

Abstract

Chronic kidney disease (CKD) is a significant and growing driver of the global non-communicable diseases (NCD) burden, responsible for 1.2 million deaths in 2016. While previous research has estimated the out of pocket costs of CKD treatment and resulting levels of catastrophic health expenditures, less is known about the impact of such costs on access to, and maintenance of, care. Our study seeks to fill this gap by synthesizing available evidence on cost as a determinant of CKD treatment discontinuation. We searched for studies which considered the financial burden of treatment and medication for CKD patients *and* the extent to which this burden was associated with patients forgoing or discontinuing treatment. We identified 14 relevant studies, five from high-income countries and nine from low-middle income countries. All suggest that cost adversely influences adherence to CKD medication and dialysis treatment. In poorer countries, those entering treatment programs were typically diagnosed late, under-dialysed and suffered very high levels of mortality. Identified studies present consistent findings regardless of study context: cost is barrier to treatment and a driver of non-adherence and discontinuation, with poorer house-holds worst affected. This is in line with previous research. Major gaps in the literature remain, however, in relation to differential impact of the cost burden on men and women, the coping strategies of poor households and the effect of insurance coverage.

Introduction

Non-communicable or chronic diseases (NCDs) have emerged as the leading causes of death globally and were responsible for 39.5 million deaths in 2016 [1]. NCDs also present a major challenge to the Universal Health Coverage (UHC) target of the United Nations' Sustainable Development Goals.

Chronic conditions typically require multiple medications and long-term treatment, imposing high economic costs on both individuals and the health system [2]. The UHC target recognizes the growing consensus that removing or reducing financial barriers is necessary to improve equitable access to health care [3] through a commitment to '*financial risk protection*' alongside '*access to quality, essential health care*'.

Chronic kidney disease (CKD) is a significant component of the NCD epidemic: global prevalence has been estimated at 13.4% [4], and is expected to rise further alongside the growing epidemics of diabetes and hypertension [5]. Unless diagnosed and treated early, CKD progresses to end-stage kidney disease (ESKD) in a large proportion of cases. The only treatment for ESKD is renal replacement therapy (RRT) – either dialysis or a kidney transplant – complex and costly procedures that are financially unaffordable for many [6].

Delayed diagnosis is most likely the result of poor access to appropriate health care and low awareness of CKD, though cost may also be a factor. In high-income countries, screening for CKD is cost-effective when targeted at high-risk groups [7] however the affordability and feasibility of screening in low-income environments is unclear [7, 8] and at present there is very limited surveillance or screening for those at risk for CKD in these contexts.[8] Even in high-income countries there is low-awareness of CKD amongst both patients and health care providers, studies from US, Taiwan and Italy suggest [8]. Low-income countries struggle to address the even the leading causes of CKD, hypertension and diabetes. Globally over half of people that have diabetes don't know they have it, rising to 69 per cent in Africa and 57 per cent in south-east Asia.[9] For those that have been diagnosed, access to appropriate medication and care is limited.[10] Similarly, access to blood

pressure lowering medications needed to manage hypertension is extremely constrained LICs and middle-income countries. [11] Global Burden of Disease (GBD) estimates suggest that in 2016 CKD was the 11th leading cause of death worldwide, responsible for 1.2 million deaths, a 29% increase over 2006 [1]. Liyanage et al [12] estimated that, in 2010, 2.3 million people died prematurely because they could not access the therapy.

There are major global inequities in access to RRT treatment [13], with the largest treatment gap being in low-income countries [12]. In these contexts, even when patients can access care, the quality is often poor. In sub-Saharan Africa, patients requiring RRT experience late diagnosis, poor availability of appropriate care, high drop-out rates and high levels of mortality [14, 15]. Other studies have highlighted the clinical complications associated with low quality care in adults with CKD, including patients being ‘under-dialysed’ (treated intermittently) likely for reasons of affordability [16, 17].

Essue et al [2] estimated that in low- and middle-income countries (LMICs) 35.6% of people with renal disease (defined as CKD or Kidney Disease) experience catastrophic health expenditure – some 185 million people annually. Similarly, large financial costs were found to impact families of those accessing end-stage renal care in India where RRT is provided predominantly by the private sector [6]. These findings are in line with those of studies on the economic burden of the NCD epidemic [18].

While previous reviews strongly suggest that out of pocket costs are a significant barrier to accessing or maintaining care for those with CKD, none address this question directly. Our study seeks to fill this gap by synthesizing available evidence on cost as a determinant of CKD treatment discontinuation, and its role in the decision to forgo treatment.

Methods

We searched Medline, PsychInfo, PubMed and Global Health electronic databases from inception to December 2017 using a combination of key words and MESH terms, including: “dialysis”, “renal dialysis”, “treatment refusal”, “patient dropout”, “medication adherence”, “non-adherence”, “compliance”, “default”, “lost to follow up”, “no-show” and “out of pocket”. The full search strategy is presented in Supplementary Table 1. The search was limited to studies published in English.

The review aimed to identify all relevant published studies which considered the financial burden of treatment and medication for CKD patients, *and* the extent to which this burden caused patients to forgo or discontinue treatment. Specifically, we were looking for studies that described:

- Patients presenting to a healthcare facility with CKD or kidney failure (KF), diagnosed as such, and subsequently prescribed or put on dialysis treatment;
- The number of CKD or KF patients who decide to forgo, postpone or abandon their treatment; or undertake less treatment or medication than advised;
- The role of out of pockets costs – in the form of costs incurred or patient concerns about these costs – in this decision.

Full inclusion and exclusion criteria are presented in Box 1.

Box 1: Selection criteria	
Inclusion	<ul style="list-style-type: none"> • reported data on numbers diagnosed with chronic kidney disease or kidney failure and referred for or receiving renal dialysis; rates of discontinuation or abandonment; and financial reasons for discontinuation • reported reasons patient chose to <i>forgo</i> renal replacement therapy (if assessed role of financial considerations in this decision) • any stage of chronic kidney disease • all locations (high, low and middle-income settings; any population group) • observational (i.e., cohort) studies, case-control studies, cross-sectional studies and qualitative studies • published in English
Exclusion	<ul style="list-style-type: none"> • no data on discontinuation rates • did not consider economic factors as reasons for discontinuation • did not consider direct costs borne by patients

The results of searches were combined and duplicate references removed. Two authors (RD, AP) independently screened all titles and abstracts of studies identified by the initial search for relevance. All potentially relevant studies were retrieved as full text papers and independently reviewed by one author (RD) for inclusion. The reference lists of included articles were also reviewed to identify other relevant studies. Data abstraction was undertaken by one author (RD) initially and verified by a second author (AP) against the original studies. Disagreements were resolved by consensus.

To appraise study quality, articles were independently appraised by two authors (RD and AP) using the Critical Appraisal Skills Programme (CASP) tools [19]. Each study was evaluated in relation to the three CASP domains: i) aims and methodological appropriateness; ii) study design and conduct; and iii) clarity of findings and value of research. Articles were then categorised into three groups: 'fully addresses CASP items', 'mainly addresses CASP items' or 'partially addresses CASP items' [20]. Four of the 14 included studies were deemed to fully address CASP items, eight mainly addressed these items and two partially addressed them. Given the small amount of literature uncovered in the topic area, all studies were included in the final review since it was thought they all provided insights into cost as a determinant of CKD treatment discontinuation. The quality categorisation of included articles is provided in Table 1.

The study aimed to provide only a narrative description of the data and to identify gaps in the literature related to reasons for financially-driven abandonment of dialysis treatment.

Results

The literature search returned 47 articles after duplicates had been removed, and a further 20 articles identified from reference lists and snowballing. Of these, 30 were selected for full text review of which a further 16 were excluded (see Figure 1). The main reasons for exclusion at the

full-paper screen were that papers did not provide any information on the role of cost in the decision to forgo or discontinue treatment or that treatment costs were presented but no link made to patients' access to treatment.

<Insert Figure 1 here>

Table 1 provides an overview of all included literature and cohort demographics. Table 2 summarises findings on adherence to dialysis treatment and associated mortality rates for those studies providing this information.

Cost as a determinant of medication adherence

Only four studies explicitly set out to measure cost as a determinant of treatment adherence, of which three examined adherence to medication. Two were large cohort studies [21, 22], the third was a small cross-sectional survey [23]; all focussed on high-income country populations.

Park et al. [21] studied treatment adherence amongst US-resident patients eligible for Medicare Part D, which reimburses 75% of outpatient medicine costs up to a specified cost limit, known as the 'benefit gap'. Once this limit is reached, patients must pay 100% of medication costs out of pocket until they reach a second threshold of catastrophic coverage, at which point the subsidy resumes. The study found that those who reached the benefit gap "were significantly more likely to be non-adherent to medications for diabetes, hypertension, and a range of other related conditions" than before they reached the gap. However, the study also found some anomalies; notably, that the lowest adherence rates were among those who had not yet reached the coverage gap. The authors suggest this is likely because these patients anticipate the gap and give up early or seek to delay reaching it, for example by reducing drug use. Equally, the highest adherence rate was amongst those who had reached catastrophic coverage – this may be because patients are sicker (have been ill for longer) and/or already demonstrated persistence through the gap period.

Similarly, Hirth et al [22] examined the relationship between drug costs and non-adherence among dialysis patients across 12 OECD countries and found cost to be a strong predictor, noting *“increased risk of non-adherence associated with higher cost pressures in most countries”*. As with Park’s study, the relationship was not ‘perfect’ – e.g., in Sweden patients bear a high cost burden (relative to other OECD countries) but have high rates of adherence, while in Australia/New Zealand and Germany the opposite is true: i.e., these countries had below average adherence relative to cost. In those countries, however, a high proportion of patients bear some cost, suggesting (the authors’ believe) that facing any out-of-pocket cost might be a more important determinant of non-adherence than the absolute magnitude of the burden – and pointing to the importance of exemption policies. The authors also suggest that cultural factors, health systems organization (including the incentives on providers to promote adherence), and overall levels of patient income influence behaviour, alongside cost considerations.

Another study used a questionnaire to gather information on medication compliance (over 24 hours) amongst patients registered at an urban dialysis clinic in the US. A third of patients said they did not take their medication as directed. The main reason cited was forgetfulness, followed by inconvenience. Cost ranked third, with 11% saying cost of prescriptions prohibited them from taking medication. However, 35% of respondents noted that cost was “always a concern” and a further 40% noted it was “sometimes a concern”. The authors note that cost might have been more of a concern if the survey had been conducted later in the year, when patients were approaching the ‘benefit gap’ (as described in the Park study).

Cost as a determinant of dialysis adherence

One Thai study looked at the economic impact of out-of-pocket RRT costs on households and the subsequent effect on treatment adherence [24]. At the time of the study, RRT was not covered by Thailand’s UHC scheme, so patients were liable for all treatment costs. Twenty households were included in the study, which found that RRT consumed 25-68% of total household expenditure. The

most common coping strategy was to reduce the frequency of haemodialysis and erythropoietin injections, with poorer households worst affected. The study found that poor patients received haemodialysis on average once a week, compared to twice a week for richer patients, and by the end of the 3-month study period 4 of the 9 poorest patients had died.

A further eight studies looked at the outcomes from, and the challenges associated with, providing, haemodialysis in a resource constrained setting. In line with our inclusion criteria, all studies included some consideration of the role of out-of-pocket costs in determining whether patients had haemodialysis, and its frequency. However, in all but two studies the quality of information on out-of-pocket costs was poor. Typically, it is presented as an observation or conclusion of the authors and is not backed with quantitative data obtained from patients. Table 2 summarises the findings of these studies.

Arogundade et al. [25] present the most comprehensive study, covering a 19-year period. It looked at a range of factors affecting presentation and management outcomes among ESRD patients in one facility in Nigeria and found that 25% of referred patients did not begin dialysis “as they could not afford RRT” or had a blood borne disease which made them non-eligible to use dialysis machines. The authors also recorded drop-out rates among those patients who began HD after 1, 4, and 12 weeks – noting only 5% sustained treatment longer than 12 weeks. They concluded the reasons for drop out were largely due to cost, noting that “payment for RRT in our setting is borne by patients out of pocket expenses, except for the extremely few number assisted by corporate organizations.”

Other studies took a similar approach, though typically over a much shorter period. These either reviewed medical records [26] or tracked outcomes [27]; [28]; [29]; [30] among dialysis patients in a single clinical setting. Each of these studies recorded high drop-out rates and/or high-levels of under-dialysis, and all reported high levels of associated mortality (Table 2). One study looked at the relationship between number of dialysis sessions and survival, and found a strong positive correlation [27].

All studies in this group pointed to affordability of dialysis as a major determinant of access, noting that dialysis sessions had to be paid out of pocket. In Nigeria, the cost of a single session of dialysis was estimated at \$130-\$155 [25] [29] [30], one study noting it to be equivalent to twice the minimum monthly wage of a government employee [29]. In India, the annual cost of treatment was estimated at US\$4500 at the time of the study, 15 times per capita GDP [31].

Rao et al [31] categorised patients as either 'self-financing' or 'financed', the latter category indicating some form of financial support from an employer or other organization. It found *"adherence to a thrice weekly dialysis schedule ... correlated with availability of financial support."* Equally, those with external financial support had one third of the risk of leaving the program compared to those without such support.

A second India study [32] looked at increase in uptake of HD in Andhra Pradesh following the State Government's decision to publically fund the service. It found a four-fold increase in service uptake over the four year study period, concluding *"removal of out of pocket costs leads to increase in uptake of HD, confirming a previously high unmet need"*.

Cost as a factor in forgoing treatment

Two qualitative studies were included as they examined the role of cost considerations in patients' decision to forgo RRT. In Singapore [33], the anticipated financial burden on the family was an important factor in the decision to forgo dialysis. Other concerns included pain of treatment, deterioration in quality of life, and time spent going to and from hospital. No measure of the influence of these factors was provided.

A US study [34] of patients referred for a transplant evaluation, but who failed to attend their appointment, found that concerns about costs were a key reason for the no-show, outweighing fear of the procedure itself and associated health risks. Cost concerns related to pre-transplant medical tests, and the transplant operation.

Insurance

Four studies had some consideration of the role of insurance coverage. Two found that the higher patient co-payments had a negative influence on medication adherence [21, 22] and two suggest that extension of coverage led to an uptake of services [32] or a reduction in concerns about cost [23]. Although the number of studies examining this issues was small, a positive association was generally observed between insurance status and treatment; and a negative one between co-payment and treatment.

Discussion

Despite long-standing recognition that cost can be a major barrier to accessing treatment, especially in LMICs, we found a very limited body of literature addressing this question in relation to CKD. Just 12 studies in total were identified, with a narrow geographic spread, including five from West Africa of which four were from Nigeria. India and Thailand were the only LMICs from the Asia Pacific region where studies were found. While LMIC studies were well represented in final list of articles retrieved, only two LMIC studies provided quantitative data on the role of cost in treatment adherence. Other studies were less robust, reporting the observations of the authors without presenting evidence to verify these observations.

Despite these limitations, all studies – whether in low or high-income countries - present striking and consistent results on access to treatment and treatment outcomes: very poor adherence to any sustained program of dialysis treatment, and very high levels of mortality. Most patients were diagnosed late, when their illness was at an advanced stage, and were highly under-dialysed. Though comparison with high-income countries is difficult given the range of time periods studied and severity of patient illness on presentation, the data suggest high levels of treatment discontinuation and disproportionate levels of early mortality. This is consistent with previous estimates of a large gap in access to RRT treatment in LMICs [12], low numbers of dialysis units compared to population need [6] and high levels of premature mortality due to diabetes [35]. The evidence provided from authors' observations of their patient cohorts, in combination with economic modelling of the financial burden of NCDs in LMICs [18], suggest a clear link between out of pocket costs and treatment access/adherence.

Significantly, the majority of studies did not analyse any of their results from a gender perspective, and none of the studies reviewed examined whether women were more likely than men to discontinue treatment. This is clear gap given all the LMIC studies found a gender bias in patients entering dialysis programs. This trend is in an Indian study which found three times as many men as

women accessing HD treatment, even after financial barriers were removed [32]. A strong gender lens is needed in any future research on access to RRT.

Only two studies [22, 24] record the amount of money patients spent on treatment and only one presents this as a proportion of total household income [24]. Understanding the relationship between health costs and household income/expenditure is needed to understand the extent of financial protection and equity in health financing [18]. Further research is also needed on the relationship between treatment and the level and type of insurance coverage offered to patients (i.e., the burden of co-payments) given extremely high and persistent costs of dialysis.

The studies reviewed here strongly suggest that reducing frequency of haemodialysis visits and medication use is a common coping strategy in response to high out of pocket costs. More robust data, gathered from patients themselves, is needed to understand the interaction of costs with other factors that may influence discontinuation. Studies in high-income countries, including the Singapore study reviewed above [33] suggest that physical pain, quality of life, burden on family and carers are important factors, along with patient doubts about the point of treatment, especially as their health deteriorates.[36] To our knowledge, non-financial drivers of CKD discontinuation have not been specifically studied in low-income contexts, however studies on chronic care more broadly suggest that, along with factors identified in richer countries, limited social and support networks, interrupted drug supplies, poor quality of care, lack of referral, difficulty reaching care facilities and poor communication with clinicians are all important [37]. Further research on these influences will support health planners and practitioners in their efforts to respond to patient needs as the CKD epidemic expands.

Limitations

The main limitation of this study was the lack of quantifiable data on treatment drop-out rates due to cost or other economic considerations. A second limitation was lack of consistent terminology used to describe adherence or treatment discontinuation across studies (see Table 2). As a result, a

high proportion of the papers reviewed in this study were captured through the hand search of reference lists rather than the initial search strategy. Finally, all reviewed studies were observational, making their results potentially subject to confounding biases (such as the disproportionate number of male patients).

Conclusion

The findings from this review, albeit based on a small number of studies, provide insight into the health, social and financial impact of the CKD epidemic globally, including its inequitable burden on the poorest households and in the poorest countries.

While access to RRT is expanding, the cost and complexity of the procedure mean a significant treatment gap is likely to persist in the near term, especially in remote and poorer areas of LMICs. Investment in early diagnosis and treatment of the conditions that lead to ESRD, such as diabetes, will be important to minimise the economic burden on households, and extend life.. Equally, the high treatment drop-out and early death rates in studies reviewed here suggest there is a need to invest in palliative care, to support the large number of ESRD patients who are unable to access RRT.

CKD deaths have increased markedly in all regions of the world, and are responsible for a large and growing proportion of the global disease burden. Effective, inexpensive treatments are available for other NCDs including hypertension, diabetes and heart disease. By contrast, the high cost of CKD treatment means that many of the poorest individuals are unable to access appropriate care or, if they do, are driven into impoverishment. Addressing this cost burden is critical not only improved access the CKD treatment but also to achieving the UHC goal of financial protection.

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Table 1: Overview of included literature

Reference	Study period	Geographic focus	Type of study	Cohort size N, % male	Description of cohort condition	Mean age (years)	Extent it addresses CASP items
Arogundade, et al., 2011	1989-2007	Nigeria	Retrospective study based on medical records	1,208, 70%	ESRD	40*	Mainly
Bello et al., 2013	January 2009-September 2010	Nigeria	Retrospective descriptive survey	120, 60%	ESRD	47	Mainly
Bland et al., 2008	Not provided (one-off survey)	United States	Qualitative study using postal survey	77, 47%	On dialysis and taking 3 or more medications	Not provided	Mainly
Dageforde et al., 2001	November 2012-December 2013	United States	Qualitative study using telephone survey	104, 61%	Referred for kidney transplant	52	Mainly
Eghan et al., 2009	October 2005-December 2007	Ghana	Retrospective (observational) study	40, 56%	On dialysis	44*	Mainly
Hirth et al., 2008	2002-2004	12 OECD countries	Cross-sectional observational study	7,766, N/A^	On dialysis	60-66	Mainly
Mittal et al., 1997	May 1994-April 1995	India	Prospective observational study (adults and children)	835, 68%	Chronic Kidney Failure	43*	Partially
Okafor et al., 2012	July-December 2008	Nigeria	Prospective observational study	64, 59%	Presenting at a private dialysis centre	48	Partially
Okunola et al., 2013	January 2005-January 2010	Nigeria	Retrospective cohort study (5-year audit of HD sessions)	225, 69%	On dialysis	49*	Mainly
Park et al., 2014	January 2006-December 2007	United States	Retrospective cohort study	11,732, 56%	Medicare-eligible dialysis patients	69	Fully
Prakongsai et al., 2009	January-March 2005	Thailand	In-depth case studies	20, 60%	ESRD	53	Fully
Rao et al., 1998	April 1996-March 1997	India	Prospective cohort study (1 year)	463, 78%	ESRD	38	Fully
Seah et al., 2013	September 2010-June 2011	Singapore	Qualitative study using semi-structured interviews	9, 55%	ESRD	81**	Mainly
Shaikh et al., 2018	2008-2012	India	Retrospective study based on insurance claims data	13,118, 73%	On dialysis for ESRD	43	Fully

*includes adults and children; ** median not mean; ^ % m not provided but random sample used

ESRD, end stage renal disease; OECD, Organisation for Economic Co-operation and Development.

Table 2: Dialysis adherence studies: summary of results

Reference	Summary of dialysis access	Mortality / lost to follow up	Reasons given for discontinuation
Arogundade et al., 2011	25% of patients diagnosed with ESRD did not begin dialysis. Among those patients that begin, only 5% sustained longer than 12 weeks.	90% of undialysed patients died within two weeks of presentation. For those on treatment, 87% died within one month.	Authors observation on cost of RRT
Bello et al., 2013	3.3% of patients maintained dialysis 3 times per week; 21.7% dialysed twice weekly, 23.3% once a week.	8.3% died and 38% of patients were “lost to follow up”	Authors observation on cost of RRT
Eghan et al., 2009	50% of patients had an average of 20 sessions of haemodialysis before stopping	Overall mortality rate 36%, mortality during 1 st 90 days: 32%	Authors’ observation on cost of dialysis. Noted that dialysis not covered by national health insurance
Mittal et al., 1997	One year after initial presentation and diagnosis with CRF, 66% of ESRD patients and 34% with less severe illness had discontinued treatment	12.5%	Authors observation on high cost and limited availability on RRT
Okafor et al., 2012	Of 30 patients were diagnosed with either CKD, ESRD or AKF, 20 began haemodialysis but only two were able to sustain treatment for more than 2 months.	Not provided	Authors observation on cost of RRT
Okunola et al., 2013	Of 225 patients offered haemodialysis, 180 had CKF. Of these: only 1% (2 patients) maintained three sessions per week of dialysis a 1% maintained two sessions a week; 63% had 5 sessions or fewer.	73% (131 patients) died and 23% (41 patients) were lost to follow up.	Authors observation on cost of dialysis
Prakongsai et al., 2009	20 patients were put in three groups according to income: richer, middle and poorer. On average, richer patients received haemodialysis twice a week, and poorer patients once a week.	Four of nine richer patients died during study period.	Income data obtained from 12 households: 11 experienced catastrophic health expenditure
Rao et al., 1998	Of 463 ESRD patients, 60% left the program and 34% of maintained “definitive RRT therapy”, including renal transplant in 23%.	Overall mortality 9.5%, with 58% taking place within 1 week of starting dialysis.	External financial support positively associated with adherence to a thrice weekly dialysis schedule
Shaikh et al., (2018)	Median time on HD was 170 days for women and 198 days for men	10% of patients died and 37% dropped out within first six months. Overall mortality for study 17%, and 63.5% stopped reporting for dialysis	Other costs associated with seeking care, including travel expenses, cost of managing co-morbidities, loss of income and carer burden

AKF, acute kidney failure; CKD, chronic kidney disease; CKF, chronic kidney failure; ESRD, end stage renal disease; RRT, renal replacement therapy.

Figure 1: Summary of literature search and selection