Mortality in renal transplant receptors – causes and related factors: integrative review

Mortalidade em receptores de transplante renal – causas e fatores relacionados: revisão integrativa

Willian Alburquerque de Almeida[1] • Adriano Menis Ferreira[2] • Marcelo Alessandro Rigotti[3]
Ana Lúcia Queiroz Bezerra[4] • Adaiele Lúcia Nogueira Viera da Silva[5] • Cristiane Chagas Teixeira[6]

RESUMO

Objetivos: Analisar as produções científicas sobre os fatores associados à mortalidade em pacientes submetidos ao transplante renal. Métodos: revisão integrativa realizada no período de janeiro de 2006 a julho de 2016, cujo levantamento bibliográfico foi por meio das bibliotecas eletrônicas: PubMed, SciELO, LILACS e Cochrane Library, totalizando 777 artigos. Após a leitura dos títulos e resumos, foi excluída toda publicação duplicada e as que não correspondiam aos critérios de inclusão. A amostra compôs-se de 21 estudos os quais responderam à questão de pesquisa. Resultados: A maior incidência de publicações deu-se em periódicos internacionais, predominando estudos de coorte com nível de evidência IV. Quanto às causas da mortalidade prevaleceu a cardiovascular. Os fatores associados a mortalidade foram relacionados a função cardiovascular, processos infecciosos, metabólicos, fisiológicos, nutricionais e estruturais. Conclusões: Recomenda-se melhorias no processo de avaliação e acompanhamento dos pacientes receptores de transplante renal.

Descritores: Transplante de rim; Mortalidade; Fatores de risco; Complicações pós-operatórias; Revisão.

ABSTRACT

Objectives: To analyze the scientific production on the factors associated with mortality in patients submitted to renal transplantation. Methods: An integrative review was carried out from January 2006 to July 2016, whose bibliographic survey was done through electronic libraries: PubMed, SciELO, LILACS and Cochrane Library, totaling 777 articles. After reading the titles and abstracts, all duplicate publications and those that did not meet the inclusion criteria were excluded. The sample consisted of 21 studies which answered the question of research. Results: The highest incidence of publications occurred in international journals, predominantly cohort studies with level of evidence IV. As for the causes of mortality, cardiovascular disease prevailed. The factors associated with mortality were related to cardiovascular function, infectious, metabolic, physiological, nutritional and structural processes. Conclusions: Improvements in the evaluation and follow-up of renal transplant recipients are recommended.

Descriptors: Kidney transplantation; Mortality; Risk factors; Postoperative complications; Review.

NOTA

[1]Enfermeiro. Mestre em Enfermagem, Doutorando em Saúde e Desenvolvimento na Região Centro-Oeste pela Universidade Federal de Mato Grosso do Sul/UFMS – Campo Grande (MS), Brasil. E-mail: will_tlcity@hotmail.com

[2]Enfermeiro. Doutor em Enfermagem, Professor Associado do Curso de Enfermagem da Universidade Federal de Mato Grosso do Sul/UFMS - Três Lagoas (MS), Brasil. E-mail: a.amr@ig.com.br

[3]Enfermeiro. Doutor em Ciências da Saúde. Professor Adjunto do Curso de Enfermagem da Universidade Federal de Mato Grosso do Sul/UFMS – Três Lagoas (MS), Brasil. E-mail: marcelosaude@hotmail.com

[4]Enfermeira. Doutora em Enfermagem. Professor Associado do Curso de Enfermagem da Universidade Federal de Goiás/UFG - Goiânia (GO), Brasil. E-mail: analuciaqueiroz@uol.com.br

[5]Enfermeira. Mestre em Enfermagem. Doutoranda em Saúde e Desenvolvimento na Região Centro-Oeste pela Universidade Federal de Mato Grosso do Sul/UFMS – Campo Grande (MS), Brasil. E-mail: adaiele@hotmail.com

[6]Enfermeira. Mestre em Enfermagem. Doutoranda em Enfermagem pela Universidade Federal de Goiás/UFG - Goiânia (GO), Brasil. E-mail: cc-teixeira@hotmail.com

Artigo baseado no Trabalho de Conclusão de Curso do curso de Especialização em Captação, Doação e Transplante de Órgãos e Tecidos pela Faculdade de Ciências da Saúde Albert Einstein, São Paulo (SP), 2016.

Não há conflitos de interesse

Trabalho realizado com apoio do Programa de Desenvolvimento Institucional do Sistema Único de Saúde (PROADI-SUS).

INTRODUCTION

Renal transplantation is considered the most appropriate and necessary modality of treatment for patients with chronic renal disease in the terminal stage, and the kidney is the most frequently transplanted organ[1]. In developed countries it is considered that the accumulated costs of renal transplantation are lower than those of dialysis treatments. In addition to providing better quality of life and greater patient survival compared to dialysis, transplantation also allows better cost-effectiveness[2-3].

The transplanted patient is constantly exposed to the risks of rejection and therefore dependent on the daily use of immunosuppressive drugs. In this way, he needs to have enough information to live with the chance of rejection and the new way of life, without the hemodialysis sessions[4].

With the progressive improvement of immunopharmacology and the quality of patient care, the risk of rejection and, consequently, a reduction in mortality rates after kidney transplantation were observed over time.

However, the predominance of cardiovascular risk factors such as: systemic arterial hypertension (SAH), diabetes mellitus (DM), dyslipidemias before renal transplantation are high[6] conferring a risk of death from cardiovascular disease of 3.5% to 5% every year[7]. Thus, cardiovascular diseases (CVD) remains the main cause of death after renal transplantation[5].

Infections are another important risk factor for mortality in renal transplant patients, since patients are highly susceptible to bacterial, fungal, and viral infections due to the use of immunosuppressants[8].

The study of the risk factors involved in the disease and treatment of the renal patient, provides information about the impact of the renal transplant care process.

In view of the importance of this context, it was analyzed the scientific production on the factors associated with mortality in adult patients submitted to renal transplantation.

METHOD

We opted for an integrative review of the scientific literature, whose method allows us to analyze and summarize existing research.9 In order to minimize possible flaws that could negatively influence the quality of the review. The following steps were taken in the elaboration of the study: 1) definition of the problem and formulation of the guiding question; 2) criteria for selection of the sample and search in the pertinent literature; 3) survey of the relevant data to be extracted from the selected studies; 4) full reading and careful analysis of included studies; 5) explanation of results, interpretation of data and presentation of knowledge review / synthesis[9-11].

The PICO strategy (acronym for patient, intervention, comparison, outcomes) was used to elaborate the integrative review research question. The use of this strategy to formulate the research question in the conduction of revision methods allows the identification of keywords, which help in locating relevant primary studies in the databases (12). Thus, the research question delimited was: "What causes and factors are related to mortality in the renal transplantation of adult patients?".

The first element of the strategy (P) consists of the transplanted kidney patient; the second (I), studies on the causes of mortality and related factors; and the fourth element (O) causes mortality and related factors. It should be noted that, depending on the review method, not all elements of the PICO strategy are used. In this integrative review, the third element, that is, the comparison, was not used.

The search for the studies occurred in July 2016, in the following electronic libraries: *Biomedical Literature Ciattions* and *Abstracts* (PubMed), Scientific Electronic Library Online (SciELO) and Cochrane Library and in the Latin American and Caribbean Literature database. Health Sciences (LILACS). The selected controlled descriptors were the following Health Sciences Descriptors (DeCS): "kidney transplantation"; "mortality"; "Risk factors", with the respective English translations, standardized in MeSH (Medical Subject Heading): "Kidney transplantation"; "Mortality"; "Risk factors".

Os termos foram combinados de diferentes formas para garantir busca ampla, cujos cruzamentos em todas as bases de dados foram realizados concomitantemente com os operadores booleanos *AND* e *OR* os três descritores e palavras na base de dados LILACS ("Transplante de rim") OR "Transplante de rim [Palavras] AND ("Mortalidade") OR "Mortalidade" [Palavras] AND ("Fatores de risco") OR "Fatores de risco" [Palavras]; cruzamentos concomitantemente com o operador booleano *AND* os MeSH Terms no PubMed ("kidney transplantation"[MeSH Terms] AND "mortality"[MeSH Terms]) AND "risk factors"[MeSH Terms]), cruzamentos concomitantemente com o operador booleano *AND* todos os índices na biblioteca eletrônica SciELO (Transplante de rim [Todos os índices] AND Mortalidade [Todos os índices] AND Fatores de Risco [Todos os índices]), cruzamentos concomitantemente com o operador booleano *AND* entre os keywords "kidney transplantation" in Keywords and "mortality" in Keywords and "risk factor" in Keywords in Trials' na biblioteca Cochrane.

The inclusion criteria of the selected studies for this integrative review were: complete articles available in Portuguese, English or Spanish; studies on adult patients submitted to renal transplantation; risk factors for mortality after transplantation; infectious complications that occurred up to one year after renal transplantation, and publication period from January 2006 to July 2016. We

chose to consider the literature of this period, because it is a relevant subject that has only recently been investigated, but which is gradually arousing the attention of the researchers.

In the initial search, 777 articles were found, 07 in the LILACS database, 745 in PubMed, 03 in SciELO and 22 in the Cochrane Library. After reading the titles and abstracts, duplicate publications were excluded and read in full of the selected studies and in accordance with the inclusion criteria. After this step, the sample consisted of 21 studies, which were presented in the flow chart (Figure 1), as recommended by the PRISMA group[13].

To the included studies, an instrument was elaborated by the authors aiming the extraction of the following information: title, author, year, objectives, methodological characteristics, results, discussion and conclusion. The extraction of the data occurred in a descriptive way as presented in the research, that is, without manipulation by the reviewers.

To evaluate the quality of the articles in the sample, a classification was used according to the level of evidence (14) as described: I - systematic reviews or meta-analysis of relevant clinical trials; II - evidence of at least one well-delineated randomized controlled trial; III - well-delineated clinical trials without randomization; IV - well-delineated cohort and case-control studies; V- systematic review of descriptive and qualitative studies; VI - evidence derived from a single descriptive or qualitative study; VII - opinion of authorities or committees of experts including interpretations of information not based on research.

The data extracted from the articles are presented in a descriptive way, in two synoptic tables, containing information referring to the titles of the article, type of study, level of evidence, database, periodical, year of publication and descriptive table with factors associated with mortality of the patients after renal transplantation.

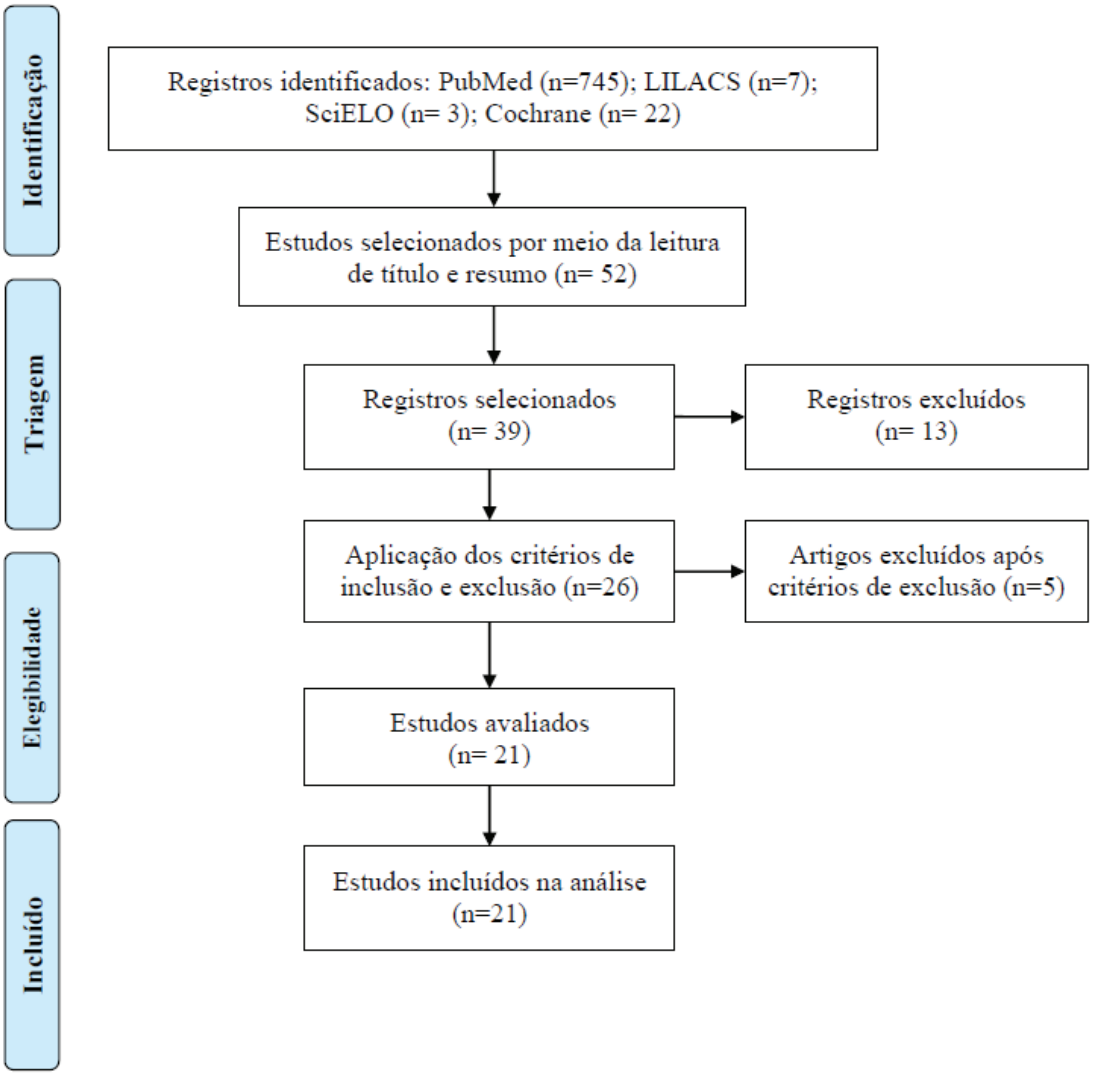

FIGURE 1 – Description of the selection process of the studies included in the integrative review. São Paulo, SP, Brazil, 2016.

RESULTS

The researches in the databases gave rise to twenty-one studies, six (28.58%) articles in 2014, followed by four (19.05%) in 2015, and no studies were identified in the years 2006 and 2016. Of the twenty one compiled articles, eighteen (85.8%) are cohort studies and of these ten (47.7%) are retrospective cohort studies, and eight (38.0%) prospective cohort studies, with a predominance of level of evidence IV in 85.8% of the studies analyzed. The highest incidence of publications occurred in international journals, with 19 (86.3%) publications and two (9.5%) in national journals. The evaluation of the journals presented the total number of renal transplant recipients, cause of mortality and the possible factors related to mortality as described in table 1.

Regarding the causes of mortality, cardiovascular disease prevailed in thirteen (61.91%) studies, followed by infection in nine (42.9%) articles analyzed. As shown in the investigations, the number of deaths due to cardiovascular and non-cardiovascular causes are described in Table 1, based on all the deaths described in the studies analyzed.

DISCUSSION

As for the place of origin of the selected articles, they were produced predominantly in North America and Europe.

Regarding the type of study used, most of the articles

TABLE 1 – Description of studies included in the integrative review, second title, type of study, level of evidence, data source, periodical, causes and factors related to mortality in renal transplant recipients and year of publication. São Paulo, SP, Brazil, 2016.

N	Article Title	Type of Study	Evidence Level	Data source	Periodic	Cause of mortality	Factors Associated with Mortality	Year
1	Frailty and mortality in kidney transplant recipients	Longitudinal Prospective	VI	PubMed	American Journal of Transplantation	• Not described	• Fragility	2015
2	Causal path analyses of the association of protein intake with risk of mortality and graft failure in renal transplant recipients	Prospective Cohort	IV	PubMed	Clinical Transplantation	• Cardiovascular • Infection • Neoplasm • Unknown • Others	• Low protein consumption	2015
3	Initial kidney graft resistance index and the long-term cardiovascular mortality in transplanted patients: a paired grafts analysis	Prospective Cohort	IV	PubMed	Nephrology Dialysis Transplantation	• Cardiovascular	• Increased intra-renal resistance index	2015
4	Long-term evolution in renal transplantation of the elderly	Retrospective Cohort	IV	SciELO	Brazilian Journal of Nephrology	• Infection • Cardiovascular • Neoplasm • Others • Unknown	• Diabetes Mellitus in patients older than 60 years	2015
5	The impact of early cytomegalovirus infection after kidney transplantation on long-term graft and patient survival	Prospective Cohort	IV	PubMed	Clinical Transplantation	• Cardiovascular • Neoplasm • Infection • Others	• Cytomegalovirus (CMV) infection	2014
6	Association of pre-transplant blood pressure with posttransplant outcomes	Prospective Cohort	IV	PubMed	Clinical Transplantation	• Cardiovascular	• Pre-transplant blood pressure increase	2014
7	Clopidogrel use as a risk factor for poor outcomes after kidney transplantation	Retrospective Cohort	IV	PubMed	The American Journal of Surgery	• Not described	• Use of clopidogrel for up to 90 or more than 90 days combined with coronary artery disease, cerebrovascular disease and / or peripheral vascular disease.	2014
8	Mortality predictors in renal transplant recipients with severe sepsis and septic shock	Observational Retrospective	V	PubMed	Public Library of Science one	• Septic shock	• Male • Admission of wards • Worst score on the first day • Hematologic dysfunction • Mechanical ventilation • Late graft dysfunction	2014

9	Recipient-related risk factors for graft failure and death in elderly kidney transplant recipients	Retrospective Cohort	IV	PubMed	Public Library of Science one	• Infection • DAC * • Stroke † • Neoplasm • Liver Disease • Bleeding • Unknown	• Low dose on prophylaxis with ganciclovir • Long dialysis time	2014
10	Symmetric dimethylarginine as predictor of graft loss and all-cause mortality in renal transplant recipients	Randomized, double-blind, placebo-controlled	II	Cochrane Database	Transplantation	• Cardiovascular • Infection • Neoplasm	• Increased symmetrical dimethylarginine	2014
11	Predictors of graft failure and death in elderly kidney transplant recipients	Prospective Cohort	IV	PubMed	Clinical and Translational Research	• Not described	• Congestive Heart Failure and Coronary Artery Disease in ≥ 65 years	2013
12	Rate of renal graft function decline after one year is a strong predictor of all-cause mortality	Retrospective Longitudinal	IV	PubMed	American Journal of Transplantation	• Cardiovascular • Neoplasm • Infection • Liver disease • Poor nutrition • Diabetes Mellitus • Respiratory • Unknown	• Decreased glomerular filtration rate	2013
13	Left atrial diameter and survival among renal allograft recipients	Retrospective Cohort	IV	PubMed	Clinical Journal of the American Society of Nephrology	• Cardiovascular • Infection • Neoplasm • Others	• Enlarged left atrium diameter - Cardiac death	2013
14	Endogenous plasma erythropoietin, cardiovascular mortality and all-cause mortality in renal transplant recipients	Prospective Cohort	IV	PubMed	American Journal of Transplantation	• Cardiovascular • Others	• Increased rates of erythropoietin	2012
15	Análise da sobrevida e fatores associados à mortalidade em receptores de transplante renal em Hospital Universitário no Maranhão	Retrospective Observational	IV	PubMed	Brazilian Journal of Nephrology	• Septic shock • Cardiovascular • Hypovolemic shock • Cerebral toxoplasmosis • Varicella • Lung cancer	• Age> 40 years • Surgical Intercurrence	2012
16	Serum phosphate and calcium concentrations are associated with reduced patient survival following kidney transplantation	Prospective Cohort	IV	PubMed	Clinical Transplantation	• Others	• High levels of phosphate and calcium in the serum.	2011
17	The association of early post-transplant glucose levels with long-term mortality	Prospective Cohort	IV	PubMed	Diabetology	• Cardiovascular • Neoplasm • Infection • Others • Unknown	• Hyperglycemia	2011
18	Risk factors associated with graft loss and patient survival after kidney transplantation	Retrospective Cohort	IV	PubMed	Transplantation Proceedings	• Not described	• Not described	2009
19	Associations between pre-kidney-transplant risk factors and post-transplant cardiovascular events and death	Retrospective Cohort	IV	PubMed	Transplant International	• Not described	• Advanced age • Cardiovascular event history • Cerebrovascular disease • Diabetic Nephropathy	2008
20	The association between recipient alcohol dependency and long-term graft and recipient survival	Retrospective Cohort	IV	PubMed	Nephrology, Dialysis, Transplantation	• Not described	• Alcohol dependence in end-stage renal disease	2007
21	Decreased serum retinol is associated with increased mortality in renal transplant recipients	Retrospective Cohort	IV	PubMed	Clinical Chemistry	• Cardiovascular • Non-cardiovascular • Unknown	• Low levels of Retinol (Vitamin A)	2007

*DAC – Doença da artéria coronária; †AVC – Acidente Vascular Cerebral

TABLE 1 – Maximum, minimum, mean ± standard deviation (Median) of the causes of mortality of renal transplant recipient patients as described in Table 3. São Paulo, SP, Brazil, 2016. (n = 21)

Variables	Max	Min	Average±DP	Medium
Causas da mortalidade				
Cardiovascular	194,00	0,00	36,67±49,99	14,00
Infecção	76,00	0,00	18,00±25,96	0,00
Neoplasia	65,00	0,00	10,71±18,50	0,00
Outros	22,00	0,00	2,66±5,79	0,00
Desconhecido	57,00	0,00	12,66±17,83	4,00

were composed of cohort studies, in which there is the difficulty to control bias[15], it should be pointed out that cohort studies are used in a classic way to evaluate results of exposures to risks[16]. Thus, in the evaluation of risk factors for mortality after renal transplantation, this would be one of the most recommended guidelines for this type of investigation.

The risk factors for renal transplant recipients mortality were distributed in categories according to frequency, namely: Fragility; Nutrition; Diabetes; Infection; Cardiovascular and Infection.

The fragility was prospectively evaluated in 537 renal transplant recipients, showing that, after five years of transplantation, the survivors were 91.5%, 86.0% and 77.5% for the non-fragile, intermediate and fragile renal transplant recipients , respectively and concluded that regardless of age, frailty is a strong and independent risk factor for post-transplant renal mortality. Studies evaluating other situations such as patients of all ages undergoing hemodialysis and elderly patients undergoing percutaneous coronary interventions showed that the fragility was associated with an increased risk of mortality in those patients who were fragile[17-18].

The nutritional part of the renal transplant recipient has been shown to be an important factor in the survival of these patients. One study found that a relatively high intake of proteins is associated with a reduced risk of mortality and graft failure in transplanted patients[19]. A cohort of 940 renal transplant recipients showed that protein intake is inversely associated with mortality and graft failure[20]. Another study evaluating serum vitamin A levels found that low retinol (Vitamin A) concentration is significantly associated with all-cause mortality in renal transplant patients, since these patients are on immunosuppressants and are very more susceptible to infections[21]. One study showed that inadequate concentrations of vitamin A intensify the severity of infectious processes[22] leading to a higher chance of mortality.

There are several comorbidities related to early graft loss and mortality in renal transplant, including DM. The impact of hyperglycaemia on patient survival after renal transplantation is unknown. Some studies indicate an association between post-transplant diabetes mellitus and mortality[23-25], while others do not[26-27]. One study showed that metabolic syndrome and post-transplantation diabetes mellitus were strongly associated but did not allow for any possible association between post-transplant diabetes mellitus and renal and / or patient survival[28], while other studies point to a reduction in graft survival and[29-30], which shows the need for further studies to identify the direct effects of diabetes on renal transplant recipients.

The prevalence of cardiovascular risk factors in renal transplant candidates is high; a study of 50 chronic renal patients showed that 78% of the participants were hypertensive, with hypertension being one of the main causes of chronic renal failure[31]. A better understanding of the relationship between these risk factors and cardiovascular morbidity and mortality is needed to improve transplant outcome. Diabetic nephropathy and cardiovascular disease were important predictors of all-cause mortality being the most important for cardiovascular events and all-cause mortality after renal transplantation[32].

Another important factor associated with mortality is the relationship of blood pressure where low post-dialysis systolic pressure and predialysis low diastolic blood pressure are associated with a lower risk of post-transplant death, while very high post-dialysis diastolic pressure is associated with a higher mortality in renal transplant recipients. Changes in blood pressure in dialysis patients prior to renal transplantation may influence the posttransplant outcome, which warrants additional studies[33]. Several pre-transplant risk factors have been identified in recent years, but the association between pre-transplant blood pressure and post-transplant mortality has not been previously assessed. It is pointed out that due to the lack of data, most guidelines on the evaluation of renal transplant candidates did not include recommendations on the ideal blood pressure of patients on the waiting list[34-37].

The recent recommendation of the American Society of Transplantation has noted that SHP (BP ≥ 140/90 mm

Hg or taking antihypertensive drugs) is a risk factor for ischemic heart disease and other atherosclerotic diseases but has not provided an ideal blood pressure range during the waiting period[35]. The European Best Practice Guideline and the UK assessment guidance did not report updated blood pressure data on dialysis patients on the waiting list[36-37].

Recently a study analyzed the effect of intra-renal resistance and revealed higher cardiovascular mortality and all causes among patients with higher initial values of intra-renal resistance, being a strong predictor of cardiovascular death, independent of previous cardiovascular events. The most important finding is that among patients transplanted with kidneys acquired from the same donor, those with the highest intra-renal resistance values measured in the renal graft during the first days after transplantation present a significantly higher risk of death cardiovascular during the long time observation[38].

Studies have pointed out the relationship of cytomegalovirus (CMV) infection with mortality in renal transplant recipients. A prospective observational cohort study reported effects of CMV on graft and patient survival in 471 renal transplant recipients between 1994 and 1997. None of the patients received prophylaxis for cytomegalovirus or preventative treatment. During a median of 13.7 (7.1-14.9) years, the number of graft losses censored by death was 118 (25%) and patient deaths were 224 (48%). In univariate analysis, CMV infection was significantly associated with loss of graft censored by death, suggesting that early cytomegalovirus infection is associated with an increase in overall long-term mortality[39].

Another study that analyzed risk factors for death and graft loss renal transplant recipients found that even patients taking ganciclovir for prophylaxis of cytomegalovirus infections at low doses was a risk factor for mortality in recipients aged> 60 years. This factor represents a potential target for interventions aimed at improving graft and patient survival in elderly recipients. According to the same study prophylaxis with ganciclovir at high doses should be widely used in elderly recipients to decrease the incidence of cytomegalovirus infection. However, prospective, randomized, multicenter studies are needed to confirm these findings[40].

Limitations of the study are related to the period of data collection and the reduced number of databases, making it difficult to generalize the results. Further studies of this nature are suggested, in order to generate new knowledge about the incidence of renal transplantation complications and mortality, as well as prevention strategies.

CONCLUSION

This study allowed us to conclude that several factors are associated with mortality in renal transplant recipients, these being factors related to cardiovascular function, infectious, metabolic, physiological, nutritional and structural processes. Investigations related to renal transplantation allow new studies to be proposed to propose improvements in the evaluation and follow-up of renal transplant recipients. For this reason, the present study may have implications that may instigate new research in order to determine the best recommendations to ensure graft and receptor survival, contributing to a better quality of life for the patient.

REFERENCES

1. British Transplant Society/Renal Association. United kingdom guidelines for living donor kidney transplantation. 3a.ed. Londres: BTS/RA; 2011.
2. Farney AC, Rogers J, Orlando G, al-Geizawi S, Buckley M, Farooq U, et al. Evolving experience using kidneys from deceased donors with terminal acute kidney injury. J Am Col Surg. 2013;216(4):645-55.
3. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;341(23):1725-30.
4. Lira ALBC, Lopes MVO. Renal transplant patients: analysis of the association of nursing diagnoses. Rev. Gaúcha Enferm. 2010;31(1):108-14.
5. Salermo MP, Zichichi E, Rossi E, Favi E, Gargiulo A, Spagnoletti G, *et al*. Evolution of causes of mortality in renal transplantation in the last 10 years. Transplant Proc. 2010; 42:1077-9.
6. Fellström B, Jardine AG, Soveri I, Cole E, Neumayer HH, Maes B, *et al*. Renal dysfunction is a strong and independent risk factor for mortality and cardiovascular complications in renal transplantation. Am J Transplant. 2005;5:1986-91.
7. Ojo AO. Cardiovascular complications after renal transplantation and their prevention. Transplantation. 2006;82:603-11.
8. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med. 2007; 357:2601-14.
9. Mendes KDS, Silveira RCCP, Galvão CM. Integrative review: research method for the incorporation of evidence in health and nursing. Texto e contexto enferm. 2008;17(4):758-64.
10. Souza MT, Silva MD, Carvalho R. Integrative review: what it is and how to do it. Einstein. 2010;8:102-6.
11. Teixeira E, Medeiros HP, Nascimento MHM, Silva BAC, Rodrigues. Integrative Review of Step-by-step Literature and Convergences with Other Review Methods. Rev Enferm UFPI. 2013;2(spe): 3-7.
12. Fineout-Overholt E, Stillwell SB. Asking compelling, clinical questions. In: Melnyk BM, Fineout-Overholt E. Evidence-based practice in nursing & healthcare: a guide to best practice. Philadelphia: Wolters Kluwer, Lippincot Williams & Wilkins; 2011. p. 25-39.
13. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. PLoS Med. 2009;6(6):e1000097.
14. Melnyk BM, Fineout-Overholt E. Making the case for evidence-based practice. In: Melnyk BM, Fineout-Overholt E. Evidence-based practice in nursing & healthcare: a guide to best practice. Philadelphia: Lippincot Williams & Wilkins; 2011, p. 3-24.
15. Carlson MDA, Morrison RS. Study Design, Precision, and Validity in Observational Studies. J Palliat Med. 2009;12(1):77-82.
16. Lazcano-Ponce E, Fernández E, Salazar-Martínez E, Hernández-Ávila M. Cohort studies. Metodología, sesgos y aplicación. Salud Pública Méx. 2000;42(3):230-41.
17. McAdams-Demarco MA, Law A, Salter M, Boyarsky B, Gimenez L, Jaar BG, *et al*. Frailty as a novel predictor of mortality and hospitalization in hemodialysis patients of all ages. J Am Geriatr Soc. 2013;61(6):896-901.
18. Singh M, Rihal CS, Lennon RJ, Spertus JA, Nair KS, Roger VL. Influence of frailty and health status on outcomes in patients with coronary disease undergoing percutaneous revascularization. Circ Cardiovasc Qual Outcomes. 2011;4(5):496-502.
19. Said MY, Deetman PE, de Vries AP, Zelle DM, Gans RO, Navis G, *et al*. Causal path analyses of the association of protein intake with risk of mortality and graft failure in renal transplant recipients. Clin Transplant. 2015;29(5):447-57.
20. Deetman PE Said MY, Kromhout D, Dullaart RP, Kootstra-Ros JE, Sanders JS, *et al*. Urinary urea excretion and long-term outcome after renal transplantation. Transplantation. 2015;99(5):1009-15.
21. Connolly GM, Cunningham R, Maxwell AP, Young IS. Decreased serum retinol is associated with increased mortality in renal transplant recipients. Clin Chem. 2007;53(10):1841-6.
22. Cribb VL, Northstone K, Hopkins D, Emmett PM. Sources of vitamin A in the diets of pre-school children in the Avon Longitudinal Study of Parents and Children (ALSPAC). Nutrients. 2013;5:1609-21.
23. Orlandi PF, Cristelli MP, Aldworth CAR, Freitas TVS, Felipe CR, Silva Junior HT, *et al*. Long-term evolution in renal transplantation of the elderly. J Bras Nefrol. 2015;37(2):212-220.
24. Valderhaug TG, Hjelmesæth J, Hartmann A, Røislien J, Bergrem HA, Leivestad T, *et al*. The association of early post-transplant glucose levels with long-term mortality. Diabetologia. 2011;54(6):1341–1349.
25. Aalten J, Hoogeveen EK, Roodnat JI, Weimar W, Borm GF, de Fijter JW, *et al*. Associations between pre-kidney-transplant risk factors and post-transplant cardiovascular events and death. Transpl Int. 2008;21(10):985-91.
26. Hjelmesaeth J, Hartmann A, Leivestad T, Holdaas H, Sagedal S, Olstad M, *et al*. The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. Kidney Int. 2006;69(3):588-95.
27. Miles AM, Sumrani N, Horowitz R, Homel P, Maursky V, Markell MS, *et al*. Diabetes mellitus after renal transplantation: as deleterious as non-transplantassociated diabetes? Transplantation. 1998;15;65(3):380-4.
28. Teixeira APSF, Fernandes NMS, Mata GF, Chaoubah A, Paula RB, Bastos MG. Prevalence of metabolic syndrome and its associated factors in renal transplant recipients. J Bras Nefrol. 2012;34(1):16-21.
29. Crutchlow MF, Bloom RD. Transplant-Associated Hyperglycemia: A New Look at an Old Problem. Clin J Am Soc Nephrol. 2007;2(2):343-355.

30. Van Laecke S, Van Biesen W, Verbeke F, De Bacquer D, Peeters P, Vanholder R. Posttransplantation Hypomagnesemia and Its Relation with Immunosuppression as Predictors of New-Onset Diabetes after Transplantation. Am J Transplant. 2009;9(9):2140-9.
31. Fidelis CI, Balbino CM, Souza MMT, Rodrigues LMS, Silvino ZR, Passos JR. Dificulties faced by the renal patient for the treatment. Rev Enferm Atual. 2016; 77:16-21.
32. Aalten J, Hoogeveen EK, Roodnat JI, Weimar W, Borm GF, De Fijter JW, *et al.* Associations between pre-kidney-transplant risk factors and post-transplant cardiovascular events and death. Transpl Int. 2008;21(10):985-91.
33. Molnar MZ, Foster CE, Sim JJ, Remport A, Krishnan M, Kovesdy CP. Association of Pre-Transplant Blood Pressure with Post-Transplant Outcomes. Clin Transplant. 2014;28(2):166–176.
34. Pilmore H. Cardiac assessment for renal transplantation. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2006;6(4):659.
35. Kasiske BL, Cangro CB, Hariharan S, Hricik DE, Kerman RH, Roth D, *et al.* The evaluation of renal transplantation candidates: clinical practice guidelines. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2001;1(Suppl 2):3.
36. Dudley, C.; Harden, P. Assessment of the Potential Kidney Transplant Recipient. 5th Edition ed. UK Renal Association. 2011.
37. European Best Practice Guidelines for Renal Transplantation (part 1). Nephrol Dial Transplant. 2000;15(Suppl 7):1.
38. Kolonko A, Chudek J, Więcek A. Initial kidney graft resistance index and the long-term cardiovascular mortality in transplanted patients: a paired grafts analysis. Nephrol Dial Transplant. 2015;30(7):1218-24.
39. Smedbraten YV, Sagedal S, Leivestad T, Mjøen G, Osnes K, Rollag H, *et al.* The impact of early cytomegalovirus infection after kidney transplantation on long-term graft and patient survival. Clin Transplant. 2014;28(1):120-6.
40. Lai X, Chen G, Qiu J, Wang C, Chen L. Recipient-related risk factors for graft failure and death in elderly kidney transplant recipients. PLoS One. 2014;9(11):e112938.