Nephrol Dial Transplant (2022) 37: 1529–1544
https://doi.org/10.1093/ndt/gfac010
Advance Access publication date 23 February 2022

ORIGINAL ARTICLE

Survival of patients who opt for dialysis versus conservative care: a systematic review and meta-analysis

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Protocol registration: PROSPERO CRD42018103379.
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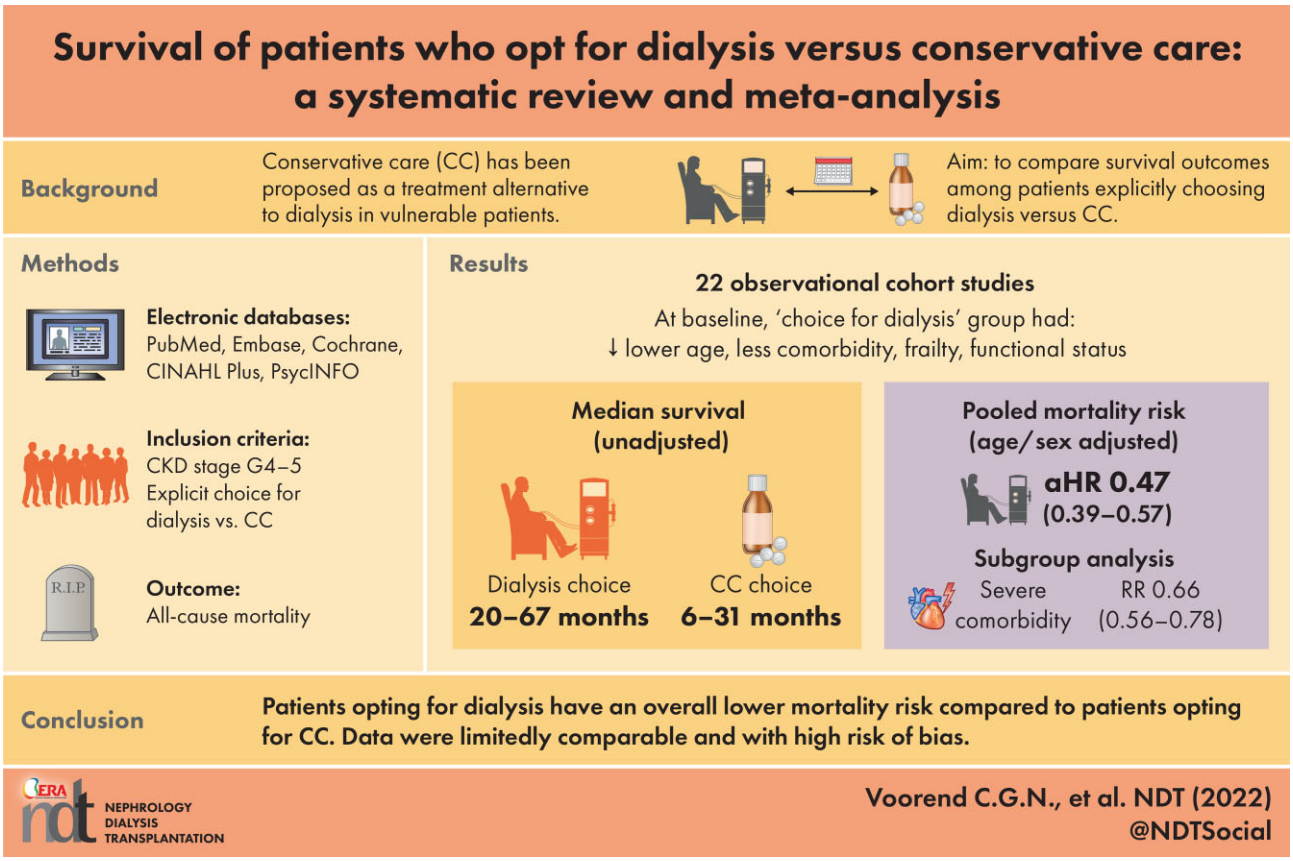
GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What is already known about this subject?

- Previous systematic reviews reported a survival advantage in patients treated with dialysis compared with conservative care (CC) and suggested that this survival benefit is substantially reduced for patients with older age or severe comorbidity.
- However, these reviews did not limit their inclusion to studies in which patients made an explicit treatment choice, e.g. the CC group included patients in whom dialysis treatment was withheld for medical reasons. This may have underestimated the survival of CC.
- An update of current data on survival outcomes is needed to evaluate and inform patients and healthcare providers whether CC is a viable alternative to dialysis in terms of survival outcomes.

What this study adds?

- With the use of a comprehensive search strategy, 22 observational cohort studies were identified in which survival outcomes were assessed in patients who explicitly opted for either dialysis or CC.
- This study confirms significant confounding and high susceptibility to bias in studies assessing survival outcomes for dialysis treatment versus CC.
- Our meta-analysis demonstrates that, on average, patients who choose dialysis have half the risk of mortality as patients who opt for CC. This decreased risk persists in patients with severe comorbidity and older age, albeit more limited.

What impact this may have on practice or policy?

- Although no individual patient predictions can be made based on these results, improved insights into survival differences between dialysis and CC can be used in shared decision making: a process in which other factors like quality of life, treatment burden and patients' goals of care are also taken into account.
- Future prospective studies on survival differences between CC and dialysis should assess survival from the moment the treatment choice is made (limiting selection bias) and adjust for more baseline discrepancies, such as frailty and other geriatric impairments (limiting confounding by indication).

ABSTRACT

Background. Non-dialytic conservative care (CC) has been proposed as a treatment option for patients with kidney failure. This systematic review and meta-analysis aims at comparing survival outcomes between dialysis and CC in studies where patients made an explicit treatment choice.

Methods. Five databases were systematically searched from origin through 25 February 2021 for studies comparing survival outcomes among patients choosing dialysis versus CC. Adjusted and unadjusted survival rates were extracted and meta-analysis performed where applicable. Risk of bias analysis was performed according to the Cochrane Risk Of Bias In Non-randomized Studies of Interventions.

Results. A total of 22 cohort studies were included covering 21 344 patients. Most studies were prone to selection bias and confounding. Patients opting for dialysis were generally younger and had fewer comorbid conditions, fewer functional impairments and less frailty than patients who chose CC. The unadjusted median survival from treatment decision or an estimated glomerular filtration rate <15 mL/min/1.73 m^2 ranged from 20 and 67 months for dialysis and 6 and 31 months for CC. Meta-analysis of 12 studies that provided adjusted hazard ratios (HRs) for mortality showed a pooled adjusted HR of 0.47 (95% confidence interval 0.39–0.57) for patients choosing dialysis compared with CC. In subgroups of patients with older age or severe comorbidities, the reduction of mortality risk remained statistically significant, although analyses were unadjusted.

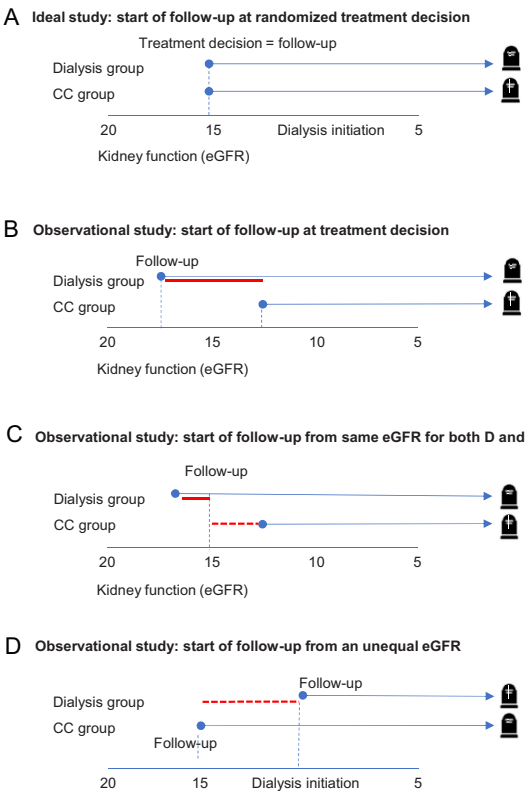
Conclusions. Patients opting for dialysis have an overall lower mortality risk compared with patients opting for CC. However, a high risk of bias and heterogeneous reporting preclude definitive conclusions and results cannot be translated to an individual level.

Keywords: conservative care, dialysis, end-stage kidney disease, mortality, systematic review

INTRODUCTION

Dialysis is the most frequently chosen treatment for patients with kidney failure. Current guidelines recommend presenting comprehensive conservative care (CC) as a treatment alternative to vulnerable patients [1, 2]. CC captures a range of pharmacological, clinical and lifestyle interventions, except dialysis, to delay the progression of kidney disease, minimize risks and complications and provide active symptom management and psychosocial support [1]. Although CC is generally more focused on maintaining health-related quality of life (HRQoL) than potentially increasing survival, reliable estimation of the survival outcomes of both CC and dialysis might help to inform patients and healthcare professionals in shared decision making.

Previous attempts have been made to systematically compare survival data for kidney failure patients choosing between dialysis and CC [3–6]. Most recent reviews suggest a survival benefit for dialysis over CC but highlight the heterogeneity of included studies [5, 6]. Comparability between both groups is hampered due to confounding by indication, which occurs



A: Ideal study: a design where therapy decision is randomized at a similar eGFR (on average). In an ideal observational study follow-up starts from treatment decision, which should be at a similar eGFR for all patients (on average). Please note that in observational studies, even when the start of follow-up is aligned at the treatment decision, other biases, such as indication bias, remain an important limitation.

B. Follow-up from treatment decision. Selection bias occurs in observational studies when the time between, in this example, eGFR 17 and 12 mL/min/1.73m^2 is immortal for CC patients: individuals who died soon after treatment decision will be missing from analyses. If not adequately discounted, the CC group has a survival advantage (i.e. over- or underestimation of the effect).

C: Follow-up from a specific eGFR threshold (e.g. eGFR of 15 mL/min/1.73m^2 for both the dialysis and CC groups). Selection bias of the dialysis group and CC group is reduced but still present. For the dialysis group, follow-up time (from, in this example, eGFR 17 to 15mL/min/1.73m^2 on average), and individuals who died soon after their treatment decision, will be missing from analyses. For the CC group, patients have had to survive up until the moment of start of treatment decision.

D: Follow-up does not start at an equal time point for both groups; at dialysis initiation versus eGFR <15 mL/min/1.73m^2 for CC group**.** Selection bias occurs when patients choosing dialysis, but dying before dialysis is initiated, are not included in the cohort.

FIGURE 1: Visualization of selection bias. In this figure, the course of eGRF also reflects the course of time.

when CC is more often chosen by or offered to patients deemed to have a worse prognosis, e.g. older or more frail patients. Additionally, the start of CC is difficult to define compared with dialysis, potentially resulting in selection bias [7]. Using both the explicit treatment decision and aligning the starting point for survival analysis is therefore critical.

The aim of this systematic review was to compare the survival of patients with kidney failure who made an explicit choice for a dialysis pathway versus CC, e.g. excluding studies where dialysis was withheld on medical grounds, in line with a recently published systematic review on HRQoL [8]. Additionally, we looked at subgroups of patients >80 years of age and those with severe comorbidity and frailty. We aimed at including studies that evaluated outcomes from predefined time points, preferably the moment of treatment decision, as an equivalent time point for treatment start itself is difficult to identify in both treatment pathways [9].

MATERIALS AND METHODS

We conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. The protocol was announced in advance on PROSPERO (CRD42018103379) [9].

Search strategy

Electronic databases PubMed, Embase, Cochrane, CINAHL Plus and PsycINFO were systematically searched from origin through 25 February 2021. Potentially relevant citations were derived with the use of a structured search strategy, tested and reviewed by a clinical librarian, using search terms related to or describing the patient population of interest [i.e. chronic kidney disease with severely reduced glomerular filtration rate (Kidney Disease: Improving Global Outcomes stage G4) or kidney failure (stage G5)], the intervention (any form of maintenance dialysis) and the comparative intervention (CC). The full search strategy is provided in Supplementary data, Table S1. Additional studies were identified by checking reference lists and citations of the included studies via Scopus and consultation with experts.

Study selection

All records were screened by title and abstract by a minimum of two authors independently (W.V., I.W., C.V. and M.O.). Consecutively, full-text articles were screened for eligibility by the same authors using predefined eligibility criteria (Supplementary data, Table S1).

All studies that reported and compared survival outcomes of patients choosing either dialysis or CC were considered for inclusion. Ideally, included studies should use a randomized controlled design and assess survival from the moment the decision for either CC or dialysis is made using an intention-to-treat approach, with an average equal kidney function between both groups, to rule out selection bias (Figure 1A). In such an ideal trial, as opposed to observational studies, confounding factors such as age, comorbidities, frailty, functional status and cognitive status are expected to be equal in both groups due

to randomization. In observational studies, confounding by indication affects this ideal comparison. In our review, at a minimum, both treatment strategies should be presented as reasonable options and an explicit choice for either dialysis or CC had to be made. CC had to be applied as non-dialytic care for kidney failure, intended to be provided until death and not just to delay the start of dialysis [1]. We defined the dialysis pathway as a choice for haemodialysis (HD) and/or peritoneal dialysis (PD), both including patients who would eventually start dialysis or were yet to start. For patient selection within the studies, where reported data allowed us to do so, we excluded patients with short-term dialysis for acute kidney injury or where the decision to withhold dialysis was the nephrologist's decision based on medical grounds only. Articles were excluded if they were non-English language or when the study solely reported on patients approaching kidney failure who had not yet decided on a preferred treatment yet. In the case of disagreements, we strove for consensus with a third reviewer (W.B.). If necessary, authors of original studies were approached for additional information. In the case of overlapping study populations, we aimed at including the study with the longest follow-up and most patients.

Data extraction

Data were extracted on bibliography, study design, risk of bias, (definitions of) exposure(s), outcomes, characteristics of study participants, numerical results and effect estimates by three authors (W.V., I.W. and C.V.) using a predefined and pilot tested data extraction form. Disagreements in screening for inclusion and data extraction were resolved through consensus discussion.

Risk of bias assessment

The risk of bias of the included studies was assessed by two authors (C.V. and M.O.) independently using the Cochrane Risk Of Bias in Non-randomized Studies of Interventions (ROBINS-I) [11, 12]. ROBINS-I addresses seven domains of potential bias. The risk of confounding was assessed for the most relevant confounding factors: age and comorbidities. Selection bias was considered if follow-up time was missing due to the selection of patients, e.g. because not all eligible patients were included or if follow-up time was inequal between both groups, and may lead to selection bias (Figure 1). In addition, ROBINS-I defines the risk of bias in the classification of interventions, deviations from the intended interventions, missing data, measurement of outcomes and selection of the reported results. All domains address internal validity as distinct from issues of generalizability. Discrepancies in the risk of bias assessment were resolved through discussion with a third author (W.B.).

Data synthesis and analysis

The main outcome of interest were the hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality. The median survival (in months) and 1-, 2- and 5-year survivals in both groups were extracted to estimate absolute survival. If necessary, outcomes were reconstructed from graphs (Kaplan–Meier) using WebPlotDigitizer version 4.2 [13]. Three predefined subgroup analyses were conducted. First, we aggregated the results from studies using four starting points for survival analyses: estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m^2, treatment decision, eGFR <15 mL/min/1.73 m^2 and eGFR <10 mL/min/1.73 m^2 or the putative start of dialysis (as dialysis is, on average, commonly initiated around eGFR 10 mL/min/1.73 m^2). Second, unadjusted survival outcomes were assessed, when possible, according to different age groups ($\geq$70, $\geq$75, $\geq$80 and $\geq$85 years). Third, if available, separate analyses were intended for patients with severe comorbidity, by using the study's own definition of severe comorbidity, and for frail patients. Patients were analysed as a combined 'choice for dialysis' group, assuming the best-fitted modality was chosen.

Statistical analysis

We conducted random-effects meta-analysis using DerSimonian and Laird's method [14] to estimate the pooled adjusted HR. If HRs were presented for (choice of) HD and PD modalities only, these ratios from a single study were pooled using a weighted fixed-effects model. Publication bias was considered low by means of a funnel plot (Supplementary data, Figure S1). The I^2 statistic was used to describe the percentage of variation between the studies due to heterogeneity (values of $<25\%$, 25–50% and $>50\%$ indicating low, moderate and high heterogeneity, respectively) [15]. To estimate the effect of adjustment for confounding, we compared the adjusted HR with unadjusted risk ratios (RRs) for 1- and 2-year mortality, which were calculated using the random-effects Mantel–Haenszel method [16, 17]. The meta-analysis of unadjusted 1- and 2-year survival data was performed for subgroups of patients >80 years of age and with severe comorbidity.

RESULTS

Search results

The search resulted in 7634 records, of which 353 full-text articles were assessed for eligibility (Figure 2). Authors of five studies were contacted for clarification of the CC definition, of whom four responded. Based on their answers, patient groups did not match our definition of explicit choice for CC, and all five articles were excluded (Supplementary data, Table S2). One study was excluded that stopped follow-up at dialysis start [18] and two because of overlapping study populations [19, 20]. Two other studies partly overlapped and the smaller study [21] was excluded from the main (meta-)analyses. Our analyses were performed on 22 cohort studies and no randomized controlled trials were found.

Study characteristics

Table 1 presents the characteristics of the 22 included studies [21–42]. The sample size varied from 87 [42] to 14 071 [40] patients, resulting in a total of 21 344 patients. The proportion of patients opting for CC varied between 6% and

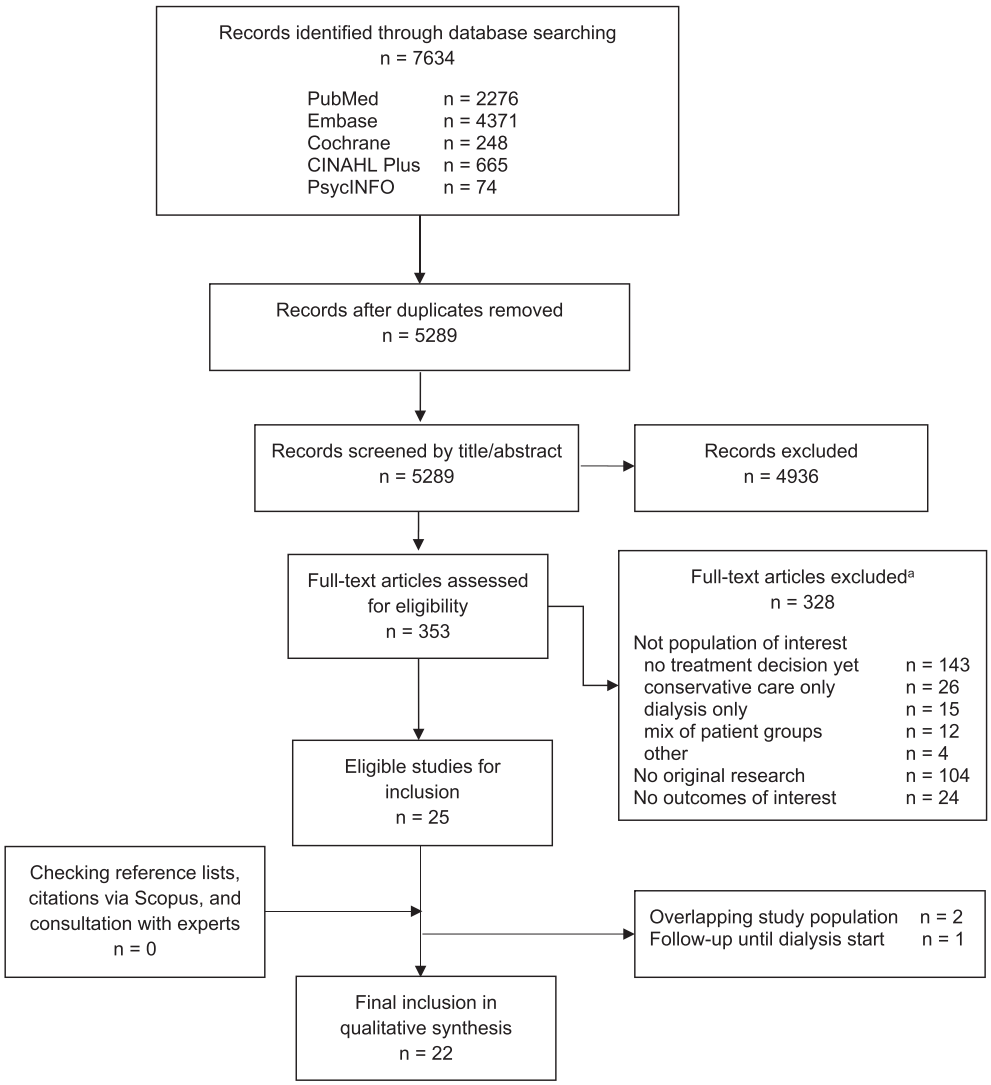


FIGURE 2: Study inclusion and exclusion flowchart. [a]Explanation of reasons for exclusion: no treatment decision yet includes patients with advanced CKD who did not, or did not have to, decide on preferred treatment yet (commonly referred to as 'pre-dialysis patients' or 'non-dialysis dependent CKD patients'), including five studies discussed with the authors to clarify their patient groups (Supplementary data, Table S2). Mix of patient groups means a mix of different patient categories into one patient group without subgroup analyses (e.g. mix of patients who have not made a decision yet and patients who chose conservative care). No original research, e.g. reviews, opinion papers or study protocols.

77% (median 31%) [35, 40]. The majority of the studies were restricted in age, ranging from ≥65 to ≥80 years old [18, 21, 23, 26, 27, 30, 31, 33–37, 39, 41, 42]. The mean age in the studies ranged from 61 to 86 years (median 78).

Choice for dialysis included mostly combined HD and PD treatment [21–23, 26, 30, 31, 35, 38, 39], occasionally together with a choice for pre-emptive transplantation (encompassing <5% of the study population) [25, 29, 32, 41]. Four studies did not specify dialysis modalities [28, 33, 36, 40]. CC comprised ongoing care of a multidisciplinary team, symptom control, medication management and some form of palliative care or advanced care planning. Eight studies did not specify the CC strategy [25–27, 30, 31, 38, 40, 41].

The reference point for survival analysis in most studies was the time when eGFR decreased to <15 mL/min/1.73 m^2 (n = 10) [21, 24, 29, 32, 35–38, 40, 42], followed by eGFR <10 mL/min/1.73 m^2 or putative dialysis start (n = 6) [23, 25, 27, 28, 31, 34], eGFR <20 mL/min/1.73 m^2 (n = 1) [30] and treatment decision (n = 1) [41]. Four studies assessed multiple starting points for their survival analyses [22, 26, 33, 39].

Risk of bias assessment

The risk of confounding was serious in the majority of the studies (Figure 3 and Supplementary data, Table S3). In 11 studies, results were not adjusted for age and comorbidity status [23, 25, 27–30, 33–35, 38, 40]. Seven studies were of serious or critical risk of selection bias [25–27, 31, 34, 40, 42], as the start of follow-up probably did not coincide for the included patients, leading to a risk of lead time or immortal time bias. The risk of bias due to unclear classification of interventions was considered serious in two studies where the intervention was not well-defined [25, 42]. The risk of bias

Table 1. Characteristics of studies included in the systematic review

Study	Design[a]	Cohort era	*N*	Inclusion criteria	Dialysis patient group	Reported CC strategy	Starting point survival analysis	Follow-up
Brown *et al.* [22], Australia	Prospective	2009–13	395	CKD stage G4/G5 No age criterion	Choice D, 34% started during follow-up (HD 60%, PD 40%)	Usual nephrology care and renal supportive care clinic	From first attendance to clinic after decision; and from eGFR <15 mL/min/1.73 m^2	Until death or study end, median 10 months (IQR 4–21) months
Carson *et al.* [23], UK	Prospective	1997–2003	202	Dialysis start or eGFR <10.8 mL/min/1.73 m^2 (CC) ≥70 years	On D (HD 69%, PD 31%)	Active medical treatment, multidisciplinary care, dietary input and end-of-life care	(Putative) dialysis start: eGFR = 10.8 mL/min/1.73 m^2	Until death, study end, transplantation, referral to other centre or loss to follow-up, maximum 107
Chandna *et al.* [32], UK	Retrospective	1990–2008	844	eGFR <15 or >10 mL/min/1.73 m^2 No age criterion	Mix of choice D and on D, 97% started (HD, PD, KTx)[b]	Active medical treatment and multidisciplinary care	From first eGFR <15 mL/min/1.73 m^2	Over period of 18 years. Until death or study end
Chandna *et al.* [21], UK	Retrospective	1995–2010	250	eGFR <15 mL/min/1.73 m^2 >75 years	Mix of choice D and on D, 91% started (HD, PD)[b]	Active medical treatment and multidisciplinary care	From first eGFR <15 mL/min/1.73 m^2	Until death, transfer to other centre or study end. Minimum 3 years, maximum 8 years over period of 18 years
Da Silva-Gane *et al.* [24], UK	Prospective	2005–7	154	Late stage G4/G5 No age criterion	Choice on HD (65%; 59% started) or PD (35%; 52% started)	Active medical treatment and multidisciplinary care	From date of recruitment (duration to decision up to 15 months)	Until death, study end or transplantation. Minimum 30 months, median 31.9 months (IQR 25.1)
García-Testal *et al.* [42], Spain	Retrospective	2014–17	87	CKD stage G5, ≥80 years	On HD	Medical and nursing consultation, including symptom control, active medical treatment and dietary advise	Date that eGFR <15 mL/min/1.73 m^2 (diagnosed ESKD)	Minimum 3.5 months, maximum 51.5 months
Hussain *et al.* [33], UK	Retrospective	2006–10	441	eGFR <20 mL/min/1.73 m^2 >70 years	Choice on D, 44.6% started[b]	Supportive care by a palliative medicine consultant	eGFR<20, <15 or <12 mL/min/1.73 m^2	Until death or study end (May 2011)
Joly *et al.* [34], France	Retrospective[c]	1989–2000	144	eGFR <10 mL/min/1.73 m^2 >80 years	On HD	Continued palliative care strategy: i.e. management of fluid overload, relief of uremic symptoms and pain, nonpharmacologic supportive measures	Start dialysis (first session), or date of written decision for CC	Until death or study end (April 2001)
Kwok *et al.* [35], Hong Kong	Retrospective	2005–13	558	eGFR <15 mL/min/1.73 m^2 ≥65 years	Choice on D, 98.4% started (HD 23%, PD 77%)	Multidisciplinary care in palliative care clinic, and symptom control	Date of advanced care planning interview (median duration until decision was 10 days)	Until death, loss to follow-up or study end (minimum 1 year, maximum 10 years)
Moranne *et al.* [30], France	Prospective (*n* = 24)	2009–10	269	eGFR <20 mL/min/1.73 m^2 for at least 3 months >75 years	Choice HD or PD (mostly HD), 50% started	NR	Date of inclusion in cohort (approximates date of treatment decision)	5-year follow-up (median 34.5 ±21 months)
Morton *et al.* [25], Australia	Prospective (*n* = 66)	2009	721[d]	eGFR <15 mL/min/1.73 m^2 No age criterion	On HD (77%), PD (23%), 96% started or KTx (4%)	Differed per renal unit, not further specified	Start dialysis, or decision for CC	3 years, until study end (2012)

Table 1. Continued

Study	Design[a]	Cohort era	*N*	Inclusion criteria	Dialysis patient group	Reported CC strategy	Starting point survival analysis	Follow-up
Murtagh *et al.* [36], UK	Retrospective, ($n = 4$)	2003–4	129	CKD stage G5 >75 years	Choice on D, 53.8% started[b]	Active multidisciplinary care, including educational, dietary, social and psychological support	First eGFR <15 mL/min/1.73 m^2	Until death or study end (2005)
Pyart *et al.*, [41], UK	Retrospective	2004–16	1216	eGFR <20 mL/min/1.73 m^2 ≥70 years	Choice HD (79%), PD (21%), home HD (2%), pre-emptive transplant (1%), 50.5% started	Maximal conservative management (not specified)	Final choice	5 years
Raman *et al.* [26], UK	Prospective[e]	NR	204	eGFR <15 mL/min/1.73 m^2 ≥75 years	Choice D, 42.3% started (HD, PD)[b]	NR	eGFR <15 or <10 mL/min/1.73 m^2	Until death or study end (2015), mean 35.1 ± 22.1 months
Seow *et al.* [27], Singapore	Prospective	2007–9	101	eGFR 8–12 mL/min/1.73 m^2 ≥75 years or age-adjusted CCI ≥8	Choice D, 100% started[b]	NR	Random moment (time of inclusion) at renal ward or outpatient clinic	24 months
Shum *et al.* [37], Hong Kong	Retrospective	2003–10	199	eGFR <15 mL/min/1.73 m^2 ≥65 years	Choice on PD, 71.8% started	Optimization of medical management and symptom control	First eGFR <15 mL/min/1.73 m^2	Until death or minimum 1.5 years until study end (2011), median 2.0 years (IQR 0.9–3.6)
Smith *et al.* [28], UK	Prospective	1996–2000	321[d]	Approaching ESKD No age criterion	Choice/recommendation on D, 72% started[b]	Active medical treatment and multidisciplinary care	(Putative) start of dialysis: eGFR = 10 mL/min/1.73 m^2	Until death or study end (2000)
Teo *et al.* [38], Singapore	Retrospective	2005	159	Diagnosed ESKD[f] No age criterion	Choice HD (71%), PD (29%); all started	NR	Date of diagnosis with ESRD	1 year (after ESKD diagnosis)
Teruel *et al.* [29], Spain	Prospective (registry) and retrospective	2013–14	232	eGFR <15 mL/min/1.73 m^2 No age criterion	Choice HD (57%), PD (39%), KTx (4%); 44.4% started	Chronic renal disease division (similar care protocol as dialysis group) or palliative care unit	Date of inclusion in the registry (i.e. first visit to the nephrology service)	Maximum 1 year. Mean 4.9 ± 3.2 months for CC, 7.2 ± 3.7 for D
Van Loon *et al.* [31], Netherlands	Prospective ($n = 17$)	2014–17	281	Starting dialysis or eGFR <15 mL/min/1.73 m^2 (CC) ≥65 years	On HD (77%), PD (23%)	Maximal conservative management (not specified)	Start of dialysis, or decision for CC	12 months
Verberne *et al.* [39], Netherlands	Retrospective	2004–16	366	CKD stage G4/G5 ≥70 years	Choice HD (79%), PD (21%), 60.8% started	Active medical treatment and multidisciplinary care	Date of decision, date of first eGFR <20, <15 or <10 mL/min/1.73 m^2	Until death, KTx (censored), loss to follow-up or study end (2016)
Wong *et al.* [40], USA	Retrospective, (registry)	2000–9	14 071	eGFR <15 mL/min/1.73 m^2 (second measure drawn after minimum 90 days) Adults	On D (group 1) Choice on D (group 2)	NR	eGFR<15 mL/min/1.73 m^2 (sustained; second measurement after 90 days)	Until death or study end (2011)

Choice on D, patients who had chosen but not yet started dialysis; D, dialysis (including all dialysis modalities); NA, not applicable; NR, not reported; KTx, pre-emptive kidney transplantation [25, 32] or preferred predialysis living donor renal transplantation [29].

[a]Study setting is a single centre or indicated if otherwise. All were observational cohort studies.

[b]The number of patients for the specific treatment modalities was unknown.

[c]Retrospective analysis of a mostly prospectively followed cohort.

[d]Fewer patients were included in the survival analysis; $n = 663$ [25] and $n = 222$ [28], respectively.

[e]Retrospective selection of patients, but data prospectively collected.

[f]Serum creatinine concentration ≥880 µmol/L.

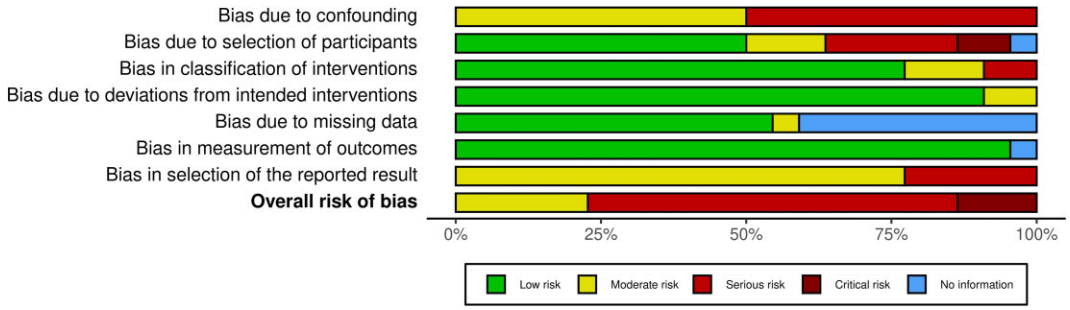


FIGURE 3: The risk of bias as assessed with the ROBINS-I for all 22 included studies.

on missing data often could not be assessed, because nine studies lacked a statement on the number of patients lost to follow-up or missing data [21, 22, 25–27, 29, 32, 38, 39, 41]. The risk of selective reporting of results was at least moderate since none of the studies prespecified survival outcomes in a published protocol. Bias in other domains (deviations of intended interventions, missing data and measurements of outcomes) was in general low or unclear, but moderate in some instances.

Characteristics of study subjects

Patients opting for CC were generally older than patients who chose dialysis treatment in all studies [Table 2; median 7.0 years (range 1.0–21.6)]. Both groups consisted of more men than women. Half of the studies reported more comorbidities in the CC group than in the dialysis group [21, 22, 24, 27–29, 32, 33, 35, 40]. In the other studies, no clear difference in overall comorbidity score was found [23, 31, 34, 36, 37, 39, 41, 42] or was not presented [25, 26, 30, 38]. CC patients had a lower functional and cognitive status, as reported in seven (of nine) and five (of seven) studies, respectively (Supplementary data, Table S4). Correspondingly, frailty was more common in patients choosing CC, although assessed in only two studies [31, 41].

Adjusted mortality outcomes

A total of 12 studies reported adjusted HRs for mortality and were included in this analysis (Figure 4A and Table 3). The study of Moranne *et al.* [30] was excluded, as dialysis start was used as a censoring event in their adjusted survival analysis. All outcomes were adjusted for age. Two studies did not adjust for comorbidity [25, 38]. Meta-analysis showed a pooled adjusted HR for mortality of 0.47 (95% CI 0.39–0.57) comparing choice for dialysis with CC, with high heterogeneity between studies (Figure 4A; $I^2 = 55\%$). For an impression of the effect of adjustment for confounding by the variables age and comorbidity, the unadjusted effect for the same studies was RR 0.38 (95% CI 0.27–0.52) for 1-year survival (Figure 4B) and RR 0.41 (95% CI 0.32–0.53) for 2-year survival.

Outcomes on median, 1-, 2- and 5-year survival

Absolute median survival was longer in all studies for choice of dialysis compared with CC, ~22 months (2.3 times) longer (Figure 5). Survival was shorter with lower kidney function (i.e. eGFR <10 mL/min/1.73 m^2) compared with higher kidney function (i.e. from treatment decision, eGFR <20 mL/min/1.73 m^2 or eGFR <15 mL/min/1.73 m^2), especially for CC patients. Unadjusted 1-, 2- and 5-year survival ranged widely between studies (Table 4, Supplementary data, Table S5), but was consistently higher in the population choosing dialysis compared with those opting for CC.

Survival for patients of older age

Studies appraising survival at age >80 years were limited in number, had small sample sizes and mostly had outcomes unadjusted for confounding variables. Despite this heterogeneity, the lower mortality risk for dialysis seems to decrease with older age (Supplementary data, Figure S2). For patients >80 years of age, most studies reported a lower mortality risk for patients opting for dialysis, albeit statistically non-significant [26, 31, 33, 35, 39]. In two studies this difference was statistically significant [34, 42]. Pooled unadjusted survival analysis indicated a lower mortality risk for dialysis in the five studies available [33–35, 39, 42] (Supplementary data, Figure S3A and B).

Survival for patients with severe comorbidities or frailty

Eight studies presented a subanalysis for patients with high comorbidity scores, using different definitions of high or severe comorbidity (Supplementary data, Table S6). Although all studies concluded that with severe comorbidity the lower mortality risk for patients choosing dialysis is substantially reduced or lost, pooled unadjusted RRs from seven studies suggested that the lower mortality risk for these patients from an eGFR <15 mL/min/1.72 m^2 was still present, i.e. for 1-year [unadjusted RR 0.55 (95% CI 0.42–0.73)] and 2-year [unadjusted RR 0.66 (95% CI 0.56–0.78)] mortality (Figure 6).

The mortality risk of severe comorbid patients adjusted or restricted for age was only rarely reported, sample sizes were small and findings were contradictory (Supplementary data, Table S6). Two studies observed a lower mortality risk for patients choosing dialysis [22, 41], while one study found no decreased risk [21]. Heterogeneity across and within studies is potentially high, as none of the studies provided separate baseline tables for these subgroup analyses. Survival data specifically in frail patients were presented in one study only. Survival did not statistically differ between frail patients

Table 2. Characteristic of the dialysis and conservative kidney management patients in the included studies

Study	Number of patients		Mean age (years)		Female (%)		Mean eGFR at baseline		Severe comorbidity		Median follow-up time, months (IQR)	
	D	CC	D	CC	D	CC	D	CC	D	CC	D	CC
Brown *et al.* [22]	273	122	67	82	33	45	16	16	18% ≥3 comorbidities [a]	38% ≥3 comorbidities [a]	16 (7–26)	10 (4–21)
Carson *et al.* [23]	173	37	76	82	31	41	11[b]	NR	Mean CCI 4.0 (SD 1.6)	Mean CCI 3.7 (SD 1.8)		
Chandna *et al.*, 2011 [32]	689	155	59	76	33	41	13	13	17% high comorbidity [c]	50% high comorbidity [c]	NR	NR
Chandna *et al.*, 2016 [21]	92	158	79	82	21	40	13	13	29% high comorbidity [c]	44% high comorbidity [c]	NR	NR
Da Silva-Gane *et al.* [24]	HD: 80 PD: 44	30	61 48	78	24 50	30	13 14	14	35% high comorbidity [d] 14% high comorbidity [d]	74% high comorbidity[d]	NR	NR
García-Testal *et al.* [42]	33	54	83	87	70	33	NR	NR	Mean CCI 9.6 (1.9)	Mean CCI 9.4 (1.9)		
Hussain *et al.* [33]	269	172	77	82	40	49	NR	NR	Mean CCI 7.7 Mean Davies score 1.9	Mean CCI 8.3 Mean Davies score 2	NR	NR
Joly *et al.* [34]	101	43	83	84	45	62	NR	NR	21% ≥3 comorbidities [e]	32% ≥3 comorbidities[e]		
Kwok *et al.* [35]	126	432	74	80	49	58	9	10	Mean CCI 7.8	Mean CCI 9.0	NR	NR
Moranne *et al.* [30]	215	54	81[b]	85[b]	40	56	12[b]	12[b]	[f]	[f]	NR	NR
Morton *et al.* [25]	619[g]	102[g]	61	79	40	49	NR	NR	[h]	[h]	NR	NR
Murtagh *et al.* [36]	52	77	80[b]	83[b]	35	34	NR	NR	19.2% high (Davies grade 2)	18.2% high (Davies grade 2)	19 (2–72)	18 (0–72)
Pyart *et al.* [41]	841	375	76[b]	83[b]	64	56	16[b]	15[b]	Median CCI 5 (IQR 3–6)	Median CCI 4 (IQR 3–5)	NR	NR
Raman *et al.* [26]	123	81	79	84	33	44	13	13	[i]	[i]	35.1 ± 22.1[j]	
Subgroup: eGFR <10	73	42	80	85	36	52	9	9	[i]	[i]	26.9 ± 23.4 [j]	
Seow *et al.* [27]	38	63	71[b]	78[b]	47	44	10[b]	10[b]	Median CCI 5 (IQR 3–5)[k]	Median CCI 5 (IQR 5–6)[k]		
Shum *et al.* [37]	157	42	73	75	48	57	6	7	Mean CCI 4.3 (SD 1.5)	Mean CCI 4.6 (SD 1.8)	NR	NR
Smith *et al.* [28]	258[l]	63[l]	59	71	43	38	NR	NR	Mean score: 2.1 (2.4)[c]	Mean score: 4.7 (SD 3.0)[c]		
Teo *et al.* [38]	HD: 102 PD: 41	16	59 61	67	44 66	63	NR	NR	[m]	[m]	NR	NR

Table 2. Continued

Study	Number of patients		Mean age (years)		Female (%)		Mean eGFR at baseline		Severe comorbidity		Median follow up time, months (IQR)	
	D	CC	D	CC	D	CC	D	CC	D	CC	D	CC
Teruel *et al.* [29]	142	90	68[b]	83[b]	37	42	12	11	Mean CCI 4.7 (SD 2.1)[k]	Mean CCI 5.8 (SD 1.9)[k]	7.2 ± 3.7[j]	4.9 ± 3.2[j]
Van Loon *et al.* [31]	192	89	75	82	33	44	8	12	41% high comorbidity[n]	44% high comorbidity[n]	NR	NR
Verberne *et al.* [39]	240	126	76	83	33	46	13	16	30% severe (Davies ≥3)	32% severe (Davies ≥3)	NR	NR
Wong *et al.* [40]	503 (not started) 12 756 (started)	812	<65 years: 34%; 65–74: 29%; 75–84: 30%; ≥85: 7% <65 years: 37%; 65–74: 31%; 75–84: 28%; ≥85: 3%	<65 years: 18%; 65–74: 21%; 75–84: 43%; ≥85: 18%	1 1	1	12 11	12	33% high comorbidity[o] 24% high comorbidity[o]	43% high comorbidity[o]		

CCI, Charlson Comorbidity Index; CIRS-G, Cumulative Illness Rating Scale–Geriatric; D, patients who chose or started with dialysis; IQR, interquartile range.

[a]Comorbidities included ischaemic heart disease or cardiac failure, cerebrovascular or peripheral vascular disease, chronic liver or lung disease, diabetes and dementia.

[b]Median presented.

[c]Scores of 0 (no disease)–4 (advanced disease) were attributed to the following condition categories: cardiac disease, peripheral vascular disease, cerebrovascular disease, respiratory disease and cancer, and cirrhosis was scored as a 4. Scores were summed. High comorbidity was designated to patients with scores of 4 in one condition category or with total scores >4.

[d]Same scoring as described under note c, but 'high comorbidity' was defined when patients had summed scores >3 or a score of 3 derived from a single category.

[e]Comorbidities included malignancy, ischaemic heart disease, cardiac failure, dysrhythmia, peripheral vascular disease, sequelae of stroke and/or overt, dementia and diabetes.

[f]No overall score was presented. No significant differences in diabetes, cancer, congestive heart failure, dysrhythmia, cerebrovascular disease and chronic respiratory disease.

[g]For dialysis and conservative care, $n = 571$ and $n = 92$, respectively, were included in the survival analysis, but no separate baseline data were provided.

[h]Data on comorbidities were not systematically recorded.

[i]No overall score was presented. Patients choosing D over CC were less likely to have peripheral vascular disease (33% versus 15%; $P = 0.005$). The percentage of patients suffering from coronary artery disease, heart failure, chronic obstructive pulmonary disease, diabetes and cerebrovascular accident did not significantly differ.

[j]Mean follow-up (for total group).

[k]Non-age adjusted.

[l]For survival analysis, $n = 186$ dialysis patients and $n = 26$ conservative care patients were included but no separate baseline data was provided.

[m]No overall score was presented.

[n]The CIRS-G was used in which ≥2 score 3 or ≥1 score 4 was considered high comorbidity.

[o]Comorbid burden was categorized by tertile of Gagne comorbidity score as having low (score <4), moderate (score 4–6) or high (score >6).

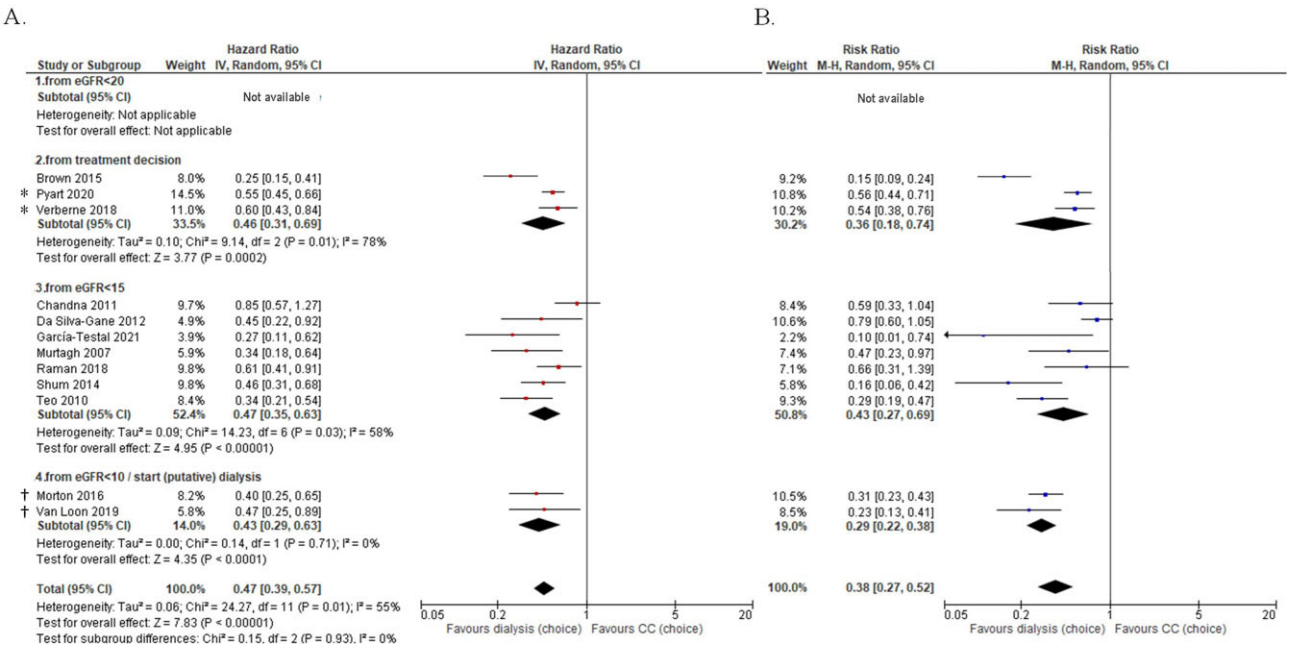


FIGURE 4: Meta-analysis of (**A**) adjusted survival and (**B**) unadjusted 1-year survival comparing choice of dialysis with choice of conservative care. *Considered as the best studies in addressing confounding and selection bias. †These studies used a different starting point for the dialysis (initiation of dialysis) versus the CC group (eGFR <15 mL/min/1.73 m^2)

(Clinical Frailty Scale score ≥6) choosing dialysis or CC [HR 1.2 (95% CI 0.69–2.06; $P = .52$) adjusted for sex, comorbidity and age] in this study [41].

DISCUSSION

This systematic review and meta-analysis shows an overall lower mortality risk for patients choosing dialysis compared with those opting for CC: dialysis is associated with half the risk for mortality and a longer (unadjusted) median survival from the time of treatment decision for this group. Our data suggest that in patients with severe comorbidity and/or older age, the lower risk for mortality was still present, albeit more limited. It is important to note that the included 22 observational cohort studies were heterogeneous for age distribution, comorbidities and the starting point and/or reference kidney function from which survival was assessed. Additionally, the risk of selection bias and (residual) confounding was high. Results on lower mortality risk for dialysis should therefore be interpreted cautiously and cannot be translated to an individual level.

Our analysis updates and extends a previously published systematic review of survival outcomes for dialysis versus CC pathways with five studies [5]. More importantly, our scope was to only include studies where patients made an explicit treatment choice, e.g. choice for CC rather than patients who did not receive dialysis treatment. Therefore, after consultation with authors, three studies [43–45]—which were included in the review by Fu *et al.* [5]—were omitted.

Regardless of these differences, we found an adjusted risk for mortality [HR 0.47 (95% CI 0.39–0.57)] comparable with the findings of Fu *et al.* [5] [HR 0.47 (95% CI 0.32–0.69)] and Wongrakpanich *et al.* [6] [HR 0.53 (95% CI 0.30–0.91)], yet with less—but still high—heterogeneity (lower I^2 statistic). Similar to Foote *et al.* [4], we also found a lower mortality risk for patients opting for dialysis when only assessing patients with an older age or severe comorbidity. Studies that did not find any difference could have been underpowered. The median survival in our analysis was similar to findings of Wrongapanic *et al.* [6]: 20–67 months for patients choosing dialysis and 6–31 months for those opting for CC. Interestingly, in a review published a decade ago, the median survival for CC patients ranged only up to 23 months [3]. Our results, adding five studies with a higher median survival for CC, may indicate that CC has evolved as a treatment option over time.

While patients who choose dialysis generally live longer than those who choose CC, treatment choice is not based on survival outcomes alone. Our recent review on HRQoL and symptoms concluded that, despite a higher burden of kidney disease after starting dialysis, no distinct advantage was found for either one of the treatment options [8]. Taken together, these reviews show that overall, dialysis patients live longer while HRQoL is comparable. Ultimately patients' treatment decisions are the result of shared decision making between nephrologists, patients and caregivers, tailored to each patient's individual situation. For individual patient goals of care, social arguments may play an important role along with medical conditions. Also, reasons for choosing either dialysis or CC are likely to differ among patients, caretakers and physicians [33, 46–48], and decisions may change over time. Therefore a well-informed, continuous, shared decision-making process between patients, caretakers and healthcare professionals is needed [49, 50].

The strength of our systematic review is the wide-ranging search in multiple databases directed by the PRISMA

Table 3. Adjusted HR for mortality per starting point comparing dialysis with CC

Authors	Age, in years	Kidney function at start of survival analysis	Comparison	Adjusted HR (95% CI)	Adjustment variables
Brown *et al.* [22]	>75	eGFR <15 mL/min/1.73 m^2	D versus CC	0.22 (0.11–0.45)	Age, sex, diabetes and ischemic heart disease
	–	Treatment decision	D versus CC[a]	**0.25 (0.15–0.42)**[a]	Age, sex, diabetes and ischemic heart disease
			D-started versus CC	0.30 (0.13–0.67)	
			D-not started versus CC	0.23 (0.12–0.41)	
Chandna *et al.* [32]	>75	eGFR <15 but >10 mL/min/1.73 m^2	D versus CC	**0.85 (0.57–1.27)**	Age, diabetes, high/low comorbidity, sex and ethnicity
Da Silva-Gane *et al.* [24]	–	Late stage G4/G5	D versus CC	**0.45 (0.22–0.91)**[a]	Age, comorbidity, performance score, physical health score and propensity score
			HD versus CC	0.47 (0.20–1.10)	
			PD versus CC	0.39 (0.10–1.48)	
García-Testal *et al.* [42]	>80	eGFR <15 mL/min/1.73 m^2	D versus CC	**0.27 (0.11–0.62)**	Age, sex, CCI and diabetes mellitus
Moranne *et al.* [30]	>75	eGFR <20 mL/min/1.73 m^2	D versus CC[b]	0.61 (0.37–0.99)[c]	Age, sex, systolic blood pressure, BMI, diabetes, active cancer, chronic respiratory failure, congestive heart failure, dysrhythmia, cerebrovascular disease, peripheral vascular disease, behavioural disorders, mobility, living at home, haemoglobin and proteinuria
Morton *et al.* [25]	–	eGFR <15 mL/min/1.73 m^2 /on dialysis	D versus CC (on 3 years mortality)	**0.40 (0.25–0.65)**	Age, sex, home language, marital status, socio-economic status, remoteness, health insurance, late referral to a nephrologist, serum albumin and haemoglobin
				0.46 (0.29–0.72)	Age, sex and baseline serum albumin (other model)
Murtagh *et al.* [36]	>75	Stage G5	D versus CC	**0.34 (0.18–0.63)**	Age, Davies score, Ischemic heart disease and modality choice
Pyart *et al.* [41]	>70	Treatment decision	D versus CC	**0.55 (0.45–0.66)**	Age, sex and CCI
Raman *et al.* [26]	>75	eGFR <15 mL/min/1.73 m^2	D versus CC	**0.61 (0.41–0.91)**	Age, living alone and peripheral vascular disease
	>75	eGFR <10 mL/min/1.73 m^2	D versus CC	0.36 (0.21–0.62)	Age and peripheral vascular disease
	>85	eGFR <15 mL/min/1.73 m^2	D versus CC	0.72 (0.25–2.08)	Age, living alone and peripheral vascular disease?
	>85	eGFR <10 mL/min/1.73 m^2	D versus CC	0.15 (0.02–1.19)	Age and peripheral vascular disease?
Shum *et al.* [37]	>65	Stage G5	PD versus CC	**0.46 (0.31–0.68)**	Age, modified CCI and basic activities of daily living impairment
Teo *et al.* [38]	–	ESRD (creatinine 880 µmol/L)	D versus CC	**0.34 (0.21–0.54)**[a]	Age, sex, race and ejection fraction >50%, type of therapy centre (charities/private)
			PD versus CC	0.44 (0.22–0.86)	
			HD versus CC	0.26 (0.13–0.51)[d]	
Van Loon *et al.* [31]	≥65	Start dialysis/decision CC	D versus CC	**0.47 (0.25–0.89)**	Age, comorbidity level and GFR category
Verberne *et al.* [39]	>70	Treatment decision	D versus CC	**0.60 (0.42–0.84)**	Age, sex and Davies comorbidity score

Bold HRs were used for the meta-analysis.

[a]The HR given for multiple dialysis groups (i.e. HD and PD groups [24, 38] or patients who started on dialysis and who had not started yet [22]), were pooled using a fixed-effects model.

[b]The CC group was defined as 'no-dialysis by patient'.

[c]The HR and CI were calculated by dividing the HR of the 'dialysis indication' group divided by the 'no-dialysis patient' group and using the standard error of the 'no-dialysis patient' group by 'no-dialysis nephrologist' group. The study is not included in the meta-analysis since dialysis initiation was a competing event.

[d]The HR was calculated using standard errors of the HR of PD versus CC.

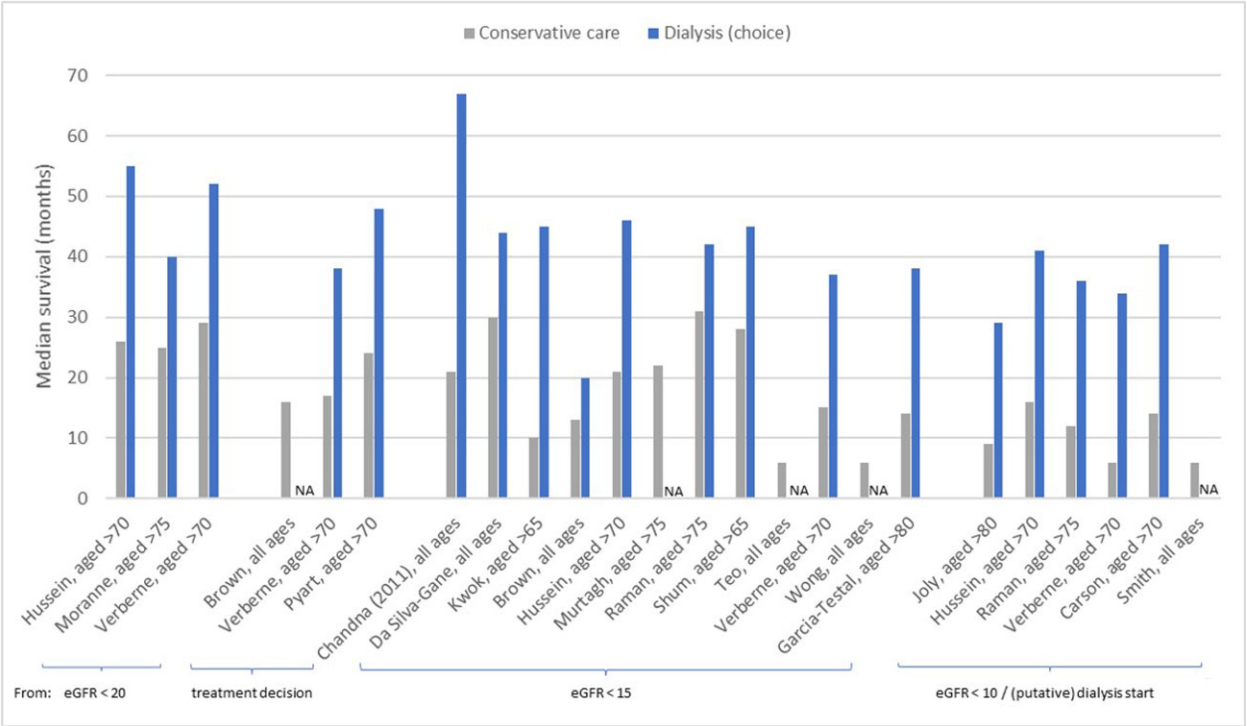


FIGURE 5: Unadjusted median survival outcomes, grouped per reference point of survival analysis. The minimum age for inclusion in each study is shown if applicable. Note that as these data are unadjusted, (sometimes large) imbalances between the dialysis and conservative care groups may exist, including older age, greater presence of severe comorbidity, more frailty, worse functional performance and worse cognitive performance in the group opting for CC. Please refer to Table 2 and Supplementary data, Table S4 for more details.

Table 4. Ranges of unadjusted survival outcomes between studies

	From treatment decision (if not available: eGFR <20 or <15 mL/min/1.73 m^2)			From start of dialysis (or eGFR <10 mL/min/1.73 m^2)		
Survival	*n*	D	CC	*n*	D	CC
Median (months)	14	20–67	6–31	6	29–42	6–16
1 year	13	72–97	31–85	8	74–92	29–66
2 years	11	46–89	13–64	7	60–79	13–41
5 years	8	11–55	1–20	2	32–43	4–21

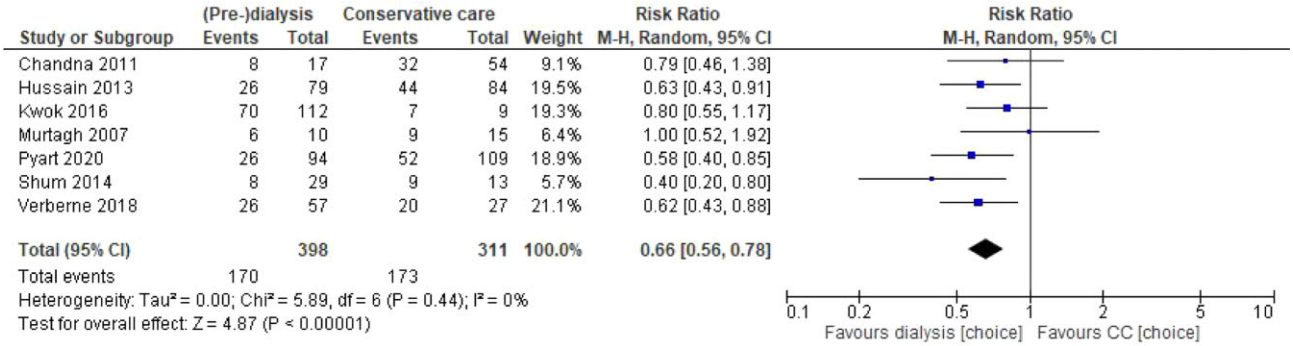


FIGURE 6: Unadjusted 2-year RRs for patients with severe comorbidity.

guidelines. Also, we focused on studies reporting an explicit choice for either dialysis or CC treatment pathways and comparing survival (from intention to treat) between both groups. Authors were contacted if the population of interest or the presence of an explicit treatment decision was not clear. Our approach limited the risk of including selected patients for whom the nephrologist decided that dialysis was not appropriate. A limitation of our systematic review is that not all articles could be included in the formal meta-analysis due to clinical and methodological heterogeneity among the

studies and, primarily, a lack of adjustment for confounders. Additional heterogeneity was introduced by the inclusion of a small number of as-treated analyses [28, 35, 40]. Besides the likely significant (residual) confounding when comparing groups, we could not assess the validity of the assumptions of the models used in the included studies. All studies reporting adjusted HRs used Cox proportional hazards models, but only two studies reported checking any of the assumptions [39, 41].

Using observational data, it is important to consider the risk of bias and generalizability, for multiple reasons. First, our results on both unadjusted and adjusted survival should be taken with caution because of (residual) confounding. Patients opting for dialysis were younger and had fewer comorbid conditions. Adjustment for these factors showed only a relatively small effect, likely explained by other confounding factors. Several other geriatric impairments, including frailty, have been associated with increased mortality in prior studies [51–53]. Although numerous studies have shown a higher prevalence of frailty and functional and cognitive impairments in the CC group [22, 24, 28–31, 33–35, 40, 41], none adjusted for these discrepancies. The study by Pyart *et al.* [41] showed that frailty better predicts outcomes compared with comorbidity. This would imply that the lower mortality risk found in patients treated with dialysis could be partly explained by the severity of disease in the CC group, meaning that (due to residual confounding) the actual survival benefit of dialysis may be less. This is also illustrated by two studies [39, 41] in which significantly more patients choosing CC, compared with those choosing dialysis, died before they would (putative) have started dialysis. For a more adequate comparison of survival between CC and dialysis, future non-randomized studies should take factors such as frailty, cognitive impairment and other confounders, e.g. functional status [35] and the rate of decline of kidney function [21, 54], into account.

Second, the moment of treatment decision differs between patients, potentially leading to selection bias. Ideally, to limit this bias, our review would have focused solely on treatment decision as the starting point for survival analysis. However, as this was only available in three studies [22, 39, 41], we chose to also present results of other starting points. Furthermore, although guidelines suggest starting education on different treatment modality options early [1, 2], it has been reported that older patients may articulate their decision at a late stage of disease course or switch from their initial intention to treat [30, 49].

Third, the generalizability of the study findings may be an issue for interpretation of our outcomes, particularly on absolute survival, because of stringent inclusion and exclusion criteria in several studies (e.g. concerning severe comorbidities [26], reduced life expectancy [27], acute referrals [38], sex [40] or high numbers of transplanted patients [29]). The percentage of patients undergoing CC in the different studies varied widely (6–77%), illustrating differences in study populations and/or the delivery and acceptability of CC as a viable treatment option among countries [55, 56].

Future studies reporting survival comparisons between dialysis and CC should include a clear definition of CC (i.e. distinguishing between CC and delaying the dialysis decision with a stable clinical status in terms of eGFR and limited clinical uraemic symptoms), report outcomes on multiple and comparable starting points of survival analysis and ensure the comparability of groups. Randomized controlled trials, such as the ongoing Prepare for Kidney Care study [57], are the ideal study design for this; however, study populations in randomized trials tend to differ significantly from real-world populations due to (explicit or implicit) selection. Non-randomized studies should prospectively look at intention-to-treat analysis, not only adjusting for the common confounding factors such as age and comorbidities, but also using essential data on the impact of frailty and functional and cognitive status [31, 33, 41]. One study, which incorporates geriatric assessment for this purpose, is ongoing in The Netherlands [58]. Furthermore, including patients opting for CC in national renal registries may provide opportunities to further comprehend the prognosis and outcomes, guide tailored treatment decisions and stimulate research improving their management [33].

In conclusion, our systematic review and meta-analysis demonstrate that patients opting for dialysis have an overall lower mortality risk compared with patients opting for CC, even patients with severe comorbidity and older age, granting that data were limitedly comparable, and the current evidence is insufficient to provide conclusions on absolute survival benefit. High-quality prospective studies are needed to substantiate and extend these methodologically conditional findings and to extend findings for individual prediction of survival outcomes in clinical practice.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

ACKNOWLEDGEMENTS

We thank clinical librarian Carla Sloof for her help and feedback on our search strategy.

FUNDING

The study was funded by an unrestricted grant from the Nephrosearch Foundation and Zilveren Kruis Healthcare Insurance Company. The funders played no role in study design; collection, analysis and interpretation of data; writing of the article or in the decision to submit the article for publication.

AUTHORS' CONTRIBUTIONS

C.G.N.V., W.R.V., A.C.A., M.v.B, S.P.M. and W.J.W.B were involved in the research idea and study design. C.G.N.V., M.v.O., W.R.V. and I.D.v.d.W. were responsible for data acquisition. C.G.N.V., M.v.O., W.R.V., I.D.v.d.W., A.C.A., F.W.D., O.D, S.P.M., M.v.B. and W.J.W.B. were involved in data analysis and interpretation. W.J.W.B. was involved in supervision or mentorship. All authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

Outside the submitted work, C.G.N.V. has received grant support from the Dutch Kidney Foundation and Nephrosearch Foundation; W.R.V. has received grant support from Zilveren Kruis; W.J.W.B. has received grant support from Zilveren Kruis and the Dutch Kidney Foundation; and M.v.B has received grant support from the Dutch Kidney Foundation and Healthcare Evaluation Leading the Change. The remaining authors declare that they have no conflicts of interest.

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Received: 17.8.2021; Editorial decision: 7.1.2022