitating a reduction in their waiting time[20]. Transplant candidates who start dialysis in advanced age (› 65 years) are less likely to be transplanted[16]. About half of transplant candidates over 60 years of age quite likely die while waiting for a kidney transplant from a deceased donor[21].

According to UNOS, Expanded Criteria Donors (ECD) are defined as donors older than 60 or older than 50 years with at least two of the following criteria: creatinine › 1.5 mg/dl, history of hypertension or stroke as cause of death. Transplant candidates deemed 'extra risk' are defined as being older than 60 or older than 50 with at least one of the following: coronary artery disease, peripheral arterial disease,

or diabetes[20]. Prolonged waiting time for a transplant in older patients negatively affects both patient survival as well as the graft itself. This problem can only be circumvented by requisition of living donors or with the use of ECD to reduce waiting times[22].

Transplant recipients of an ECD have an increased risk of organ rejection compared to recipients of optimal donors, however, the former still have a survival benefit compared with patients on dialysis[23]. This benefit of transplantation with ECD is directly proportional to the increase in waiting time on dialysis[24].

At risk transplant candidates have a very poor prognosis while awaiting an organ from a standard donor which is further worsened by increased duration of dialysis; meanwhile, the healthiest candidates may benefit from waiting longer for a standard donor instead of being transplanted with an ECD[6].

It also stands to reason that post-circulatory death donors can be an appropriate and valuable contribution to increase the number of organs available for transplantation. The use of these donors for transplantation translates into augmented opportunities for transplant candidates and reduction of waiting times[25].

HLA

The anti-HLA antibodies are mainly developed in patients undergoing blood transfusions, pregnancies or previous transplants. Patients with high levels of anti-HLA antibodies (hypersensitised) have their transplantation rates drastically reduced due to the immunological barrier of an increased risk of rejection[26]. Hypersensitized patients are fated to spend long periods of time on dialysis[27] which in itself is a risk factor for patient and graft survival.

Panel reactive antibody (PRA) is defined as the percentage of an HLA antigen panel that reacts with the serum of the patient and may reflect the percentage of donors expected to react with patient sera[28]. This positive crossmatch probability can also be represented by the calculated PRA (cPRA) which is based on HLA antigens to which the patient is sensitized[29]. The PRA or the cPRA are the only immunity parameters that give prospective information about the possible response of a patient to an organ transplant.

Hypersensitised patients have two major drawbacks: 1) Lower probability of finding a donor with a negative crossmatch and, therefore, tendency toward longer waiting time for a transplant, and 2) When transplanted, even with a negative crossmatch, higher risk of rejection episodes and graft lost[30].

The options of renal transplant candidates sensitised to a large number of HLA antigens are limited. The Australian experience shows that the distribution of living kidney donors on the basis of acceptable mismatches is an effective way to identify donors for some hypersensitised candidates within a relatively short space of time[31]. The concept of acceptable mismatches (AMM's) assumes that antibody recognition of epitopes in HLA molecules occurs in certain areas of the HLA epitopes and that some of these are similar in different HLAs. The HLA Matchmaker algorithm validated by Eurotransplant uses the functional epitopes on areas of molecules of class I and II HLA[32].

The anti-HLA antibodies can be identified by microlymphocytotoxicity – complement dependent cytotoxicity (CDC), enzyme-linked immunosorbent assay (ELISA), Luminex, and methods for flow cytometry using a panel of known antigens, beads or HLA class I and II cells[28].

With the development of laboratory and diagnostic techniques to determine the immune humoral response, it is possible to identify which anti-HLA antibody is injurious to the patient, thereby increasing the likelihood of success of a future transplant[33]. Although very sensitive solid phase tests have been available and in use for several years, their impact on the prediction of successful transplantation is controversial, particularly when it is necessary to identify right cut-off values for the most sensitive tests, such as the positivity of the single antigen test or in the definition of unacceptable anti-HLA antibodies[33].

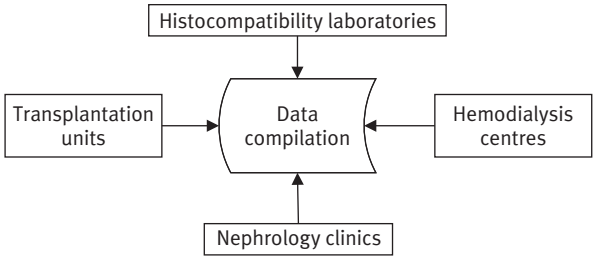
METHODS

The population in study consists of patients that have been or still were present on the kidney transplant waiting list. Data must be collected from several sources that manage these patients, i.e., nephrology clinics, haemodialysis facilities, histocompatibility laboratories and transplantation centres (Fig. 1).

Immunological data: presence of anti-HLA antibodies, ABO blood type, maximum percentage of PRA; clinical and biological data: presence of comorbidities, body mass index, date of first RRT, date of registration on the waiting list for registered patients and date of transplantation for transplanted patients, dialysis modality and serum albumin; social and demographic data: age, gender, the distance between the patient's residence and the transplantation centre calculated in kilometres, ethnicity, income and education; these are some examples of the data that must be collected and analysed.

Figure 1

Data origin and flow of kidney transplant candidates



Here we have described some statistics that should be used routinely in order to form a systematic picture of end-stage renal disease (ESRD) patients.

Incidence and prevalence of Renal Replacement Therapy (RRT) are two of the most common metrics used to characterize a population of ESRD patients. The unadjusted RRT incidence per million age-related population (p.m.a.r.p) is defined as the number of new patients on RRT in a year per age group (e.g. ≥ 65 years of age) divided by the mid-year general population in that age group. The unadjusted prevalence of RRT p.m.a.r.p. is defined as the number of patients receiving RRT by or on the thirty-first of December of each year, per age group, divided by the mid-year general population in that age group.

For instance, point prevalence counts (candidates alive on the waiting list for kidney transplant by or on December thirty-first of each year) and new candidate counts by year. Organ waiting list numbers of all active patients compared on December thirty-first of each year will allow us to analyse efficiency of the policies applied to the management of waiting lists. Time on dialysis applies to the time that transplant recipients were on dialysis until transplantation and median waiting time to transplantation can be defined as the time on dialysis did it take before 50% of the waiting list patients in a given year received a transplant[13,34].

The number of performed transplants per million population (p.m.p.) must be examined for each year combining different age groups. The number of performed transplants p.m.p. per year is defined as the number of transplants performed in a year divided by the mid-year general population. Statistics on potential donor numbers, effective donor numbers, referral patterns by month, cause of death, type of donor, donor age, reason for denial of donation, mean organ yield per donor, percentage of effective donors per organ, number of transplants per organ, number of organ transplanted per million inhabitants can explain variations on organ waiting lists.

Survival rates calculated with life tables and actuarial methods and curves compared with Mantel-Hanzel test will allow us to calculate patients' and graft survival including death with a functioning graft, as well as graft loss; this data will enable us to compare existing kidney allocation programmes and their merits. Other factors that can influence transplant outcome can and must be identified.

A Cox proportional hazards regression, left-truncated for time since start of dialysis, can be used to assess time to kidney transplantation, with either a living or cadaveric kidney donor. Using a Cox multivariate hazard regression model with a time-dependent covariate, access to kidney transplantation can be analysed and modifiable factors that influence access can be identified[35].

CONCLUSION

Kidney transplantation is the preferred treatment for many ESRD patients; however, the small number of organs for transplantation does not allow all patients to have access to this scarce resource. Pooling of transplant data grouping pathologies leading to terminal renal disease will be valuable to clarify HLA matching role and adapt different allocation criteria and different transplant strategies to different patient groups.

For this reason it is of utmost importance to define objective and systematic metrics with clinical utility that allow making informed decisions when health policies are established for the distribution of an organ.

Conflict of interest statement: None declared

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