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Review

Mortality in Elderly Waiting-List Patients Versus Age-Matched Kidney Transplant Recipients: Where is the Risk?

Domingo Hernández[a] Juana Alonso-Titos[a] Ana María Armas-Padrón[b] Pedro Ruiz-Esteban[a] Mercedes Cabello[a] Verónica López[a] Laura Fuentes[a] Cristina Jironda[a] Silvia Ros[a] Tamara Jiménez[a] Elena Gutiérrez[a] Eugenia Sola[a] Miguel Angel Frutos[a] Miguel González-Molina[a] Armando Torres[c]

[a]Nephrology Department, Carlos Haya Regional University Hospital and University of Malaga, IBIMA, Málaga, [b]La Cuesta Primary Health Care Centre, La Laguna, Tenerife, [c]Nephrology Department, Hospital Universitario de Canarias, CIBICAN, University of La Laguna, Tenerife and Instituto Reina Sofía de Investigación Renal, IRSIN, Spain

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Abstract
The number of elderly patients on the waiting list (WL) for kidney transplantation (KT) has risen significantly in recent years. Because KT offers a better survival than dialysis therapy, even in the elderly, candidates for KT should be selected carefully, particularly in older waitlisted patients. Identification of risk factors for death in WL patients and prediction of both perioperative risk and long-term post-transplant mortality are crucial for the proper allocation of organs and the clinical management of these patients in order to decrease mortality, both while on the WL and after KT. In this review, we examine the clinical results in studies concerning: a) risk factors for mortality in WL patients and KT recipients; 2) the benefits and risks of performing KT in the elderly, comparing survival between patients on the WL and KT recipients; and 3) clinical tools that should be used to assess the perioperative risk of mortality and predict long-term post-transplant survival. The acknowledgment of these concerns could contribute to better management of high-risk patients and prophylactic interventions to prolong survival in this particular population, provided a higher mortality is assumed.

Domingo Hernández, MD

Nephrology Department, Carlos Haya Regional University Hospital,
Avda. Carlos Haya s/n., E-29010 Málaga (Spain)
Tel. +34 952907411, Fax +34 951291557, E-Mail domingohernandez@gmail.com

Introduction

Because nearly half of all incident end-stage renal disease (ESRD) patients worldwide are older than 65 years [1, 2], nephrologists will need to decide which of these many elderly patients are suitable candidates for kidney transplantation (KT). In the current context of donor shortage, elderly patients (e.g. >65 years) are less frequently placed on the waiting list (WL), due to uremia-related life-threatening comorbidities, and, if they are listed, they have fewer chances of receiving a KT than their younger counterparts, partly owing to emergent events (cardiovascular disorders, infections, neoplasias, etc.) that can modify their transplant status whilst on the WL [3, 4]. In addition, assessment of elderly KT candidates is complex and evidence-based clinical guidelines for the management of this particular population are lacking [4–8]. Moreover, many transplant teams are still reluctant to include elderly patients on the WL for KT as objective selection criteria for transplantation in this population are poorly defined [3, 4, 9]. Misconceptions regarding the inclusion criteria for elderly patients for KT could delay early referral to a transplant center or delay WL inclusion, leading to a longer time spent on dialysis.

Although many studies have demonstrated that KT is relatively safe and provides a better survival compared with age-matched dialysis patients [10–14], the benefits in survival could be tapered by risk in elderly patients, especially in those who have spent a prolonged time on the WL [3, 15–17]. Indeed, elderly KT recipients also have an increased risk of cardiovascular (CV) diseases, infections and neoplastic events, leading to higher post-transplant mortality than younger patients.

In this review, we focus on the clinical results of relevant reports concerning the benefits and risks of performing KT in elderly ESRD patients as opposed to remaining on the WL. We aim to answer the following questions: 1) Do we know the specific risk factors for mortality in elderly KT candidates?; 2) Is mortality in elderly patients on the WL for KT higher than in age-matched KT recipients?; and 3) What clinical tools should be used to assess the perioperative risk of mortality or to predict post-transplant survival in the long-term.

Risks of death on the waiting-list

Given the emerging evidence of the benefits of KT on survival in the elderly ESRD population, the age of patients on the WL for KT has risen significantly over the last decades worldwide [3, 4, 18–21]. However, previous reports have documented that approximately half of elderly KT candidates (>60 years) in the United States die on the WL before receiving a deceased-donor transplant [22]. The annual mortality rate for all patients on the WL varies between 5-10% worldwide, but increases greatly in the older dialysis population [22, 23]. As expected, the most common causes of mortality in these patients during the first year on dialysis are CV disorders followed by infectious complications [21]. This higher mortality in elderly patients on the WL can be explained by the increasing comorbidities in this particular population. There are few clinical conditions that join together as many risk factors as uremia, especially in elderly patients. Indeed, the risk of death in older KT candidates increases significantly as their time on dialysis therapy increases. In the US population, several socio-demographic factors, such as older age, race, unemployment status, smoking, diabetes, CV comorbidity and prior history of admissions, are independent risk factors for mortality on dialysis therapy, including patients on the WL [24, 25]. Likewise, these same factors plus psychiatric disorders and a prior history of neoplasia have also been associated with an increased risk of death in European dialysis patients [26]. Unfortunately, not all are modifiable risk factors that can be addressed by targeted therapeutic interventions. Recently, competing risk models showed that older age, the presence of a central venous cathether at the start of hemodialysis therapy, unemployment and a Charlson Comorbidity index (CCI) score [27] higher than 3 were risk factors associated with mortality in Southern European

KT candidates [21]. In addition, the presence of peripheral vascular disease (PVD) in patients on the WL has been related to a higher risk for mortality in large cohort studies of both the American and the European dialysis population [28–30]. In particular, PVD was associated with a 1.9-2.9 fold increased risk of mortality in wait-listed patients for KT. Furthermore, in KT candidates there may be a high prevalence of poor health indicators, recently established by American health authorities, such as obesity, physical inactivity, smoking, low income or low cultural levels, which could all increase the risk of death on the WL for KT [31, 32]. To further complicate this alarming situation, comorbidities can progress throughout ESRD [33], including those waitlisted for KT. Finally, other barriers to accessing KT, such as socio-demographic factors (obesity, female patients, patients who live in rural areas or far from transplant centers, among others) could increase the time on the WL and favor the onset or impairment of non-desirable comorbidities while still on the WL, leading to a higher mortality [19, 34–36]. However, there may be a high overlap in the risk profile and life-expectancy of patients waitlisted for KT and those who are not [24], suggesting that accurate assessment of the risk of death should be performed in order to prioritize or properly assign a KT. Thus, early and accurate identification of risk factors for mortality, mainly modifiable risk factors, plus knowledge of WL inclusion criteria in elderly patients could help to target prophylactic interventions in this particular population. Consequently, comorbidity-based prediction of mortality in the short- and long-term could be crucial for making the best clinical decisions in elderly patients on the WL for KT, always considering that lack of KT is likely the biggest risk for dying in this particular population.

Risk of mortality in elderly KT recipients

A priori, elderly KT recipients have a greater risk of infections, CV events and neoplasia than younger patients. This is an obvious issue because ageing is associated with a higher risk of mortality in all populations. As expected, most reports have shown that the mortality risk increases with age, including in recipients from expanded criteria living kidney donors [37–41]. With ageing, an interaction between great CV comorbidity and infections and neoplastic processes within the framework of immunosuppressive therapy seems likely, leading to excessive post-transplant mortality [8, 42–44]. In addition, the risk of death in older KT recipients increases with increased comorbidity during the first post-transplant year [39, 45]. Finally, older KT recipients are susceptible to cognitive impairment, poor functional status and frailty, increasing hospital readmission and mortality risk [46–50]. However, death-censored graft survival in the elderly, including KT recipients 80 years and older, appears to be comparable to or even better than that in younger KT recipients in the long term [40, 51, 52]. It is plausible, therefore, that, given the immunosenescence of the elderly, the use of lower doses of immunosuppressants and a more careful surveillance could minimize these life-threatening side effects, while still being able to provide adequate levels of immunosuppression. Given this background, careful selection of elderly candidates for KT based on a thoroughly comprehensive medical, psychosocial and functional evaluation would be recommendable, with emphasis on a CV work-up, to make the best clinical decisions in order to decrease post-transplant mortality, as reported [4]. Unfortunately, the optimal method of screening for CV diseases in these patients is still unclear.

Comparing mortality risk on waiting-list versus post-transplantation

An appropriate candidate for KT is a patient whose survival and quality of life (QOL) are expected to improve after KT as compared with remaining on dialysis. However, whether this holds true for all elderly WL patients is uncertain. For instance, consider a theoretical 83-year-old patient with advanced chronic renal disease secondary to nephrosclerosis, a non-

smoker with no diabetes, hypertension, or prior cardiovascular disease, with a functioning arterio-venous fistula, hemoglobin blood levels of 12 g/dL and CCI of 6 points (Patient A); would it be safe for this patient to receive a KT? Would the likelihood of death during dialysis be greater than after a KT?. For practical purposes and in another clinical setting, let us also consider a hypothetical 80-year-old patient with renal disease secondary to insulin-dependent diabetes, former smoker, and hypertension, a healed myocardial infarction of 6 months previously, a central venous catheter for hemodialysis and CCI of 12 points (Patient B). What would be the likelihood of death during dialysis and after a KT for this patient?

Based on a recent review on criteria for and appropriateness of KT in elderly patients, the European Renal Association-European Dialysis and Transplant Association (Descartes Working Group and European Renal Best Practice) recommends KT for carefully selected ESRD patients because KT is superior to dialysis in terms of patient survival, QOL and cost-effectiveness, as evidenced by multiple studies carried out in older ESRD patients [7, 11–13, 16, 52–59], including those on home-dialysis therapy [60]. This potential benefit of KT can vary greatly between countries. Indeed, survival on dialysis appears to be better in Europe than the US. Thus, the expected survival benefit with transplantation could be lower in Europe compared with the US [61, 62]. Additionally, virtually all guidelines agree that patients should not be deemed ineligible for KT based on age alone [4]. However, prolonged waiting times dramatically decrease the clinical and economic benefits of KT, suggesting that living donor transplantation may be of particular benefit in this population [16].

Focusing on patients waitlisted for KT, observational studies have shown that the mortality risk is significantly higher in the WL patients than in age-matched KT recipients, regardless of the type of transplant, although these differences were mainly observed beyond the third month after KT [9, 11–14, 56, 63]. Additionally, two recent observational studies have shown that utilization of kidneys with a high Kidney Donor Profile Index (>85%) or deceased diabetic donor kidneys also provides a higher survival in older recipients compared with waitlisted patients [64, 65]. However, an elegant Dutch observational study performed in elderly KT patients receiving deceased-donor grafts from elderly donors (≥65 years) demonstrated an increased mortality risk compared with waitlisted elderly patients remaining on dialysis [66]. A higher incidence rate of delayed graft function, impaired renal function and rejection in elderly recipients who receive kidneys from elderly donors could have explained this concerning finding. Table 1 shows the survival benefit for KT recipients over potential candidate patients for KT in several observational studies, including the elderly population.

A few years ago, Tonelli et al. performed a systematic review of cohort studies involving 110 eligible studies with a total of 1, 922, 300 participants and comparing outcomes between chronic dialysis patients and KT recipients [67]. Most studies found a significantly lower mortality as well as a lower rate of CV events associated with KT. Additionally, the magnitude of the clinical benefits seemed to increase over time. More interestingly, similar findings were observed in the subset of 10 studies including 97, 873 waitlisted patients, supporting the clinical benefit of KT compared with dialysis therapy, regardless of age and comorbidity. Similarly, a recent cohort study of the Danish Nephrology Registry showed a significantly better survival in KT recipients compared with waitlisted patients despite high comorbidity [17]. Nonetheless, it is possible that the beneficial effect on survival of KT is not so robust in patients aged >70 years, diabetics and those with chronic obstructive pulmonary disease, as previously reported by Perez-Saez et al. [68], suggesting that this benefit may not be extrapolatable to older patients. However, a later systematic review carried out by these same authors showed an overall better patient survival at the fifth year post-transplantation in elderly KT recipients compared with age-matched waitlisted patients [69].

In summary, mortality risk is significantly higher in WL patients than in age-matched KT recipients, especially in elderly patients. Transplanting with low-quality allografts could lead to higher mortality, which underlines the importance of proper selection and preservation if the allocation of elderly donors to elderly recipients is to be expanded.

Table 1. Observational studies comparing the benefit on survival of a kidney transplant over potential candidate patients for transplantation, including elderly population. Abbreviations: Tx, transplantation; WL, waiting-list; SCD, standard cadaveric donor; ECD, expanded cadaveric donor; LD, living donor; DDT, deceased donor transplant; KDPI, Kidney Donor Profile Index

Reference	Transplant period	Recipient population	Transplanted vs. Waitlisted patients	Patient survival or mortality risk
Wolfe et al.,[11] 1999	1991-1997	All ages	23275/22889	Adjusted mortality risk Tx vs. WL: age 40-59: 0.3 (95% CI: 0.3-0.4); Age 60-74 y: 0.4 (95% CI 0.3-0.5)
Ojo et al., [12] 2001	1992-1997	All ages	41892/71295	Adjusted 5 y-survival: ideal Tx 85%; marginal Tx 75%: Adjusted mortality Tx vs WL: ideal Tx 0.5; marginal Tx 0.7 (P=0.001)
Rao et al., [13] 2007	1990-2004	>70 y.	2436/3229	At 4 y-survival, TX: 66% (overall adjusted mortality risk: 0.6, 95% CI 05-0.7); WL: 51%
Heldal et al., [56] 2010	1990-2005	>70 y.	233/53	Period 1990-99: Survival at 1st, 2nd and 5th year: Tx 79%, 60% and 39% vs. WL 93%, 66%, 29% Period 2000-2005: Tx 89%, 74%, 64% vs. WL 98%, 56%, 33%
Gill et al., [71] 2013	1995-2007	≥65 y. Low, intermediate and high CV risk	11072/4396	Mortality risk ECD >SCD >LD Days to equal survival Tx/WL: High risk patients: LD 130 days, SCD 368 days; ECD 521 days.
Sorensen et al, [17] 2016	1995-2011	All ages	2349/825	Adjusted mortality risk for elderly (>65 y) Tx patients receiving DDT: 0.45 (95% CI 0.26-0.75)
Pérez-Sáez et al, [68] 2016	1990-2013	All ages	389/2040	Overall mortality risk for Tx: 0.44 (95% CI 0.32-0.62); if recipient 65-69 y: HR 0.56 (95% CI 0.34-0.92)
Peters-Sengers et al., [66] 2017	2002-2012	<65 y (N=2883) and ≥65 y (N=714)	3597/504	5-year mortality elderly patients (>65 y): Tx 60% vs WL 61.3%
Chen et al., [63] 2017	2006-2013	>70 y	2397/79681	5-year mortality: low risk patients (scoring 1): Tx 19% vs WL 50%; high risk patients (scoring 5): Tx 40% vs WL 90%
Jay et al., [64] 2017	2003-2012	>60 y	4359/74394	Adjusted 1-2 year mortality risk using donor with KDPI score >85%: 0.52 (95% CI 0.45-0.61)
Cohen et al., [65] 2017	>1994	All ages (>18 y.)	134,661/302,958	Adjusted mortality risk in overall cohort with diabetic donor: Tx 0.91 (95% CI 0.84-0.98)

Assessment of perioperative risk in elderly candidates for KT

Cardiovascular diseases are the most common cause of death in KT recipients, with the highest rates in the peritransplant period. Older age is considered a very important risk factor for mortality in the perioperative and early post-transplant period in comparison with age-matched waitlisted dialysis patients, and this risk can increase greatly according to the quality of graft [66, 70, 71]. Thus, potential elderly candidates for KT should have a careful medical evaluation of their CV comorbidities. Furthermore, evaluation of risk in the peritransplant period can be crucial to properly assign a KT. Accordingly, an important issue for older patients undergoing a transplant assessment is their likelihood of an unfavorable perioperative outcome. Most guidelines recommend that patients with either a reduced life-expectancy or high perioperative risk of death should not be waitlisted for KT, but this principle is often not easy to apply in daily clinical practice [72]. Indeed, multiple prognostic indices are available to assess perioperative mortality risk. These have been validated in both the general population and renal patients, but no clear guidelines on the criteria for their use in patients waitlisted for KT are currently available. Moreover, there is limited information on the use of these scores for predicting the risk of early death in elderly candidates for KT. Accurate assessment of the perioperative surgical risk could allow us to undertake a careful selection of waitlisted patients in order to minimize early mortality post-transplantation. But do we have clinical tools to accurately estimate early mortality

Table 2. Surgical risk scores frequently used in the general population. *Dialysis patients without other comorbidities are considered as ASA III

Risk score	Assessment/Risk stratification
The ASA classification* The American Society of Anesthesiologists Fitz-Henry, J Ann R Coll Surg Engl 2011; 93: 185–187	Assessment: ASA I – ASA VI Scoring based on: • Normal healthy patients (ASA I) • Systemic disease mild (ASA II) or severe (ASA III) • Life-threatening systemic disease (ASA IV) • Moribund patients (ASA V) • Deceased-donor (ASA VI)
Revised Cardiac Risk Index Lee TH, Circulation. 1999;100:1043–1049 https://www.mdcalc.com/revised-cardiac-risk-index-pre-operative-risk	Assessment: Class I (very low risk) – Class IV (high risk) Scoring based on: • High risk surgery • Cardiovascular disease: coronary artery disease, congestive heart failure, cerebrovascular disease • Diabetes on insulin • Serum creatinine >2 mg/dL
ACS NSQIP® Surgical Risk Calculator American College of Surgeons (ACS) Winoker JS, 2017; J Urol 2017 https://riskcalculator.facs.org/RiskCalculator/	Assessment: Percent risk - chance of outcome - predicted length of hospital stay Scoring based on: • Surgical procedure • Age, gender, ASA class, steroid use, comorbidities (diabetes, hypertension, sepsis, cancer, CHF, COPD, acute renal failure), dialysis, smoker, BMI
Gupta Index: perioperative myocardial infarction or cardiac arrest risk calculator Gupta PK, Circulation. 2011;124:381-387 https://www.qxmd.com/calculate/calculator_245/gupta-perioperative-cardiac-risk	Assessment: percentile of risk/percent risk Scoring based on: • Age, ASA class, serum creatinine, functional status, surgical procedure
Detsky's Modified Cardiac Risk Index Detsky AS 1986, J Gen Intern Med 1; 213 http://www.fpnotebook.com/CV/Surgery/DtskysMdfdCrdcRskIndx.htm	Assessment: Class 1 (low risk), class 2 (moderate risk), class 3 (high risk) Scoring based on: • Age • Cardiac conditions: prior MI, angina pectoris, pulmonary edema, critical aortic stenosis • Emergency • General medical status
Surgical Outcome Risk Tool (SORT) K.L. Protopapa KL, 2014; Br J Surg 101; 1774-1783. The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) www.ncepod.org.uk	Assessment: percent risk (high risk>5%; critical care if ≥10%) Scoring based on: • Procedure, severity, ASA class, urgency • Thoracic, gastrointestinal or vascular surgery • Cancer • Age

in this particular population? Table 2 shows some surgical risk scores frequently used in the general population, which could be applied in elderly waitlisted patients, showing the clinical information necessary for inclusion on the list and, thus, to calculate the risk [73–78]. Although these risk indices are not universally applied in daily clinical transplant practice, efforts should made to apply those indices involving renal impairment, especially when assessing death risk in elderly patients before performing KT. For instance, applying the American Society of Anesthesiology (ASA) classification to assess the perioperative risk based on comorbidity conditions and renal disease of our 83-year-old Patient A mentioned above would give an intermediate risk, but not a high risk [73]. By contrast, this same classification would give a higher perioperative risk for our Patient B (Table 3). The Revised Cardiac Index, which includes age, cardiac disorders and renal function, assigns our Patient A a total score of 2; that is, an intermediate and assumable perioperative risk (https://www.mdcalc.com/revised-cardiac-risk-index-pre-operative-risk) [74]. However, this risk score assigns our Patient B a total score of 3 (high perioperative risk). The Surgical Risk Calculator of the American College of Surgeons includes dialysis therapy as well as age and other comorbid conditions in patients who are due to undergo major surgery, as is transplant (https://riskcalculator.facs.org/RiskCalculator/) [75]. A priori, our elderly Patient A would have a moderate risk of early death post-transplantation, but not a high risk. However, our Patient B would have a moderate-high risk of early death post-transplantation (Table 3). Finally, the Surgical Outcome Risk Tool (SORT score) includes age, comorbidities and the ASA classification (www.ncepod.org.uk) [78]. Again, our Patient A would have an intermediate and manageable perioperative risk whereas our Patient B would have a high mortality risk. Thus, assessing perioperative risk at the time of listing may help determine the advisability of undergoing transplant or continuing on dialysis therapy. Accordingly, it is plausible to perform a KT in carefully selected elderly waiting-list patients, using risk indices

Table 3. Risk stratification in our two different typical risk patients according to several prediction models. WL, waiting-list; TX, transplantation; ASA, The American Society of Anesthesiology; CCI, Charlson comorbidity index

Application of Risk score	Risk stratification Patient A	Risk stratification Patient B
Perioperative risk		
The ASA Classification The American Society of Anesthesiologists Fitz-Henry, J Ann R Coll Surg Engl 2011;93:185–187	ASA classification: intermediate risk (ASA III)	ASA classification: high risk (ASA IV)
Revised Cardiac Risk Index Lee TH, Circulation. 1999;100:1043–1049 https://www.mdcalc.com/revised-cardiac-risk-index-pre-operative-risk	Points 2: Class III, Intermediate perioperative risk (6.6% complications)	Points 3: Class IV High perioperative risk (>11% complications)
ACS NSQIP® Surgical Risk Calculator American College of Surgeons (ACS) Winoker JS, 2017; J Urol 2017 https://riskcalculator.facs.org/RiskCalculator/	Moderate risk of early death post-TX (4%)	Moderate-high risk of early death post-TX (9%)
Gupta Index: perioperative myocardial infarction or cardiac arrest (MICA) risk calculator Gupta PK, Circulation. 2011;124:381-387 https://www.qxmd.com/calculate/calculator_245/gupta-perioperative-cardiac-risk	Estimated risk probability for perioperative MICA 0.56%	Estimated risk probability for perioperative MICA 1.4%
Detsky's Modified Cardiac Risk Index Detsky AS 1986, J Gen Intern Med 1; 213 http://www.fpnotebook.com/CV/Surgery/DtskysMdfdCrdcRskIndx.htm	Class 1: Points 0-15 Low risk	Class 2: Points 20-30 Intermediate risk
Surgical Outcome Risk Tool (SORT) K.L. Protopapa KL, 2014; Br J Surg 101; 1774-1783. The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) www.ncepod.org.uk	Medium mortality risk (3.7%)	High mortality risk (>5%)
Risk Prediction in Dialysis or WL patients, and transplant patients	Low comorbidity (CCI< 5) 5-year post-TX expected survival 90%	High comorbidity (CCI≥5) 5-year post-TX expected survival 70%
Wu et al., [111] 2005		
Hernandez et al.,[108] 2005	5-y survival post-TX: 78%	5-y survival post- TX: 70%
van Walraven et al., [94] 2010	WL: 5-y expected survival 30% TX: 5-y expected survival 60%	WL: 5-y expected survival 20% TX: 5-y expected survival 45%
Grams et al., [32] 2012	3-y survival post-TX: 75%	3-y survival post-TX: 69%
Floege et al., [98] 2015	Intermediate mortality risk on dialysis: 1-year mortality 9%; 2-year mortality 20%	High mortality risk on dialysis: 1-year mortality 20%; 2-year mortality 35%
Dusseux et al., [100] 2015	WL: 3-y expected survival 70% (Score 6) May be suitable for TX evaluation	WL: 3-y expected survival 43% (score 10) May not be suitable for TX evaluation
Couchoud et al., [99] 2015	Low risk (score 4) 3-month expected mortality after initiating dialysis 5%	Intermediate risk (score 12) 3-month expected mortality after initiating dialysis 24%
Laging et al., [124] 2016	5-year post-TX mortality 6%	5-year post-TX mortality 30%
Lorent et al., [125] 2016	The cumulative probability of death after the 1st y. post-TX is 0.46	The cumulative probability of death after the 1st y. post-TX is 0.26
Chen et al., [63] 2017	WL: 5-year mortality 60%, score -4 (suitable for transplant) Transplant: 5-year mortality	WL: 5-year mortality 80%, score 4 (a priori no suitable for transplant) Transplant: 5-year mortality
Molnar et al., [127] 2017	1-year post-TX mortality 12%; 5-year post-TX mortality 28%	1-year post-TX mortality 16%; 5-year post-TX mortality 50%

that involve renal impairment, provided an increase in early post-operative risk is accepted. Nevertheless, prospective studies in elderly WL patients incorporating a more detailed risk prediction based on preoperative risk scores and graft quality scores are needed.

Prediction of mortality and comorbidity in waiting-list patients and kidney transplant recipients

Prediction of mortality and comorbidity, such as ischemic heart disease (IHD), in both waitlisted patients and KT recipients may be crucial for performing the most timely therapeutic measures in order to decrease mortality in these patients. Accordingly, prognostic indices should include comorbidity risk factors as well as secondary survival measures to estimate survival accurately and to make targeted therapeutic decisions or to guide eligibility for KT properly. The CCI has been considered a useful tool for predicting the risk of mortality in both the general population and renal patients, but it does not incorporate other uremia-related risk factors that can have a negative impact on survival [27, 79]. Similarly, the Framingham risk score, which is widely used in the general population, can also underestimate the CV risk in renal patients, especially in those with poor health indicators [80]. Consequently, several comorbidity scores have been proposed to predict mortality in renal patients [63, 79, 81–103] (Table 4). However, most previous studies have reported models that are difficult to use, based on odds ratios or hazard ratios from many variables. In addition, most of these lack a mortality analysis exclusively for elderly patients (e.g., >70 years) on the WL or mostly do not assess simultaneously mortality risk after KT as compared with remaining on the WL. Thus, further studies are clearly needed to determine the accuracy of predictive tools based on common clinical parameters and to relate their performance to more sophisticated predictors of clinical outcome. With this framework, a large Canadian cohort study developed and validated a prediction model to assess simultaneously survival in three patient groups: patients on the WL, patients who could receive a deceased-donor KT, and potential KT recipients from a living donor. After sample randomization in two subpopulations, a score was obtained from a Cox multivariate analysis, giving a total risk score for each patient, such that as the risk score increases, the risk of death increases exponentially after 5 years [94]. Applying this risk score, the 5-year expected survival in our elderly Patient A would be 30% if he remains on the WL. By contrast, a survival of 60% would be expected if this patient receives a deceased-donor KT. The 5-year expected survival rates for our Patient B would be 20% and 45% if he remains on the WL or if he receives a successful deceased-donor KT, respectively (Table 3). More recently, Floege et al. developed a mortality risk score in 11, 508 European incident hemodialysis patients with a mean age of 64 years using covariates such as age, smoking, body mass index (BMI), vascular access, comorbidities and certain biochemical parameters. Patients were stratified into a low, intermediate or high risk accordingly, but not all patients were on the WL or were elderly [98], which could be an important limitation for applying this risk score in elderly waitlisted patients. Nonetheless, based on this risk score our Patient A would have an intermediate risk of death at the first and second post-transplant year (9% and 20%, respectively). By contrast, our Patient B would have a high risk of death in the same post-transplant periods (20% and 35%, respectively). Couchoud et al. also developed a mortality risk score in a large cohort of elderly hemodialysis patients (>75 years old) from the National French Registry based on age, gender, frailty, serum albumin, BMI and other comorbidities, classifying patients into a low, intermediate or high risk of death [99]. The 3-month expected mortality after initiating dialysis in our Patient A is 5% (low risk), whereas our Patient B would have a higher mortality risk after starting dialysis therapy (24%) (Table 3). Similarly, a large French cohort study carried out in 16, 337 elderly dialysis patients (>70 years old) developed a risk score for death post-inclusion on the WL using age, gender, diabetic condition, mobility status, BMI and comorbidities [100]. The probability of patients being alive within 3 years after listing was around 70% for the lowest quintile (0-6 points), representing about 20% of incident patients, as in our Patient A. By contrast, the 3-year expected survival of our Patient B would only be 43% (score 10), and, thus, he would not be suitable for transplant evaluation (Table 3). Finally, Chen et al. recently created a 5-year mortality prediction score in elderly (70 years or older) incident dialysis patients, potentially suitable candidates for KT, from the United States Renal Data System.

Table 4. Comorbidity indices to predict mortality in renal patients. Abbreviations: ARO, Analyzing Data, Recognizing Excellence and Optimizing Outcomes; AUC, area under curve; HD, hemodialysis; CCI, Charlson comorbidity index; CHADS2, Score for atrial fibrillation stroke risk; DOPPS, Dialysis Outcomes Practice Patterns; HR, Hazard ratio; ICED, index of coexistent disease; OR, odd ratio; KT, kidney transplantation; NHIRD, Nation Health Insurance system of Taiwan; PD, peritoneal dialysis; REMIS, Renal Management Information System; REIN, French National Renal Epidemiology and Information Network; UNOS, United Network for Organ Sharing transplant; USRDS, United States Renal Data System

Reference/year	Study data/ Patients	Population	Variables	Assessment/ Risk stratification
Hutchinson et al.,[81] 1982	Multicenter N=220	Starting dialysis	Age, length of diabetes, left ventricular failure	Low (<30), medium (30-70), high (>70)
Wright [82] 1991	Single center N=138	HD	Age and comorbidity	Low-medium-high
Khan et al.,[83] 1993	Single center N=375	HD	Age, diabetes and comorbidity	Low-medium-high
Davies et al.,[84] 1995	Single center N=97	PD	Age, comorbidity, albumin,	Low-medium-high
Barrett et al.,[85] 1997	Multicenter N=822	Starting dialysis	Age, comorbidity	Low (0-4), medium (5-9), high (>9)
Fried et al.,[86] 2001	Single center N=268	PD	Age, comorbidity, albumin	HR, increase in the CCI
Beddhu et al.,[87] 2002	Single center N=97	PD	Age. comorbidity,	HR, increase in the CCI
Van Manen et al.,[88] 2002	Multicenter N=1205	Starting dialysis	Comorbidity	Low-medium-high
Van Manen et al.,[79] 2003	Multicenter N=1041	Starting dialysis	Comorbidity (Khan, Davies and CCI indices)	Low-medium-high
Miskulin et al.,[89] 2003	Multicenter N=1772	HD	ICED	Low (0-1), Medium (2), High (3)
Miskulin et al.,[90] 2004	Multicenter N=1779	HD	ICED, Wright-Khan, Davies, CCI,	AUC
Hemmelgarn et al.,[91] 2003	Single center N=237	HD and PD	Comorbidity (CCI)	HR, CCI score
Couchad et al.,[92] 2009	French Rein Registry N=2500	Starting dialysis	Frailty, comorbidity	OR, Risk Score 0-9
Cohen et al.,[93] 2010	Multicenter N=449	HD	Age, comorbidity, physician´s impression	Risk quintiles
van Walraven et al.,[94] 2010	USRDS N=169,393	HD, PD, KT	Age, comorbidity, race, BMI, listed-year	Increase in risk score
Liu et al.,[95] 2010	REMIS, UNOS, N=244,651	Incident and prevalent	Age, race, comorbidity, CCI	HR, Increase in risk score (≤3, 4-7, 7-9, ≥10)
Wagner et al.,[96] 2011	Multicenter N=5447	HD, PD	Age, race, comorbidity, blood parameters	Increases in the HR
Couchad et al.,[99] 2015	REIN N=24,348	Starting dialysis	Age, gender, frailty, comorbidity, albumin	OR, Low, Intermediate, High
Floege et al.,[98] 2015	ARO and DOPPS cohorts N=11,508	Incident HD patients	Age, comorbidity, vascular access, blood parameters	Low-Intermediate-High risk
Dusseaux et al.,[100] 2015	REIN N=16,337	Incident dialysis patients	Age, gender, comorbidity, mobility	Risk score 6-18
Reuter et al.,[101] 2016	Single center N=347	Waitlisted patients	Procam, Framinghan, ESC-score, Muenster scores	Increase in standard point-scoring systems
Yang, et al.,[103] 2016	NHIRD N=3046	HD	CHADS2, CHA2DS2 and CCI scores	Risk score, AUC
Ivory et al.,[97] 2017	Australia-New Zealand Registry N=23,658	Starting dialysis	Age, comorbidity, late referral	OR, AUC
Ma et al.,[102] 2017	Single center N=461	Incident PD patients	CCI, Hemmelgarn score, and Liu score	Increase in risk score
Chen et al., [63] 2017	USRDS N=159,362	Incident dialysis patients	Age, BMI<18, comorbidity and being institutionalized	Increase in risk score groups

Predictors of mortality included age >80 years, body mass index <18 kg/m^2, congestive heart failure, chronic pulmonary disease, immobility and being institutionalized. A scoring system was internally validated, such that 5-year mortality was 47% for the lowest risk score group and >90% for the highest risk population [63]. The application of this risk score in our two elderly patients is also shown in Table 3. These risk scores could well be used to estimate mortality risk in elderly patients who initiate dialysis, but not all waitlisted patients for KT. Additionally, the prediction capacity could differ substantially depending on specific

variables or comorbidities included in the models, as recently reported [101–103]. Lastly, a composite risk model has been developed in exclusively waitlisted patients for KT using age, CCI, the presence of a central venous catheter and employment status. Patient survival in patients without risk factors was compared with that in patients with one or more risk factors; the mortality risk increased significantly at each risk level [21]. This could be useful to prioritize selection in high-risk patients waitlisted for KT.

What is the situation in KT recipients? Despite poorer outcomes compared with younger KT recipients, older KT patients show a significant improvement in survival compared with age-matched waitlisted patients. However, death with a functioning graft is still the second most common cause of graft loss, especially in the elderly population [42, 52]. Predicting mortality and comorbidity in these patients could be very convenient to determine the most timely therapeutic measures and thus decrease mortality. Given that application of prognostic indices used in the general population (e.g. Framingham score) could underestimate the mortality risk in the transplant population [104, 105], an appropriate assessment of survival in these patients should include both classical and non-classical risk factors plus transplant-related factors and community-based health indicators in the predictive models, because traditional risk factors alone do not sufficiently explain the high mortality [43]. Finally, frailty has also been recently associated with high mortality in KT recipients [47, 106].

Recent years have seen the development and validation of several prognostic indices for mortality and comorbidity (mainly IHD) in KT recipients [12, 32, 40, 55, 63, 94, 107–128] (Table 5) and several e-resources (e.g. www.transplantscore.com, www.transplantmodels.com or www.renalmed.co.uk/risk-calculator) driven from these risk scores are now available for this population [129]. Some of these indices are based on risk scores applied to the general population [109, 111, 118, 124], whereas others have also included pre- and post-transplant variables (Table 5). In general, they all accurately predict the risk of death or appearance of IHD and some attempts have been made to internally validate or compare the performance of these predictive models, mostly using registry data, but as yet, few have been externally validated in prospective studies. The creation of standardized and validated processes for risk model development, using data from national registries, could help transplant teams worldwide and facilitate international comparisons in order to improve transplant outcomes, as previously suggested [130]. Additionally, very few models have exclusively assessed patient survival in advanced-age recipients or they have only focused on the effect of age on survival [32, 40, 41, 55, 63, 108, 112, 116, 118]. As a consequence, there is currently no consensus about the optimal survival prediction risk score for elderly KT. Meanwhile, transplant clinicians should implement the most useful risk model according to their own transplant center or characteristics patients. Table 6 shows several risk scores to predict mortality in KT recipients. These scores have been internally and/or externally validated and they can be used to help transplant physicians in their decision-making in daily clinical practice. For instance, a prognostic index for mortality developed in a single-center cohort study assigned older patients (>60 years) without additional comorbidities to the highest-risk group for death after KT [108], as would be expected in our Patient A (78% survival at the fifth year post-transplantation), which can be considered as an acceptable mortality and a clinically manageable situation. By contrast, this figure for our Patient B would be 70% at the same post-transplantation time (Table 3). Grams et al, using a cohort of 6988 KT recipients 65 years or older, developed a prediction model for mortality by logistic regression involving 4 demographic and 15 comorbidity variables [32]. Application of the model to our Patient A gives an acceptable predicted 3-year post-transplant survival (75%), being considered a priori a good candidate for KT. The predicted 3-year post-transplant survival of our Patient B would be 69%. In a sub-analysis of 67 elderly patients (70 years or older) who received a KT, performed by Dusseux et al. using logistic regression in a cohort of ESRD patients from the French national registry, patients with a risk score <6 points showed a good prognosis at the first three years post-transplantation [100]. Using a recent predictive score proposed by Molnar et al. [127], our elderly Patient A would have a probability of death at the first

Table 5. Predictive models for death and ischemic heart disease in kidney transplantation from deceased or living donors. Abbreviations: ANNs, artificial neural networks; CCI, Charlson Comorbidity Index; CORR, Canadian Organ Replacement Registry; GF, graft failure; HR, hazard ratio; IHD, ischemic heart disease; MACE, major adverse cardiac events, including cardiac death; OPTN, Organ Procurement and Transplantation Network; OR, odds ratio; SIUT, Sindh Institute of Urology and Transplantation database; SRTR, Scientific Registry of Transplant Recipients; UNOS, United Network for Organ Sharing; USRDS, US Renal Data System

Reference, year published	Study data, patients, (Transplant dates)	Outcomes	Time of comorbidity assessment	Risk prediction method
Ojo et al.,[107] 2000	USRDS, 86,502 (1988-1997)	Death	Pretransplant	HR
Ojo et al.,[12] 2001	USRDS, UNOS 41,892 (1992-1998)	Death, GF	Pretransplant	HR
Hernandez et al.,[108] 2005	Single center, 1,293 (1981-2001)	Death	Pretransplant and peritransplant	HR
Jassal et al.,[109] 2005	CORR, 6,324 (1988-1999)	Death	Pretransplant	HR, increase in the CCI
Jassal et al.,[110] 2005	CORR, 6,324 (1988-1999)	Death	Pretransplant	HR
Wu et al.,[111] 2005	Single center, 715 (1998-2007)	Death, GF	Pretransplant	Cut-off CCI≥ 5 vs.<5
Cardinal et al.,[112] 2005	Single center, 256 (1985-2000)	Death, GF	Pretransplant	HR
Schaeffner et al.,[113] 2006	Single center, 710 (1996-1998)	Death, GF	Post-transplant	HR
Lin et al.,[114] 2008	USRSD, UNOS 57,389 (1995-2002)	Death, GF	Pretransplant	ANNs, HR, AUC
Cosio et al.,[115] 2008	Single center, 933 (1998-2006)	Death	Pretransplant	HR
Moers et al.,[116] 2009	UNOS, 99,860 (1994-2006)	Death, GF	Pretransplant	OR, HR
Hernandez et al.,[117] 2009	Multicenter, 4,928 (1990-2002)	Death	Pretransplant and 1 y. post-transplant	HR
Heldal et al.,[118] 2009	Single center, 1494 (1990-2005)	Death, GF	Pretransplant and post-transplant, including CCI	HR
Machniki et al.,[119] 2009	USRDS, 25,270 (1995-2002)	Death, GF	Pretransplant	HR
Israni et al.,[120] 2010	Multicenter, 23,575 (>1990)	IHD	Pretransplant and post-transplant	HR
van Walraven et al.,[94] 2010	USRDS, 169,393 (1995-2006)	Death	Wait-list time	Points from HR
Kasiske et al.,[121] 2010	USRDS and OPTN, 59,091 (2000-2006)	GF, Death	Pretransplant, 1 w. and 1 y. post-transplant	HR
Heldal et al.,[55] 2011	Single center, 160 2000-2005	Death	Pretransplant and post-transplant	HR
Soveri et al.,[122] 2012	Multicenter, 2012 (1996-1997)	MACE	Pretransplant and post-transplant	HR
Molnar et al.,[40] 2012	SRTR, 145,470 (all patients up to 2006)	Death, GF	Pretransplant	HR
Grams et al.,[32] 2012	UNOS, USRDS 6988 (1999-2006)	Death	Pretransplant	OR
Dahle et al.,[123] 2015	Single center, 1497 (2007-2012)	Death	Pretransplant and post-transplant	HR
Laging et al.,[124] 2016	Single center, 1728 (2000-2013)	Death, GF	Pretransplant, CCI	HR
Lorent et al.,[125] 2016	Multicenter, 3439 (2000-2012)	Death	Pretransplant and 1-year post-transplant	HR
Zafar et al.,[126] 2016	SIUT database, 2283 (1993-2009)	Death, GF	Pretransplant	HR
Molnar et al.,[127] 2017	USRDS 15,125 (2001-2006)	Death, GF	Pretransplant	HR
Seoane-Pillado et al.,[128] 2017	Single center, 2029 (1981-2011)	Death, MACE	Pretransplant and post-transplant	HR
Chen et al., [63] 2017	USRDS, 2397 (2006-2014)	Death	Age, BMI<18, comorbidity and being institutionalized	Points from HR

and fifth year post-transplantation of 12% and 28%, respectively. By contrast, our Patient B would have a higher mortality risk (16% and 50%, respectively), as shown in Table 3. Lastly, as an alternative to the CCI, Laging et al. developed the Rotterdam Comorbidity in Kidney Transplantation (RoCKeT) score using comorbidities similar to those in the CCI, including age [124]. Not surprisingly, comorbidity was highest (75%) in the oldest age group (70-79 years). However, 50% of the patients in the highest comorbidity group survived more than 10 years. Accordingly, the authors concluded that patients with severe comorbidity should not, a priori, be excluded from KT because transplant offers better survival than dialysis therapy. Here, the 5-year post-transplant mortality in our Patient A would be 6%, whereas it would be 30% for our Patient B (Table 3). When the risk scoring system elaborated by

Table 6. Several published scores, internally and/or externally validated in other populations, to predict mortality after kidney transplant. Abbreviations: CCI, comorbidity Charlson Index; TX, kidney transplant, CVD, cardiovascular disease; WL, waiting list; PVD, peripheral vascular disease; CVA, cerebrovascular accident; HIV, human immunodeficiency virus; RRS, Recipient Risk Score; MACE, major adverse cardiovascular events

Reference, year published, (transplant dates)	Population	Assessment/risk stratification
Wu et al., [111] 2005 (1998-2003)	All ages (>18 y)	Assessment: cut-off of pretransplant CCI score (CCI<5 vs. ≥5) • Scoring based on: age and CCI
Hernandez et al., [108] 2005 (1981-2001)	All ages (>18 y)	Assessment: Patients were stratified into three risk groups (low, medium, and high) by combining peritransplant risk factors for mortality after hospitalization and using beta-coefficient from multivariate Cox analysis • Scoring based on: age, selected pretransplant comorbidities, renal dysfunction at discharge, diabetes, time on dialysis, and acute tubular necrosis
Cardinal et al., [112] 2005 (1985-2000)	≥60 ys.	Assessment: Relative risk of mortality and crude rates of patient survival at 1, 5, and 10 years post-transplant Scoring based on: smoking, BMI, time on dialysis before TX
Hernandez et al., [117] 2009 (1990-2002)	All ages (>18 y)	Assessment: The probability of 3-year post-transplant mortality by score risk quartiles, using beta-coefficient from multivariate Cox analysis • Scoring based on: age, hepatitis C, diabetes (Pre and post-TX), proteinuria and renal function at the 1st y, and immunosuppressants
Machnicki et al., [119] 2009 (1995-2002)	All ages (>18 y)	Assessment: Adjusted hazard risks for death using multivariate Cox regression models • Score based on: pretransplant comorbidities from Medicare claims with the Clinical Classifications Software (CCS), Charlson and Elixhauser comorbidities
van Walraven et al., [94] 2010 (1995-2006)	All ages (>18 y)	Assessment: Scoring system: An individual patient's index score can be calculated by summing up the points for each applicable risk factor • Scoring based on: age stratus, BMI, cause of renal disease, race, year of transplant, comorbidities and time on WL
Kasiske et al., [121] 2010 (2000-2006)	All ages (>18 y)	Assessment: The final prediction models can be used to estimate predicted probability of both all-cause mortality and graft failure within 5 years of transplant from each of 3 times: at the time of transplant, 7 days post-transplant, and 1 year post-transplant • Scoring based on: pretransplant, 1st week and 1-year post-transplant clinical variables
Soveri et al., [122] 2012 (1996-1997) Cardiovascular Risk Calculator for Renal Transplant Recipients, http://www.anst.uu.se/insov254/calculator/	All ages (>18 y)	Assessment: MACE-Free Survival Calculation (probability of 7-year MACE-free survival) • Scoring based on: recipient age, smoking, coronary heart disease, diabetes, creatinine, renal replacement therapy and number of transplants
Grams et al., [32] 2012 (1999-2006)	≥65 y.	Assessment: quintile of predicted 3-year post-transplantation survival (top quintile, excellent candidates; quintiles 2 and 3, good candidates; quintiles 4 and 5, remaining candidates. • Scoring based on: age recipient, time on dialysis, drug-depent, selected comorbidities, smoking and transplant year >1999
Sorensen et al., [17] 2016 (1995-2011)	All ages (>18 y)	Assessment: Mortality risk combining recipient age, type of transplant and CCI (<2, 3-4 and ≥5) • Scoring based on: recipient age (five stratus), type of transplant and CCI
Laging et al., [124] 2016 (2000-2013)	All ages (>18 y)	Assessment: two comorbidity scores: The Rotterdam Comorbidity in Kidney Transplantation score (four strati: 0, 1-2, 3-4, 5-9) and CCI • Scoring based on: age, diabetes, malignancy. HIV, PVD, CVA, liver disease and lung disease or CCI
Lorent et al., [125] 2016 (two cohorts: 2000-2012 and 2008-2012)	All ages (>18 y)	Assessment: 1-year mortality scoring system: cut-off at 0.03 for the 1-year RRS and 2.24 for the RRS • Scoring based on: recipient age, time on dialysis, pretransplant CVD and 1-year serum creatinine or RRS
Molnar et al., [127] 2017 (2001-2006) www.TransplantScore.com	>65 y	Assessment: estimated post-transplant survival using beta-coefficients from multivariable model for mortality • Scoring based on: recipient age, race, cause and length of renal disease, biochemical parameters, selected comorbidities, donor characteristics, diabetes status and type of insurance
Chen et al., [63] 2017 (2006-2013)	>70 y	Assessment: scoring system: 1 (low risk) to 5 (high risk) points • Scoring based on: recipient age>80 y; BMI<18; comorbidities; immobilization; institutionalized patients

Chen at al for elderly dialysis patients was applied to KT recipients, the 5-year mortality was approximately 40% in the highest risk score, whereas it was 90% for age-matched high risk candidates for KT [63]. The fact that use of expanded criteria donor kidneys has not

been associated with increased mortality in recipients older than 70 years supports these findings [40].

Conclusion

Advanced age should not be an absolute contraindication to KT in carefully selected ESRD patients, because KT offers a higher survival rate than dialysis therapy, even in the elderly. Waitlisted patients, especially older patients, have a higher mortality risk than age-matched KT recipients. Thus, identification of risk factors for death in waitlisted patients, especially elderly candidates, could help to allocate and prioritize high-risk patients for KT. As the number of organs is limited worldwide, decisions should be based on the best clinical evidence to afford equal opportunities of receiving KT in both high-risk and low-risk waitlisted elderly patients. Finally, older KT recipients have a significantly higher mortality, mainly those receiving low-quality grafts, than younger KT patients. Thus, risk scores to predict both perioperative and early post-transplant mortality could contribute to the better management of high-risk patients and the use of prophylactic interventions to prolong survival, provided a higher mortality is assumed.

Disclosure Statement

The authors declare they have no conflicts of interest regarding the publication of this article.

Abbreviations

ASA (American Society of Anesthesiology); BMI (body mass index); CCI (Charlson Comorbidity index); CV (cardiovascular); ESRD (end-stage renal disease); IHD (ischemic heart disease); KT (kidney transplantation); PVD (peripheral vascular disease); QOL (quality of life); WL (waiting list).

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