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SYSTEMATIC REVIEW

Humanistic burden and economic impact of chronic kidney disease: a systematic literature review [version 1; peer review: 1 approved, 2 not approved]

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Abstract

Background: Chronic kidney disease (CKD) is increasing in prevalence worldwide. Progression of CKD to end-stage renal disease (ESRD) can result in the requirement for renal replacement therapy, which incurs considerable healthcare costs and imposes restrictions on patients' daily living. This systematic review was conducted to inform understanding of the humanistic and economic burden of CKD by collecting quality of life (QoL), symptom burden, and cost and resource use data, with a focus on the impact of disease progression.

Methods: Embase, MEDLINE, the Cochrane Library, and conference proceedings were searched in May 2017 according to predefined inclusion criteria. Data were extracted for full publications reporting either QoL or symptom burden (published 2007–2017; reporting data from ≥ 100 patients) or costs and resource use (published 2012–2017). Relevant QoL studies were those that used the 6-dimension or 8-, 12-, or 36-item Short-Form Health Surveys, 5-dimension EuroQol questionnaire, Healthy Days/Health-Related Quality of Life questionnaire, or Kidney Disease Quality of Life Questionnaire.

Results: Data were extracted from 95 studies reporting QoL data, 47 studies reporting cost and resource use data, and eight studies reporting descriptions of symptoms; 12 studies (seven QoL; five costs/resource use) reported data for patients with and without CKD, and 15 studies (seven QoL; eight costs/resource use) reported data by disease stage. Patients with CKD, including those with ESRD, had worse QoL than those with normal kidney function, and incurred higher healthcare costs. Disease progression was associated with cost increases, particularly for later stages and in patients receiving dialysis. Increasing CKD severity was also associated with reductions in QoL, although not all studies identified showed a consistent decrease with increasing disease stage.

Conclusions: The presence of CKD and CKD progression are

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Any reports and responses or comments on the article can be found at the end of the article.

associated with reductions in patients' QoL and increased economic impact. This may be mitigated by interventions that slow progression.

Keywords

chronic kidney disease, end-stage renal disease, quality of life, healthcare costs, disease severity, systematic review, humanistic burden, economic burden

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Introduction

Chronic kidney disease (CKD) is characterized by a gradual loss of kidney function over time. With an estimated global prevalence of 11–13%, CKD is a common condition that is associated with a significant economic burden across the world¹. The prevalence of the disease is rising, owing in part to an increase in the median age of populations worldwide, and the growing number of individuals with diabetes mellitus (DM) or hypertension¹. These conditions are the two main causes of CKD and are commonly present in patients with diminished renal function². In the USA, for example, approximately 40% of people with CKD also have DM, and 32% of people with CKD have hypertension³.

When CKD progresses, patients may experience complications such as anaemia, cardiovascular disease (CVD), peripheral arterial disease, pruritus, and increased risk of infection. Both disease progression and its associated complications require medical treatment, which further impacts patients' quality of life (QoL) and contributes to the humanistic and economic burden of CKD^{4,5}. Moreover, progression to end-stage renal disease (ESRD) has a significant effect on patients' daily lives and is often associated with considerable costs due to the common requirement for renal replacement therapy (RRT) via dialysis or kidney transplantation¹. Therefore, slowing the rate of progression of CKD to advanced stages, in particular to ESRD, is an important medical objective⁴.

Many studies have investigated the humanistic and economic burden of CKD, although quantification of this remains challenging owing to differences between methodologies and patient populations across studies. To gain a better understanding of the current evidence, and evidence gaps, we conducted systematic reviews (SRs) to identify relevant evidence on the humanistic burden of CKD, defined here as the effect of CKD on patients' QoL, and the economic burden, comprising resource use and healthcare costs associated with CKD. In particular, we reviewed data on QoL and costs for patients with CKD compared with the general population, and across disease stages.

Methods

Systematic literature review

Two systematic searches, one on humanistic burden/QoL and one on economic burden, were performed in MEDLINE and MEDLINE In-Process, Embase, and the Cochrane Library via Ovid. Cut-off dates were January 2002 and May 2017 for the humanistic burden SR and January 2007 and May 2017 for the economic burden SR; the shorter review window for the economic burden SR was specified because economic data are considered to decrease in relevance more quickly than QoL data. As supplementary searches, congress abstracts published between 2015 and 2017 (or the most recent 2 years available) from relevant health economics and outcomes research and nephrology meetings were reviewed. The search strings used to identify evidence are listed in *Extended data: Supplementary content 1*⁶.

Citation screening and full text review

Abstracts and titles identified were screened by an independent reviewer to determine whether they met the PICOS (patient,

interventions, comparisons, outcomes, and study design) eligibility criteria ([Table 1](#)), in accordance with 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁷. All publications that met entry criteria for review were obtained as full articles and reassessed against the predefined inclusion criteria. Owing to the large number of citations meeting these criteria, a decision was taken to restrict the extraction of data from eligible studies. For both SRs, data were extracted only from full publications. This meant that, although congress abstract screening was performed, no data from congress abstracts were extracted. For the humanistic burden SR, study publication dates for data extraction were restricted to 2007–2017; for the economic burden SR, the relevant time period was restricted to 2012–2017. Furthermore, for the humanistic burden SR, data were not extracted if the study population included fewer than 100 patients with CKD or if the study did not use any of the following instruments:

- 36-item Short-Form Health Survey (SF-36)
- 12-item Short-Form Health Survey (SF-12)
- 8-item Short-Form Health Survey (SF-8)
- 6-dimension Short-Form Health Survey (SF-6D)
- 5-dimension EuroQol questionnaire (EQ-5D)
- Healthy Days/Health-Related Quality of Life (HRQoL) questionnaire
- Kidney Disease Quality of Life Questionnaire (KDQoL).

Data extraction

For each publication, information was extracted into a data extraction table. Studies were listed according to inclusion of QoL, symptom burden or cost, and resource use data. For each study, patients' CKD stage, RRT status [pre-dialysis, dialysis (including dialysis modality) or renal transplant], age, and comorbidities including CVD and the presence of DM were recorded. No risk of bias assessment between or within studies was performed.

Focus of this review

These SRs were conducted to collect information on the overall impact of CKD development and progression on patients' QoL or their healthcare costs. Therefore, we chose to focus this review on studies that compared QoL or costs for patients with CKD and individuals without CKD, or that compared by CKD severity, defined by either disease stage or estimated glomerular filtration rate (eGFR) category. Other studies identified in the SRs are grouped into key themes and listed separately to indicate the scope of the evidence identified in our searches.

Results

Search results

In total, 5219 papers were identified in the initial searches, of which 1114 papers were removed as duplicates, and 4105 were included for screening by abstract and title. This screening identified 3539 papers that did not meet the inclusion criteria. In total, 444 papers were included for full paper review. Following full paper review, 284 references were identified for inclusion,

Table 1. Eligibility criteria for identification of studies reporting the humanistic and economic burden of chronic kidney disease.

Population	Patients with CKD <ul style="list-style-type: none"> Adults (≥ 18 years old) Stages 2, 3 (3a and 3b), 4, and 5 (dialysis and non-dialysis) and ESRD eGFR < 75 mL/min/1.73 m²
Interventions	Any or no intervention
Outcomes	Humanistic burden SR <ul style="list-style-type: none"> Clinical features/symptoms (as described by clinician) QoL as measured by generic or condition-specific questionnaires Symptom burden, QoL, and health status as reported by patient, clinician, or carer HSUVs as measured using direct or indirect methods Mapping algorithms (to allow HSUVs to be estimated from generic or condition-specific measures) Economic burden SR <ul style="list-style-type: none"> Direct costs (including any intervention costs) Cost drivers Resource utilization Total costs
Study design	Humanistic burden SR <ul style="list-style-type: none"> Observational or interventional studies <ul style="list-style-type: none"> To refine scope, the patient burden SR identified only publications that reported QoL, PRO, and symptom burden outcomes within a study setting or by assessment using a survey (search terms for both observational and interventional studies were implemented) Economic burden SR <ul style="list-style-type: none"> Should include clear objective to assess costs or resource use
Date restrictions	Humanistic burden SR <ul style="list-style-type: none"> January 2002 to May 2017 Economic burden SR <ul style="list-style-type: none"> January 2007 to May 2017
Language restrictions	<ul style="list-style-type: none"> English only (foreign publications with an English abstract were considered for inclusion)
Country	<ul style="list-style-type: none"> Australia, Canada, China, Denmark, France, Germany, Italy, Japan, Mexico, Netherlands, Norway, Spain, Sweden, UK, USA

CKD, chronic kidney disease. eGFR, estimated glomerular filtration rate. ESRD, end-stage renal disease. HSUV, health state utility value. PRO, patient-reported outcome. QoL, quality of life. SR, systematic review.

plus 79 abstracts identified in supplementary searches. In total, data were extracted from 95 references reporting QoL data, 47 references reporting cost and resource use data, and eight references reporting descriptions of symptoms. A PRISMA flow diagram is shown in [Figure 1](#). Details of the patient populations in the studies discussed in this review are given in [Table 2](#). [Figure 2](#) shows all studies identified in these SRs, grouped into key themes according to the data reported.

QoL in patients with CKD compared with the general population

Several studies compared the QoL of patients with CKD with that of individuals in the general population. These studies reported overall measures associated with QoL, as well as physical component summary (PCS), mental component summary (MCS), and individual domain scores from the SF-36.

Across the studies identified, patients with CKD experienced lower physical and mental QoL compared with the general population. A study by Davison *et al.* that measured QoL using the SF-6D found that a mixed population of patients with CKD who were either pre-dialysis (CKD stage 3–4, anticipated to require dialysis within 12 months; 34%) or dialysis-dependent (66%) reported lower QoL than an age-matched subset of the general population (SF-6D score: 0.67 vs 0.79)⁸. A study by Nguyen *et al.* found that patients with pre-dialysis CKD (stages 3–5), the majority (69.1%) of whom had CKD stage 3a, spent, on average, a greater number of days over a 30-day period inactive owing to poor physical and mental health (3.1 vs 1.5 days; $P < 0.001$) and a greater number of days with poor physical health (5.1 vs 3.0 days; $P < 0.01$) compared with a sample of the US general population⁹. However, a study conducted by Agarwal *et al.* in the USA, which measured only sleep quality, found no difference between

Figure 1. PRISMA flow diagram, showing the flow of studies identified through the systematic review process. ^aThe congresses included in this search were the International Society for Pharmacoeconomics and Outcomes Research US and European congresses, the European Renal Association–European Dialysis and Transplant Association congress, the World Congress of Nephrology, the American Society of Nephrology Kidney Week, and the National Kidney Foundation Spring Clinical Meeting. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. QoL, quality of life. SR, systematic review.

patients with pre-dialysis CKD or dialysis-dependent ESRD and a matched population without CKD¹⁰.

Compared with the general population, patients receiving dialysis experienced lower QoL. In total, four studies reported SF-12/SF-36 scores in patients receiving dialysis compared with the general population^{11–14}. Studies by Wan *et al.* and Wang *et al.* reported a statistically significant reduction in SF-12 and SF-36 PCS scores (9.9% and 37.6%, reductions, respectively; both $P < 0.001$; Figure 3)^{12,13}. Boini *et al.* also reported a reduction in SF-12 PCS scores in patients undergoing dialysis compared with the general population of the USA and France (21.0% and 21.5%, respectively; Figure 3); however, no statistical analysis was

reported¹¹. Boini *et al.*¹¹ and Wang *et al.*¹³ reported a decrease in SF-12 (USA: 14.2%; France: 9.1%; $P = \text{NR}$) and SF-36 (23.0%; $P < 0.001$) MCS scores, respectively, in patients who were dialysis-dependent compared with the general population, whereas Wan *et al.*¹² reported a statistically significant increase in SF-12 MCS scores (9.8%; $P < 0.001$) in patients receiving dialysis compared with the general population of Hong Kong (Figure 3).

The studies by Wan *et al.*, Wang *et al.*, and Yong *et al.* reported individual SF-12 and SF-36 domain scores for patients undergoing dialysis compared with the general population^{12–14}. Wan *et al.* found that patients receiving dialysis reported significantly higher scores for the mental health domain (7.0%;

Table 2. Summary of studies that reported quality of life or costs and resource use by presence of CKD or disease severity.

Study characteristics		Lowest severity (or reference category)		Highest severity	Data
Quality of life in patients with CKD compared with the general population					
Agarwal 2011 USA	Instrument: KDQoL Dialysis: NR DM: CKD: 59% ESRD: 40%	No CKD	vs	Patients with CKD or ESRD	KDQoL sleep quality
Boini 2011 France	Instrument: KDQoL Dialysis: NR DM: NR	General population (France) General population (USA)	vs	ESRD	SF-12 PCS SF-12 MCS
Davison 2009 Canada	Instrument: SF-6D Dialysis: 34% DM: 43%	General population (community-dwelling subjects)	vs	CKD stage 4–5	SF-6D
Nguyen 2017 USA	Instrument: HRQoL-4 Dialysis: NR DM: 32%	No CKD	vs	CKD stage 3a–5	HRQoL-4
Wan 2015 China	Instrument: SF-12 Dialysis: 100% DM: NR	General population (Hong Kong)	vs	ESRD	SF-12 PCS SF-12 MCS All SF-12 domains
Wang 2016 China	Instrument: SF-36 Dialysis: 100% DM: NR	National average	vs	ESRD	SF-36 PCS SF-36 MCS All SF-36 domains
Yong 2009 China	Instrument: SF-36 Dialysis: dialysis group: 100% palliative care group: none DM: 42%	General population (Hong Kong)	vs	ESRD (dialysis) ESRD (palliative care)	All SF-36 domains

Study characteristics		Lowest severity (or reference category)					Highest severity	Data
Quality of life in patients with increasing severity of CKD								
Campbell 2013 USA	Instrument: SF-8 Dialysis: excluded DM: 100% (type NR)	eGFR ≥ 90 mL/min/1.73 m ²	75–89	60–74	45–59	30–44	eGFR ≤29 mL/min/1.73 m ²	SF-8 PCS
								SF-8 MCS
Eriksson 2016 (A) France, Germany, Italy, Spain, UK	Instrument: EQ-5D, SF-12 Dialysis: 35% DM: 100% (type 2)	CKD stage 3			CKD stage 4		Dialysis	EQ-5D
								SF-12 PCS
								SF-12 MCS
McClellan 2010 USA	Instrument: SF-12 Dialysis: NR DM: 21% (type NR)	eGFR > 90 mL/min/1.73 m ²	60–89		45–59	30–44	eGFR 15–29 mL/min/1.73 m ²	SF-12 PCS
								SF-12 MCS
Porter 2012 USA	Instrument: SF-36 Dialysis: NR DM: 9% (type NR)	eGFR > 60 mL/min/1.73 m ²	50–60		40–50	30–40	eGFR < 30 mL/min/1.73 m ²	SF-36 PCS
								SF-36 MCS
Rajian 2013 USA	Instrument: SF-36/SF-12 Dialysis: 3% ^a DM: 100% (type NR)	CKD stage 0/1	2	3a	3b	4	ESRD/dialysis	SF-36/12 PCS
								SF-36/12 MCS
Rounellotti 2010 USA	Instrument: SF-36 Dialysis: CKD group: 0% ESRD group: 100% DM: 35%	CKD			vs		ESRD	SF-36 PCS
								SF-36 MCS
								SF-36 domains
Wolfgram 2017 USA	Instrument: EQ-5D Dialysis: NR DM: excluded	eGFR ≥ 60 mL/min/1.73 m ²	> 44–< 60				eGFR ≤ 44 mL/min/1.73 m ²	EQ-5D

Study characteristics		Lowest severity (or reference category)		Highest severity	Data
Costs and resource use in patients with CKD compared with the general population					
Kim 2016 USA	Dialysis: pre-dialysis or dialysis DM: normal kidney function: 19% pre-dialysis CKD: 33% ESRD: 54% Other: hip fracture	Normal kidney function	CKD, pre-dialysis	ESRD (dialysis or renal transplant)	Hospitalizations; LoS; hospital cost
Kumar 2012 USA	Dialysis: pre-dialysis or dialysis DM: normal kidney function: 18% pre-dialysis CKD: 34% ESRD: 38% Other: pulmonary embolism	Normal kidney function	CKD, pre-dialysis	ESRD (dialysis)	Hospitalizations; LoS
Puenpatom 2017 USA	Dialysis: NR DM: no CKD: 23% CKD/ESRD: 62% Other: hepatitis C	No CKD	vs	CKD or ESRD	Total healthcare costs
Qian 2017 USA	Dialysis: 0% DM: no CKD: 25% CKD: 29% Other: bone metastases	No CKD	vs	CKD stage 3–5	Total and constituent healthcare costs; hospitalizations; ED visits; outpatient visits; LoS
Wyld 2015 Australia	Dialysis: pre-dialysis DM: no CKD: 7% CKD stage 1–2: 31% CKD stage 3–5: 15%	No CKD	vs	CKD stage 1–2, 3, or 4–5	Direct healthcare costs
Costs and resource use in patients with increasing severity of CKD					
Wyld 2015 Australia	Dialysis: pre-dialysis DM: no CKD: 7% CKD stage 1–2: 31% CKD stage 3–5: 15%	No CKD	CKD stage 1–2	CKD stage 3 4–5	Direct healthcare costs
Turchetti 2016 Italy	Dialysis: pre-dialysis DM: 35%	CKD stage 4	vs	CKD stage 5	Direct medical costs

Study characteristics		Lowest severity (or reference category)	Highest severity			Data	
Costs and resource use in patients with increasing severity of CKD							
Smith 2016 USA	Dialysis: NR DM: 37%	CKD stage 3a with comorbidities	CKD stage 3b			CKD stage 4–5	Total insurance claims costs
McQueen 2017 USA	Dialysis: included DM: 100% (type NR)	CKD stage 1	CKD stage 2	CKD stage 3a	CKD stage 3b	CKD stage 4 ^b	Annual costs
Vupputuri 2014 USA	Dialysis: pre-dialysis at baseline DM: 100% (T2)	CKD stage 0–2, no disease progression	CKD stage 0–2, any disease progression	CKD stage 3, no disease progression	CKD stage 3, any disease progression	CKD stage 4, no disease progression	Total medical costs (baseline and incremental follow-up)
Arjara 2013 Australia	Dialysis: included DM: CKD stage 1–2: 21% CKD stage 3: 31% CKD stage 4–5: 53% Other: percutaneous coronary intervention	CKD stage 1–2	CKD stage 3			CKD stage 4–5	Total direct cardiovascular costs
Eriksson 2016 (B) Sweden	Dialysis: pre-dialysis, dialysis, and renal transplant DM: > 30% except the transplanted group	CKD stage 4–5, pre-dialysis	vs			ESRD (HD, PD, or renal transplant)	Total and constituent costs; hospitalizations; outpatient visits; LoS
Escuredo-Villaplana 2013 Spain	Dialysis: pre-dialysis and PD DM: NR Other: anaemia	CKD stage 2–5, pre-dialysis	vs			PD	Monthly cost of ESAs

CKD, chronic kidney disease. DM, diabetes mellitus. eGFR, estimated glomerular filtration rate. EQ-5D, 5-dimension EuroQol questionnaire. ESA, erythropoietin-stimulating agent. ESRD, end-stage renal disease. HD, haemodialysis. HRQoL-4, 4-item Healthy Days/Health-Related Quality of Life questionnaire. KDQoL, Kidney Disease Quality of Life questionnaire. LoS, length of stay. MCS, mental component summary. NR, not reported. PCS, physical component summary. PD, peritoneal dialysis. SF-6D, 6-dimension Short-Form Health Survey. SF-8/12/36, 8-/12-/36-item Short-Form Health Survey. ^aTaken as those reported as in the ESRD/dialysis category. ^b14.4% of patients at CKD stage 4 in this study were receiving dialysis. ^c70.3% of patients at CKD stage 5 in this study were receiving dialysis.

Figure 2. Summary of evidence identified in these systematic reviews, showing the number of studies identified, grouped according to the key data presented. ^aSome studies fell into more than one category. CKD, chronic kidney disease. HRQoL, health-related quality of life.

$P = 0.006$) but lower scores in the physical functioning (20.3%; $P < 0.001$), role-limiting (physical; 9.8%; $P = 0.004$), bodily pain (10.0%; $P = 0.004$), and general health (20.0%; $P < 0.001$) domains than those without CKD (Figure 3)¹². In studies by Wang *et al.* and Yong *et al.*, a statistically significant reduction in scores across all domains of the SF-36 ($P < 0.001$ and $P < 0.05$, respectively) was reported in patients receiving dialysis compared with the general population (Figure 3)^{13,14}. Yong *et al.* also reported lower SF-36 domain scores in patients with ESRD undergoing palliative care compared with the general population. A statistically significant difference was found only in the physical functioning ($P < 0.001$), role-limiting (physical; $P = 0.027$), social functioning ($P < 0.001$), and vitality ($P = 0.036$) domains (Figure 3)¹⁴.

QoL by severity of CKD

Several studies reporting QoL data stratified by CKD stage were identified, in addition to studies that examined the impact of demographic factors and comorbidities on the relationship between disease severity and QoL.

Overall, later stages of CKD were associated with worse QoL, but the trends for physical QoL were slightly different from those for mental QoL. In a study by Roumelioti *et al.*, patients receiving maintenance dialysis had a near-significant decrease (17.7%; $P = 0.05$) in the SF-36 physical functioning domain score compared with patients with advanced CKD (eGFR < 30 mL/min/1.73 m²)¹⁵. Similarly, in two US studies by McClellan *et al.* and Porter *et al.*, decreasing eGFR was

Figure 3. Scores across all domains of the Short-Form Health Survey in patients with end-stage renal disease or those undergoing dialysis compared with the general population, which provides a graphical representation of the distribution of scores across individual domains of the Short-Form Health Survey for different patient populations¹¹⁻¹⁴. ^aMH, $P < 0.01$ versus GP; RL-P and BP, $P < 0.005$ versus GP; PCS, MCS, PF, and GHP, $P < 0.001$ versus GP. ^bFor all domains, $P < 0.001$ versus average. ^cPatients with ESRD versus GP (age- and sex-adjusted): BP, $P < 0.05$ versus GP; MH, $P < 0.005$ versus GP; PF, RL-P, GHP, V, SF, RL-M, $P < 0.001$ versus GP. Patients on palliative care versus GP (age- and sex-adjusted): RL-P and V, $P < 0.05$ versus GP; PF and SF, $P < 0.001$ versus GP. ^dNo statistical analysis reported. ^eFor the general population of the USA, MCS and PCS scores were both reported as 50. BP, bodily pain, CKD, chronic kidney disease. ESRD, end-stage renal disease. GP, general population. HD, haemodialysis. MH, mental health. PF, physical functioning. RL-M, role-limiting (mental). RL-P, role-limiting (physical). SF, social functioning. SF-12/36, 12-/36-item Short-Form Health Survey. V, vitality.

associated with lower SF-12 ($P = 0.001$) and SF-36 ($P = 0.004$) PCS scores, but there was no apparent relationship between eGFR and MCS scores (data shown in *Extended data: Supplementary content 2*¹⁶⁻¹⁸). McClellan *et al.* reported results from an unadjusted analysis as well as from an analysis adjusted for sociodemographic status and comorbidities; a correlation between eGFR and SF-12 PCS score was identified in both analyses ($P < 0.001$)¹⁶. Porter *et al.* reported results from an unadjusted analysis only¹⁷.

In several studies, the presence of comorbidities affected whether worsening CKD severity was linked to reductions in QoL. Porter *et al.* found that patients with a greater number of comorbidities experienced overall worse physical and mental QoL, assessed by SF-36 scores, than those with fewer comorbidities (mean PCS/MCS score: no comorbidities, 43.0/47.9; one comorbidity, 39.3/45.8; two or three comorbidities, 36.8/44.4; four or more comorbidities, 31.2/36.0; $P < 0.001$ for PCS and MCS)¹⁷. Furthermore, studies conducted by Campbell *et al.* and

Wolfgram *et al.* in the USA found that adjustment for comorbidities and sociodemographic factors affected the relationship between QoL scores and eGFR^{19,20}. Campbell *et al.* found that in an unadjusted analysis, patients with an eGFR of less than 60 mL/min/1.73 m² reported a statistically significant reduction in SF-8 PCS scores ($P < 0.05$) compared with patients with an eGFR greater than 90 mL/min/1.72 m² (reference group), whereas those with an eGFR of 60–89 mL/min/1.72 m² reported higher SF-8 PCS scores ($P < 0.05$) than the reference group [mean PCS score by eGFR (mL/min/1.72 m²): ≥ 90 , 44.04; 75–89, 44.97; 60–74, 45.00; 45–59, 42.32; 30–44, 40.41; ≤ 29 , 40.02]¹⁹. However, following full adjustment for demographic factors and comorbidities, there were no significant differences between patients in any eGFR category and the reference group (*Extended data: Supplementary content 2*)¹⁸. Interestingly, there was a statistically significant difference in SF-8 MCS scores between patients who had the most severe disease (eGFR less than 29 mL/min/1.73 m²) and patients with the least severe disease in both unadjusted and adjusted analyses (fully adjusted analysis

data shown in (*Extended data: Supplementary content 2*)^{18,19}. Similarly, a study by Wolfram *et al.*, also in the USA, found that decreasing eGFR was associated with significantly lower EQ-5D scores in both the unadjusted analysis [mean EQ-5D score by eGFR (mL/min/1.72 m²): ≥ 60 , 0.85; > 44 to < 60 , 0.85; ≥ 44 , 0.82] and an analysis adjusted for sociodemographic factors [mean EQ-5D score by eGFR (mL/min/1.72 m²): ≥ 60 , 0.84; > 44 to < 60 , 0.84; ≥ 44 , 0.82]²⁰. However, in an analysis adjusted for sociodemographics and comorbidities, including CVD, no relationship between eGFR and QoL was found [mean EQ-5D score by eGFR (mL/min/1.72 m²): ≥ 60 , 0.73; > 44 to < 60 , 0.75; ≥ 44 , 0.73]²⁰.

Studies by Rajan *et al.* and Eriksson *et al.* assessed the impact of increasing disease severity in patient populations with specific comorbidities^{21,22}. Rajan *et al.* reported QoL scores for patients with DM that was either prevalent (longer than 3 years) or recent-onset (less than 3 years)²². In both patient populations, scores for the physical functioning and role-limiting (physical) domains of the SF-36 were lower with increasing CKD stage; however, scores for the mental health domain increased up to stage 3, but were lower for stage 4 and lower still for stage 5 (*Extended data: Supplementary content 2*)^{18,22}. The authors acknowledged that many of the patients with CKD stage 0/1 had claims for International Classification of Diseases (Ninth Revision) codes relating to mental illness, which may account for the lower scores in the mental health domain in this subgroup²². Eriksson *et al.* reported QoL in patients with pre-dialysis CKD (stage 3–4) or receiving dialysis, with or without anaemia²¹. Lower SF-12 and EQ-5D scores were reported by patients with CKD stage 4 than those with CKD stage 3, and the lowest scores were reported by patients receiving dialysis; however, no statistical analysis of the difference between stages was reported. This trend was present both in patients with anaemia and in those without anaemia (*Figure 4*)²¹.

Other QoL studies and symptom burden studies

Studies were identified that reported QoL data associated with treatment modality and setting^{8,12,23–41}; comorbidities in CKD^{17,20–22,41–60}; mental health^{61,62}; sleep quality^{10,59,63–65}; patient support, care, and disease management^{11,66–83}; sociodemographic factors^{84,85}; and other factors predictive of CKD development^{15,86–103}. These studies are listed in *Extended data: Supplementary content 3*¹⁰⁴. A total of eight studies were identified on symptom burden in patients with CKD, of which two studies^{105,106} discussed the symptoms experienced by patients with CKD stage 5 who were not receiving dialysis, and six studies^{24,34,67,107–109} discussed symptom burden in patients receiving dialysis (*Extended data: Supplementary content 3*)¹⁰⁴.

Costs for CKD or ESRD, compared with normal kidney function

The SR identified several studies that compared costs and resource use between individuals with CKD and those with normal kidney function. Some of the studies differentiated between patients with pre-dialysis CKD and those who required RRT, and the patients in several of the studies had additional comorbidities.

Figure 4. Quality of life with increasing disease severity in patients with and without anaemia: (a) SF-12 PCS scores; (b) SF-12 MCS scores; (c) EQ-5D scores, showing the change in quality of life as CKD stage increases²¹. No statistical analysis of the between-stage difference was reported. EQ-5D, 5-dimension EuroQol questionnaire. MCS, mental component summary. PCS, physical component summary. SF-12, 12-item Short-Form Health Survey.

Across all studies, pre-dialysis CKD and ESRD requiring RRT were associated with significant increases in cost and resource use. Kim *et al.* found that patients with pre-dialysis CKD were significantly more likely to experience hip fracture-related hospitalization than patients with normal kidney function, and those receiving RRT were at higher risk than patients with pre-dialysis CKD. Median hospital costs were significantly greater in patients with CKD than for the general population and were highest for patients requiring RRT. This trend was also observed in the length of hospital stay, although the absolute differences between groups were small (*Figure 5*)¹¹⁰. Kumar *et al.* found

Figure 5. Hospitalizations in patients with normal kidney function, chronic kidney disease, or end-stage renal disease, showing the number of hospitalizations per 1000 individuals in patient with different severity of disease^{110,111}. ^aP < 0.001 for each pairwise comparison. ^bIncluded patients receiving dialysis or renal transplant. ^cIncluded patients receiving dialysis. ^dP < 0.05 versus normal kidney function. CKD, chronic kidney disease. ESRD, end-stage renal disease. IQR, interquartile range. LoS, length of stay. USD, US dollars.

very similar results in a study examining hospitalization rates and length of stay for pulmonary embolism in patient populations with normal kidney function, with pre-dialysis CKD or receiving dialysis (Figure 5)¹¹². In a study of patients with hepatitis C, total healthcare costs were 2.9 times higher for those who had CKD, compared with those who had hepatitis C without CKD (USD 548 vs USD 1922; P < 0.001)¹¹². Some patients with CKD in this study were defined as having ESRD; however, patients' dialysis or transplant status was not specified. In a fourth study, patients with bone metastases and impaired kidney function incurred 60% higher total healthcare costs than a control group of patients with bone metastases and normal kidney function (USD 142,267 vs USD 88,839; P < 0.001). These increased costs were driven by hospital admission, emergency department and outpatient visits, longer length of stay in hospital, and higher pharmacy costs¹¹³. An Australian study by Wyld *et al.* also showed that patients with any stage of pre-dialysis CKD incurred significantly higher costs than individuals with no CKD (Figure 6a)¹¹⁴.

Costs by severity of CKD

In total, six studies reported costs for patient populations stratified by CKD stage. Across the evidence base, later-stage disease was associated with comparatively higher costs, both in studies including only patients with pre-dialysis CKD and in those in which some patients were receiving RRT.

Wyld *et al.* showed that costs increased significantly across pre-dialysis CKD stages (Figure 6a)¹¹⁴. Patients with CKD stage 3 incurred approximately 28% higher direct annual healthcare costs than those with CKD stage 1–2; however, there was a

much larger cost increase for CKD stage 4–5, with patients in this group incurring more than fourfold higher costs than patients with CKD stage 3. This cost increase was apparent in subgroups of patients both with and without DM, suggesting that the high costs associated with CKD stage 4 and 5 were not attributable solely to the presence of DM. However, only 18 patients in this study had CKD stage 4–5, meaning that the results may have been skewed by a small number of individuals who incurred exceptionally high healthcare expenditure.

Two studies examined the costs of CKD across stages 4–5 or 3–5. An Italian study by Turchetti *et al.* of patients with pre-dialysis CKD showed a 31% increase in the direct annual medical costs associated with CKD stage 5, compared with CKD stage 4 (P < 0.01; Figure 6b)¹¹⁵. DM and CVD were shown to have an impact on costs incurred by patients at either CKD stage. Smith *et al.*, who conducted a study in the USA, found that patients with CKD stage 3a who had comorbidities and patients with CKD stage 3b incurred similar monthly costs associated with health insurance claims (Figure 6c)¹¹⁶. Those with CKD stage 4–5, however, incurred more than double these costs (P < 0.05). Patients' dialysis status was not specified in the study publication, but a breakdown of costs was reported. Later-stage CKD was associated with higher inpatient, outpatient, and professional services costs than CKD stage 3a or 3b, whereas the highest prescription costs were incurred by patients with CKD stage 3b.

Several studies examining costs by CKD stage included patients who had progressed to RRT and therefore incurred additional costs^{117,118}. Two studies were conducted in patient populations

Figure 6. Total costs for patients with chronic kidney disease (pre-dialysis or dialysis status not specified), by disease stage, showing the total cost of healthcare for patients with different severity of disease from three studies in Australia, Italy, and the USA^{114–116}. ^aOne-way ANOVA. ^bDialysis status not specified. ^cHypertension, DM, history of CHF, hyperkalaemia, or proteinuria. ANOVA, analysis of variance. AUD, Australian dollars. CHF, congestive heart failure. CKD, chronic kidney disease. DM, diabetes mellitus. EUR, euros. USD, US dollars.

with CKD and DM in the USA. McQueen *et al.* found an increase in annual costs for each successive CKD stage, with the exception of CKD stage 2, which was associated with slightly lower costs than CKD stage 1. As in other studies, the largest increase was between the later disease stages, with a 71% increase in costs for stage 5 compared with stage 4 (Figure 7a)¹¹⁷. A similar cost increase was reported by Vupputuri *et al.* who compared costs between patients whose disease progressed and those who remained stable. Individuals who progressed to RRT incurred 77% higher annual medical costs than patients who remained at CKD stage 4 (Figure 7b)¹¹⁸. In a third study, Ariyaratne *et al.* examined the impact of CKD stage on patients undergoing

percutaneous coronary intervention (PCI) in Australia. Direct cardiovascular costs, assessed 1 year after PCI, did not increase significantly for CKD stage 3 from stage 1–2 (AUD 4851 vs AUD 4442; 9% increase; $P = 0.052$), whereas patients with CKD stage 4–5, some of whom were receiving dialysis, incurred significantly higher costs than those at stage 1–2 (AUD 6958; 57% increase; $P < 0.001$)¹¹⁹.

Costs for pre-dialysis CKD compared with RRT

Two studies were identified that compared costs for patients with pre-dialysis CKD with those for patients receiving dialysis (Extended data: Supplementary content 4)^{120–122}.

Figure 7. Total costs for patients with diabetes mellitus and chronic kidney disease by disease stage, including patients receiving dialysis, providing a graphical representation of annual costs across disease stage in two US studies^{117,118}. ^a14.4% of patients at CKD stage 4 had a procedure code for dialysis during the baseline period. ^b70.3% of patients at CKD stage 5 had a procedure code for dialysis during the baseline period. ^cESRD was defined as a requirement for dialysis or renal transplant, and was considered to be equivalent to CKD stage 5 in this study. CKD, chronic kidney disease. ESRD, end-stage renal disease. NS, nonsignificant. T2DM, type 2 diabetes mellitus. USD, US dollars.

Eriksson *et al.* compared costs and resource use in Sweden between four treatment groups: patients with pre-dialysis CKD (stage 4–5), those receiving haemodialysis, those receiving peritoneal dialysis, and patients with renal transplant. Patients with pre-dialysis CKD incurred the lowest total costs and had the lowest rate of outpatient visits of any treatment group, but had a slightly higher hospitalization rate and a greater mean number of hospital days annually than those who had received a renal transplant¹²¹. Both types of dialysis incurred higher inpatient and outpatient costs than pre-dialysis CKD or renal transplant, with more than 70% of the costs associated with haemodialysis contributed by

outpatient care. All types of RRT were associated with additional expenditure on drugs, compared with pre-dialysis CKD. In addition, a study by Escudero-Vilaplana *et al.* showed that among patients receiving erythropoietin-stimulating agents (ESAs), the monthly cost of ESA therapy was significantly higher for patients receiving peritoneal dialysis than for those with pre-dialysis CKD (stage 2–5)¹²².

Other cost and resource use studies

The other studies identified in the economic burden SR did not compare patients with CKD with the general population or

report data by disease severity. Data from these studies are not reported in this manuscript; however, the studies are listed in *Extended data*: Supplementary content 3¹⁰⁴ to illustrate key trends and groupings in the economic evidence base for CKD. The studies that we identified reported data on the costs associated with different treatment modalities or settings^{26,121,123–127}; on the cost of comorbidities in CKD, including DM, cardiovascular complications, and anaemia^{112–115,117–119,122,128–141}; on hospitalization costs and rates for patients with CKD^{62,66,142–148}; and on other costs in CKD^{149–155}.

Discussion

The studies identified in these SRs clearly illustrate the humanistic and economic impact of CKD. Patients with pre-dialysis CKD as well as patients who require RRT are likely to have worse QoL than the general population, and also incur higher healthcare costs. Several studies indicated that increasing CKD severity is associated with a gradual reduction in physical QoL; however, evidence for the impact of CKD on mental QoL was inconsistent. The economic burden SR identified strong evidence that costs and resource use are higher for patients with CKD than for the general population. Costs are especially high for patients at the most severe stage of CKD, for whom dialysis is often required. In patients with pre-dialysis CKD, costs increase incrementally with disease severity, particularly when comparing CKD stages 4–5 with stages 2–3. These findings underline the importance of early intervention in CKD to prevent patients from progressing to late-stage CKD and dialysis.

Several studies identified in these SRs report data concerning the impact of comorbidities on QoL or costs. It is likely that some of the humanistic and economic burden associated with CKD, particularly later-stage disease, is linked to comorbidities. Patients with CKD may be more likely to have comorbidities than the general population; furthermore, CKD is itself a risk factor for several complications and comorbidities, which contribute to the effect that the disease has on long-term outcomes. By examining subgroups of patients with particular comorbidities, as in the study by Wyld *et al.*, it is possible to gain an understanding of the relative contribution of various comorbidities to overall disease burden. However, in order to study the burden of CKD specifically, analyses should be adjusted only for comorbidities that are unrelated to or are risk factors for CKD, but not comorbidities that are usually consequences of CKD. Exact differentiation between these types of comorbidities is not always possible, which can confound attempts to determine the true burden of CKD as distinct from co-existing conditions.

In this review, the impact of disease severity has been inferred almost exclusively from cross-sectional data; only one longitudinal study was identified. The economic study by Vupputuri *et al.* examined the impact and long-term consequences of increasing CKD severity in a patient cohort over time by comparing patients who remained at the same CKD stage and those whose disease progressed; however, the remaining economic studies and all QoL studies were cross-sectional. A longitudinal cohort study of patients with early-stage CKD could provide additional insights into the within-patient effects of CKD progression, the development

of comorbidities and complications, and the competing risk of death, helping to quantify the extent to which this results in over-representation of relatively young patients or patients with few comorbidities in the later CKD stages, due to their better overall survival.

Moreover, definitions of CKD stage and grouping of patients into categories were not consistent across the evidence base, and in some cases eGFR category was used as a measure for disease severity but did not correspond exactly to the CKD stages used in other studies. Patients' dialysis status differed between studies, as did the definition of ESRD, which was defined as the requirement for dialysis only in some studies and was expanded to include renal transplant in others. Similarly, CKD stage 5 was considered a pre-dialysis disease stage in some studies, but in others was analogous to RRT. For QoL, the use of different instruments across studies also contributed to the difficulty in drawing comparisons between different data sets. Therefore, it was not possible to strengthen our findings by performing a meta-analysis using the data identified.

These SRs identified a broad range of studies reporting QoL or cost and resource use data for patients with CKD, including the impact of treatment modality and the effect of comorbidities. In the majority of studies, however, the scope of the data reported was relatively limited or comparisons were made between two groups of patients with CKD, differentiated by other factors, such as sociodemographic characteristics or treatment; these studies were outside the scope of this review. Owing to the design of the SRs, in which restrictions were applied to publication type, population size, and QoL instrument, it is also possible that some studies of interest may not have been examined in detail. Furthermore, no assessment of risk of bias was performed.

Conclusions

Our findings indicate that the development and progression of CKD are associated with both a reduction in patients' QoL and an increase in healthcare costs. Interventions and initiatives to prevent CKD progression, especially to later stages of disease and the requirement for dialysis, could improve patients' well-being and may limit the growing economic burden of CKD. We have also identified the need for further research, particularly longitudinal studies, as well as studies that collect full information on patients' disease history, treatment status, and comorbidities, and adjust for these factors when necessary. Such studies will be vital to quantify the impact of slowing CKD progression on the disease's humanistic and economic burden.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Figshare: Freeman *et al.* Supplementary content 1 – Table S1. <https://doi.org/10.6084/m9.figshare.10011476>.

This project contains Table S1: Electronic search strategy.

Figshare: Freeman *et al.* Supplementary content 2 – Figure S1. <https://doi.org/10.6084/m9.figshare.10011683>¹⁸.

This project contains Figure S1: Physical and mental component summary scores with increasing severity of chronic kidney disease.

Figshare: Freeman *et al.* Supplementary content 3 – Table S2. <http://doi.org/10.6084/m9.figshare.10011692>¹⁰⁴.

This project contains Table S2: Additional quality of life, symptom burden and cost and resource use studies identified in the systematic review.

Figshare: Freeman *et al.* Supplementary content 4 – Table S3. <https://doi.org/10.6084/m9.figshare.10011710>¹²⁰.

This project contains Table S3: Summary of studies that compared costs for patients with chronic kidney disease by renal replacement therapy status.

Figshare: Freeman *et al.* Supplementary content 5 – Protocol. <https://doi.org/10.6084/m9.figshare.11112578>¹⁵⁶.

This project contains the protocol for this systematic review.

Reporting guidelines

Figshare: PRISMA checklist for ‘Humanistic burden and economic impact of chronic kidney disease: a systematic literature review’. <http://doi.org/10.6084/m9.figshare.10011893>¹⁵⁷.

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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Freeman *et al.* started an ambitious project by reporting meta-analyses on both the quality of life (QoL) and the cost of treatment of patients with chronic kidney disease (CKD)

The overall conclusion confirms existing knowledge that progressing CKD is associated with a reduction in QoL and increasing costs.

I have several concerns:

1. To describe and analyse the QoL over all stages of kidney disease is a major undertaking. So is meta-analyzing the costs. The authors do not clearly describe why they decided to perform two meta-analyses and report it in one manuscript. In their manuscript, the authors in essence describe two meta-analyses. In clinical practice, and in governing healthcare, it is important to know the effects of a disease and its treatment on both QoL and costs. I miss a clear rationale for why both topics are presented combined in this manuscript. The manuscript reads like a manuscript on QoL and a second on costs. The authors do not make a clear connection between the two.
I would invite the authors to better connect the two topics or consider writing two separate manuscripts, one focusing on QoL and one focusing on costs.
2. The cut off date used for both analyses was May 2017. Both QoL of kidney patients and costs of kidney care are topics of major interest in recent years. Many studies have been published since. For a manuscript to be published in 2020, an update of the search is essential
3. The literature was screened by a single independent reviewer. Reviewing by two reviewers is the accepted norm in meta-analyses.
4. The authors do not provide a table stating the risks of bias in the studies analyzed (Prisma checklist item 12)

5. In table 2 the authors provide an overview of the literature reported in both meta-analyses. In the first column the text is rotated 90 degrees, making this column illegible (on my laptop). In the current lay-out I can not read which studies are reviewed!
6. It is difficult to summarize studies with different ways of staging CKD, using different measurement tools. The authors mainly describe the results of individual studies, both in the figures and in the text of the manuscript. Prisma guidelines suggest providing a summary and a synthesis of results (Prisma items 13,14). Not all studies selected use the standard KDIGO staging of CKD and not all use the same measures of QoL and costs. I would suggest a synthesis of results from those studies that do use the standard KDIGO classification of CKD and do use the same measures of QoL and costs.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Partly

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Nephrology, outcomes of care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 09 July 2020

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Boris Bikbov

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The manuscript by Freeman *et al.* presents the results of a systematic review on changes in quality

of life (QoL) and the economic burden of chronic kidney disease (CKD). The authors performed a search in several databases, collected valuable information and made important conclusions. However, there are several issues that should be improved or further detailed, as explained below:

1. In the "Introduction" the authors refer to a meta-analysis on CKD prevalence suggesting 11-13% of population having the disease. A more recent study on global CKD prevalence is available that estimates the CKD prevalence as substantially lower 9.1% ([https://doi.org/10.1016/S0140-6736\(20\)30045-3](https://doi.org/10.1016/S0140-6736(20)30045-3)).
2. It is unclear why the authors limited their systematic search by May 2017.
3. The search strategy (described in detail in the supplement at https://figshare.com/articles/Freeman_et_al_Supplementary_content_1_Table_S1/10011476) has a potential pitfall of low sensitivity because it applies exclusion of bibliographic records based on the presence of the word "acute" in a title or an abstract. However, in the abstract of data sources describing the QoL or economy of CKD the word "acute" could occur just to identify that acute kidney diseases were not considered in a given data source. The exact influence of this feature applied by the authors is not known, but it should be discussed in the "Limitations" as a potential reason for lowering search strategy sensitivity, or additional searches should be performed to demonstrate this feature has not led to the exclusion of useful data sources.
4. The "Methods" indicates that "Abstracts and titles identified were screened by an independent reviewer", while the current recommendation is to perform screening by 2 reviewers in order to lower the risk of selection bias or a human error.
5. The phrase "Owing to a large number of citations meeting these criteria, a decision was taken to restrict the extraction of data from eligible studies." in the "Methods" is not clear and should be explained in detail.
6. The authors screened congress abstracts, but stated that "This meant that, although congress abstract screening was performed, no data from congress abstracts were extracted." It would be more logical not to mention congress abstracts at all if they have not been used.
7. In the inclusion criteria, the authors listed CKD stages from 2 to 5, and it is unclear why they excluded CKD stage 1. They also stated that the inclusion criteria was "eGFR < 75 mL/min/1.73 m²", but this threshold is very unusual since it does not correspond to KDOQI nor to KDIGO classifications (which use threshold eGFR < 60 mL/min/1.73 m²), and thus the criteria used by the authors identified both healthy persons (with eGFR > 60) and CKD patients (with eGFR < 60) but excluded persons with eGFR > 75 who represent a majority of the general population. The authors identified a list of countries they used as the inclusion/exclusion criteria but this list is not inclusive: it includes some countries of Western Europe but not others, it includes China but not includes Taiwan which has great data on the topic.
8. All these methodological pitfalls decrease the value of the review and its results, and should be explained in the "Methods" and discussed in the "Limitations".

9. In the “Results” it is stated that “plus 79 abstracts identified in supplementary searches”, but in the “Methods” the authors indicated they excluded abstracts from the consideration.
10. “Figure 2” could be presented as a table, without repetition of some rows’ headings.
11. At figure 3 the labels “dialysis-dependent CKD” and “dialysis-dependent ESKD” leave some doubts on how the authors use the terminology.
12. The authors describe the included studies in the “Results” but perform this in a way that certainly requires improvements. First, it is much better to present all studies in a structured table than in a less-structured text with only some highlights from the included papers. Second, it would be better to group the included papers by whether they consider only pre-dialysis CKD or only ESKD. Neither the main text nor the supplements do not provide enough details of the included papers in this structured way.
13. The presentation of “Results” looks more like a listing of the studies but not an exhaustive summary and detailed analysis. I would suggest to put the majority of the extracted data into the tables as described above, and use the “Results” to indicate the most important findings or patterns as already partially done.
14. The “Discussion” consists of only the authors’ text and does include only one reference, even without appropriate citation. Actually, the “Discussion” in its current view is more similar to “Conclusion”. In any way, the “Discussion” should be strengthened.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: chronic kidney disease, acute kidney disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 11 June 2020

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This manuscript describes a systematic literature review on quality of life, symptom burden, and healthcare resource utilization and costs of CKD across different CKD stages and comparing to the general population without CKD. The literature search process, decisions on which publications to include, the summary of review results, and limitations are clearly stated.

My only suggestion is to remove the following sentence from Methods, Citation Screening and Full Text Review on page 3 because this information is duplicate from the previous subsection Systemic Literature Review:

- "For the humanistic burden SR, study publication dates for data extraction were restricted to 2007–2017; for the economic burden SR, the relevant time period was restricted to 2012–2017."

I recommend acceptance with this minor edit.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Oncology, autoimmune diseases, cardiovascular diseases, chronic kidney disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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