Vanorio-Vega et al. Renal Replacement Therapy (2021) 7:28
https://doi.org/10.1186/s41100-021-00346-8

Renal Replacement Therapy

REVIEW

Open Access

Additional cost of end-stage kidney disease in diabetic patients according to renal replacement therapy modality: a systematic review

Isabella Vanorio-Vega[1,2*], Panayotis Constantinou[1], Philippe Tuppin[1] and Cécile Couchoud[2]

Abstract

The prevalence of end-stage kidney disease (ESKD) is growing worldwide; the survival of these patients requires renal replacement therapy (RRT, a complex and costly treatment). Over 20% of the patients that start RTT had diabetes. Limited evidence on the effect of comorbidities on the cost of RRT exists. This review summarizes the available evidence on the effect of diabetes mellitus (DM) on the cost of RRT. Electronic databases were searched using key words that combined RRT with DM and cost. References were identified with title, abstract, and full-text screening. The studies included were published in English and presented data on the cost of RRT in ESKD patients with comparison between DM status. Seventeen studies were included in this review. The crude and adjusted cost of care estimates for patients on dialysis was generally higher for DM patients. The cost of care of ESKD patients differed according to various treatment modalities and these differences, mainly driven by inpatient costs. Overall, we found an increased cost of RRT care in patients with DM regardless of the type of treatment. Future analysis of the effects of multiple comorbidities should be considered to better understand the effect of DM on the cost of RRT.

Keywords: Cost, Diabetes, Dialysis, Renal replacement therapy, Renal transplant

Background

The prevalence of end-stage kidney disease (ESKD) is continuing to increase worldwide. Long-term survival of these patients is dependent on renal replacement therapy (RRT) (hemodialysis [HD], peritoneal dialysis [PD], and/or kidney transplant). In Europe, over 20% of the RTT incident cases had diabetes, over 10% a cardiovascular disease, and over 50% are 65 years old or older [1]. ESKD has been recognized as a public health concern due to the financial and human burden, the complexity of care, and the growing prevalence of the disease [2]. In Europe, the number of prevalent patients increased from 641.6 per million population (pmp) in 1997 to 823 pmp in 2016 [3, 4]. This increase has been attributed to a surge of the prevalence of conditions that lead to chronic kidney disease (CKD), such as diabetes, cardiovascular disease, and older age [5].

In the USA, 47% of incident ESKD patients are attributed to diabetes [6]. Total spending for ESKD patients accounts for 7% of the Medicare budget and allocated to 1% of the population [7]. In France, 22.2% of the ESKD incident patients are attributed to diabetes [6]. The cost of RRT represented 3% of the total budget of the French national health insurance fund in 2013 and served less than 1% of the population [8]. Studies have found that the most clinically

* Correspondence: Isabella.vanoriovega@assurance-maladie.fr
[1]Direction de la stratégie des études et des statistiques, Caisse nationale de l'assurance maladie (CNAM), Avenue du Professeur André Lemierre, 75020 Paris, France
[2]Agence de la biomédecine, 1 Avenue du Stade de France, 93212 Saint-Denis, France

effective and cost-effective treatment modality is kidney transplantation [9]. However, transplant availability is limited, and this modality is not suitable for all ESKD patients, particularly patients with one or several comorbidities [10], which limit the eligibility for kidney transplantation and self-care dialysis. Multiple comorbidities have been associated with an increased pattern of cost [11]; nonetheless, the available evidence remains limited.

Diabetes mellitus (DM) is recognized as the primary cause of ESKD in the USA, Europe, and other regions of the world, with a prevalence ranging between 23 and 39% in ESKD patients [1, 12, 13]. Diabetic patients on HD have a poorer quality of life, an increased risk of developing/worsening of cardiovascular disease, neurological diseases, and an increased mortality [14–16]. As the prevalence of diabetes is increasing worldwide [17], it is expected that a greater number of patients will develop diabetic chronic kidney disease and eventually ESKD [18]. In this narrative review, we will summarize the available evidence on the effect of DM on the cost of RRT according to the treatment modality.

Methods

Literature search

Seven electronic databases were searched from data inception to mid-February 2018 with no time or methodology restrictions through focused and highly sensitive search strategies: NHS Economic Evaluation Database, Health Technology Assessment (via EBM Reviews), Embase (via the Ovid platform), EconLit (via EBSCO), Cochrane library, APAIS Health (via Informit), and Medline (search from inception to July 2020). Databases were searched for medical subject headings (MeSH) and keywords, combining terms related to dialysis or kidney transplantation with terms related to DM and terms related to cost information (“cost”, “expenditure”, “costing”, “cost evaluation”). A manual search for grey literature was conducted to retrieve government documents or commission reports.

Inclusion criteria

This review included studies in English reporting data on costs in ESKD patients treated by RRT (HD and/or PD and/or kidney transplantation) and comparing patients with DM and patients without DM, regardless of the type of diabetes.

Exclusion criteria

Studies that did not report separate costs for DM patients, studies that reported costs for combined comorbidities, non-primary studies (review articles, commentaries, letters, editorials), and studies including only post-transplant DM were not included.

Study selection

Titles and abstracts were screened, removing irrelevant records (either not related to our topic or irrelevant study design (reviews or non-original data). Full texts were sourced for the remaining records, and their eligibility was assessed for inclusion. We extracted the following information: first author, year of publication, setting (i.e., country), study design, definition of DM, type of dialysis, data sources, perspective, currency, cost, cost categories, time period considered for calculation of costs. A narrative approach was used to synthesize the current findings.

Cost assessment

To assess and categorize costs, we will use the terminology adopted by the French National Authority for Health to evaluate medico-economic strategies in the management of end-stage kidney disease. Costs related to consumption of hospital, ambulatory care, transportation, health program, and prescribed medications will be categorized as direct costs. Indirect costs refer to the impact of the disease on an individual’s ability or not to work as a result of reduced survival [19]. A top-down estimation refers to the estimation of costs using overall cost of a service of component; consequently, the estimation of unitary costs when using this method is the average cost; therefore, insensitive to between-patient variability. A bottom-up approach provides detailed information about the cost components per patient and identifies patient-specific unit costs. Person-based methods can more accurately assess and adjust for between-patient variability [20, 21].

Appraisal and quality assessment

Quality assessment used the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. This scale considers three major issues: selection (source of the population and its representativeness, sample size, missing values, exposure analysis), comparability (most important factor, other factors), and outcome (evaluation, statistical test).

Results

Literature search

The database searches performed in 2018 and 2020 identified 1416 records. After removing duplicate and irrelevant articles, 43 articles were submitted to full-text review. No studies of interest were identified in the grey literature. Twenty-five of these 43 references were excluded, as they did not report costs for diabetic patients or presented the costs of combined stages of CKD. At the end of the process, we identified 18 references (Fig. 1) [11, 22–38] (corresponding

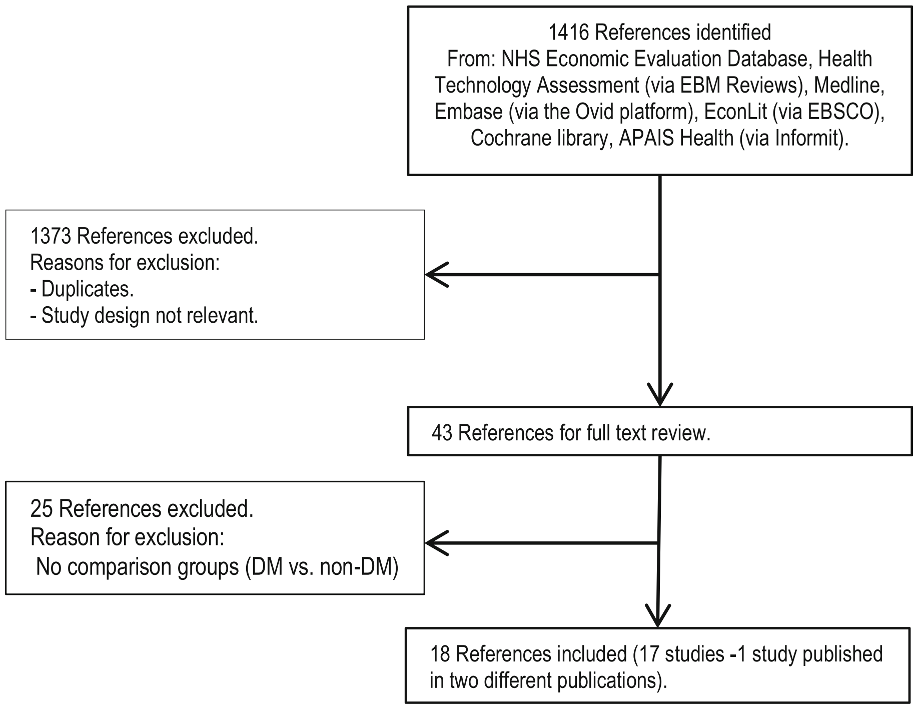

Fig. 1 Study selection process

to 17 studies, as one study was published in 2 parts [11, 22]).

Study characteristics

The 17 studies comprised no randomized controlled trials, 9 cohort studies [22, 24, 27, 29, 32–34, 36, 37], and 8 cross-sectional studies [11, 22, 25, 26, 28, 30, 31, 35, 38] (see Tables 1 and 2 for characteristics of the included studies). Four studies included incident patients [11, 22, 29, 32, 33], 2 studies included incident and prevalent patients [23, 34], and the rest of the studies included prevalent patients [24–28, 30, 31, 35–38]. Only 6 studies included transplanted patients [11, 29, 30, 35–37]. One article considered patients that were diagnosed with DM before and after kidney transplantation [37]. The proportion of diabetic patients ranged from 18 to 49% in the different groups and subgroups, except one article where DM patients were matched to non-DM [26].

Resource use and costs

All of the studies included in this review reported direct cost of care; none of the studies reported indirect cost of RRT. Three studies reported bottom-up cost estimates [24, 25, 28], 1 study reported a mix of bottom-up and top-down estimates [27], and the remaining studies used a top-down approach. Ten studies adopted an insurance perspective [11, 22, 24, 26, 28, 30, 31, 33, 34, 36], 4 studies adopted a provider perspective [25, 29, 32, 35], and 2 studies adopted a societal perspective [23, 27]. Five studies were based on national databases [11, 22, 24, 30, 37]. The types of costs reported in the studies in this review included inpatient in 7 studies [11, 22, 24, 26, 28, 30, 31, 35], outpatient in 6 studies [11, 22, 24, 28, 30, 31, 33], reimbursement in 4 studies [32, 33, 36, 37], transportation in 4 studies [27, 30, 31, 35], drugs in 3 studies [30, 35, 38], and dialysis procedure in 2 studies [31, 34]. The following were reported in individual studies: social services and patient out-of-pocket expenditure [23], amount paid by healthcare providers [25], caregiver costs [27], laboratory tests [35]. Six studies presented adjusted results [11, 22, 23, 27, 31, 32].

Quality appraisal of the studies

The overall study quality assessed by the CHEERS checklist was moderate to low, details in Table 2. Almost half of the studies included less than 400 patients, while the remaining studies comprised populations ranging between 1146 and 290,537 patients. Most of the studies are not representative of the general population, none of the studies addressed missing data, and only a few studies considered additional factors. Heterogeneous variables selected to adjust for confounders across studies (age, gender, comorbidities, income, and other variables) and the method of identification of DM varied (by medication consumption or previous medical records).

Impact of DM on costs

In the group of studies that reported cost analysis using crude results, 2 studies did not find any statistical

Table 1 General characteristics of the studies included in the review

Author	Year	Country	Population	Period inclusion	Source	Outcome currency	Perspective	Costs included	Total	Sub-group 1	Sub-group 2	Sub-group 3
Li et al. [11, 22]	2015	UK	Incident RRT	2003–2006	The UK Renal Registry (UKRR); Hospital Episode Statistics (HES)	Mean costs during the first year ( )	Insurance	Top-bottom cost estimation. In-patient cost from Health Resource Group (HRG), 2012 tariff. Outpatient cost (appointments).		HD n= 12, 068 Mean age = 68 DM= 34%	PD *n*= 4018 Mean age = 68 DM= 29%	TX *n*= 4149 Mean age = 68 DM= 27%
	2016					Generalized linear model parameter				Dialysis n= 15, 869 DM= 34%	TX *n*= 4511 DM= 26%	
Grun et al. [23]	2003	UK	Incident and prevalent dialysis in patients 70 yrs. or older	1995–1996	North Thames dialysis Study medical records.		Societal	Top-bottom cost estimation. Medical and social services. Privately borne costs.	Dialysis n= 171 HD= 56% Mean age= 77 DM= 20%			
Kao et al. [24]	2013	Taiwan	Prevalent dialysis adults, no cancer, no dialysis out of hospital	1997–2005	National Health Insurance (NHI)	Total lifetime cost. Cost per patient per year (US$)	Insurance	Bottom up costs estimation. Out-patient medical expenses Inpatient medical expenses.		HD n= 36, 539 Mean age = 61 DM= 49%	PD n= 3137 Mean age = 53 DM= 34%	
Su et al. [25]	2010	Taiwan	Prevalent dialysis patients	2005–2006	National Health Insurance Bureau's (NHIB) medical records	Use of medical resources during dialysis.	Provider	Bottom-up cost estimation. Fixed and variable during dialysis	Dialysis n= 177 Mean age= 62 DM= 50% HD=? %			
Yang et al. [26]	2001	Taiwan	Prevalent dialysis patients > 1 yr. dialysis	1999	3 medical centers	Annualized cost per patient-year at risk (US$)	Insurance	Top-bottom cost estimation. Out-patient medical expenses Inpatient medical expenses.	Dialysis n= 212 1/1-paired DM			
Hynes et al. [27]	2012	USA	Prevalent dialysis patients	2001–2003	Healthcare use Medicare claims databases Self-report	Adjusted 12-month total cost (US$)	Societal	Mix of bottom-up and top-bottom estimation. Direct cost (including travel and caregivers).		HD n= 334 Mean age=		

Table 1 General characteristics of the studies included in the review *(Continued)*

Author	Year	Country	Population	Period inclusion	Source	Outcome currency	Perspective	Costs included	Total	Sub-group 1	Sub-group 2	Sub-group 3
										62.2 DM= 50% DM Comp= 39%		
Bruns et al. [28]	1997	USA	Prevalent dialysis patients	1994–1995	Medical records University of Pittsburgh Hospital	Annualized costs per patient-year (US$)	Insurance	Bottom-up cost estimation. All transaction - Inpatient - Outpatient	Dialysis n= 148 >65 yrs. =32% DM= 25%			
Salonen et al. [29]	2003	Finland	Incident adult patients	1991–1996	Tempere University hospital	Mean cost (US$)	Provider	Bottom-up costs estimation. Direct health cost including overhead costs		HD n= 138 Mean age = 58.6 DM= 32%	CAPD n= 76 Mean age = 51 DM= 42%	TX n= 55 Mean age = 45 DM= 25%
Couillerot et al. [30]	2017	France	Prevalent adult RRT patients	2009–2010	French national health insurance information system (SNIIRAM). French national hospital computerized medical information system (PMSI).	Monthly cost (€)	Insurance	Bottom-up cost estimation. Direct costs: - Outpatient - Inpatient -Drugs -Transport	RRT n= 65, 662 Mean age = 61 DM= 23%	HD n= 33, 405	PD n= 2473	TX n= 22, 768
Icks et al. [31]	2010	Germany	Prevalent dialysis patients	2006	Medical records	Dialysis-related costs	Insurance	Top-down cost estimation. Direct medical cost: dialysis treatment, related admissions, outpatient contacts, related Drugs and patient transportation		HD n= 344 Mean age = 69		
Joyce et al. [32]	2004	USA	Incident (new onset ESKD) patients	1998–2002	PharMetrics Patient-Centric Database	First-year annual cost (US$)	Provider	Top-down cost estimation. Direct cost (health plan reimbursements)	RRT n= 4190 >65 yrs. =26% DM= 48%			
Mau et al. [33]	2010	USA	Incident patients aged 67 or older	1995–2005	Medicare	First-year annual cost (US$)	Insurance	Top-down cost estimation. Medicare allowable cost		HD n= 290, 537 Mean age = 75.6–		

Table 1 General characteristics of the studies included in the review *(Continued)*

Author	Year	Country	Population	Period inclusion	Source	Outcome currency	Perspective	Costs included	Total	Sub-group 1	Sub-group 2	Sub-group 3
										77.4 DM= 54.2–64.1%		
Wong et al. [34]	2012	Australia	Incidence and prevalence	2004–2008	Refined diagnosis-related group and Medicare benefits schedule Australia	Total cost of dialysis and receiving a deceased donor liver	Insurance	Top-down cost estimation. Total cost of dialysis and receiving a deceased donor liver				
Ghoddousi et al. [35]	2007	Iran	Prevalence	2000–2005	Patient's hospital records	Total cost of rehospitalizations after Tx (PPP$)	Provider	Top-down cost estimation. Total hospital costs including hotel, medications, surgery, lab. test, imaging tests, health personnel, transportation.	Hx n=387 DM= 18%			
Smith et al. [36]	1989	USA	Prevalence	1981–1983	Michigan Kidney Registry	Annual Medicare allowable charges	Insurance	Top-down cost estimation. Sum of the reimbursed amount paid by providers	n=1146 DM= 21%	HD n=1106 $\bar{X}$ age 58,7 DM= 21%	PERI n=69 DM= 27.5%	Tx n=167 DM= 27%
Woodward et al. [37]	2011	USA	Prevalence	1998–2002	US Renal Data System	The lump sum of daily average Medicare payments per patient (8 yrs.)	Insurance	Top-down cost estimation. Institutional claims and physician's supplier claims	n=24, 816 DM= 46.4% NODAT= 20%	Tx patients Total= 24,816 DM= 46.4% NODAT= 20%		
Manley et al. [38]	2005	USA	Prevalence	2003	Dialysis Clinic Inc. DCI	Average monthly cost of drugs taken at home by patients that receive dialysis	Provider	Top-down cost estimation. Medications used at home	n=10, 230	HD= 10203 DM 40%		

UKRR The UK Renal Registry, *HES* Hospital Episode Statistics, *HD* hemodialysis, *PD* peritoneal dialysis, *CAPD* continuous ambulatory peritoneal dialysis, *RRT* renal replacement therapy, *ESKD* end-stage kidney disease, *NODAT* new onset DM after transplant

Table 2 Quality assessment of included articles

Author	Year	Design	Prospective Retrospective	Data source	Comorbidities definition	Confounder	Adjustment	Selection				Comparability		Outcome		Total
								Source diversity	Sample size	Missing data	Exposure Analysis	Main factor	Other factors	Evaluation	Stat test	
Li et al. [11, 22]	2015	Cross-sectional	Retrospective	National	Discharge codes from hospitalizations prior to starting RRT-ICD 10	None	None	*	*		*			*	*	5
	2016					MRM	Age, sex, years since starting RRT, treatment modality, events, comorbidities	*	*			*	*	*	*	6
Grun et al. [23]	2003	Cohort	Prospective	4 dialysis units	At baseline	None	Sex, age, treatment modality, comorbid conditions, cohort, length of time since initiation					*	*	*	*	4
Kao et al. [24]	2013	Cohort	Retrospective	National		Stratification	Stratification by matched HD-PD on age, sex, DM status	*	*					*		3
Su et al. [25]	2010	Cross-sectional	Prospective	One district		MRM	Comorbidities, age					*		*	*	3
Yang et al. [26]	2001	Cross-sectional	Prospective	3 medical centers		Matching	Matched DM–no DM on age, sex, duration of dialysis					*		*		2
Hynes et al. [27]	2012	Cohort	Prospective	Veterans Affairs facilities	Year prior the index date-ICD 9	MRM	Age, gender, race, income, insurance, comorbidities, quality of well-being				*	*	*	*	*	5
Bruns et al. [28]	1997	Cross-sectional	Retrospective	1 medical center		Stratification	Stratification by age							*		1
Salonen et al. [29]	2003	Cohort	Prospective	1 medical center		MRM	Stratification by treatment modality							*	*	2
Couillerot et al. [30]	2017	Cross-sectional	Retrospective	National	Use of drugs for DM	Stratification	Stratification on age and	*	*		*			*		4

Table 2 Quality assessment of included articles *(Continued)*

Author	Year	Design	Prospective Retrospective	Data source	Comorbidities definition	Confounder	Adjustment	Selection				Comparability		Outcome		Total
								Source diversity	Sample size	Missing data	Exposure Analysis	Main factor	Other factors	Evaluation	Stat test	
							RRT modality, events									
Icks et al. [31]	2010	Cross-sectional	Prospective	1 medical center		MRM	Gender, age, ESKD duration, time of dialysis					*		*	*	3
Joyce et al. [32]	2004	Cohort	Retrospective	Commercially insured patients in 61 Health Plans	Year prior the index date-ICD 9	MRM	Age, gender, insurance, comorbidities, region, medication use. No adjustment on RRT modality.		*		*			*	*	4
Mau et al. [33]	2010	Cohort	Retrospective	National	2 years prior the index date-ICD 9	MRM	Age, gender, race, comorbidities, Hb, eGFR, albumin, BMI, hospital days pre-onset	*	*		*	*		*	*	6
Ghoddousi et al. [35]	2007	Cross-sectional	Retrospective	1 medical center	Reported in the EMR	None	None		*		*			*		3
Smith et al. [36]	1989	Cohort	Retrospective	Michigan database		None	None	*	*			*				3
Woodward et al. [37]	2011	Cohort	Retrospective	US Renal Data System	ICD 9	None	None	*	*		*	*		*	*	6
Wong et al. [34]	2012	Cohort	Retrospective	National	Australian Refined Diagnosis Related Groups	Stratification	None	*			*	*	*	*		5
Manley et al. [38]	2005	Cross-sectional	Retrospective	National		None	None	*	*			*		*		4

* used to mark the charateristic as present in the study
MRM multiple regression model, *RRT* renal replacement therapy, *ESKD* end-stage kidney disease

differences in terms of crude mean cost between patients with or without DM receiving dialysis (HD and PD grouped together) (Table 3) [23, 25]. One study found a 23% difference for the cost per patient-year, varying according to age from 61% in the 65–74 years age-group vs −22% in DM patients ≥ 75 years [28]. One study found a 12% difference in total cost per patient-year, mainly explained by the difference in terms of utilization of resources during hospitalization between non-DM and DM patients [26]. The last study to report differences within the HD+PD group showed increased annual costs among DM patients for all comparator groups ranging from 17 to 44%, except for the annual costs related to at-home continuous ambulatory peritoneal dialysis training (CAPDTR) that were 3% lower among DM patients [36].

Table 4 contains details of the studies that reported HD and PD cost estimates separately. In the HD group, four studies found a higher cost for DM patients between 4 and 32%, regardless of the comparator used or the age group or the treatment modality [11, 29, 30, 38]. Among PD patients, three studies found a higher cost in DM patients, between 4 and 52%, regardless of the comparator used or the age group or the type of PD [11, 29, 30]. One study found a lower total lifetime cost in DM patients with −48 and −42% for HD and PD. The differences expressed in terms of life years were 23 and 32%, respectively [24].

In transplanted patients (Table 5), four studies found a higher cost in DM patients regardless of the comparator ranging between 14 and 100% [11, 30, 35, 37]. Salonen et al. reported a lower cost for DM in the comparator group for the first 6 months (−4%) and during the second year after transplant (−10%) [29]. Two studies presented cost estimates for all RRT patients, and both reported higher costs for DM patients, ranging between 5 and 50% [32, 34].

Six studies presented adjusted cost analyses (Table 6), and 3 of these studies reported significant results suggesting a positive relationship between DM and increased cost [22, 32]. Three studies, based on relatively small sample sizes, did not find any statistical association between DM and costs [23, 27, 31].

Discussion

Our narrative review shows for the first time to our knowledge the different costs of care between DM and non-DM patients by type of RRT. This review found that higher costs are generally reported for patients with DM in RRT. The costs most commonly reported were inpatient costs and outpatient costs. The difference between DM and non-DM patients was observed

Table 3 Crude cost estimate reported in dialysis patients (HD + PD)

Author	Year	comparator	Stratification	Value of non-DM (SD)	Value of DM (SD)	Diff	p
Grun et al. [23]	2003	Mean cost per day (£)	None	68.5 (30.5)	68.1 (28.1)	−1%	0.94
Su et al. [25]	2010	Dialysis cost (NT)	None	1467.53 (220.9)	1481.6 (209.13)	1%	0.664
Yang et al. [26]	2001	Total cost (US$/patient-year)	None	24,146	26,988	12%	
		Outpatient (US$/patient-year)	None	22,820	22,311	−2%	
		Dialysis and EPO	None	21,209	19,841	−6%	
		Other clinic	None	1611	2470	53%	
		Hospitalization (US$/patient-year)	None	1325	4677	253%	
		Dialysis and EPO	None	409	1093	167%	
		Others	None	916	3584	291%	
Bruns et al. [28]	1997	Costs per patient-year ($)	All	55,581	68,228	23%	
			20–44	48,927	51,884	6%	
			45–64	65,707	72,643	11%	
			65–74	48,062	77,418	61%	
			≥75	59,594	46,746	−22%	
Smith et al. [36]	1989	Annual charges HD in centers	None	23,470	27,463	17%	
		Annual charges PERI in centers	None	22,529	26,486	18%	
		Annual charges CAPDTR	None	18,408	17,879	−3%	
		Annual charges CAPDH	None	22,753	29,435	29%	
		Annual charges Other	None	28,342	40,779	44%	
		Weighted average	None	24,976	29,671	19%	

NT New Taiwan, *EPO* erythropoietin, *PERI* in center peritoneal dialysis, *CAPDTR* continuous ambulatory peritoneal dialysis training, *CAPDH* combinations of dialysis treatments

Table 4 Crude cost estimate reported in HD and PD separate groups.

Author	Year	Comparator	HD patients					PD patients				
			Stratification	Value of non-DM (SD)	Value of DM (SD)	Diff	p	Strata	Value of non-DM (SD)	Value of DM (SD)	Diff	p
Li et al. [11, 22]	2015	Mean inpatient cost (£)	None	6685 (6415, 6956)*	8454 (8049, 8858)*	26%	< 0.0005		4492 (4215, 4770)*	6814 (6321, 7307)*	52%	< 0.0005
		Mean outpatient cost (£)	None	1081 (1051, 1110)*	1346 (1303, 1389)*	25%	< 0.0005		1789 (1453, 1543)*	2064 (1976, 2152)*	15%	< 0.0005
Kao et al. [24]	2013	Total lifetime (US$)	None	216,457 (12,853)	112,516 (5318)	−48%			157,374 (10,531)	90,945 (10,935)	−42%	
		Per life-year (US$)	None	20,724	25,519	23%			17,163	22,732	32%	
Salonen et al. [29]	2003	Mean cost 0–6 months (US$)	None	32,741	34,006	4%		CAPD	23,323	29,882	28%	
		Mean 7–12 months (US$)	None	26,155	28,908	11%		CAPD	20,982	29,897	42%	
		Mean year 2 (US$)	None	52,287	63,781	22%		CAPD	42,386	51,027	20%	
Couillerot et al. [30]	2017	Mean monthly health care costs (euros) for a stable prevalent patient	18–44 yrs.									
			In-center	6915 (2455)	8298 (2429)	20%		Non-ass CAPD	3214 (1269)	4382	36%	
			Home	4739 (1791)	5886 (1811)	24%		Non-ass APD	4208 (1370)	5376 (2071)	28%	
			Self-care	4083 (1567)	5360 (2021)	31%		Ass CAPD	4850	6018	24%	
			Home	4159 (1759)	5038	21%		Ass APD	5550	6717	21%	
			45–69 yrs.									
			In-center	6964 (2306)	7992 (2306)	15%		Non-ass CAPD	3856 (1344)	4093 (1253)	6%	
			Home	5136 (1672)	5810 (1641)	13%		Non-ass APD	4324 (1410)	4984 (1446)	15%	
			Self-care	4304 (1461)	4940 (1698)	15%		Ass CAPD	4899 (1885)	6497 (2406)	33%	
			Home	4118 (1825)	5439 (2190)	32%		Ass APD	6275 (1520)	6543 (2054)	4%	
			70+ yrs.									
			In-center	6916 (1867)	7736 (2014)	12%		Non-ass CAPD	3462 (1348)	4295 (1287)	24%	
			Home	5003 (1632)	5425 (1756)	8%		Non-ass APD	4085 (1390)	5118 (1691)	25%	
			Self-care	4340 (1282)	4696 (1349)	8%		Ass CAPD	4932 (1565)	5923 (1848)	20%	
			Home	3484 (1251)	4374	26%		Ass APD	5265 (1653)	5796 (2069)	10%	
		Cost of the first month of treatment for incident patients.	18–44 yrs.	7716 (13683)	9467 (6999)	23%			10,882 (11,691)	13,345 (9978)	23%	
			45–69 yrs.	7797 (10717)	8632 (6809)	11%			9647 (9441)	9654 (7981)	0%	
			70+ yrs.	7851 (6767)	8667 (7434)	10%			8810 (8276)	11,244 (8860)	28%	

Table 4 Crude cost estimate reported in HD and PD separate groups. *(Continued)*

Author	Year	Comparator	HD patients					PD patients				
			Stratification	Value of non-DM (SD)	Value of DM (SD)	Diff	p	Strata	Value of non-DM (SD)	Value of DM (SD)	Diff	p
Manley	2005	Monthly cost of ambulatory medications.	None	571.04 (287.36)	691.04 (271.59)	21%						

*95% CI limits

CAPD continuous ambulatory peritoneal dialysis; *Non-ass CAPD* non-assisted CAPD, *Ass CAPD* assisted CAPD

regardless of the treatment modality (dialysis or transplantation) and was mainly driven by the higher costs of hospitalization.

The results should be interpreted cautiously, 8 of the studies were published over 10 years ago, and there are numerous methodological pitfalls the observational studies included. A quality score higher than 5 was observed for only 3 studies. Thirteen studies were based on local databases and were less representative of the general population. Six studies adjusted for patient

Table 5 Crude cost estimate reported in transplanted and unspecified RRT patients:

Author	Year	Comparator	Stratification	Value of non-DM (SD)	Value of DM (SD)	Diff	p
Transplanted patients							
Li et al. [11, 22]	2015	Mean inpatient cost (£)	None	3626 (3439, 3813)*	5921 (5499, 6343)*	63%	< 0.0005
		Mean outpatient cost (£)	None	3963 (3890, 4036)*	4520 (4376, 4665)*	14%	< 0.0005
Salonen et al. [29]	2003	Mean cost 0–6 months (US$)	None	38,946	37,299	−4%	
		Mean cost 7–12 months (US$)	None	7216	8497	18%	
		Mean cost 2nd year (US$)	None	11,972	10,802	−10%	
Couillerot et al. [30]	2017	Mean monthly health care costs (euros) fort a stable prevalent patient	18–44 years	1043 (1188)	2091 (1998)	100%	
			45–69 years	1075 (1065)	1640 (1337)	53%	
			70+ years	1038 (888)	1475 (1129)	42%	
Ghoddousi et al. [35]	2007	Total cost (PPP $ rehospitalization)	None	863.93 (1165.2)	1261.98 (1930.5)	46%	
Smith et al. [36]	1989	Year of transplant annual charges LTRAN	None	41,553	46,797	13%	
		Year of transplant annual charges CTRAN	None	42,074	61,493	46%	
		Year of transplant annual charges FTRAN	None	58,672	63,670	9%	
		Year after transplant annual charges LTRAN	None	3836	4320	13%	
		Year after transplant annual charges CTRAN	None	5696	8325	46%	
		Year after transplant annual charges FTRAN	None	47,057	50,584	7%	
Woodward et al. [37]	2011	DM before transplant. Cumulative cost per patient from 3 years before transplant to 5 years after transplant	None	114,686	162,048	29%	
		NODAT before transplant. Cumulative cost per patient from 3 years before transplant to 5 years after transplant	None	114,686	146,915	22%	
RRT							
Joyce et al. [32]	2004	Annual cost for the 12 months post onset of ESKD ($)	None	57,249	86,081	50%	
Wong et al. [34]	2012	Total costs ($)	45 years old	119,329	136,677	13%	
		Total costs ($)	60 years old	143,004.98	151,168.29	5%	

ESKD end-stage kidney disease, *DM* diabetes mellitus, *PPP* power parity dollar, *LTRAN* living related donor, *CTRAN* cadaver donor, *FTRAN* failed, *NODAT* new onset DM after transplant

Table 6 Adjusted cost estimations of patients receiving RRT (DM and non-DM patients)

Author	Year	Stratification	Comparator	Estimation	Adjusted results ($,£,€ (95%CI)	p-value
TX patients						
Li et al. [22]	2016	None	Increase in mean annual costs ($, GLM coefficient) for inpatient GLM		1046 (734, 1359)	<0.05
			Increase in mean annual costs (GLM coefficient) for outpatient GLM		593 (515, 671)	<0.05
Dialysis patients (HD + PD)						
Li et al. [22]	2016	None	Increase in mean annual costs ($, GLM coefficient) for inpatient GLM		1191 (929, 1453)	<0.05
			Increase in mean annual costs (GLM coefficient) for outpatient GLM		248 (211, 284)	<0.05
Grun et al. [23]	2003		Adjusted difference of means cost per day (, linear regression) linear		−0.8 (−11.8, 10.1)	0.88
HD patients						
Hynes et al. [27]	2012	DM	Adjusted annual cost difference ($, GLM marginal effect)		−1623 (−14,973; 11,727)	0.81
		Complicated DM			8763 (−10,331; 27,857)	0.37
Icks et al. [31]	2010	None	Relative cost differences (euros, GLM)		1.04 (0.98,1.10)	
Mau et al. [33]	2010	None	Case-mix-adjusted estimate		0.0275 (0.0014)	
			Relative cost		1.03	<0.001
RRT patients						
Joyce et al. [32]	2004	None	Adjusted annual cost difference ($, GLM marginal effect)		42,361	<0.001

DM diabetes mellitus, *TX* transplant patients, *GLM* generalized linear model

characteristics for cost modelling. Most studies did not consider comorbidities. Social, transport, and out-of-pocket expenses were not considered in the majority of studies. The diversity of comparators, populations, sources of costs, and the perspectives used in the various studies prevented us from performing a dollar-to-dollar comparison between the various studies or a meta-analysis.

There is evidence in the literature for a higher healthcare cost in the DM population regardless of their kidney disease status that is mainly driven by inpatient costs due to long hospital stays [39]. Yang et al. showed that the number of hospitalizations, and the mean length of hospital stay were the main drivers of the increased costs among DM patients [40]. Other studies in our review do not provide any insight into the drivers for higher costs for DM patients.

Higher costs for DM patients can also be explained by the number and total cost of medications, as patients with DM were more frequently prescribed cardiovascular, gastrointestinal, and endocrine drugs than non-DM patients treated by RRT [38], which is consistent with the metabolic complications intrinsic to DM and the high rate of vascular and neurological comorbidities in the DM population [41].

Wong et al. and Kao et al. [24, 34] reported lifetime costs of DM. In their study, the overall cost of RRT was higher for non-DM patients. However, when corrected by the expected years of life, the cost of RRT was higher in DM patients, as DM patients with ESKD are known to have a shorter life expectancy than non-DM patients [15, 42, 43].

A more marked difference in costs between non-DM and DM patients was generally observed in the younger population, which could likely be explained by the lower rate of comorbidities in young non-DM patients. Younger patients are more likely to have type 1 DM; insulin therapy represents a high proportion of the cost of treatment for these patients. Younger patients have also been reported to have a higher first month cost when starting treatment as a result of training to perform PD independently and clinical evaluations for inclusion on transplant waiting lists [30]. This interesting point should be taken into account when performing future analyses of the costs associated with comorbidities and differences according to age groups and the reference time-points to be used. In the study by Bruns et al., the greatest difference was observed in an older age group (between the ages of 65 and 74). The distribution of the population in this study was slightly different from that of the general population, as outliers were likely to have an impact in the 65- to 74-year age group.

Only one of the studies provided data concerning the various types of living donor or cadaver transplant and graft loss. One study in our review included information on the cost for patients with or without DM related to the time since transplant. Costs were particularly high during the first year compared to the second year in both groups [29], supporting evidence that kidney transplantation is the RRT modality associated with the greatest economic benefits after the first year regardless of DM status [43].

Conclusions

We found an increased cost of RRT in patients with DM regardless of the treatment modality when compared to patients without DM. Given the increased prevalence of DM in the population, we can anticipate higher healthcare cost for this group of patients. The effects of presence of multiple comorbidities (in non-DM and DM patients), life expectancy, and specificity of type of dialysis treatment should be taken into account in future studies to obtain a better understanding of the effect of DM in RRT care. Additional information is also needed on indirect costs.

Abbreviations

CAPDTR: Continuous ambulatory peritoneal dialysis training; CHEE RS: Consolidated Health Economic Evaluation Reporting Standards; CKD: Chronic kidney disease; DM: Diabetes mellitus; ESKD: End-stage kidney disease; HD: Hemodialysis; PD: Peritoneal dialysis; RRT: Renal replacement therapy

Acknowledgements

We want to aknowledge CIFRE for providing us the oportunity to develop our researh.

Authors' contributions

CC developed the idea and performed the preliminary search and screening. IV performed screening of abstracts and titles as well as full-text screening and data extraction and wrote the manuscript. CP and PT reviewed and edited the manuscript. All authors discussed and approved the manuscript.

Funding

No specific funding.

Availability of data and materials

The references used are available in the following databases: NHS Economic Evaluation Database, Health Technology Assessment (via EBM Reviews), Medline, Embase (via the Ovid platform), EconLit (via EBSCO), Cochrane library, APAIS Health (via Informit).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 9 March 2021 Accepted: 14 May 2021
Published online: 31 May 2021

References

1. Kramer A, Pippias M, Noordzij M, Stel VS, Andrusev AM, Aparicio-Madre MI, et al. The European renal association – European dialysis and transplant association (ERA-EDTA) registry annual report 2016: a summary. Clin Kidney J. 2019 Oct 1;12(5):702–20. https://doi.org/10.1093/ckj/sfz011.
2. Wang V, Vilme H, Maciejewski ML, Boulware LE. The economic burden of chronic kidney disease and end-stage renal disease. Semin Nephrol. 2016 Jul;36(4):319–30. https://doi.org/10.1016/j.semnephrol.2016.05.008.
3. Kramer A, Stel V, Zoccali C, Heaf J, Ansell D, Gronhagen-Riska C, et al. An update on renal replacement therapy in Europe: ERA-EDTA registry data from 1997 to 2006. Nephrol Dial Transplant. 2009 Dec 1;24(12):3557–66. https://doi.org/10.1093/ndt/gfp519.
4. ERA-EDTA Registry Annual Report 2017. 2017;152.
5. Hallan SI, Dahl K, Oien CM, Grootendorst DC, Aasberg A, Holmen J, et al. Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey. BMJ. 2006 Nov 18;333(7577):1047. https://doi.org/10.1136/bmj.39001.657755.BE.
6. 2020 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. Bethesda,: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2020.
7. USRDS. US Renal Data System 2019 Annual Data Report: epidemiology of kidney disease in the United States. 2019.
8. Assurance Maladie. Améliorer la qualité du système de santé et maîtriser les dépenses 2 juillet 2015 Propositions de l'Assurance Maladie pour 2016. 2015 juillet. 2015.
9. Tataradze A, Managadze G, Beglarashvili L, Kipshidze N, Managadze L, Chkhotua A. Comparative costs of different renal replacement therapies in lower middle income countries on the example of Georgia. Int J Clin Med. 2016;07(07):437–44. https://doi.org/10.4236/ijcm.2016.77046.
10. Ceretta ML, Noordzij M, Luxardo R, De Meester J, Abad Diez JM, Finne P, et al. Changes in co-morbidity pattern in patients starting renal replacement therapy in Europe—data from the ERA-EDTA registry. Nephrol Dial Transplant. 2018;33(10):1794–804. https://doi.org/10.1093/ndt/gfx355.
11. Li B, Cairns J, Fotheringham J, Tomson C, Forsythe J, Watson C, et al. Understanding cost of care for patients on renal replacement therapy: looking beyond fixed tariffs. Nephrol Dial Transplant. 2015;30(10):1726–34. https://doi.org/10.1093/ndt/gfv224.
12. Masakane I, Taniguchi M, Hasegawa T, Nakai S, Goto S, Wada A, et al. Annual dialysis data report 2017, JSDT renal data registry. Ren Replace Ther. 2019;5(1):53.
13. Burrows NR, Hora I, Geiss LS, Gregg EW, Albright A. Incidence of end-stage renal disease attributed to diabetes among persons with diagnosed diabetes — United States and Puerto Rico, 2000–2014. MMWR Morb Mortal Wkly Rep. 2017;66(43):1165–70. https://doi.org/10.15585/mmwr.mm6643a2.
14. Sørensen VR, Mathiesen ER, Watt T, Bjorner JB, Andersen MVN, Feldt-Rasmussen B. Diabetic patients treated with dialysis: complications and quality of life. Diabetologia. 2007;50(11):2254–62. https://doi.org/10.1007/s00125-007-0810-1.
15. Soleymanian T, Kokabeh Z, Ramaghi R, Mahjoub A, Argani H. Clinical outcomes and quality of life in hemodialysis diabetic patients versus non-diabetics. Journal of Nephropathology. 2017;
16. Arsalan W, Syed AHB, Sidra B, Ayyaz AK. Quality of life in diabetic and non diabetic patients on hemodialysis therapy. J Diabetes Endocrinol. 2014;5(2):9–18. https://doi.org/10.5897/JDE2013.0068.
17. Zhou, Y., Abel, G.A., Hamilton, W., Pritchard-Jones, K., Gross, C.P., Walter, F.M., Renzi, C., Johnson, S., McPhail, S., Elliss-Brookes, L. and Lyratzopoulos, G. Diagnosis of cancer as an emergency: a critical review of current evidence. Nat Rev Clin Oncol. 2016/11/03 ed. 2017 14(1):45–56.
18. Gilbertson DT, Liu J, Xue JL, Louis TA, Solid CA, Ebben JP, et al. Projecting the number of patients with end-stage renal disease in the United States to the year 2015. J Am Soc Nephrol. 2005;16(12):3736–41. https://doi.org/10.1681/ASN.2005010112.
19. Bongiovanni I, Couillerot-Peyrondet A-L, Sambuc C, Dantony E, Elsensohn M-H, Sainsaulieu Y, et al. Évaluation médico-économique des stratégies de prise en charge de l'insuffisance rénale chronique terminale en France. Néphrologie Thérapeutique. 2016;12(2):104–15. https://doi.org/10.1016/j.nephro.2015.10.004.
20. Tan SS, Rutten FFH, van Ineveld BM, Redekop WK, Hakkaart-van RL. Comparing methodologies for the cost estimation of hospital services. Eur J Health Econ. 2009;10(1):39–45. https://doi.org/10.1007/s10198-008-0101-x.
21. Larg A, Moss JR. Cost-of-illness studies: a guide to critical evaluation. PharmacoEconomics. 2011;29(8):653–71. https://doi.org/10.2165/11588380-000000000-00000.
22. Li B, Cairns J, Fotheringham J, Ravanan R, Ravanan R. Predicting hospital costs for patients receiving renal replacement therapy to inform an economic evaluation. Eur J Health Econ. 2016;17(6):659–68. https://doi.org/10.1007/s10198-015-0705-x.

23. Grun RP. Costs of dialysis for elderly people in the UK. Nephrol Dial Transplant. 2003;18(10):2122–7. https://doi.org/10.1093/ndt/gfg354.
24. Kao T-W, Chang Y-Y, Chen P-C, Hsu C-C, Chang Y-K, Chang Y-H, et al. Lifetime costs for peritoneal dialysis and hemodialysis in patients in Taiwan. Perit Dial Int J Int Soc Perit Dial. 2013;33(6):671–8. https://doi.org/10.3747/pdi.2012.00081.
25. Su B-G, Tsai K-L, Yeh S-H, Ho Y-Y, Liu S-Y, Rivers PA. Risk factor and cost accounting analysis for dialysis patients in Taiwan. Health Serv Manag Res. 2010;23(2):84–93. https://doi.org/10.1258/hsmr.2009.009017.
26. Yang W-C, Hwang S-J, Chiang S-S, Chen H-F, Tsai S-T. The impact of diabetes on economic costs in dialysis patients: experiences in Taiwan. Diabetes Res Clin Pract. 2001;54:47–54. https://doi.org/10.1016/S0168-8227(01)00309-6.
27. Hynes DM, Stroupe KT, Fischer MJ, Reda DJ, Manning W, Browning MM, et al. Comparing VA and private sector healthcare costs for end-stage renal disease. Med Care. 2012;50(2):161–70. https://doi.org/10.1097/MLR.0b013e31822dcf15.
28. Bruns F, Seddon P, Saul P, Zeidel M. The cost of caring for end-stage kidney disease patients: an analysis based on hospital financial transaction records. American Society of Nephrology. 1997;12.
29. Salonen T, Reina T, Oksa H, Sintonen H, Pasternack A. Cost analysis of renal replacement therapies in Finland. Am J Kidney Dis. 2003 Dec;42(6):1228–38. https://doi.org/10.1053/j.ajkd.2003.08.024.
30. Couillerot-Peyrondet A-L, Sambuc C, Sainsaulieu Y, Couchoud C, Bongiovanni-Delarozière I. A comprehensive approach to assess the costs of renal replacement therapy for end-stage renal disease in France: the importance of age, diabetes status, and clinical events. Eur J Health Econ. 2017;18(4):459–69. https://doi.org/10.1007/s10198-016-0801-6.
31. Icks A, Buckhard H, Afschin G, Chernyak N, Rathmann W, Giani G, et al. Cost of dialysis-a regional population-based analysis. Nephrology Dialysis Transplantation. 2009;
32. Joyce AT, Iacoviello JM, Nag S, Sajjan S, Jilinskaia E, Throop D, et al. End-stage renal disease-associated managed care costs among patients with and without diabetes. Diabetes Care. 2004;27(12):2829–35. https://doi.org/10.2337/diacare.27.12.2829.
33. Mau L-W, Liu J, Qiu Y, Guo H, Ishani A, Arneson TJ, et al. Trends in patient characteristics and first-year medical costs of older incident hemodialysis patients, 1995-2005. Am J Kidney Dis. 2010;55(3):549–57. https://doi.org/10.1053/j.ajkd.2009.11.014.
34. Wong G, Howard K, Chapman JR, Chadban S, Cross N, Tong A, et al. Comparative survival and economic benefits of deceased donor kidney transplantation and dialysis in people with varying ages and co-morbidities. van Baal PHM, editor. PLoS ONE. 2012 Jan 18;7(1):e29591.
35. Ghoddousi K, Ramezani MK, Assari S, Lankarani MM, Amini M, Khedmat H, et al. Primary kidney disease and post-renal transplantation hospitalization costs. Transplant Proc. 2007;39(4):962–5. https://doi.org/10.1016/j.transproceed.2007.03.007.
36. DG Smith, LC Harlan, VM Hawthorne. The charges for ESRD treatment of diabetics. 1989.
37. Woodward RS, Flore MC, Machnicki G, Brennan DC. The long-term outcomes and costs of diabetes mellitus among renal transplant recipients: tacrolimus versus cyclosporine. Value Health. 2011;14(4):443–9. https://doi.org/10.1016/j.jval.2010.10.030.
38. Manley, HJ, Cannella, CA. Nondialysis (home) medication utilization and cost in diabetic and nondiabetic hemodialysis patients. Nephrology News & Issues. 2005
39. Cheng S-W, Wang C-Y, Ko Y. Costs and length of stay of hospitalizations due to diabetes-related complications. J Diabetes Res. 2019;2019:1–6. https://doi.org/10.1155/2019/2363292.
40. Yang M, Fox CH, Vassalotti J, Choi M. Complications of progression of CKD. Adv Chronic Kidney Dis. 2011;18(6):400–5. https://doi.org/10.1053/j.ackd.2011.10.001.
41. Webb L, Gilg J, Feest T, Fogarty D. Chapter 4: comorbidities and current smoking status amongst patients starting renal replacement therapy in England, Wales and Northern Ireland from 2008 to 2009. Nephron Clin Pract. 2011;119(s2):c85–96. https://doi.org/10.1159/000331754.
42. Couchoud C, Stengel B, Landais P, Aldigier J-C, de Cornelissen F, Dabot Cet al. The renal epidemiology and information network (REIN): a new registry for end-stage renal disease in France. Nephrol Dial Transplant 2006; 21(2):411–418, DOI: https://doi.org/10.1093/ndt/gfi198.
43. Vijayan M, Radhakrishnan S, Abraham G, Mathew M, Sampathkumar K, Mancha NP. Diabetic kidney disease patients on hemodialysis: a retrospective survival analysis across different socioeconomic groups. Clin Kidney J. 2016;9(6):833–8. https://doi.org/10.1093/ckj/sfw069.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.