ISSN 2220-3230 (online)

World Journal of *Transplantation*

Quarterly Volume 14 Number 1 March 18, 2024

Published by Baishideng Publishing Group Inc

World Journal of Transplantation

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INDEXING/ABSTRACTING

The *WJT* is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The *WJT*'s CiteScore for 2022 is 2.8 and Scopus CiteScore rank 2022: Transplantation is 23/51.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Transplantation

ISSN
ISSN 2220-3230 (online)

LAUNCH DATE
December 24, 2011

FREQUENCY
Quarterly

EDITORS-IN-CHIEF
Maurizio Salvadori, Sami Akbulut, Vassilios Papalois, Atul C Mehta

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https://www.wjgnet.com/2220-3230/editorialboard.htm

PUBLICATION DATE
March 18, 2024

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World Journal of Transplantation

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World J Transplant 2024 March 18; 14(1): 90149

DOI: 10.5500/wjt.v14.i1.90149

ISSN 2220-3230 (online)

EDITORIAL

Predicting outcomes after kidney transplantation: Can Pareto's rules help us to do so?

Fernando M Gonzalez, Francisca Gonzalez Cohens

Specialty type: Transplantation

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Markic D, Croatia; Tsoulfas G, Greece

Received: November 24, 2023
Peer-review started: November 24, 2023
First decision: November 30, 2023
Revised: January 13, 2024
Accepted: February 5, 2024
Article in press: February 5, 2024
Published online: March 18, 2024

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Abstract

Kidney transplantation is the best option for kidney replacement therapy, even considering that most of the times the grafts do not survive as long as their recipients. In the Khalil *et al*'s experience, published in this issue of the Journal, they analyze their second kidney graft survival and describe those significant predictors of early loss. This editorial comments on the results and put in perspective that most of the times, long-term graft survival could be inadvertently jeopardized if the immunosuppressive therapy is reduced or withdrawn for any reason, and that it could happen frequently if the transplant physician intends to innovate with the clinical care without proper evidence-based data.

Key Words: Kidney transplantation; Graft survival; Acute rejection; Interstitial fibrosis and tubular atrophy; Immunosuppression

Core Tip: Most of the times, kidney graft and recipient survivals do not match because of earlier graft failure. Apart from surgical or urological complications, the reason frequently is the appearance of donor-specific antibodies that mediate acute and chronic allograft damage because treating physicians intend to construct a tailor-made immunosuppressive therapy to each of their patients.

Citation: Gonzalez FM, Cohens FG. Predicting outcomes after kidney transplantation: Can Pareto's rules help us to do so? *World J Transplant* 2024; 14(1): 90149
URL: https://www.wjgnet.com/2220-3230/full/v14/i1/90149.htm
DOI: https://dx.doi.org/10.5500/wjt.v14.i1.90149

INTRODUCTION

Kidney transplantation is the best option for kidney replacement therapy, even considering that most of the times the grafts do not survive as long as their recipients. In those patients who experience the failure of the transplanted graft, it is still possible to perform a second, or even a third, transplant, because these organs still perform better than dialysis.

From a process management perspective, the best option to prolong the survival of those patients suffering from end-stage renal disease is to optimize dialysis quality while they are waiting for a transplant. Then, efforts should be taken to try to prolong the survival of their first kidney graft. The question is how to accomplish this last issue in the real world.

In 1906, Vilfredo Pareto postulated that 80% of the consequences come from 20% of causes[1] and from this perspective, the main causes of transplant failures should be few. In the Khalil *et al*'s experience[2], published in this issue of the Journal, they state that the first graft failed mainly because of two drivers: Primary non-function, explained by a recipient high body mass index ($P = 0.009$), and first graft loss because of acute rejection ($P = 0.025$). They also found that the survival of the second graft was reduced if the first one presented delayed graft function ($P = 0.008$ and $P < 0.001$, respectively), and also if the first graft underwent an acute rejection in the first year after the first transplant ($P = 0.053$) [2]. It is possible to think that Khalil *et al*[2] describe two main determinants that explain their failures: Rejection due to primary non-function, and immunological and inflammatory progressive damage to the graft. The first determinant may be explained by organ donor maintenance quality before organ harvesting, cold and warm ischemia times lasting too long, and not enough expertise of the implanting surgeons, which are expected to decrease as the procurement and surgical teams get experience, as it is observed in countries with high rates of kidney transplants[3]. Regarding the second determinant, it is more difficult to avoid having acute rejection episodes because there are several graft-recipient pair factors that intervene in their development, such as human leukocyte antigen mismatches, prior sensitization, immunosuppressive schemes, drug quality, and patient compliance.

Putting our focus on rejection, there are several experiences that analyze graft biopsies from failing kidney transplants with an intention to answer why those kidney grafts fail in the medium-to-long term. Most of the time, either graft rejection (9%-64%) or non-specific chronic injury or, in other words, interstitial fibrosis and tubular atrophy (IFTA, 24%-47%), is found[4]. It is also found that the rejection types and IFTA vary in parallel with the recipients' age and time after transplantation. But characteristically, there are more T-cell mediated rejections in the first 5 years after transplantation, and more antibody mediated rejections (ABMR) and IFTA after that period, while other causes of graft failure happen in young recipients[5].

By the way, what is IFTA? Is it synonymous with the term chronic allograft nephropathy (CAN)? At the end of last century, some experts thought that as grafts get older, they accumulate specific and non-specific damage resulting in sclerosis, increase in the interstitium collagen content, and tubular atrophy. This hypothesis was endorsed in a prospective protocol biopsy cohort of both kidney and pancreas transplantation in type 1 diabetics[6]. In fact, in this experience, Nankivell *et al*[6] showed that rejections predominated soon after transplantation, and both chronic damage and arteriolar hyalinosis predominated later on. Regrettably, a secondary hypothesis resulting from this experience was that calcineurin inhibitors (CNI), mostly cyclosporine, could be the culprit, which stimulated the transplant community to take non-evidence-based action to decrease or even withdraw the use of CNI. Some years later, we observed the appearance of donor-specific antibodies (DSA), and subsequently, of ABMR and graft losses as consequences. The histological morphology of these grafts reminded of the old CAN and, at the same time, the newer term IFTA, closing the circle of the main cause of the mismatch of kidney graft and transplanted recipient survivals, which is a chronic allograft rejection due to insufficient immunosuppression.

Nevertheless and sadly, this is not the whole story. Not providing enough immunosuppression could happen also because some doctors aspire to prescribe "patient-tailored therapies" based on their own perceptions/experiences, and believe more on that than on evidence-based medicine. There are several experiences, systematic reviews, and meta-analyses that show us that decreasing, or even worse, withdrawing any of the chronic immunosuppressive agents such as CNI, antiproliferatives, or steroids, is associated with the appearance of DSA, ABMR, and IFTA. These pathogenic mechanisms would be responsible for the decrease in graft survival and early graft loss[7-11].

Another explanatory variable could be frequent mycophenolate dose reduction, to even 50% below the standard and approved dose, occurring soon after transplantation, which is further associated with an increase in IFTA[12,13]. Moreover, this unintended and naïve behavior, which tries to ameliorate drug-related adverse events, could be accompanied with a decrease in CNI dose, resulting in less immunosuppression than prudence suggests[14].

CONCLUSION

From Khalil *et al*'s data[2], it is interesting to learn that for achieving a long kidney transplant survival, it is advisable to be prepared in different frontlines: (1) Having a well-trained team in order to surpass surgical technical difficulties, such as

primary non-function because of recipient's body mass index; and (2) prescribing a well-balanced immunosuppressive therapy to maximize patients' adherence, and minimize the probability of DSA, ABMR, IFTA, and of course, drug-related adverse effects, issues that may threaten the task of prolonging the survival of a first (or second) transplanted allograft, with the objective of matching it with the survival of the recipient blessed by that transplant.

FOOTNOTES

Author contributions: Gonzalez FM is main author and mostly wrote the manuscript; Cohens FG contributed to bibliographic searches and core idea construction, and edited the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Li L
L-Editor: Wang TQ
P-Editor: Zhao S

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