BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038401
Article Type:	Original research
Date Submitted by the Author:	12-Mar-2020
Complete List of Authors:	Sullivan, Michael; University of Glasgow, Institute of Cardiovascular and Medical Sciences Rankin, Alastair; University of Glasgow, Institute of Cardiovascular and Medical Sciences Jani, Bhautesh; University of Glasgow, General Practice and Primary Care, Institute of Health and Wellbeing Mair, Frances; University of Glasgow, General Practice and Primary Care, Institute of Health and Wellbeing Mark, Patrick; University of Glasgow, Institute of Cardiovascular & Medical Sciences
Keywords:	Chronic renal failure < NEPHROLOGY, Dialysis < NEPHROLOGY, Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, Ischaemic heart disease < CARDIOLOGY, End stage renal failure < NEPHROLOGY

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Associations between multimorbidity and adverse clinical outcomes in patients with chronic kidney disease: a systematic review and meta-analysis

Michael Sullivan[1], Alastair Rankin[1], Bhautesh Dinesh Jani[2], Frances S Mair[2], Patrick B Mark[1]

1 – Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

2 – General Practice and Primary Care, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK

Corresponding author:

Michael Sullivan

Address: Institute of Cardiovascular and Medical Sciences, University of Glasgow, 126 University Place, Glasgow, G12 8TA, UK

Telephone: +44(0) 141 330 2677

Email: Michael.sullivan@glasgow.ac.uk

Twitter Handle: @sullivanmk8

Keywords: chronic kidney disease, dialysis, comorbid, multimorbidity, diabetes, cardiovascular

Abstract

Objective: To systematically review the literature exploring the associations between multimorbidity (the presence of two or more LTCs) and adverse clinical outcomes in patients with CKD.

Data sources: MEDLINE, EMBASE, CINAHL, Cochrane Library and SCOPUS (1946-2019). The main search terms were “Chronic Kidney Failure” and “Multimorbid*”.

Participants: adults over the age of 18 with CKD stages three to five i.e. eGFR less than 60ml/minute/1.73m^2.

Exposure: Multimorbidity quantified by Measures.

Outcome measures: all-cause mortality, renal progression, hospitalisation and cardiovascular events.

Study analysis: Newcastle Ottawa Scale for quality appraisal and fixed-effects meta-analysis.

Results: Of 1852 papers identified, 26 met the inclusion criteria. 21 papers involved patients with advanced CKD and no studies were from low or middle income countries. All-cause mortality was an outcome in all studies. Patients with multimorbidity were at higher risk of mortality compared to patients without multimorbidity (Total risk ratio 2.28 (95% confidence interval 1.81-2.88)). The risk of mortality was higher with increasing multimorbidity (Total hazard ratio 1.31 (1.27-1.36)) and both concordant and discordant LTCs were associated with heightened risk. Multimorbidity was associated with renal progression in four studies, hospitalisation in five studies and cardiovascular events in two studies.

Limitations: Outcomes did not include all of those prioritised by patients e.g. quality of life. Meta-analysis could only include 10 of 26 papers as the methodologies of studies were heterogeneous.

Conclusions: There are associations between multimorbidity and adverse clinical outcomes in patients with CKD. However, most data relate to mortality risk in patients with advanced

CKD. There is limited evidence regarding patients with mild to moderate CKD, outcomes such as cardiovascular events, types or patterns of LTCs and regarding patients from low or middle income countries.

Prospero Registration: CRD42019147424.

Article Summary

Strengths and limitations of this study

- This review is the first to synthesise the existing evidence on multimorbidity in patients with CKD and it included a range of settings.
- The outcomes of interest were chosen by researchers and these do not include all outcomes that are important to patients e.g. quality of life.
- Two authors independently performed paper selection, data extraction and quality appraisal.
- Meta-analysis was performed, but only included selected papers because of methodological heterogeneity of papers.

Introduction

Multimorbidity is the presence of two or more long-term conditions (LTCs)[1]. In a Scottish study of 1.8 million patients, it was found to affect 23% of the whole population and in particular those from areas of lower socioeconomic status[2]. It is a problem for individual patients because it is associated with complex treatment regimens that result in a high burden of treatment and reduced quality of life[3]. For clinicians and health services, caring for these individuals represents a huge workload and equates to approximately two thirds of health care spending[4]. The current disease-orientated approaches of guidelines and healthcare are inadequate for patients with multiple LTCs and complex needs[5].

Multimorbidity is more common in patients with chronic kidney disease (CKD) than any other LTC: e.g. among 2.5 million Canadians, patients with CKD had more co-morbid LTCs than patients with lung disease (mean 4.2 LTCs versus 2.8)[6]. The prevalence of CKD is around 12%[7] and as this rises globally, the adverse effects of CKD and multimorbidity on quality of life are increasing[8]. The leading cause of death in patients with CKD is cardiovascular disease and although this is partly related to risk factors common to both conditions, low estimated glomerular filtration rate (eGFR) and proteinuria are predictors of cardiovascular mortality[9, 10]. The higher cardiovascular risk observed among CKD patients is independent of traditional atherosclerotic risk factors such as hypertension and dyslipdaemia, but the reasons for this and the influence of multimorbidity on CKD are incompletely understood. CKD and multimorbidity therefore occur together frequently and there are a number of issues common to both problems such as polypharmacy and significant treatment burden[11].

We undertook this systematic review to establish the current evidence concerning associations between multimorbidity and adverse clinical outcomes in patients with CKD.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines were followed[12] and this review was registered with the International Prospective Register of Systematic Reviews (CRD42019147424).

Literature Search

A comprehensive search strategy identified studies of patients with CKD that investigated the associations between multimorbidity and adverse clinical outcomes (see Supplementary File 1 for search terms). We included observational studies; in particular those using electronic health care records. There was no restriction on sample size. The databases searched included studies from 1946 to 2019. The search was limited to papers published in English. Databases searched were MEDLINE (OVID interface), EMBASE (OVID interface), CINAHL Complete (EBSCO interface), The Cochrane Library (OVID interface), and SCOPUS. Selected medical subject headings were combined with keywords relating to multimorbidity and CKD to create a search strategy which was produced for use in MEDLINE and amended for use in the other databases, using controlled vocabulary, Boolean operators and search symbols. The search was carried out to include literature published up to 29th August 2019. The results were supplemented with searches of reference lists of included studies. Search data were stored and merged using Endnote X9 (Clarivate Analytics, Philadelphia, USA) and papers were shared and assessed using DistillerSR (Evidence Partners, Ottawa, Canada).

Study Selection

We included empirical quantitative studies that contained data on associations between Multimorbidity Measures and all-cause mortality or additional outcomes in adults with CKD. We accepted any Multimorbidity Measure, which included simple counts of LTCs and co-morbidity scoring systems. Additional outcomes were hospitalisation, cardiovascular events, cardiovascular deaths, heart failure hospitalisations and renal progression (40% reduction

in eGFR, doubling of serum creatinine or initiation of renal replacement therapy (RRT)). Review articles, drug intervention studies, qualitative studies, case reports and conference abstracts were excluded. Studies that analysed the relationship between a Multimorbidity Measure and any of our outcomes of interest were included in adults over the age of 18 with CKD stages three to five i.e. eGFR less than 60ml/minute/1.73m^2 including those requiring RRT i.e. haemodialysis (HD), peritoneal dialysis (PD) or renal transplantation. Exclusion criteria were children or adolescents aged 18 or under, animal studies and individuals without CKD.

The study selection process was conducted by two reviewers (MS, AR). Title screening was followed by abstract and full paper review, where necessary. Any inter-reviewer disagreements were resolved by a third reviewer (PM).

Data extraction

As recommended by the Cochrane Handbook[13], data were extracted in a Population, Exposure, Comparator, Outcomes (PECO) approach:

Population: We extracted data on the characteristics of study populations: country, sample size, follow-up time and setting i.e. CKD, HD, PD, renal transplant and conservative care.

Exposure: We extracted the Multimorbidity Measure used in each study and whether LTCs were categorised into different types for analysis.

Comparator: We extracted the details provided of comparator groups i.e. patients with CKD with less than two LTCs. We did not count CKD as an LTC.

Outcomes: We extracted details of the statistical analyses employed to evaluate the relationship between Multimorbidity Measure and outcomes. Risks were expressed as effect sizes with 95% confidence intervals, where available.

Data synthesis and analysis

Results were presented in a narrative format. Where possible, fixed effects meta-analysis was performed for the primary outcome, all-cause mortality. Quantification of statistical heterogeneity was assessed by means of I^2, which shows the percentage of total variation across studies due to heterogeneity[13]. These analyses were carried out using RevMan Version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). Meta-analysis was limited by heterogeneous methodologies: variable Multimorbidity Measures, use of effect sizes (Hazard ratios (HRs), Risk ratios (RRs), Kaplan Meier curves) and the use of multimorbidity as a continuous and categorical variable. We therefore performed meta-analysis where several studies used similar methodologies. Data on numbers of deceased patients were not available for all studies and so we contacted study authors for their primary data. Where necessary and possible, we calculated RRs for studies, comparing patients with multimorbidity to those without multimorbidity. HRs could not be calculated as there were no individual time-to-event data.

Quality appraisal

Two researchers conducted quality appraisal independently (MS, AR). Studies were assessed using an adapted Newcastle-Ottawa quality assessment scale (NOS), as informed by the Cochrane Handbook[13] (see Supplementary File 2). Studies were not excluded based on quality appraisal.

Results

Search results

Figure 1 demonstrates the literature search flow. After the removal of duplicate papers, 1852 papers were identified. 1756 papers were excluded as they were not relevant and so 96 full papers were screened and 26 papers met our eligibility criteria and were included in the review[14-39].

Study characteristics

Table 1 lists the characteristics of the 26 included studies. The studies were published between 1995 and 2019 and all used a cohort design. The size of populations was between 69 and 821,334. Fourteen studies examined subjects predominantly on dialysis[14, 16-21, 24, 26, 29, 32, 34, 32, 39]; five included patients with CKD stages 3 to 5[15, 23, 23, 33, 35] including two with mild CKD [23, 33]; two involved patients with CKD stage 5 including those not on RRT or conservative care[28, 30]; two included those receiving conservative care[22, 37]; three included renal transplant recipients[25, 31, 38].

Table 2 shows the number of studies using each Multimorbidity Measure and how the corresponding effect sizes were presented: as a categorical or a continuous variable. In addition to these, three studies examined more than one Multimorbidity Measure: comparing how effectively each measure predicted outcomes[21, 26, 36]. Ten studies used the Charlson Comorbidity Index (CCI) or a modification of this scale (mCCI)[14, 16, 24, 25, 29, 30, 32, 34, 38, 39]. Seven studies used the number of LTCs i.e. condition count[15, 22, 23, 27, 28, 35, 37]. Two studies used the Stoke comorbidity grade, which uses condition count to divide patients into low, intermediate and high grades[19, 20]. Two studies used the Comorbidity severity score[17, 18]. One study compared those with CKD, diabetes and heart failure to those with just CKD and heart failure[33]. One study used the Kidney Transplant Morbidity Index[31].

All studies reported the effect of multimorbidity on all-cause mortality. Five studies reported the effect of multimorbidity on hospitalisation[14, 18, 33-35] and four on renal progression[25, 27, 31, 38]. One study reported the effect of multimorbidity on heart failure hospitalisation and cardiovascular death[33] and one study reported the effect of multimorbidity on myocardial infarction[35]. Twelve studies expressed effect sizes using multimorbidity as a categorical variable[15-17, 23, 25, 27, 31-33, 35, 38, 39], nine as a continuous variable[14, 18-20, 24, 28, 29, 34, 37] and one as both[30]. One study gave a narrative comparison of groups[22] and two used Kaplan-Meier

curves[26, 36]. Two studies categorised LTCs into types: both used concordant and discordant as types and one also specified mental health and chronic pain LTCs[15, 35].

Main findings

The results of the included studies were summarised in Supplementary File 3. Unadjusted HRs were quoted as adjusted HRs were not available for all studies. Where multimorbidity was used as a categorical variable, 12 of 13 studies found that patients with multimorbidity had higher rates of mortality than patients without multimorbidity. In the one study that did not detect a difference, Lee *et al*'s primary outcome was renal progression[27]. For all-cause mortality, the authors provided event rates and Kaplan Meier Curves but there were no HRs with adjustments for confounding variables.

Where multimorbidity was used as a continuous variable, 10 of 11 studies found that with each increase in Multimorbidity Measure, all-cause mortality was higher. In the one study to not detect a difference, Ellam *et al* was a study of just 69 conservatively-managed patients[22].

Of the four studies that reported renal progression, three were in renal transplant recipients[25, 30, 31]. All four studies demonstrated higher rates of renal progression in patients with multimorbidity (HRs from each study 2.97 (1.53-5.76), 2.44 (1.19-5.02), 3.11 (2.55-3.80), 1.42 (1.02-1.97). Renal progression was defined by graft loss or RRT initiation and one paper reported significant annual reductions in eGFR by increasing number of LTCs[27]. Five studies reported rates of hospitalisation and all of these identified an association between multimorbidity and hospitalisation[14, 18, 33-35].

One paper reported rates of Heart Failure Hospitalisation and Cardiovascular Death[33]: patients with multimorbidity had higher rates of both outcomes than patients without multimorbidity. One paper reported higher rates of Myocardial Infarction in patients with multimorbidity[35].

Two papers described the influence of concordant and discordant LTCs on adverse outcomes[15, 35]. These papers found that both types of LTC were associated with higher rates of mortality. One paper found that the rates of outcomes were higher in patients with at least one discordant LTC compared to patients with only concordant LTCs[15]. No association was identified between mental health and chronic pain LTCs and Myocardial Infarction[35].

Meta-analysis

We performed meta-analysis for all-cause mortality where several studies used comparable methodologies. Figure 2 included studies that used CCI as a continuous variable, demonstrating that with each increase in CCI, the risk of mortality was higher (Total HR 1.31 (95% confidence interval 1.27-1.36)). Figure 3 included studies that used condition count as a categorical variable: demonstrating that patients with multimorbidity were at higher risk of mortality compared to patients without multimorbidity (Total RR 2.28 (95% confidence interval 1.81-2.88)). There was considerable statistical heterogeneity in the studies included in each meta-analysis (I^2 97% in figure 2 and 78% in figure 3).

Risk of bias (See Supplementary File 4)

All studies selected patients with and without multimorbidity from the same cohort and used either secure medical records or structured interviews to collect data. Most studies included just one group of patients with CKD such as HD patients and only three studies included patients with a true range of mild to severe CKD[15, 27, 35]. All but two studies controlled for factors such as ischaemic heart disease, age or diabetes[17, 22]. Only one study made a statement about subjects who were lost to follow-up[26]. However, as all the studies were based on health care databases, it is reasonable to assume complete or near-complete follow-up. All studies followed up patients for more than one year, but there was variation in the average length of follow-up (from 13.1 to 81.6 months). Four studies did not specify the average follow-up time but from their survival analyses, it was clear that patients were followed up for at least one year[25, 30, 36, 39].

The NOS score evaluation of each study was between five and seven stars. The two studies that did not control for confounding factors were “poor” quality as per Agency for Healthcare Research and Quality standards[17, 22, 40]. The remainder were “good” quality[14-16, 18-21, 23-39].

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to synthesise the existing evidence on the effects of multimorbidity specific to patients with CKD. It is increasingly recognised that multimorbidity and the management of patients with disease clusters are challenging problems[41]. The medical profession has been given a mandate to improve the care of patients affected by multimorbidity and to do so, improving our understanding of the issues will be fundamental. Multimorbidity has been studied in the general population, with clear associations reported between it and high rates of mortality[42]. It is time for researchers to build a body of evidence about patients with kidney disease. Our review demonstrates that for patients with CKD, multimorbidity is associated with high rates of mortality, and the risk is higher with increasing numbers of LTCs. Unfortunately, the literature provides little detail beyond this association. Of the papers in the review, only two categorised LTCs and studied whether the type of LTCs influenced outcomes. Tonelli *et al* and Bowling *et al* found that concordant LTCs such as diabetes were associated with high rates of mortality, but so were discordant or unrelated LTCs like cancer and depression[15, 35]. Bowling *et al* found that the presence of one or more discordant LTC conferred higher risk compared to patients with only concordant LTCs. This suggests that there are groups of patients in whom it is not just the number but also the type of LTCs that puts them at elevated risk. Further research is needed into what patterns or clusters of disease exist to help clinicians understand the risks faced by patients with CKD and multimorbidity.

Patients require clinicians to help with their overall health and quality of life, not just the status of individual LTCs. As seen in the Standardized Outcomes in [illegible](SONG-HD) initiative, patients usually wish to understand the

risks they face. However, there is often a mismatch between the outcomes regarded as important by patients to those emphasised in clinical guidelines[43, 44]. It is therefore imperative that we consider patient-oriented outcomes when studying multimorbidity and ensure that research leads to improvements in care for patients. A limitation of our review is that we did not summarise outcomes prioritised by patients. The merit in investigating multimorbidity in patients with CKD will be that patients and clinicians will have an improved understanding of the risks they face. They will therefore be able to prioritise particular interventions such as cardiovascular risk factor modification and vascular access creation.

Despite the methodological and clinical heterogeneity of the studies in our review, the findings are consistent with existing literature[11]. We have confirmed associations between multimorbidity and adverse clinical outcomes in RRT and non-RRT settings, and in a range of countries. 21 of 26 studies included patients with advanced CKD including those on RRT. However, it should be noted that there was no information available from low or middle income countries. Mild to moderate CKD was also under-represented, despite this constituting 99% of the patients with CKD[45]. Multimorbidity in patients with CKD from low and middle income countries and in those with mild to moderate CKD should therefore be targets for future research. Only two studies assessed the influence of multimorbidity on cardiovascular outcomes[33, 35]. Cardiovascular morbidity and mortality is the most significant risk for patients with CKD and many of the LTCs that occur in patients with CKD are risk factors for cardiovascular events[10]. Further research is therefore needed to explore how multimorbidity influences cardiovascular events in patients with CKD. Of the four studies that examined the influence of multimorbidity on renal progression, all but one were in patients with renal transplants. The study in non-transplant patients identified an association between multimorbidity and renal progression[27]. This risk is a significant one, particularly for the patients who develop the need for RRT. Many patient cohorts around the world have

ample follow-up data and so the influence of multimorbidity on renal progression in non-transplant cohorts should be studied in greater detail.

The studies included in our review are heterogenous. Clinical heterogeneity is evident in the range of populations studied: stage 3 CKD, HD, PD, transplant and conservative care. There are high levels of methodological and statistical heterogeneity. There is no consensus as to which Multimorbidity Measure should be used, and which measure is the most effective at predicting adverse outcomes[46]. CCI was the most commonly used measure, although a number of modifications have been made for use in populations with CKD. Three studies included in this review compared different Multimorbidity Measures. CCI was found to effectively predict mortality risk, with other scoring systems performing comparably and none superior to the rest. Although our work demonstrates that various Multimorbidity Measures are associated with adverse clinical outcomes, we have not identified the best Multimorbidity Measure for risk prediction.

It has been recognised that there are fewer randomised controlled trials (RCTs) to assess the efficacy of interventions in patients with CKD than in other medical specialties and that patients with CKD are often excluded from RCTs[47, 48]. Furthermore, patients with advanced CKD that are included in RCTs are not representative of the wider population of those with CKD[49]. Similar observations have been made in other fields, whereby subjects with multimorbidity are underrepresented in trials of novel interventions[50]. Therefore, to improve outcomes for patients with CKD, both epidemiological studies and RCTs need to account for the range of multimorbidity in patients with CKD. A strength of our review is that it brings together information about the effects of multimorbidity in patients with CKD from various settings to create a comprehensive picture of the effects on different outcomes. Although the studies are challenging to summarise given the heterogeneity, the data are ample and clinically acceptable and therefore likely to be correct. Meta-analysis was performed with data from only 10 studies. The data from 16 studies, including those with large sample sizes,

therefore did not contribute to full data analysis. If a uniform Multimorbidity Measure were agreed and established in guidelines, the comparability and synthesis of data in future would be improved. The evaluation of the effects of types of LTCs on outcomes was limited because only two studies examined this issue. A key focus of research should therefore be what patterns of multimorbidity or disease clusters exist in groups of patients with CKD.

In conclusion, this review provides evidence of associations between multimorbidity and heightened risk of adverse clinical outcomes in patients with CKD. Our findings emphasise the need for further research into the details of how multimorbidity influences different outcomes. In particular, evidence gaps exist for patients with mild to moderate CKD, for outcomes other than mortality such as renal progression and cardiovascular events, for patients with CKD from low and middle income countries and for the patterns of multimorbidity that contribute to heightened risk.

Acknowledgements

We thank Paul Cannon of the University of Glasgow Library for assistance with the literature search. We used the MOOSE checklist when writing our report[51].

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Conflicts of Interest

The results presented in this paper have not been published previously in whole or part.

Michael Sullivan, Alastair Rankin, Bhautesh Jani and Frances Mair have no conflicts of interest. Patrick Mark reports personal fees and non-financial support from Vifor, personal fees from Astrazeneca, grants from Boehringer Ingelheim, personal fees and non-financial support from Pharmacosmos, personal fees from Janssen, personal fees from Novartis, personal fees from Pfizer, personal fees from Bristol Myers Squibb, personal fees and non-financial support from Napp, outside the submitted work.

Author Contributions

All authors contributed to conceptualisation, appraisal of results, writing (review and editing) and manuscript approval. MS, AR and PM performed data analysis extraction. MS and AR performed data extraction. MS prepared the original manuscript draft.

Word Count

3282 words.

Figure Legends

Figure 1. PRISMA flow diagram

Figure 2. Mortality risk for each increase in CCI (Generic Inverse Variance Method, Fixed Effects Model)

Figure 3. Mortality risk for patients with multimorbidity (Mantel-Haenszel Method, Fixed Effects Model)

Data availability statement

All relevant data are included in the article or uploaded as supplementary information.

Patient and public involvement

No patients involved.

Tables

Reference	Country	Setting	Sample size	Average follow-up (months)	Outcome(s)	
					Mortality	Others
DIALYSIS						
Beddhu 2000	USA	HD/PD	268	13.1	✓	Hospitalisation
Chae 2010	South Korea	HD	456	40.6	✓	
Chandna 1999	UK	HD/PD	292	63	✓	Hospitalisation
Chandna 2010	UK	CC/RRT	844	58.7*	✓	
Davies 1995	UK	PD	97	30	✓	
Davies 2002	UK	PD	303	72.0*	✓	
Di Iorio 2004	Italy	HD	515	15	✓	
Fried 2001	USA	PD	268	16.9	✓	
Hemmelgarn 2003	Canada	HD/PD	237	26.3	✓	
Park 2015	South Korea	HD	24738	47.7	✓	
Rattanasompattikul 2012	USA	HD	893	72	✓	
Shum 2013	China	PD/CC	157	23.5	✓	Hospitalisation
van Manen 2002	Netherlands	HD/PD	589	NK	✓	
Wu 2013	Taiwan	HD/PD	79645	NK	✓	
NON-RRT CKD						
Bowling 2016	USA	CKD 3-5	821334	81.6	✓	
Fraser 2015	UK	CKD 3	1741	43.2	✓	
Lee 2018	Taiwan	CKD 3-5	1463	76.7	✓	Renal progression
Lhotta 2003	Austria	CKD 5	75	48	✓	

Ritchie 2009	USA	CKD/Heart failure	1974	32.6	✓	Hospitalisation, HF hospitalisation, CV death
Tonelli 2015	Canada	CKD 3-5	530771	48	✓	Hospitalisation, Myocardial Infarction
TRANSPLANT						
Fernandez 2019	USA	Tx assessment	2086	NK	✓	
Grosso 2012	Italy	Tx recipients	223	NK	✓	Renal Progression
Pieloch 2015	USA	Tx recipients	100261	36	✓	Renal Progression
Wu 2005	USA	Tx recipients	715	40.2	✓	Renal Progression
CONSERVATIVE CARE						
Ellam 2008	UK	CC	69	21*	✓	
Wong 2007	UK	CC	73	23.4*	✓	

Table 1. Study characteristics. HD, haemodialysis; PD, peritoneal dialysis; CKD, chronic kidney disease; RRT, renal replacement therapy; CC, conservative care; Tx, transplant; NK, Not Known. *Median survival

Variable Type	Multimorbidity Measure: number of studies				
	CCI	Condition Count	CSS	KTMI	Heart failure and CKD versus Heart failure, CKD and diabetes
Categorical	6	4	1	1	1
Continuous	6	4	1	0	0

Table 2. Studies using each Multimorbidity measure. CCI, Charlson Comorbidity Index; CSS, Comorbidity Severity Score; KTMI, Kidney Transplant Morbidity Index.

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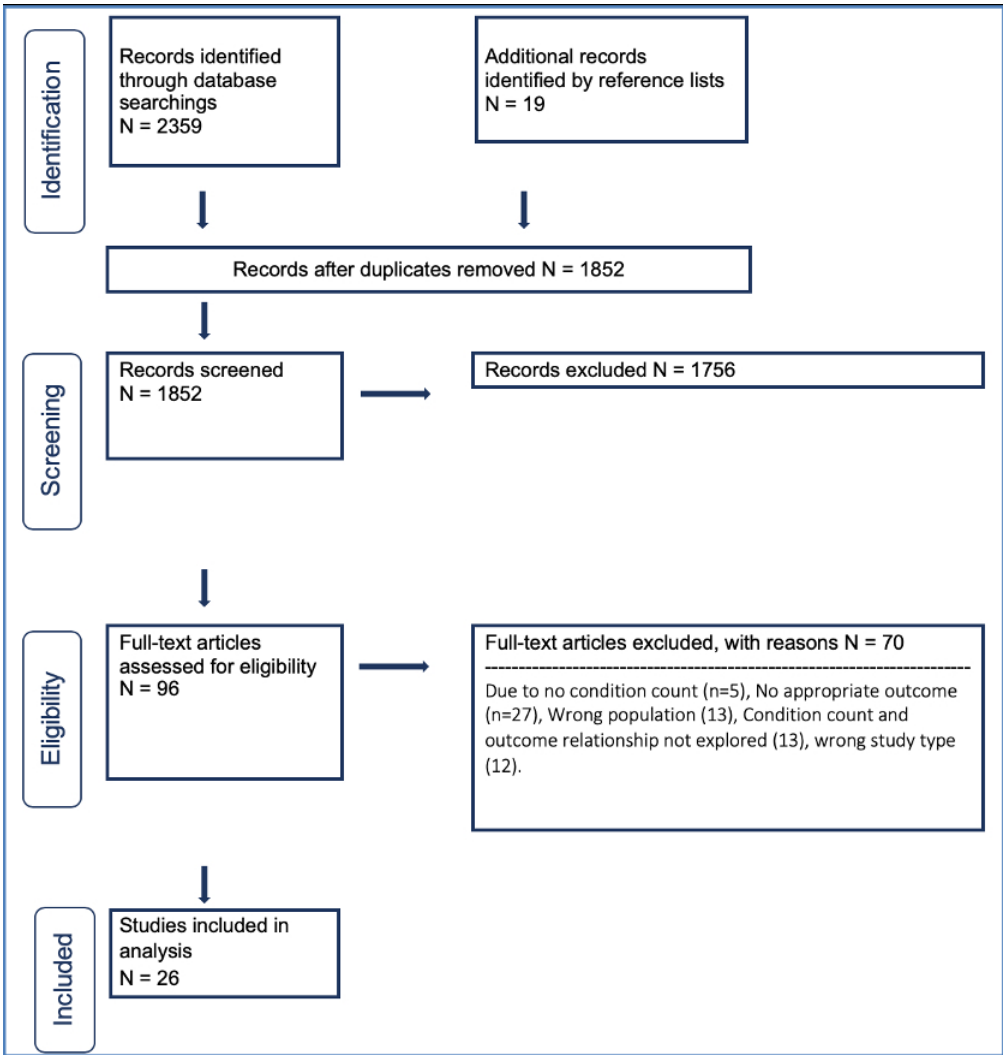
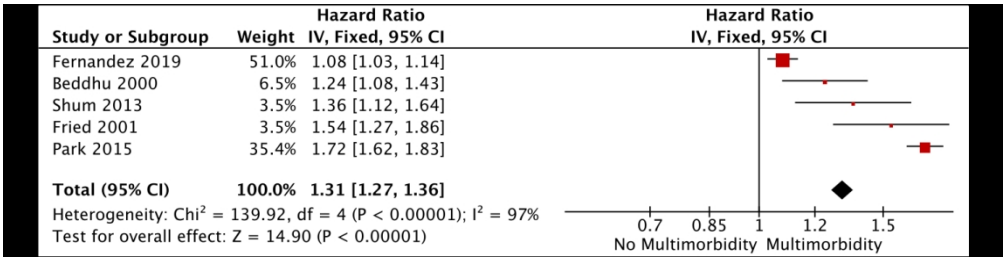
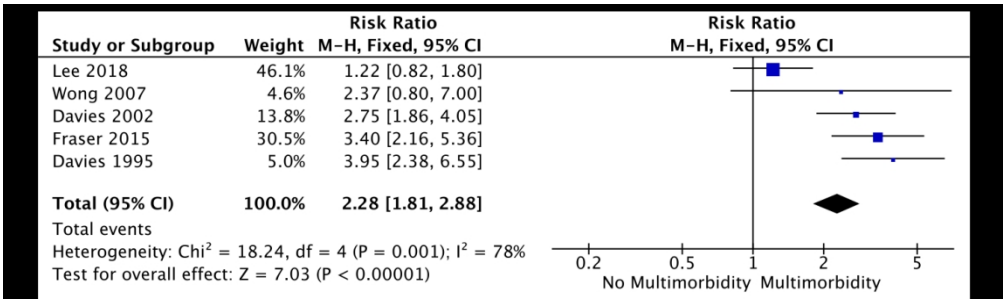


PRISMA flow diagram



Mortality risk for Charlson Comorbidity Index as a continuous variable (Generic Inverse Variance Method, Fixed Effects Model)



Mortality risk for patients with multimorbidity (Mantel-Haenszel Method, Fixed Effects Model)

! "##$%&%'()*+,-.$%,/0,1)()2)3%,!%)*45,6%*&3,

Subject headings	Chronic Kidney Failure Kidney Failure Chronic Renal Insufficiency Renal Insufficiency Kidney Disease Kidney Dysfunction Mild renal impairment Moderate renal impairment Severe renal impairment Subclinical renal impairment Renal replacement therapy Hemodialysis Peritoneal Dialysis Continuous Ambulatory Peritoneal DIalysis Kidney transplantation Kidney graft	Multimorbidity Multiple Chronic Conditions	Humans Adult
Textwords	Chronic kidney or chronic renal CKF, CKD, CRF or CRD Predialysis or pre-dialysis Renal failure or kidney failure Kidney disease Renal insufficienc* Hemodialysis or Haemodialysis Hemodiafiltration or haemodiafiltration Dialysis Endstage renal or endstage kidney Peritoneal dialysis CAPD or APD or CCPD or PD Kidney Transplant	Multimorbid* or multi morbid Condition count Multiple condition or multicondition or multi condition Multiple disease or multidisease or multi disease Multiple disorder or multidisorder or multi disorder Multiple comorbidities or multiple co morbidities Discordant comorbidities or concordant comorbidities	Adult* or aged* or elderly

! "##$%&%'()*+,-.$%,70,89 : ; < ! 6=9,>,?66< : <,@A<=B6C,< ! ! 9 ! ! D986,! ; <=9,

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort ie CKD with multimorbidity (MM)
   a) truly representative of the average CKD/MM population in the community *
   b) somewhat representative of the average CKD/MM population in the community *
   c) selected group of users eg only one disease group
   d) no description of the derivation of the cohort

2) Selection of the unexposed cohort ie CKD without MM
   a) drawn from the same community as the exposed cohort *
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort
   d) no control group

3) Ascertainment of CKD/MM status
   a) secure record (eg medical records) *
   b) structured interview *
   c) written self report
   d) no description

4) Demonstration that outcomes were not present at start of study
   a) yes *
   b) no

Comparability

1) Comparability of cohorts on the basis of the design ie are exposed/non-exposed individuals matched or do the authors actively control for confounding factors?
   a) study controls for ischaemic heart disease *
   b) study controls for additional factor(s) *
   Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

Outcomes

1) Assessment of outcome(s)
   a) independent blind assessment *
   b) record linkage *
   c) self report
   d) no description

2) Was follow-up long enough ie > 1 year
   a) yes *
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for *
   b) subjects lost to follow up unlikely to introduce bias - small number lost to follow up, or description provided of those lost) *
   c) high lost to follow up rate and no description of those lost
   d) no statement

Total stars /8

Supplementary File 3. Results from included studies

Reference	Effect size	CCI groups	Effect size (95% CI)
CATEGORICAL PRESENTATION OF EFFECT SIZE			
Chae 2010	HRs	**! "#$%& ' (&) (# * *+#, &)-& . /01#**	
		Quartile 1 (CCI 2)	Ref
		Quartile 2 (CCI 4-5)	9.22 (3.29-25.84)
		Quartile 3 (CCI 6)	16.77 (5.97-47.11)
		Quartile 4 (CCI 7-11)	22.37 (8.08-61.93)
		2"# * *+#034/5 (-' 6#&60#& ' (# (-& . 0%01#	
		Tertile 1 (CCI 2)	Ref
		Tertile 2 (CCI 3)	1.39 (1.01-2.05)
		Tertile 3 (CCI 4-8)	1.98 (1.25-3.14)
Wu 2005	HRs	*** *+#034/5 (-' 6#&60#**	
		CCI < 5	Ref
		CCI ≥ 5	2.88 (1.90-4.37)
Grosso 2012	HRs	**7 8 (-9-0 (# * *+#** 1 point: myocardial infarction, heart failure, peripheral vascular disease, COPD, connective tissue disease or mild liver disease 2 points: diabetes mellitus, cerebrovascular accident, solid tumour or leukaemia	
		CCI ≤ 1	Ref
		CCI > 1#	3.87 (1.06-14.06)#
Rattanasompattikul 2012	HRs	*** *+#034/5 (-' 6#&60#& ' (#)0 ' &/# (-10&10**	
		Quartile 1 (CCI 0)	Ref
		Quartile 2 (CCI 1-2)#	1.72 (1.26-2.36)
		Quartile 3 (CCI 3)	2.60 (1.13-3.26)
		Quartile 4 (CCI 4-9)#	3.40 (2.41-4.79)
Wu 2013	HRs	*** *+#034/5 (-' 6#&60**	
		CCI ≤ 3	Ref
		CCI 4-6	2.49 (2.35-2.63)
		CCI 7-9	3.53 (3.34-3.73)
		CCI 10-12	3.66 (3.45-3.88)
		CCI 13-15	4.12 (3.84-4.42)
		CCI > 15	4.42 (4.02-4.86)

CONTINUOUS PRESENTATION OF EFFECT SIZES			
Beddhu 2000	HRs	**78(-9-0(#**+#** 1 point: coronary artery disease, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, mild liver disease, diabetes 2 points: hemiplegia, moderate or severe renal disease, diabetes with end-organ damage, any tumour, leukaemia, lymphoma 3 points: moderate or severe liver disease 6 points: metastatic solid tumour, AIDS	
		Each increase in CCI	1.24 (1.11-1.39)#
Fried 2001	Relative risk	**$%&'(&)(#**+#,&)-&./01**	
		Each increase in CCI	1.54 (1.36-1.74)
Park 2015	HRs	**!"#$%&'(&)(#**+#,&)-&./01**	
		Each increase in CCI	1.42 (1.39-1.45)
		2"#78(-9-0(#+#-'#-'4-(0'%#:&0;8(-&/<1-1#=&%-0'%1#** Details not provided	
		Each increase in CCI	1.72 (1.66-1.78)
Shum 2013	HRs	**>$?@#78(-9-0(#**+**	
		Each increase in CCI (PD group only)#	1.36 (1.18-1.56)
CONTINUOUS AND CATEGORICAL PRESENTATION OF EFFECT SIZES			
Fernandez 2019	HRs	**>$?@#78(-9-0(#**+#**	
		Each increase in CCI#	1.08 (1.03-1.13)
		Low comorbidity burden CCI 0-1	Ref
		High comorbidity burden CCI ≥ 2	1.38 (1.01-1.89)

Results from studies using Charlson Comorbidity Index (CCI) as Multimorbidity Measure

Reference	Effect size#	Conditions and groups#	Effect size (95% CI)#
CATEGORICAL PRESENTATION OF EFFECT SIZE			
Bowling 2016	HRs	22 conditions: hypertension, hyperlipidemia, coronary heart disease, atrial fibrillation, heart failure, peripheral arterial disease, arthritis, osteoporosis, gout, diabetes, hypothyroidism, cancer, prostate cancer, anaemia, cerebrovascular disease, depression, dementia, epilepsy, Parkinson's disease, gastroesophageal reflux disease/peptic ulcer disease, benign prostatic hypertrophy and COPD/asthma	
		1	Ref
		2	0.95 (0.93-0.97)
		3	1.03 (1.01-1.05)
		4	1.24 (1.21-1.26)
		5	1.43 (1.39-1.47)
		≥ 6	1.72 (1.64-1.80)

Fraser 2015	HRs	11 conditions: hypertension, diabetes, ischaemic heart disease, heart failure, peripheral vascular disease, cerebrovascular disease, chronic respiratory disorder, depression, chronic painful condition, thyroid disorder and anaemia	
		0-1	Ref
		2	2.31 (1.36-3.94)
		≥ 3	4.58 (2.85-7.38)
Lee 2018	10-year survival rates	12 conditions: diabetes, hypertension, gout, heart failure, ischemic heart disease, cerebrovascular disease, liver disease, malignancy, tuberculosis, hyperlipidaemia, anaemia and connective tissue disease	
		0	93.7%
		1	94.3%
		2	92.9%
		≥ 3	92.7%
Tonelli 2015	HRs	29 conditions: alcohol misuse, asthma, atrial fibrillation, lymphoma, non-metastatic cancer, metastatic cancer, heart failure, chronic pain, COPD, chronic hepatitis B, cirrhosis, severe constipation, dementia, depression, diabetes, epilepsy, hypertension, hypothyroidism, inflammatory bowel disease, irritable bowel syndrome, multiple sclerosis, myocardial infarction, Parkinson's disease, peptic ulcer disease, peripheral vascular disease, psoriasis, rheumatoid arthritis, schizophrenia, and stroke or transient ischemic attack	
		0	Ref
		1	1.57 (1.50-1.63)
		2	2.34 (2.24-2.44)
		3	3.43 (3.29-3.58)
		4	4.81 (4.60-5.02)
		≥ 5	7.74 (7.43-8.07)
CONTINUOUS PRESENTATION OF EFFECT SIZES			
Davies 1995	HRs	@0,0/8=;0'%#89#%:0#$%8A0#*8;8).-(-%<#B)&(0# 11 conditions: ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, left ventricular dysfunction, diabetes mellitus, systemic collagen vascular disease, COPD, pulmonary fibrosis, pulmonary tuberculosis, asthma and cirrhosis Low grade: 0 conditions Intermediate grade: 1-2 conditions High grade: ≥ 3 conditions	
		Each increase in grade	2.66 (1.55-4.55)
Davies 2002	Relative risk	$%8A0#*8;8).-(-%<#B)&(0#	
		Each increase in grade	2.4 (1.4-4.1)
Ellam 2008	Narrative	$%8A0#*8;8).-(-%<#B)&(0#	"No statistically significant effect on survival"
Wong 2007	HRs	$%8A0#*8;8).-(-%<#B)&(0#	
		Each increase in grade	2.53 (1.32-4.83)
Lhotta 2003	HRs	Five conditions: diabetes, heart failure, coronary artery disease, cerebrovascular disease and peripheral vascular disease	
		Each increase in comorbidity score	1.78 (1.32-2.40)

Results from studies using Condition Count as Multimorbidity Measure. COPD; chronic obstructive pulmonary disease

Reference#	Effect size measure#	Multimorbidity measure and groups#	Effect size (95% CI)#
Chandna 1999#	HRs	*8 ; 8) . - (-%<#10 , 0)-%<#148)0#C * $ $D# Cardiac score, according to New York Heart Association, respiratory disease score (1-4), cerebrovascular disease score (1-4), peripheral vascular disease score (1-4), cirrhosis (4), and malignancy score (1-4)	
		Each increase in CSS	1.238 (1.145-1.338)
Chandna 2010#	HRs	*8 ; 8) . - (-%<#10 , 0)-%<#148)0	
		Low comorbidity (CSS ≤ 4)	Ref
		High comorbidity (CSS > 4)	1.823 (1.255-2.650)
Pieloch 2015#	HRs	E-(' 0<#F)& ' 1=/& ' %# 7 8) . - (-%<#+ ' (03	
		0	Ref
		1	1.85 (1.45-2.36)
		2	3.11 (2.46-3.94)
		3	5.00 (3.96-6.31)
		4	7.37 (5.83-9.32)
		5	9.41 (7.41-11.94)
		6	12.15 (9.45-15.63)
		≥ 7	13.03 (9.68-17.54)
Ritchie 2009#	HRs	G0&)%#9&-/5)0H# * E@#& ' (#(-& . 0%01#	
		Heart failure and CKD	Ref
		Heart failure, CKD and diabetes	1.25 (1.07-1.46)

Results from studies using other Multimorbidity Measures

Reference	Scores studied	Presentation of effect size
Hemmelgarn 2003	CCI Development of ESRD modified CCI	Kaplan-Meier curves
Di Iorio 2004	CCI Development of CCI modified for haemodialysis patients	Relative risk, 5.5 for CCI
van Manen 2002	CCI Khan index Davies index Development of a new index	Kaplan-Meier curves

Studies that analyse different Multimorbidity Measures

Supplementary File 4. Risk of bias: Results from NOS

Reference	Selection				Comparability	Outcome assessment			Quality score
	I#	J#	K#	L#	M#	N#	O#	P#	
Beddhu 2000		✵	✵	✵	✵	✵	✵		6
Bowling 2016	✵	✵	✵	✵	✵	✵	✵		7
Chae 2010		✵	✵	✵	✵	✵	✵		6
Chandna 1999		✵	✵	✵	✵	✵	✵		6
Chandna 2010		✵	✵	✵		✵	✵		5
Davies 1995		✵	✵	✵	✵	✵	✵		6
Davies 2002		✵	✵	✵	✵	✵	✵		6
Di Iorio 2004		✵	✵	✵	✵	✵	✵		6
Ellam 2008		✵	✵	✵		✵	✵		5
Fernandez 2019		✵	✵	✵	✵	✵	✵		6
Fraser 2015		✵	✵	✵	✵	✵	✵		6
Fried 2001		✵	✵	✵	✵	✵	✵		6
Grosso 2012		✵	✵	✵	✵	✵	✵		6
Hemmelgarn 2003		✵	✵	✵	✵	✵	✵	✵	7
Lee 2018	✵	✵	✵	✵	✵	✵	✵		7
Lhotta 2003		✵	✵	✵	✵	✵	✵		6
Park 2015		✵	✵	✵	✵	✵	✵		6
Pieloch 2015		✵	✵	✵	✵	✵	✵		6
Rattanasompattikul 2012		✵	✵	✵	✵	✵	✵		6
Ritchie 2009		✵	✵	✵	✵	✵	✵		6
Shum 2013		✵	✵	✵	✵	✵	✵		6
Tonelli 2015	✵	✵	✵	✵	✵	✵	✵		7
van Manen 2002		✵	✵	✵	✵	✵	✵		6
Wong 2007		✵	✵	✵	✵	✵	✵		6
Wu 2005		✵	✵	✵	✵	✵	✵		6
Wu 2013		✵	✵	✵	✵	✵	✵		6

Table 3. Newcastle Ottawa Scale. 1. Representativeness of the exposed cohort. 2. Selection of the non-exposed cohort. 3. Ascertainment of CKD/multimorbidity status. 4. Demonstration that outcomes were not present at start of study. 5. Comparability of cohorts on the basis of the design. 6. Assessment of outcome(s). 7. Was follow-up long enough. 8. Adequacy of follow up of cohort.

Reporting checklist for meta-analysis of observational studies.

Based on the MOOSE guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the MOOSEreporting guidelines, and cite them as:

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283(15):2008-2012.

	Reporting Item	Page Number
Title		
#1	Identify the study as a meta-analysis of observational research	1
Abstract		
#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number (From PRISMA checklist)	2, 3
Background		
#3a	Problem definition	4
#3b	Hypothesis statement	4
#3c	Description of study outcomes	5

	#3d	Type of exposure or intervention used	5
	#3e	Type of study designs used	5
	#3f	Study population	5
Methods			
Search strategy	#4a	Qualifications of searchers (eg, librarians and investigators)	N/A
Search strategy	#4b	Search strategy, including time period included in the synthesis and keywords	5
Search strategy	#4c	Effort to include all available studies, including contact with authors	5, 7
Search strategy	#4d	Databases and registries searched	5
Search strategy	#4e	Search software used, name and version, including special features used (eg, explosion)	5
Search strategy	#4f	Use of hand searching (eg, reference lists of obtained articles)	5
Search strategy	#4g	List of citations located and those excluded, including justification	7
Search strategy	#4h	Method of addressing articles published in languages other than English	5
Search strategy	#4i	Method of handling abstracts and unpublished studies	6
Search strategy	#4j	Description of any contact with authors	7
	#5a	Description of relevance or appropriateness of studies gathered for assessing the hypothesis to be tested	8
	#5b	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7
	#5c	Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	7

#5d	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7
#5e	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	7
#5f	Assessment of heterogeneity	7
#5g	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7
#5h	Provision of appropriate tables and graphics	16, 17, 18, supplemental file
Results		
#6a	Graphic summarizing individual study estimates and overall estimate	N/A
#6b	Table giving descriptive information for each study included	16, 17, 18
#6c	Results of sensitivity testing (eg, subgroup analysis)	N/A
#6d	Indication of statistical uncertainty of findings	10
Discussion		
#7a	Quantitative assessment of bias (eg. publication bias)	N/A
#7b	Justification for exclusion (eg, exclusion of non–English-language citations)	N/A
#7c	Assessment of quality of included studies	11
Conclusion		
#8a	Consideration of alternative explanations for observed results	N/A
#8b	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	12
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Notes:

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BMJ Open

Associations between multimorbidity and adverse clinical outcomes in patients with chronic kidney disease: a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038401.R1
Article Type:	Original research
Date Submitted by the Author:	21-Apr-2020
Complete List of Authors:	Sullivan, Michael; University of Glasgow, Institute of Cardiovascular and Medical Sciences Rankin, Alastair; University of Glasgow, Institute of Cardiovascular and Medical Sciences Jani, Bhautesh; University of Glasgow, General Practice and Primary Care, Institute of Health and Wellbeing Mair, Frances; University of Glasgow, General Practice and Primary Care, Institute of Health and Wellbeing Mark, Patrick; University of Glasgow, Institute of Cardiovascular & Medical Sciences
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Epidemiology, General practice / Family practice
Keywords:	Chronic renal failure < NEPHROLOGY, Dialysis < NEPHROLOGY, Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, Ischaemic heart disease < CARDIOLOGY, End stage renal failure < NEPHROLOGY

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Associations between multimorbidity and adverse clinical outcomes in patients with chronic kidney disease: a systematic review and meta-analysis

Michael Sullivan[1], Alastair Rankin[1], Bhautesh Dinesh Jani[2], Frances S Mair[2], Patrick B Mark[1]

1 – Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

2 – General Practice and Primary Care, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK

Corresponding author:

Michael Sullivan

Address: Institute of Cardiovascular and Medical Sciences, University of Glasgow, 126 University Place, Glasgow, G12 8TA, UK

Telephone: +44(0) 141 330 2677

Email: Michael.sullivan@glasgow.ac.uk

Twitter Handle: @sullivanmk8

Keywords: chronic kidney disease, dialysis, comorbid, multimorbidity, diabetes, cardiovascular

Abstract

Objective: To systematically review the literature exploring the associations between multimorbidity (the presence of two or more long term conditions (LTCs)) and adverse clinical outcomes in patients with chronic kidney disease (CKD).

Design: Systematic Review and Meta-analysis.

Data sources: MEDLINE, EMBASE, CINAHL, Cochrane Library and SCOPUS (1946-2019). The main search terms were “Chronic Kidney Failure” and “Multimorbid*”.

Eligibility Criteria: Observational studies of adults over the age of 18 with CKD stages three to five i.e. eGFR less than 60ml/minute/1.73m^2. The exposure was Multimorbidity quantified by Measures and the outcomes were all-cause mortality, renal progression, hospitalisation and cardiovascular events. We did not consider CKD as a co-morbid LTC.

Data Extraction and Synthesis: Newcastle Ottawa Scale for quality appraisal and risk of bias assessment and fixed-effects meta-analysis for data synthesis.

Results: Of 1852 papers identified, 26 met the inclusion criteria. 21 papers involved patients with advanced CKD and no studies were from low or middle income countries. All-cause mortality was an outcome in all studies. Patients with multimorbidity were at higher risk of mortality compared to patients without multimorbidity (Total risk ratio 2.28 (95% confidence interval 1.81-2.88)). The risk of mortality was higher with increasing multimorbidity (Total hazard ratio 1.31 (1.27-1.36)) and both concordant and discordant LTCs were associated with heightened risk. Multimorbidity was associated with renal progression in four studies, hospitalisation in five studies and cardiovascular events in two studies.

Limitations: Meta-analysis could only include 10 of 26 papers as the methodologies of studies were heterogeneous.

Conclusions: There are associations between multimorbidity and adverse clinical outcomes in patients with CKD. However, most data relate to mortality risk in patients with advanced CKD. There is limited evidence regarding patients with mild to moderate CKD, outcomes

such as cardiovascular events, types of LTCs and regarding patients from low or middle income countries.

Prospero Registration: CRD42019147424.

Article Summary

Strengths and limitations of this study

- This review is the first to synthesise the existing evidence on multimorbidity in patients with CKD and it included a range of settings.
- The outcomes of interest were chosen by researchers and these do not include all outcomes that are important to patients e.g. quality of life.
- Two authors independently performed paper selection, data extraction and quality appraisal.
- Meta-analysis was performed, but only included selected papers because of methodological heterogeneity of papers.

Introduction

Multimorbidity is the presence of two or more long-term conditions (LTCs)[1]. In a Scottish study of 1.8 million patients, it was found to affect 23% of the whole population and in particular those from areas of lower socioeconomic status[2]. It is a problem for individual patients because it is associated with complex treatment regimens that result in a high burden of treatment and reduced quality of life[3]. For clinicians and health services, caring for these individuals represents a huge workload and equates to approximately two thirds of health care spending[4]. The current disease-orientated approaches of guidelines and healthcare are inadequate for patients with multiple LTCs and complex needs[5].

Multimorbidity is more common in patients with chronic kidney disease (CKD) than any other LTC: e.g. among 2.5 million Canadians, patients with CKD had more co-morbid LTCs than patients with lung disease (mean 4.2 LTCs versus 2.8)[6]. The prevalence of CKD is around 12%[7] and as this rises globally, the adverse effects of CKD and multimorbidity on quality of life are increasing[8]. The leading cause of death in patients with CKD is cardiovascular disease and although this is partly related to risk factors common to both conditions, low estimated glomerular filtration rate (eGFR) and proteinuria are predictors of cardiovascular mortality[9, 10]. The higher cardiovascular risk observed among CKD patients is independent of traditional atherosclerotic risk factors such as hypertension and dyslipdaemia, but the reasons for this and the influence of multimorbidity on CKD are incompletely understood. CKD and multimorbidity therefore occur together frequently and there are a number of issues common to both problems such as polypharmacy and significant treatment burden[11].

We undertook this systematic review to establish the current evidence concerning associations between multimorbidity and adverse clinical outcomes in patients with CKD.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines were followed[12] and this review was registered with the International Prospective Register of Systematic Reviews (CRD42019147424).

Literature Search

A comprehensive search strategy identified studies of patients with CKD that investigated the associations between multimorbidity and adverse clinical outcomes (see Supplementary File 1 for search terms). We included observational studies; in particular those using electronic health care records. There was no restriction on sample size. The databases searched included studies from 1946 to 2019. The search was limited to papers published in English. Databases searched were MEDLINE (OVID interface), EMBASE (OVID interface), CINAHL Complete (EBSCO interface), The Cochrane Library (OVID interface), and SCOPUS. Selected medical subject headings were combined with keywords relating to multimorbidity and CKD to create a search strategy which was produced for use in MEDLINE and amended for use in the other databases, using controlled vocabulary, Boolean operators and search symbols. The search was carried out to include literature published up to 29th August 2019. The results were supplemented with searches of reference lists of included studies. Search data were stored and merged using Endnote X9 (Clarivate Analytics, Philadelphia, USA) and papers were shared and assessed using DistillerSR (Evidence Partners, Ottawa, Canada).

Inclusion Criteria

We included empirical quantitative studies that contained data on associations between Multimorbidity Measures and all-cause mortality or additional outcomes in adults with CKD. We accepted any Multimorbidity Measure, which included simple counts of LTCs and co-morbidity scoring systems. We did not consider CKD as a co-morbid LTC because all of the patients in our papers had CKD. Additional outcomes were hospitalisation, cardiovascular

events, cardiovascular deaths, heart failure hospitalisations and renal progression (40% reduction in eGFR, doubling of serum creatinine or initiation of renal replacement therapy (RRT)). Studies that analysed the relationship between a Multimorbidity Measure and any of our outcomes of interest were included in adults over the age of 18 with CKD stages three to five i.e. eGFR less than 60ml/minute/1.73m^2 including those requiring RRT i.e. haemodialysis (HD), peritoneal dialysis (PD) or renal transplantation.

Exclusion Criteria

Review articles, drug intervention studies, qualitative studies, case reports and conference abstracts were excluded. Studies with children or adolescents aged 18 or under, animals and individuals without CKD were excluded.

The study selection process was conducted by two reviewers (MS, AR). Title screening was followed by abstract and full paper review, where necessary. Any inter-reviewer disagreements were resolved by a third reviewer (PM).

Data extraction

As recommended by the Cochrane Handbook[13], data were extracted in a Population, Exposure, Comparator, Outcomes (PECO) approach:

Population: We extracted data on the characteristics of study populations: country, sample size, follow-up time and setting i.e. CKD, HD, PD, renal transplant and conservative care.

Exposure: We extracted the Multimorbidity Measure used in each study and whether LTCs were categorised into different types for analysis.

Comparator: We extracted the details provided of comparator groups i.e. patients with CKD with less than two LTCs. We did not count CKD as an LTC.

Outcomes: We extracted details of the statistical analyses employed to evaluate the relationship between Multimorbidity Measure and outcomes. Risks were expressed as effect sizes with 95% confidence intervals, where available.

Data synthesis and analysis

Results were presented in a narrative format. Where possible, fixed effects meta-analysis was performed for the primary outcome, all-cause mortality. Fixed effects models were applied because we assumed the direction of effect of multimorbidity on mortality would be consistent across the studies and heterogeneity would not contribute to the effect estimates. The Generic Inverse Variance method was used where multimorbidity was expressed as a continuous variable and the Mantel-Haenszel method was used where multimorbidity was expressed as a categorical variable. Quantification of statistical heterogeneity was assessed by means of I^2, which shows the percentage of total variation across studies due to heterogeneity[13]. These analyses were carried out using RevMan Version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). Meta-analysis was limited by heterogeneous methodologies: variable Multimorbidity Measures, use of effect sizes (Hazard ratios (HRs), Risk ratios (RRs), Kaplan Meier curves) and the use of multimorbidity as a continuous and categorical variable. We therefore performed meta-analysis where several studies used similar methodologies. Data on numbers of deceased patients were not available for all studies and so we contacted study authors for their primary data. For meta-analysis and where necessary and possible, we calculated RRs for studies, comparing patients with multimorbidity to those without multimorbidity. HRs could not be calculated as there were no individual time-to-event data.

Quality appraisal

Two researchers conducted quality appraisal independently (MS, AR). Studies were assessed using an adapted Newcastle-Ottawa quality assessment scale (NOS), as

informed by the Cochrane Handbook[13] (see Supplementary File 2). Studies were not excluded based on quality appraisal.

Patient and public involvement

No patients involved.

Results

Search results

Figure 1 demonstrates the literature search flow. After the removal of duplicate papers, 1852 papers were identified. 1756 papers were excluded as they were not relevant and so 96 full papers were screened and 26 papers met our eligibility criteria and were included in the review[14-39].

Study characteristics

Table 1 lists the characteristics of the 26 included studies. The studies were published between 1995 and 2019 and all used a cohort design. The size of populations was between 69 and 821,334. Fourteen studies examined subjects predominantly on dialysis[14, 16-21, 24, 26, 29, 32, 34, 32, 39]; five included patients with CKD stages 3 to 5[15, 23, 23, 33, 35] including two with mild CKD [23, 33]; two involved patients with CKD stage 5 including those not on RRT or conservative care[28, 30]; two included those receiving conservative care[22, 37]; three included renal transplant recipients[25, 31, 38].

Table 2 shows the number of studies using each Multimorbidity Measure and how the corresponding effect sizes were presented: as a categorical or a continuous variable. In addition to these, three studies examined more than one Multimorbidity Measure: comparing how effectively each measure predicted outcomes[21, 26, 36]. Ten studies used the Charlson Comorbidity Index (CCI) or a modification of this scale (mCCI)[14, 16, 24, 25, 29, 30, 32, 34, 38, 39]. Seven studies used the number of LTCs i.e. condition count[15, 22, 23, 27, 28, 35, 37]. Two studies used the Stoke comorbidity grade, which uses condition count to divide patients into low, intermediate and high grades[19, 20]. Two studies used the Comorbidity severity score[17, 18].

One study compared those with CKD, diabetes and heart failure to those with just CKD and heart failure[33]. One study used the Kidney Transplant Morbidity Index[31].

All studies reported the effect of multimorbidity on all-cause mortality. Five studies reported the effect of multimorbidity on hospitalisation[14, 18, 33-35] and four on renal progression[25, 27, 31, 38]. One study reported the effect of multimorbidity on heart failure hospitalisation and cardiovascular death[33] and one study reported the effect of multimorbidity on myocardial infarction[35]. Twelve studies expressed effect sizes using multimorbidity as a categorical variable[15-17, 23, 25, 27, 31-33, 35, 38, 39], nine as a continuous variable[14, 18-20, 24, 28, 29, 34, 37] and one as both[30]. One study gave a narrative comparison of groups[22] and two used Kaplan-Meier curves[26, 36]. Two studies categorised LTCs into types: both used concordant and discordant as types and one also specified mental health and chronic pain LTCs[15, 35].

Main findings

The results of the included studies were summarised in Supplementary File 3. Some papers did not provide adjusted HRs. To make it easier to compare the studies, we therefore quoted unadjusted HRs. Where multimorbidity was used as a categorical variable, 12 of 13 studies found that patients with multimorbidity had higher rates of mortality than patients without multimorbidity. In the one study that did not detect a difference, Lee *et al*'s primary outcome was renal progression[27]. For all-cause mortality, the authors provided event rates and Kaplan Meier Curves but there were no HRs with adjustments for confounding variables.

Where multimorbidity was used as a continuous variable, 10 of 11 studies found that with each increase in Multimorbidity Measure, all-cause mortality was higher. In the one study to not detect a difference, Ellam *et al* was a study of just 69 conservatively-managed patients[22].

Of the four studies that reported renal progression, three were in renal transplant recipients[25, 30, 31]. All four studies demonstrated higher rates of renal progression in patients with multimorbidity (HRs from each study 2.97 (1.53-5.76), 2.44 (1.19-5.02), 3.11 (2.55-3.80), 1.42 (1.02-1.97). Renal progression was defined by graft loss or RRT initiation and

one paper reported significant annual reductions in eGFR by increasing number of LTCs[27]. Five studies reported rates of hospitalisation and all of these identified an association between multimorbidity and hospitalisation[14, 18, 33-35].

One paper reported rates of Heart Failure Hospitalisation and Cardiovascular Death[33]: patients with multimorbidity had higher rates of both outcomes than patients without multimorbidity. One paper reported higher rates of Myocardial Infarction in patients with multimorbidity[35].

Two papers described the influence of concordant and discordant LTCs on adverse outcomes[15, 35]. These papers found that both types of LTC were associated with higher rates of mortality. One paper found that the rates of outcomes were higher in patients with at least one discordant LTC compared to patients with only concordant LTCs[15]. No association was identified between mental health and chronic pain LTCs and Myocardial Infarction[35].

Meta-analysis

Data synthesis was problematic because each study reported different effect sizes for different categorical groups. We therefore performed meta-analysis for all-cause mortality where several studies used comparable methodologies. Figure 2 included studies that used CCI as a continuous variable, demonstrating that with each increase in CCI, the risk of mortality was higher (Total HR 1.31 (95% confidence interval 1.27-1.36)). Figure 3 included studies that used condition count as a categorical variable: demonstrating that patients with multimorbidity were at higher risk of mortality compared to patients without multimorbidity (Total RR 2.28 (95% confidence interval 1.81-2.88)). Risk ratio were used here because time to event data were not available for all these studies and so hazard ratios could not be calculated. There was considerable statistical heterogeneity in the studies included in each meta-analysis (I^2 97% in figure 2 and 78% in figure 3). Sub-group analyses were not possible such as for patients with mild-moderate CKD because there were inadequate studies.

Risk of bias

All studies selected patients with and without multimorbidity from the same cohort and used either secure medical records or structured interviews to collect data. Most studies included just one group of patients with CKD such as patients receiving HD and only three studies included patients with a true range of mild to severe CKD[15, 27, 35]. All but two studies controlled for factors such as ischaemic heart disease, age or diabetes[17, 22]. Only one study made a statement about subjects who were lost to follow-up[26]. However, as all the studies were based on health care databases, it is reasonable to assume complete or near-complete follow-up. All studies followed up patients for more than one year, but there was variation in the average length of follow-up (from 13.1 to 81.6 months). Four studies did not specify the average follow-up time but from their survival analyses, it was clear that patients were followed up for at least one year[25, 30, 36, 39].

The NOS score evaluation of each study was between five and seven stars (See Supplementary File 4). The two studies that did not control for confounding factors were "poor" quality as per Agency for Healthcare Research and Quality standards[17, 22, 40]. The remainder were "good" quality[14-16, 18-21, 23-39].

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to synthesise the existing evidence on the associations between multimorbidity and outcomes specific to patients with CKD. It is increasingly recognised that multimorbidity and the management of patients with disease clusters are challenging problems[41]. The medical profession has been given a mandate to improve the care of patients affected by multimorbidity and to do so, improving our understanding of the issues will be fundamental. Multimorbidity has been studied in the general population, with clear associations reported between it and high rates of mortality[42]. It is time for researchers to build a body of evidence about patients with kidney disease. Our review demonstrates that for patients with CKD,

multimorbidity is associated with high rates of mortality, and the risk is higher with increasing numbers of LTCs. Unfortunately, the literature provides little detail beyond this association. Of the papers in the review, only two categorised LTCs and studied whether the type of LTCs influenced outcomes. Tonelli *et al* and Bowling *et al* found that concordant LTCs such as diabetes were associated with high rates of mortality, but so were discordant or unrelated LTCs like cancer and depression[15, 35]. Bowling *et al* found that the presence of one or more discordant LTC conferred higher risk compared to patients with only concordant LTCs. This suggests that there are groups of patients in whom it is not just the number but also the type of LTCs that puts them at elevated risk. Further research is needed into what patterns or clusters of disease exist to help clinicians understand the risks faced by patients with CKD and multimorbidity.

Patients require clinicians to help with their overall health and quality of life, not just the status of individual LTCs. As seen in the Standardized Outcomes in Nephrology−Hemodialysis (SONG-HD) initiative, patients usually wish to understand the risks they face. However, there is often a mismatch between the outcomes regarded as important by patients to those emphasised in clinical guidelines[43, 44]. It is therefore imperative that we consider patient-oriented outcomes when studying multimorbidity and ensure that research leads to improvements in care for patients. A limitation of our review is that we did not summarise outcomes prioritised by patients. The merit in investigating multimorbidity in patients with CKD will be that patients and clinicians will have an improved understanding of the risks they face. They will therefore be able to prioritise particular interventions such as cardiovascular risk factor modification and vascular access creation.

Despite the methodological and clinical heterogeneity of the studies in our review, the findings are consistent with existing literature[11]. We have confirmed associations between multimorbidity and adverse clinical outcomes in RRT and non-RRT settings, and in a range of countries. 21 of 26 studies included patients with advanced CKD including those on RRT.

However, it should be noted that there was no information available from low or middle income countries. Mild to moderate CKD was also under-represented, despite this constituting 99% of the patients with CKD[45]. Multimorbidity in patients with CKD from low and middle income countries and in those with mild to moderate CKD should therefore be targets for future research. Only two studies assessed the influence of multimorbidity on cardiovascular outcomes[33, 35]. Cardiovascular morbidity and mortality is the most significant risk for patients with CKD and many of the LTCs that occur in patients with CKD are risk factors for cardiovascular events[10]. Further research is therefore needed to explore how multimorbidity influences cardiovascular events in patients with CKD. Of the four studies that examined the influence of multimorbidity on renal progression, all but one were in patients with renal transplants. The study in non-transplant patients identified an association between multimorbidity and renal progression[27]. This risk is a significant one, particularly for the patients who develop the need for RRT. Many patient cohorts around the world have ample follow-up data and so the influence of multimorbidity on renal progression in non-transplant cohorts should be studied in greater detail.

The studies included in our review are heterogenous. Clinical heterogeneity is evident in the range of populations studied: stage 3 CKD, HD, PD, transplant and conservative care. There are high levels of methodological and statistical heterogeneity. There is no consensus as to which Multimorbidity Measure should be used, and which measure is the most effective at predicting adverse outcomes[46]. CCI was the most commonly used measure, although a number of modifications have been made for use in populations with CKD. Three studies included in this review compared different Multimorbidity Measures. CCI was found to effectively predict mortality risk, with other scoring systems performing comparably and none superior to the rest. Although our work demonstrates that various Multimorbidity Measures are associated with adverse clinical outcomes, we have not identified the best Multimorbidity Measure for risk prediction.

It has been recognised that there are fewer randomised controlled trials (RCTs) to assess the efficacy of interventions in patients with CKD than in other medical specialties and that patients with CKD are often excluded from RCTs[47, 48]. Furthermore, patients with advanced CKD that are included in RCTs are not representative of the wider population of those with CKD[49]. Similar observations have been made in other fields, whereby subjects with multimorbidity are underrepresented in trials of novel interventions[50]. Therefore, to improve outcomes for patients with CKD, both epidemiological studies and RCTs need to account for the range of multimorbidity in patients with CKD. A strength of our review is that it brings together information about the effects of multimorbidity in patients with CKD from various settings to create a comprehensive picture of the effects on different outcomes. Although the studies are challenging to summarise given the heterogeneity, the data are ample and clinically acceptable and therefore likely to be correct. Meta-analysis was performed with data from only 10 studies. The data from 16 studies, including those with large sample sizes, therefore did not contribute to full data analysis. If a uniform Multimorbidity Measure were agreed and established in guidelines, the comparability and synthesis of data in future would be improved. The evaluation of the effects of types of LTCs on outcomes was limited because only two studies examined this issue. A key focus of research should therefore be what patterns of multimorbidity or disease clusters exist in groups of patients with CKD.

In conclusion, this review provides evidence of associations between multimorbidity and heightened risk of adverse clinical outcomes in patients with CKD. Our findings emphasise the need for further research into the details of how multimorbidity influences different outcomes. In particular, evidence gaps exist for patients with mild to moderate CKD, for outcomes other than mortality such as renal progression and cardiovascular events, for patients with CKD from low and middle income countries and for the patterns of multimorbidity that contribute to heightened risk.

Acknowledgements

We thank Paul Cannon of the University of Glasgow Library for assistance with the literature search.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Conflicts of Interest

The results presented in this paper have not been published previously in whole or part.

Michael Sullivan, Alastair Rankin, Bhautesh Dinesh Jani and Frances S. Mair have no conflicts of interest. Patrick B. Mark reports personal fees and non-financial support from Vifor, personal fees from Astrazeneca, grants from Boehringer Ingelheim, personal fees and non-financial support from Pharmacosmos, personal fees from Janssen, personal fees from Novartis, personal fees from Pfizer, personal fees from Bristol Myers Squibb, personal fees and non-financial support from Napp, outside the submitted work.

Author Contributions

Michael Sullivan, Alastair Rankin, Bhautesh Dinesh Jani, Frances S. Mair and Patrick B. Mark contributed to conceptualisation, appraisal of results, writing (review and editing) and manuscript approval. Michael Sullivan, Alastair Rankin and Patrick B. Mark performed data analysis. Michael Sullivan and Alastair Rankin performed data extraction. Michael Sullivan prepared the original manuscript draft.

Word Count

3739 words.

Figure Legends

Figure 1. PRISMA flow diagram

Figure 2. Mortality risk for each increase in Charlson Comorbidity Index (Generic Inverse Variance Method, Fixed Effects Model)

Figure 3. Mortality risk for patients with multimorbidity (Mantel-Haenszel Method, Fixed Effects Model)

Data availability statement

All relevant data are included in the article or uploaded as supplementary information.

Tables

Reference	Country	Setting	Sample size	Average follow-up (months)	Outcome(s)	
					Mortality	Others
DIALYSIS						
Beddhu 2000	USA	HD/PD	268	13.1	✓	Hospitalisation
Chae 2010	South Korea	HD	456	40.6	✓	
Chandna 1999	UK	HD/PD	292	63	✓	Hospitalisation
Chandna 2010	UK	CC/RRT	844	58.7*	✓	
Davies 1995	UK	PD	97	30	✓	
Davies 2002	UK	PD	303	72.0*	✓	
Di Iorio 2004	Italy	HD	515	15	✓	
Fried 2001	USA	PD	268	16.9	✓	
Hemmelgarn 2003	Canada	HD/PD	237	26.3	✓	
Park 2015	South Korea	HD	24738	47.7	✓	
Rattanasompattikul 2012	USA	HD	893	72	✓	
Shum 2013	China	PD/CC	157	23.5	✓	Hospitalisation
van Manen 2002	Netherlands	HD/PD	589	NK	✓	
Wu 2013	Taiwan	HD/PD	79645	NK	✓	
NON-RRT CKD						
Bowling 2016	USA	CKD 3-5	821334	81.6	✓	
Fraser 2015	UK	CKD 3	1741	43.2	✓	
Lee 2018	Taiwan	CKD 3-5	1463	76.7	✓	Renal progression

Lhotta 2003	Austria	CKD 5	75	48	✓	
Ritchie 2009	USA	CKD/Heart failure	1974	32.6	✓	Hospitalisation, HF hospitalisation, CV death
Tonelli 2015	Canada	CKD 3-5	530771	48	✓	Hospitalisation, Myocardial Infarction
TRANSPLANT						
Fernandez 2019	USA	Tx assessment	2086	NK	✓	
Grosso 2012	Italy	Tx recipients	223	NK	✓	Renal Progression
Pieloch 2015	USA	Tx recipients	100261	36	✓	Renal Progression
Wu 2005	USA	Tx recipients	715	40.2	✓	Renal Progression
CONSERVATIVE CARE						
Ellam 2008	UK	CC	69	21*	✓	
Wong 2007	UK	CC	73	23.4*	✓	

Table 1. Study characteristics. HD, haemodialysis; PD, peritoneal dialysis; CKD, chronic kidney disease; RRT, renal replacement therapy; CC, conservative care; Tx, transplant; NK, Not Known. *Median survival

Variable Type	Multimorbidity Measure: number of studies				
	CCI	Condition Count	CSS	KTMI	Heart failure and CKD versus Heart failure, CKD and diabetes
Categorical	6	4	1	1	1
Continuous	6	4	1	0	0

Table 2. Studies using each Multimorbidity measure. CCI, Charlson Comorbidity Index; CSS, Comorbidity Severity Score; KTMI, Kidney Transplant Morbidity Index.

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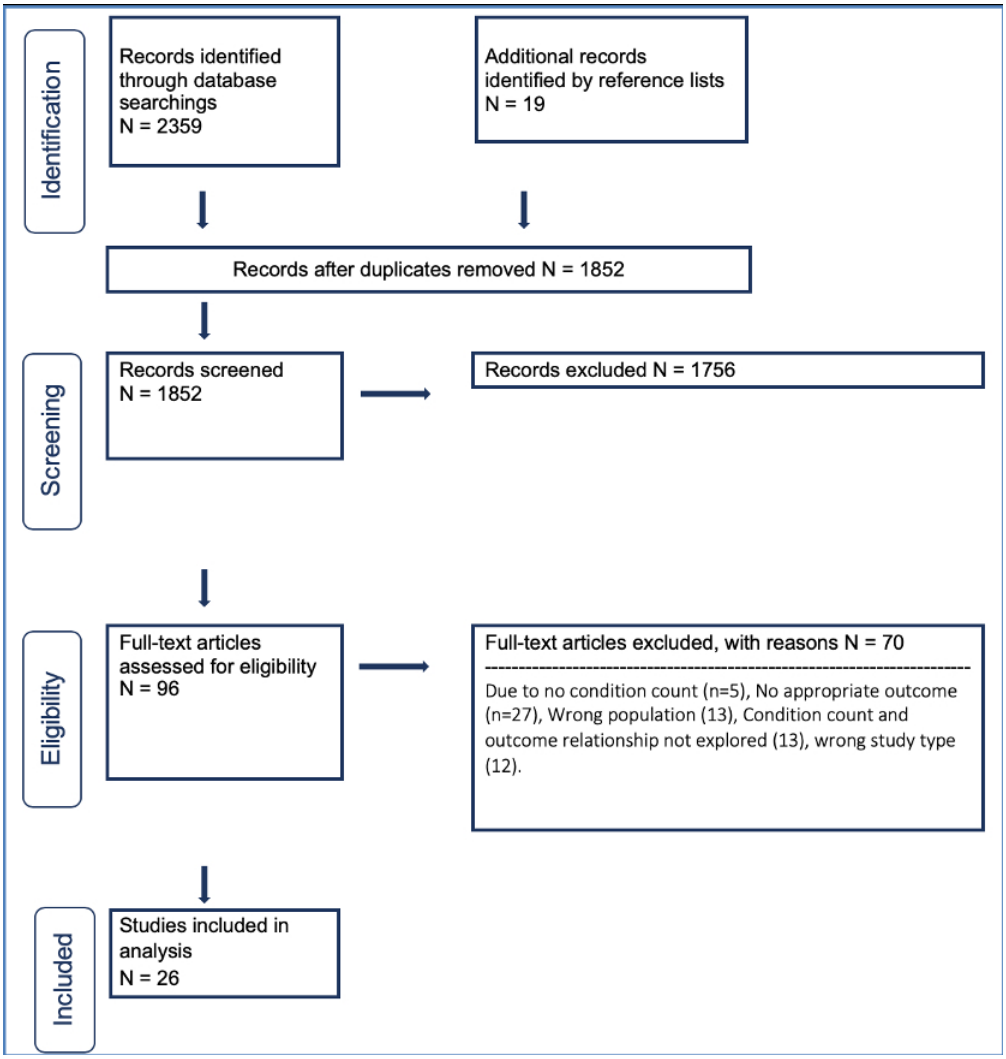
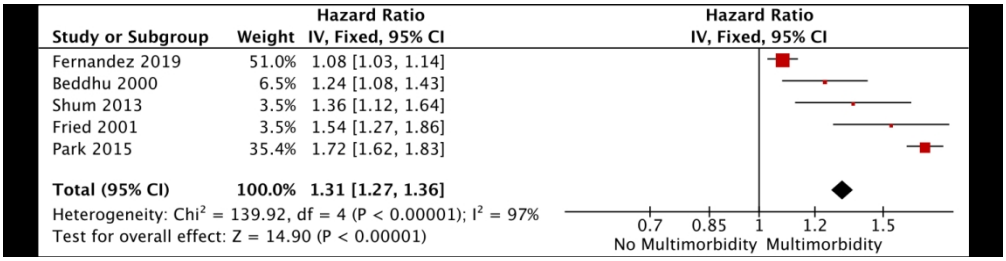
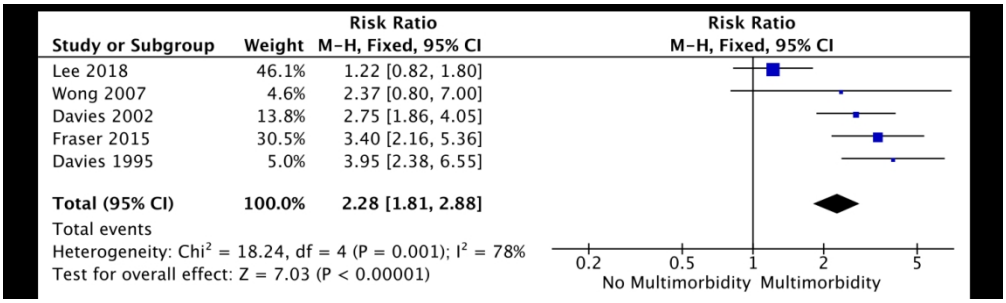


PRISMA flow diagram



Mortality risk for Charlson Comorbidity Index as a continuous variable (Generic Inverse Variance Method, Fixed Effects Model)



Mortality risk for patients with multimorbidity (Mantel-Haenszel Method, Fixed Effects Model)

Supplementary File 1. Database Search Terms

Subject headings	Chronic Kidney Failure Kidney Failure Chronic Renal Insufficiency Renal Insufficiency Kidney Disease Kidney Dysfunction Mild renal impairment Moderate renal impairment Severe renal impairment Subclinical renal impairment Renal replacement therapy Hemodialysis Peritoneal Dialysis Continuous Ambulatory Peritoneal DIalysis Kidney transplantation Kidney graft	Multimorbidity Multiple Chronic Conditions	Humans Adult
Textwords	Chronic kidney or chronic renal CKF, CKD, CRF or CRD Predialysis or pre-dialysis Renal failure or kidney failure Kidney disease Renal insufficienc* Hemodialysis or Haemodialysis Hemodiafiltration or haemodiafiltration Dialysis Endstage renal or endstage kidney Peritoneal dialysis CAPD or APD or CCPD or PD Kidney Transplant	Multimorbid* or multi morbid Condition count Multiple condition or multicondition or multi condition Multiple disease or multidisease or multi disease Multiple disorder or multidisorder or multi disorder Multiple comorbidities or multiple co morbidities Discordant comorbidities or concordant comorbidities	Adult* or aged* or elderly

Supplementary File 2. NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort ie chronic kidney disease (CKD) with multimorbidity (MM)
   a) truly representative of the average CKD/MM population in the community *
   b) somewhat representative of the average CKD/MM population in the community *
   c) selected group of users eg only one disease group
   d) no description of the derivation of the cohort

2) Selection of the unexposed cohort ie CKD without MM
   a) drawn from the same community as the exposed cohort *
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort
   d) no control group

3) Ascertainment of CKD/MM status
   a) secure record (eg medical records) *
   b) structured interview *
   c) written self report
   d) no description

4) Demonstration that outcomes were not present at start of study
   a) yes *
   b) no

Comparability

1) Comparability of cohorts on the basis of the design ie are exposed/non-exposed individuals matched or do the authors actively control for confounding factors?
   a) study controls for ischaemic heart disease *
   b) study controls for additional factor(s) *
   Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

Outcomes

1) Assessment of outcome(s)
   a) independent blind assessment *
   b) record linkage *
   c) self report
   d) no description

2) Was follow-up long enough ie > 1 year
   a) yes *
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for *
   b) subjects lost to follow up unlikely to introduce bias - small number lost to follow up, or description provided of those lost) *
   c) high lost to follow up rate and no description of those lost
   d) no statement

Total stars /8

Supplementary File 3. Results from included studies

Reference	Effect size	CCI groups	Effect size (95% Confidence Interval)
CATEGORICAL PRESENTATION OF EFFECT SIZE			
Chae 2010	HRs	**A. Standard CCI variables**	
		Quartile 1 (CCI 2)	Ref
		Quartile 2 (CCI 4-5)	9.22 (3.29-25.84)
		Quartile 3 (CCI 6)	16.77 (5.97-47.11)
		Quartile 4 (CCI 7-11)	22.37 (8.08-61.93)
		B. CCI excluding age and diabetes	
		Tertile 1 (CCI 2)	Ref
		Tertile 2 (CCI 3)	1.39 (1.01-2.05)
		Tertile 3 (CCI 4-8)	1.98 (1.25-3.14)
Wu 2005	HRs	**CCI excluding age**	
		CCI < 5	Ref
		CCI ≥ 5	2.88 (1.90-4.37)
Grosso 2012	HRs	**Modified CCI** 1 point: myocardial infarction, heart failure, peripheral vascular disease, COPD, connective tissue disease or mild liver disease 2 points: diabetes mellitus, cerebrovascular accident, solid tumour or leukaemia	
		CCI ≤ 1	Ref
		CCI > 1	3.87 (1.06-14.06)
Rattanasompattikul 2012	HRs	**CCI excluding age and renal disease**	
		Quartile 1 (CCI 0)	Ref
		Quartile 2 (CCI 1-2)	1.72 (1.26-2.36)
		Quartile 3 (CCI 3)	2.60 (1.13-3.26)
		Quartile 4 (CCI 4-9)	3.40 (2.41-4.79)
Wu 2013	HRs	**CCI excluding age**	
		CCI ≤ 3	Ref
		CCI 4-6	2.49 (2.35-2.63)
		CCI 7-9	3.53 (3.34-3.73)
		CCI 10-12	3.66 (3.45-3.88)
		CCI 13-15	4.12 (3.84-4.42)
		CCI > 15	4.42 (4.02-4.86)

CONTINUOUS PRESENTATION OF EFFECT SIZES			
Beddhu 2000	HRs	**Modified CCI** 1 point: coronary artery disease, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, mild liver disease, diabetes 2 points: hemiplegia, moderate or severe renal disease, diabetes with end-organ damage, any tumour, leukaemia, lymphoma 3 points: moderate or severe liver disease 6 points: metastatic solid tumour, AIDS	
		Each increase in CCI	1.24 (1.11-1.39)
Fried 2001	Relative risk	**Standard CCI variables**	
		Each increase in CCI	1.54 (1.36-1.74)
Park 2015	HRs	**A. Standard CCI variables**	
		Each increase in CCI	1.42 (1.39-1.45)
		B. Modified CCI in incident haemodialysis patients Details not provided	
		Each increase in CCI	1.72 (1.66-1.78)
Shum 2013	HRs	**ESRD Modified CCI**	
		Each increase in CCI (PD group only)	1.36 (1.18-1.56)
CONTINUOUS AND CATEGORICAL PRESENTATION OF EFFECT SIZES			
Fernandez 2019	HRs	**ESRD Modified CCI**	
		Each increase in CCI	1.08 (1.03-1.13)
		Low comorbidity burden CCI 0-1	Ref
		High comorbidity burden CCI ≥ 2	1.38 (1.01-1.89)

Results from studies using Charlson Comorbidity Index (CCI) as Multimorbidity Measure. HR; hazard ratio. COPD; Chronic Obstructive Pulmonary Disease. AIDS; Acquired Immune Deficiency Syndrome. PD; peritoneal dialysis.

Reference	Effect size	Conditions and groups	Effect size (95% Confidence Interval)
CATEGORICAL PRESENTATION OF EFFECT SIZE			
Bowling 2016	HRs	22 conditions: hypertension, hyperlipidemia, coronary heart disease, atrial fibrillation, heart failure, peripheral arterial disease, arthritis, osteoporosis, gout, diabetes, hypothyroidism, cancer, prostate cancer, anaemia, cerebrovascular disease, depression, dementia, epilepsy, Parkinson's disease, gastroesophageal reflux disease/peptic ulcer disease, benign prostatic hypertrophy and COPD/asthma	
		1	Ref
		2	0.95 (0.93-0.97)
		3	1.03 (1.01-1.05)
		4	1.24 (1.21-1.26)
		5	1.43 (1.39-1.47)
		≥ 6	1.72 (1.64-1.80)

Fraser 2015	HRs	11 conditions: hypertension, diabetes, ischaemic heart disease, heart failure, peripheral vascular disease, cerebrovascular disease, chronic respiratory disorder, depression, chronic painful condition, thyroid disorder and anaemia	
		0-1	Ref
		2	2.31 (1.36-3.94)
		≥ 3	4.58 (2.85-7.38)
Lee 2018	10-year survival rates	12 conditions: diabetes, hypertension, gout, heart failure, ischemic heart disease, cerebrovascular disease, liver disease, malignancy, tuberculosis, hyperlipidaemia, anaemia and connective tissue disease	
		0	93.7%
		1	94.3%
		2	92.9%
		≥ 3	92.7%
Tonelli 2015	HRs	29 conditions: alcohol misuse, asthma, atrial fibrillation, lymphoma, non-metastatic cancer, metastatic cancer, heart failure, chronic pain, COPD, chronic hepatitis B, cirrhosis, severe constipation, dementia, depression, diabetes, epilepsy, hypertension, hypothyroidism, inflammatory bowel disease, irritable bowel syndrome, multiple sclerosis, myocardial infarction, Parkinson's disease, peptic ulcer disease, peripheral vascular disease, psoriasis, rheumatoid arthritis, schizophrenia, and stroke or transient ischemic attack	
		0	Ref
		1	1.57 (1.50-1.63)
		2	2.34 (2.24-2.44)
		3	3.43 (3.29-3.58)
		4	4.81 (4.60-5.02)
		≥ 5	7.74 (7.43-8.07)
CONTINUOUS PRESENTATION OF EFFECT SIZES			
Davies 1995	HRs	**Development of the Stoke Comorbidity Grade** 11 conditions: ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, left ventricular dysfunction, diabetes mellitus, systemic collagen vascular disease, COPD, pulmonary fibrosis, pulmonary tuberculosis, asthma and cirrhosis Low grade: 0 conditions Intermediate grade: 1-2 conditions High grade: ≥ 3 conditions	
		Each increase in grade	2.66 (1.55-4.55)
Davies 2002	Relative risk	**Stoke Comorbidity Grade**	
		Each increase in grade	2.4 (1.4-4.1)
Ellam 2008	Narrative	**Stoke Comorbidity Grade**	"No statistically significant effect on survival"
Wong 2007	HRs	**Stoke Comorbidity Grade**	
		Each increase in grade	2.53 (1.32-4.83)
Lhotta 2003	HRs	Five conditions: diabetes, heart failure, coronary artery disease, cerebrovascular disease and peripheral vascular disease	
		Each increase in comorbidity score	1.78 (1.32-2.40)

Results from studies using Condition Count as Multimorbidity Measure. COPD; chronic obstructive pulmonary disease. HR; hazard ratio.

Reference	Effect size measure	Multimorbidity measure and groups	Effect size (95% Confidence Interval)
Chandna 1999	HRs	**Comorbidity severity score (CSS)** Cardiac score, according to New York Heart Association, respiratory disease score (1-4), cerebrovascular disease score (1-4), peripheral vascular disease score (1-4), cirrhosis (4), and malignancy score (1-4)	
		Each increase in CSS	1.238 (1.145-1.338)
Chandna 2010	HRs	**Comorbidity severity score**	
		Low comorbidity (CSS ≤ 4)	Ref
		High comorbidity (CSS > 4)	1.823 (1.255-2.650)
Pieloch 2015	HRs	**Kidney Transplant Morbidity Index**	
		0	Ref
		1	1.85 (1.45-2.36)
		2	3.11 (2.46-3.94)
		3	5.00 (3.96-6.31)
		4	7.37 (5.83-9.32)
		5	9.41 (7.41-11.94)
		6	12.15 (9.45-15.63)
		≥ 7	13.03 (9.68-17.54)
Ritchie 2009	HRs	**Heart failure, CKD and diabetes**	
		Heart failure and CKD	Ref
		Heart failure, CKD and diabetes	1.25 (1.07-1.46)

Results from studies using other Multimorbidity Measures. HR; hazard ratio. CKD; chronic kidney disease.

Reference	Scores studied	Presentation of effect size
Hemmelgarn 2003	CCI Development of ESRD modified CCI	Kaplan-Meier curves
Di Iorio 2004	CCI Development of CCI modified for haemodialysis patients	Relative risk, 5.5 for CCI
van Manen 2002	CCI Khan index Davies index Development of a new index	Kaplan-Meier curves

Studies that analyse different Multimorbidity Measures. CCI; Charlson Comorbidity Index

Supplementary File 4. Risk of bias: Results from Newcastle Ottawa Scale

Reference	Selection				Comparability	Outcome assessment			Quality score
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Beddhu 2000		✸	✸	✸	✸	✸	✸		6
Bowling 2016	✸	✸	✸	✸	✸	✸	✸		7
Chae 2010		✸	✸	✸	✸	✸	✸		6
Chandna 1999		✸	✸	✸	✸	✸	✸		6
Chandna 2010		✸	✸	✸		✸	✸		5
Davies 1995		✸	✸	✸	✸	✸	✸		6
Davies 2002		✸	✸	✸	✸	✸	✸		6
Di Iorio 2004		✸	✸	✸	✸	✸	✸		6
Ellam 2008		✸	✸	✸		✸	✸		5
Fernandez 2019		✸	✸	✸	✸	✸	✸		6
Fraser 2015		✸	✸	✸	✸	✸	✸		6
Fried 2001		✸	✸	✸	✸	✸	✸		6
Grosso 2012		✸	✸	✸	✸	✸	✸		6
Hemmelgarn 2003		✸	✸	✸	✸	✸	✸	✸	7
Lee 2018	✸	✸	✸	✸	✸	✸	✸		7
Lhotta 2003		✸	✸	✸	✸	✸	✸		6
Park 2015		✸	✸	✸	✸	✸	✸		6
Pieloch 2015		✸	✸	✸	✸	✸	✸		6
Rattanasompattikul 2012		✸	✸	✸	✸	✸	✸		6
Ritchie 2009		✸	✸	✸	✸	✸	✸		6
Shum 2013		✸	✸	✸	✸	✸	✸		6
Tonelli 2015	✸	✸	✸	✸	✸	✸	✸		7
van Manen 2002		✸	✸	✸	✸	✸	✸		6
Wong 2007		✸	✸	✸	✸	✸	✸		6
Wu 2005		✸	✸	✸	✸	✸	✸		6
Wu 2013		✸	✸	✸	✸	✸	✸		6

Table 3. Newcastle Ottawa Scale. 1. Representativeness of the exposed cohort. 2. Selection of the non-exposed cohort. 3. Ascertainment of chronic kidney disease/multimorbidity status. 4. Demonstration that outcomes were not present at start of study. 5. Comparability of cohorts on the basis of the design. 6. Assessment of outcome(s). 7. Was follow-up long enough. 8. Adequacy of follow up of cohort.

Reporting checklist for meta-analysis of observational studies.

Based on the MOOSE guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the MOOSEreporting guidelines, and cite them as:

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283(15):2008-2012.

	Reporting Item	Page Number
Title		
#1	Identify the study as a meta-analysis of observational research	1
Abstract		
#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number (From PRISMA checklist)	2, 3
Background		
#3a	Problem definition	4
#3b	Hypothesis statement	4
#3c	Description of study outcomes	5

	#3d	Type of exposure or intervention used	5
	#3e	Type of study designs used	5
	#3f	Study population	5
Methods			
Search strategy	#4a	Qualifications of searchers (eg, librarians and investigators)	N/A
Search strategy	#4b	Search strategy, including time period included in the synthesis and keywords	5
Search strategy	#4c	Effort to include all available studies, including contact with authors	5, 7
Search strategy	#4d	Databases and registries searched	5
Search strategy	#4e	Search software used, name and version, including special features used (eg, explosion)	5
Search strategy	#4f	Use of hand searching (eg, reference lists of obtained articles)	5
Search strategy	#4g	List of citations located and those excluded, including justification	7
Search strategy	#4h	Method of addressing articles published in languages other than English	5
Search strategy	#4i	Method of handling abstracts and unpublished studies	6
Search strategy	#4j	Description of any contact with authors	7
	#5a	Description of relevance or appropriateness of studies gathered for assessing the hypothesis to be tested	8
	#5b	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7
	#5c	Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	7

#5d	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7
#5e	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	7
#5f	Assessment of heterogeneity	7
#5g	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7
#5h	Provision of appropriate tables and graphics	16, 17, 18, supplemental file
Results		
#6a	Graphic summarizing individual study estimates and overall estimate	N/A
#6b	Table giving descriptive information for each study included	16, 17, 18
#6c	Results of sensitivity testing (eg, subgroup analysis)	N/A
#6d	Indication of statistical uncertainty of findings	10
Discussion		
#7a	Quantitative assessment of bias (eg. publication bias)	N/A
#7b	Justification for exclusion (eg, exclusion of non–English-language citations)	N/A
#7c	Assessment of quality of included studies	11
Conclusion		
#8a	Consideration of alternative explanations for observed results	N/A
#8b	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	12
#8c	Guidelines for future research	12
#8d	Disclosure of funding source	15

Notes:

- 5h: 16, 17, 18, supplemental file Reproduced with permission from JAMA. 2000. 283(15):2008-2012. Copyright © 2000 American Medical Association. All rights reserved.This checklist was completed on 09. March 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Associations between multimorbidity and adverse clinical outcomes in patients with chronic kidney disease: a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038401.R2
Article Type:	Original research
Date Submitted by the Author:	01-Jun-2020
Complete List of Authors:	Sullivan, Michael; University of Glasgow, Institute of Cardiovascular and Medical Sciences Rankin, Alastair; University of Glasgow, Institute of Cardiovascular and Medical Sciences Jani, Bhautesh; University of Glasgow, General Practice and Primary Care, Institute of Health and Wellbeing Mair, Frances; University of Glasgow, General Practice and Primary Care, Institute of Health and Wellbeing Mark, Patrick; University of Glasgow, Institute of Cardiovascular & Medical Sciences
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Epidemiology, General practice / Family practice
Keywords:	Chronic renal failure < NEPHROLOGY, Dialysis < NEPHROLOGY, Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, Ischaemic heart disease < CARDIOLOGY, End stage renal failure < NEPHROLOGY

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Associations between multimorbidity and adverse clinical outcomes in patients with chronic kidney disease: a systematic review and meta-analysis

Michael Sullivan[1], Alastair Rankin[1], Bhautesh Dinesh Jani[2], Frances S Mair[2], Patrick B Mark[1]

1 – Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

2 – General Practice and Primary Care, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK

Corresponding author:

Michael Sullivan

Address: Institute of Cardiovascular and Medical Sciences, University of Glasgow, 126 University Place, Glasgow, G12 8TA, UK

Telephone: +44(0) 141 330 2677

Email: Michael.sullivan@glasgow.ac.uk

Twitter Handle: @sullivanmk8

Keywords: chronic kidney disease, dialysis, comorbid, multimorbidity, diabetes, cardiovascular

Abstract

Objective: To systematically review the literature exploring the associations between multimorbidity (the presence of two or more long term conditions (LTCs)) and adverse clinical outcomes in patients with chronic kidney disease (CKD).

Design: Systematic Review and Meta-analysis.

Data sources: MEDLINE, EMBASE, CINAHL, Cochrane Library and SCOPUS (1946-2019). The main search terms were “Chronic Kidney Failure” and “Multimorbid*”.

Eligibility Criteria: Observational studies of adults over the age of 18 with CKD stages three to five i.e. eGFR less than 60ml/minute/1.73m^2. The exposure was Multimorbidity quantified by Measures and the outcomes were all-cause mortality, renal progression, hospitalisation and cardiovascular events. We did not consider CKD as a co-morbid LTC.

Data Extraction and Synthesis: Newcastle Ottawa Scale for quality appraisal and risk of bias assessment and fixed-effects meta-analysis for data synthesis.

Results: Of 1852 papers identified, 26 met the inclusion criteria. 21 papers involved patients with advanced CKD and no studies were from low or middle income countries. All-cause mortality was an outcome in all studies. Patients with multimorbidity were at higher risk of mortality compared to patients without multimorbidity (Total risk ratio 2.28 (95% confidence interval 1.81-2.88)). The risk of mortality was higher with increasing multimorbidity (Total hazard ratio 1.31 (1.27-1.36)) and both concordant and discordant LTCs were associated with heightened risk. Multimorbidity was associated with renal progression in four studies, hospitalisation in five studies and cardiovascular events in two studies.

Limitations: Meta-analysis could only include 10 of 26 papers as the methodologies of studies were heterogeneous.

Conclusions: There are associations between multimorbidity and adverse clinical outcomes in patients with CKD. However, most data relate to mortality risk in patients with advanced CKD. There is limited evidence regarding patients with mild to moderate CKD, outcomes

such as cardiovascular events, types of LTCs and regarding patients from low or middle income countries.

Prospero Registration: CRD42019147424.

Article Summary

Strengths and limitations of this study

- This review is the first to synthesise the existing evidence on multimorbidity in patients with CKD and it included a range of settings.
- The outcomes of interest were chosen by researchers and these do not include all outcomes that are important to patients e.g. quality of life.
- Two authors independently performed paper selection, data extraction and quality appraisal.
- Meta-analysis was performed, but only included selected papers because of methodological heterogeneity of papers.

Introduction

Multimorbidity is the presence of two or more long-term conditions (LTCs)[1]. In a Scottish study of 1.8 million patients, it was found to affect 23% of the whole population and in particular those from areas of lower socioeconomic status[2]. It is a problem for individual patients because it is associated with complex treatment regimens that result in a high burden of treatment and reduced quality of life[3]. For clinicians and health services, caring for these individuals represents a huge workload and equates to approximately two thirds of health care spending[4]. The current disease-orientated approaches of guidelines and healthcare are inadequate for patients with multiple LTCs and complex needs[5].

Multimorbidity is more common in patients with chronic kidney disease (CKD) than any other LTC: e.g. among 2.5 million Canadians, patients with CKD had more co-morbid LTCs than patients with lung disease (mean 4.2 LTCs versus 2.8)[6]. The prevalence of CKD is around 12%[7] and as this rises globally, the adverse effects of CKD and multimorbidity on quality of life are increasing[8]. The leading cause of death in patients with CKD is cardiovascular disease and although this is partly related to risk factors common to both conditions, low estimated glomerular filtration rate (eGFR) and proteinuria are predictors of cardiovascular mortality[9, 10]. The higher cardiovascular risk observed among CKD patients is independent of traditional atherosclerotic risk factors such as hypertension and dyslipdaemia, but the reasons for this and the influence of multimorbidity on CKD are incompletely understood. CKD and multimorbidity therefore occur together frequently and there are a number of issues common to both problems such as polypharmacy and significant treatment burden[11].

We undertook this systematic review to establish the current evidence concerning associations between multimorbidity and adverse clinical outcomes in patients with CKD.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines were followed[12] and this review was registered with the International Prospective Register of Systematic Reviews (CRD42019147424).

Literature Search

A comprehensive search strategy identified studies of patients with CKD that investigated the associations between multimorbidity and adverse clinical outcomes (see Supplementary File 1 for search terms). We included observational studies; in particular those using electronic health care records. There was no restriction on sample size. The databases searched included studies from 1946 to 2019. The search was limited to papers published in English. Databases searched were MEDLINE (OVID interface), EMBASE (OVID interface), CINAHL Complete (EBSCO interface), The Cochrane Library (OVID interface), and SCOPUS. Selected medical subject headings were combined with keywords relating to multimorbidity and CKD to create a search strategy which was produced for use in MEDLINE and amended for use in the other databases, using controlled vocabulary, Boolean operators and search symbols. The search was carried out to include literature published up to 29th August 2019. The results were supplemented with searches of reference lists of included studies. Search data were stored and merged using Endnote X9 (Clarivate Analytics, Philadelphia, USA) and papers were shared and assessed using DistillerSR (Evidence Partners, Ottawa, Canada).

Inclusion Criteria

We included empirical quantitative studies that contained data on associations between Multimorbidity Measures and all-cause mortality or additional outcomes in adults with CKD. We accepted any Multimorbidity Measure, which included simple counts of LTCs and co-morbidity scoring systems. We did not consider CKD as a co-morbid LTC because all of the patients in our papers had CKD. Additional outcomes were hospitalisation, cardiovascular

events, cardiovascular deaths, heart failure hospitalisations and renal progression (40% reduction in eGFR, doubling of serum creatinine or initiation of renal replacement therapy (RRT)). Studies that analysed the relationship between a Multimorbidity Measure and any of our outcomes of interest were included in adults over the age of 18 with CKD stages three to five i.e. eGFR less than 60ml/minute/1.73m^2 including those requiring RRT i.e. haemodialysis (HD), peritoneal dialysis (PD) or renal transplantation.

Exclusion Criteria

Review articles, drug intervention studies, qualitative studies, case reports and conference abstracts were excluded. Studies with children or adolescents aged 18 or under, animals and individuals without CKD were excluded.

The study selection process was conducted by two reviewers (MS, AR). Title screening was followed by abstract and full paper review, where necessary. Any inter-reviewer disagreements were resolved by a third reviewer (PM).

Data extraction

As recommended by the Cochrane Handbook[13], data were extracted in a Population, Exposure, Comparator, Outcomes (PECO) approach:

Population: We extracted data on the characteristics of study populations: country, sample size, follow-up time and setting i.e. CKD, HD, PD, renal transplant and conservative care.

Exposure: We extracted the Multimorbidity Measure used in each study and whether LTCs were categorised into different types for analysis.

Comparator: We extracted the details provided of comparator groups i.e. patients with CKD with less than two LTCs. We did not count CKD as an LTC.

Outcomes: We extracted details of the statistical analyses employed to evaluate the relationship between Multimorbidity Measure and outcomes. Risks were expressed as effect sizes with 95% confidence intervals, where available.

Data synthesis and analysis

Results were presented in a narrative format. Where possible, fixed effects meta-analysis was performed for the primary outcome, all-cause mortality. Previous systematic reviews including patients from the general population have demonstrated consistent associations between multimorbidity and mortality[14]. We assumed the direction of effect of multimorbidity on mortality would be consistent across our studies, barring sampling errors and differences in sample size, and so we applied fixed effects models. However, random effects models were also performed as sensitivity analysis, as this approach would be more helpful if the participants in the included studies were inherently different. The Generic Inverse Variance method was used where multimorbidity was expressed as a continuous variable and the Mantel-Haenszel method was used where multimorbidity was expressed as a categorical variable. Quantification of statistical heterogeneity was assessed by means of I^2, which shows the percentage of total variation across studies due to heterogeneity[13]. These analyses were carried out using RevMan Version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). Meta-analysis was limited by heterogeneous methodologies: variable Multimorbidity Measures, use of effect sizes (Hazard ratios (HRs), Risk ratios (RRs), Kaplan Meier curves) and the use of multimorbidity as a continuous and categorical variable. We therefore performed meta-analysis where several studies used similar methodologies. Data on numbers of deceased patients were not available for all studies and so we contacted study authors for their primary data. For meta-analysis and where necessary and possible, we calculated RRs for studies, comparing patients with multimorbidity to those without multimorbidity. HRs could not be calculated as there were no individual time-to-event data.

Quality appraisal

Two researchers conducted quality appraisal independently (MS, AR). Studies were assessed using an adapted Newcastle-Ottawa quality assessment scale (NOS), as informed by the Cochrane Handbook[13] (see Supplementary File 2). Studies were not excluded based on quality appraisal.

Patient and public involvement

No patients involved.

Results

Search results

Figure 1 demonstrates the literature search flow. After the removal of duplicate papers, 1852 papers were identified. 1756 papers were excluded as they were not relevant and so 96 full papers were screened and 26 papers met our eligibility criteria and were included in the review[15-40].

Study characteristics

Table 1 lists the characteristics of the 26 included studies. The studies were published between 1995 and 2019 and all used a cohort design. The size of populations was between 69 and 821,334. Fourteen studies examined subjects predominantly on dialysis[15, 17-22, 25, 27, 30, 33, 35, 33, 40]; five included patients with CKD stages 3 to 5[16, 24, 24, 34, 36] including two with mild CKD [24, 34]; two involved patients with CKD stage 5 including those not on RRT or conservative care[29, 31]; two included those receiving conservative care[23, 38]; three included renal transplant recipients[26, 32, 39].

Table 2 shows the number of studies using each Multimorbidity Measure and how the corresponding effect sizes were presented: as a categorical or a continuous variable. In addition to these, three studies examined more than one Multimorbidity Measure: comparing how effectively each measure predicted outcomes[22, 27, 37]. Ten studies used the Charlson Comorbidity Index (CCI) or a modification of this scale (mCCI)[15, 17, 25, 26, 30, 31, 33, 35, 39, 40].

Seven studies used the number of LTCs i.e. condition count[16, 23, 24, 28, 29, 36, 38]. Two studies used the Stoke comorbidity grade, which uses condition count to divide patients into low, intermediate and high grades[20, 21]. Two studies used the Comorbidity severity score[18, 19]. One study compared those with CKD, diabetes and heart failure to those with just CKD and heart failure[34]. One study used the Kidney Transplant Morbidity Index[32].

All studies reported the effect of multimorbidity on all-cause mortality. Five studies reported the effect of multimorbidity on hospitalisation[15, 19, 34-36] and four on renal progression[26, 28, 32, 39]. One study reported the effect of multimorbidity on heart failure hospitalisation and cardiovascular death[34] and one study reported the effect of multimorbidity on myocardial infarction[36]. Twelve studies expressed effect sizes using multimorbidity as a categorical variable[16-18, 24, 26, 28, 32-34, 36, 39, 40], nine as a continuous variable[15, 19-21, 25, 29, 30, 35, 38] and one as both[31]. One study gave a narrative comparison of groups[23] and two used Kaplan-Meier curves[27, 37]. Two studies categorised LTCs into types: both used concordant and discordant as types and one also specified mental health and chronic pain LTCs[16, 36].

Main findings

The results of the included studies were summarised in Supplementary File 3. Some papers did not provide adjusted HRs. To make it easier to compare the studies, we therefore quoted unadjusted HRs. Where multimorbidity was used as a categorical variable, 12 of 13 studies found that patients with multimorbidity had higher rates of mortality than patients without multimorbidity. In the one study that did not detect a difference, Lee *et al*'s primary outcome was renal progression[28]. For all-cause mortality, the authors provided event rates and Kaplan Meier Curves but there were no HRs with adjustments for confounding variables.

Where multimorbidity was used as a continuous variable, 10 of 11 studies found that with each increase in Multimorbidity Measure, all-cause mortality was higher. In the one study to not detect a difference, Ellam *et al* was a study of just 69 conservatively-managed patients[23].

Of the four studies that reported renal progression, three were in renal transplant recipients[26, 31, 32]. All four studies demonstrated higher rates of renal progression in patients with multimorbidity (HRs from each study 2.97 (1.53-5.76), 2.44 (1.19-5.02), 3.11 (2.55-3.80), 1.42 (1.02-1.97). Renal progression was defined by graft loss or RRT initiation and one paper reported significant annual reductions in eGFR by increasing number of LTCs[28]. Five studies reported rates of hospitalisation and all of these identified an association between multimorbidity and hospitalisation[15, 19, 34-36].

One paper reported rates of Heart Failure Hospitalisation and Cardiovascular Death[34]: patients with multimorbidity had higher rates of both outcomes than patients without multimorbidity. One paper reported higher rates of Myocardial Infarction in patients with multimorbidity[36].

Two papers described the influence of concordant and discordant LTCs on adverse outcomes[16, 36]. These papers found that both types of LTC were associated with higher rates of mortality. One paper found that the rates of outcomes were higher in patients with at least one discordant LTC compared to patients with only concordant LTCs[16]. No association was identified between mental health and chronic pain LTCs and Myocardial Infarction[36].

Meta-analysis

Data synthesis was problematic because each study reported different effect sizes for different categorical groups. We therefore performed meta-analysis for all-cause mortality where several studies used comparable methodologies. Figure 2 included studies that used CCI as a continuous variable, demonstrating that with each increase in CCI, the risk of mortality was higher (Total HR 1.31 (95% confidence interval 1.27-1.36)). All studies included in this meta-analysis had HRs available. Figure 3 included studies that used condition count as a categorical variable: demonstrating that patients with multimorbidity were at higher risk of mortality compared to patients without multimorbidity (Total RR 2.28

(95% confidence interval 1.81-2.88)). Risk ratio were used here because time to event data were not available for all these studies and so hazard ratios could not be calculated. There was considerable statistical heterogeneity in the studies included in each meta-analysis (I^2 97% in figure 2 and 78% in figure 3). Sub-group analyses were not possible such as for patients with mild-moderate CKD because there were inadequate studies. Where random effects models were fitted, there remained significant associations between multimorbidity and all-cause mortality (Supplemental File 4). For studies that used CCI as a continuous variable, the risk of mortality was higher for each increase in CCI (Total HR 1.37 (95% confidence interval 1.07-1.75)). For studies that used condition count as a categorical variable, patients with multimorbidity were at higher risk of mortality compared to patients without multimorbidity (Total RR 2.53 (95% confidence interval 1.57-4.07)).

Risk of bias

All studies selected patients with and without multimorbidity from the same cohort and used either secure medical records or structured interviews to collect data. Most studies included just one group of patients with CKD such as patients receiving HD and only three studies included patients with a true range of mild to severe CKD[16, 28, 36]. All but two studies controlled for factors such as ischaemic heart disease, age or diabetes[18, 23]. Only one study made a statement about subjects who were lost to follow-up[27]. However, as all the studies were based on health care databases, it is reasonable to assume complete or near-complete follow-up. All studies followed up patients for more than one year, but there was variation in the average length of follow-up (from 13.1 to 81.6 months). Four studies did not specify the average follow-up time but from their survival analyses, it was clear that patients were followed up for at least one year[26, 31, 37, 40].

The NOS score evaluation of each study was between five and seven stars (See Supplementary File 5). The two studies that did not control for confounding factors were

"poor" quality as per Agency for Healthcare Research and Quality standards[18, 23, 41]. The remainder were "good" quality[15-17, 19-22, 24-40].

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to synthesise the existing evidence on the associations between multimorbidity and outcomes specific to patients with CKD. It is increasingly recognised that multimorbidity and the management of patients with disease clusters are challenging problems[42]. The medical profession has been given a mandate to improve the care of patients affected by multimorbidity and to do so, improving our understanding of the issues will be fundamental. Multimorbidity has been studied in the general population, with clear associations reported between it and high rates of mortality[43]. It is time for researchers to build a body of evidence about patients with kidney disease. Our review demonstrates that for patients with CKD, multimorbidity is associated with high rates of mortality, and the risk is higher with increasing numbers of LTCs. Unfortunately, the literature provides little detail beyond this association. Of the papers in the review, only two categorised LTCs and studied whether the type of LTCs influenced outcomes. Tonelli *et al* and Bowling *et al* found that concordant LTCs such as diabetes were associated with high rates of mortality, but so were discordant or unrelated LTCs like cancer and depression[16, 36]. Bowling *et al* found that the presence of one or more discordant LTC conferred higher risk compared to patients with only concordant LTCs. This suggests that there are groups of patients in whom it is not just the number but also the type of LTCs that puts them at elevated risk. Further research is needed into what patterns or clusters of disease exist to help clinicians understand the risks faced by patients with CKD and multimorbidity.

Patients require clinicians to help with their overall health and quality of life, not just the status of individual LTCs. As seen in the Standardized Outcomes in Nephrology−Hemodialysis (SONG-HD) initiative, patients usually wish to understand the

risks they face. However, there is often a mismatch between the outcomes regarded as important by patients to those emphasised in clinical guidelines[44, 45]. It is therefore imperative that we consider patient-oriented outcomes when studying multimorbidity and ensure that research leads to improvements in care for patients. A limitation of our review is that we did not summarise outcomes prioritised by patients. The merit in investigating multimorbidity in patients with CKD will be that patients and clinicians will have an improved understanding of the risks they face. They will therefore be able to prioritise particular interventions such as cardiovascular risk factor modification and vascular access creation.

Despite the methodological and clinical heterogeneity of the studies in our review, the findings are consistent with existing literature[11]. We have confirmed associations between multimorbidity and adverse clinical outcomes in RRT and non-RRT settings, and in a range of countries. 21 of 26 studies included patients with advanced CKD including those on RRT. However, it should be noted that there was no information available from low or middle income countries. Mild to moderate CKD was also under-represented, despite this constituting 99% of the patients with CKD[46]. Multimorbidity in patients with CKD from low and middle income countries and in those with mild to moderate CKD should therefore be targets for future research. Only two studies assessed the influence of multimorbidity on cardiovascular outcomes[34, 36]. Cardiovascular morbidity and mortality is the most significant risk for patients with CKD and many of the LTCs that occur in patients with CKD are risk factors for cardiovascular events[10]. Further research is therefore needed to explore how multimorbidity influences cardiovascular events in patients with CKD. Of the four studies that examined the influence of multimorbidity on renal progression, all but one were in patients with renal transplants. The study in non-transplant patients identified an association between multimorbidity and renal progression[28]. This risk is a significant one, particularly for the patients who develop the need for RRT. Many patient cohorts around the world have

ample follow-up data and so the influence of multimorbidity on renal progression in non-transplant cohorts should be studied in greater detail.

The studies included in our review are heterogenous. Clinical heterogeneity is evident in the range of populations studied: stage 3 CKD, HD, PD, transplant and conservative care. There are high levels of methodological and statistical heterogeneity. There is no consensus as to which Multimorbidity Measure should be used, and which measure is the most effective at predicting adverse outcomes[47]. CCI was the most commonly used measure, although a number of modifications have been made for use in populations with CKD. Three studies included in this review compared different Multimorbidity Measures. CCI was found to effectively predict mortality risk, with other scoring systems performing comparably and none superior to the rest. Although our work demonstrates that various Multimorbidity Measures are associated with adverse clinical outcomes, we have not identified the best Multimorbidity Measure for risk prediction.

It has been recognised that there are fewer randomised controlled trials (RCTs) to assess the efficacy of interventions in patients with CKD than in other medical specialties and that patients with CKD are often excluded from RCTs[48, 49]. Furthermore, patients with advanced CKD that are included in RCTs are not representative of the wider population of those with CKD[50]. Similar observations have been made in other fields, whereby subjects with multimorbidity are underrepresented in trials of novel interventions[51]. Therefore, to improve outcomes for patients with CKD, both epidemiological studies and RCTs need to account for the range of multimorbidity in patients with CKD. A strength of our review is that it brings together information about the effects of multimorbidity in patients with CKD from various settings to create a comprehensive picture of the effects on different outcomes. Although the studies are challenging to summarise given the heterogeneity, the data are ample and clinically acceptable and therefore likely to be correct. Meta-analysis was performed with data from only 10 studies. The data from 16 studies, including those with large sample sizes,

therefore did not contribute to full data analysis. If a uniform Multimorbidity Measure were agreed and established in guidelines, the comparability and synthesis of data in future would be improved. The evaluation of the effects of types of LTCs on outcomes was limited because only two studies examined this issue. A key focus of research should therefore be what patterns of multimorbidity or disease clusters exist in groups of patients with CKD.

In conclusion, this review provides evidence of associations between multimorbidity and heightened risk of adverse clinical outcomes in patients with CKD. Our findings emphasise the need for further research into the details of how multimorbidity influences different outcomes. In particular, evidence gaps exist for patients with mild to moderate CKD, for outcomes other than mortality such as renal progression and cardiovascular events, for patients with CKD from low and middle income countries and for the patterns of multimorbidity that contribute to heightened risk.

Acknowledgements

We thank Paul Cannon of the University of Glasgow Library for assistance with the literature search.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Conflicts of Interest

The results presented in this paper have not been published previously in whole or part.

Michael Sullivan, Alastair Rankin, Bhautesh Dinesh Jani and Frances S. Mair have no conflicts of interest. Patrick B. Mark reports personal fees and non-financial support from Vifor, personal fees from Astrazeneca, grants from Boehringer Ingelheim, personal fees and non-financial support from Pharmacosmos, personal fees from Janssen, personal fees from Novartis, personal fees from Pfizer, personal fees from Bristol Myers Squibb, personal fees and non-financial support from Napp, outside the submitted work.

Author Contributions

Michael Sullivan, Alastair Rankin, Bhautesh Dinesh Jani, Frances S. Mair and Patrick B. Mark contributed to conceptualisation, appraisal of results, writing (review and editing) and manuscript approval. Michael Sullivan, Alastair Rankin and Patrick B. Mark performed data analysis. Michael Sullivan and Alastair Rankin performed data extraction. Michael Sullivan prepared the original manuscript draft.

Word Count

3739 words.

Figure Legends

Figure 1. PRISMA flow diagram

Figure 2. Mortality risk for each increase in Charlson Comorbidity Index (Generic Inverse Variance Method, Fixed Effects Model)

Figure 3. Mortality risk for patients with multimorbidity (Mantel-Haenszel Method, Fixed Effects Model)

Data availability statement

All relevant data are included in the article or uploaded as supplementary information.

Tables

Reference	Country	Setting	Sample size	Average follow-up (months)	Outcome(s)	
					Mortality	Others
DIALYSIS						
Beddhu 2000	USA	HD/PD	268	13.1	✓	Hospitalisation
Chae 2010	South Korea	HD	456	40.6	✓	
Chandna 1999	UK	HD/PD	292	63	✓	Hospitalisation
Chandna 2010	UK	CC/RRT	844	58.7*	✓	
Davies 1995	UK	PD	97	30	✓	
Davies 2002	UK	PD	303	72.0*	✓	
Di Iorio 2004	Italy	HD	515	15	✓	
Fried 2001	USA	PD	268	16.9	✓	
Hemmelgarn 2003	Canada	HD/PD	237	26.3	✓	
Park 2015	South Korea	HD	24738	47.7	✓	
Rattanasompattikul 2012	USA	HD	893	72	✓	
Shum 2013	China	PD/CC	157	23.5	✓	Hospitalisation
van Manen 2002	Netherlands	HD/PD	589	NK	✓	
Wu 2013	Taiwan	HD/PD	79645	NK	✓	
NON-RRT CKD						
Bowling 2016	USA	CKD 3-5	821334	81.6	✓	
Fraser 2015	UK	CKD 3	1741	43.2	✓	
Lee 2018	Taiwan	CKD 3-5	1463	76.7	✓	Renal progression

Lhotta 2003	Austria	CKD 5	75	48	✓	
Ritchie 2009	USA	CKD/Heart failure	1974	32.6	✓	Hospitalisation, HF hospitalisation, CV death
Tonelli 2015	Canada	CKD 3-5	530771	48	✓	Hospitalisation, Myocardial Infarction
TRANSPLANT						
Fernandez 2019	USA	Tx assessment	2086	NK	✓	
Grosso 2012	Italy	Tx recipients	223	NK	✓	Renal Progression
Pieloch 2015	USA	Tx recipients	100261	36	✓	Renal Progression
Wu 2005	USA	Tx recipients	715	40.2	✓	Renal Progression
CONSERVATIVE CARE						
Ellam 2008	UK	CC	69	21*	✓	
Wong 2007	UK	CC	73	23.4*	✓	

Table 1. Study characteristics. HD, haemodialysis; PD, peritoneal dialysis; CKD, chronic kidney disease; RRT, renal replacement therapy; CC, conservative care; Tx, transplant; NK, Not Known. *Median survival

Variable Type	Multimorbidity Measure: number of studies				
	CCI	Condition Count	CSS	KTMI	Heart failure and CKD versus Heart failure, CKD and diabetes
Categorical	6	4	1	1	1
Continuous	6	4	1	0	0

Table 2. Studies using each Multimorbidity measure. CCI, Charlson Comorbidity Index; CSS, Comorbidity Severity Score; KTMI, Kidney Transplant Morbidity Index.

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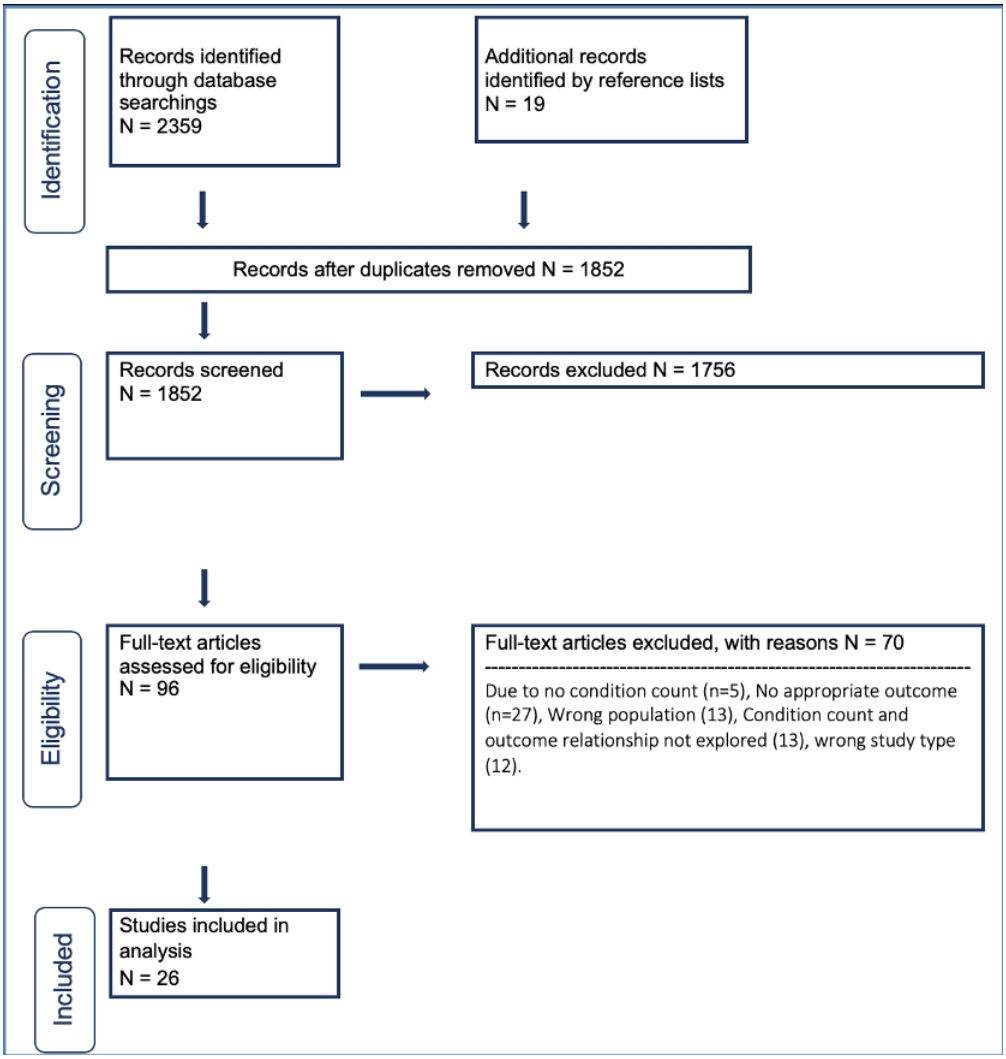
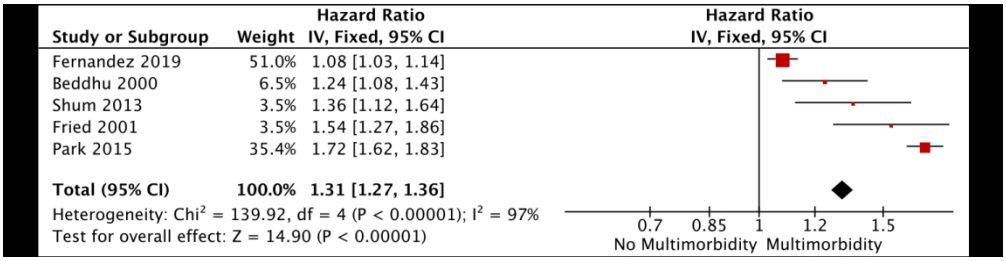
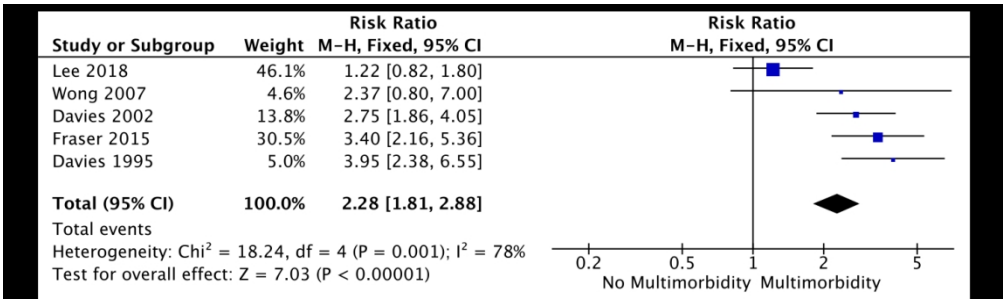


PRISMA flow diagram



Mortality risk for Charlson Comorbidity Index as a continuous variable (Generic Inverse Variance Method, Fixed Effects Model)



Mortality risk for patients with multimorbidity (Mantel-Haenszel Method, Fixed Effects Model)

Supplementary File 1. Database Search Terms

Subject headings	Chronic Kidney Failure Kidney Failure Chronic Renal Insufficiency Renal Insufficiency Kidney Disease Kidney Dysfunction Mild renal impairment Moderate renal impairment Severe renal impairment Subclinical renal impairment Renal replacement therapy Hemodialysis Peritoneal Dialysis Continuous Ambulatory Peritoneal DIalysis Kidney transplantation Kidney graft	Multimorbidity Multiple Chronic Conditions	Humans Adult
Textwords	Chronic kidney or chronic renal CKF, CKD, CRF or CRD Predialysis or pre-dialysis Renal failure or kidney failure Kidney disease Renal insufficienc* Hemodialysis or Haemodialysis Hemodiafiltration or haemodiafiltration Dialysis Endstage renal or endstage kidney Peritoneal dialysis CAPD or APD or CCPD or PD Kidney Transplant	Multimorbid* or multi morbid Condition count Multiple condition or multicondition or multi condition Multiple disease or multidisease or multi disease Multiple disorder or multidisorder or multi disorder Multiple comorbidities or multiple co morbidities Discordant comorbidities or concordant comorbidities	Adult* or aged* or elderly

Supplementary File 2. NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort ie chronic kidney disease (CKD) with multimorbidity (MM)
   a) truly representative of the average CKD/MM population in the community *
   b) somewhat representative of the average CKD/MM population in the community *
   c) selected group of users eg only one disease group
   d) no description of the derivation of the cohort

2) Selection of the unexposed cohort ie CKD without MM
   a) drawn from the same community as the exposed cohort *
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort
   d) no control group

3) Ascertainment of CKD/MM status
   a) secure record (eg medical records) *
   b) structured interview *
   c) written self report
   d) no description

4) Demonstration that outcomes were not present at start of study
   a) yes *
   b) no

Comparability

1) Comparability of cohorts on the basis of the design ie are exposed/non-exposed individuals matched or do the authors actively control for confounding factors?
   a) study controls for ischaemic heart disease *
   b) study controls for additional factor(s) *
   Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

Outcomes

1) Assessment of outcome(s)
   a) independent blind assessment *
   b) record linkage *
   c) self report
   d) no description

2) Was follow-up long enough ie > 1 year
   a) yes *
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for *
   b) subjects lost to follow up unlikely to introduce bias - small number lost to follow up, or description provided of those lost) *
   c) high lost to follow up rate and no description of those lost
   d) no statement

Total stars /8

Supplementary File 3. Results from included studies

Reference	Effect size	CCI groups	Effect size (95% Confidence Interval)
CATEGORICAL PRESENTATION OF EFFECT SIZE			
Chae 2010	HRs	**A. Standard CCI variables**	
		Quartile 1 (CCI 2)	Ref
		Quartile 2 (CCI 4-5)	9.22 (3.29-25.84)
		Quartile 3 (CCI 6)	16.77 (5.97-47.11)
		Quartile 4 (CCI 7-11)	22.37 (8.08-61.93)
		B. CCI excluding age and diabetes	
		Tertile 1 (CCI 2)	Ref
		Tertile 2 (CCI 3)	1.39 (1.01-2.05)
		Tertile 3 (CCI 4-8)	1.98 (1.25-3.14)
Wu 2005	HRs	**CCI excluding age**	
		CCI < 5	Ref
		CCI ≥ 5	2.88 (1.90-4.37)
Grosso 2012	HRs	**Modified CCI** 1 point: myocardial infarction, heart failure, peripheral vascular disease, COPD, connective tissue disease or mild liver disease 2 points: diabetes mellitus, cerebrovascular accident, solid tumour or leukaemia	
		CCI ≤ 1	Ref
		CCI > 1	3.87 (1.06-14.06)
Rattanasompattikul 2012	HRs	**CCI excluding age and renal disease**	
		Quartile 1 (CCI 0)	Ref
		Quartile 2 (CCI 1-2)	1.72 (1.26-2.36)
		Quartile 3 (CCI 3)	2.60 (1.13-3.26)
		Quartile 4 (CCI 4-9)	3.40 (2.41-4.79)
Wu 2013	HRs	**CCI excluding age**	
		CCI ≤ 3	Ref
		CCI 4-6	2.49 (2.35-2.63)
		CCI 7-9	3.53 (3.34-3.73)
		CCI 10-12	3.66 (3.45-3.88)
		CCI 13-15	4.12 (3.84-4.42)
		CCI > 15	4.42 (4.02-4.86)

CONTINUOUS PRESENTATION OF EFFECT SIZES			
Beddhu 2000	HRs	**Modified CCI** 1 point: coronary artery disease, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, mild liver disease, diabetes 2 points: hemiplegia, moderate or severe renal disease, diabetes with end-organ damage, any tumour, leukaemia, lymphoma 3 points: moderate or severe liver disease 6 points: metastatic solid tumour, AIDS	
		Each increase in CCI	1.24 (1.11-1.39)
Fried 2001	Relative risk	**Standard CCI variables**	
		Each increase in CCI	1.54 (1.36-1.74)
Park 2015	HRs	**A. Standard CCI variables**	
		Each increase in CCI	1.42 (1.39-1.45)
		B. Modified CCI in incident haemodialysis patients Details not provided	
		Each increase in CCI	1.72 (1.66-1.78)
Shum 2013	HRs	**ESRD Modified CCI**	
		Each increase in CCI (PD group only)	1.36 (1.18-1.56)
CONTINUOUS AND CATEGORICAL PRESENTATION OF EFFECT SIZES			
Fernandez 2019	HRs	**ESRD Modified CCI**	
		Each increase in CCI	1.08 (1.03-1.13)
		Low comorbidity burden CCI 0-1	Ref
		High comorbidity burden CCI ≥ 2	1.38 (1.01-1.89)

Results from studies using Charlson Comorbidity Index (CCI) as Multimorbidity Measure. HR; hazard ratio. COPD; Chronic Obstructive Pulmonary Disease. AIDS; Acquired Immune Deficiency Syndrome. PD; peritoneal dialysis.

Reference	Effect size	Conditions and groups	Effect size (95% Confidence Interval)
CATEGORICAL PRESENTATION OF EFFECT SIZE			
Bowling 2016	HRs	22 conditions: hypertension, hyperlipidemia, coronary heart disease, atrial fibrillation, heart failure, peripheral arterial disease, arthritis, osteoporosis, gout, diabetes, hypothyroidism, cancer, prostate cancer, anaemia, cerebrovascular disease, depression, dementia, epilepsy, Parkinson's disease, gastroesophageal reflux disease/peptic ulcer disease, benign prostatic hypertrophy and COPD/asthma	
		1	Ref
		2	0.95 (0.93-0.97)
		3	1.03 (1.01-1.05)
		4	1.24 (1.21-1.26)
		5	1.43 (1.39-1.47)
		≥ 6	1.72 (1.64-1.80)

Fraser 2015	HRs	11 conditions: hypertension, diabetes, ischaemic heart disease, heart failure, peripheral vascular disease, cerebrovascular disease, chronic respiratory disorder, depression, chronic painful condition, thyroid disorder and anaemia	
		0-1	Ref
		2	2.31 (1.36-3.94)
		≥ 3	4.58 (2.85-7.38)
Lee 2018	10-year survival rates	12 conditions: diabetes, hypertension, gout, heart failure, ischemic heart disease, cerebrovascular disease, liver disease, malignancy, tuberculosis, hyperlipidaemia, anaemia and connective tissue disease	
		0	93.7%
		1	94.3%
		2	92.9%
		≥ 3	92.7%
Tonelli 2015	HRs	29 conditions: alcohol misuse, asthma, atrial fibrillation, lymphoma, non-metastatic cancer, metastatic cancer, heart failure, chronic pain, COPD, chronic hepatitis B, cirrhosis, severe constipation, dementia, depression, diabetes, epilepsy, hypertension, hypothyroidism, inflammatory bowel disease, irritable bowel syndrome, multiple sclerosis, myocardial infarction, Parkinson's disease, peptic ulcer disease, peripheral vascular disease, psoriasis, rheumatoid arthritis, schizophrenia, and stroke or transient ischemic attack	
		0	Ref
		1	1.57 (1.50-1.63)
		2	2.34 (2.24-2.44)
		3	3.43 (3.29-3.58)
		4	4.81 (4.60-5.02)
		≥ 5	7.74 (7.43-8.07)
CONTINUOUS PRESENTATION OF EFFECT SIZES			
Davies 1995	HRs	**Development of the Stoke Comorbidity Grade** 11 conditions: ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, left ventricular dysfunction, diabetes mellitus, systemic collagen vascular disease, COPD, pulmonary fibrosis, pulmonary tuberculosis, asthma and cirrhosis Low grade: 0 conditions Intermediate grade: 1-2 conditions High grade: ≥ 3 conditions	
		Each increase in grade	2.66 (1.55-4.55)
Davies 2002	Relative risk	**Stoke Comorbidity Grade**	
		Each increase in grade	2.4 (1.4-4.1)
Ellam 2008	Narrative	**Stoke Comorbidity Grade**	"No statistically significant effect on survival"
Wong 2007	HRs	**Stoke Comorbidity Grade**	
		Each increase in grade	2.53 (1.32-4.83)
Lhotta 2003	HRs	Five conditions: diabetes, heart failure, coronary artery disease, cerebrovascular disease and peripheral vascular disease	
		Each increase in comorbidity score	1.78 (1.32-2.40)

Results from studies using Condition Count as Multimorbidity Measure. COPD; chronic obstructive pulmonary disease. HR; hazard ratio.

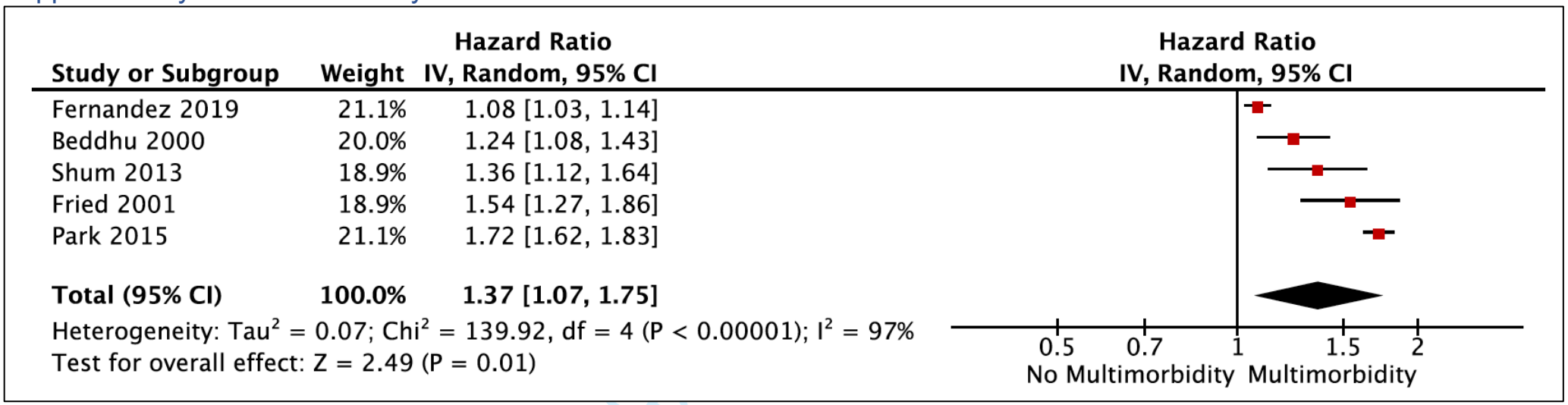
Reference	Effect size measure	Multimorbidity measure and groups	Effect size (95% Confidence Interval)
Chandna 1999	HRs	**Comorbidity severity score (CSS)** Cardiac score, according to New York Heart Association, respiratory disease score (1-4), cerebrovascular disease score (1-4), peripheral vascular disease score (1-4), cirrhosis (4), and malignancy score (1-4)	
		Each increase in CSS	1.238 (1.145-1.338)
Chandna 2010	HRs	**Comorbidity severity score**	
		Low comorbidity (CSS ≤ 4)	Ref
		High comorbidity (CSS > 4)	1.823 (1.255-2.650)
Pieloch 2015	HRs	**Kidney Transplant Morbidity Index**	
		0	Ref
		1	1.85 (1.45-2.36)
		2	3.11 (2.46-3.94)
		3	5.00 (3.96-6.31)
		4	7.37 (5.83-9.32)
		5	9.41 (7.41-11.94)
		6	12.15 (9.45-15.63)
		≥ 7	13.03 (9.68-17.54)
Ritchie 2009	HRs	**Heart failure, CKD and diabetes**	
		Heart failure and CKD	Ref
		Heart failure, CKD and diabetes	1.25 (1.07-1.46)

Results from studies using other Multimorbidity Measures. HR; hazard ratio. CKD; chronic kidney disease.

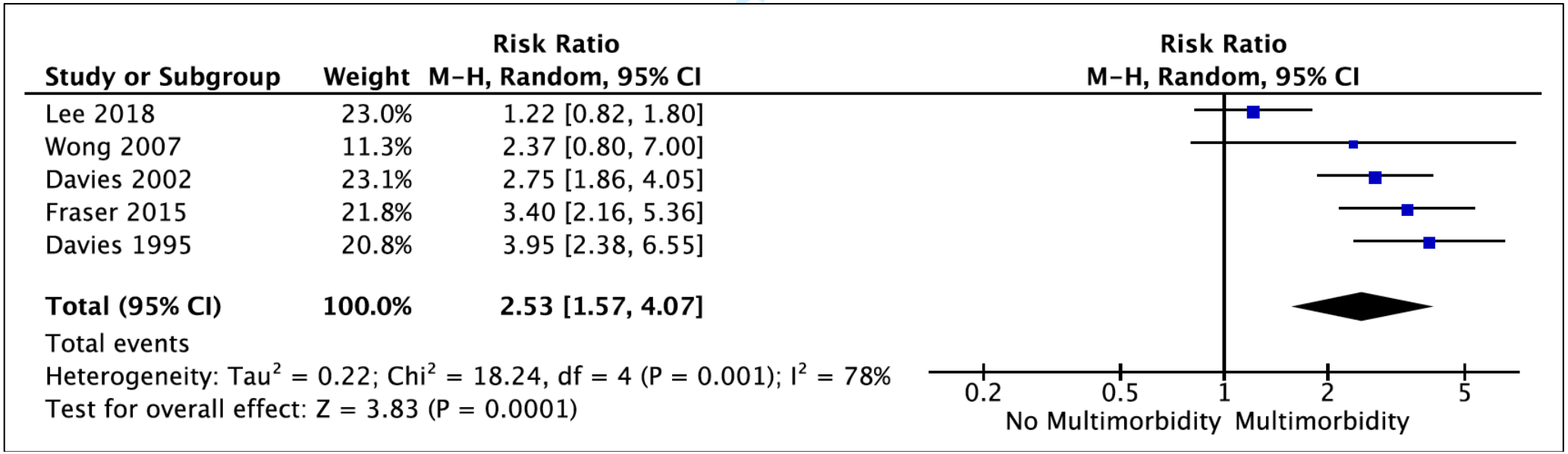
Reference	Scores studied	Presentation of effect size
Hemmelgarn 2003	CCI Development of ESRD modified CCI	Kaplan-Meier curves
Di Iorio 2004	CCI Development of CCI modified for haemodialysis patients	Relative risk, 5.5 for CCI
van Manen 2002	CCI Khan index Davies index Development of a new index	Kaplan-Meier curves

Studies that analyse different Multimorbidity Measures. CCI; Charlson Comorbidity Index

Supplementary File 4. Meta-analysis with random effects models



Mortality risk for Charlson Comorbidity Index as a continuous variable (Random Effects Model)



Mortality risk for patients with multimorbidity (Random Effects Model)

Supplementary File 5. Risk of bias: Results from Newcastle Ottawa Scale

Reference	Selection				Comparability	Outcome assessment			Quality score
	1	2	3	4	5	6	7	8	
Beddhu 2000		✸	✸	✸	✸	✸	✸		6
Bowling 2016	✸	✸	✸	✸	✸	✸	✸		7
Chae 2010		✸	✸	✸	✸	✸	✸		6
Chandna 1999		✸	✸	✸	✸	✸	✸		6
Chandna 2010		✸	✸	✸		✸	✸		5
Davies 1995		✸	✸	✸	✸	✸	✸		6
Davies 2002		✸	✸	✸	✸	✸	✸		6
Di Iorio 2004		✸	✸	✸	✸	✸	✸		6
Ellam 2008		✸	✸	✸		✸	✸		5
Fernandez 2019		✸	✸	✸	✸	✸	✸		6
Fraser 2015		✸	✸	✸	✸	✸	✸		6
Fried 2001		✸	✸	✸	✸	✸	✸		6
Grosso 2012		✸	✸	✸	✸	✸	✸		6
Hemmelgarn 2003		✸	✸	✸	✸	✸	✸	✸	7
Lee 2018	✸	✸	✸	✸	✸	✸	✸		7
Lhotta 2003		✸	✸	✸	✸	✸	✸		6
Park 2015		✸	✸	✸	✸	✸	✸		6
Pieloch 2015		✸	✸	✸	✸	✸	✸		6
Rattanasompattikul 2012		✸	✸	✸	✸	✸	✸		6
Ritchie 2009		✸	✸	✸	✸	✸	✸		6
Shum 2013		✸	✸	✸	✸	✸	✸		6
Tonelli 2015	✸	✸	✸	✸	✸	✸	✸		7
van Manen 2002		✸	✸	✸	✸	✸	✸		6
Wong 2007		✸	✸	✸	✸	✸	✸		6
Wu 2005		✸	✸	✸	✸	✸	✸		6
Wu 2013		✸	✸	✸	✸	✸	✸		6

Table 3. Newcastle Ottawa Scale. 1. Representativeness of the exposed cohort. 2. Selection of the non-exposed cohort. 3. Ascertainment of chronic kidney disease/multimorbidity status. 4. Demonstration that outcomes were not present at start of study. 5. Comparability of cohorts on the basis of the design. 6. Assessment of outcome(s). 7. Was follow-up long enough. 8. Adequacy of follow up of cohort.

Reporting checklist for meta-analysis of observational studies.

Based on the MOOSE guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the MOOSEreporting guidelines, and cite them as:

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283(15):2008-2012.

	Reporting Item	Page Number
Title		
#1	Identify the study as a meta-analysis of observational research	1
Abstract		
#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number (From PRISMA checklist)	2, 3
Background		
#3a	Problem definition	4
#3b	Hypothesis statement	4
#3c	Description of study outcomes	5

	#3d	Type of exposure or intervention used	5
	#3e	Type of study designs used	5
	#3f	Study population	5
Methods			
Search strategy	#4a	Qualifications of searchers (eg, librarians and investigators)	N/A
Search strategy	#4b	Search strategy, including time period included in the synthesis and keywords	5
Search strategy	#4c	Effort to include all available studies, including contact with authors	5, 7
Search strategy	#4d	Databases and registries searched	5
Search strategy	#4e	Search software used, name and version, including special features used (eg, explosion)	5
Search strategy	#4f	Use of hand searching (eg, reference lists of obtained articles)	5
Search strategy	#4g	List of citations located and those excluded, including justification	7
Search strategy	#4h	Method of addressing articles published in languages other than English	5
Search strategy	#4i	Method of handling abstracts and unpublished studies	6
Search strategy	#4j	Description of any contact with authors	7
	#5a	Description of relevance or appropriateness of studies gathered for assessing the hypothesis to be tested	8
	#5b	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7
	#5c	Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	7

#5d	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7
#5e	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	7
#5f	Assessment of heterogeneity	7
#5g	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7
#5h	Provision of appropriate tables and graphics	16, 17, 18, supplemental file
Results		
#6a	Graphic summarizing individual study estimates and overall estimate	N/A
#6b	Table giving descriptive information for each study included	16, 17, 18
#6c	Results of sensitivity testing (eg, subgroup analysis)	N/A
#6d	Indication of statistical uncertainty of findings	10
Discussion		
#7a	Quantitative assessment of bias (eg. publication bias)	N/A
#7b	Justification for exclusion (eg, exclusion of non–English-language citations)	N/A
#7c	Assessment of quality of included studies	11
Conclusion		
#8a	Consideration of alternative explanations for observed results	N/A
#8b	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	12
#8c	Guidelines for future research	12
#8d	Disclosure of funding source	15

Notes:

- 5h: 16, 17, 18, supplemental file Reproduced with permission from JAMA. 2000. 283(15):2008-2012. Copyright © 2000 American Medical Association. All rights reserved.This checklist was completed on 09. March 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai