Risk Factors of Rejection in Renal Transplant Recipients

Subjects: Transplantation

Contributor: Arianeb Mehrabi

Kidney transplantation (KTx) is the treatment of choice for end-stage renal diseases (ESRD). Multiple factors influence graft rejection after KTx. Pre-operative factors affecting graft function and survival include donor and recipient characteristics such as age, gender, race, and immunologic compatibility. In addition, several peri- and post-operative parameters affect graft function and rejection, such as cold and warm ischemia times, and post-operative immunosuppressive treatment. Exposure to non-self-human leucocyte antigens (HLAs) prior to transplantation up-regulates the recipient's immune system. A higher rate of acute rejection is observed in transplant recipients with a history of pregnancies or significant exposure to blood products because these patients have higher panel reactive antibody (PRA) levels. Identifying these risk factors will help physicians to reduce the risk of allograft rejection, thereby promoting graft survival.

kidney transplantation rejection recipient

1. Introduction

Kidney transplantation (KTx) improves the patients' quality of life and life expectancy compared with other renal replacement therapies such as dialysis. Furthermore, advances in immunosuppressive therapies have substantially improved KTx outcomes [1]. Although long-term graft outcomes have improved noticeably through recent decades, survival of KTx recipients is fourfold lower than in individuals without end-stage renal diseases (ESRD). Graft rejection is one of the main causes of graft loss after KTx, so understanding the factors affecting graft rejection is important for promoting graft survival.

Multiple factors influence graft rejection after KTx [2][3]. Pre-operative factors affecting graft function and survival include donor and recipient characteristics such as age, gender, race, and immunologic compatibility [4][5]. In addition, several peri- and post-operative parameters affect graft function and rejection, such as cold and warm ischemia times, and post-operative immunosuppressive treatment [6][7][8]. Identifying these risk factors will help physicians to reduce the risk of allograft rejection, thereby promoting graft survival.

2. Donor-Related Factors

2.1. Donor Gender

Using the large Collaborative Transplant Study database, Zeier et al. showed that death-censored graft survival and five-year graft survival were significantly lower in patients receiving grafts from female donors [9]. The rate of graft loss among patients receiving organs from female donors was noticeably higher during the first five years after KTx [10]. However, a retrospective survival analysis of 766 KTx patients showed comparable graft survival rates between organs from male and female donors [11]. In terms of short-term outcomes, some studies have shown that grafts from female donors have fewer nephrons and are more susceptible to immunosuppressive-induced nephrotoxicity than grafts from male donors [12]. However, the protective and stimulatory effects of female hormones, such as estradiol, improve graft function and reduce cellular infiltration, thereby providing better long-term outcomes [12]. These findings are supported by a prospective study, which suggested a higher risk of acute rejection when grafts were transplanted from a female donor, and a higher risk of complete graft loss after five years when grafts were transplanted from a male donor.

2.2. Donor Age

Donor age is a better predictor of KTx outcome than donor gender. Allografts from older donors have a higher risk of post-transplant complications, delayed graft function, acute rejection, and graft failure [13]. Transplantation from both very young and very old donors is a risk factor for poor transplant outcome [9]. The risk ratio was higher when kidneys were donated by younger female donors (16 to 45 years) than by older female donors (>45 years) and then transplanted into male recipients [14].

2.3. Living versus Deceased Donor

Organs procured from living donors provide several benefits by reducing warm and cold ischemia times and the immunological characteristics can be precisely evaluated before transplantation [14]. Living donor grafts reduced the rate of short-term morbidity and mortality, and increased graft survival. Living donors with diabetes mellitus and hypertension are disqualified from donating organs because of the increased risk for ESRD [15]. Immunological activation is also lower in living donors; 53% of deceased-donor renal allografts had increased neutrophil infiltration compared with 0% of living-donor grafts. However, there are still reasons to consider deceased-donor transplantation. The risk of mortality is 68% lower in deceased-donor kidney recipients than in similar patients who do not receive a transplant [14].

2.4. Non-Marginal and Marginal Donors

Extended donor criteria were defined by Port et al. in 2002. However, the marginal kidney donor criteria remain unclear, despite progressive expansion of transplant waiting lists [16]. Physicians mostly might not follow the defined or their own center's criteria for organ procurement, particularly regarding circulatory death of the donor. In the literature, different criteria have been suggested for definition of marginal kidney donors. Kidney donors with brain dead were considered marginal, if were aged >60 years, or >50 years with any of the following conditions: (1) hypertension, (2) cerebro-vascular cause of brain death or (3) pre-retrieval serum creatinine (SCr) level > 1.5 mg/dL, with a degree of glomerulosclerosis >15% and prolonged cold ischemia. Additionally, marginal living donors are considered to be older (>70 years old), obese (>35 kg/m^2), and have hypertension, diabetes, nephropathies,

and kidney cysts [17]. The one-year graft function was comparable between organs obtained from marginal and non-marginal donors, but rates of interstitial fibrosis/tubular atrophy and acute rejection were higher in organs from marginal donors. Dual-kidney transplant from marginal donors into a single recipient increases the available organs and prevents disqualification of marginal organs. Recent studies have shown a diminished risk of adverse effects after KTx from marginal donors when the CIT was short [18].

3. Recipient-Dependent Factors

3.1. Recipient Race

African American populations are at a higher risk of suboptimal renal transplantation [19]. According to several trials and large transplant cohorts, African American patients have higher rates of acute rejection and early graft failure compared with Caucasians [19].

3.2. Recipient Age

A younger age of recipients is associated with an elevated risk of suboptimal allograft outcomes. The absorption, delivery, and excretion of immunosuppressive drugs is different in pediatric and adult patients, and pediatric patients have a higher relative risk of acute rejection [20][21]. Current immunosuppression and standardized induction therapy have reduced the probability of acute graft rejection in pediatric patients and have increased the long-term allograft survival [21][22].

3.3. Concomitant Diseases

Concomitant diseases, such as infectious disease, coagulopathies, and malignancies can affect post-KTx outcomes [23]. The leading cause of death after KTx is cardiovascular disease, particularly in patients suffering from autoimmune diseases such as lupus erythematous. Antiphospholipid antibodies and cardiovascular disease should be evaluated before KTx, with due attention to the increased risk of intravascular thrombosis and the recurrence of lupus nephritis.

3.4. Re-Transplantation

Acute rejection rates are high (from 33% to 69%) among renal re-transplant patients [24], and there are growing numbers of patients awaiting re-transplantation. Managing these patients is challenging because the rate of hyperimmunity increases with positive crossmatch KTx [24]. In addition, human leucocyte antigens (HLA) mismatch could lead to increase rate of acute rejection among this group of patients [25]. Previously, presence of repeated HLA antigen mismatched from the first transplant was associated with rapid and early alloimmune damage as well as graft loss, by rechallenging the immune system of recipient. However, recent studies have showed that patients with repeated HLA antigen mismatched class II, who are sensitized or nephrectomized have higher tendency to develop rejection and graft loss after re-transplantation. Although re-transplantation recipients are at risk of delayed

graft function due to early acute rejection (prior sensitization), re-transplantation still offers considerable benefits [26][27].

4. Donor-Recipient Compatibility

4.1. ABO Blood Types

The ABO blood typing system is based on a group of antigens located on the erythrocyte surface. These antigens induce antibody development upon exposure to a foreign host immune system. Incompatibility with the main blood group antigens (A, B, AB, and A1) is clinically important because of naturally circulating immunoglobulin (Ig)M and IgG antibodies. Transplantation between individuals who are not blood-group-compatible results in hyperacute rejection, and this incompatibility has traditionally been considered a contraindication to transplantation. Because of the organ shortage, pre-transplant splenectomy, plasmapheresis, and immunosuppression have been performed to overcome compatibility issues [28].

4.2. Human Leucocyte Antigen Typing

Exposure to non-self HLAs increases the risk of graft rejection and early graft failure. Pre-transplantation sensitivity to HLA antigens in the recipient stimulates clonal proliferation of lymphocytes and antibodies to donor tissue [29]. Graft survival in patients with peak or current panel reactive antibody (PRA) level ≥ 50% is half that of patients with a PRA level <50% [30][31]. This consequence is exacerbated in re-transplant recipients whose survival of the graft declines by an estimated rate of 10% [32]. Transplant patients with a history of abortions or extensive exposure to blood products have a greater risk of acute rejection, which might be associated with peak or elevated PRA levels [32]. However, the current standardization of single antigen has diminished the popularity of the PRA. It has been shown that a complement-dependent lymphocytotoxic crossmatch (CDC-XM) test can predict the possible immunological risks in KTx. Therefore, this method has been established as the gold standard test for graft allocation and could be utilized before renal transplantation. Nevertheless, this test could not detect specifically the preexisting donor-specific HLA antibodies (HLA-DSA). In this regard, new methods with solid-phase assays helped us to detect HLA antibodies more sensitive and specific [33]. As a new method, the analysis of serum with the beads covered by a single HLA antigen (single antigen bead-SAB) has been developed to improve the sensitivity of HLA antibody detection to prevent graft rejection [34].

5. Perioperative Factors

Ischemia/Reperfusion Injury

Ischemia/reperfusion injury is one of the most common complications after renal transplantation. It is influenced by the warm ischemia time (WIT) and CIT. Adenosine triphosphate production is decreased in tubular cells because of oxygen deficiency after prolonged periods of ischemia, which alters enzyme activity. After reperfusion, free-oxygen radical production induces local inflammation and stimulates the complement and coagulation cascade. While

preservation solutions and cold temperature maintain electrolyte balance by diminishing the rate of metabolism in the tubular cells, prolonged ischemia increases anaerobic respiration [35]. Ischemia/reperfusion injury delays graft activity, which is characterized by acute tubular necrosis.

Several studies have shown that prolonged CIT and WIT increases graft alloreactivity and acute graft rejection [36]. The CIT and WIT has the greatest impact on the survival of grafts from deceased donors and marginal donors, so reducing the ischemia time will improve the longevity and utility of these marginal donor kidneys [37]. Prolonged CIT increases the humoral antibody response [38].

6. Post-Transplant Factors

6.1. Delayed Graft Function

The frequency of delayed graft function varies from 4 to 10% in living donor transplants and from 5 to 50% in deceased-donor kidney transplants. Although the association between delayed graft function and rates of rejection has not been yet clearly described by the studies, it has been suggested that early detection of patients at risk of delayed graft function will allow early post-operative hemodynamic and immunosuppressive treatment to promote graft function [39]. T-cell-depletion (e.g., using calcineurin inhibitors) might improve perfusion and recovery of the graft by delaying nephrotoxic immunosuppression [39][40][41].

6.2. Immunosuppressive Regimen

New immunosuppressive regimens are accompanied with better monitoring and desensitization strategies have been utilized to extend the donor criteria [42][43]. Currently, immunosuppressive agents can be classified into three categories: “induction agents”, “maintenance therapy” and “treatment for rejection”. Induction agents are typically polyclonal antibodies (anti-thymocyte globulins) and interleukin (IL)-2 receptor antagonists (basiliximab). New induction agents include alemtuzumab, efalizumab and alefacept. The four drug classes that comprise maintenance regimens include calcineurin inhibitors (cyclosporine and tacrolimus), mTOR inhibitors (sirolimus and everolimus), antiproliferative agents (azathioprine and mycophenolic acid), and corticosteroid. Nowadays, the current standard of care for kidney transplant immunosuppression is a calcineurin inhibitor–based immunosuppressive regimen with tacrolimus and mycophenolate [44].

7. Conclusions

Graft rejection and graft loss after KTx depend on multiple factors. These risk factors can be categorized into donor-related, recipient-related, donor-recipient compatibility, and peri- and post-operative factors. Female gender, early and advanced ages, deceased donors, and concomitant diseases such as hypertension and diabetes mellitus are the main donor-related risk factors for graft rejection and graft loss. In addition, prolonged CIT might be associated with a higher risk of ischemia/perfusion injury that influences long-term graft function and survival. African American KTx recipients are vulnerable to acute rejection and graft loss. Furthermore, old age, obesity,

underlying disease, prolonged dialysis, and re-transplantation are the main recipient-related risk factors that increase the probability of graft loss after KTx. Identifying these risk factors helps clinicians to avoid sub-optimal organ allocation and improves the short- and long-term outcomes of KTx. Development of new biomarkers, meticulous surgical techniques, and intensive post-transplant care, together with due attention to these risk factors, might help determine the risk of graft loss, optimize graft allocation, and improve KTx outcomes.

References

1. Lim, M.A.; Kohli, J.; Bloom, R.D. Immunosuppression for kidney transplantation: Where are we now and where are we going? Transplant. Rev. 2017, 31, 10–17.
2. Lemoine, M.; Beauport, D.T.; Lobbedez, T.; Choukroun, G.; de Ligny, B.H.; Hazzan, M.; Guerrot, D.; Bertrand, D. Risk factors for early graft failure and death after kidney transplantation in recipients older than 70 years. Kidney Int. Rep. 2019, 4, 656–666.
3. Foroutan, F.; Friesen, E.L.; Clark, K.E.; Motaghi, S.; Zyla, R.; Lee, Y.; Kamran, R.; Ali, E.; De Snoo, M.; Orchanian-Cheff, A.; et al. Risk factors for 1-year graft loss after kidney transplantation: Systematic review and meta-analysis. Clin. J. Am. Soc. Nephrol. 2019, 14, 1642–1650.
4. Naderi, G.; Azadfar, A.; Yahyazadeh, S.R.; Khatami, F.; Aghamir, S.M.K. Impact of the donor-recipient gender matching on the graft survival from live donors. BMC Nephrol. 2020, 21, 5.
5. Schold, J.D.; Augustine, J.J.; Huml, A.M.; Fatica, R.; Nurko, S.; Wee, A.; Poggio, E.D. Effects of body mass index on kidney transplant outcomes are significantly modified by patient characteristics. Am. J. Transplant. 2021, 21, 751–765.
6. Cavaleri, M.; Veroux, M.; Palermo, F.; Vasile, F.; Mineri, M.; Palumbo, J.; Salemi, L.; Astuto, M.; Murabito, P. Perioperative goal-directed therapy during kidney transplantation: An impact evaluation on the major postoperative complications. J. Clin. Med. 2019, 8, 80.
7. Gao, Y.; Yu, X.; Feng, X.; Zhang, Y. Factors related to postoperative prognosis of kidney transplant recipients: A retrospective analysis of 127 patients. Front. Lab. Med. 2018, 2, 63–67.
8. Lim, J.-H.; Cho, J.-H.; Jung, H.-Y.; Choi, J.-Y.; Park, S.-H.; Kim, Y.-L.; Kim, H.-K.; Huh, S.; Yoo, E.S.; Won, D., II; et al. Excellent outcome after desensitization in high immunologic risk kidney transplantation. PLoS ONE 2019, 14, e0222537.
9. Zeier, M.; Döhler, B.; Opelz, G.; Ritz, E. The effect of donor gender on graft survival. J. Am. Soc. Nephrol. 2002, 13, 2570–2576.
10. Ge, F.; Huang, T.; Yuan, S.; Zhou, Y.; Gong, W. Gender issues in solid organ donation and transplantation. Ann Transpl. 2013, 18, 14.
11. Chen, P.-D.; Tsai, M.-K.; Lee, C.-Y.; Yang, C.-Y.; Hu, R.-H.; Lee, P.-H.; Lai, H.-S. Gender differences in renal transplant graft survival. J. Formos. Med. Assoc. 2013, 112, 783–788.

12. Puoti, F.; Ricci, A.; Nanni-Costa, A.; Ricciardi, W.; Malorni, W.; Ortona, E. Organ transplantation and gender differences: A paradigmatic example of intertwining between biological and sociocultural determinants. Biol. Sex Differ. 2016, 7, 35.
13. Akoh, J.A.; Mathuram Thiyagarajan, U. Renal transplantation from elderly living donors. J. Transplant. 2013, 2013.
14. Saat, T.C.; van den Akker, E.K.; IJzermans, J.N.; Dor, F.J.; de Bruin, R.W. Improving the outcome of kidney transplantation by ameliorating renal ischemia reperfusion injury: Lost in translation? J. Transl. Med. 2016, 14, 20.
15. Lentine, K.L.; Segev, D.L. Health outcomes among non-Caucasian living kidney donors: Knowns and unknowns. Transpl. Int. 2013, 26, 853–864.
16. De Rosa, P.; Muscogiuri, G.; Sarno, G. Expanded criteria donors in kidney transplantation: The role of older donors in a setting of older recipients. Int. Sch. Res. Not. 2013, 2013, 301025.
17. Cantarelli, C.; Cravedi, P. Criteria for living donation from marginal donors: One, no one, and one hundred thousand. Nephron 2019, 142, 227–232.
18. Maggiore, U.; Cravedi, P. The marginal kidney donor. Curr. Opin. Organ Transplant. 2014, 19, 372–380.
19. Dharnidharka, V.R.; Seifert, M.E. Kidney transplant results in children: Progress made, but blacks lag behind. Kidney Int. 2015, 87, 492–494.
20. Dharnidharka, V.R.; Lamb, K.E.; Zheng, J.; Schechtman, K.B.; Meier-Kriesche, H.U. Across all solid organs, adolescent age recipients have worse transplant organ survival than younger age children: A US national registry analysis. Pediatr. Transplant. 2015, 19, 471–476.
21. Mehrabi, A.; Golriz, M.; Khajeh, E.; Ghamarnejad, O.; Kulu, Y.; Wiesel, M.; Müller, T.; Majlesara, A.; Schmitt, C.; Tönshoff, B. Surgical outcomes after pediatric kidney transplantation at the University of Heidelberg. J. Pediatr. Urol. 2019, 15, 221.e1–221.e8.
22. Pratschke, J.; Dragun, D.; Hauser, I.A.; Horn, S.; Mueller, T.F.; Schemmer, P.; Thaiss, F. Immunological risk assessment: The key to individualized immunosuppression after kidney transplantation. Transplant. Rev. 2016, 30, 77–84.
23. Mehrabi, A.; Golriz, M.; Maier, J.; Fonouni, H.; Garoussi, C.; Hafezi, M.; Fard, N.; Faridar, A.; Rezaei, N.; Wiesel, M.J.E.; et al. Long-Term Follow-Up of Kidney Transplant Recipients with Polycystic Kidney Disease. Exp. Clin. Transplant. Off. J. Middle East Soc. Organ Transplant. 2015, 13, 413–420.
24. Salvadori, M.; Bertoni, E. Renal transplant allocation criteria, desensitization strategies and immunosuppressive therapy in retransplant renal patients. J. Nephrol. 2012, 25, 890.

25. Santos, A.H.; Casey, M.J.; Womer, K.L. Analysis of risk factors for kidney Retransplant outcomes associated with common induction regimens: A study of over twelve-thousand cases in the United States. J. Transplant. 2017, 2017, 8132672.
26. Campos, A.; Malheiro, J.; Tafulo, S.; Santos, S.; Dias, L.; Martins, L.S.; Almeida, M.; Pedroso, S.; Henriques, A.C.; Cabrita, A. Increase of allosensitization after a kidney graft failure: Predictors and effect on retransplantation outcomes. Nefrología 2017, 37, 397–405.
27. Zhu, L.; Fu, C.; Lin, K.; Wang, Z.; Guo, H.; Chen, S.; Lin, Z.; Chen, Z.; Chen, G. Patterns of early rejection in renal retransplantation: A single-center experience. J. Immunol. Res. 2016, 2016, 2697860.
28. Song, G.W.; Lee, S.G.; Hwang, S.; Kim, K.H.; Ahn, C.S.; Moon, D.B.; Ha, T.Y.; Jung, D.H.; Park, G.C.; Kim, W.J.; et al. ABO-incompatible adult living donor liver transplantation under the desensitization protocol with rituximab. Am. J. Transplant. 2016, 16, 157–170.
29. Süsal, C.; Opelz, G. Current role of human leukocyte antigen matching in kidney transplantation. Curr. Opin. Organ Transplant. 2013, 18, 438–444.
30. Mehra, N.; Baranwal, A.K. Clinical and immunological relevance of antibodies in solid organ transplantation. Int. J. Immunogenet. 2016, 43, 351–368.
31. Opelz, G.; Süsal, C.; Ruhenstroth, A.; Döhler, B. Impact of HLA compatibility on lung transplant survival and evidence for an HLA restriction phenomenon: A collaborative transplant study report. Transplantation 2010, 90, 912–917.
32. Opelz, G.; Döhler, B. Multicenter analysis of kidney preservation. Transplantation 2007, 83, 247–253.
33. Lefaucheur, C.; Loupy, A.; Hill, G.S.; Andrade, J.; Nochy, D.; Antoine, C.; Gautreau, C.; Charron, D.; Glotz, D.; Suberbielle-Boissel, C. Preexisting donor-specific HLA antibodies predict outcome in kidney transplantation. J. Am. Soc. Nephrol. 2010, 21, 1398–1406.
34. Amico, P.; Hönger, G.; Mayr, M.; Steiger, J.; Hopfer, H.; Schaub, S. Clinical relevance of pretransplant donor-specific HLA antibodies detected by single-antigen flow-beads. Transplantation 2009, 87, 1681–1688.
35. Kalogeris, T.; Baines, C.P.; Krenz, M.; Korthuis, R.J. Cell biology of ischemia/reperfusion injury. Int. Rev. Cell Mol. Biol. 2012, 298, 229–317.
36. Kulu, Y.; Fathi, P.; Golriz, M.; Khajeh, E.; Sabagh, M.; Ghamarnejad, O.; Mieth, M.; Ulrich, A.; Hackert, T.; Müller-Stich, B.P.; et al. Impact of surgeon’s experience on vascular and haemorrhagic complications after kidney transplantation. Eur. J. Vasc. Endovasc. Surg. 2019, 57, 139–149.

37. Wong, G.; Teixeira-Pinto, A.; Chapman, J.R.; Craig, J.C.; Pleass, H.; McDonald, S.; Lim, W.H. The impact of total ischemic time, donor age and the pathway of donor death on graft outcomes after deceased donor kidney transplantation. Transplantation 2017, 101, 1152–1158.
38. Yong, C.; Hosgood, S.A.; Nicholson, M.L. Ex-vivo normothermic perfusion in renal transplantation: Past, present and future. Curr. Opin. Organ Transplant. 2016, 21, 301–307.
39. Sadeghi, M.; Daniel, V.; Lahdou, I.; Döhler, B.; Naujokat, C.; Renner, F.C.; Weimer, R.; Fonouni, H.; Mehrabi, A.; Schmidt, J.; et al. Association of pretransplant soluble glycoprotein 130 (sgp130) plasma levels and posttransplant acute tubular necrosis in renal transplant recipients. Transplantation 2009, 88, 266–271.
40. Mohty, M.; Bacigalupo, A.; Saliba, F.; Zuckermann, A.; Morelon, E.; Lebranchu, Y. New directions for rabbit antithymocyte globulin (Thymoglobulin®) in solid organ transplants, stem cell transplants and autoimmunity. Drugs 2014, 74, 1605–1634.
41. Zaza, G.; Tomei, P.; Granata, S.; Boschiero, L.; Lupo, A. Monoclonal antibody therapy and renal transplantation: Focus on adverse effects. Toxins 2014, 6, 869–891.
42. Filippone, E.J.; Farber, J.L. Humoral immune response and allograft function in kidney transplantation. Am. J. Kidney Dis. 2015, 66, 337–347.
43. Morath, C.; Zeier, M.; Döhler, B.; Opelz, G.; Süsal, C. ABO-incompatible kidney transplantation. Front. Immunol. 2017, 8, 234.
44. Wojciechowski, D.; Wiseman, A. Long-term immunosuppression management: Opportunities and uncertainties. Clin. J. Am. Soc. Nephrol. 2021, 16, 1264–1271.