Prevalence, patterns, and impacts of multimorbidity on adverse clinical outcomes in chronic kidney disease: A systematic review.

Samin Chowdhury, NIHR Academic Clinical Fellow General Practice

Lancaster Medical School, Lancaster University, UK

Email: samin.chowdhury@lancaster.ac.uk

Contact: 07709716065

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Abstract

Background: Multimorbidity is the concurrent presence of two or more long-term health conditions in the same individual. It fragments healthcare delivery and affects quality of life. Chronic kidney disease (CKD) often occurs with multimorbidity. The prevalence of CKD is rising. However, there is a lack of evidence on the prevalence, patterns, and impacts of multimorbidity on adverse clinical outcomes in patients with CKD.

Methods: This was a systematically conducted literature review. A search was conducted in EMBASE, MEDLINE, CINAHL, and SCOPUS (2019-2023). The main search terms were "chronic kidney disease" and "multimorbidity." The eligibility criteria were observational studies with adult participants with all stages of CKD (CKD stages 1-5, including those on renal replacement therapy). The exposure was multimorbidity quantified by measures. All-cause mortality, kidney disease progression, hospitalisation, and cardiovascular events were outcomes. The Joanna Briggs Institute (JBI) checklist was used for the risk of bias assessment. Due to heterogeneity in design and methods, Jennie Popay's narrative synthesis was used for data synthesis.

Results: Of 6879 papers, nine papers met the inclusion criteria. Most studies included participants with all stages of CKD (CKD stage 1-5). The prevalence of multimorbidity ranged from 86.6% to 99.1%. Hypertension was the most prevalent comorbidity. The combination of concordant multimorbidity (hypertension, diabetes, and cardiovascular diseases) was highly prevalent. Multimorbidity was significantly associated with mortality, cardiovascular events, kidney disease progression, and hospitalisation. While older people had more

multimorbidity burdens, younger patients with CKD were at a higher risk of death from multimorbidity. Severe CKD with clusters of cardiovascular diseases, diabetes, chronic pain, and depression was significantly associated with all-cause mortality.

Conclusion: There are associations between multimorbidity and adverse clinical outcomes in patients with CKD. However, there is a lack of data on Black, Asian, and Minority Ethnic participants and from low- and middle-income countries. Further research is needed to investigate the high prevalence of chronic pain and depression in chronic kidney disease.

Keywords:

Multimorbidity, chronic kidney disease, mortality, hospitalisation, kidney function, cardiovascular events.

Background

Multimorbidity is having two or more long-term health conditions (LTCs) simultaneously in the same person (1). With the advent of modern medicine, more people are living longer, thereby developing multimorbidity (2). A recent systematic review reported that the global age-adjusted prevalence of multimorbidity is approximately 37.2% (3). Multimorbidity affects approximately 50 million people in the European Union (4). It is also becoming more common in lower and middle-income countries (LMICs) (4, 5). In England and Scotland, 27.2% and 23.2% of people have multimorbidity (2, 6). Multimorbidity affects life expectancy, the amount of treatment needed, daily function, and quality of life. It makes healthcare delivery more complicated and makes it harder to coordinate care. People with multimorbidity use health services more than those with only one health condition.

Therefore, the Academy of Medical Sciences (AMS) and the National Institute for Health and Care Research (NIHR) identified multimorbidity as a priority area of research (4, 7).

Chronic kidney disease (CKD) is a progressive loss of kidney function or damage to the structure of the kidney lasting for at least three months (8). It affects approximately 10% of the global population and is often linked to multimorbidity (9, 10). It has five stages based on the range of kidney function measured by estimated glomerular filtration rate (eGFR). People with chronic kidney disease have the highest death rate of anyone with a long-term health condition (11-13). CKD patients also need more hospital admission than those without (14). Multimorbidity makes it more likely that kidney function will worsen, leading to the need for dialysis, kidney transplant, and higher healthcare costs (12, 15, 16). Therefore, Kidney Research UK has recently identified the need for investigating the link between multimorbidity and CKD (17).

To improve patient outcomes, it is becoming more apparent how important it is to determine how common and “clustered” multiple health conditions are (7). When a person has multiple health conditions, health guidelines and care usually focus on treating each condition separately. This disjointed way of giving care does not always meet the complex needs of people with multimorbidity. For example, guidelines do not consider how different medicines interact or how severe each health condition is in a person with multimorbidity (18, 19). People with CKD often have heart disease and diabetes, examples of "Concordant multimorbidity". This means conditions with the exact cause and disease pathways (11, 20, 21). They also have health problems that are not directly linked to CKD, such as mental health problems, including depression ("discordant multimorbidity") (22, 23). Therefore, it is

important to find these "clusters" of conditions so that early, focused interventions can be made to improve clinical outcomes. (24, 25).

While Sullivan et al. (2020) published a similar systematic review to assess the impacts of multimorbidity on mortality in patients with CKD stages 3-5, there is a lack of evidence on how patterns or clusters of multimorbidity in all-stage CKD (including mild-moderate CKD) affect other important clinical outcomes (26). Therefore, this study aims to examine the current research to determine the prevalence and patterns of multimorbidity in all-stage CKD. The study also aims to determine how multimorbidity is linked to adverse clinical outcomes in people with all-stage CKD.

Methods

A systematically conducted literature review. The Guidance on conducting systematic reviews and meta-analyses of observational studies of etiology (COSMOS-E) was followed to conduct this review. (27). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for reporting. (See additional file appendix 6). The review was not registered with the International Prospective Register of Systematic Reviews (PROSPERO).

Research questions

1. What are the prevalence and patterns of multimorbidity in adult patients with chronic kidney disease (CKD)?
2. How does multimorbidity affect clinical outcomes in adult patients with chronic kidney disease (CKD)?

Objectives

-Determine the prevalence and patterns of multimorbidity in patients with any stage of CKD to understand the extent and "clusters" of multimorbidity associated with CKD.

-Investigate the association between multimorbidity and adverse clinical outcomes in patients with CKD to understand the impact. This will help develop targeted clinical interventions.

Design:

A systematic review without meta-analysis.

Inclusion criteria

-Studies investigating the prevalence or patterns of multimorbidity in CKD or reduced renal function (estimated glomerular filtration rate <90 ml/min/1.73 m^2). Any multimorbidity measures were accepted, including simple counts or a comorbidity scoring system.

-Studies that investigated the association between multimorbidity and adverse clinical outcomes in patients with CKD. Outcomes were hospitalisation, mortality, cardiovascular events including myocardial infarction or stroke, progression of CKD to kidney failure or renal replacement therapy, and association of multimorbidity with CKD severity.

-Studies that counted CKD as a multimorbidity.

-Adult participants aged 18 and over.

-Studies published in English.

Exclusion criteria:

-Qualitative studies as the outcomes studied are quantitative in nature.

-Narrative or systematic reviews.

-Drug intervention studies.

-Randomised controlled trials as they often exclude multimorbid participants.

-Case reports or conference abstracts.

-Studies with children or adolescents below 18. Kidney functions differ between adults and children.

-Animal or other experimental preclinical studies.

Search strategy

Selected medical subject headings (MeSH) terms were combined with keywords relating to CKD and multimorbidity to create a search strategy. This was first developed for MEDLINE and then was adapted for other online databases. (See additional file Appendix 1). On May 31, 2023, SC conducted a literature search using MEDLINE, EMBASE, CINAHL, and SCOPUS online databases. Because a similar systematic review was published in 2020, the search includes papers published between 1 January 2019 and 31 May 2023. Due to the lack of time and resources for translation services, only articles published in English were included. No geographical restriction was placed. Search results were stored and merged in EndNote 20 (Clarivate Analytics, Philadelphia, USA). Papers were screened using Rayyan Intelligent systematic review software. Search terms were set out below:

((TITLE-ABS-KEY ("Chronic Kidney Failure" OR "Renal Insufficiency" OR "Chronic Renal Insufficiency" OR "Kidney Diseases")) OR (TITLE-ABS-KEY ("Renal Replacement Therapy" OR "Continuous Renal Replacement Therapy" OR "Dialysis" OR "Peritoneal Dialysis" OR "Hemodialysis")) OR (TITLE-ABS-KEY ("end stage renal

disease")) OR (TITLE-ABS-KEY ("kidney function" OR "renal function" OR trend)) OR (TITLE-ABS-KEY (ckd OR crf OR ckf OR crd OR "kidney disease*" OR "kidney injur*" OR "kidney fail*" OR "kidney insufficienc*"))) AND ((TITLE-ABS-KEY ("multimorbidity" OR "multiple chronic conditions")) OR (TITLE-ABS-KEY ("multiple comorbidity")) OR (TITLE-ABS-KEY (((((multimorbid* OR "multi morbidity" OR multimorbidity OR multimorbidity) OR multiple AND diseas* OR multipl e AND condition* OR multi AND condition* OR (multiple AND comorbid* OR multiple AND comorbidities) OR ("multiple disorder" OR multidisorder OR multidisorder) OR discordant AND comorbid* OR conco rdant AND comorbid*)))))) AND ((TITLE-ABS-KEY ("Treatment Outcomes" OR "health outcome" OR "clinical outcome")) OR (TITLE-ABS-KEY ((health OR outcom* OR clinical AND outcom* OR adverse AND outcom*))) OR (TITLE-ABS-KEY ("Kidney Function Tests" OR "kidney function" OR "Hospitalisation" OR "hospitalisation" OR "Death" OR "Mortality" OR "Ho spital Mortality" OR "cardiovascular outcome" OR "cancer mortality")) OR (TITLE-ABS-KEY ("Prevalence" OR "cluster")) OR (TITLE-ABS-KEY ("all cause mortality" OR "cardiovascular mortality"))) AND (LIMIT-TO (PUBYEAR , 2023) OR LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019))

Study selection

SC screened all the papers against the eligibility criteria. The full text was only accessed when there was insufficient information to decide eligibility for inclusion.

Data extraction

SC conducted data extraction. A data extraction form was created in MS Excel before the search to extract relevant data from the included studies. Data extraction included study authors, year of publication, study design, setting, sample size, median follow-up time, study results, and outcomes studied. (Table 1).

Data synthesis

The results are presented in a narrative format. The general framework of the narrative synthesis by Popay et al. (2006) was used. This is because considerable heterogeneity was observed in the included studies regarding methods, sample size, study designs, and outcomes (28).

Quality assessment:

SC conducted the quality appraisal of all the selected studies. The studies included were either cross-sectional or cohort studies. Based on this, the methodological quality of the included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist for cross-sectional and cohort studies. The JBI tool has eight questions for cross-sectional studies and 11 for cohort studies to assess the risk of bias in a study's design, conduct, and analysis (see Additional file Appendix 2, Appendix 3). (29). Based on subjective scoring, studies were rated high, moderate, and low quality. Studies were not excluded based on the quality appraisal. The overall quality of the review was assessed using the SANRA (a scale of the quality assessment of the narrative review articles) checklist (see Additional file Appendix 5) (30).

Patient and public involvement:

No patient or the public was involved.

Results

Search results

The search retrieved 6879 papers. After deduplication, the titles and abstracts of 5229 articles were screened, and 11 papers were included. After the full-text screening, two of these 11 papers were excluded because they were conference abstracts. Therefore, nine articles were included in the final analysis. Figure 1 demonstrates the literature search flow.

A. Developing a preliminary synthesis.

Table 1 lists the study characteristics. Six studies were prospective cohorts, and three were cross-sectional. The sample size of the included studies ranged between 252 and 892,005. Most of the studies were conducted in Europe and the USA. Seven studies examined patients with CKD stages 3-5 who were not on dialysis. Six of them included participants with mild-moderate CKD (CKD stage 1-3, eGFR≥30 ml/min/1.73m^2) (31-36). Four studies included patients without CKD. Only one study involved patients on renal replacement therapy, including dialysis. (37). Except for Sullivan et al. (2021), all the studies measured multimorbidity by simply counting them ("condition count").

B. Exploring relationships within and between studies.

The main findings of the included studies are summarised. (Table 2). Full results with effect estimates of the included studies are summarised. (See Additional file Appendix 4).

Prevalence of multimorbidity in CKD

The prevalence of multimorbidity, including CKD, was higher in most studies, ranging from 86.6% to nearly 99.1%, as reported by five studies (33, 34, 36, 38, 39). When CKD was excluded, the prevalence of two or more comorbidities was reported at 25%-57.3% by three studies (33, 34, 39). Both Palo et al. (2023) and Sullivan et al. (2022) reported a higher number of comorbidities in more severe CKD (CKD stages 4 and 5) than in mild to moderate CKD (CKD 1-3) (32, 39). As reported by three studies, older patients with CKD had a higher multimorbidity burden than the younger population (34, 35, 37). Only three studies collected data from the Black, Asian, and Minority Ethnic (BAME) populations. (31, 33, 39).

Multimorbidity patterns

Hypertension was the most prevalent comorbidity, as reported by seven studies (31-34, 36-39). Two studies reported a higher presence of hypertension and musculoskeletal conditions (33, 39). The combination of hypertension, diabetes, and cardiovascular diseases was highly prevalent in three studies (31, 36, 37).

Outcomes

Multimorbidity was significantly associated with mortality, major adverse cardiovascular and kidney events, and hospitalisation (32, 36, 37). While older people had more multimorbidity burdens, younger patients with CKD were at a higher risk of death from multimorbidity (36, 37). Severe CKD (eGFR <30 ml/min/1.73m^2) with clusters of heart failure, peripheral vascular disease, atrial fibrillation, diabetes, chronic pain, and depression was significantly associated with all-cause mortality and major cardiovascular events (32).

C. Assessing the robustness of the synthesis.

All cohort studies were of good quality with a low risk of bias (Table 3). Two were at risk of selection bias, as they did not describe the loss to follow-up in adequate detail. In contrast, more than half of the cross-sectional studies had a moderate to high risk of selection and misclassification bias (Table 4). The overall quality of this narrative review was deemed "Good" using a well-validated appraisal checklist. The PRISMA reporting checklist has been provided. (See Additional file appendix 6).

Discussion

The study shows that CKD patients have a high rate of multimorbidity. This is similar to a recent systematic review examining adverse outcomes for CKD patients with multimorbidity (12). The literature shows that some diseases, such as high blood pressure, diabetes, and heart disease, are very common in people with CKD. Several studies have reported that complications of CKD, such as mineral malabsorption, oxidative stress, and chronic inflammation, can cause this clustering (13). This study also shows that multimorbidity is strongly linked to mortality, hospitalisation, and major cardiovascular events. This is not an unexpected finding. There is well-established evidence that these conditions are linked in their disease pathways and have poor outcomes (14). This group may benefit from an integrated clinic that can meet their complex medical needs. Integrated clinics have been shown to help people with CKD by reducing high blood pressure, high cholesterol, and high blood sugar (40).

This review shows that multimorbidity is strongly linked to reduced kidney function. It is also linked to the progression of CKD to kidney failure that needs dialysis or a kidney transplant. This result is similar to an earlier study that showed that multimorbidity was associated with the progression of CKD to dialysis (16). This shows the importance of frequent monitoring of kidney function in this cohort of patients.

The review showed that depression and chronic pain, which are discordant multimorbidities, are linked to more advanced CKD (stages 4 and 5) (eGFR<30 ml/min/1.73 m^2). This is similar to other studies that showed that depression is common in people with advanced CKD. However, it is often misdiagnosed and undertreated (41). Depression in people with CKD makes it harder for them to take medicines. Moreover, antidepressants work less well with reduced kidney function. A systematic review found that depression-focused interventions were the most effective in multimorbidity (42). These goal-based interventions might be useful for people with both CKD and depression. However, there is a lack of evidence on why chronic pain is so common in CKD (34, 38).

The strength of the review lies in the robustness of its methodology. The process of selecting the studies was transparent. Both individual papers and the review itself were judged using well-validated appraisal checklists.

In 2020, a systematic review was performed to examine the adverse outcomes of multimorbidity in people with chronic kidney disease (26). To the best of the author's knowledge, this is the first study since the review was published to look at the trends of multimorbidity and its associated adverse outcomes in people with CKD. In their systematic

312 review, Sullivan et al. (2020) said that there were not enough data to determine how
313 patients with mild-to-moderate CKD (eGFR>30 ml/min/1.73 m^2) would fare if they had
314 multimorbidity (26). Almost all the studies in this review looked at people with mild to
315 moderate CKD, and one study also looked at people who had kidney transplants (33).
316
317 However, this study has some limitations. Over half of the studies were cross-sectional. This
318 made it harder to explore the longitudinal change in multimorbidity patterns. Additionally, in a
319 few studies, there was a risk of selection bias because people self-reported their
320 multimorbidity (43). Some studies used a single test of eGFR to define CKD without
321 measuring it after three months, making the exposure inadequate (44, 45). There was
322 not enough information about people who dropped out of the study. All the studies used
323 health databases to collect data. However, a few of them did not provide a reference for the
324 diagnostic codes used. This might have introduced misclassification bias (46).
325
326 It is well known that people from BAME (Black, Asian, and Minority Ethnic) groups are more
327 likely to develop CKD. They also disproportionately suffer CKD-related diseases such as
328 diabetes and high blood pressure (5, 47). Nevertheless, most of the people in almost all
329 studies were White. CKD affects more people in lower- and middle-income countries than in
330 high-income countries (48). However, eight of the studies in this review were conducted in
331 countries with high incomes, which makes it difficult to generalise the results.
332 It would be helpful to see how the severity of different comorbidities affects the results.
333 However, none of the studies looked at this link, which could be an important confounder
334 (49).
335

Conclusions

This study shows that people with all stages of CKD are more likely to have multimorbidity. Older CKD patients tend to have a higher number of comorbidities. Younger people with CKD can also have multiple health problems, making them more likely to die than older people. High blood pressure, diabetes, and heart conditions often occur together with CKD. These “clusters” are also linked to poor clinical outcomes, such as hospital admission and mortality. The review provides evidence that depression and chronic pain, which seem to have nothing to do with CKD, often coexist.

Recommendations for future research

For future studies to have more results, they should include more Black, Asian and minority ethnic participants. More research needs to be done to investigate the link between CKD and discordant multimorbidity. To date, most studies have investigated the effects of multimorbidity on clinician-centred outcomes. In future studies, multimorbidity should be examined in terms of patient-focused outcomes. This includes outcomes such as quality of life, disease burden, fatigue, and insomnia. Patients with CKD and multimorbidity are often excluded from randomised controlled studies. Therefore, CKD patients with multimorbidity need more pragmatic controlled trials using large databases. This should reduce selection bias and improve the generalisability of the results. Last, lower and middle-income countries should conduct more research in this area. This will help them understand the pattern and outcomes of multimorbidity in CKD. This will help these countries make decisions about treatment and healthcare policy.

List of abbreviations

UK= United Kingdom

CKD= Chronic kidney disease

AIMS= Academy of Medical Sciences

NIHR= National Institute for Health and Care Research

LTCs= Long-term health conditions

eGFR= estimated glomerular filtration rate

SANRA= A Scale of the Quality Assessment of Narrative Review Articles

PROSPERO= International Prospective Register of Systematic Reviews

MeSH= Medical Subject Headings

MS Excel= Microsoft Excel

JBI= Joanna Briggs Institute

USA= United States of America

SCREAM= Stockholm Creatinine Measurements Project

SAIL=Secure anonymised information linkage databank

RRT= Renal Replacement Therapy

BMI= Body Mass Index

CHF= Congestive Heart Failure

ACM= All-cause mortality

MACE= Major Adverse Cardiovascular Events

CVD= Cardiovascular disease

COPD= chronic obstructive pulmonary disease

MAKE= major adverse kidney events

BAME= Black, Asian, and Minority Ethnic

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