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Early versus late nephrology referral and patient outcomes in chronic kidney disease: an updated systematic review and meta-analysis

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Abstract

Background Nephrology referral has been recognized as a modifiable factor influencing patient outcomes. The study aimed to compare clinical outcomes among patients referred early versus late to nephrologists.

Methods We searched online database from inception to June 1, 2022, to obtain all eligible literature reporting outcomes of patients referred early versus late to nephrologists. The early and late referral was defined by the time at which patients were referred to nephrologists before dialysis onset.

Results Seventy-two studies with over 630,000 patients met the inclusion criteria. A lower likelihood of all-cause mortality (HR = 0.67, 95% CI: 0.62–0.72) was achieved among patients referred early to nephrologists. The survival advantage of early referral was apparent in the first 6 months and extended to the 5th year after dialysis onset (6 months: HR = 0.52, 95% CI: 0.40–0.68; 5 years: HR = 0.67, 95% CI: 0.60–0.74). The early referral was associated with shorter durations of initial hospitalization, a higher rate of kidney transplantation (RR = 1.41, 95% CI: 1.12–1.78), a lower likelihood of emergency start (RR = 0.39, 95% CI: 0.28–0.54), a higher likelihood of permanent access creation (RR = 3.34, 95% CI: 2.43–4.59), increased initial use of permanent access (RR = 2.60, 95% CI: 2.18–3.11), and reduced initial catheter use (RR = 0.43, 95% CI: 0.32–0.58).

Conclusions Our study showed a lower risk of mortality, shorter lengths of initial hospitalization, and better preparations for renal replacement therapy among patients referred early to nephrologists. Early nephrology care should be promoted to improve the management of advanced chronic kidney disease.

Keywords Chronic renal insufficiency, Referral, Meta-analysis, Mortality

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Background

As a public health problem, chronic kidney disease (CKD) has attracted more and more attention due to its increasing prevalence and mortality. The global prevalence of chronic kidney disease is estimated between 11%–13% with the majority stage 3 [1]. A systematic review including 123 countries or region register systems has reported that 2.6 million people received renal replacement therapy (RRT) in 2010 and is estimated to exceed 5.4 million in 2030 [2]. Chronic kidney disease resulted in 1.2 million deaths worldwide in 2017 and is predicted to become the fifth leading cause of mortality globally by 2040 [3, 4].

Numerous studies have shown that consulting a nephrologist can affect the clinical outcome of patients with chronic kidney disease. A meta-analysis in 2005 showed that patients referred to nephrologists early had lower mortality rates and fewer early hospitalizations compared to those referred late [5]. The other meta-analysis in 2014, consistent with the previous analysis, showed a decrease in mortality and better dialysis access preparation in patients with early nephrology referrals [6]. However, the benefits of early referral remain controversial due to heterogeneity and bias from confounding factors (i.e., comorbidity, age, and residual renal function). Pooled analysis using adjusted estimates is necessary for minimizing bias and enhancing the generalizability of the findings. Besides, an increasing number of studies have compared the clinical outcomes among patients with early versus late referral to nephrologists in the past few years. There is a growing need for an updated meta-analysis to identify the patient outcomes associated with referral patterns based on the latest research. Therefore, we performed an updated meta-analysis to examine outcomes related to referral patterns in patients with advanced CKD. The study with subgroup analyses also examined whether the mortality risk of early versus late nephrology referral is influenced by dialysis duration, dialysis modalities, and referral entry points.

Methods

A systematic review and meta-analysis was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The pre-specified protocol for this study was registered with PROSPERO (CRD42023423608).

Search strategy and study selection

We searched for randomized clinical trials, cohort studies, and case–control studies that compared outcomes in patients with early referral versus patients with late referral using PubMed, Embase, and the Cochrane Library until June 1, 2022. We designed search strategies by combining all relevant terms of referral, chronic kidney disease (Supplementary Appendix S1). Two authors (LC, YC) independently screened all records by title and abstract and retrieved the full text of potential records. The third author (NH) independently made a determination in case of any disagreement. For inclusion, the studies had to meet all criteria as follows: (1) being a randomized clinical trial or a case–control or a cohort study; (2) defining late and early nephrology referral by the time at which patients were referred to nephrologists; (3) including patients with stage 4–5 of CKD or ESRD; (4) being English literature, and (5) reporting either all-cause mortality, emergency start, initial use of catheter, arteriovenous access creation or initial use of arteriovenous access. Studies were excluded for either one of the criteria as follows: (1) participants younger than 18 years old; (2) patients on pre-existing renal replacement therapy; and (3) defining late and early nephrology referral by either referral frequency, preparation of vascular access or estimated glomerular filtration rate (eGFR).

Data extraction and quality assessment

Two authors (LC, YC) collected data into a chart independently, including data source, the definition of late and early nephrology referral, follow-up duration, dialysis modality, sample size, age, sex, eGFR or creatinine clearance (Ccr) at the first referral and the first dialysis session, and adjusted confounders of all-cause mortality. We evaluated the methodological quality according to criteria from the Newcastle–Ottawa Scale including selection, comparability, and outcome. More than 5 points were regarded as a low risk of bias.

Outcome measures

The primary outcome of interest was all-cause mortality risk after initiation of dialysis in the early referral (ER) versus late referral (LR) patients. The secondary outcomes included various clinical parameters in the ER versus LR group, including the length of initial hospital stay, the rate of kidney transplantation, the emergency start of dialysis, initial catheter use, arteriovenous access creation, and initial use of arteriovenous access. Initial hospitalization was in connection with the start of renal replacement therapy. Renal transplant recipients included patients receiving transplantation before and after dialysis. The emergency start was defined as the first dialysis within 24 h after medical consultation or unavoidable first dialysis for life-threatening disorders including severe hyperkalemia, pulmonary edema, encephalopathy, pericarditis, and metabolic acidosis. Catheters included non-tunneled and tunneled catheters. Arteriovenous access included arteriovenous fistula and arteriovenous graft.

Statistical analysis

We summarized data using the risk ratio and 95% confidence interval (CI) for dichotomous variables, mean and deviation means or median and range for quantitative variables, percentages for categorical variables, and hazard ratio (HR) and 95% CI for time-to-event data. When estimates of effect were unavailable directly, we calculated relevant effect estimates by extracting data from figures or transforming them from raw data. If adjusted estimates were available in the studies, we used the best-adjusted estimates of effect for each study, otherwise, we used the unadjusted estimates. We measured heterogeneity among studies by I^2 statistic. If severe heterogeneity cannot be avoided ($I^2 > 50\%$), we chose the Random-effects inverse-variance model with the DerSimonian-Laird method for the meta-analysis, otherwise, we used the fixed-effect model. We assessed the publication bias using funnel plot and Egger test. We used the trim-and-fill method to obtain the pooled estimates adjusted for publication bias. To examine the robustness of the meta-analysis, we performed a sensitivity analysis by removing each included study. For all analyses, statistical significance was considered when a two-tailed $p < 0.05$. Engauge Digitizer version 11.1 was used to extract data from graphs. R version 4.1.3 (The R Foundation for Statistical Computing) was used to perform all analyses.

Results

Characteristics of the included studies

A total of 19,850 publications were identified based on the search strategy and 142 were retrieved in the full text. Finally, 72 cohort or case–control studies with a total sample size of more than 630,000 patients were included in this review (Fig. 1) [7–78]. There was no randomized clinical trial regarding referral patterns and outcomes. The baseline characteristics of eligible studies are given in Table 1. The studies were published between 1998 and 2019, with follow-up duration ranging from 2 months to 5 years. A total of 31 studies enrolled patients before 2003, 25 studies enrolled patients after 2003, one study did not specify the enrollment period, and 16 studies spanned across 2003. Among the patients, more than 321,000 were ER patients and more than 309,000 were LR patients. The average age of patients was 35.5 to 87.4 years and the proportion of males was 38.3% to 78%. The cut-off point of late and early nephrology referral varied among studies. The cut-off point of 1, 3, 4, 6,

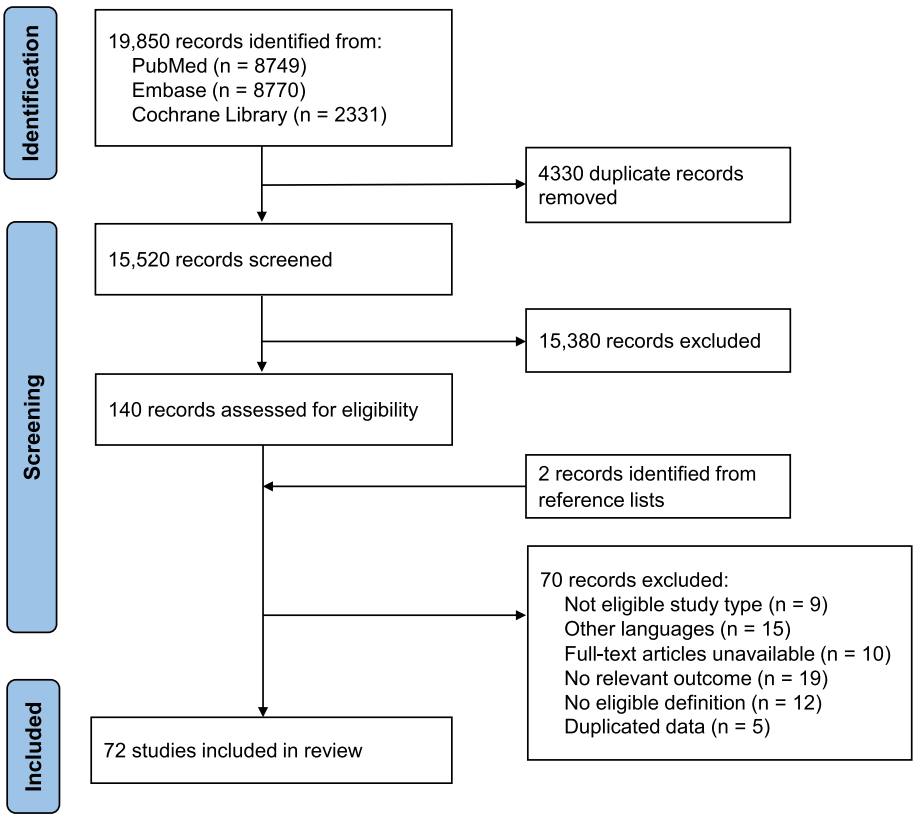

Fig. 1 Flow diagram of studies identified, included, and excluded

Table 1 Baseline characteristics of included studies

Study	Data source	Dialysis modality	Definition of LR (Month)	Enrollment period (Year)	Follow-up duration	LR:ER (n)	Age (Year)	Male (%)	Creatine at first referral (mg/dl) (LR: ER)	Creatine at dialysis initiation (mg/dl) (LR: ER)	eGFR/ CCr at first referral (ml / min/1.73m^2) (LR: ER)	eGFR/CCr at dialysis initiation (ml / min/1.73m^2) (LR: ER)	GFR-estimating equations	Adjustment for variables of mortality
Cass 2002 [7]	The ANZDATA database	HD; PD	< 3	1995–1998	Until Mar 31, 2000	4243 (1141: 3102)	56.6	56.6	NA	NA	NA	NA	NA	Age, sex, number of comorbidities, presence of primary renal disease, and Indigenous status.
Goransson 2001 [8]	Central Hospital of Rogaland, Norway	HD; PD	< 3	1984–1998	5 years	89 (25: 64)	59.3	67.4	NA	7.8 (7.8: 7.8)[a]	NA	NA	NA	NA
Hommel 2012 [9]	The Danish Nephrology Registry	HD; PD	< 4	1999–2006	Until Dec 2007	4495 (1727: 2768)	63.8	62.7	NA	NA	NA	NA	NA	Age, sex, emigration, comorbidity, and renal diagnosises
Avorn 2002 [10]	The Medicare or Medicaid programs	HD	< 3	1990–1996	NA	2398 (839: 1559)	NA	56.3	NA	NA	NA	NA	NA	NA.
Leimbach 2014 [11]	Charite Universitätsmedizin Berlin	HD	< 3	2001–2012	Until Dec 31, 2012	76 (21: 55)	82.5	57.9	NA	NA	NA	NA	NA	NA.
Spigolon 2016 [12]	The BRAZPD II cohort	PD	< 3	2004–2011	60 months	4107 (2000: 2107)	61.1	51.1	6.1 (6.3: 6.0)[c]	NA	NA	NA	NA	Demographics, clinical variables, and biochemical variables.
Stack 2003 [13]	The USRDS	HD; PD	< 4	1996–1997	Up to 2 years	2159 (717: 1442)	58.1	53.9	NA	8.5 (8.8: 8.3)[b]	NA	7.5 (7.4: 7.5)[a]	MDRD	NA
Avorn 2002 [14]	The New Jersey Medicaid and Medicare programs	HD; PD	< 3	1991–1996	1 year	3014 (1039: 1975)	NA	56.2	NA	NA	NA	NA	NA	Age, race, socioeconomic status, and renal diagnoses.
Obialo 2005 [15]	Grady Memorial Hospital	NA	< 3	1999–2002	4 years	460 (380: 80)	51.0	56.0	11.6 (9.4: 13.8)[e]	NA	6.0 (7: 6)[e]	NA	MDRD	NA.
Ratcliffe 1984 [16]	The Oxford renal unit	HD; PD	< 1	1981	Mean, 4.1 years	55 (32: 23)	NA	NA	NA	NA	NA	NA	NA	NA.

Table 1 (continued)

Study	Data source	Dialysis modality	Definition of LR (Month)	Enrollment period (Year)	Follow-up duration	LR:ER (n)	Age (Year)	Male (%)	Creatine at first referral (mg/dl) (LR: ER)	Creatine at dialysis initiation (mg/dl) (LR: ER)	eGFR/ CCr at first referral (ml / min/1.73m^2) (LR: ER)	eGFR/CCr at dialysis initiation (ml / min/1.73m^2) (LR: ER)	GFR-estimating equations	Adjustment for variables of mortality
Roubicek 2000 [17]	Sainte-Marguerite University Hospital	HD	< 4	1989–1996	NA	270 (93: 177)	56.0	60.0	NA	9.7 (10.9: 9.1)[d]	NA	7.7 (7.0: 8.0)[c]	Cockcroft-Gault	NA.
Lin 2004 [18]	Chang-Gung Memorial Hospital, Taiwan	HD; PD	< 6	2000–2003	6 months	105 (60: 45)	61.4	42.9	NA	NA	NA	NA	NA	Age, hemoglobin, albumin, cholesterol.
Kim 2013 [19]	The Comprehensive Prospective Study of the Clinical Research Center for End Stage Renal Disease	HD; PD	< 12	2008–2011	Maxium, 36 months	1028 (429: 599)	57.0	59.6	4.8 (2.6: 7.2)[d]	8.4 (8.5: 8.3)[a]	24.5 (11.4: 36.1)[d]	7.6 (7.7: 7.5)[a]	MDRD	BMI, mCCI, serum calcium, high-density lipoprotein cholesterol, triglycerides, total cholesterol, hemoglobin, intact parathyroid hormone, uric acid, and eGFR.
Baek 2014 [20]	Seoul National University Hospital in Korea	HD	< 3	2000–2010	25.1 months	820 (390: 430)	76.3	60.5	NA	6.0 (5.8: 6.2)[b]	NA	10.5 (11.2: 9.9)[d]	MDRD	Age, gender, diabetes mellitus, hypertension, serum creatinine, albumin, comorbidites, and type of vascular access at the first dialysis.
Chen 2010 [21]	One medical center and 1 regional hospital in Southern Taiwan	HD	< 6	1997–2006	Mean, 92 months	192 (44: 148)	63.6	45.3	12.2 (11.5: 12.4)[a]	NA	3.8 (4.1: 3.8)[a]	NA	MDRD	Demographic and comorbid conditions.
Lawton 2015 [22]	The ANZDATA database	HD; PD	< 3	1995–2009	Until Dec 31, 2011	27488 (6350: 21138)	35.3	59.3	NA	NA	NA	NA	NA	Age, sex, comorbid conditions, and BMI.

Table 1 (continued)

Study	Data source	Dialysis modality	Definition of LR (Month)	Enrollment period (Year)	Follow-up duration	LR:ER (n)	Age (Year)	Male (%)	Creatine at first referral (mg/dl) (LR: ER)	Creatine at dialysis initiation (mg/dl) (LR: ER)	eGFR/ CCr at first referral (ml / min/1.73m^2) (LR: ER)	eGFR/CCr at dialysis initiation (ml / min/1.73m^2) (LR: ER)	GFR-estimating equations	Adjustment for variables of mortality
Jungers 2001 [23]	Necker Hospital	HD; PD	< 6	1989–1998	Until Apr 1, 1999	1057 (258: 799)	54.5	67.4	NA	NA	NA	7.1 (6.6: 7.6)[e]	Cockcroft-Gault	NA.
Roderick 2002 [24]	Six units in England	HD; PD	< 4; < 1; < 12	1996–1997	At least 6 months	353 (124: 229)	60.0	58.4	NA	9.7 (10.2: 9.5)[b]	NA	NA	NA	NA.
Kazmi 2004 [25]	The USRDS	HD; PD	< 4	1996–1997	Mean, 739.8 days	2195 (730: 1465)	57.9	54.0	7.9 (8.0: 7.8)[a]	NA	8.7 (9.1: 8.7)[b]	NA	MDRD	Insurance status, angina, education level, employment status, treatment modality and ESRD network.
Schwenger 2006 [26]	Heidelberg University	HD	< 2	1998–2001	Until Jan 31, 2003	254 (119: 135)	63.0	NA	NA	NA	NA	NA	NA	NA.
Goncalves 2003 [27]	Federal University of São Paulo	HD	< 3	1997–1999	Mean, 295 days	101 (59: 42)	51.0	61.4	NA	8.8 (8.2: 9.6)[a]	NA	NA	NA	NA.
Wu 2003 [28]	Chang-Gung Memorial Hospital	PD	< 6	1998–2000	Mean, 39.1 months	52 (36: 16)	59.0	61.5	NA	NA	NA	4.0 (3.4: 5.3)[d]	NA	NA.
Stoves 2001 [29]	St Jame's University Teaching Hospital	HD; PD	< 3	1980–1999	NA	1260 (467: 793)	52.6	60.6	NA	NA	NA	NA	NA	NA.
Ellis 1998 [30]	Dulwich Hospital	HD; PD	< 3	1996–1997	Until Jul 1998	198 (64: 134)	59.6	58.6	NA	NA	NA	NA	NA	NA.
Roderick 2002 [31]	Bristol and Portsmouth renal units	HD; PD	< 4	1997–1998	6 months	250 (96: 154)	57.0	58.0	NA	NA	NA	NA	NA	NA.
Bersan 2013 [32]	The Brazail database of health care plan provider	HD	< 4	2004–2008	60 months	212 (32: 180)	62.0	55.6	NA	NA	NA	NA	NA	Age, diabetes, and hospitalizations.
Kessler 2003 [33]	Lorraine	HD; PD	< 1; < 4; < 12	1997–1999	Median, 22.2 months	502 (156: 346)	62.8	59.4	NA	7.8 (NA)	NA	10 (NA)	NA	NA.

Table 1 (continued)

Study	Data source	Dialysis modality	Definition of LR (Month)	Enrollment period (Year)	Follow-up duration	LR:ER (n)	Age (Year)	Male (%)	Creatine at first referral (mg/dl) (LR: ER)	Creatine at dialysis initiation (mg/dl) (LR: ER)	eGFR/ CCr at first referral (ml / min/1.73m^2) (LR: ER)	eGFR/CCr at dialysis initiation (ml / min/1.73m^2) (LR: ER)	GFR-estimating equations	Adjustment for variables of mortality
Al-Jaishi 2015 [34]	Canadian Organ Replacement Register, Ontario Health Insurance Plan, Discharge Abstract Database, and Registered Persons Database	HD	< 3	2001–2010	NA	17183 (6892: 10291)	65.8	60.0	NA	NA	NA	9.0 (NA)	MDRD	NA.
Kinchen 2016 [35]	The CHOICE Study	HD; PD	< 4	1995–1998	Median, 2.2 years	828 (399: 429)	NA	55.2	NA	NA	NA	NA	NA	NA.
Yanay 2014 [36]	Hillel Yaffe Medical Center	HD	< 3	2006–2009	Median, 3.1 years	200 (82: 118)	70.1	56.0	NA	NA	NA	NA	NA	Age, gender, and diabetes mellitus.
Povlsen 2008 [37]	Aarhus University Hospital	PD	< 3	2000–2004	At least 2 years	100 (42: 58)	74.6	56.0	NA	6.1 (6.1:5.6)[a]	NA	NA	NA	NA.
Pena 2006 [38]	The San Jorge Hospital of Huesca and the Hospital of Barbastro	HD	< 4	1991–2001	Until Dec 31, 2001	178 (39: 139)	59.2	61.8	NA	8.7 (10.2:8.3)[b]	NA	NA	NA	NA.
Dhanorkar 2022 [39]	Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India	HD; PD	< 12	2018–2020	Mean, 16.7 months	992 (517: 475)	47.6	72.2	NA	NA	23.0 (15.3: 31.5)[c]	NA	CKD-EPI	Age, BMI, education, occupation, socioeconomic class, eGFR, duration of follow-up, primary physician, underlying kidney disease.
Chow 2007 [40]	The Chinese University of Hong Kong	PD	< 3	2003–2004	Median, 36.8 months	102 (41: 61)	55.2	61.8	NA	NA	3.8 (3.4: 4.1)[a]	NA	NA	Baseline serum albumin concentration, age, diabetes, and residual glomerular filtration rate.

Table 1 (continued)

Study	Data source	Dialysis modality	Definition of LR (Month)	Enrollment period (Year)	Follow-up duration	LR:ER (n)	Age (Year)	Male (%)	Creatine at first referral (mg/dl) (LR: ER)	Creatine at dialysis initiation (mg/dl) (LR: ER)	eGFR/ CCr at first referral (ml / min/1.73m^2) (LR: ER)	eGFR/CCr at dialysis initiation (ml / min/1.73m^2) (LR: ER)	GFR-estimating equations	Adjustment for variables of mortality
Jager 2010 [41]	The NECOSAD study	HD; PD	< 12	1996–2004	1 year	1438 (456: 982)	60.0	62.0	NA	NA	NA	3.7 (3.4: 3.9)[b]	The mean of creatinine and urea clearance and corrected for body surface area and as weekly kt/Vurea	NA.
Iwata 2019 [42]	Osaka General Medical Center	HD	< 4; < 6; < 8; < 12; < 16; < 20; < 24	2006–2015	Median, 34 months	1117 (283: 834)	68.6	64.0	NA	8.1 (8.1: 8.0)[a]	NA	5.4 (5.4: 5.3)[a]	MDRD	Age, etiology, cardiovascular history, malignancy history, temporary catheter use, BMI, systolic blood pressure, pulse rate, eGFR, albumin, corrected calcium, and CRP.
Liu 2018 [43]	The Dialysis Measurement Analysis and Reporting system	HD; PD	< 6 < 4; < 12	2004–2014	Median, 10.5 months	569 (264: 305)	64.0	61.0	NA	NA	7.3 (7.2: 7.3)	NA	NA	Age, sex, dialysis programs, serum albumin, and comorbidities.
Stojceva-Taneva 2006 [44]	University Clinical Centre	HD	< 3	2001	1 months	189 (110: 79)	55.9	50.8	NA	NA	NA	NA	NA	NA.
Foley 2014 [45]	The USRDS Medical Evidence Report	HD; PD	< 6	2005–2009	1 year	481377 (259679: 221698)	NA	56.1	NA	NA	NA	< 15: 82.6% (81.4%: 82.9%); ≥ 15: 17.4% (18.6%: 17.1%)	NA	NA.
Gubensek 2014 [46]	The Slovenian Renal Replacement Therapy Registry	HD	< 3	2004–2010	Until Dec 31, 2010	156 (54: 102)	83.0	49.0	NA	7.6 (NA)	NA	7.3 (NA)	MDRD	Age, phosphate, nephrology referral, AVF, and starting HD in hospital.
Yamagata 2012 [47]	The JSDT registry	HD; PD	< 1; < 3; < 4; < 6; < 12	2007	12 months	9685 (6030: 3655)	67.5	64.0	NA	8.2 (8.1: 8.3)	NA	6.5 (7.9: 6.3)	MDRD	NA.

Table 1 (continued)

Study	Data source	Dialysis modality	Definition of LR (Month)	Enrollment period (Year)	Follow-up duration	LR:ER (n)	Age (Year)	Male (%)	Creatine at first referral (mg/dl) (LR: ER)	Creatine at dialysis initiation (mg/dl) (LR: ER)	eGFR/ CCr at first referral (ml / min/1.73m^2) (LR: ER)	eGFR/CCr at dialysis initiation (ml / min/1.73m^2) (LR: ER)	GFR-estimating equations	Adjustment for variables of mortality
Bradbury 2007 [48]	DOPPS phases I and II	HD	< 1	1996–2001; 2002–2004	365 days	4623 (1115: 3508)	NA	56.3	NA	NA	NA	NA	NA	Age, gender, race, BMI, cause of ESRD, vascular access type, laboratory characteristics, comorbidities, and EPO use.
Hayashi 2016 [49]	Rinku General Medical Center and other 5 hospitals in Japan	HD	< 6	2001–2009	Median, 31.1 months	604 (346: 258)	68.0	56.6	NA	8.1 (7.8: 8.42)[d]	NA	5.3 (5.4: 4.9)[c]	MDRD	Referral timing, age, etiology, cardiovascular history, pre-dialysis ESA use, emergency induction, temporary catheter use, eGFR, calcium, ferritin, total cholesterol, CRP, and mean blood pressure.
Nakamura 2007 [50]	The National Cardiovascular Center Hospital	HD	< 6	1983–2003	41 months	366 (172: 194)	63.0	78.0	3.6 (5.7: 2.7)[d]	10.0 (9.6: 10.6)[a]	NA	NA	NA	Age, diabetes mellitus, CVD, systolic blood pressure and serum albumin.
Okazaki 2018 [51]	Seventeen clinical centers in Japan	HD; PD	< 3	2011–2013	Median, 2.2 years	1475 (275: 1200)	67.5	68.1	NA	NA	NA	5.5 (5.9: 5.4)[c]	MDRD	Age, sex, history of volume overload, history of malignancy, comorbidities of diabetes mellitus, atherosclerotic disease, serum albumin, phosphate, and hemoglobin.

Table 1 (continued)

Study	Data source	Dialysis modality	Definition of LR (Month)	Enrollment period (Year)	Follow-up duration	LR:ER (n)	Age (Year)	Male (%)	Creatine at first referral (mg/dl) (LR: ER)	Creatine at dialysis initiation (mg/dl) (LR: ER)	eGFR/ CCr at first referral (ml / min/1.73m^2) (LR: ER)	eGFR/CCr at dialysis initiation (ml / min/1.73m^2) (LR: ER)	GFR-estimating equations	Adjustment for variables of mortality
Santos 2019 [52]	Centro Hospitalar do Porto	HD; PD	< 3; < 12	2009–2016	Until Aug 30, 2017	421 (83: 338)	75.1	53.7	NA	6.3 (NA)	NA	6.6 (NA)	CKD-EPI	NA.
Singhal 2014 [53]	Health administrative databases of the Institute for Clinical Evaluative Sciences in Canada	HD; PD	< 6	1998–2008	1 year	12,143 (2929: 9214)	63.6	59.0	NA	NA	NA	NA	NA	NA.
Yoon 2009 [54]	Dialysis centers of 8 hospitals of the Catholic University of Korea	HD	< 3	2006–2007	6 months	291 (95: 196)	59.0	53.3	NA	NA	NA	NA	NA	NA.
Atieh 2020 [55]	Ramallah Hemodialysis Center	HD	< 3	2018	NA	120 (25: 95)	55.0	59.0	NA	NA	NA	NA	NA	NA.
Schmidt 1998 [56]	West Virginia University	HD; PD	< 1	1990–1997	Until Nov 30, 1997	238 (58: 180)	61.0	46.0	NA	NA	NA	NA	NA	NA
Astor 2001 [57]	The CHOICE Cohort Study	HD	< 1; < 4; < 12	1995–1998	6 months	356 (142: 214)	NA	57.3	NA	NA	NA	NA	NA	NA.
Herget-Rosenthal 2010 [58]	Seven nephrological centres	HD; PD	< 4	2003–2004	1 year	149 (46: 103)	61.2	54.4	7.0 (6.8: 7.1)[a]	NA	10.2 (10.4: 10.1)[a]	NA	MDRD	NA.
Lin 2016 [59]	Chang Gung Memorial Hospital	HD	< 6	1998–2001	Mean, 58.9 months	115 (62: 53)	64.1	46.1	NA	NA	NA	3.4 (2.5: 4.5)[d]	NA	Good glycemic control, age at dialysis, hemoglobin, albumin, cholesterol, and residual renal function.
Diegoli 2014 [60]	Vale do Itajaí University	HD	< 3	2008–2011	Until Feb 2013	111 (67: 44)	61.0	63.1	NA	NA	NA	NA	NA	NA.
Hamadah 2019 [61]	Prince Hamza Hospital	HD	< 12	2018	NA	50 (11: 39)	50.0	52.0	NA	NA	NA	NA	NA	NA.
Kumar 2012 [62]	Manipal University	NA	< 3	NA	1 year	50 (32: 18)	58.4	70.0	NA	NA	23.7 (11.4: 45.6)[d]	NA	MDRD	NA.

Table 1 (continued)

Study	Data source	Dialysis modality	Definition of LR (Month)	Enrollment period (Year)	Follow-up duration	LR:ER (n)	Age (Year)	Male (%)	Creatine at first referral (mg/dl) (LR: ER)	Creatine at dialysis initiation (mg/dl) (LR: ER)	eGFR/ CCr at first referral (ml / min/1.73m^2) (LR: ER)	eGFR/CCr at dialysis initiation (ml / min/1.73m^2) (LR: ER)	GFR-estimating equations	Adjustment for variables of mortality
Parameswaran 2011 [63]	The Postgraduate Institute of Medical Education and Research	HD; PD	< 3; < 12	2006–2007	6 months	2490 (1868: 622)	44.0	70.2	NA	NA	NA	NA	NA	NA.
Oliva 2013 [64]	The Andalusian Registry of Chronic Renal Patients	HD	< 6	2004–2007	Until Dec 31, 2007	704 (500: 204)	79.3	55.0	NA	NA	NA	NA	NA	NA.
Ravani 2003 [65]	Two Italian centers	HD; PD	< 3	1999–2002	NA	229 (84: 145)	64.4	62.0	NA	NA	NA	8.7 (8.9: 8.5)[a]	Cockcroft-Gault	NA.
Lorenzo 2004 [66]	Three dialysis facilities in Spain	HD	< 3	1996–2001	Mean, 23.7 months	538 (257: 281)	65.0	38.3	NA	NA	10.8 (10.0: 11.6)[d]	NA	MDRD	NA.
Fan 2002 [67]	St Bartholomew's and The Royal London Hospital	PD	< 1	1998–1999	1 year	98 (27: 71)	51.2	59.2	NA	NA	NA	NA	NA	NA.
Descamps 2011 [68]	Lyon Sud Hospital	HD; PD	< 6	1995–2006	Until Dec 31, 2007	495 (104: 391)	62.1	63.0	NA	NA	NA	NA	NA	NA.
Kanno 2019 [69]	Japan Community Health Care Organization Sendai Hospital	HD	< 3	2008–2013	1 year	122 (83: 39)	87.4	52.0	NA	NA	NA	NA	MDRD	NA.
Arora 1999 [70]	The New England Medical Center	HD; PD	< 4	1992–1997	NA	135 (30: 105)	59.7	48.1	NA	NA	NA	7.8	MDRD	NA.
Caskey 2003 [71]	Seven countries in Europe	HD; PD	< 1	1998–1999	At least 2 months	262 (66: 196)	59.4	60.0	NA	NA	NA	8.2 (7.7: 8.4)[a]	Cockcroft-Gault	NA.
Dogan 2005 [72]	Yuzuncu Yil University Hospital	HD; PD	< 3	1998–2002	NA	101 (61: 40)	44.8	53.5	NA	NA (10.0: 7.9)[c]	NA	NA	NA	NA.
Shin 2007 [73]	St. Vincent's Hospital in Suwon	HD	< 3	1999–2004	60 months	119 (52: 67)	52.9	52.1	NA	9.8 (10.1: 9.5)[a]	NA	6.5 (6.4:6.6)[a]	NA	NA.

Table 1 (continued)

Study	Data source	Dialysis modality	Definition of LR (Month)	Enrollment period (Year)	Follow-up duration	LR:ER (n)	Age (Year)	Male (%)	Creatine at first referral (mg/dl) (LR: ER)	Creatine at dialysis initiation (mg/dl) (LR: ER)	eGFR/ CCr at first referral (ml / min/1.73m^2) (LR: ER)	eGFR/CCr at dialysis initiation (ml / min/1.73m^2) (LR: ER)	GFR-estimating equations	Adjustment for variables of mortality
Winkelmayer 2003 [74]	The Medicaid, Medicare, or Pharmaceutical Assistance for the Aged and Disabled programs in the state of New Jersey	HD; PD	< 3	1991–1996	1 year	3014 (1039: 1975)	NA	56.2	NA	NA	NA	NA	NA	NA.
Marron 2016 [75]	Twenty-five ICS clinics in Poland, Hungary, and Romania	HD; PD	< 3	2012	1 year	547 (266: 281)	Median, 64.0	61.0	NA	Median, 6.1 (6.8: 5.2)[d]	NA	Median, 9.0 (9: 8)[a]	MDRD	NA.
Foote 2014 [76]	Australia and New Zealand Dialysis and Transplant Registry	HD; PD	< 3	1999–2010	NA	25009 (5897: 19112)	60.7	59.9	NA	NA	NA	7.3 (7.0: 8.2)[d]	MDRD	NA.
Blunt 2015 [77]	Hospital Episode Statistics	HD; PD	< 3	2010–2011	NA	3928 (1336: 2592)	NA	63.4	NA	NA	NA	NA	NA	NA.
Hughes 2013 [78]	The STARRT study	HD; PD	< 12	2009–2010	NA	436 (209: 227)	67.0	57.6	NA	NA	NA	NA	NA	NA.

Data are presented in mean (SD), or proportion if not otherwise mentioned

Abbreviations: *ANZDATA* Australia and New Zealand Dialysis and Transplant Registry, *DOPPS* Dialysis Outcomes and Practice Patterns Study, *USRDS* US Renal Data System, *BRAZPD* the Brazilian Peritoneal Dialysis study, *CHOICE* The Choices for Healthy Outcomes in Caring for ESRD, *REIN* The French Renal Epidemiology and Information Network, *CKD-EPI* the Chronic Kidney Disease Epidemiology Collaboration, *MDRD* The Modification of Diet in Renal Disease, *ESRD* end stage renal disease, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *CVD* cardiovascular disease, *AVF* arteriovenous fistula, *HD* hemodialysis, *PD* peritoneal dialysis, *mCCI* modified Charlson comorbidity index, *CRP* C-reative protein, *EPO* erythropoietin, *ESA* erythropoiesis- stimulating agents, *NA* not available

[a] ns

[b] $p < 0.05$

[c] $p < 0.01$

[d] $p < 0.001$

[e] $p < 0.0001$

and 12 months before dialysis initiation was used in 9, 35, 15, 14, and 12 studies, respectively. The average eGFR/Ccr was from 3.8 to 23.7 ml/min/1.73 m^2 at the first visit to nephrologists. Thirty-one out of 72 studies reported either serum creatinine, eGFR, or Ccr of the cohorts at the initiation of dialysis. Among these, 25 studies compared residual kidney function between the LR and ER groups. The eGFR at the initiation of dialysis in the LR and ER groups varied across studies, whether in the pre-2003 or post-2003 cohorts. Eight of the 14 studies in the pre-2003 cohort and 4 of the 11 studies in the post-2003 cohort reported significant differences in eGFR between the LR and ER groups. The average eGFR at initiation of dialysis ranged from 3.4 to 10 mL/min/1.73 m^2 in the pre-2003 cohort and from 5.3 to 10.5 mL/min/1.73 m^2 in the post-2003 cohort. ER patients initiated dialysis at an eGFR of 3.9 to 8.5 mL/min/1.73 m^2 and 4.9 to 9.9 mL/min/1.73 m^2 in the pre- and post-2003 cohorts, respectively, while LR patients initiated dialysis at an eGFR of 3.4 to 8.9 mL/min/1.73 m^2 and 5.4 to 11.2 mL/min/1.73 m^2 in the respective cohorts. According to the Newcastle–Ottawa Scale, the majority of studies presented a low risk of bias (Supplementary Table S2).

All-cause mortality

In the 56 studies reporting all-cause mortality, more than 245,000 ER patients and 275,000 LR patients were assessed. The all-cause mortality rate of ER patients was 33% lower than that of LR patients (HR = 0.67, 95% CI: 0.62–0.72, Fig. 2). Adjusted estimates from each study were combined to reduce potential bias from confounding. Of note, mortality outcomes were adjusted for different sets of variable factors. Among 22 studies available, 20, 16, and 9 studies were adjusted for age, comorbidity, and residual renal function, respectively. Pooled analysis showed that the adjusted mortality rate was 27% lower in ER patients than in LR patients (HR = 0.73, 95% CI: 0.69–0.78). The unadjusted HR was 0.63 (95% CI: 0.56–0.71) in the 34 studies.

Further analysis of mortality rates stratified by follow-up duration is presented in Fig. 3. The 6-month, 1-year, 2-year, 3-year, 4-year, and 5-year mortality rates between ER and LR were reported in 22, 41, 21, 18, 15, and 17 studies, respectively. ER patients had a lower risk of mortality at 6 months, 1 year, and 2, 3, 4, and 5 years after the start of dialysis compared to LR patients (6 months: HR = 0.52, 95% CI: 0.40–0.68; 1 year: HR = 0.57, 95% CI: 0.51–0.65; 2 years: HR = 0.54, 95% CI: 0.47–0.63; 3 years: HR = 0.62, 95% CI: 0.53–0.71; 4 years: HR = 0.63, 95% CI: 0.54–0.73; 5 years: HR = 0.67, 95% CI: 0.60–0.74). To evaluate the short- and long-term effect of referral timing, the survival outcomes at 6-month and 5-year dialysis were obtained. Figure 4 shows the relative mortality risk and absolute survival rates of ER versus LR at 6-month and 5-year dialysis when cut-off points were set at 3, 4, and 6 months before the first dialysis. Compared to LR patients, patients who were referred for at least 3 and 6 months had a lower likelihood of 6-month and 5-year mortality. Among ER patients, the survival rate increased with longer durations of pre-RRT care from ≥ 3 months to ≥ 6 months.

The mortality risk of ER versus LR patients on hemodialysis (HD) and peritoneal dialysis (PD), HD only, and PD only was reported in 27, 22, and 6 studies, respectively (Fig. 5). Compared to LR patients, ER patients showed a lower likelihood of mortality risk, irrespective of dialysis modalities (HD and PD: HR = 0.68, 95% CI: 0.62–0.75; HD: HR = 0.61, 95% CI: 0.53–0.69; PD: HR = 0.83, 95% CI: 0.72–0.95).

Six and 10 studies reported adjusted mortality risk for cohorts initiating dialysis before and after 2003, respectively. A lower mortality risk was observed in ER patients in both time periods (pre-2003: HR = 0.69, 95% CI: 0.59–0.81; post-2003: HR = 0.72, 95% CI: 0.60–0.87) (Supplementary Fig. S1). Pooled data from 6 post-2003 cohorts with a mean age above 60 showed a 20% lower mortality risk in the ER group (HR = 0.80, 95% CI: 0.71–0.89) (Supplementary Fig. S2).

Other clinical outcomes

Secondary outcomes of interest were durations of initial hospitalization, kidney transplantation, arteriovenous access creation, emergency first dialysis, initial use of arteriovenous access, and first catheter use before dialysis initiation, which were reported in 9, 10, 8, 14, 21, and 23 studies, respectively. Relative risk for each outcome between ER patients versus LR patients was highly heterogeneous with the I^2 ranging from 81 to 99% (Fig. 6). All 9 studies reported that ER patients had shorter hospital stays beginning at dialysis than LR patients. Compared to LR patients, ER patients were more likely to undergo kidney transplantation during a follow-up period ranging from 4 months to 34.4 months in the included studies (RR = 1.41, 95% CI: 1.12–1.78, Fig. 6a). ER patients presented a higher likelihood of arteriovenous access creation (RR = 3.34, 95% CI: 2.43–4.59, Fig. 6b) and initial use of arteriovenous access (RR = 2.60, 95% CI: 2.18–3.11, Fig. 6c). Besides, ER patients were less likely to undergo emergency first dialysis (RR = 0.39, 95% CI: 0.28–0.54, shown in Fig. 6d) or start dialysis with catheters (RR = 0.43, 95% CI: 0.32–0.58, Fig. 6e).

Sensitivity analysis

We conducted a sensitivity analysis by excluding each included study. The pooled HR was not significantly

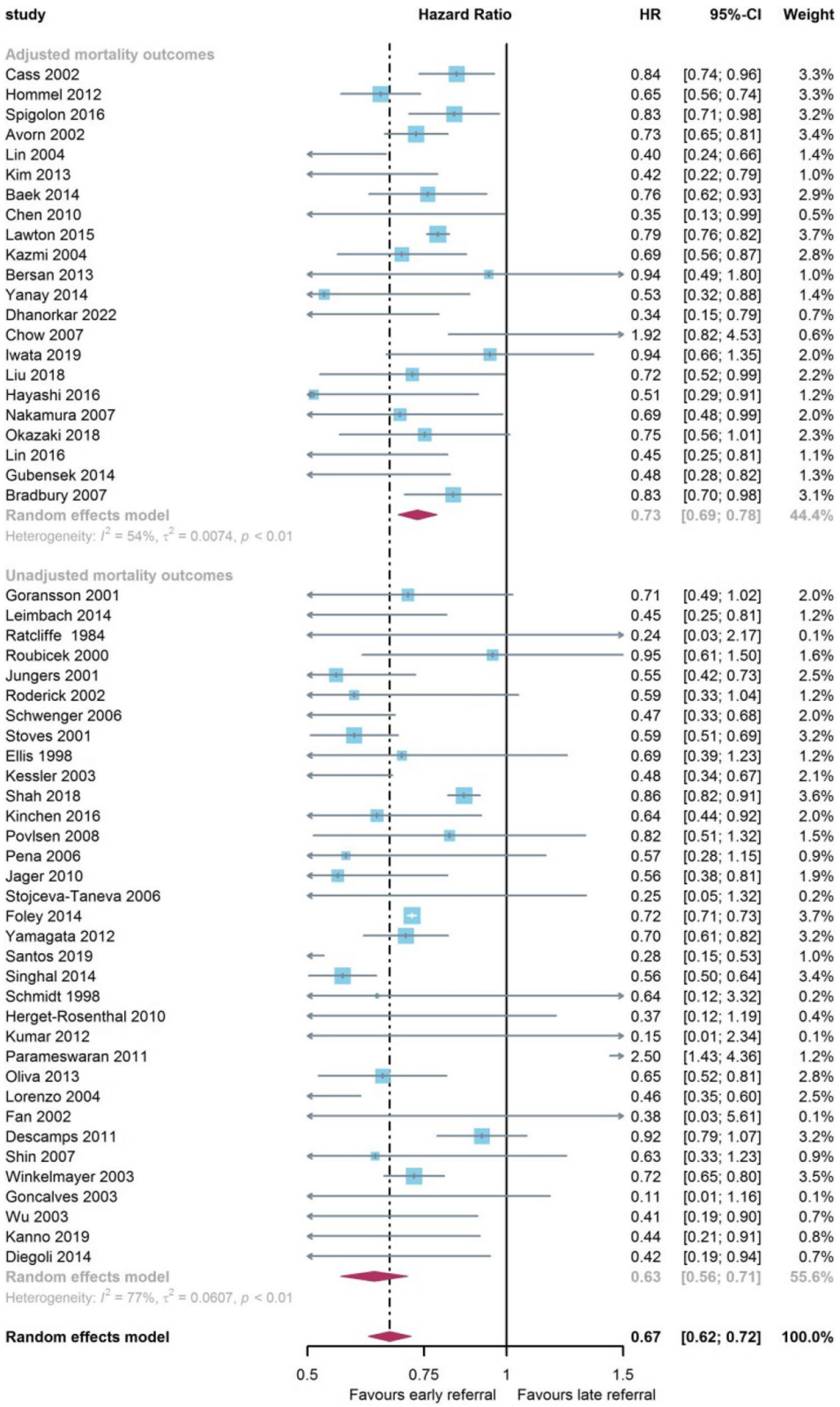

Fig. 2 Forest plot for all-cause mortality overall of early versus late referral. ER patients were associated with a lower risk of all-cause mortality than their LR counterparts. The pooled HRs and their 95% CI were estimated using random effects models. Abbreviations: ER, early referral; LR, late referral; CI, confidence interval

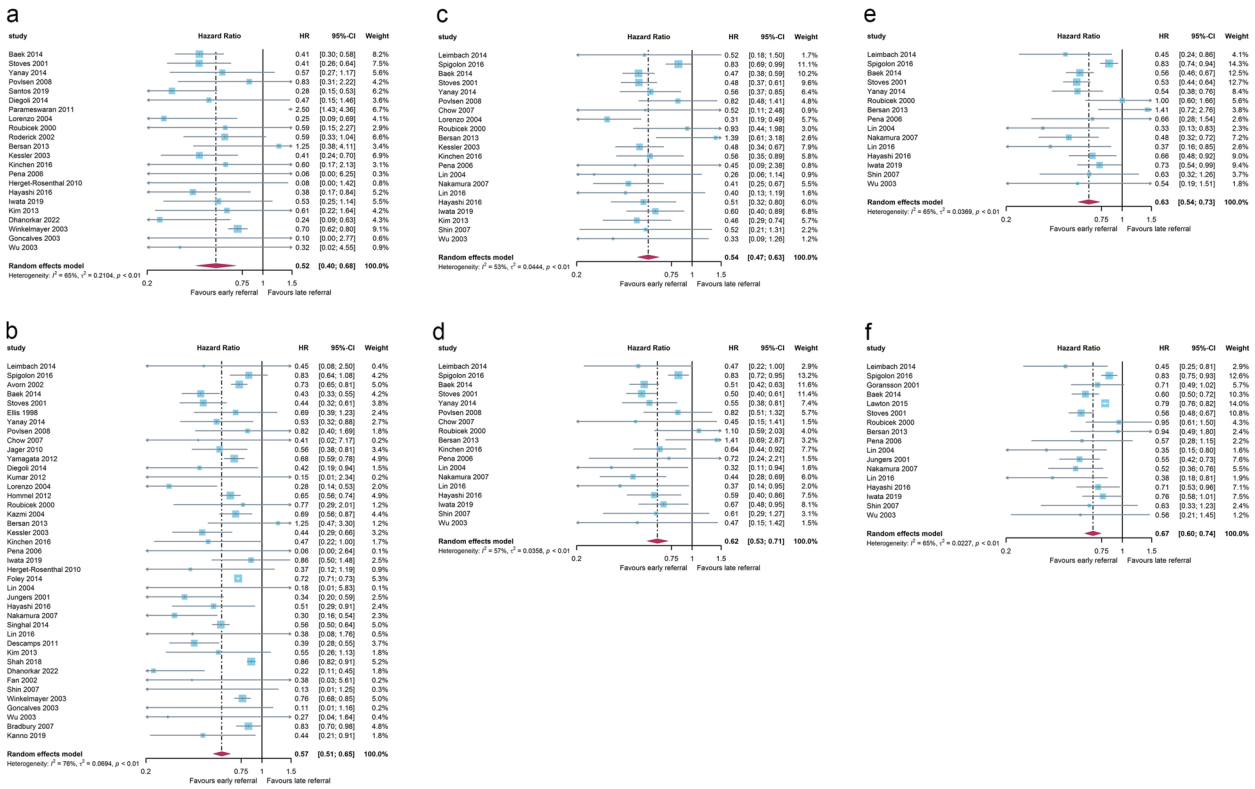

Fig. 3 Forest plot for all-cause mortality overall of early versus late referral stratified by dialysis duration. **a** 6 months; **b** 1 year; **c** 2 years; **d** 3 years; **e** 4 years and **f** 5 years. ER patients showed a lower mortality risk at 6 months, 1 year, and 2, 3, 4, and 5 years after dialysis initiation than LR patients. The pooled HRs and their 95% CI were estimated using random effects models. Abbreviations: ER, early referral; LR, late referral; CI, confidence interval

altered, indicating that the result was relatively robust (Supplementary Fig. S3).

Publication bias

The publication bias was assessed regarding the outcome of all-cause mortality, with the largest number of included studies. There was significant publication bias by Egger 's test ($p=0.037$) and funnel plot. Therefore, a sensitivity analysis was conducted using the trim-and-fill method. After adding 17 unpublished studies, the trim-and-fill analysis showed a similar result (HR = 0.72, 95% CI: 0.66–0.78, Supplementary Fig. S4).

Discussion

In the analysis of 72 studies involving more than 630,000 patients, we showed the survival benefits of early nephrology referral among pre-dialysis populations, irrespective of dialysis modalities. Further, we identified that patients referred earlier had shorter lengths of initial hospitalization and better preparation for renal replacement therapy. Nephrology care involves patient education, complication management, consultations of treatment modality, and preparation of dialysis access. Timely pre-RRT nephrology care provides enough time for multidisciplinary cooperation to optimize strategies in advanced CKD and generally leads to improved outcomes. Kidney Disease: Improving Global Outcomes (KDIGO) guidelines have recommended timely nephrology consultations for RRT planning in people with progressive CKD [79].

However, population heterogeneity and selection bias were potentially high in this meta-analysis. Results from observational studies may be confounded by case-mix characteristics and clinical statuses, such as age, laboratory parameters, and comorbidity. Our study suggested a trend toward initiating dialysis at slightly higher eGFR levels over the past two decades. eGFR at the initiation of dialysis has proven to be a significant risk factor influencing patient prognosis. Data from the Initiating Dialysis Early and Late randomized controlled trial showed no significant differences in mortality risk or adverse event frequency between early- and late-start groups (eGFR of 10–14 mL/min/1.73 m^2 vs. 5–7 mL/min/1.73 m^2) [80]. Moreover, a meta-analysis of 15 cohort studies found that a higher adjusted mortality risk was associated with initiating dialysis at higher GFRs, even after accounting for

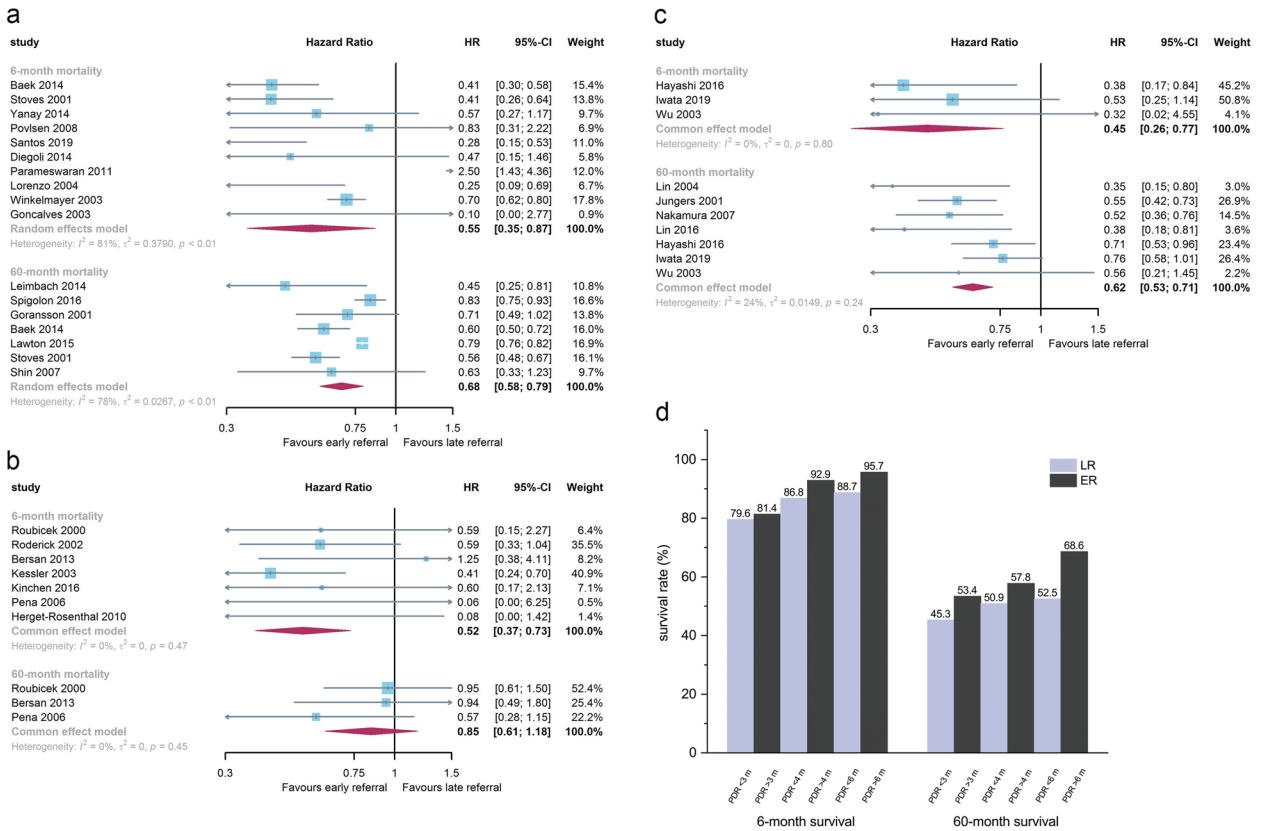

Fig. 4 All-cause mortality overall of early versus late referral stratified by cut points of first nephrology care. **a** 3 months; **b** 4 months; **c** 6 months; and **d** absolute survival rates by cut points. Patients referred at least 3 and 6 months showed a lower likelihood of 6-month and 60-month mortality than their LR counterparts. Patients referred at least 4 months showed a lower of 6-month mortality risk but similar 60-month mortality risk compared to LR patients. Compared to those referred earlier than 3 and 4 months prior to the first dialysis, patients who were referred at least 6 months showed the highest absolute survival rate during 6-month and 60-month dialysis (6 months: 95.7%; 60 months: 68.6%). The biggest survival difference was observed between ER and LR when the cut-off point was set at 6 months than at 3 and 4 months. The pooled HRs and their 95% CI were estimated using random effects models. Abbreviations: ER, early referral; LR, late referral; CI, confidence interval; PDR: pre-dialysis referral

confounding factors [81]. Therefore, eGFR at dialysis initiation was included as a key confounder in our analysis. Additionally, age and comorbidity are prognostic factors affecting patients' survival. The differences in confounders for adjustment existed across studies. Riley et.al proposed to define at least a minimum set of factors for adjustment to reduce confounding bias in meta-analysis of observational studies [82]. To minimize the effect of confounding factors, we presented pooled mortality risk using estimates adjusted for potential confounding factors such as age, comorbidity, and eGFR. We observed a 27% reduction in adjusted mortality risk associated with early nephrology referral. The persistent survival benefits of early referral were observed in both the post-2003 cohort and older populations, demonstrating that early nephrology referral continues to be a critical factor in improving patient outcomes. Additionally, in line with previous meta-analyses, the present study found that the survival benefits from early nephrology care persisted for years after dialysis initiation.

The hypothesis of survival benefits in ER patients could be partly caused by a lower likelihood of emergency start and initial catheter use and a higher likelihood of permanent access creation and permanent access first use. Data from the French Renal Epidemiology and Information Network have shown that emergency first dialysis is independently associated with worse three-year survival [83]. Non-tunneled CVCs (central venous catheters) are typically applied in short-term, inpatient dialysis including emergency induction [84, 85]. Central venous catheters are associated with a higher likelihood of death, cardiovascular events, and infection [84, 85]. Arhuidese et al. showed that reliable arteriovenous access positively impacted prognosis in patients receiving chronic dialysis [86].

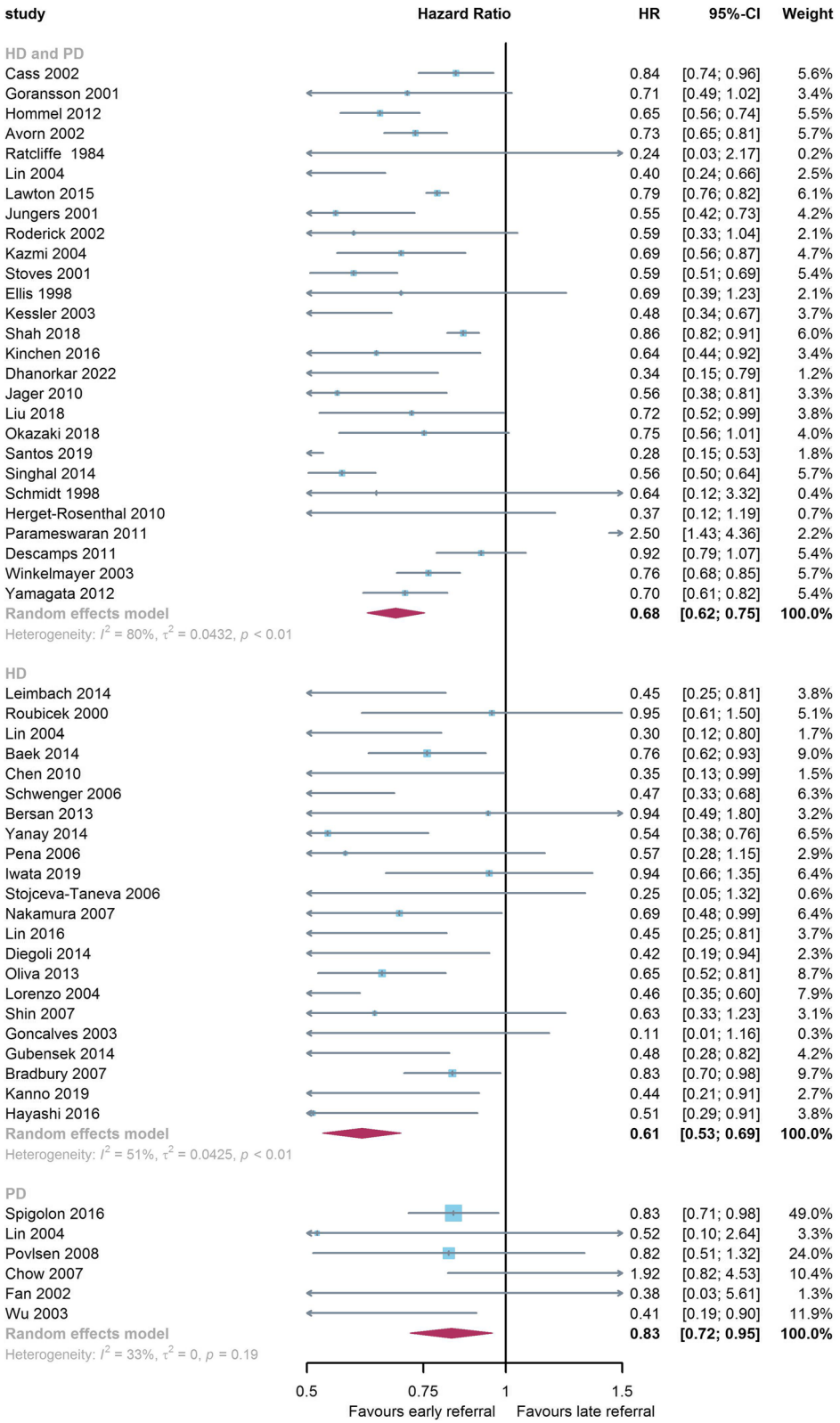

Fig. 5 Forest plot for all-cause mortality overall of early versus late referral stratified by dialysis modality. Compared to LR patients, ER patients showed a lower likelihood of mortality risk in HD only, PD only and two modality groups, respectively. The pooled HRs and their 95% CI were estimated using random effects models. Abbreviations: ER, early referral; LR, late referral; HD: hemodialysis; PD: peritoneal dialysis; CI, confidence interval

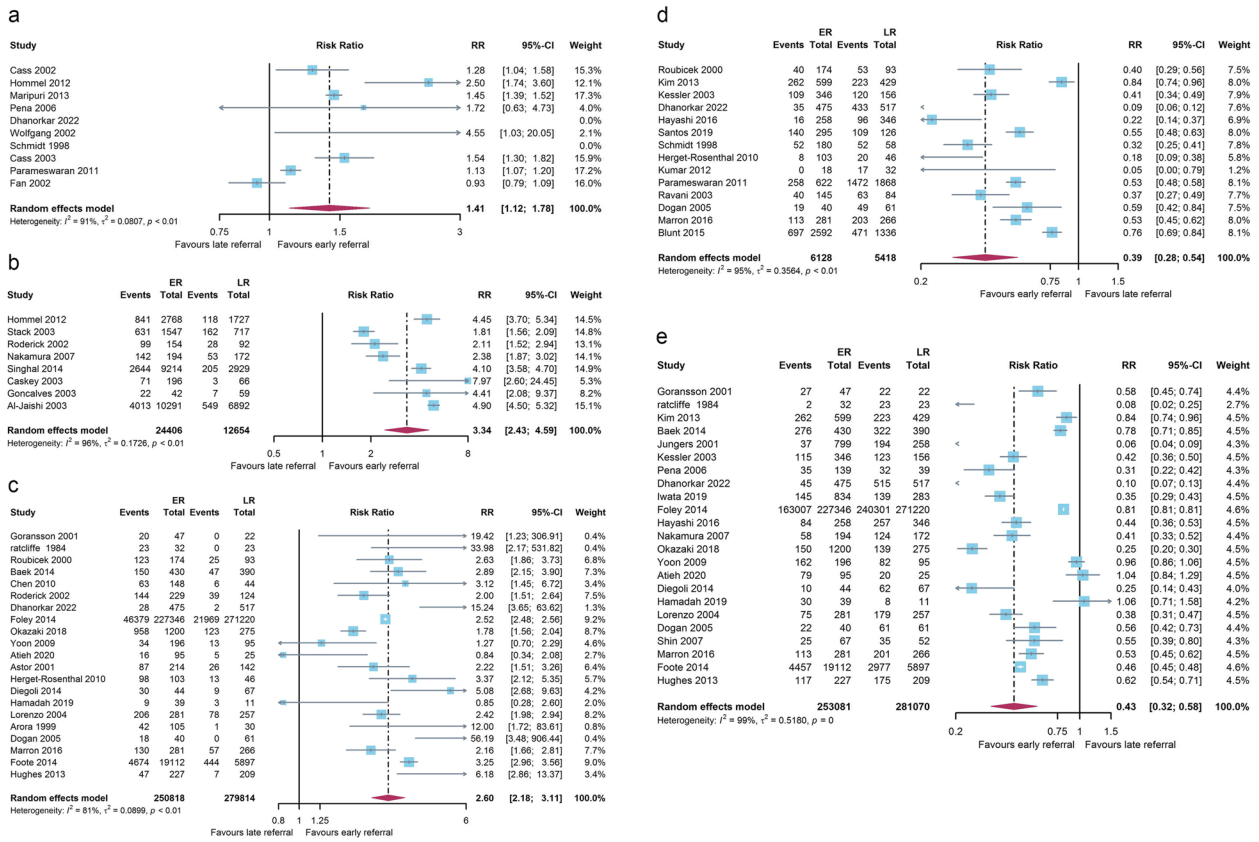

Fig. 6 Forest plot for secondary outcomes of early versus late referral. **a** kidney transplantation; **b** arteriovenous access creation; **c** initial use of arteriovenous access; **d** initial catheter use; and **e** emergency start. ER patients were associated with a higher rate of kidney transplantation, a higher likelihood of arteriovenous access creation, increased arteriovenous access use, reduced initial catheter use, and a lower likelihood of emergency start compared to LR patients. The pooled RRs and their 95% CI were estimated using random effects models. Abbreviations: ER, early referral; LR, late referral; CI, confidence interval

Kidney transplantation is the best therapy for kidney failure, with proven benefits in life quality and survival over dialysis [87]. Our findings showed that the ER patients had a higher rate of transplantation compared to LR patients, again reiterating that adequate nephrology care plays a role in further prospective management of CKD patients. The steps prior to kidney transplantation are multiple, involving patient education, referral to transplant clinics, medical evaluation, and wait-listing [88]. Gill et al. suggested that the death rate increased with a longer waiting time before transplantation [89]. Early nephrology referral has been associated with preemptive kidney waiting-list placement and transplantation [90, 91], suggesting better nephrology care drives referral to transplant clinics. Early RRT planning discussions with patients at high risk of ESRD should be promoted.

As chronic kidney disease is common and represents a heavy societal burden, there is a need to explore the proper timing of nephrology consultations for adequate preparation of RRT. Pooled analysis of survival data with different referral points showed an increasing trend of survival rate with longer durations of nephrologist follow-ups. However, caution is needed in interpreting these results, as selection bias cannot be completely avoided. Saggi et.al suggested that preparation for RRT should begin early enough in the course of CKD to consider therapy modality and establish permanent access for dialysis choice [92]. Given the burden and integrated care associated with advanced CKD, KDIGO guidelines suggest at least 1 year is required to ensure appropriate education, understanding, and referrals to other practitioners (e.g., vascular access surgeons, transplant team, etc.) [79].

The current study has several strengths. Firstly, our findings involved a large cohort of CKD patients and enhanced statistical power to quantify the association of referral patterns and outcomes. Secondly, our study focused on significant outcomes related to ESRD patients including mortality and kidney

transplantation. The latter was not reported in previous systematic reviews. Further analysis explored associations of survival and length of nephrology care. However, our study is limited by the observational nature of the included studies. The heterogeneity across studies is largely attributed to population selection criteria, sample size, statistical methodology, and referral practices. The referral pattern was defined as months before dialysis initiation without considering eGFR. Besides, the sample population for analysis consists of patients with CKD at different stages and thus, lead-time bias cannot be avoided. Additionally, our meta-analysis included pre-2003 cohorts, which limited its ability to accurately reflect the current dialysis population. Therefore, a subgroup analysis was conducted to assess the mortality risk associated with the two referral patterns, focusing on cohorts from before and after 2003. Furthermore, publishing bias existed in this study. Studies with negative findings that are less likely to be published might affect the results. However, it is not feasible to conduct randomized controlled trials to address this issue due to ethical limitations. A large-scale prospective study is awaited to draw a conclusion.

To conclude, our study showed that early referral to nephrologists for patients with advanced CKD was associated with a reduced risk of mortality, shorter initial hospitalization durations, and improved readiness for RRT. Early nephrology care should be promoted to improve the management of advanced chronic kidney disease.

Abbreviations

CKD	Chronic kidney disease
ESRD	End-stage renal disease
eGFR	Estimated glomerular filtration rate
Ccr	Creatinine clearance
ER	Early referral
LR	Late referral
CI	Confidence interval
HR	Hazard ratio
HD	Hemodialysis
PD	Peritoneal dialysis
RRT	Renal replacement therapy
CVCs	Central venous catheters

Supplementary Information

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Supplementary Material 1.

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Clinical trial number
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Authors' contributions
YC conceived the study, executed its design, and revised the manuscript. LC had full access to data collection, statistical analysis, interpretation, and manuscript drafting. DS, NH, and LL participated in data collection and analysis. All authors had access to the data and approved the final manuscript for submission.

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Data availability
All data generated or analyzed in this study are presented in this article and its supplementary materials. Further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
An ethics statement is not applicable because this study is based exclusively on the published literature. The consent is not required because the study does not retrieve individual patients' data.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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