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Review – Renal Disease

Kidney Transplant Outcomes in Elderly Population: A Systematic Review and Meta-analysis

Alberto Artiles [a,†], *Ana Domínguez* [a,†], *José Daniel Subiela* [a], *Romain Boissier* [b,c], *Riccardo Campi* [d,e], *Thommas Prudhomme* [f], *Alessio Pecoraro* [d], *Alberto Breda* [g], *Francisco Javier Burgos* [a], *Angelo Territo* [g,‡], *Vital Hevia* [a,‡,*], *on behalf of the EAU-YAU Kidney Transplantation Working Group*

[a] *Urology Department, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Alcalá University, Madrid, Spain;* [b] *Aix-Marseille University, Marseille, France;* [c] *Department of Urology & Renal Transplantation, La Conception University Hospital, Assistance-Publique, Marseille, France;* [d] *Unit of Urological Robotic Surgery and Renal Transplantation, Careggi Hospital, University of Florence, Florence, Italy;* [e] *Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy;* [f] *Department of Urology and Kidney Transplantation, Rangueil University Hospital, Toulouse, France;* [g] *Urology Department, Fundación Puigvert, University Autónoma of Barcelona, Barcelona, Spain*

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Abstract

Context: Owing to population ageing, a growing number of kidney transplants (KTs) in elderly population are being performed. KT is the best treatment for patients with end-stage renal disease (ESRD). However, in older patients, the decision between dialysis and KT can be difficult due to potential inferior outcomes. Few studies have been published addressing this issue, and literature outcomes are controversial.
Objective: To conduct a systematic review and meta-analysis to appraise the evidence about outcomes of KT in elderly patients (>70 yr).
Evidence acquisition: A systematic review and meta-analysis (PROSPERO registration: CRD42022337038) was performed. Search was conducted on PubMed and LILACS databases. Comparative and noncomparative studies addressing outcomes (overall survival [OS], graft survival [GS], complications, delayed graft function [DGF], primary nonfunction, graft loss, estimated glomerular filtrate rate, or acute rejection) of KT in people older than 70 yr were included.
Evidence synthesis: Of the 10 357 yielded articles, 19 met the inclusion criteria (18 observational studies, one prospective multicentre study, and no randomised controlled trials), enrolling a total of 293 501 KT patients. Comparative studies reporting enough quantitative data for target outcomes were combined. There were significant inferior 5-yr OS (relative risk [RR], 1.66; 95% confidence interval [CI], 1.18–2.35) and 5-yr GS in the elderly group (RR, 1.37; 95% CI, 1.14–1.65) to those in the <70-yr group. Short-term GS at 1 and 3 yr was similar between groups, and

† These authors contributed equally to this manuscript and share first authorship.
‡ These authors contributed equally to this manuscript and share senior authorship.
* Corresponding author. Urology, Ctra Colmenar km 9,100, Madrid 28034, Spain. Tel. +34 645 946 800; Fax: +34 913 368 760.
E-mail address: vital.hevia.uro@gmail.com (V. Hevia).

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similar findings occurred with DGF, graft loss, and acute rejection rates. Few data about postoperative complications were reported.
Conclusions: Elderly recipients have worse OS at all time points and long-term GS compared with younger recipients (<70 yr). Postoperative complications were under-reported and could not be assessed. The DGF, acute rejection, death with functioning graft, and graft loss were not inferior in elderly recipients. Geriatric assessment in this setting might be useful for selecting better elderly candidates for KT.
Patient summary: Compared with younger population, kidney transplant in elderly patients has inferior patient and graft survival outcomes in the long term.

1. Introduction

Kidney transplant (KT) is considered the best treatment for end-stage renal disease (ESRD) [1], as it supposes a survival benefit as well as an improvement of health-related quality of life (QoL) compared with dialysis regardless of age [2]. The percentage of elderly patients on the waiting list for KT is growing in the past decades, as the number of KTs in this population is also increasing; population over 70 yr accounted for 12% of all recipients in France [1] and 17% of patients in the waiting list in Norway [3]. This group of patients will become clinically more relevant in the near future, as the number of people aged 75–84 yr in the European Union (EU) is projected to increase by 60.5% from 2018 to 2050 [4]. In Europe, the average age of recipients has increased by 10 yr over the past two decades, while in the USA, the proportion of patients aged 65–74 yr included in the waiting list increased from 2% in the 1990s to >10% in 2012 [1].

The definition of elderly people remains controversial, with different cut-off points existing in medical literature. Old people are defined by the United Nations in the World Population Ageing 2013 Report [4] as those aged >60 yr and very old as those aged >85 yr, while the World Health Organization (WHO) states that older people in developed countries are those aged >65 yr.

Undoubtedly, ageing implies complex medical conditions such as multiple comorbidities, frailty, and cognitive impairment, which can pose real barriers to KT and threaten its outcomes and patient status. Additionally, older population usually have immunity disorders, and all these issues may expose elderly patients to a higher risk of complications such as infections and post-transplant malignancies [2]. There is considerable debate in transplant community about the potential benefit of KT in elderly patients. Some studies in literature have reported their outcomes in recipients aged >70 yr with variable outcomes. In contrast to liver transplantation field, in which systematic reviews (SRs) have been performed to assess outcomes in elderly patients [5], to date there is no SR addressing the outcomes of KT in this population.

The aim of this study was to perform an SR and meta-analysis to appraise all available evidence about outcomes of KT in elderly patients (>70 yr). This age limit was decided by the European Association of Urology Young Academic Urologists (EAU-YAU) Kidney Transplantation Working Group, as it represents, to our knowledge, the elderly age in developed countries' literature. The primary objectives were to assess graft survival (GS)—noncensored for death, patient overall survival (OS), and complications (according to the Clavien-Dindo classification) of patients aged >70 yr receiving a KT and to compare these with those in younger population.

The secondary objectives were as follows: (1) delayed graft function (DGF), defined as the need for dialysis during

Table 1 – Baseline characteristics of population receiving a kidney transplant (KT) in the included studies stratified by age (>70 and <70 yr)

	>70 yr	<70 yr
N = 293 501	23 917	269 584
Age (yr), median (range)	73.5 (70.3–81.6)	57.4 (46.4–67.2)
Donor age (yr), median (range)	55.0 (45.4–77.0)	47.7 (39.0–71.6)
Follow-up (yr), median (range)	50.9 (38.8–72.7)	64.2 (47.0–72.0)
BMI	26.5 (25.5–28.0)	27.4 (26.3–29.0)
Hypertension, % (*n*)	28.1% (3122/11 102)	3.6% (5285/147 786)
Diabetes, % (*n*)	20.0% (4556/22 734)	13.7% (36 145/264 555)
Coronary disease, % (*n*)	9.4% (1477/15 759)	3.4% (6254/183 035)
Time on dialysis prior to KT (mo), median (range)	23.0 (6.2–47.7)	37.0 (6.9–64.1)
Type of dialysis, % (*n*)		
Haemodialysis	67.0 (817/1219)	82.2 (37/45)
Peritoneal	15.8 (193/1219)	17.8 (8/45)
Type of donor, % (*n*)		
LD	27.3 (6340/23 239)	35.0 (93 249/266 419)
DBD	46.4 (5009/10797)	18.5 (21 163/114 490)
ECD	18.5 (3575/19 638)	2.7 (6824/256 417)
DCD	4.3 (582/13 546)	2.1 (2581/123 511)
Number of KT, % (*n*)		
1st	98.7 (17402/17 638)	91.1 (114 311/125 431)
Retransplant	1.3 (236/17 638)	8.9 (11 120/125 431)
CIT (h), median (range)	13.8 (2.0–26.0)	13.3 (2.2–24.9)
WIT (min), median (range)*	51.2	48.0

BMI = body mass index; CIT = cold ischaemia time; DBD = donor after brain death; DCD = donor after cardiocirculatory death; ECD = expanded criteria donor; LD = living donor; WIT = warm ischaemia time.

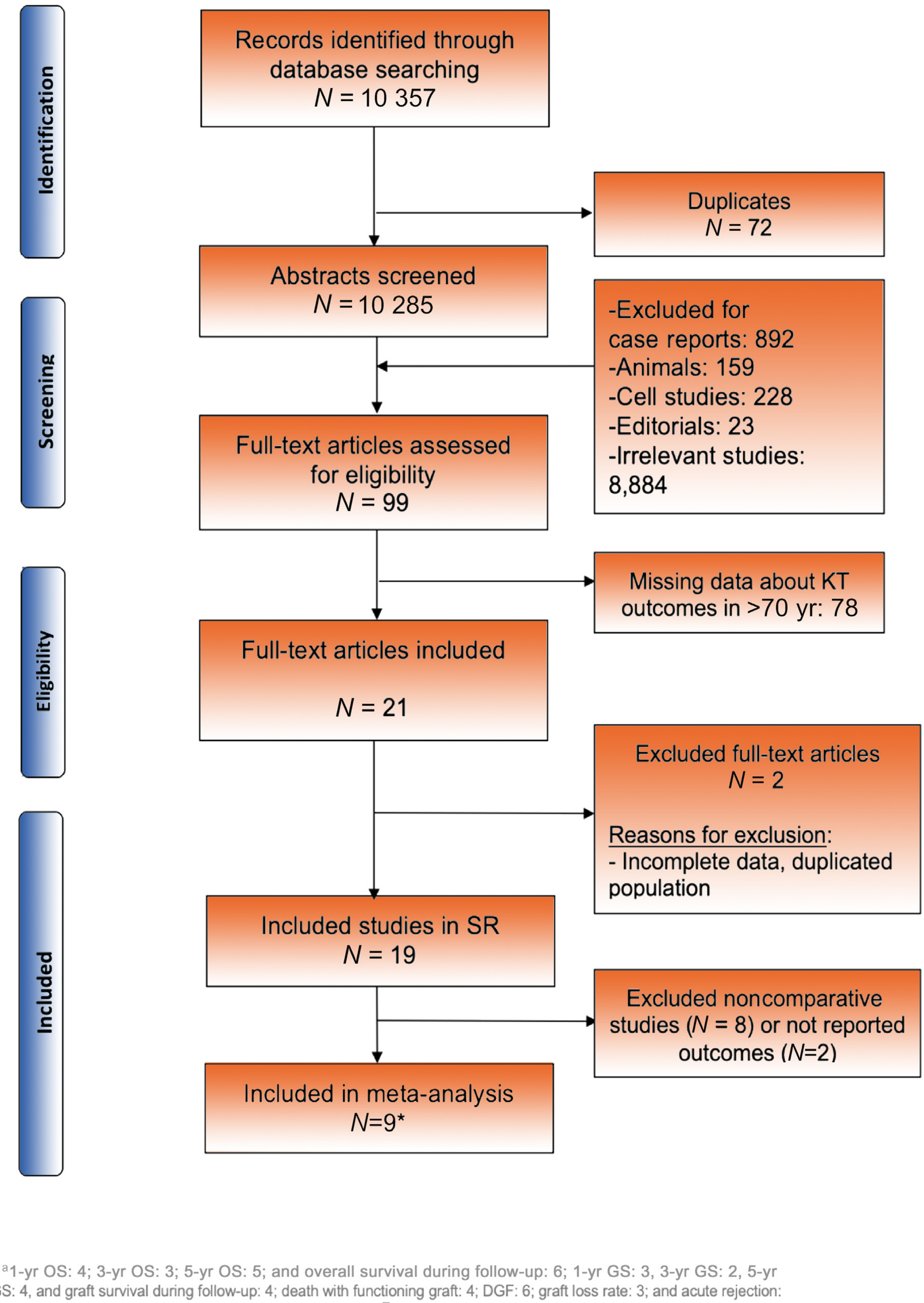

Fig. 1 – PRISMA diagram. DGF = delayed graft function; GS = graft survival; KT = kidney transplant; OS = overall survival; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; SR = systematic review.

1st week after KT; (2) primary nonfunction (PNF), defined as a permanent loss of allograft function starting immediately after transplantation; (3) graft loss rate, defined as the return to dialysis, retransplantation, or death; (4) estimated

Table 2 – Characteristics of the included studies

Study	Design	Country	Type of study	Recruitment period	Total number of KT (n)	No. of patients >70 yr	No. of patients <70 yr	Follow-up >70 yr (mo)	Follow-up <70 yr (mo)	Whole study (mo)
Doucet (2021) [10]	Prospective	Australia	Multicentre	2000–2015	12 983	299	12 684	44.4	72.0	71.4
Zompolas (2021) [8]	Retrospective	Germany	Single centre	2010–2018	85	40	45	50.9	47.0	49.0
Pletcher (2020) [15]	Retrospective	USA	Multicentre	2001–2016	83 058	3862	79 196	–	–	–
Cabrera (2020) [38]	Retrospective	Spain	Single centre	2002–2015	2037	138	0	38.8	–	38.8
Lemoine (2019) [39]	Retrospective	France	Multicentre	2000–2014	171	171	0	–	–	–
Thiessen (2017) [16]	Retrospective	USA	Single centre	1987–2013	10 511	2730	7781	–	–	–
Ravinuthala (2017) [7]	Retrospective	USA	Multicentre	1988–2013	298 455	471	-	–	–	–
Lønning (2016) [43]	Retrospective	Norway	Single centre	1983–2015	411	411	0	–	–	–
Saucedo-Crespo (2016) [17]	Retrospective	USA	Multicentre	2003–2013	2624	300	2324	–	–	–
Al-Shraideh (2014) [18]	Retrospective	USA	Single centre	2001–2012	884	104	780	–	–	70.0
Molnar (2012) [11]	Retrospective	USA	Multicentre	1998–2006	145 470	5566	139 904	–	–	48.6
Boesmueller (2011) [12]	Retrospective	Austria	Single centre	1999–2009	83	19	56	72.7	64.2	–
Heldal (2011) [3]	Retrospective	Norway	Single centre	2000–2005	160	160	0	61.2	–	–
Huang (2010) [9]	Retrospective	USA	Multicentre	2000–2008	31 179	6302	24 877	–	–	–
Sener (2009) [13]	Retrospective	USA	Single centre	1992–2007	3297	188	3109	–	–	–
Heldal (2009) [14]	Retrospective	Norway	Single centre	1990–2005	2310	354	1140	–	–	–
Rao (2007) [44]	Retrospective	USA	Multicentre	1990–2005	2438	2438	0	–	–	–
Macrae (2005) [45]	Retrospective	USA	Multicentre	1994–2000	80 217	258	-	–	–	–
Albrechtsen (1995) [46]	Prospective	Norway	Single centre	1983–1993	126	126	0	–	–	–

KT = kidney transplant.

glomerular filtrate rate (eGFR); and (5) acute graft rejection confirmed histologically.

2. Evidence acquisition

2.1. Data sources and searches

This SR has been conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The protocol for the review was uploaded in the PROSPERO database (CRD42022337038). Databases searched were PubMed/Medline and LILACS. Full strategy search, PICOTS (Population, Intervention, Comparator, Outcome, Type of study, Timing, and Setting) table, and inclusion criteria are shown in the Supplementary material.

No language or year restrictions were applied, and the database was complemented by screening the reference list of the included studies.

2.2. Inclusion criteria and study eligibility

Studies eligible for inclusion were those reporting outcomes (at least one primary or secondary endpoint) of patients older than 70 yr who underwent KT (in single-arm studies) and those younger than 70 yr (in comparative ones). All study designs were eligible for inclusion, except reviews, editorials, letter to the editor, case reports, and studies published only as a conference abstract. Studies included were comparative studies and single-arm case series (incorporating a single intervention of KT in patients over 70 yr of age). All studies must have a minimum follow-up of 1 yr.

All identified abstracts were placed in a bibliography management software program (Mendeley) and sorted according to inclusion and exclusion folders by drag and drop. Titles and abstracts of all identified studies were reviewed independently by three authors (A.A., A.D., and J. D.S.), and discrepancies were resolved by a fourth reviewer (V.H.). The detailed inclusion criteria are summarised in the Supplementary material.

2.3. Data extraction

Data from eligible reports were extracted independently (A. A., A.D., and J.D.S.), and discrepancies were resolved by a fourth reviewer (V.H.). A data-extraction sheet was created a priori including author name, year of publication, study type, country, recruitment period, follow-up (months), total number of KTs performed in the period, number of patients aged $\leq$70 and >70 yr, age, body mass index, hypertension, diabetes, coronary disease, duration of dialysis prior to KT, dialysis modality, donor type, donor age, number of transplantations (first transplant or retransplant), Charlson Comorbidity Index (CCI), Karnofsky, Eastern Cooperative Oncology Group (ECOG), Clinical Frailty Scale, Frail Scale, cold ischaemia time (CIT), warm ischaemia time (WIT), operation time (minutes), GS, OS, DGF, PNF, creatinine level and eGFR, and complications according to the Clavien grading system.

In this SR, GS (noncensored for death) refers to the time from the date of transplantation to the date of irreversible graft failure signified by return to long-term dialysis (or retransplantation) or the date of the last follow-up during the period when the transplant was still functioning or the date of death.

2.4. Risk of bias assessment

Risk of bias assessment was performed independently (A.A. and A.D.) using the ROBINS-I tool for nonrandomised studies [6]. Study characteristics were extracted by one author, and a second author checked data extractions for accuracy. Any disagreements were resolved by discussion with a third author (V.H.). Since nonrandomised studies were included, this tool was extended with a list of important potential confounders established a priori by the YAU Kidney Transplantation Working Group. The confounders included were time on dialysis, donor type and age, and number of prior transplants. For each study, it was assessed whether each confounder was considered and whether, if necessary, the confounder was controlled for in the analysis.

2.5. Data synthesis

This review tabulates quantitative information and systematic descriptions of all studies included. Frequencies and percentages were used to report categorical variables; mean and standard deviation were used to report continuous variables. Measures of association were assessed using data reported in each study. Meta-analyses were conducted using studies with directly comparable groups, as determined by the existence of two categories (≤70 and >70 yr). Therefore, single-arm studies were excluded and only observational studies were included in meta-analysis, as there were no eligible randomised controlled studies with comparable groups. Relative risks (RRs) between two comparable groups were estimated using DerSimonian-Laird random-effect models. Heterogeneity was evaluated using the I^2 statistic, and I^2 thresholds of <25%, 25–49%, 50–75%, and >75% were considered to represent low, moderate, high, and very high heterogeneity, respectively. RRs and their 95% confidence intervals (CIs) were calculated and pooled with STATA v.15 (StataCorp, College Station, TX, USA). Statistical significance was defined as $p < 0.05$. Additionally, Egger linear regression and Begg's test were used to examine publication bias. A p value of <0.05 was defined as a significant publication bias.

3. Evidence synthesis

3.1. Search results

The search retrieved 10 357 articles. After removing duplicates (n = 72), abstracts of 10 285 papers were screened.

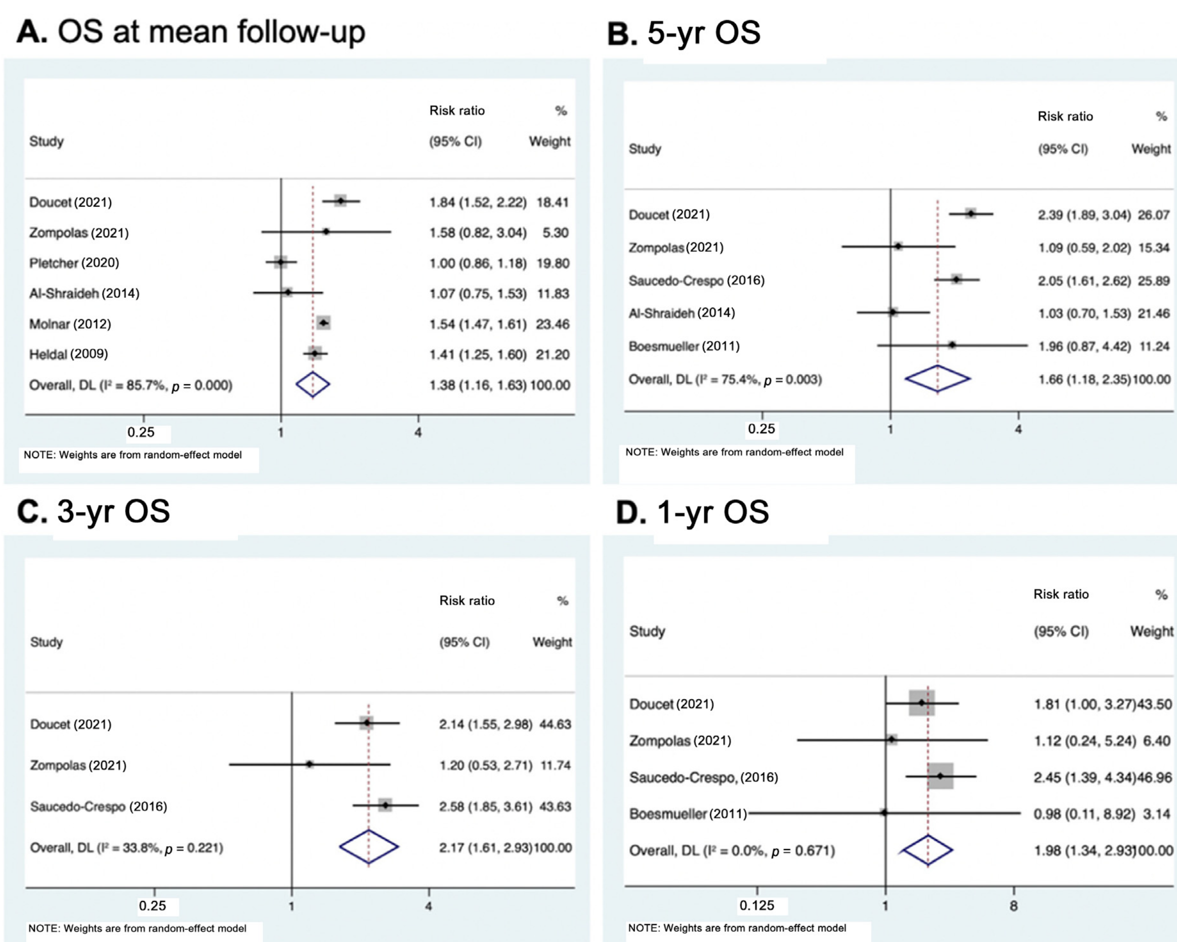

Fig. 2 – Forest plots of the pooled RRs for OS at (A) the mean follow-up, and (B) 5 yr, (C) 3 yr, and (D) 1 yr of follow-up. There was worst OS at all time points in the >70-yr group (RR, 1.66; 95% CI, 1.18–2.35; p = 0.003). CI = confidence interval; OS = overall survival; RR = relative risk.

Table 3 – Survival outcomes in percentage of population receiving a kidney transplant (KT)

N	Study	1-yr GS		3-yr GS		5-yr GS		GS		1-yr OS		3-yr OS		5-yr OS		OS		Death with functioning graft		Graft loss	
		>70 yr	<70 yr	>70 yr	<70 yr	>70 yr	<70 yr	>70 yr	<70 yr	>70 yr	<70 yr	>70 yr	<70 yr	>70 yr	<70 yr	>70 yr	<70 yr	>70 yr	<70 yr	>70 yr	<70 yr
1	Doucet (2021) [10]	94.0	95.0	85.5	90.5	76.5	85.5	69.0	77.0	96.5	98.0	88.5	95.0	80.0	92.5	71.0	86.0	74.4	43.2	31.0	23.0
2	Zompolas (2021) [8]	–	90.7	–	79.4	–	68.0	–	–	92.9	92.9	75.3	79.4	62.0	68.0	55.0	76.0	61.1	72.7	–	–
3	Pletcher (2020) [15]	–	–	–	–	–	–	90.0	94.5	–	–	–	–	–	–	88.5	96.5	–	–	–	–
4	Cabrera (2020) [38]	95.6	–	–	–	93.1	–	–	–	82.1	–	–	–	60.1	–	54.3	–	84.1	–	13.0	–
5	Lemoine (2019) [39]	82.6	–	78.7	–	75.4	–	–	–	90.1	–	82.5	–	68.1	–	76.6	–	–	–	23.4	–
6	Thiessen (2017) [16]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
7	Ravinuthala (2017) [7]	85.0	–	67.0	–	51.0	–	–	–	89.0	–	72.0	–	57.0	–	–	–	–	–	–	–
8	Lønning (2016) [43]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
9	Saucedo-Crespo (2016) [17]	98.0	98.0	96.0	96.0	91.0	94.0	–	–	95.0	98.0	86.0	95.0	77.0	90.0	–	–	–	–	–	–
10	Al-Shraideh (2014) [18]	–	–	–	–	72.0	73.7	61.5	61.4	–	–	–	–	78.0	78.8	73.5	75.4	20.0	27.0	38.5	37.4
11	Molnar (2012) [11]	–	–	–	–	–	–	90.6	85.6	–	–	–	–	–	–	71.7	83.3	–	–	9.4	14.3
12	Boesmueller (2011) [12]	95.0	98.1	–	–	82.0	92.7	–	–	95.0	94.4	–	–	57.0	82.4	–	–	–	–	–	–
13	Heldal (2011) [3]	82.3	–	–	–	–	–	–	–	–	–	–	–	–	–	46.0	–	43.0	–	–	–
14	Huang (2010) [9]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
15	Sener (2009) [13]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
16	Heldal (2009) [14]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	31.0	59.5	58.0	30.5	–	–
17	Rao (2007) [44]	93.1	–	89.2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
18	Macrae (2005) [45]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	50.1	–	–	–	–	–
19	Albrechtsen (1995) [46]	79.0	–	–	–	63.0	–	57.9	–	77.0	–	–	–	67.0	–	59.5	–	83.0	–	–	–

GS = graft survival; OS = overall survival.

Of these, 10 186 were excluded and 99 met the abstract inclusion criteria. Finally, after full-text screening, a total of 19 studies were included (Fig. 1). In total, nine studies were included in the meta-analysis and pooled estimates were obtained for different outcomes: OS at 1 yr (four studies), 3 yr (three studies), 5 yr (five studies), and overall (six studies); GS at 1 yr (three studies), 3 yr (two studies), 5 yr (four studies), and overall (four studies); death with functioning graft (four pooled studies); DGF (six studies); graft loss (three studies); and acute rejection (AR; seven pooled studies).

3.2. *Characteristics of studies, population, and interventions*

The 19 studies included a total of 293 501 patients. Table 1 summarises baseline characteristics of both groups, with a total of 23 917 recipients aged >70 yr and 269 584 younger than 70 yr. Donor age was higher in the >70-yr group: 55.0 (45.4–77.0) versus 47.7 (39.0–71.6) yr. Furthermore, a higher number of expanded criteria donors (ECDs) in >70-yr recipients was identified (18.5% vs 2.7%). Regarding other potential confounders, time on dialysis was longer in the <70-yr group (37.0 vs 23.0 mo), while both groups had similar CIT (13.8 vs 13.3 h). The median follow-up for the >70-yr group was 50.9 mo (interquartile range [IQR] 38.8–72.7) and 64.2 mo (IQR 47.0–72.0) in the <70-yr group.

Table 2 shows general features of the 19 included studies. Ravinuthala et al [7] published the study including the largest number of patients (298 455). Eleven comparative studies (ten retrospective and one prospective) were included, while the remaining eight were case series (>70 yr).

3.3. *Primary outcomes*

A quantitative analysis (meta-analysis) was performed to pool and compare outcomes between both groups. Figure 2 represents the forest plot of the pooled RR for OS. The pooled meta-analysis showed a significant decrease in 5-yr OS in patients aged >70 yr (RR: 1.66; 95% CI: 1.18–2.35). A significant difference between both groups was also observed at 1 yr (RR: 1.98; 95% CI: 1.34–2.93) and 3 yr (RR: 2.17; 95% CI: 1.61–2.93) of follow-up.

Five-year GS ranged from 51.0% to 93.1% in the elderly (>70 yr) versus 68.0 to 94.0% in the younger group (<70 yr). Table 3 contains the survival outcomes of the included studies, and Figure 3 shows the forest plot of the pooled RRs for GS. There was significantly better 5-yr GS in recipients aged <70 yr (RR, 1.37; 95% CI, 1.14–1.65), without significant differences in short term. The pooled RR of GS was 1.18 (95% CI, 0.79–1.75) at 1 yr and 1.33 (95% CI, 0.94–1.87) at 3 yr.

Concerning complications, in the studies included in this SR, very few reported complication rates and only Zompolas et al. [8] did it according to the Clavien-Dindo classification system, without complications Clavien >III in both groups.

3.4. Secondary outcomes

Figure 4 shows the forest plot of the pooled RR for DGF, AR, death with functioning graft, and graft loss.

DGF rates ranged from 19.4% to 53.6% in elderly recipients (>70 yr) and from 18.1% to 60.0% in younger ones (<70 yr; Table 4), without significant differences between both groups (RR, 1.08; 95% CI, 0.86–1.36).

Three comparative studies reported the graft loss rate. It ranged from 9.3% to 38.5% in the older group versus 14.3% to 37.4% in the younger group, without reaching statistical significance (RR, 0.95; 95% CI, 0.61–1.48).

Regarding AR, it is the most frequently reported indicator among comparatives studies (seven studies included in meta-analysis). In recipients aged >70 yr, rejection rates range from 4.3% to 40.0%, while in the younger group the rates are 4.7–50%. The pooled analysis showed no increased likelihood of AR in >70-yr old patients (RR, 0.87; 95% CI, 0.80–0.93).

Only two studies reported PNF rates. Huang et al. [9] described 1.3% for the elderly group compared with 1.2% in the younger population. Moreover, eGFR and creatinine levels were poorly reported.

3.5. Risk of bias assessment of the included studies and publication bias

Of the 11 comparative studies, five had a high [10–14] and six a moderate risk of bias [8,9,15–18]. Figure 5 includes the traffic-light plot for the risk of bias domains in ROBINS-I tool for the 11 comparative studies included in this SR. Most of the studies exhibited a moderate or high risk of bias according to this tool. Neither Egger's nor Begg's test demonstrated a significant publication bias across the articles included in the meta-analysis for any endpoint ($p > 0.05$; Supplementary material).

3.6. Discussion

3.6.1. Findings in the context of existing literature

This SR and meta-analysis highlight a gap in knowledge and research regarding outcomes of KT in older population. Along with the growing pool of elderly KT recipients, several large studies assessing KT outcomes in these patients have been published over recent years. In this scenario, it is crucial to determine outcomes and to select which patients may benefit from KT and who are at a high risk of post-transplant complications. With that purpose,

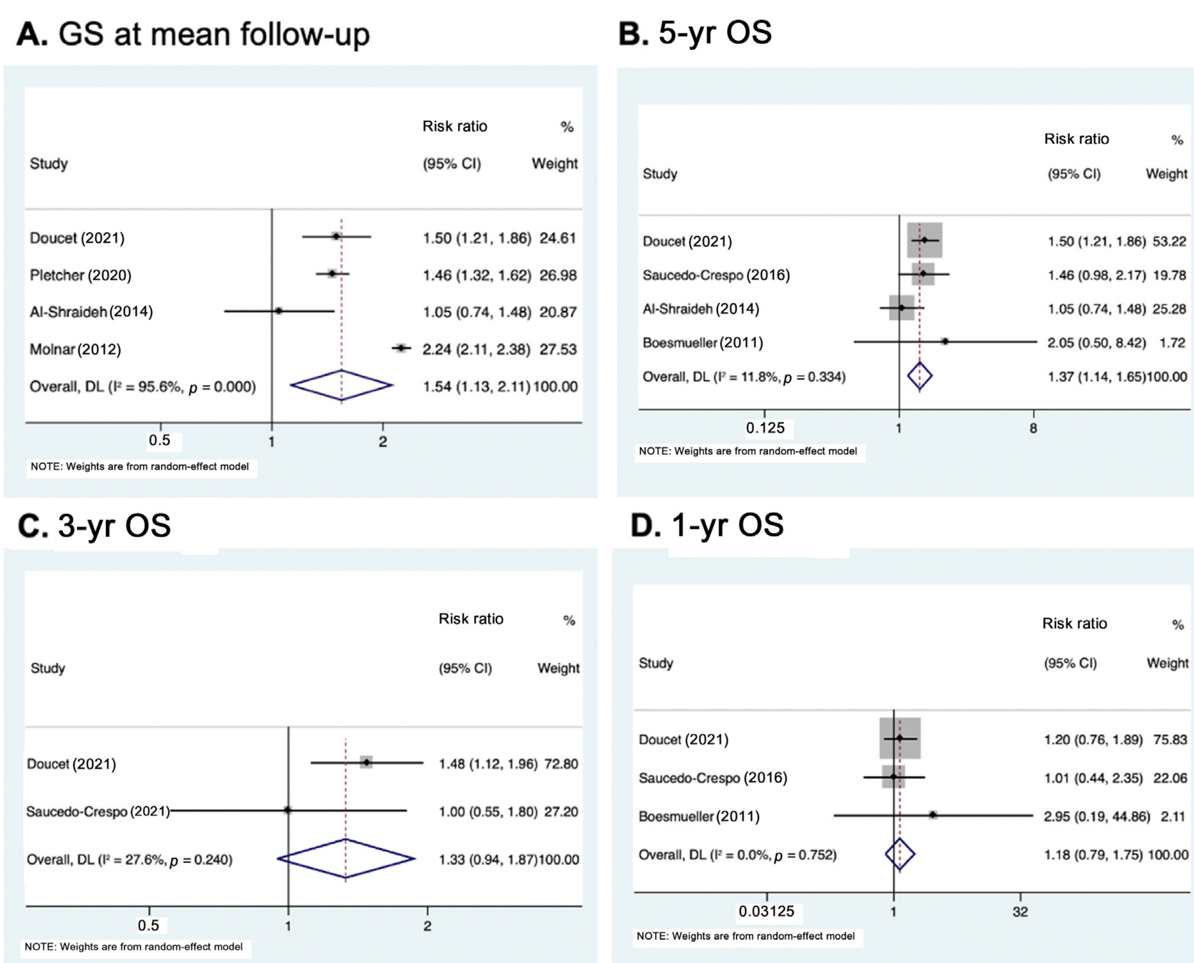

Fig. 3 – Forest plots of the pooled RRs for graft survival (GS) at (A) the mean follow-up, and (B) 5 yr, (C) 3 yr, and (D)1 yr of follow-up. There was worst GS since 5-yr time point in the >70-yr group (RR, 1.37; 95% CI, 1.14–1.65; p = 0.334). CI = confidence interval; GS = graft survival; RR = relative risk.

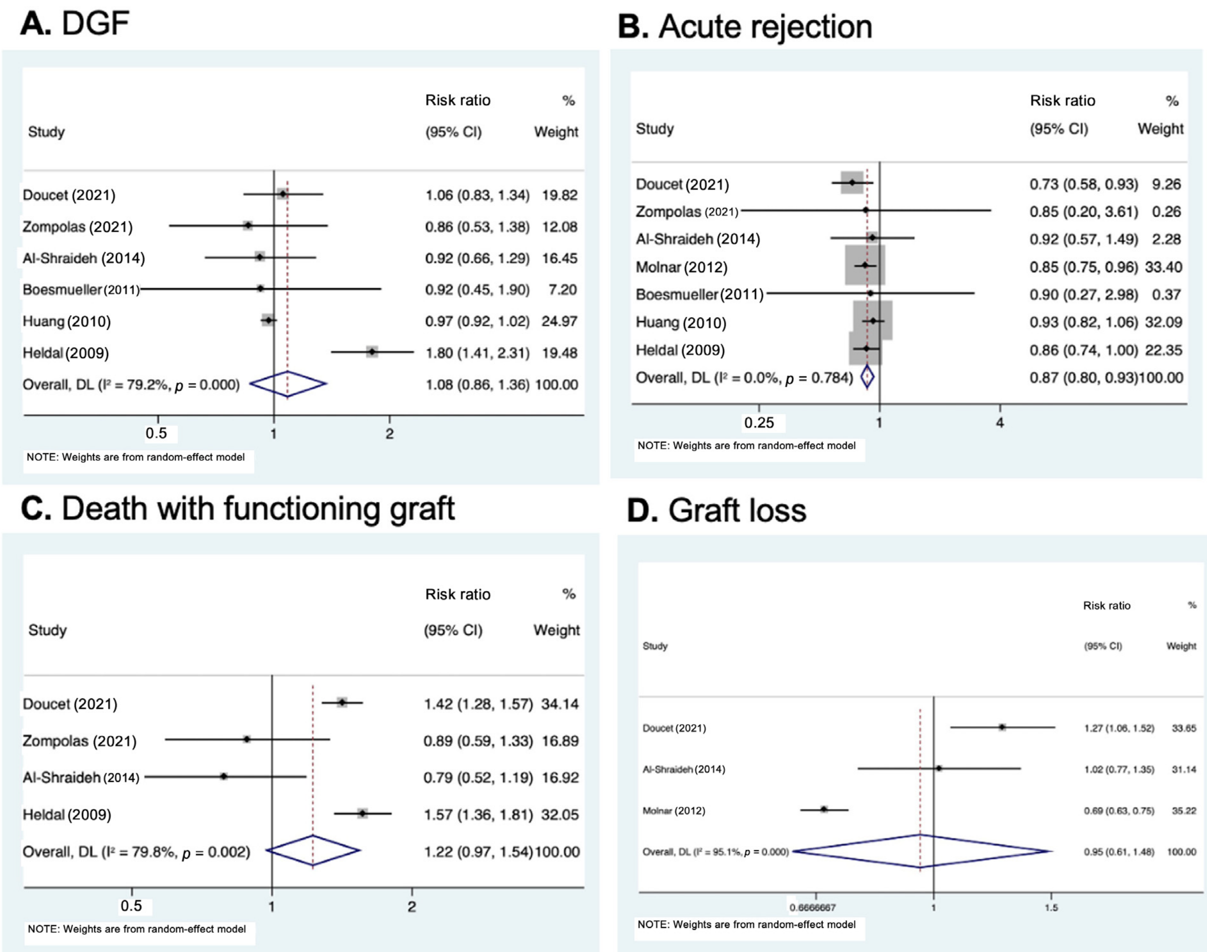

Fig. 4 – Forest plots of the pooled RRs for (A) DGF (B) acute rejection, (C) death with functioning graft, and (D) graft loss. There were no worse outcomes in the >70-yr group for any secondary endpoint. CI = confidence interval; DGF = delayed graft function; RR = relative risk.

we conducted this SR including a large number of recipients, which contributes to widen the evidence about this renal replacement therapy in this vulnerable population.

Regarding primary objectives, elderly (>70 yr) recipients have worse OS at all time points (Fig. 2), while GS remains comparable with that for young recipients (<70 yr) in the short term (1 and 3 yr) but becomes worse in the long term (5 yr and end of follow-up; Fig. 3). Complication rates, a relevant primary objective of the present study, were underreported and so could not be analysed properly.

Concerning secondary objectives, the elderly group did not have worse DGF, AR, death with functioning graft, or graft loss (Fig. 4).

3.6.2. Ageing and KT

It has been estimated that by 2030, 60% of patients with chronic kidney disease needing renal replacement therapy will be older than 65 yr [19]. Several studies have pointed out the benefit of KT compared with dialysis in terms of QoL in the majority of older recipients [20]. Moreover, this benefit in elderly population has also been observed in terms of survival compared with dialysis [21]. However, at advanced ages, a decision between dialysis and KT can be difficult mainly due to comorbidities and geriatric syndromes such as cognitive impairment or frailty [20].

Elderly population is a heterogeneous group. Medical research commonly defines people as elderly when they are aged 65 yr or above. Nevertheless, defining elderly age by chronology alone has its limitations [22]. Variability among elderly definitions depends on the life expectancy variations experienced by the population during the past decades. Indeed, a geriatric patient is not specifically age defined but rather characterised by a high degree of frailty and multiple active diseases that become more common in the age group above 80 yr, according to the Geriatric Medicine Section of the European Union of Medical Specialists [23]. In this SR, the limit of 70 yr was established by the YAU Kidney Transplantation Working Group, trying to present updated research adapted to developed countries' demography. In fact, and according to the *Eurostat Report* [24], in 2020, the life expectancy at birth in the EU was 80.4 yr. Furthermore, considering the mean age of KT recipients in our context as developed countries, in Spain, the proportion of >70-yr-old recipients transplanted has been increasing constantly during the past decade, reaching 19.2% in 2021 [25]. Very few studies have explored the outcomes of KT in the very old recipients (>80 yr). According to

Table 4 – Comparative functional outcomes and complications of KT recipients according to study groups (<70- and >70-yr old)

	DGF		PNF		Acute rejection		UTI		Haematoma		Vascular complication		Ureteral stricture		Lymphocele	
	>70 yr	<70 yr	>70 yr	<70 yr	>70 yr	<70 yr	>70 yr	<70 yr	>70 yr	<70 yr	>70 yr	<70 yr	>70 yr	<70 yr	>70 yr	<70 yr
Doucet (2021) [10]	19.4% (54/279)	18.1% (1880/10 372)	–	–	19.0% (53/279)	28.0% (2904/10 372)	–	–	–	–	–	–	–	–	–	–
Zompolas (2021) [8]	47.5% (19/40)	60.0% (27/45)	–	–	7.5% (3/40)	8.9% (4/45)	–	–	–	–	0% (0/40)	2.2% (1/45)	–	–	–	–
Pletcher (2020) [15]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cabrera (2020) [38]	53.6% (74/138)	–	6.5% (9/138)	–	15.2% (21/138)	–	41.3% (57/138)	–	10.1% (14/138)	–	11.6% (16/138)	–	2.2% (3/138)	–	5.8% (8/138)	–
Lemoine (2019) [39]	30.6% (48/171)	–	–	–	20.9% (33/171)	–	18.7% (29/171)	–	11.1% (19/171)	–	5.3% (9/171)	–	10.5% (18/171)	–	11.1% (19/171)	–
Thiessen (2017) [16]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Ravinuthala (2017) [7]	23.3% (110/471)	–	–	–	5.7% (27/471)	–	–	–	–	–	–	–	–	–	–	–
Lønning (2016) [43]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Saucedo-Crespo (2016) [17]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Al-Shraideh (2014) [18]	28.8% (30/104)	32.0% (251/780)	–	–	15.4% (16/104)	17.0% (132/780)	–	–	–	–	–	–	–	–	–	–
Molnar (2012) [11]	–	–	–	–	4.3% (239/5566)	5.1% (7067/139 904)	–	–	–	–	–	–	–	–	–	–
Boesmueller (2011) [12]	36.8% (7/19)	41.1% (23/56)	–	–	15.8% (3/19)	17.8% (10/56)	–	–	–	–	5.3% (1/19)	3.6% (2/56)	10.5% (2/19)	0% (0/56)	–	–
Heldal (2011) [3]	52.5% (84/160)	–	–	–	22.0% (35/160)	–	–	–	–	–	–	–	–	–	–	–
Huang (2010) [9]	24.9% (1572/6302)	–	1.3% (82/6302)	1.2% (299/24 877)	4.4% (274/6302)	4.7% (1169/24 877)	–	–	–	–	–	–	–	–	–	–
Sener (2009) [13]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Heldal (2009) [14]	24.0% (85/354)	–	–	–	40.0% (142/354)	50.0% (570/1140)	–	–	–	–	–	–	–	–	–	–
Rao (2007) [44]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Macrae (2005) [45]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Albrechtsen (1995) [46]	59.0% (74/126)	–	–	–	59.0% (74/126)	–	–	–	–	–	–	–	–	–	–	–
Total (%)	26.4% (2157/8164)	23.5% (8761/37 270)	1.4% (91/6440)	1.2% (299/24 877)	6.9% (920/13 306)	6.7% (11 856/177 174)	27.8% (86/309)	NR	10.7% (33/309)	NR	7.1% (26/368)	3.0% (3/101)	7% (23/328)	0% (0/56)	8.7% (27/309)	NR

DGF = delayed graft function; KT = kidney transplant; NR = not reported; PNF = primary nonfunction; UTI = urinary tract infection.

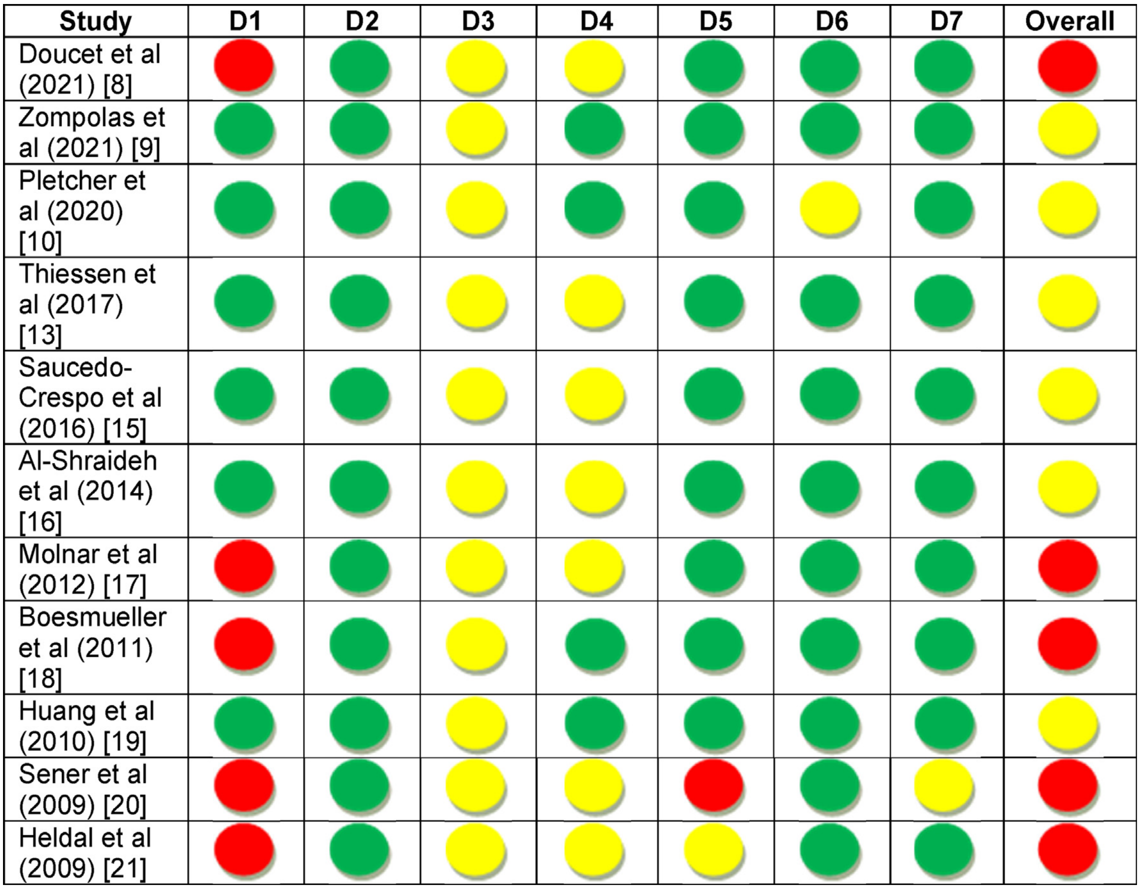

Fig. 5 – "Risk of bias" assessment for each included study. D1 = confounding; D2 = selection of participants; D3 = classification of interventions; D4 = deviations from intended interventions; D5 = missing data; D6 = measurement of outcomes; and D7 = selection of the reported result.

Ravinuthala et al. [7], octogenarians have significantly increased length of stay, perioperative mortality, and rates of graft loss.

Several authors have established an age of 65 yr to classify older KT recipients, such as McAdams-DeMarco et al. [26], who encountered that these recipients represented 18.4% of the transplanted population, a five-fold rise from 3.4% in 1990s.

To avoid a bias due to the differences between heterogeneous groups, an age-stratified analysis of outcomes, mainly survival, should ideally be performed. Nevertheless, preliminary search revealed a lack of papers analysing similar age subgroups. Recently, Vanhove et al. [27] assessed outcomes in first-time single KT recipients through multistate models and encountered that in the elderly (>75 yr), the absolute overestimation of death risk with functioning graft was four-fold higher than in the <55-yr group, concluding that these multistate models provide a comprehensive assessment of KT outcomes, particularly in older recipients, who are more prone to event rate overestimation and for whom outcomes after graft failure are worse than for younger population.

3.6.3. *Comparison between KT and dialysis*

According to the recent SR by Schoot et al. [20] assessing QoL outcomes of renal replacement therapies, these improve in the majority of the older KT recipients and were superior to dialysis. Moreover, functional status was worse, and the incidence of serious fall injuries increased in many older dialysis patients.

Dialysis patients have 10–20 times higher cardiac mortality rates than the general population, and although this risk is lessened after transplant, patients carry the burden of their time spent living with ESRD and on dialysis, and cardiac mortality rates remain high. According to Wyld et al. [28], of 5089 deaths in 16 329 KT recipients, 18% were cardiac: older age, longer dialysis duration, and earlier era of transplantation were associated with this outcome.

3.6.4. *The use of frailty and comorbidity scores*

Based on the Consensus Guidelines of the Canadian Society of Transplantation, advanced age per se is not a contraindication for KT, so older patients with ESRD without medical or surgical contraindications should be considered candidates [21]. Age-associated comorbidities expose elderly recipients to a high risk of postoperative complications [19]. Particularly, many older patients on dialysis have cardiovascular disease that can be a barrier for KT [19]. Among KT candidates, 21% are frail and 55% have cognitive impairment, and both conditions increase the risk of mortality [29]. Moreover, the KTOP study among KT recipients estimated cognitive impairment and frailty in 36.4% and 15.8%, respectively [30], while other authors encountered 19.8% of frailty in KT recipients, assessing it through the

"Fried score" [31]. In this context, a refined assessment of elderly patients who are candidates for KT might be performed. Potential elderly recipients must be assessed precisely to exclude serious cardiovascular disease, cancer, and other comorbidities. Some indicators have been proposed to improve candidate selection. According to a recent SR, frailty is associated with higher rates of DGF and length of stay [32], so this parameter has become a popular indicator.

KT recipients present higher rates of pre-existing comorbidities, in particular diabetes mellitus, hypertension, and cardiac disease [33]. In Table 1, we can observe higher percentages of hypertension (28.1% vs 3.6%), diabetes (20.0% vs 13.7%), and coronary disease (9.4% vs 3.4%) rates in elderly patients. The CCI can be used to describe comorbidities in patients who are going to receive an intervention such as KT, but it has not proved its usefulness predicting mortality in the population age >70 yr [14]. In this SR, an attempt was made to extract data regarding frailty and comorbidity scales (CCI, Karnofsky, ECOG, Clinical Frailty Scale, and Frail Scale), but no paper except that of Heldal et al. [14] reported any information. Given the expected demographic evolution in developed countries, it would be advisable to include geriatric assessments using tools such as those mentioned above to refine recipient selection and to be able to predict complications.

3.6.5. *Heterogeneous outcomes*

Over the past decades, many studies in developed countries have reported outcomes of KT in elderly patients, assessing patient's risks and determining the age effect on GS. However, consensus has not been reached, although its safety has been reported in selected elderly patients [34]. Data are somewhat heterogeneous, mainly due to different age thresholds and nonstandardised data regarding KT outcomes, particularly from a surgical point of view. According to the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry Study, with 10 651 recipients, elderly people may have inferior OS and GS [10]. On the contrary, other researchers have published encouraging data, with lower rejection rates and better GS, although with inferior OS because of higher cardiovascular risk factors [35]. Older patients with comorbidities are less likely to be recommended for inclusion in the waiting list [36], although KT in elderly patients has been growing in the last decades [10]. Improved OS and GS with current immunosuppressive protocols have broadened the application of KT to selected elderly patients, and a rising number of patients aged >65 yr are receiving transplants [21]. Moreover, recipient's preoperative optimisation as well as effective and safe anaesthesia during KT and postoperative care contributes to successful outcomes [37].

In the present SR, 5-yr GS ranged from 51.0% to 93.1% in >70-yr and from 68.0% to 94.0% in <70-yr old recipients, with pooled RRs of 1.37 (95% CI, 1.14–1.65; I^2 11.8%, p = 0.334) at 5 yr and 1.54 (95% CI, 1.13–2.11; I^2 95.6%, p = 0.000) at the end of follow-up (Fig. 3). Concerning patient survival, there was significantly lower OS at all time points in the >70-yr group (at 5 yr of follow-up: RR, 1.66; 95% CI, 1.18–2.35; I^2 75.4%, p = 0.003; Fig. 2). Although probably explained in part by age, this finding makes it necessary to be cautious when deciding to go for KT in elderly patients.

In the current meta-analysis, the pooled RR for graft loss rates was 0.95 (0.61–1.48, p = 0.000; Fig. 4). In this sense, it seems to be constant throughout literature that similar AR and graft loss rates are described between older and younger recipients; Molnar et al. [11] reported a graft loss rate of 9.4% in elderly recipients compared with 14.3% in younger recipients. Regarding other functional outcomes, results from the meta-analysis indicate that there was not a significant difference in DGF between both groups (RR, 1.08; 95% CI, 0.86–1.36; p = 0.0000). The largest study reporting DGF rates by Doucet et al. [10] reports a rate of 19.4% in elderly versus 18.1% in younger population.

The eGFR and creatinine outcomes were lacking in the included studies, with only seven papers reporting them [3,8,10,12,18,38,39]. Extracted outcomes were quite similar between both groups: median eGFR at the last follow-up was 47.1 ml/min in the >70-yr control group versus 48.0 ml/min in the younger group, while the median creatinine level was 1.76 (range 1.5–2.0) versus 1.8 (range 1.7–1.9) mg/dl in the >70-yr versus <70-yr group.

3.6.6. *Surgical risk and postoperative complications*

Older recipients are usually at a greater risk of perioperative complications, including death, mainly due to infection and cardiovascular disease [21]. However, a lack of reported data about postoperative complications has been identified, particularly from a surgical point of view. Urinary leak (10.1%, 14/138) or surgical site infection rates (18.8%, 26/138) have been reported only in one study for older patients [38], while only Zompolas et al. [8] stratified them according to the Clavien system (7.1% in the >70-yr vs 11.1% in the <70-yr group with Clavien III complications).

Advanced age of donors and recipients usually brings substantial increased complexity in KT surgery [40]. Atherosclerosis commonly affects ESRD patients on dialysis and especially the elderly [41], and this condition can make surgery very challenging. Vascular complication rates have been described poorly in the studies included in this SR—only in two comparative studies [8,12] (5.3% in the >70-yr compared with 3.6% in the <70-yr group [12]). Furthermore, since retransplant rates have increased drastically to almost 25% over the past decades, this issue represents a challenge, especially in elderly population that could potentially need a subsequent KT [42]. However, the retransplant rate in this group is lower.

Concerning WIT, which is directly related to surgical complexity, only one study addressed this parameter. WIT in the <70-yr group was 48.0 versus 52.6 min in the >70-yr group [8]. Another indicator of surgical complexity is the number of prior transplants. Retransplant rate, understood as the proportion of patients undergoing subsequent transplants after graft failure, was significantly lower in the >70-yr group (1.3% vs 8.9% in the <70-yr group; Table 1). This fact probably reflects a more meticulous selection of elderly recipients when considering a potential KT, which undoubtedly introduces a bias that should lead us to a cautious interpretation of the outcomes for this old-age group.

3.6.7. Donor selection

In many KT programmes, transplantation teams attempt to match by allocating ECD organs to older recipients. Compared with organs from standard criteria donors, ECD kidneys are associated with worse GS outcomes, but with increased life expectancy over dialysis in older recipients [19]. This effect of donor age poses a major confounder in the assessment of KT outcomes in elderly population when comparing with younger cohorts. Thus, as represented in Table 1, donor age was higher in the >70-yr group (55.0 vs 47.7 in the <70-yr group), with a higher proportion of ECDs (18.5% vs 2.7%), a higher proportion of donors after cardiocirculatory death (4.3% vs 2.1%), and a lower proportion of living donors (27.3% vs 35.0%).

3.6.8. Strengths and limitations

Several limitations of the present SR need to be mentioned. The first and main limitation was the difficulty for determining a homogeneous age threshold, as there are no standardised cut-offs in the literature, where these range from >60 yr in the 1990s' studies to >80 yr in the most recent studies. Moreover, most of the papers about old population lack a geriatric assessment and/or frailty or comorbidity scores. In addition, the existence of studies analysing patients from US nationwide databases in different periods may lead to duplicated populations. Lastly, some confounders such as donor features or time on dialysis have not been controlled.

However, to our knowledge, this work has several strengths. Its relevance, according to demographic evolution in developed countries, makes it of great interest to transplant and urological communities, as it reports outcomes about the real population that we will have to face over the next years. Furthermore, it reports outcomes and meta-analyses of a very large number of transplanted patients, highlighting the potential need of geriatric or frailty assessment and stressing the importance of reporting surgical complications as an important part of KT outcomes, particularly in this old-age setting where it becomes even more relevant when selecting potential candidates.

4. Conclusions

Elderly KT recipients (>70 yr) have worse OS at all time points and long-term GS compared with younger recipients (<70 yr). Postoperative complications were under-reported and could not be assessed. The DGF, AR, death with functioning graft, and graft loss in elderly population were not inferior to those in younger population. Considering progressive and constant ageing of population in developed countries, the addition of geriatric assessment in this setting might be useful for selecting better elderly candidates for KT.

Author contributions: Vital Hevia had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Territo, Hevia, Campi, Boissier, Prudhomme, Pecoraro.
Acquisition of data: Artiles, Domínguez, Subiela, Hevia.
Analysis and interpretation of data: Artiles, Domínguez, Subiela, Hevia.
Drafting of the manuscript: Artiles, Domínguez, Subiela, Hevia.
Critical revision of the manuscript for important intellectual content: Artiles, Domínguez, Subiela, Hevia, Burgos, Breda, Territo, Campi, Boissier, Prudhomme, Pecoraro.
Statistical analysis: Artiles, Domínguez, Subiela, Hevia.
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Appendix A. Supplementary data

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