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GFR at Initiation of Dialysis and Mortality in CKD: A Meta-analysis

Paweena Susantitaphong, MD[1,3], **Sarah Altamimi, MBBS**[1], **Motaz Ashkar, MBBS**[1], **Ethan M. Balk, MD, MPH**[2,3], **Vianda S. Stel, PhD**[4], **Seth Wright, MD**[5], and **Bertrand L. Jaber, MD, MS**[1,3]

[1]Department of Medicine, Division of Nephrology, Kidney and Dialysis Research Laboratory, St. Elizabeth's Medical Center, Boston, MA [2]Center for Clinical Evidence Synthesis, Tufts Clinical and Translational Science Institute, Tufts University, Boston, MA [3]Department of Medicine, Tufts University School of Medicine, Boston, MA [4]Department of Medical Informatics, ERA-EDTA Registry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands [5]Department of Medicine, Brigham and Women's Hospital, Boston, MA

Abstract

Background—The proportion of patients with advanced chronic kidney disease (CKD) initiating dialysis at higher glomerular filtration rate (GFR) has increased over the past decade. Recent data suggest that higher GFR may be associated with increased mortality.

Study Design—A meta-analysis of cohort studies and trials.

Setting & Population—Patients with advanced CKD.

Selection Criteria for Studies—We performed a systematic literature search in MEDLINE, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, American Society of Nephrology abstracts, and bibliographies of retrieved articles to identify studies reporting on GFR at dialysis initiation and mortality.

Predictor—estimated or calculated GFR at dialysis initiation.

Outcome—Pooled adjusted hazard ratio (HR) of continuous GFR for all-cause mortality.

Results—Sixteen cohort studies and one randomized controlled trial were identified (n=1,081,116). By meta-analysis, restricted to the 15 cohorts (n=1,079,917), higher GFR at dialysis initiation was associated with a higher pooled adjusted HR for all-cause mortality (1.04; 95% CI, 1.03–1.05; P<0.001). However, there was significant heterogeneity (I^2=97%; P<0.001). The association persisted among the 9 cohorts that adjusted analytically for nutritional covariates (HR 1.03; 95% CI 1.02, 1.04; P<0.001; residual I^2=97%). The highest mortality risk was observed in hemodialysis cohorts (HR 1.05; 95% CI 1.02, 1.08; P<0.001) whereas there was no association between GFR and mortality in peritoneal dialysis cohorts (HR 1.04; 95% CI 0.99, 1.08, P=0.11;

ADDRESS FOR CORRESPONDENCE: Bertrand L. Jaber, MD, MS; St. Elizabeth's Medical Center; 736 Cambridge Street, Boston, MA 02135; Phone (617) 562-7832; Facsimile (617) 562-7797; bertrand.jaber@steward.org.
*Drs. Susantitaphong, Altamimi, and Ashkar contributed equally to this study.

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residual I^2=98%). Finally, higher GFR was associated with a lower mortality risk in cohorts that calculated GFR (HR 0.80; 95% CI 0.71, 0.91; P=0.003), contrasting with a higher mortality risk in cohorts that estimated GFR (HR 1.04; 95% CI 1.03, 1.05; P<0.001; residual I^2=97%).

Limitations—Paucity of randomized controlled trials; different methods for determining GFR; and substantial heterogeneity.

Conclusions—Higher estimated rather than calculated GFR at dialysis initiation is associated with a higher mortality risk among patients with advanced CKD, independent of nutritional status. Although there was substantial heterogeneity of effect size estimates across studies, this observation requires further study.

Keywords

ESRD; CKD; hemodialysis; peritoneal dialysis; early initiation; late initiation; GFR; mortality

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The number of patients with stage-5 chronic kidney disease (CKD) is increasing worldwide[1–4]. In 2008, close to 110,000 patients initiated dialysis in the US[4], and in 2020, 800,000 prevalent patients are projected to receive dialysis[3]. The care of patients with stage-5 CKD is associated with significant resource consumption and healthcare expenditure, close to 5.9% of the total Medicare budget in the US alone[4]. From 1996 to 2008, the proportion of patients initiating dialysis in the US at an estimated glomerular filtration rate (eGFR) of greater than 10 ml/min/1.73 m^2 has more than doubled from 20% to 52%[3]. A similar trend has also been observed in Europe and Canada[5,6]. Likely reasons for this trend are the widespread adoption of clinical practice guidelines on management of advanced CKD, and the belief that malnutrition might develop in patients who start dialysis late[7], thus affecting survival[8].

Currently published clinical practice guidelines vary with respect to eGFR cutoffs below which dialysis therapy should be initiated but they unanimously recommend assessing for symptoms or signs of uremia[8–13]. However, typical uremic symptoms that constitute clear indications to initiate dialysis including, pericarditis, and encephalopathy, generally occur at very low of GFR[14,15]. In one study, symptoms such as nausea, vomiting, and progressive deterioration in nutritional status accounted for less than one-third of dialysis indications in the elderly[16].

Patients with advanced CKD who transition to dialysis often experience significant physical and emotional stress. Health-related quality of life benefits observed following initiation of dialysis are debatable, and early initiation of dialysis is associated with higher costs[17]. Recent data also suggest that initiation of dialysis at higher GFR might be associated with worse clinical outcomes[18–21]. These controversial findings have prompted several commentaries[22–27]. Although a systematic review of 10 studies recently examined this question, the analysis was qualitative in nature and the results somewhat inconclusive[28]. To gain more information on this subject, we performed a quantitative meta-analysis of all available studies of patients with advanced CKD that examined the association of kidney function at the start of dialysis, as assessed by level of GFR, with all-cause mortality. We also explored potential sources of heterogeneity among studies.

METHODS

Data Sources and Searches

We searched MEDLINE (inception-March 2011), the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov to identify eligible studies using the medical subject headings (MeSH) search terms and keywords provided in Table S1 (available as

online supplementary material). The search strategy was limited to human studies with no language restrictions. We also reviewed the *American Society of Nephrology* abstracts (2003–2010 meetings) and the bibliographies of retrieved articles.

Study Selection

In light of the paucity of randomized controlled trials, we focused primarily on cohort studies that examined the association of GFR at dialysis initiation with mortality. We included studies that compared early *vs.* late initiation of dialysis as defined in the individual reports. No restrictions were placed on sample size or study duration. Two authors (SA and MA) screened the electronic citations and then re-screened the full-text of potentially relevant articles.

Data Extraction and Quality Assessment

Data were extracted from full-text articles independently by 3 authors (SA, MA and PS). Disagreements were resolved through consensus and arbitration by a fourth author (BLJ). We extracted data on study characteristics including the country of origin, year of publication, study design, data source, accrual period, number of patients, initial dialysis modality (hemodialysis [HD], peritoneal dialysis [PD], or both), maximum duration of follow-up, and cohort characteristics including, mean age, percentage of men and diabetics, mean body mass index, and mean serum albumin. We also extracted data on the mean estimated GFR (eGFR) (estimated by the Modification of Diet in Renal Disease [MDRD] study equation), calculated GFR (cGFR) (defined as the average of creatinine and urea clearance from a 24 hour urine collection), or creatinine clearance (estimated by the Cockcroft-Gault equation). Outcomes of interest were the total number of deaths, all-cause mortality rates including those within GFR categories (if applicable), and the effect estimates of Cox-regression analyses examining the association of eGFR or cGFR (per 1-ml/min/1.73 m^2 increment) with mortality, which consisted of adjusted odds ratios and hazard ratios (with 95% confidence intervals). We grouped the adjustment variables used in these regression analyses into demographic and socioeconomic factors, causes of kidney failure, co-morbid conditions, nutritional factors, anemia parameters, treatment variables, and miscellaneous. Corresponding authors of studies were contacted for data clarification and to provide additional analyses.

The quality of the cohort studies was assessed using an adaptation of the Newcastle-Ottawa Scale[29]. This scale assesses the quality of observational studies, and allocates a maximum of 9 points for quality of selection (up to 4 points), comparability (up to 2 points), and outcome (up to 3 points) of study participants. Overall study quality was arbitrarily defined as poor (score 0–3), fair (score 4–6), or good (score 7–9). The Jadad score was used to assess the quality of randomized controlled trials.

Data Synthesis and Analysis

Most cohort studies performed multivariable Cox proportional-hazards regression analyses and reported the adjusted hazard ratio of eGFR or cGFR for all-cause mortality. Consequently, to minimize confounding, we performed a random-effects model meta-analysis of the pooled adjusted hazard ratio of estimated or calculated GFR (per 1-mL/min/1.73 m^2 increment) reported in the cohort studies for all-cause mortality among patients initiating dialysis.

The heterogeneity of effect size estimates across studies was described with the I^2 index and Q statistic P value. We investigated heterogeneity by performing univariate random-effects model meta-regressions of the adjusted hazard ratios against study characteristics including, methods of GFR assessment, initial dialysis modality, inclusion of nutritional covariates in

the multivariable models, duration of follow-up (< *vs.* ≥ median), study sample size (< *vs.* ≥ 10,000), and quality scores. All the analyses were performed using Comprehensive Meta-Analysis version 2.0, and the *metan* and *metareg* commands of Stata 11 (College Station, TX). Publication bias was assessed using funnel plots and the Egger test[30].

RESULTS

Study Characteristics and Quality

A total of 2,792 potentially relevant citations were identified and screened; 39 articles were retrieved for detailed evaluation, of which 17 fulfilled eligibility criteria (Figure 1)[18–21,31–43]. Characteristics of the studies are displayed in Table 1. There were 16 cohort studies and one randomized controlled trial. In the single randomized controlled trial, Initiating Dialysis Early and Late (IDEAL)[19], 828 adults with progressive CKD were randomly assigned to initiate dialysis when the eGFR reached 10–14 mL/min/1.73 m^2 or 5–7 mL/min/1.73 m^2. 56% of study participants were initiated on HD and 44% on PD. The cohort studies spanned approximately 10 years, varied in sample size (100–896,546 patients) and maximum duration of follow up (1–11 years), and involved patients initiating HD, PD, or a mixture of the two modalities. Most studies had more men (range, 45–67%) with a mean age of 58 (range 46–67) years. The percentage of diabetics varied from 8.4–100%. Among studies that reported the baseline values, the meta-analyzed mean body mass index was 25.9 (95% CI, 25.6–26.2) kg/m^2, and mean serum albumin 3.32 (95% CI, 3.30–3.35) gm/dL. Fourteen studies estimated the GFR using a variant (4-, 5- or 6-variable) of the MDRD Study equation[18–21,34–43], and 1 study estimated GFR using the Cockcroft-Gault equation[33]. Two studies calculated GFR using the average of creatinine and urea clearance derived from a 24-hour urine collection (Table S2)[31,32].

Corresponding authors of 16 studies were contacted[18–21,32–43], and 7 provided additional information[18,20,21,33,35,40,41], including adjusted hazard ratios according to the initial dialysis modality[40]. One study included 2 cohorts with different accrual periods that were analyzed separately[40]. There was an overlap of patient populations between 2 cohort studies[21,35]; thus, in the larger and more recent report, those patients were excluded (overlap period of 1996–1999) to avoid duplication of the cohort[21]. Among cohort studies reporting adjusted hazard ratios for mortality, 15 modeled continuous GFR (per 1 mL/min/1.73 m^2 increment)[18,20,21,31–35,37,38,40–43], and 11 modeled pre-defined GFR categories (Table 2).

We only meta-analyzed the Cox regression models that examined continuous GFR, and therefore excluded from the analysis 2 cohort studies[36,39] and the IDEAL trial[19]. All 15 analyzable cohorts used multivariable adjustments, but only in 9 cohorts, analyses were adjusted for selected nutritional covariates including, weight, body mass index, serum albumin, and/or serum bicarbonate (Table 2). According to the Newcastle Ottawa Scale, most cohort studies were considered of fair (scale of 4–6) to good (scale of 7–9) quality (Table 1).

Association of GFR at Dialysis Initiation with All-Cause Mortality

The IDEAL trial found that over a median follow-up duration of 3.6 years, the early-start group had a hazard ratio of 1.04 (95% CI, 0.83–1.30) for all-cause mortality compared with the late-start group.

The 15 cohorts reporting the adjusted hazard ratio of continuous GFR included a total of 1,079,917 analyzable patients. By meta-analysis, higher GFR (per 1 mL/min/1.73 m^2 increment) at dialysis initiation was associated with a significantly higher adjusted hazard ratio for all-cause mortality (HR, 1.04; 95% CI, 1.03–1.05; P<0.001; Figure 2). The test for heterogeneity was highly significant (I^2=97%; P<0.001).

Subgroup analyses were explored. Among the 9 cohorts that included nutritional indicators in their multivariable models, GFR remained independently associated with a 3% risk increase in mortality (adjusted HR, 1.03; 95% CI, 1.02–1.04; P<0.001), but had a significantly smaller effect compared with the 6 cohorts that did not include nutritional covariates (P=0.008; residual I^2=97%; Figure 3A). Among the 5 cohorts initiating HD (139,797 analyzable patients), the association between higher GFR and increased mortality was significant (adjusted HR, 1.05; 95% CI, 1.02–1.08; P<0.001), contrasting with the 4 cohorts restricted to PD as the initial dialysis modality (2,820 analyzable patients) where higher GFR was not associated with mortality (adjusted HR, 1.04; 95% CI, 0.99–1.08; P=0.1). However, there was no significant difference in the effect between these 2 subgroups (P=0.6; residual I^2=98%; Figure 3B). Higher GFR was also associated with a lower mortality risk in the 2 cohorts (486 analyzable patients) that calculated GFR (adjusted HR=0.80; 95% CI 0.71, 0.91; P=0.003), contrasting with a higher mortality risk in the 13 cohorts (1,079,431 analyzable patients) that estimated GFR (adjusted HR=1.04; 95% CI 1.03, 1.05; P<0.001). The effect between these 2 subgroups was significant (P<0.001; residual I^2=97%; Figure 3C). Cohorts that had a maximum follow-up period ≥5 years (adjusted HR=1.03; 95% CI 1.02, 1.04; P<0.001) had significantly smaller effect (P=0.04; residual I^2=97%) compared to those with a follow-up period <5 years (adjusted HR=1.05; 95% CI 1.04, 1.06). Cohorts that included ≥10,000 patients (adjusted HR=1.04; 95% CI 1.03, 1.05; P<0.001) had near-significantly larger effect (P=0.07; residual I^2=97%) compared to those with <10,000 patients (adjusted HR=1.03; 95% CI 1.02, 1.04).

In a sensitivity analysis that excluded the 2 largest studies that contributed collectively 914,200 patients [21,35], higher GFR remained associated with mortality (adjusted HR=1.04; 95% CI 1.02, 1.05; P<0.001; residual I^2=97%). In another sensitivity analysis where we excluded the report by Rosansky et al that might have had potential population overlap with the study by Wright et al, higher GFR remained associated with higher mortality (adjusted HR=1.04; 95% CI 1.03, 1.05; P<0.001; residual I^2=97%).

Study quality did no significantly affect the pooled estimates (data not shown). Finally, funnel plots were symmetric suggesting less susceptibility to publication bias (Figure S1) and the Egger test was not significant (P=0.7).

DISCUSSION

In the present meta-analysis of cohort studies, we demonstrate that among patients with advanced CKD, higher GFR at the initiation of dialysis is associated with a higher mortality risk. Across studies, a 1-mL/min/1.73 m^2 GFR increment was associated with a 4% higher adjusted hazard for all-cause mortality. This association persisted across a broad range of sensitivity and subgroup analyses. Indeed, restricting to studies that used nutritional covariates in their multivariable models demonstrated an attenuated but persistent association of GFR with a 3% risk increase in mortality. Furthermore, the mortality risk was the highest at 5% in studies restricted to patients initiating HD. By contrast, in studies restricted to patients initiating PD, higher GFR appeared to not be associated with mortality. However, the lack of significant difference in the effect between the 2 subgroups and the relatively small sample size of the pooled PD cohorts precludes definitive conclusions. Finally, the mortality risk was 20% lower in the few studies that derived the GFR from a 24-hour urine collection contrasting with a higher mortality risk among the many studies that estimated GFR.

The proportion of patients initiating dialysis at higher eGFR has been increasing over the past decade. This may be the result of a widespread adoption of clinical practice guidelines that provide eGFR cutoff values below which dialysis therapy should be considered[8–12],

coupled to the belief that early dialysis initiation might prevent the progressive decline in nutritional status[7], and might possibly allow for better vascular access planning and avoidance of dialysis catheters[44–46]. Unfortunately, there is no definitive evidence to support this approach. In a post-hoc analysis of the IDEAL study, which is the only randomized controlled trial comparing early (eGFR of 10–14 mL/min/1.73 m^2) with late (eGFR of 5–7 mL/min/1.73 m^2) initiation of dialysis, the authors failed to demonstrate a survival benefit between the 2 groups[19]. However, 76% of the patients in the late-start group needed to initiate dialysis due to uremic symptoms when their eGFR was far above the 5 to 7 mL/min/1.73 m^2. In fact, the mean eGFR at the start of dialysis in the early- and late-start group was 9.0 and 7.2 mL/min/1.73 m^2, respectively. We can only speculate as to whether the absolute difference in eGFR between the two groups was too small to detect a survival difference. Furthermore, the wide 95% confidence interval of the HR with early dialysis initiation (1.04; 95% CI, 0.83, 1.30) observed in this trial is consistent with our observational data. Overall, the trial results suggest that the decision to initiate dialysis is not only determined by eGFR, but also by the clinical condition of the patient. In a subsequent pre-specified analysis of the IDEAL trial, early start was not cost-effective, with mean direct dialysis-related costs that were significantly greater in the early-start group by $10,777[17]. The present meta-analysis of cohort studies leaves us with the impression that higher eGFR at dialysis initiation, adjusted for confounders, might either be harmful or does not affect survival.

In the present report, we condensed the different “GFR” evaluation methods into a single rubric for the purpose of the analysis. The Cockcroft-Gault and MDRD Study equations, which incorporate the serum creatinine, tend estimate endogenous creatinine clearance not GFR, and are highly influenced by the muscle mass. Consequently, sarcopenia, which is the loss of muscle mass, especially in the elderly, is associated with lower serum creatinine, which would result in higher eGFR levels. Consequently, these equations are very poor estimates of GFR in advanced CKD. By contrast, 24-hour urine collections that measure endogenous creatinine or creatinine and urea clearance calculate GFR most accurately in advanced CKD, which was our population of interest. In one of our subgroup analyses, we demonstrated an association between higher calculated GFR (derived from a 24-hour urine collection), which is less likely to be influenced by the muscle mass, and lower mortality risk, contrasting with an association between higher estimated GFR (derived from the MDRD Study and Cockcroft-Gault equation) and higher mortality risk. Endogenous creatinine clearance (cGFR) seems to be the best markers, reflecting real kidney function. Therefore, the patients had the real worsening of kidney function; the initiation of dialysis did not result in high mortality. Although our results are consistent with a recent study that found an association between higher eGFR and increased mortality risk, but not cGFR [47], our analysis was restricted to a small sample of only 486 patients. In a large study of patients initiating dialysis, higher eGFR values were found to represent lower creatinine production rather than higher creatinine clearance, calling into question the reliability of estimating GFR with serum creatinine in advanced CKD [48]. In that same study, the risk for mortality in early dialysis starters was greatly attenuated when endogenous creatinine clearance was used as the method to assess GFR[48]. As a consequence of these emerging data, a recently published updated guideline on when to start dialysis introduced cGFR derived from a 24-hour urine collection as the best GFR assessment in advanced kidney failure[49].

A recently published qualitative systematic review that did not conduct a quantitative analysis was inconclusive regarding timing of dialysis initiation in patients with advanced CKD [28]. However, the authors noted higher mortality rates in early-starters of HD but lower mortality in early-starters of PD[28]. Our subgroup analysis is supportive of this finding, whereby higher GFR in patients starting HD was associated with the highest adjusted mortality risk, whereas in the fewer studies restricted to PD populations, higher GFR appeared to not be associated with mortality. In a reanalysis of the CANUSA study, a 5 L/

week/1.73 m^2 (the equivalent of 0.5 mL/min/1.73 m^2) increment in GFR (mean of urea and creatinine clearance) obtained 1 month after initiating PD, was associated with an adjusted 12% risk reduction in mortality, which disappeared once the 24-hour urine volume was forced into the model[50]. These authors suggested that the effect of GFR on mortality might be mediated in part by urine volume. This hypothesis needs to be tested. Although the IDEAL study failed to demonstrate a survival benefit of early *vs.* late start of dialysis[19], the dialysis modality choice was made by the patient and treating physician. This might have confounded the results of the trial as the treatment modality might be associated with a different mortality risk.

Our data synthesis has several strengths. This is the first meta-analysis and largest systematic review of cohort studies of patients with advanced CKD (1,079,917 analyzable patients) that examines the association of GFR at dialysis initiation with mortality. In addition, the analyses used adjusted hazard ratios to minimize the confounding relation of GFR with mortality by including patient and treatment characteristics. Furthermore, particular emphasis was placed on studies that adjusted for nutritional indicators, as the main non-GFR determinant of serum creatinine is muscle mass, which is a reflection of nutritional status.

There are several limitations that should be noted. Multiple definitions were used to quantify severity of kidney impairment including the MDRD Study equation (and its variants), the Cockroft-Gault equation, and 24-hour urine collection. The studies included varied greatly in duration of follow-up. Our meta-analysis was subject to several potential biases including lead-time bias, survival bias, and publication bias, as well as confounding and variable methodological quality inherent to the use of observational studies. There was also a potential overlap in the populations of two US-based cohort studies that utilized the same dialysis registry[18,20,21,33,35,40,41]. However, a sensitivity analysis excluding the smaller-size study[18,20,21,33,35,40,41], yielded similar results. The symmetric funnel plots coupled to a non-significant Egger test are suggestive of less susceptibility to publication bias. Confounding by indication is frequently encountered in observational studies, and is a more concerning bias and an important limitation of the analysis[51]. Indeed, the profile of early dialysis starters, as defined by a higher GFR level, might be related to the risk of adverse outcomes rather than the treatment variable of interest (i.e., higher GFR). Consequently, it remains unclear if persons with higher comorbidity profiles were more likely to initiate dialysis earlier. Since poor nutritional status at dialysis initiation is a known predictor of mortality in patients with CKD[52–54], we attempted to minimize this potential bias by using hazard ratios that were adjusted for several patient characteristics including nutritional indicators. However, the observational design of our analysis limits causal inference, and full adjustment for known and unknown confounders. This is an important limitation as some of the comorbidity assessment tools used in national data registries that collect, analyze, and distribute information on dialysis patients might under-report certain diagnoses[55,56].

Finally, the absence of differences in the pooled effect estimates according to study quality argues against biases resulting from flaws in the design of the individual studies included in our meta-analysis. Overall, these well-founded concerns call into question the design of clinical trials that rely on creatinine-based eGFR in patients with advanced CKD for treatment allocation.

In conclusion, the present meta-analysis of 15 cohort studies with 1,079,917 analyzable patients with advanced CKD found that higher GFR level at initiation of dialysis is associated with a higher adjusted mortality risk in observational studies, independent of nutritional status. This association might be strongest among patients initiating HD. Although there was substantial heterogeneity of effect size estimates across studies, The

association between higher GFR and mortality in patients with advanced CKD requires further study, and calls for the design of a large trial to formally test the appropriate timing of dialysis initiation preferably using better kidney function assessment tools such as measured or calculated GFR or non-creatinine-based GFR markers to minimize misclassification bias and nutritional confounding. Such trial should ideally be restricted to a particular dialysis modality due to the potential confounding effect of the modality on outcomes. In the meantime, the timing of dialysis initiation in individuals with advanced CKD will continue to focus on the burden of uremic symptoms, treatment availability, physician preferences, and patient choices[25].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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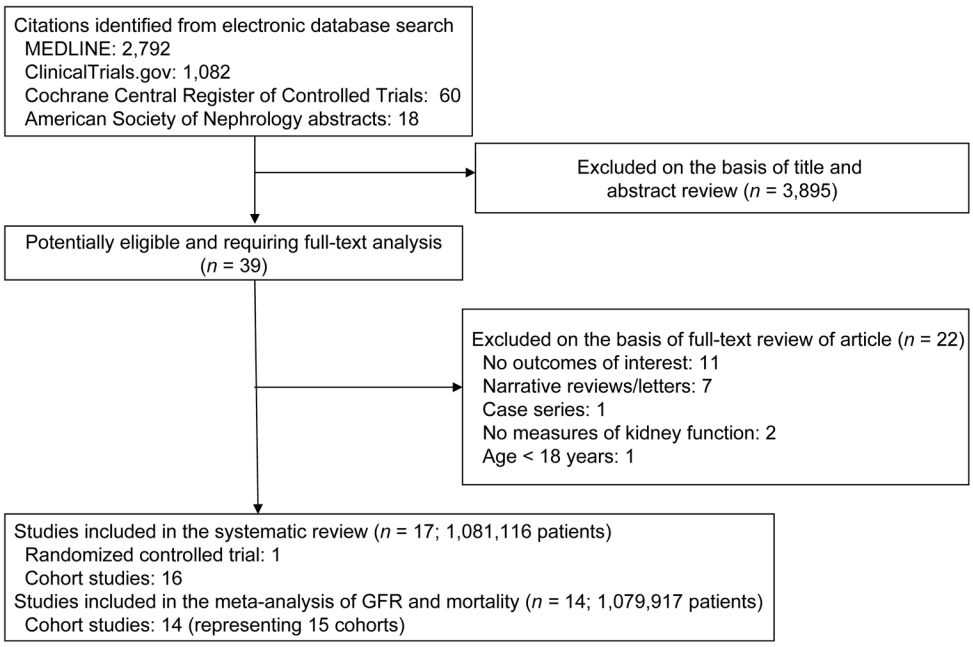

Figure 1.
Study selection flow diagram.

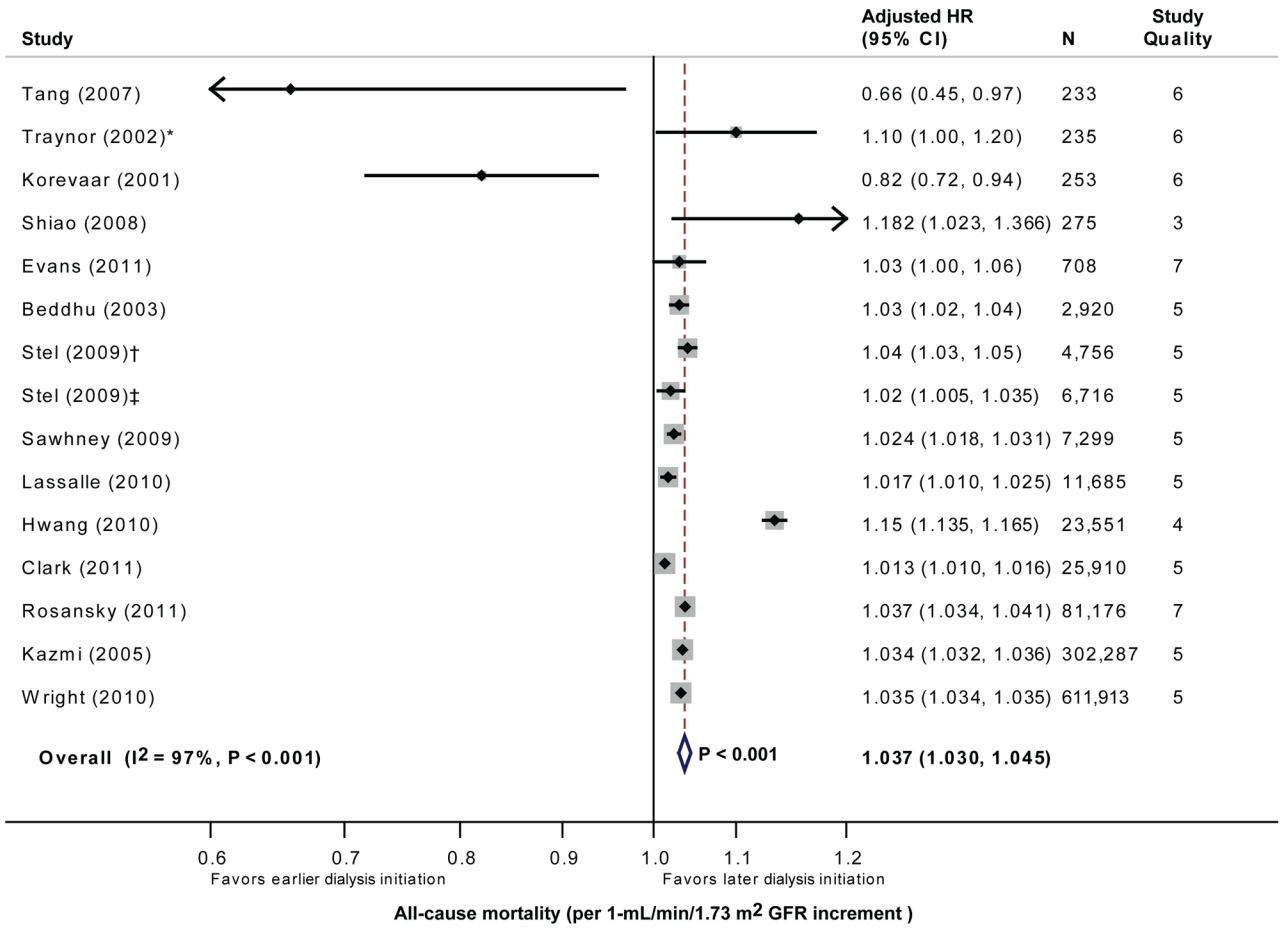

Figure 2.

Forest plot of the glomerular filtration rate (GFR) (per 1 mL/min/1.73 m^2 increment) adjusted hazard ratio (with 95% confidence interval) for all-cause mortality. * The GFR is reported in mL/min and is not normalized to body surface area. The study by Stel et al included 2 cohorts with 2 accrual periods († cohort initiating dialysis in 1999; ‡ cohort initiating dialysis in 2003). The test for heterogeneity is significant (I^2=97% and P<0.001 by Q test).

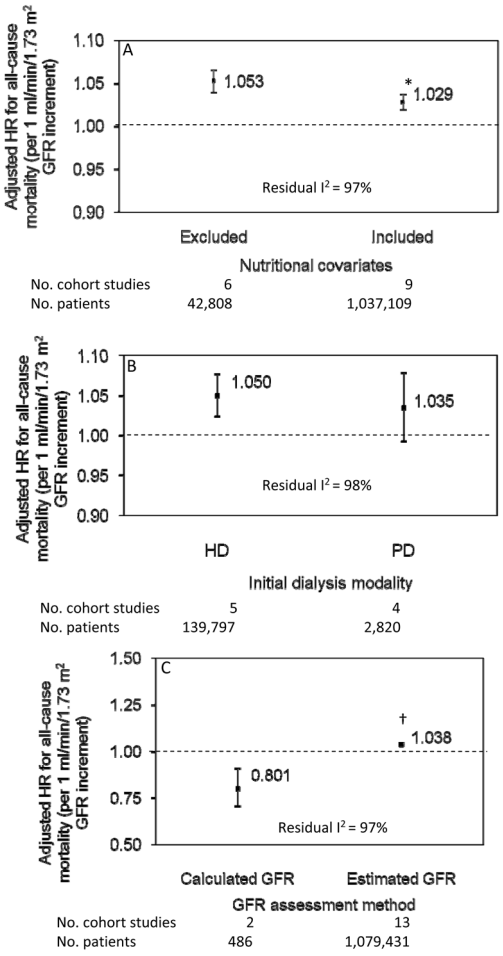

Figure 3.

Subgroup analyses displaying the glomerular filtration rate (GFR) (per 1 mL/min/1.73 m^2 increment) adjusted hazard ratio (with 95% confidence interval) for all-cause mortality stratified by (3A) use of nutritional covariates in the multivariable models; (3B) initial dialysis modality; and (3C) GFR assessment method. * P=0.008 *vs.* cohorts that excluded nutritional covariates; † P<0.001 *vs.* cohorts that calculated GFR. The test for heterogeneity is significant (residual I^2=97%, 98% and 97%, respectively).

Table 1

Characteristics of the studies included in the meta-analysis

Author	Country	Year	Study Design	Data Source	Accrual Period	No. of Patients	Initial Dialysis Modality	Max F/U Length	Mean Age (y)	Mean eGFR	Men (%)	DM (%)	Study Quality
Korevaar	NL	2001	PCS	NECOSAD	1997–1999	253	HD, PD	3 y	57	6.3	62	NR	6
Traynor	GB[a]	2002	RCS	Glasgow Royal Infirmary's Electronic Records	1987–2000	235	HD, PD	10 y	55[*]	8.3	67	22	6
Beddhu	US	2003	RCS	DMMS II	1996–1997	2920	HD, PD	2 y	59	8.2	53	42	5
Kazmi	US	2005	RCS	CMS Program	1996–1999	302,287	HD, PD	5 y	62	8.4	53	48	5
Wilson	CA	2007	RCS	Single Center	2001–2005	271	HD	2 y	66	NR	61	51	5
Tang	HK	2007	PCS	Single Center	2002–2004	233	PD	2 y	58	9.1	51	42	6
Shiao	TW	2008	RCS	Single Center	1997–2005	275	PD	6 y	51	4.8	45	19	3
Sawhney	GB[a] + CA	2009	RCS	Scottish Renal Registry + BC Provincial Renal Agency	2000–2005	7,299	HD, PD	5 y	51	8.3	58	NR	5
Coronel	ES	2009	RCS	Single Center	1982–2004	100	PD	5 y	53	8.3	65	100	3
Stel	NL	2009	RCS	ERA-EDTA Registry	1999, 2003	11,472	HD, PD	2 y	64	7.9; 8.6	61	8.4[†]	5
Lassalle	FR	2010	RCS	French REIN Registry	2002–2009	11,685	HD, PD	4 y	67	8.8	62	36	5
Hwang	TW	2010	RCS	The Bureau of National Health Insurance (TW)	2001–2004	23,551	HD	1 y	62	4.7	48	50	4
Cooper	AU	2010	RCT	Multi-Center (AU & NZ)	2000–2008	828	HD, PD	7 y	60	8.1	66	43	3[**]
Wright	US	2010	RCS	US Renal Data System	1995, 2000–2006	611,913	HD, PD	5 y	65	9.8	54	57	5
Rosansky	US	2011	RCS	CMS Program	1996–2006	81,176	HD	11 y	46	7.1	58	0	7
Clark	CA	2011	RCS	Canadian Organ Replacement Registry	2001–2007	25,910	HD	7 y	65	9.8	60	46	5
Evans	SE	2011	PCS	Multi-Center	1996–1998	708	HD, PD	7 y	57	7.6	66	NR	7

[*] Median age

[**] Jadad score

[†] reported in the 2003 cohort

PCS, prospective cohort study; RCS, retrospective cohort study; RCT, randomized controlled trial; DMMS II, Dialysis Morbidity Mortality Study Wave II; BC, British Columbia (Canada); HD, hemodialysis; PD, peritoneal dialysis; ERA-EDTA, European Renal Association–European Dialysis and Transplant Association; NL, The Netherlands; GB, Great Britain; US, United States; CA, Canada; HK, Hong Kong; TW, Taiwan; ES, Spain; FR, France; AU, Australia; SE, Sweden; NECOSAD, Netherland Cooperative Study on the Adequacy of Dialysis; NZ, New Zealand; CMS, Centers for Medicare and Medicaid Services; DM, diabetes mellitus; max, maximum; f/u, follow up; eGFR, estimated glomerular filtration rate

[a] Scotland

Table 2

Adjusted hazard ratios of estimated GFR for all-cause mortality in the studies included in the meta-analysis.

Author	eGFR* category	Mean eGFR	All-cause mortality**	Adjustment variables				
				Demographic & socioeconomic factors	Cause of kidney failure	Comorbid conditions	Nutritional factors	Anemia parameters, treatment factors, & misc
Korevaar	Timely starters [a]	7.1	0.60 (0.35–1.05)	Age, sex	DM, GN, RVD, other	Wright/Khan co-morbidity index score	-	-
	Late starters[a]	4.9	1.00 (reference)					
	Per 1-unit ↑	-	0.82 (0.72–0.94)					
Traynor	≥ 8.3	10.4[b]	0.95[c]	Age, sex	-	Wright/Khan co-morbidity index score	Albumin, weight	Hb, WBC, vascular access, dialysis modality, MAP
	< 8.3	6.7[b]	1.00 (reference)					
	≥ 8 (non-DM)	9.8[b]	0.62[c]					
	< 8 (non-DM)	6.3[b]	1.00 (reference)					
	Per 1-mL/min ↑	-	1.10 (1.00–1.20)					
Beddhu	> 7.5	10.9	NR	Age, sex, race, insurance status, smoking	-	CAD, CHF, LVH, CBVD, PVD, DM, malignancy, chronic lung disease, AIDS, functional impairment	Albumin, bicarbonate, BMI, clinical diagnosis of malnutrition	Hct, dialysis modality
	≤ 7.5	5.6	NR					
	Per 1-unit ↑		1.03 (1.02–1.04)					
Kazmi	> 10.0	13.8	1.42 (1.38–1.46)	Age, sex, race/ ethnicity, employment, insurance status	DM, GN, HTN, other	CAD, CHF, HTN, CBVD, PVD, DM, COPD	Albumin, BMI	Hct, dialysis initiation y, network
	7.6–10.0	8.6	1.19 (1.15–1.21)					
	5.0–7.5	6.3	1.09 (1.06–1.12)					
	< 5.0	3.9	1.00 (reference)					
	Per 1-unit ↑	-	1.03 (1.03–1.04)					
Wilson	> 10	NR	1.68 (0.65–4.32)[c]	Age, sex, race, employment status	-	CAD, PVD, antihypertensive use, DM	-	Predialysis nephrology care
	5–10	NR	1.58 (0.54–4.65)[c]					
	< 5	NR	1.00 (reference)					
Tang	Elective starters (≤10)	9.2	0.33 (0.11–0.76)	Age, sex	-	DM	-	First eGFR
	Initial refusers	8.9	1.00 (reference)					
	Per 1-unit ↑	-	0.66 (0.45–0.97)					

Author	eGFR* category	Mean eGFR	All-cause mortality**	Adjustment variables				
				Demographic & socioeconomic factors	Cause of kidney failure	Comorbid conditions	Nutritional factors	Anemia parameters, treatment factors, & misc
Shiao	≥ 5	6.8	NR	Age, sex	-	CAD, DM	Albumin, nPCR	Hb, WBC, total & renal CCr/wk, total & renal Kt/V, Catheter late implantation
	< 5	3.5	NR					
	Per 1-unit ↑	-	1.18 (1.02–1.37)					
Sawhney	≥ 15.0	18.6	1.65 (1.39–1.95)	Age, sex, standardized mortality ratio, registry	DM, GN, RVD, PKD, drug-induced, congenital, other, unknown	-	-	Hb, dialysis initiation y, dialysis modality
	10.0–14.9	11.6	1.37 (1.19–1.59)					
	5.0–9.9	7.2	1.17 (1.02–1.34)					
	< 5.0	4.2	1.00 (reference)					
	Per 1-unit ↑	-	1.02 (1.02–1.03)					
Coronel	> 7.7	10.6	0.96[d]	Age	-	CAD, CHF, HTN, valvulopathy, CBVD, PVD	Albumin	-
	≤ 7.7	5.4	1.00 (reference)					
Stel***	≥ 10.5	14.3[e]	1.45 (1.32–1.62)	Age, sex	DM, GN, RVD, HTN, other	-	-	Dialysis modality, country
	8.0–10.5	9.1[e]	1.14 (1.04–1.25)					
	< 8.0	5.9[e]	1.00 (reference)					
	Per 1-unit ↑	-	1.04 (1.03–1.05)					
	≥ 10.5	14.3[e]	1.38 (1.19–1.61)	Age, sex	DM, GN, RVD, HTN, other	CAD, CBVD, PVD, DM, Malignancy	-	Dialysis modality, country
	8–10.5	9.1[e]	1.17 (1.01–1.36)					
	< 8.0	5.9[e]	1.00 (reference)					
	Per 1-unit ↑	-	1.02 (1.01–1.04)					
	Per 1-unit ↑	-	1.03 (1.03–1.04)	-	-	-	-	-
Lassalle	> 20	NR	NR	Age, sex	-	CAD, CHF, PVD, DM, dysrhythmia, malignancy, disability	Albumin, BMI	Hb, ESA use, planned/ unplanned dialysis initiation, wait listing, transplant status
	16–20	NR	NR					
	11–15	NR	NR					
	6–10	NR	NR					
	≤ 5	NR	NR					
	Per 1-unit ↑	-	1.02 (1.01–1.03)					
Hwang	≥ 6.52	7.7	2.44 (2.11–2.81)	Age, sex	DM, GN, HTN,	CAD, CHF, HTN, CVD, DM,	-	Hct, dialysis initiation year

Author	eGFR* category	Mean eGFR	All-cause mortality**	Adjustment variables				
				Demographic & socioeconomic factors	Cause of kidney failure	Comorbid conditions	Nutritional factors	Anemia parameters, treatment factors, & misc
	5.21–6.51	5.8	1.66 (1.43–1.93)		chronic TIN, other, unknown	malignancy, liver cirrhosis, TB, others		
	4.28–5.20	4.7	1.21(1.04–1.41)					
	3.29–4.27	3.8	1.18 (1.01–1.37)					
	< 3.29	2.6	1.00 (reference)					
	Per 1-unit ↑	-	1.15 (1.14–1.17)					
Cooper	10–14	9	1.04 (0.83–1.30)		NA			
	5–7	7.2	1.00 (reference)					
Wright	> 15.0	19.0 *f*	1.48 (1.47–1.50)	Age, sex, race, height	DM, GN, HTN, PKD, urological causes, other, unknown	CMI score, DM	Weight	Predialysis care duration, dialysis type, vascular access
	10.0–15.0	12.1 *f*	1.16 (1.15–1.17)					
	5.0–10	7.5 *f*	1.00 (reference)					
	≤ 5.0	3.9 *f*	0.87 (0.86,0.88)					
	Per 1-unit ↑	-	1.04 (1.03–1.03)					
Rosansky	≥ 15.0	18.9 *f*	1.74 (1.64–1.85)	Age, sex, race, ethnicity	GN, HTN, PKD, urological causes, other, unknown	-	Albumin, BMI	Hb, dialysis initiation year
	10–14.9	11.8 *f*	1.47 (1.41–1.54)					
	5–9.9	7.1 *f*	1.23 (1.19–1.27)					
	< 5.0	3.7 *f*	1.00 (reference)					
	Per 1-unit ↑	-	1.04 (1.03–1.04)					
Clark	>10.5		1.18 (1.13–1.23)	Age, sex, ethnicity	DM, GN, RVD, other, unknown	Modified CMI score, CAD, CHF, HTN, CVD, PVD, DM, lung disease, malignancy	Albumin	Vascular access, transplants status, late referral
	≤ 10.5	7.1	1.00 (reference)					
	Per 1-unit ↑	-	1.01 (1.01–1.02)					
Evans	≥ 7.5–20	10.8	1.19 (0.91–1.56)	Age, sex, smoking, alcohol use, education	DM, GN, HTN, other, unknown	CMI score	BMI	Clinical status, first eGFR, decline in eGFR,
	< 7.5	5.5	1.00 (reference)					
	Per 1-unit ↑	-	1.03 (1.00–1.06)					

*a*Timely starters defined as eGFR >10.5 mL/min/1.73 m^2 (equivalent to standardized Kt/V_{urea} = 2.0) or eGFR ≤ 10.5 mL/min/1.73 m^2 and in equivalent of total nitrogen appearance normalized to body weight (nPNA) > 0.8g/kg/d, and BMI >20 kg/m^2;

*b*Median eGFR at the start of dialysis;

[c] Adjusted odds ratio;

[d] Unadjusted odd ratio;

[e] Mean eGFR of each category in the combined cohort;

[f] Data received directly from corresponding author.

[*] units are mL/min/1.73 m^2 unless otherwise indicated

[**] Adjusted hazard ratio (95% confidence interval)

[***] analysis adjusted for general characteristics is based on 1999 data; the unadjusted analysis and the analysis adjusted for general characteristics and comorbidity are both based on 2003 data.

AIDS, acquired immune deficiency syndrome; eGFR, estimated glomerular filtration rate; ESA, erythropoietin-stimulating agent; BMI, body mass index; WBC, white blood cell; CCr/wk, weekly creatinine clearance; nPCR, normalized protein catabolic rate; CAD, coronary artery disease; CHF, congestive heart failure; LVH, left ventricular hypertrophy; HTN, hypertension; CBVD, cerebrovascular disease; PVD, peripheral vascular disease; DM, diabetes mellitus; GN, glomerulonephritis; RVD, renal vascular disease; PKD: polycystic kidney disease; TIN, tubulointerstitial nephritis; TB, tuberculosis; Hct, hematocrit; Hb, hemoglobin, MAP, mean arterial pressure; CMI, Charlson comorbidity index; misc, miscellaneous; NR, not reported; y, year.