Health-related quality of life and symptoms of conservative care versus dialysis in patients with end-stage kidney disease: a systematic review

Verberne, W.R.; Wittenboer, I.D. van den; Voorend, C.G.N.; Abrahams, A.C.; Buren, M. van; Dekker, F.W.; ... ; Bos, W.J.W.

Nephrol Dial Transplant (2021) 36: 1418–1433
doi: 10.1093/ndt/gfaa078
Advance Access publication 14 June 2020

ORIGINAL ARTICLE

Health-related quality of life and symptoms of conservative care versus dialysis in patients with end-stage kidney disease: a systematic review

Wouter R. Verberne [1,2], Iris D. van den Wittenboer[1], Carlijn G.N. Voorend[2], Alferso C. Abrahams[3], Marjolijn van Buren[2,4], Friedo W. Dekker[5], Brigit C. van Jaarsveld[6], Ismay N. van Loon[3], Simon P. Mooijaart[7], Gurbey Ocak[1], Johannes J.M. van Delden[8] and Willem Jan W. Bos[1,2]

[1]Department of Internal Medicine, St Antonius Hospital, Nieuwegein, The Netherlands, [2]Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands, [3]Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, The Netherlands, [4]Department of Nephrology, Haga Hospital, The Hague, The Netherlands, [5]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands, [6]Department of Nephrology and Amsterdam Cardiovascular Sciences, Amsterdam University Medical Centers, VU University, Amsterdam, The Netherlands, [7]Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands and [8]University Medical Center Utrecht, Julius Center for Health Sciences and Primary Care, Utrecht, The Netherlands

Correspondence to: Wouter R. Verberne; E-mail: w.verberne@antoniusziekenhuis.nl

ABSTRACT

Background. Non-dialytic conservative care (CC) has been proposed as a viable alternative to maintenance dialysis for selected older patients to treat end-stage kidney disease (ESKD). This systematic review compares both treatment pathways on health-related quality of life (HRQoL) and symptoms, which are major outcomes for patients and clinicians when deciding on preferred treatment.

Methods. We searched PubMed, Embase, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus and PsycINFO from inception to 1 October 2019 for studies comparing patient-reported HRQoL outcomes or symptoms between patients who chose either CC or dialysis for ESKD.

Results. Eleven observational cohort studies were identified comprising 1718 patients overall. There were no randomized controlled trials. Studies were susceptible to selection bias and confounding. In most studies, patients who chose CC were older and had more comorbidities and worse functional status than patients who chose dialysis. Results were broadly consistent across studies, despite considerable clinical and methodological heterogeneity. Patient-reported physical health outcomes and symptoms appeared to be worse in patients who chose CC compared with patients who chose dialysis but had not yet started, but similar compared with patients on dialysis. Mental health outcomes were similar between patients who chose CC or dialysis, including before and after dialysis start. In patients who chose dialysis, the burden of kidney disease and impact on daily life increased after dialysis start.

Conclusions. The available data, while heterogeneous, suggest that in selected older patients, CC has the potential to achieve similar HRQoL and symptoms compared with a dialysis pathway. High-quality prospective studies are needed to confirm these provisional findings.

Keywords: conservative care, health-related quality of life, renal dialysis, symptoms, systematic review

INTRODUCTION

The number of patients with end-stage kidney disease (ESKD) is increasing worldwide [1, 2]. The fastest-growing group is represented by older patients. Among older patients, dialysis has become the most common treatment for ESKD [3]. Nowadays, the majority of patients on maintenance dialysis are >65 years of age in many countries [4, 5]. Older patients are more often frail, have multiple chronic conditions and have greater functional impairment than younger patients [6]. Since dialysis is an intensive treatment, its suitability in older patients has been questioned [7]. Non-dialytic conservative care (CC) has been proposed as an alternative to dialysis for selected older patients with ESKD [8–10]. With the intention to be provided until death, CC aims to preserve quality of life with adequate symptom control by active medical treatment and multidisciplinary care, including all interventions needed except dialysis [8].

Data on patient-relevant outcomes are needed to evaluate whether CC is a viable alternative to dialysis and, if so, to help inform the shared decision-making process between patients

KEY LEARNING POINTS

What is already known about this subject?

- Most comparative studies have focused on survival and show that in selected patients the survival benefit of a dialysis pathway is limited or absent compared with conservative care (CC), particularly in the oldest patients and patients with multiple comorbidities.
- Data on more patient-relevant outcomes, such as health-related quality of life (HRQoL) and symptoms, are needed to evaluate whether CC is a viable alternative to dialysis.

What this study adds?

- Using a comprehensive search strategy, we identified 11 observational cohort studies in which HRQoL outcomes and symptoms were measured in patients who chose either CC or dialysis for end-stage kidney disease (ESKD).
- This systematic review demonstrates that in selected older patients CC has the potential to achieve similar physical and mental health outcomes and symptoms compared with a dialysis pathway, although data were limited and of suboptimal quality.
- In patients who chose dialysis, the burden of kidney disease and its impact on daily life increased after dialysis start.

What impact does this have on practice or policy?

- The findings on HRQoL and symptoms support current guideline recommendations that, in selected older patients, CC might be a viable alternative to a dialysis pathway for ESKD.
- CC should be discussed in the shared decision-making process by older patients and clinicians when determining the preferred treatment for ESKD.
- The data on HRQoL and symptoms can be used in this shared decision-making process.

and healthcare professionals on possible treatments for ESKD [11, 12]. Most studies, however, have assessed survival only. These observational studies have shown that in selected patients the survival benefit of a dialysis pathway is limited or absent compared with CC, particularly in the oldest patients and patients with multiple comorbidities [13, 14]. Patients consider outcomes other than survival to be important as well when deciding on CC or dialysis, including health-related quality of life (HRQoL) and symptoms [15–19]. The need for more patient-relevant data on both treatment pathways has recently been recognized as a research priority by patients, clinicians and organizations such as Kidney Disease: Improving Global Outcomes (KDIGO) [8, 20–23]. Six systematic reviews have been performed to summarize evidence on HRQoL and symptoms in patients who chose either CC or a dialysis pathway [24–29], but these studies included limited search strategies [24–29] or have become outdated [24, 28, 29]. An updated and more comprehensive overview of current evidence on HRQoL and symptoms in both treatment pathways is needed.

The aim of this systematic review was to compare patient-reported outcomes on HRQoL and symptoms between patients who chose either CC or a dialysis pathway for ESKD. We aimed to include studies that evaluated outcomes from the moment of treatment decision or subsequent time points, as an equivalent time point for treatment start itself is difficult to identify in both treatment pathways [30].

MATERIALS AND METHODS

We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [31]. Methods of the analysis and selection criteria were documented in advance in a protocol published on PROSPERO [32].

Search strategy

We identified studies by searching PubMed, Embase, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus and PsycINFO from inception to 1 October 2019. A proposal for search terms was pilot tested and reviewed by an external clinical librarian. The final search strategy included terms relating to or describing the intervention (CC), the comparative intervention (dialysis pathway) and the patient population [advanced chronic kidney disease (CKD) or ESKD]. Supplementary data, Table S1 shows the full search terms. We searched for additional studies by checking the reference lists and citations of included studies via Scopus and by expert consultation.

Study selection

Two authors (W.V. and I.W.) independently screened the titles and abstracts of all search hits for eligibility. Full texts of potentially relevant studies were retrieved and independently assessed for final eligibility. Pre-defined criteria on inclusion and exclusion were used (Supplementary data, Table S1). We selected original research articles if they included a comparison of patient-reported outcomes on HRQoL or symptoms between patients who chose either CC or a dialysis pathway. In all patients, an explicit decision in favour of CC or dialysis had to been made, without further selecting on how or by whom the treatment decision was made. We defined CC as non-dialytic care for ESKD intended to be provided until death (not just to postpone dialysis) [8]. Patients on a dialysis pathway included both patients who chose dialysis but had not yet started and patients who started or were already receiving dialysis. Studies in patients with acute kidney injury and non-English publications were excluded. Disagreements were resolved through consensus discussion, consultation of a third author (W.B.) and contact with authors of the original studies for additional information.

Data extraction

Data from included studies were independently extracted by two authors (W.V. and I.W.) using a standardized, pre-piloted form. The extracted data included information on study setting, study population, participant characteristics, study methodology, measurement tools and study results of HRQoL and symptoms and information to assess risk of bias. Discrepancies in data extraction were resolved through consensus discussion.

Study quality assessment

Two authors (W.V. and I.W.) independently appraised the risk of bias of included studies using the Risk of Bias Assessment Tool for Non-randomized Studies [33, 34]. This tool assesses six domains of bias with criteria to determine a low risk, high risk or unclear risk of bias (selection of participants, confounding variables, measurement of exposure, blinding of outcome assessments, incomplete outcome data and selective outcome reporting). Disagreements in the assessed risk of bias were resolved through consensus discussion and consultation of a third author (W.B.).

Data synthesis

The findings of the included studies were synthesized qualitatively. We subdivided the results of patients on a dialysis pathway according to dialysis start and modality and in patients on CC according to an estimated glomerular filtration rate (eGFR) <10 mL/min/1.73 m^2 as a surrogate time point for dialysis start. We planned to perform a meta-analysis in case of sufficiently homogeneous data [32]. After careful consideration, however, performing a meta-analysis was deemed inappropriate due to wide variability in study design, study population, exposure, analysis and reporting of study outcomes.

RESULTS

Search results

We screened 4059 unique search hits identified through database searching, leaving 338 articles for full-text assessment (Figure 1). We excluded 327 full-text articles because the studies did not include the population or outcomes of interest or described no original research. We contacted the authors of four studies to clarify the definition of their CC-like patient group. All authors responded and answered that their patient group did not correspond with our definition of CC, making these studies ineligible for inclusion (Supplementary data, Table S2). Our search resulted in 11 relevant studies comparing HRQoL outcomes or symptoms between patients who chose either CC or a dialysis pathway [35–45]. No randomized controlled trials were identified.

Study characteristics

Table 1 summarizes the characteristics of the studies included. Studies were published between 2009 and 2019 and originated from Europe, Asia and Australia. Studies were observational cohort studies performed in a single centre ($n = 8$) or multiple centres ($n = 3$). Sample size varied from 11 to 395 patients per study (1718 patients overall: 1069 on a dialysis pathway, 649 on CC). Seven studies included only older patients using a threshold in the range of $\geq$60–$\geq$75 years old [38–44]. The patient group on a dialysis pathway varied per study: some included patients in whom a decision in favour of dialysis had been made but who had not yet started on dialysis [35, 39] and other studies mixed such patients with patients who had started dialysis [36–38], while most studies included patients receiving dialysis [haemodialysis (HD), peritoneal dialysis (PD) or assisted PD (aPD)] [39–45]. Studies also used different inclusion criteria on the severity of advanced CKD, among which two studies focused on patients with an eGFR <10 mL/min/1.73 m^2 [41, 42]. The reported approach to CC was generally similar among the studies.

Six studies assessed outcomes at a single time point [36, 39–42, 45], while five studies performed multiple measurements over time, including a baseline measurement [35, 37, 38, 43, 44]. Time points of outcome measurements ranged from 3 months after treatment decision or dialysis start to 36 months after decision or recruitment or 139 months after dialysis start.

Risk of bias

Figure 2 shows that seven studies had a high risk of selection bias, particularly one study that non-randomly selected patients on HD as a rough reference [40]. Six studies had a high risk of confounding, as no adjustment for any confounder was reported [35, 36, 40, 43–45]. The risk of bias due to incomplete outcome data was high in two studies because of low response rates (49–56% [35]; 30–56% [36]). Other risk of bias domains were assessed as low or unclear due to missing information. Supplementary data, Table S3 shows the risk of bias assessment per study.

Patient characteristics

Table 2 shows the characteristics of the patient groups who chose either CC or dialysis. Patients on CC were older (mean age ranging from 73 to 84 years old) than patients on a dialysis pathway (48–83 years old) and were more often female. An exception was one study that included patients by propensity matching on age and sex [41]. The comorbidity level was higher in patients on CC compared with patients on a dialysis pathway in six studies [35–37, 40, 43, 45], while they were similar in four studies [38, 39, 41, 44]. Seven studies reported functional status and observed functional impairment in both patient groups, which was often worse in patients on CC than in patients on a dialysis pathway.

HRQoL

Ten studies reported HRQoL outcomes. Table 3 shows the results per HRQoL domain. Supplementary data, Table S4 shows the results per study, including baseline values where applicable.

Nine studies assessed physical and mental health domains using the 36-item Short Form (SF-36) or 12-item Short Form (SF-12) [35–42, 45]. Lower physical health outcomes were observed in patients who chose CC compared with patients who chose dialysis but had not yet started, including the physical component summary, physical function and general health

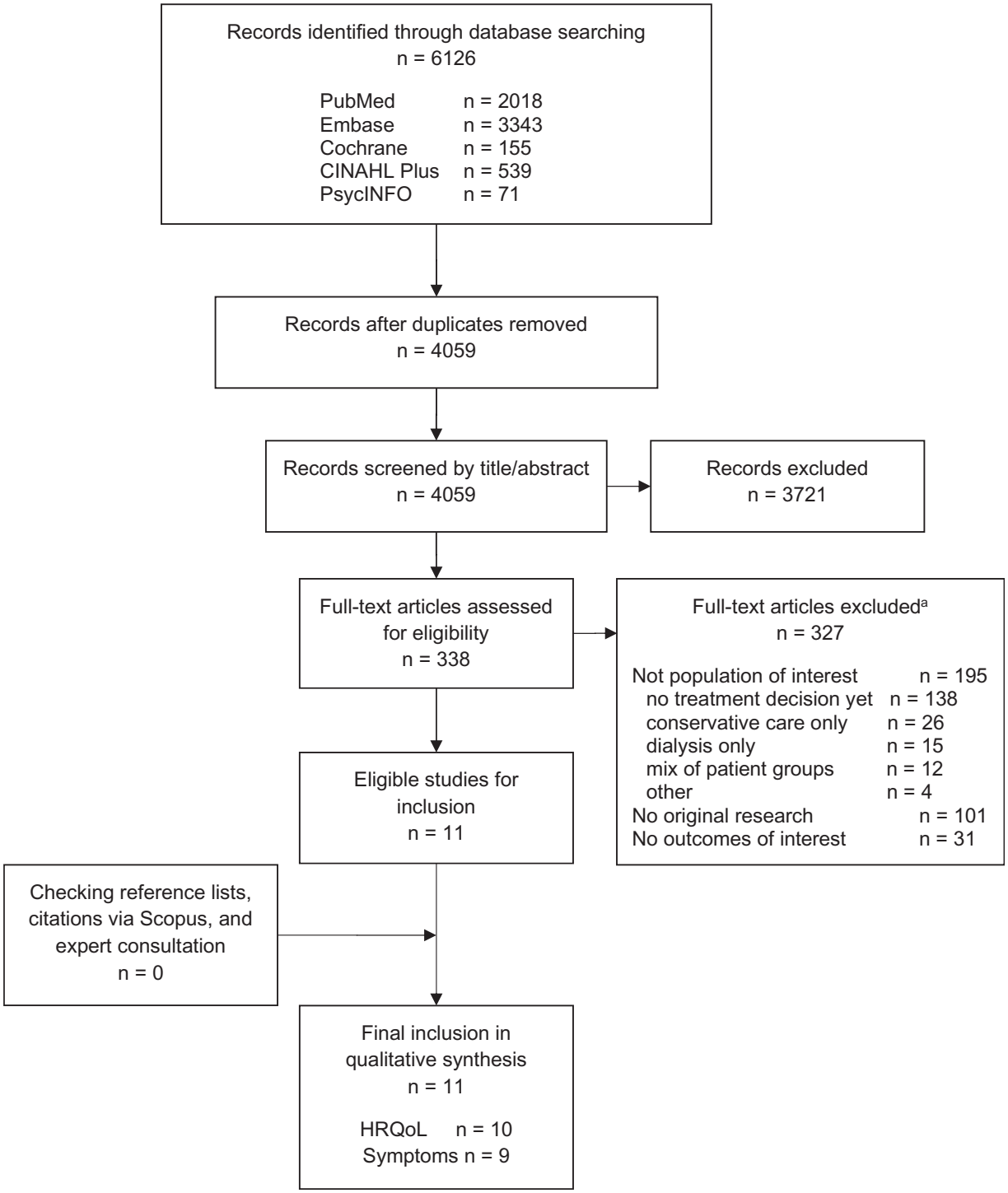

FIGURE 1: Study inclusion and exclusion flow diagram.
[a]Explanation of reasons for exclusion: No treatment decision yet includes patients with advanced CKD who did not or did not yet have to decide on preferred treatment (commonly referred to as 'non-dialysis dependent chronic kidney disease patients'), including four studies discussed with the authors to clarify their CC-like patient group (Supplementary Table S2); mix of patient groups means mix of different patient categories into one patient group without subgroup analyses (e.g. mix of patients who have not made a treatment decision yet and patients who chose CC); no original research, e.g. reviews, opinion papers or study protocols.

domains [35–37, 39]. Similar physical health outcomes were observed between patients who chose CC and patients on dialysis, including patients with an eGFR <10 mL/min/1.73 m^2 and different dialysis modalities [37–42, 45]. In repeated measurements over 12–36 months, physical health outcomes showed similar trajectories in both patient groups [35, 37, 38], including after dialysis start in patients who chose dialysis [37, 38].

Table 1. Characteristics of studies included in the systematic review

References	Country	Design[a]	*n*	Inclusion criteria	Dialysis patient group	Reported CC strategy	Patient-reported outcome measure		Time points of outcome measurement
							HRQoL	Symptoms	
Brown *et al.* [35]	Australia	Cohort	395	CKD Stage 4/5 No age criterion	Choice D	Usual nephrology care and renal supportive care clinic	SF-36	MSAS-SF	At baseline and 12 months after first visit to pre-dialysis or renal supportive care clinic
Yuen *et al.* [36]	Hong Kong	Cohort	268	CKD Stage 4/5 Adults	Mix of choice D and on D (27%, modality unknown)	Renal palliative care clinic	SF-36	NA	NR
Da Silva-Gane *et al.* [37]	UK	Cohort	154	CKD Stage 4/5 No age criterion	Choice HD, 59% started during follow-up Choice PD, 52% started	Active medical treatment and multidisciplinary care	SF-36SWLS	HADS (anxiety + depressive symptoms)	Every 3 months for up to 36 months after recruitment; until 12 months after dialysis start
Seow *et al.* [38]	Singapore	Cohort	101	eGFR 8–12 ≥75 years or age-adjusted CCI ≥ 8	Choice D, 100% started during follow-up (modality unknown)	NR	KDQOL-SF	KDQOL-SF	Multiple measurements during 24 months after recruitment
Verberne *et al.* [39]	Netherlands	Cohort	96	CKD Stage 4/5 ≥70 years	Choice D On D (76% HD, 24% PD)	Active medical treatment and multidisciplinary care	KDQOL-SF	KDQOL-SF	At median 13 (choice D), 35 (on D) and 16 months (CC) after treatment decision
De Biase *et al.* [40]	Italy	Cohort	11	eGFR < 15 >75 years	On HD	Usual nephrology care and round-the-clock telephone support service	SF-36	STAI-Y BDI	At median 17 (dialysis) and 13 months (CC); NR from which starting point
Iyasere *et al.* [41]	UK	Cohort Multicentre ($n = 21$)	84	eGFR < 10 ≥60 years >6 months life expectancy	On HD On aPD	Active non-dialysis care	SF-12 IIRS	POS-S renal HADS (depressive symptoms)	Majority at 13–60 months after dialysis start; NR for CC group
Shah *et al.* [42]	UK, Australia	Cohort Multicentre ($n = 3$)	129	eGFR < 10 ≥75 years	On D (84% HD, 16% PD)	Comprehensive conservative, non-dialytic care	KDQOL-36	KDQOL-36	NR (cross-sectional)
Tan *et al.* [43]	Australia	Cohort	20	eGFR < 15 >65 years	On D (42% HD, 58% PD)	Renal supportive care clinic	NA	POS-S renal	At baseline and 6 months after dialysis start or first visit to renal supportive care clinic
Van Loon *et al.* [44]	Netherlands	Cohort Multicentre ($n = 17$)	281	eGFR < 15 ≥65 years	On D (77% HD, 23% PD)	Maximal conservative management	EQ-5D-3L	NA	At baseline and 6 months after dialysis start or treatment decision (CC)
Yong *et al.* [45]	Hong Kong	Cohort	179	eGFR < 15 Adults	On D (20% HD, 80% PD)	Renal palliative care clinic	SF-36	Self-created symptom listBPI	At mean 139 (HD) or 49 (PD) months after dialysis start; 11 months after treatment decision (CC)

[a]Study setting is single centre or indicated if otherwise.

BDI, Beck Depression Inventory; BPI, Brief Pain Inventory; CCI, Charlson Comorbidity Index; choice D, patients who had chosen but not yet started dialysis; D, dialysis (including all dialysis modalities); eGFR (mL/min/1.73 m^2); EQ-5D-3L, EuroQOL-5D-3L; HADS, Hospital Anxiety and Depression Scale (used version is indicated); IIRS, Illness Intrusiveness Rating Scale; KDQOL-SF, Kidney Disease Quality of Life–Short Form (79 items, including the SF-36 and eight kidney disease-specific domains); KDQOL-36 (36 items, including the SF-12 and three kidney disease-specific domains); MSAS-SF, Memorial Symptom Assessment Scale; *n*, overall sample size; NA, not applicable; NR, not reported; POS-S renal, Palliative Care Outcome Scale–Symptoms (Renal); STAI-Y, State Trait Anxiety Inventory; SWLS, Satisfaction with Life Scale.

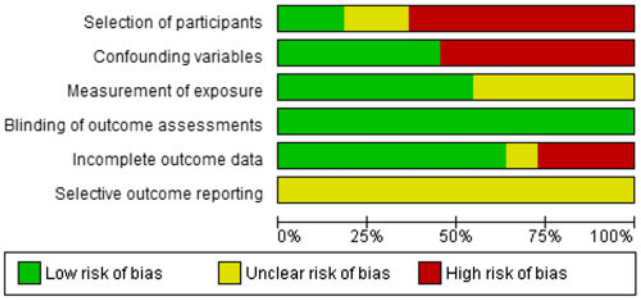

FIGURE 2: Overall risk of bias using the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS) [33]. Supplementary data, Table S3 shows the risk of bias assessment per study.

Mental health outcomes, including the mental component summary vitality, social function, role emotional and mental health domains, were similar between patients who chose CC or a dialysis pathway, including patients with an eGFR <10 mL/min/1.73 m^2, before and after dialysis start and per dialysis modality [35–42, 45]. When measured repeatedly over 12–36 months, mental health outcomes showed similar trajectories in both patient groups [35, 37, 38], including after dialysis start in patients who chose dialysis [37, 38].

Three studies examined kidney disease–specific HRQoL domains [38, 39, 42]. Patients who chose CC scored similar to [39] or better than patients on dialysis on effects of kidney disease on daily life [38, 42]. Furthermore, patients who chose CC scored better on burden of kidney disease compared with patients on dialysis [38, 39, 42]. In patients on a dialysis pathway, both domain scores decreased after dialysis start [38]. In another study, scores on life satisfaction also decreased after dialysis start [37]. Illness intrusiveness scores were similar between patients on CC or dialysis [41]. One study observed a small decline in general health status of the EuroQOL-5D after treatment decision in patients who chose CC, while patients who started dialysis scored similar after 6 months [44].

Symptoms

Table 4 shows the results of the nine studies comparing symptoms by overall symptom scores ($n = 7$) or domain scores on depressive symptoms ($n = 3$), anxiety ($n = 2$), cognitive function ($n = 2$), sleep ($n = 2$) and pain ($n = 1$) [35, 37–43, 45]. Patients who chose CC reported a higher overall symptom burden than patients who chose dialysis but had not yet started [35, 39] and patients on aPD [41], but were similar compared with patients on HD or unassisted PD [36, 39, 41–43]. When measured repeatedly over 12–24 months, two studies observed similar trajectories of symptom burden in patients on CC or a dialysis pathway [35, 38], including after dialysis start in patients who chose dialysis [38]. One small study found less improvement of symptoms after 6 months in patients on CC compared with patients started with dialysis [43]. Patients who chose CC reported more dyspnoea, drowsiness and poor mobility than patients on dialysis, but less pruritus, skin changes, halitosis, sexual problems, bloated abdomen and limb numbness [43, 45].

Two studies found more depressive symptoms in patients who chose CC compared with patients on HD [40, 41], while scores were stable over 36 months in both patient groups and did not change after dialysis start [37]. No differences between both patient groups were reported on anxiety [37, 40], cognitive function [38, 39], sleep [38, 39] and pain [45]. Patients who chose dialysis reported an improvement in cognitive function after dialysis start [38].

DISCUSSION

This systematic review summarizes patient-reported HRQoL outcomes and symptoms among patients who chose either CC or a dialysis pathway for ESKD. We identified 11 observational cohort studies that were generally small-scale and of suboptimal study quality, being susceptible to selection bias and confounding. Patients who chose CC were generally older and less fit than patients who chose dialysis. Despite considerable clinical and methodological heterogeneity, the results on HRQoL and symptoms were broadly consistent across the studies. Physical health outcomes and symptom burden appeared to be worse in patients who chose CC compared with patients who chose dialysis but had not yet started. Similar physical health outcomes and symptom burden were observed between patients who chose CC compared with patients on dialysis. Mental health outcomes were also similar between patients who chose CC or dialysis, including before and after dialysis start. In patients who chose dialysis, the burden of kidney disease and impact on daily life increased after dialysis start.

Most studies on CC and dialysis focused on survival and showed an overall survival benefit in older patients who chose a dialysis pathway compared with CC [13, 14]. However, this survival benefit was absent or limited in the oldest patients and patients with multiple comorbidities [13, 14]. Studies also found that older patients who chose CC had lower treatment burden and hospitalization rates, including at the end of life, than patients who chose dialysis, both before and after dialysis start [47–50]. For example, one study observed that older patients who chose CC spent 4% of the days survived at or in hospital compared with 48% for patients on HD [47]. The need for more patient-relevant data on CC and dialysis is increasingly recognized [8, 20, 23, 51]. Such data could help to evaluate treatment effectiveness and inform the shared decision-making process of patients and clinicians, which is recommended as a model to decide on preferred treatment for ESKD [8–10, 52–54]. The studies on HRQoL and symptoms, both major outcomes to patients and clinicians [15–19], extend the available patient-relevant data on both treatment pathways.

While heterogeneous, the results on HRQoL and symptoms were notably similar across the studies, which were mostly performed in patients >65 years old. The studies, therefore, provide provisional but valuable insight as to whether CC in older patients has the potential to achieve reasonable HRQoL outcomes and symptoms compared with a dialysis pathway. First, patients on both treatment pathways reported impaired physical health and a high symptom burden, stressing the need for improved supportive care in both pathways [8, 55–57]. Second, no distinct advantage on HRQoL outcomes and

Table 2. Patient characteristics of the dialysis and CC patient groups per included study

References	Number of patients		Mean age		Female (%)		Mean eGFR at baseline		High comorbidity		Impaired functional status or frailty	
	D	CC	D	CC	D	CC	D	CC	D	CC	D	CC
Brown *et al.* [35]	273 choice D	122	67	82	33	45	16	16	18% ≥3 comorbidities[c]	38% ≥3 comorbidities[c]	NR	NR
Yuen *et al.* [36]	79 mix D[a]	189	59	77	NR	NR	11	13	Mean mCCI 6.2	Mean mCCI 8.9	13% impaired mobility	53% impaired mobility
Da Silva-Gane *et al.* [37]	80 choice HD	30	61	78	24	30	13	14	35% high comorbidity[d]	74% high comorbidity[d]	18% KPS <70	66% KPS <70
	44 choice PD		48		50		14		14% high co-morbidity[d]		2% KPS <70	
Seow *et al.* [38]	38 choice D	63	71	78	47	44	10	10	Median CCI 5	Median CCI 5	Median KPS 60	Median KPS 60
Verberne *et al.* [39]	39 choice D	23	80	84	31	46	16	16	28% high comorbidity[e]	26% high comorbidity[e]	NR	NR
	34 on D		80		25		NA		32% high comorbidity[e]			
De Biase *et al.* [40]	5 on HD	6	79	82	NR	36	NA	8	Median number 2[f]	Median number 6[f]	Mean KPS 70	Mean KPS 84
Iyasere *et al.* [41]	28 on HD[b]	28[b]	82[b]	83[b]	57[b]	50[b]	NA	NR	Median Davies score 2[b]	Median Davies score 1[b]	Median frailty score 4[h]	Median frailty score 4[h]
	28 on aPD[b]		81[b]		50[b]				Median Davies score 2[b]		Median frailty score 5[h]	
Shah *et al.* [42]	83 on D	46	83	81	33	41	NA	NR	NR	NR	NR	NR
Tan *et al.* [43]	12 on D	8	73	84	25	50	NA	11	8% CCI >5	50% CCI >5	51% KPS <70	50% KPS <70
Van Loon *et al.* [44]	192 on D	89	82	75	31	44	8	12	41% high comorbidity[g]	44% high comorbidity[g]	77% frail[i]	88% frail[i]
Yong *et al.* [45]	134 on D	45	58	73	48	54	NA	NR	Mean mCCI 6.1	Mean mCCI 8.5	NR	NR

[a]27% were being treated with dialysis (dialysis modality unknown), the rest had not yet started dialysis.
[b]CC patients were propensity matched to HD and aPD patients by age, gender, ethnicity, diabetes status and index of deprivation.
[c]Comorbidities included ischaemic heart disease or cardiac failure, cerebrovascular or peripheral vascular disease, chronic liver or lung disease, diabetes and dementia.
[d]Comorbidity score included cardiac disease, peripheral vascular disease, central nervous disease and respiratory disease. Severity ranged from 0 (no disease) to 4 (advanced disease). Cancer was graded similarly, cirrhosis was scored as 4. Patients with summed scores >3 or a score of 3 derived from a single system were considered to have high comorbidity.
[e]The Davies comorbidity score was used, in which a score ≥3 is defined as high comorbidity.
[f]Comorbidities included dementia, diabetes mellitus, hypoacusia, heart failure, hypertension, ischaemic heart disease, osteoarthritis, stroke, arrhythmia, urinary incontinence, chronic obstructive lung disease, bedsores, neoplasms and hypothyroidism.
[g]The Cumulative Illness Rating Scale–Geriatrics was used, in which ≥2× score 3 or ≥1× score 4 was considered high comorbidity.
[h]Clinical Frailty Scale (higher scores represent increasing levels of frailty).
[i]Frailty was measured with a geriatric assessment. Impairments in ≥2 geriatric domains was considered as frail.
CCI (higher score represents higher comorbidity burden); mCCI, modified CCI (higher score represents higher comorbidity burden); choice D, patients who had chosen but not yet started dialysis; *D*, dialysis patient group; D, dialysis (modalities unspecified); eGFR (mL/min/1.73 m^2); KPS, Karnofsky performance scale (lower score represents worse functional status); mix D, mix of patients who had selected dialysis but not yet started dialysis and patients who were being treated with dialysis; on D, patients being treated with dialysis.

Table 3. Study results per outcome domain of HRQoL

Outcome	References	Effect estimate	Results dialysis patient group			Results CC		Statistical significance	Adjusted
SF-36, SF-12			Before start	After start	Combined	Combined eGFR> <10	eGFR < 10 mL/min/1.73 m2		
Physical component summary	Brown *et al.* [35]	Percent worse/stable/improved	55/4/41			63/16/21		P = 0.12	No
	Da Silva-Gane *et al.* [37]	Change per month (mean)			0.04	0.04		±0.17, 'non-significant'	Yes[a]
		Change after dialysis start (mean)		0.49				±1.7, P = 0.53	Yes[a]
	Seow *et al.* [38]	B coefficient per month	−0.29	−0.30		−0.10		P = 0.07	Yes[b]
		B coefficient after dialysis start		1.72				−0.57–4.01, P = 0.14	Yes[b]
	Verberne *et al.* [f] [39, 46]	Mean	38.3			30.9		P < 0.01	No
		B coefficient	6.61			Ref.		1.79–11.43, P < 0.01	Yes[c]
		Mean		34.2		30.9		P = 0.38	No
		B coefficient		2.2		Ref.		−2.79–7.20, P = 0.38	Yes[c]
	Iyasere *et al.* [41]	Median		29.2 (HD) 30.8 (aPD)			28.9	P = 0.62	No
		β-coefficient		1.08 (HD)			Ref.	0.89–1.29, P = 0.45	Yes[d]
		β-coefficient		1.20 (aPD)			Ref.	1.00–1.45, P = 0.05	Yes[d]
	Shah *et al.* [42]	Mean		31.2			34.3	'Non-significant'	No
		β-coefficient		−3.17			Ref.	−7.61–1.27, P = 0.16	Yes[e]
Mental component summary	Brown *et al.* [35]	Percent worse/stable/improved	45/2/53			42/5/53		P = 0.78	No
	Da Silva-Gane *et al.* [37]	Change per month (mean)			0.12	0.12		±0.32, P < 0.05	Yes[a]
		Change after dialysis start (mean)		−0.68				±5.84, P = 0.53	Yes[a]
	Seow *et al.* [38]	β-coefficient per month	0.01	−0.09		0.13		P = 0.89	Yes[b]
		β-coefficient after dialysis start		−0.26				−3.39–2.86, P = 0.87	Yes[b]
	Verberne *et al.* [f] [39, 46]	Mean	52.8			47.5		P = 0.17	No
		β-coefficient	6.45			Ref.		1.48–11.41, P = 0.01	Yes[c]
		Mean		50.5		47.5		P = 0.58	No
		β-coefficient		−0.58		Ref.		−5.80–4.64, P = 0.83	Yes[c]
	Iyasere *et al.* [41]	Median		49.9 (HD) 50.2 (aPD)			46.3	P = 0.68	No
		β-coefficient		1.03 (HD)			Ref.	0.87–1.22, P = 0.71	Yes[d]
		β-coefficient		1.07 (aPD)			Ref.	0.90–1.27, P = 0.44	Yes[d]
	Shah *et al.* [42]	Mean		47.7			46.6	'Non-significant'	No
		β-coefficient		−2.41			Ref.	−7.66–2.84, P = 0.37	Yes[e]
Physical function	Yuen *et al.* [36]	Mean			88.7	81.2		P < 0.001	No
	Verberne *et al.* [39]	Median	50			25		P < 0.001	No
		Median		30		25		P = 0.25	No
	De Biase *et al.* [40]	Mean		45		28		NR	No
	Yong *et al.* [45]	Mean		55.9		43.8		NR	No
Role physical	Yuen *et al.* [36]	Mean			81.8	75.5		P = 0.77	No
	Verberne *et al.* [39]	Median	50			25		P = 0.63	No
		Median		25		25		P = 0.83	No
	De Biase *et al.* [40]	Mean		15		25		NR	No
	Yong *et al.* [45]	Mean		42.5		53.3		NR	No
Body pain	Yuen *et al.* [36]	Mean			83.5	78.9		P = 0.12	No
	Verberne *et al.* [39]	Median	80			57.5		P = 0.10	No
		Median		73.8		57.5		P = 0.06	No

Continued

Table 3. Continued

Outcome	References	Effect estimate	Results dialysis patient group			Results CC		Statistical significance	Adjusted
SF-36, SF-12			Before start	After start	Combined	Combined eGFR> <10	eGFR < 10 mL/min/1.73 m2		
	De Biase *et al.* [40]	Mean		62		47		NR	No
	Yong *et al.* [45]	Mean		75.2		72.8		NR	No
General health	Yuen *et al.* [36]	Mean			53.9	50.3		P < 0.001	No
	Verberne *et al.* [39]	Median	50			35		P < 0.005	No
		Median		37.5		35		P = 0.57	No
	De Biase *et al.* [40]	Mean		46		41		NR	No
	Yong *et al.* [45]	Mean		38.2		42.4		NR	No
Vitality	Yuen *et al.* [36]	Mean			61.5	60.4		P = 0.94	No
	Verberne *et al.* [39]	Median	60			45		P < 0.005	No
		Median		57.5		45		P = 0.03	No
	De Biase *et al.* [40]	Mean		51		47		NR	No
	Yong *et al.* [45]	Mean		51.2		49		NR	No
Social function	Yuen *et al.* [36]	Mean			92.9	92.2		P = 0.49	No
	Verberne *et al.* [39]	Median	87.5			62.5		P = 0.01	No
		Median		62.5		62.5		P = 0.69	No
	De Biase *et al.* [40]	Mean		75		77		NR	No
	Yong *et al.* [45]	Mean		65.8		73.6		NR	No
Role emotional	Yuen *et al.* [36]	Mean			77.7	77.9		P = 0.37	No
	Verberne *et al.* [39]	Median	100			100		P = 0.81	No
		Median		100		100		P = 0.79	No
	De Biase *et al.* [40]	Mean		60		40		NR	No
	Yong *et al.* [45]	Mean		50.5		68.9		NR	No
Mental health	Yuen *et al.* [36]	Mean			74.5	75.7		P = 0.008	No
	Verberne *et al.* [39]	Median	84			76		P = 0.001	No
		Median		84		76		P = 0.03	No
	De Biase *et al.* [40]	Mean		67		67		NR	No
	Yong *et al.* [45]	Mean		67.1		73.5		NR	No
KDQOL-SF or KDQOL-36									
Effects of kidney disease on daily life	Seow *et al.* [38]	β-coefficient per month	−0.34	−0.25		0.3	81.3	P = 0.01	Yes[b]
		β-coefficient after dialysis start		−3.86			Ref.	−0.74 to −0.31, P = 0.03	Yes[b]
	Verberne *et al.* [39]	Median	92.9			82.7		P = 0.03	No
		Median		85.7		82.7		P = 0.35	No
	Shah *et al.* [42]	Mean		64.2				P < 0.001	No
		β-coefficient		−16.49				−25.98 to −6.99, P < 0.001	Yes[e]
Burden of kidney disease	Seow *et al.* [38]	β-coefficient per month	−0.58	−0.65		0.54	62.8	P < 0.001	Yes[b]
		β-coefficient after dialysis start		−25.11			Ref.	−32.2 to −18.1, P < 0.001	Yes[b]
	Verberne *et al.* [39]	Median	75			75		P = 0.70	No
		Median		43.8		75		P = 0.001	No
	Shah *et al.* [42]	Mean		34.7				P < 0.001	No
		β-coefficient		−28.59				−41.77 to −15.42, P < 0.001	Yes[e]

Other PROMs							
IIRS	Iyasere *et al.* [41]	Median	31.0 (HD)		30.5	P = 0.79	No
			32.0 (aPD)				
		β-coefficient	1.17 (HD)		Ref.	0.93–1.48, P = 0.19	Yes[d]
		β-coefficient	1.11 (aPD)		Ref.	0.86–1.42, P = 0.42	Yes[d]
SWLS	Da Silva-Gane *et al.* [37]	Change per month (mean)		0.02	0.02	±0.11, 'non-significant'	Yes[a]
		Change after dialysis start (mean)	−1.84			±4.50, P = 0.01	Yes[a]
EQ-5D index score	Van Loon *et al.* [44]	Change after 6 months (mean)	0.026		−0.047	P < 0.01	No
EQ-5D self-rated health score	Van Loon *et al.* [44]	Change after 6 months (mean) (scale 0–10)	0.3		−0.4	P < 0.01	No

[a]Mean changes were adjusted for age, sex, comorbidity score, Karnofsky performance score and propensity score [37].
[b,c]coefficients were adjusted for age, comorbidity score, Karnofsky performance score, primary renal disease and change in eGFR [38].
[c]β-coefficients were adjusted for sex and way of administration. Similar results when also adjusted for age and comorbidity score [39, 46].
[d]All analyses were performed in propensity-matched patients. β-coefficients were adjusted for age, sex, comorbidity score, frailty and dialysis vintage [41].
[e,f]coefficients were adjusted for age, sex, country, education and health insurance [42].
[f]Results on the PCS and MCS were included from a reanalysis in which the same scoring algorithm as in similar studies was used [39, 46].
eGFR (mL/min/1.73 m^2); EQ-5D (score of 1 is perfect health); IIRS (score range: 13–91, higher scores represent more illness intrusion); KDQOL-SF (79 items, including the SF-36 and eight kidney disease-specific domains; score range: 0–100, higher scores represent better quality of life); KDQOL-36 (36 items, including the SF-12 and three kidney disease–specific domains; score range: 0–100, higher scores represent better quality of life); PROMs, patient-reported outcome measures; Ref., reference group; SF-12 (score range: 0–100, higher scores represent better quality of life); SF-36 (score range: 0–100, higher scores represent better quality of life); SWLS (score range: 5–35, higher scores represent higher satisfaction with life).

symptoms of one treatment pathway over the other could be identified when comparing both treatment pathways, particularly between patients who chose CC and patients on dialysis. An exception is the higher burden of kidney disease reported by patients who chose dialysis, especially after dialysis start, compared with patients who chose CC. These findings on HRQoL and symptoms support current guideline recommendations that in selected older patients, CC might be a viable alternative to a dialysis pathway for ESKD [8–10].

Patients, their families and clinicians are likely to have specific reasons to choose or recommend CC or a dialysis pathway [15, 16, 18]. Therefore an important consideration of the observational data on HRQoL and symptoms is the risk of selection bias and confounding. Substantial differences in characteristics were observed between both patient groups, which may have resulted in a biased comparison of HRQoL outcomes and symptoms in the younger and likely more fit patients choosing dialysis compared with the older and less fit patients choosing CC. However, this makes the similarities in HRQoL outcomes and symptoms between both patient groups even more remarkable. Furthermore, younger and more well patients are in general more likely to complete HRQoL measures. We determined a high risk of incomplete outcome data in three studies [35, 36, 42], but it remains unclear whether more missing data were seen in older patients or other specific subgroups. Five studies adjusted for a set of confounders in multivariable analyses or by propensity matching to better compare the effect of both treatment pathways [37–39, 41, 42], but residual confounding by unmeasured and unknown determinants is likely. Data on health status and frailty as assessed in a comprehensive geriatric assessment are associated with outcomes and might enable more accurate comparisons [6, 58, 59]. Such data could also improve outcome prediction and help identify modifiable risk factors [58, 60].

The validity of the used outcome measures in our patient population of interest, comprising older patients and patients on the relatively new treatment pathway of CC, is less clear [61–64]. Most studies used the SF-36 or SF-12 to assess HRQoL outcomes, which are well-validated in many populations and diseases, including ESKD [20, 65, 66]. A recent validation study of the SF-36 in patients on CC, however, showed that the summary scores on physical and mental health (PCS and MCS) are more appropriate to use rather than the scores on individual subscales [61]. More validation studies are needed to specifically assess the validity and reliability of patient-reported outcome measures of HRQoL and symptoms in this growing older patient population.

Another methodological issue in the studies on HRQoL and symptoms is whether equivalent time points in CC and dialysis pathways were used for patient inclusion and outcome comparisons. Although all studies used eGFR thresholds, most studies compared outcomes in patients who chose CC with a mean eGFR >10 mL/min/1.73 m^2 to patients on dialysis, which is generally started at an eGFR <10 mL/min/1.73 m^2. Equivalent time points in both treatment pathways are necessary to avoid potential lead time bias in outcome comparisons [30]. While time of dialysis start and an equivalent in patients who chose CC enables evaluation of treatment itself, this time

Table 4. Results on symptoms per study

References	PROM	Outcome domain	Effect estimate	Results dialysis patient group			Results CC		Statistical significance	Adjusted for
				Before start	After start	Combined	Combined eGFR <10	eGFR $<10 <10$ mL/min/1.73 m^2		
Brown *et al.* [35]	MSAS-SF	Symptom score	Mean at baseline	9.1			12.2		$P<0.001$	Not adjusted
			Percent worse/stable/improved after 12 months	58/31/10			38/57/5		$P=0.12$	
Da Silva-Gane *et al.* [37]	HADS	Anxiety	Mean at baseline	5.5 (HD)			6.9		$P=0.04$	Age, sex, co-morbidity score, KPS score and propensity score (mean changes)
			Mean at baseline	4.7 (PD)			6.9		$P=0.02$	
			Change per month (mean)			−0.004	−0.004		±0.14, 'non-significant;	
			Change after dialysis start (mean)		−0.02				±2.6, $P=0.95$	
		Depressive symptoms	Mean at baseline	6.1 (HD)			5.2		'Non-significant'	
			Mean at baseline	6.4 (PD)			5.2		'Non-significant'	
			Change per month (mean)			−0.03	−0.03		±0.10, 'non-significant'	
			Change after dialysis start (mean)		−0.57				±1.7, $P=0.10$	
Seow *et al.* [38]	KDQOL-SF	Symptoms/problems	β-coefficient per month	−0.21	−0.17		0.002		$P=0.10$	Age, co-morbidity score, KPS score and primary renal disease, change in eGFR
			β-coefficient after dialysis start		2.63				−0.01–5.28, $P=0.05$	
		Cognitive function	β-coefficient per month	0.3	−0.22		−0.09		$P=0.001$	
			β-coefficient after dialysis start		7.58				3.50–11.65, $P<0.001$	
		Sleep	β-coefficient per month	−0.54	−0.15		0.14		$P=0.08$	
			β-coefficient after dialysis start		2.4				−2.06–6.86, $P=0.29$	
Verberne *et al.* [39]	KDQOL-SF	Symptoms/problems	Median	86.4			72.6		$P=0.03$	Not adjusted
			Median		83.3		72.6		$P=0.05$	
		Cognitive function	Median	86.7			73.3		$P=0.01$	
			Median		86.7		73.3		$P=0.09$	
		Sleep	Median	70			65		$P=0.19$	
			Median		66.3		65		$P=0.66$	
Shah *et al.*[42]	KDQOL-36	Symptoms/problems	Mean		70.7			76.6	'Non-significant'	Age, sex, country, education and health insurance (b coefficient)
			β-coefficient		−5.93			Ref.	−14.61–2.73, $P=0.18$	
De Biase *et al.* [40]	STAI-Y	Anxiety	Percent with anxiety		0		0		NR	Not adjusted
	BDI	Depressive symptoms	Percent with depressive symptoms		20		50			
Iyasere *et al.* [41]	POS-S renal	Symptom score	Median		22 (HD) 16 (aPD)			20	$P=0.10$	Age, sex, co-morbidity score, frailty score, dialysis vintage (β-coefficients)
			β-coefficient		0.90 (HD)			Ref.	0.66–1.21, $P=0.48$	
	HADS		β-coefficient		0.62 (aPD)			Ref.	0.43–0.90, $P=0.01$	
		Depressive symptoms	Median		5 (HD) 7.5 (aPD)			7	$P=0.03$	
			Percent score >7		25 (HD) 54 (aPD)			46	$P=0.07$	Propensity matched patients (all analyses)
			β-coefficient		0.70 (HD)			Ref.	0.52–0.92, $P=0.01$	
			β-coefficient		0.86 (aPD)			Ref.	0.86–1.12, $P=0.24$	

Tan *et al.* [43]	POS-S renal	Symptom score	Mean at baseline[a]	9	9	NR	Not adjusted
		Symptom score	Mean change >6 months	−7.6	−1.5	P = 0.002	
		Pain	Percent at baseline; percent at 6 months	33; 25	88; 25	P = 0.015; P = 0.10	
		Shortness breath	Percent at baseline; percent at 6 months	42; 8	63; 63	P = 0.39; P = 0.01	
		Weakness	Percent at baseline; percent at 6 months	83; 50	50; 50	P = 0.12; P = 0.99	
		Nausea	Percent at baseline; percent at 6 months	17; 0	0; 0	P = 0.25; n/a	
		Vomiting	Percent at baseline; percent at 6 months	17; 0	0; 0	P = 0.25; n/a	
		Poor appetite	Percent at baseline; percent at 6 months	50; 8	25; 25	P = 0.29; P = 0.33	
		Constipation	Percent at baseline; percent at 6 months	25; 17	50; 38	P = 0.27; P = 0.32	
		Mouth problems	Percent at baseline; percent at 6 months	0; 0	13; 25	P = 0.23; P = 0.07	
		Drowsiness	Percent at baseline; percent at 6 months	17; 0	25; 40	P = 0.67; P = 0.004	
		Poor mobility	Percent at baseline; percent at 6 months	25; 8	63; 63	P = 0.10; P = 0.01	
		Itching	percent at baseline; percent at 6 months	50; 8	38; 25	P = 0.61; P = 0.33	
		Difficulty sleeping	Percent at baseline; percent at 6 months	58; 17	50; 38	P = 0.73; P = 0.32	
		Restless legs	Percent at baseline; percent at 6 months	8; 8	25; 25	P = 0.33; P = 0.33	
		Feeling anxious	Percent at baseline; percent at 6 months	25; 8	50; 25	P = 0.27; P = 0.33	
		Feeling depressed	Percent at baseline; percent at 6 months	42; 0	13; 25	P = 0.18; P = 0.07	
		Skin changes	Percent at baseline; percent at 6 months	17; 17	0; 25	P = 0.25; P = 0.67	
		Diarrhea	Percent at baseline; percent at 6 months	0; 0	0; 0	n/a	
Yong *et al.* [45]	Symptom list	Overall	Mean number	9.3	8.2	P = 0.24	Not adjusted
		Fatigue	Percent; intensity (NRS scale)	75; 5.5	69; 5.9	P = 0.39; P = 0.90	
		Cold aversion	Percent; intensity (NRS scale)	69; 5.5	78; 5.1	P = 0.24; P = 0.12	
		Pruritus	Percent; intensity (NRS scale)	66; 5.6	58; 4.3	P = 0.34; P = 0.02	
		Difficulty sleeping	Percent; intensity (NRS scale)	62; 5.4	49; 5.8	P = 0.12; P = 0.11	
		Lower torso weakness	Percent; intensity (NRS scale)	60; 5.3	58; 5.7	P = 0.82; P = 0.10	
		Skin changes	Percent; intensity (NRS scale)	55; 5.1	29; 4.4	P = 0.003; P = 0.84	
		Halitosis	Percent; intensity (NRS scale)	34; 4.4	18; 4.5	P = 0.045; P = 0.27	
		Sexual problem	Percent; intensity (NRS scale)	34; 6.8	9; 3.3	P = 0.001; P = 0.04	
		Dyspnea	Percent; intensity (NRS scale)	30; 4.4	47; 5.1	P = 0.04; P = 0.60	
		Change in taste	Percent; intensity (NRS scale)	19; 5.1	16; 3.3	P = 0.57; P = 0.03	
		Bloated abdomen	Percent; intensity (NRS scale)	28; 4.9	22; 3.5	P = 0.48; P = 0.04	

Continued

Table 4. Continued

References	PROM	Outcome domain	Effect estimate	Results dialysis patient group			Results CC	Statistical significance	Adjusted for
				Before start	After start	Combined	Combined eGFR $<10 <$ 10 mL/min/1.73 m^2		
		Limb numbness	Percent; intensity (NRS scale)	50; 4.4		42; 3.8		P = 0.37; P = 0.04	
		Other						No significant differences in prevalence and intensity of dry mouth, cough, pain, loss of appetite, muscle cramp, dizziness, limb swelling, constipation, nausea, hearing impairment and restless legs	
	BPI	Pain intensity scores	Worst pain (mean)	5.2		4.8		P = 0.18	
			Least pain (mean)	3.1		3		P = 0.99	
			Average pain (mean)	4.1		4.2		P = 0.43	
			Pain now (mean)	2.7		3		P = 0.20	

[a]Results were estimated from the reported figure.

point ignores the period between treatment decision making and actual dialysis start. Since patients could change their decision during this period [67], using time of dialysis start brings potential selection bias. For clinical practice, using time of treatment decision is more informative, being more applicable to patients during decision making, although such data represent the results of a chosen treatment pathway rather than of treatment itself.

High-quality studies are needed to confirm, and extend, current findings on HRQoL and symptoms in patients who chose CC or a dialysis pathway, including at different eGFR levels and both before and after dialysis start. Theoretically, a randomized controlled trial including intention-to-treat analysis could offer the best study design to deal with the limitations of current outcome data on both treatment pathways. In practice, however, such trials pose difficult ethical questions and might be difficult to perform [68]. One randomized controlled trial is currently ongoing in the UK (https://doi.org/10.1186/ISRCTN17133653). Non-randomized studies should prospectively follow patients on both treatment pathways from an equivalent starting point with intention-to-treat analysis and reasonable adjustment for confounders. Standardization should be considered as a matter of importance to increase the efficacy of studies and patient input [69].

For HRQoL, both generic and kidney disease–specific domains provided relevant outcome data and should be further explored, including separate analyses per dialysis modality. For symptom burden, more insight is needed into whether specific symptoms are more prevalent or severe in CC or a dialysis pathway. For example, two studies observed more dyspnoea in patients on CC, which might be a consequence of not being treated with dialysis [43, 45]. Patients should ideally be followed until the end of life to assess outcomes during the entire trajectory [70]. Finally, researchers and clinicians should develop and test best practices of both CC and integrated supportive care in dialysis pathways to improve care quality in patients with ESKD [8, 55–57].

In clinical practice, CC should become more available and appropriately offered as one of the possible treatment pathways for ESKD in older patients [17, 71, 72]. A dynamic shared decision-making process by the patient, the patient's family and the healthcare team is needed. Such a process should involve ongoing discussion and evaluation of what matters to the patient in order to decide on a treatment pathway for ESKD that fits best with the patient [18].

The strengths of our systematic review are its comprehensive search using broad search terms in multiple databases and that PRISMA guidelines were followed. We also carefully assessed whether studies included the population of interest, particularly for CC-like patient groups, since many different terms were used. Our definition of CC was based on the consensus definition from KDIGO [8]. We focused on comparative studies in patients who had made a decision on treatment for ESKD. Outcomes in patients who postponed a decision and in patients with acute kidney injury need further research. A limitation might be our exclusion of non-English publications. No meta-analysis was performed due to the substantial clinical and methodological heterogeneity among the studies, providing too

limited homogeneous data on similar effect estimates with comparable adjustment for confounders.

Our systematic review demonstrated that in selected older patients, CC has the potential to achieve similar patient-reported HRQoL outcomes and symptoms compared with a dialysis pathway, although data were limited and of suboptimal quality. High-quality prospective studies are needed to confirm and extend the provisional findings on these patient-relevant outcomes. Considered together with evidence on survival and treatment burden [13, 14, 46–49], we conclude that CC could be a viable alternative to dialysis in selected older patients. CC should therefore be part of the shared decision-making process of older patients and clinicians on the preferred treatment for ESKD.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

ACKNOWLEDGEMENTS

We thank clinical librarian Carla Sloof for reviewing and piloting our search strategy.

FUNDING

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

AUTHORS' CONTRIBUTIONS

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

CONFLICT OF INTEREST STATEMENT

C.G.N.V. has received grant support from Nephrosearch Foundation and Dutch Kidney Foundation (A1D3P04) during the conduct of the study. A.C.A. has received grant support from ZonMW, Dutch Kidney Foundation, Baxter, Fresenius, Dirinco, Dutch Healthcare Insurance outside the submitted work. W.R.V. and W.J.W.B. have received grant support from Zilveren Kruis Insurance during the conduct of the study. The remaining authors declare that they have no potential conflicts of interest.

REFERENCES

1. Couser WG, Remuzzi G, Mendis S *et al.* The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. *Kidney Int* 2011; 80: 1258–1270
2. Xie Y, Bowe B, Mokdad AH *et al.* Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. *Kidney Int* 2018; 94: 567–581
3. Tam-Tham H, Quinn RR, Weaver RG *et al.* Survival among older adults with kidney failure is better in the first three years with chronic dialysis treatment than not. *Kidney Int* 2018; 94: 582–588
4. Kramer A, Pippias M, Noordzij M *et al.* The European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Registry annual report 2015: a summary. *Clin Kidney J* 2018; 11: 108–122
5. Saran R, Robinson B, Abbott KC *et al.* US Renal Data System 2018 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis* 2019; 73: A7–A8
6. Kallenberg MH, Kleinveld HA, Dekker FW *et al.* Functional and cognitive impairment, frailty, and adverse health outcomes in older patients reaching ESRD-A systematic review. *Clin J Am Soc Nephrol* 2016; 11: 1624–1639
7. Germain MJ, Davison SN, Moss AH. When enough is enough: the nephrologist's responsibility in ordering dialysis treatments. *Am J Kidney Dis* 2011; 58: 135–143
8. Davison SN, Levin A, Moss AH *et al.* Executive summary of the KDIGO Controversies Conference on Supportive Care in Chronic Kidney Disease: developing a roadmap to improving quality care. *Kidney Int* 2015; 88: 447–459
9. Farrington K, Covic A, Aucella F *et al.* Clinical practice guideline on management of older patients with chronic kidney disease stage 3b or higher (eGFR <45 mL/min/1.73 m^2). *Nephrol Dial Transplant* 2016; 31(Suppl 2): ii1–ii66
10. Williams AW, Dwyer AC, Eddy AA *et al.* Critical and honest conversations: the evidence behind the "Choosing Wisely" campaign recommendations by the American Society of Nephrology. *Clin J Am Soc Nephrol* 2012; 7: 1664–1672
11. Villain C, Fouque D. Choosing end-stage kidney disease treatment with elderly patients: are data available? *Nephrol Dial Transplant* 2019; 34: 1432–1435
12. Couchoud C, Hemmelgarn B, Kotanko P *et al.* Supportive care: time to change our prognostic tools and their use in CKD. *Clin J Am Soc Nephrol* 2016; 11: 1892–1901
13. Foote C, Kotwal S, Gallagher M *et al.* Survival outcomes of supportive care versus dialysis therapies for elderly patients with end-stage kidney disease: a systematic review and meta-analysis. *Nephrology (Carlton)* 2016; 21: 241–253
14. Verberne WR, Geers AB, Jellema WT *et al.* Comparative survival among older adults with advanced kidney disease managed conservatively versus with dialysis. *Clin J Am Soc Nephrol* 2016; 11: 633–640
15. Hussain JA, Flemming K, Murtagh FE *et al.* Patient and health care professional decision-making to commence and withdraw from renal dialysis: a systematic review of qualitative research. *Clin J Am Soc Nephrol* 2015; 10: 1201–1215
16. Morton RL, Tong A, Howard K *et al.* The views of patients and carers in treatment decision making for chronic kidney disease: systematic review and thematic synthesis of qualitative studies. *BMJ* 2010; 340: c112
17. Tonkin-Crine S, Okamoto I, Leydon GM *et al.* Understanding by older patients of dialysis and conservative management for chronic kidney failure. *Am J Kidney Dis* 2015; 65: 443–450
18. Verberne WR, Konijn WS, Prantl K *et al.* Older patients' experiences with a shared decision-making process on choosing dialysis or conservative care for advanced chronic kidney disease: a survey study. *BMC Nephrol* 2019; 20: 264
19. Ramer SJ, McCall NN, Robinson-Cohen C *et al.* Health outcome priorities of older adults with advanced CKD and concordance with their nephrology providers' perceptions. *J Am Soc Nephrol* 2018; 29: 2870–2878
20. Verberne WR, Das-Gupta Z, Allegretti AS *et al.* Development of an international standard set of value-based outcome measures for patients with chronic kidney disease: a report of the International Consortium for Health Outcomes Measurement (ICHOM) CKD Working Group. *Am J Kidney Dis* 2019; 73: 372–384
21. Evangelidis N, Tong A, Manns B *et al.* Developing a set of core outcomes for trials in hemodialysis: an international Delphi survey. *Am J Kidney Dis* 2017; 70: 464–475

22. Manera KE, Tong A, Craig JC *et al.* An international Delphi survey helped develop consensus-based core outcome domains for trials in peritoneal dialysis. *Kidney Int* 2019; 96: 699–710
23. Harris DCH, Davies SJ, Finkelstein FO *et al.* Increasing access to integrated ESKD care as part of universal health coverage. *Kidney Int* 2019; 95(4 Suppl): S1–S33
24. O'Connor NR, Kumar P. Conservative management of end-stage renal disease without dialysis: a systematic review. *J Palliat Med* 2012; 15: 228–235
25. Tsai HB, Chao CT, Chang RE *et al.* Conservative management and health-related quality of life in end-stage renal disease: a systematic review. *Clin Invest Med* 2017; 40: E127–E134
26. Ren Q, Shi Q, Ma T *et al.* Quality of life, symptoms, and sleep quality of elderly with end-stage renal disease receiving conservative management: a systematic review. *Health Qual Life Outcomes* 2019; 17: 78
27. Eckert K, Motemaden L, Alves M. Effect of hemodialysis compared with conservative management on quality of life in older adults with end-stage renal disease: systematic review. *J Hosp Palliat Nurs* 2018; 20: 279–285
28. Pacilio M, Minutolo R, Garofalo C *et al.* Stage 5-CKD under nephrology care: to dialyze or not to dialyze, that is the question. *J Nephrol* 2016; 29: 153–161
29. Vega-Alava KM, Luz VA. A comparison between dialysis versus conservative management as modes of treatment in the management of elderly patients with end stage renal disease: a systematic review. *Philipp J Intern Med* 2016; 54: 1–6
30. Hole B, Tonkin-Crine S, Caskey FJ *et al.* Treatment of end-stage kidney failure without renal replacement therapy. *Semin Dial* 2016; 29: 491–506
31. Moher D, Liberati A, Tetzlaff J *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6: e1000097
32. Verberne W, van den Wittenboer I, Bos W. *Patient-relevant Outcomes of Dialysis Treatment Versus Conservative Care in Older Patients with Advanced Chronic Kidney Disease: A Systematic Review*. PROSPERO 2018 CRD42018103379.https://www.crd.york.ac.uk/prospero/display_record.php? ID=CRD42018103379 (last accessed 1 February 2020)
33. Kim SY, Park JE, Lee YJ *et al.* Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol* 2013; 66: 408–414
34. Harrison JK, Reid J, Quinn TJ *et al.* Using quality assessment tools to critically appraise ageing research: a guide for clinicians. *Age Ageing* 2017; 46: 359–365
35. Brown MA, Collett GK, Josland EA *et al.* CKD in elderly patients managed without dialysis: survival, symptoms, and quality of life. *Clin J Am Soc Nephrol* 2015; 10: 260–268
36. Yuen SK, Suen HP, Kwok OL *et al.* Advance care planning for 600 Chinese patients with end-stage renal disease. *Hong Kong J Nephrol* 2016; 19: 19–27
37. Da Silva-Gane M, Wellsted D, Greenshields H *et al.* Quality of life and survival in patients with advanced kidney failure managed conservatively or by dialysis. *Clin J Am Soc Nephrol* 2012; 7: 2002–2009
38. Seow YY, Cheung YB, Qu LM *et al.* Trajectory of quality of life for poor prognosis stage 5D chronic kidney disease with and without dialysis. *Am J Nephrol* 2013; 37: 231–238
39. Verberne WR, Dijkers J, Kelder JC *et al.* Value-based evaluation of dialysis versus conservative care in older patients with advanced chronic kidney disease: a cohort study. *BMC Nephrol* 2018; 19: 205
40. De Biase V, Tobaldini O, Boaretti C *et al.* Prolonged conservative treatment for frail elderly patients with end-stage renal disease: the Verona experience. *Nephrol Dial Transplant* 2007; 23: 1313–1317
41. Iyasere O, Brown EA, Johansson L *et al.* Quality of life with conservative care compared with assisted peritoneal dialysis and haemodialysis. *Clin Kidney J* 2019; 12: 262–268
42. Shah KK, Murtagh FEM, McGeechan K *et al.* Health-related quality of life and well-being in people over 75 years of age with end-stage kidney disease managed with dialysis or comprehensive conservative care: a cross-sectional study in the UK and Australia. *BMJ Open* 2019; 9: e027776
43. Tan T, Brennan F, Brown M. Impact of dialysis on symptom burden and functional state in the elderly. *Renal Soc Australasia J* 2017; 13: 22–30
44. van Loon IN, Goto NA, Boereboom FTJ *et al.* Quality of life after the initiation of dialysis or maximal conservative management in elderly patients: a longitudinal analysis of the Geriatric assessment in OLder patients starting Dialysis (GOLD) study. *BMC Nephrol* 2019; 20: 108
45. Yong DS, Kwok AO, Wong DM *et al.* Symptom burden and quality of life in end-stage renal disease: a study of 179 patients on dialysis and palliative care. *Palliat Med* 2009; 23: 111–119
46. Verberne WR, Dijkers J, Kelder JC *et al.* Reanalysis of the physical and mental health summary scores of dialysis versus conservative care in older patients with advanced chronic kidney disease: a critical appraisal. *BMC Res Notes* 2019; 12: 722
47. Carson RC, Juszczak M, Davenport A *et al.* Is maximum conservative management an equivalent treatment option to dialysis for elderly patients with significant comorbid disease? *Clin J Am Soc Nephrol* 2009; 4: 1611–1619
48. Hussain JA, Mooney A, Russon L. Comparison of survival analysis and palliative care involvement in patients aged over 70 years choosing conservative management or renal replacement therapy in advanced chronic kidney disease. *Palliat Med* 2013; 27: 829–839
49. Teo BW, Ma V, Xu H *et al.* Profile of hospitalisation and death in the first year after diagnosis of end-stage renal disease in a multi-ethnic Asian population. *Ann Acad Med Singapore* 2010; 39: 79–87
50. Wong SPY, Yu MK, Green PK *et al.* End-of-life care for patients with advanced kidney disease in the US veterans affairs health care system, 2000–2011. *Am J Kidney Dis* 2018; 72: 42–49
51. Grubbs V, Tuot DS, Powe NR *et al.* System-level barriers and facilitators for foregoing or withdrawing dialysis: a qualitative study of nephrologists in the United States and England. *Am J Kidney Dis* 2017; 70: 602–610
52. Renal Physicians Association. *Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis (Clinical Practice Guideline)*. 2nd ed. Rockville, MD: Renal Physicians Association, 2010
53. Koncicki HM, Schell JO. Communication skills and decision making for elderly patients with advanced kidney disease: a guide for nephrologists. *Am J Kidney Dis* 2016; 67: 688–695
54. Rosansky SJ, Schell J, Shega J *et al.* Treatment decisions for older adults with advanced chronic kidney disease. *BMC Nephrol* 2017; 18: 200
55. Davison SN, Tupala B, Wasylynuk BA *et al.* Recommendations for the care of patients receiving conservative kidney management: focus on management of CKD and symptoms. *Clin J Am Soc Nephrol* 2019; 14: 626–634
56. Harrison TG, Tam-Tham H, Hemmelgarn BR *et al.* Identification and prioritization of quality indicators for conservative kidney management. *Am J Kidney Dis* 2019; 73: 174–183
57. Wong SPY, McFarland LV, Liu CF *et al.* Care practices for patients with advanced kidney disease who forgo maintenance dialysis. *JAMA Intern Med* 2019; 179: 305–313
58. van Loon IN, Wouters TR, Boereboom FT *et al.* The relevance of geriatric impairments in patients starting dialysis: a systematic review. *Clin J Am Soc Nephrol* 2016; 11: 1245–1259
59. van Loon IN, Goto NA, Boereboom FTJ *et al.* Geriatric assessment and the relation with mortality and hospitalizations in older patients starting dialysis. *Nephron* 2019; 143: 108–119
60. van Loon IN, Goto NA, Boereboom FTJ *et al.* Frailty screening tools for elderly patients incident to dialysis. *Clin J Am Soc Nephrol* 2017; 12: 1480–1488
61. Erez G, Selman L, Murtagh FE. Measuring health-related quality of life in patients with conservatively managed stage 5 chronic kidney disease: limitations of the Medical Outcomes Study Short Form 36: SF-36. *Qual Life Res* 2016; 25: 2799–2809
62. Mishra GD, Gale CR, Sayer AA *et al.* How useful are the SF-36 sub-scales in older people? Mokken scaling of data from the HALCyon programme. *Qual Life Res* 2011; 20: 1005–1010
63. Yang F, Griva K, Lau T *et al.* Health-related quality of life of Asian patients with end-stage renal disease (ESRD) in Singapore. *Qual Life Res* 2015; 24: 2163–2171
64. Laudański K, Nowak Z, Niemczyk S. Age-related differences in the quality of life in end-stage renal disease in patients enrolled in hemodialysis or continuous peritoneal dialysis. *Med Sci Monit* 2013; 19: 378–385
65. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30: 473–483

66. Gibbons E, Fitzpatrick R. *A Structured Review of Patient-Reported Outcome Measures for People with Chronic Kidney Disease*. Oxford: Department of Public Health, University of Oxford, 2009
67. Moranne O, Fafin C, Roche S *et al.* Treatment plans and outcomes in elderly patients reaching advanced chronic kidney disease. *Nephrol Dial Transplant* 2018; 33: 2182–2191
68. Korevaar JC, Feith GW, Dekker FW *et al.* Effect of starting with hemodialysis compared with peritoneal dialysis in patients new on dialysis treatment: a randomized controlled trial. *Kidney Int* 2003; 64: 2222–2228
69. Perkins GD, Jacobs IG, Nadkarni VM *et al.* Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. *Circulation* 2015; 132: 1286–1300
70. Murtagh FE, Addington-Hall J, Edmonds P *et al.* Symptoms in the month before death for stage 5 chronic kidney disease patients managed without dialysis. *J Pain Symptom Manage* 2010; 40: 342–352
71. Ladin K, Pandya R, Perrone RD *et al.* Characterizing approaches to dialysis decision making with older adults: a qualitative study of nephrologists. *Clin J Am Soc Nephrol* 2018; 13: 1188–1196
72. Ladin K, Pandya R, Kannam A *et al.* Discussing conservative management with older patients with CKD: an interview study of nephrologists. *Am J Kidney Dis* 2018; 71: 627–635

Received: 24.12.2019; Editorial decision: 18.3.2020

Nephrol Dial Transplant (2021) 36: 1433–1439
doi: 10.1093/ndt/gfaa071
Advance Access publication 8 June 2020

Acute kidney injury demographics and outcomes: changes following introduction of electronic acute kidney injury alerts—an analysis of a national dataset

Jennifer Holmes[1], Kieron Donovan[1], John Geen[2], John Williams[3] and Aled O. Phillips[3]

[1]Welsh Renal Clinical Network, Cwm Taf Morgannwg University Health Board, Pontypridd, UK, [2]Department of Clinical Biochemistry, Cwm Taf Morgannwg University Health Board, Merthyr Tydfil, UK and Faculty of Life Sciences and Education, University of South Wales, Pontypridd, UK and [3]Institute of Nephrology, Cardiff University School of Medicine, Cardiff, UK

Correspondence to: Aled O. Phillips; E-mail: phillipsao@cf.ac.uk

ABSTRACT

Background. Electronic alerts for acute kidney injury (AKI) have been widely advocated. Our aim was to describe the changes in AKI demographics and outcomes following implementation of a national electronic AKI alert programme.

Methods. A prospective national cohort study was undertaken to collect data on all cases of AKI in adult patients (≥18 years of age) between 1 April 2015 and 31 March 2019.

Results. Over the period of data collection, there were 193 838 AKI episodes in a total of 132 599 patients. The lowest incidence of AKI was seen in the first year after implementation of electronic alerts. A 30-day mortality was highest in Year 1 and significantly lower in all subsequent years. A direct comparison of mortality in Years 1 and 4 demonstrated a significantly increased relative risk (RR) of death in Year 1: RR = 1.08 [95% confidence interval (CI) 1.054–1.114 $P < 0.001$]. This translates into a number needed to treat in Year 4 for one additional patient to survive of 69.5 (95% CI 51.7–106.2) when directly comparing the outcomes across the 2 years. The increase in the number of cases and improved outcomes was more pronounced in community-acquired AKI, and was associated with a significant increase in patient hospitalization.

Conclusions. This study represents the first large-scale dataset to clearly demonstrate that a national AKI alerting system which highlights AKI is associated with a change in both AKI demographics and patient outcomes.

Keywords: AKI, epidemiology, outcomes, prognosis, survival analysis

INTRODUCTION

Acute kidney injury (AKI) is a common complication of multiple medical and surgical conditions, which carries significant morbidity and mortality and high health-associated costs [1]. The premise, that early and appropriate clinical intervention can improve the outcome for AKI [2], has driven the implementation of automated AKI electronic alerts (e-alerts) across the National Health Service (NHS) in England and Wales. Implementation of AKI e-alerts across Wales was established in