KI REPORTS
KIReports.org
CLINICAL RESEARCH

Health Care Resource Utilization and Related Costs of Patients With CKD From the United States: A Report From the DISCOVER CKD Retrospective Cohort

Juan Jose Garcia Sanchez[1], Glen James[1], Juan Jesus Carrero[2], Matthew Arnold[1], Carolyn S.P. Lam[3,4], Carol Pollock[5], Hungta (Tony) Chen[6], Stephen Nolan[1], David C. Wheeler[7] and Roberto Pecoits-Filho[8,9]

[1]AstraZeneca, Cambridge, UK; [2]Karolinska Institutet, Department of Medical Epidemiology and Biostatistics, Stockholm, Sweden; [3]National Heart Center, Department of Cardiology, Singapore, Singapore; [4]Duke-NUS Medical School, Singapore, Singapore; [5]Kolling Institute- Royal North Shore Hospital University of Sydney, Sydney, Australia; [6]AstraZeneca, Gaithersburg, United States; [7]University College London, London, United Kingdom; [8]School of Medicine- Pontifical Catholic University of Parana, Curitiba, Brazil; and [9]Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA

Introduction: It is well established that chronic kidney disease (CKD) results in a significant burden on patients' health and health care providers. However, detailed estimates of the health care resource utilization (HCRU) of CKD are limited, particularly those which consider severity, comorbidities, and payer type. This study aimed to bridge this evidence gap by reporting contemporary HCRU and costs in patients with CKD across the US health care providers.

Methods: Cost and HCRU estimates of CKD and reduced kidney function without CKD (estimated glomerular filtration rate [eGFR]: 60−75 and urine albumin-to-creatinine ratio [UACR]: <30) were derived for US patients included in the DISCOVER CKD cohort study, using linked inpatient and outpatient data from the limited claims-EMR data set (LCED) and TriNetX database. Patients with a history of transplant or undergoing dialysis were not included. HCRU and costs were stratified by CKD severity using UACR and eGFR.

Results: Overall health care costs ranged from $26,889 (A1) to $42,139 (A3), and from $28,627 (G2) to $42,902 (G5) per patient per year (PPPY), demonstrating a considerable early disease burden which continued to increase with declining kidney function. The PPPY costs of later stage CKD were particularly notable for patients with concomitant heart failure ($50,191 [A3]) and those covered by commercial payers ($55,735 [A3]).

Conclusions: Health care costs and resource use associated with CKD and reduced kidney function pose a substantial burden across health care systems and payers, increasing in line with CKD progression. Early CKD screening, particularly of UACR, paired with proactive disease management may provide both an improvement to patient outcomes and a significant HCRU and cost saving to health care providers.

Kidney Int Rep (2023) **8,** 785–795; https://doi.org/10.1016/j.ekir.2023.01.037
KEYWORDS: chronic kidney disease; cost analysis; health care providers; health care resource use; hospitalizations; United States

CKD has been estimated to affect 14.8% of adults in the US, across all stages of the disease, a proportion which is likely to increase because of an aging population and increasing incidence of type 2 diabetes (T2D), cardiovascular disease, hypertension, and other conditions with established links to CKD.[1–3] CKD is associated with substantial morbidity and mortality, as well as decreased quality of life and high health care costs from patients' more frequent and expensive interactions with health care services, due in part to strongly associated comorbidities, complications, and the frequent requirement for expensive renal replacement therapies as CKD progresses toward kidney failure.[1,4–7] US modeling projections further predict that CKD prevalence will increase in adults aged >30 years to 16.7% by 2030.[8]

Correspondence: Juan Jose Garcia Sanchez, Health Economics and Payer Evidence, Academy House, 136 Hills Road, Cambridge CB2 8PA, UK. E-mail: juanjose.garciasanchez@astrazeneca.com
Received 26 June 2022; revised 19 January 2023; accepted 24 January 2023; published online 3 February 2023

The progressive nature of CKD is characterized by a sustained reduction in kidney function with a reduction in glomerular filtration rate and generally an increase in UACR. The categorization of patients by eGFR and UACR according to the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines is crucial for accurate prognosis and patient management.[9] Patients in more at-risk categories generally experience decreased quality of life, increased health care utilization, as well as increased risk of cardiovascular disease and mortality, which have been independently linked to lower eGFR and higher UACR.[9-11] Contemporary US modeling projections show that routine UACR measurement paired with appropriate intervention could prevent CKD progression to later stages (stages G3b–G5) in approximately 1.3 million patients with associated health care savings of $16 billion between 2020 and 2025.[12]

Recent real-world studies have been published regarding the HCRU of CKD in the US setting.[13,14] One study reported HCRU and costs in a real-world population with CKD stage 2 to 4. Patients with UACR 200 to 5000 mg/g had significantly higher health care costs than patients with UACR 0 to 199 mg/g at $39,222 versus $19,547 PPPY, respectively, and increased rates of hospitalizations (0.55 vs. 0.20 PPPY) and outpatient visits (7.55 vs. 6.74 PPPY), respectively.[13] A separate study reported total health care costs of $24,029 PPPY among patients with CKD and T2D in the first year after diagnosis; in addition, annual costs of late stage CKD were substantially greater than early stage CKD (Stage 5: $110 210 vs. Stage 1: $18 529).[14]

Robust economic tools are required to inform regulatory agencies, health care providers and other budget holders of the value of new treatments for improving patient outcomes in the context of a health care system with limited resources. To conduct such evaluations, thorough HCRU estimates are required to accurately model the relevant CKD population, with data derived from real-world clinical practice providing the gold standard of evidence. In addition, granular data may be used to better inform the health sector with resourcing requirements for more efficient health care delivery. Using inpatient and outpatient care data obtained from the LCED and TriNetX database, this study describes the HCRU of patients with CKD and reduced kidney function without CKD (eGFR: 60−75 and UACR: <30) in the US, stratified by eGFR and UACR, to provide a valuable source of contemporary HCRU and cost data, with the aims of informing future economic evaluations for new and effective therapies. In addition, the classification by both eGFR and UACR in this study provides valuable granular data on patients with albuminuria, which has been linked to worsened clinical outcomes independently of eGFR.[10,15-17]

METHODS

Study Population

DISCOVER CKD is a multinational, observational cohort study in patients with CKD.[18] The patients included in the analysis reported here are a subset derived from DISCOVER CKD based on the US retrospective patient cohort, which correspond to patients recorded in the LCED and TriNetX databases. The full DISCOVER CKD study was comprised of a retrospective patient cohort capturing primary and secondary care data from established anonymized datasets and a prospective cohort collecting primary and secondary data (ClinicalTrials.gov identifier: NCT04034992).

The DISCOVER CKD eligibility criteria have been previously described,[18] but in brief the eligible patient cohort included adult patients diagnosed with CKD after January 1, 2008 and ≥1 year of medical history available before the index date. Diagnosis was defined as follows: (i) documented diagnostic code (e.g., International Classification of Diseases 10) for CKD Stages G3a through to kidney failure or (ii) 2 consecutive eGFR measures of <75 ml/min per 1.73 m^2 recorded >90 days apart (maximum 730 days).

The following additional inclusion criteria were applied for this analysis: (i) 2 consecutive eGFR measures 5 to 75 ml/min per 1.73 m^2 recorded >90 days apart (maximum 730 days), and (ii) ≥1 UACR measurement within 1 year before or any time up to 5 years after the index date. The UACR measure closest to index was used to categorize patients.

The following additional exclusion criteria were applied: (i) patients without 2 measures of eGFR <75 ml/min per 1.73 m^2 recorded at least 90 days apart on or after 1 January 2008, (ii) eGFR measures <5 ml/min per 1.73 m^2 were excluded (eGFR measures only, not the patient), (iii) death within 30 days of index date (where available in data source), (iv) history of type 1 diabetes mellitus, or (v) a history of renal transplant or dialysis at index.

Baseline patient demographics and laboratory parameters were defined as the most recent variable before index within a 1-year lookback period (1 year before index). Medication usage at baseline was defined as any treatment received at index or within the 1-year lookback period. Comorbidity history at baseline was defined as any history before index spanning the patient's entire available medical history. For any repeated measures, the nonmissing data closest to the index date were used.

The KDIGO classification system, an internationally recognized framework for appraising the severity and prognosis of CKD incorporating both eGFR and UACR measurements, was used to assess CKD severity (Supplementary Figure S1).[9] As per the KDIGO guidelines, patients with eGFR 60 to 75 and UACR <30 are

not classified as having CKD. Nonetheless, these patients make up a large portion of the population with decreased kidney function and are included in this study for information purposes. eGFR 60 to 75 is classified as mildly decreased and UACR <30 is normal to mildly increased.[9]

Study Period

This analysis covered a study period of 2012 to 2018 for LCED associated data and from 2008 to 2019 for TriNetX data. Data sources were reported separately to protect patient confidentiality. Patients were followed up until the end of data collection, database end, loss to follow-up or death, whichever occurred first. The index date corresponded with the patient's baseline and was defined as the date of the second eGFR measurement recorded >90 days after the first measurement (maximum 730 days).

Data Sources

Data used in this study were sourced from the linked IBM MarketScan and Explorys Claims-EMR data sets, in which data were linked by IBM at the individual patient level. Specifically, the 5-year LCED was used, which included electronic health records and claims data. This study also used data from TriNetX, a global federated research network of electronic health records; both databases captured inpatient and outpatient records (more details are provided in Supplementary Methods). HCRU derived from each database were analyzed and reported separately.

Study End Points

Study endpoints included in this analysis were patient follow-up, total length of hospital admission, HCRU, and costs. HCRU were recorded as the total number of events within the study period and the incidence rates. Costs associated with each resource category were reported as total and annualized costs over the study period. HCRU and costs of outpatient visits and hospitalization were captured from the LCED, costs were reported directly within the database. HCRU associated with outpatient visits, hospitalization, critical care, and emergency room (ER) visits were captured from the TriNetX database, costs were not available from TriNetX and therefore were not included in the analysis.

Statistical Analysis

Descriptive analysis for annualized HCRU or costs were undertaken across resource categories. The LCED cost analysis captured costs covered by insurance providers and employers in addition to patients' out of pocket costs. Patients were not censored for transplant or dialysis initiation during the study period to capture all types of CKD, including progression to renal replacement therapy. However, the specific costs of dialysis and transplant were not included in this analysis. Data were analyzed per database (LCED and TriNetX) for the overall cohort, stratified by eGFR and UACR categories, by comorbidity and medical history at baseline (T2D and heart failure [HF]) and by payer type for LCED cohort costs (commercial and Medicare). Costs were sourced directly from the LCED, recorded as US dollars and inflated to 2019 values. Costs recorded for the follow-up period were used to calculate annual costs across the cohort. Annualized event rates were expressed as the incidence of the outcome per 100 person-years.

RESULTS

Baseline Characteristics

DISCOVER CKD captured a large US patient cohort, including 6351 and 18,327 patients meeting the eligibility criteria of this study, with data sourced from the LCED and TriNetX databases respectively (Table 1).

The most common comorbidities at baseline were hypertension (LCED: 85.7%, TriNetX: 75.8%) and T2D (LCED: 68.4%, TriNetX: 64.9%). The majority of patients (91.0% and 82.2%) had eGFR between 45 and 75 ml/min per 1.73 m^2, and had UACR <30 mg/g (77.1% and 62.3%), corresponding to LCED and TriNetX respectively (Supplementary Tables S1 and S2).

HCRU in the Overall Cohort

HCRU of the DISCOVER CKD retrospective cohort increased with worsening measures of CKD severity. Rates of HCRU generally increased with worsened eGFR and UACR.

The overall rates of outpatient visits were substantially greater than hospitalizations; however, the magnitude of difference between UACR subcategories was larger for hospitalization; 1.4-fold and 2.5-fold increase between A1 and A3 patients for outpatient visits and hospitalization, respectively. HCRU trends were similar between eGFR subcategories; 5.2-fold and 3.0-fold increase between G2 and G5 patients for outpatient visits and hospitalization, respectively (Table 2, LCED). The length of stay (LOS) for each hospital admission also increased with severity (mean LOS: 8.5 [A1] to 14.9 days [A3] and 9.1 [G2] to 17.5 days [G5]; Supplementary Tables S3 and S4).

Increasing hospitalization and outpatient visit rates were mirrored in the TriNetX cohort. In addition, rates of critical care and ER visits increased 4.5-fold and 1.2-fold between A1 and A3 patients, and 2.0-fold and 2.0-fold between G2 and G5 patients for critical care and ER visits, respectively. Contrary to UACR stratified data, the greatest HCRU rates across the TriNetX cohort

Table 1. Baseline characteristics

Variable	LCED cohort ($N = 6351$)	TriNetX cohort ($N = 18,327$)
Follow-up (yr), mean (SD)	3.4 (1.7)	3.2 (2.4)
Demographics		
Female, *n* (%)	3186 (50.2)	10,075 (55.0)
Age, mean (SD)	65.3 (10.5)	65.7 (11.7)
KDIGO eGFR categories, *n* (%)		
G2[a]: 60–75 ml/min per 1.73 m^2	4178 (65.8)	9,953 (54.3)
G3a: 45–<60 ml/min per 1.73 m^2	1599 (25.2)	5,119 (27.9)
G3b: 30–<45 ml/min per 1.73 m^2	454 (7.1)	2,208 (12.0)
G4: 15–<30 ml/min per 1.73 m^2	103 (1.6)	830 (4.5)
G5: 0–<15 ml/min per 1.73 m^2	17 (0.3)	217 (1.2)
KDIGO UACR categories, n (%)		
A1: <30 mg/g	4895 (77.1)	11,423 (62.3)
A2: 30–<300 mg/g	1140 (17.9)	4995 (27.3)
A3: ≥300 mg/g	316 (5.0)	1909 (10.4)
Laboratory values, median (IQR)		
eGFR, ml/min per 1.73 m^2	65.0 (56.3–70.5)	61.7 (50.1–69.2)
UACR, mg/g	7.8 (3.7–21.3)	17.0 (7.0–62.5)
Hb, g/dl	13.6 (12.5–14.7)	13.2(12.0–1 4.4)
Medical History/Comorbidities at baseline, *n* (%)		
History of HF	533 (8.4)	1735 (9.5)
History of coronary heart disease	1422 (22.4)	3657 (20.0)
History of myocardial infarction	368 (5.8)	998 (5.4)
History of hypertension	5440 (85.7)	13,898 (75.8)
History of T2D	4345 (68.4)	11,892 (64.9)
History of stroke	983 (15.5)	1669 (9.1)
History of hyperkalemia	166 (2.6)	504 (2.8)
Baseline medication use, *n* (%)		
RAAS inhibitors (ACE inhibitors and ARBs)	4248 (66.9)	8953 (48.9)
Diuretics (MRAs, loop diuretics and thiazide diuretics)	3039 (47.9)	7097 (38.7)
Anticoagulants	926 (14.6)	3262 (17.8)
Antiplatelets (aspirin, clopidogrel, and other agents)	1258 (19.8)	4920 (26.8)
Antihypertensive therapies (calcium channel blockers [DHP and non-DHP], β-blockers and α-blockers)	3694 (58.2)	8698 (47.5)

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; DHP, dihydropyridine; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HF, heart failure; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system; T2D, type 2 diabetes; UACR, urine albumin-creatinine ratio.
[a]Restricted G2 KDIGO category based on eGFR cut-off from study inclusion criteria

were not associated with the worse eGFR groupings but were observed in the G4 category (Table 3, TriNetX).

HCRU Stratified by Comorbidity

When stratified by underlying comorbidities, rates of HCRU across the LCED cohort were comparable between those with comorbid T2D and CKD or reduced kidney function without CKD (eGFR 60−75 and UACR <30) and those without T2D; with hospitalization and outpatient visits of 23.7 versus 19.0 and 1969.8 versus 1768.2 events per 100 patient years, respectively. When stratifying by the presence of HF, HCRU rates were substantially higher in patients with comorbid HF compared to those without for both hospitalization and outpatient visits (55.9 vs. 18.8 and 2884.4 vs. 1807.9 events per 100 patient years, respectively).

HCRU across the TriNetX cohort followed the same trends. Critical care and ER visit rates were comparable between patients with and those without T2D but were substantially higher in patients with comorbid HF compared to those without (84.4 vs. 25.1 and 36.8 vs. 14.9 events per 100 patient years, respectively).

Health Care Costs in the Overall Cohort (LCED)

Total mean health care costs were $29,664 PPPY and ranged from $26,889 (A1) to $42,139 (A3) across UACR categories, and from $28,627 (G2) to $42,902 (G5) across eGFR categories (Figure 1). Although patients experienced outpatient visits at a much higher rate than hospitalizations, overall costs were substantially greater for hospitalization (mean costs: $21,382 vs. $8282 PPPY; SupplementaryTable S5).

HCRU category costs for both hospitalization and outpatient visits generally rose with increasing CKD severity (Table 4 and Figure 1). Increased hospitalization costs were driven by both an increased rate of events and an increased LOS per admission as severity increased (Supplementary Tables S3 and S4).

Annual health care costs for patients with an absence of CKD but eGFR 60 to 75 and UACR <30 are already substantial (mean costs: $25,377); comparing to patients with G3a CKD, there is only a marginal increase in costs ($28,064) which increase more substantially at later stages of CKD (Figure 1), indicating a nonlinear cost burden as CKD worsens.

Health Care Costs Stratified by Comorbidity (LCED)

When stratified by underlying comorbidity, total health care costs were comparable between patients with comorbid T2D and CKD or reduced kidney function without CKD (eGFR 60–75 and UACR <30) compared to those without T2D (mean cost: $30,260 vs. $28,321 PPPY) and were substantially higher for patients with comorbid HF compared to those without ($41,598 vs. $27,989). Costs generally increased in line with worsened UACR and eGFR (Figure 2).

Health Care Costs Stratified by Payer Type (LCED)

When stratified by payer type, total health care costs covered by commercial payers (employer sponsored private health care) were substantially greater than costs covered by Medicare (mean cost: $37,843 vs. $22,660 PPPY, respectively). As in the overall cohort, commercial and Medicare health care costs and utilization rates generally rose with CKD severity for both hospitalization and outpatient visits (Supplementary Tables S6–S11).

Table 2. Health care resource utilization from LCED cohort, stratified by eGFR and UACR

	UACR 0–<30 mg/g		UACR 30–<300 mg/g		UACR ≥300 mg/g	
	Events	Rate per 100 person yr (95% CIs)	Events	Rate per 100 person yr (95% CIs)	Events	Rate per 100 person yr (95% CIs)
Hospitalization (N = 6351)						
		(n = 4895)		(n = 1140)		(n = 316)
eGFR 60–75	1319	15.6 (14.8–16.5)	396	25.5 (23.1–28.2)	105	36.9 (30.2–44.6)
eGFR 45–<60	507	17.2 (15.8–18.8)	319	36.0 (32.2–40.2)	109	41.0 (33.7–49.5)
eGFR 30–<45	156	25.8 (21.9–30.2)	131	42.6 (35.6–50.6)	76	39.8 (31.4–49.8)
eGFR 15–<30	38	34.2 (24.2–46.9)	35	52.6 (36.6–73.1)	45	60.7 (44.2–81.2)
eGFR 0–<15	<11	113.3 (48.9–223.2)	<11	63.2 (28.9–119.9)	<11	125.1 (57.2–237.5)
Overall	2028	16.7 (16.0–17.5)	890	31.5 (29.5–33.6)	344	41.8 (37.5–46.5)
Outpatient Visits (N = 6351)						
		(n = 4895)		(n = 1140)		(n = 316)
eGFR 60–75	146,490	1734.5 (1725.6–1743.4)	28,850	1860.1 (1838.7–1881.7)	6834	2400.6 (2344.0–2458.2)
eGFR 45–<60	52,181	1773.8 (1758.6–1789.1)	19,387	2187.9 (2157.2–2218.9)	5551	2088.4 (2033.8–2144.1)
eGFR 30–<45	11,388	1883.5 (1849.0–1918.4)	7067	2298.5 (2245.2–2352.8)	4926	2580.3 (2508.8–2653.4)
eGFR 15–<30	1851	1665.4 (1590.4–1743.0)	1885	2830.8 (2704.4–2961.5)	2403	3238.9 (3110.6–3371.0)
eGFR 0–<15	164	2322.7 (1980.8–2706.6)	1247	8752.2 (8273.1–9251.8)	125	1738.0 (1446.7–2070.7)
Overall	212,074	1751.2 (1743.7–1758.6)	58,436	2068.2 (2051.5–2085.1)	19,839	2,411.3 (2377.8–2445.0)

CI, confidence interval; eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio.
NB: number of events <11 not specified for preservation of patient anonymity

However, though overall costs were greater for commercial payers, particularly for hospitalizations (Figure 3), the rates of hospitalization were higher for Medicare covered patients (25.2 vs. 17.5 events per 100 person-years; Supplementary Tables S10 and S11).

Comparatively, there was a much greater increase in commercial health care costs as eGFR and UACR worsened than Medicare covered costs, which were relatively similar across severity categories (Figure 3). A higher proportion of patients covered by Medicare had more severe eGFR (G3b–G5) compared to commercial covered patients (5.8% and 13.1%, respectively) but there were similar proportions of patients in the most severe UACR category ([A3]: 5.1% and 4.8%, respectively).

The average hospital LOS is greater for patients covered by commercial payers compared to Medicare beneficiaries (10.9 vs. 9.6 days) and is particularly disparate for patients with poor eGFR (G5: 17.3 vs. 10.3 days, respectively) and UACR (A3: 16.0 vs. 13.8 days, respectively).

DISCUSSION

This study shows that CKD represents a significant economic burden on US health care systems beyond the impacts of specialist nephrology treatment and care. Costs and resource utilization in patients with eGFR of 60 to 75 and UACR <30 without CKD were notable and continued to increase for both declining kidney function and increasing albuminuria.

Higher proportions of the study population utilized inpatient and outpatient services compared with the US nationwide average for Medicare beneficiaries. More specifically, patients in UACR categories A1, A2, and A3 incurred expenses relating the outpatient care approximately 3, 5, and 7 times greater than the average US Medicare patient.[19] The burden imposed by hospitalizations was compounded by an increasing LOS per admission as severity increased, almost doubling between the least and most severe UACR and eGFR groups (from A1–A3 and G2–G5). In addition to capturing these key drivers of health care burden, this study reported HCRU associated with critical care and ER visits which are often overlooked when evaluating direct health care burden. Because of the common overstretching of these resources, they represent areas in which a reduction in CKD-related admission could be greatly beneficial to the health care system.

With such a high prevalence, particularly where there is a shift toward the more advanced stages of the disease, CKD can be expected to pose a continued and growing burden on both patients and payers within the US health care system.[9,20]

Although higher costs in patients with lower eGFR and higher UACR were evident from this study regardless of payer type, we note that HCRU rates, particularly for hospitalizations, were higher for Medicare beneficiaries, but associated costs were higher for patients covered by commercial payers. The higher average hospital LOS for commercially insured patients somewhat explains this disparity; however, it

Table 3. Health care resource utilization from TriNetX cohort, stratified by eGFR and UACR

	UACR 0–<30 mg/g		UACR 30–<300 mg/g		UACR ≥300 mg/g	
	Events	Rate per 100 person yr (95% CIs)	Events	Rate per 100 person yr (95% CIs)	Events	Rate per 100 person yr (95% CIs)
Hospitalization (*N* = 18,327)						
	(*n* = 11,423)		(*n* = 4995)		(*n* = 1909)	
eGFR 60–75	38,801	164.3 (162.7–166.0)	17,586	250.6 (246.9–254.3)	6030	303.1 (295.5–310.9)
eGFR 45–<60	16,600	165.6 (163.1–168.2)	11,696	270.5 (265.6–275.4)	3721	256.5 (248.3–264.8)
eGFR 30–<45	6,556	220.3 (215.0–225.7)	7176	310.5 (303.3–317.7)	4770	394.2 (383.1–405.6)
eGFR 15–<30	1,766	275.3 (262.6–288.5)	3371	486.4 (470.1–503.1)	3607	486.5 (470.7–502.6)
eGFR 0–<15	215	78.0 (67.9–89.1)	596	193.6 (178.3–209.8)	1487	611.2 (580.5–643.1)
Overall	63,938	170.4 (169.0–171.7)	40,425	275.9 (273.2–278.6)	19,615	348.1 (343.2–353.0)
Outpatient visit (*N* = 18,327)						
	(*n* = 11,423)		(*n* = 4995)		(*n* = 1909)	
eGFR 60–75	225,508	955.0 (951.1–959.0)	78,574	1119.6 (1111.8–1127.4)	21,836	1097.7 (1083.1–1112.3)
eGFR 45–<60	111,939	1116.8 (1110.3–1123.4)	49,049	1134.3 (1124.3–1144.4)	17,781	1225.5 (1207.6–1243.7)
eGFR 30–<45	36,645	1231.3 (1218.7–1244.0)	33,255	1438.8 (1423.3–1454.3)	15,226	1258.4 (1238.5–1278.5)
eGFR 15–<30	10,219	1593.3 (1562.5–1624.5)	10,186	1469.8 (1441.4–1498.7)	8864	1195.5 (1170.7–1220.6)
eGFR 0–<15	3401	1233.3 (1192.2–1275.5)	3490	1133.5 (1096.2–1171.7)	2379	977.9 (938.9–1018.0)
Overall	387,712	1033.1 (1029.8–1036.3)	174,554	1191.1 (1185.6–1196.7)	66,086	1172.8 (1163.9–1181.8)
Critical care (*N* = 18,327)						
	(*n* = 11,423)		(*n* = 4995)		(*n* = 1909)	
eGFR 60–75	4252	18.0 (17.5–18.6)	2690	38.3 (36.9–39.8)	1261	63.4 (59.9–67.0)
eGFR 45–<60	1778	17.7 (16.9–18.6)	1738	40.2 (38.3–42.1)	588	40.5 (37.3–43.9)
eGFR 30–<45	503	16.9 (15.5–18.4)	1181	51.1 (48.2–54.1)	912	75.4 (70.6–80.4)
eGFR 15–<30	284	44.3 (39.3–49.7)	730	105.3 (97.8–113.3)	816	110.1 (102.6–117.9)
eGFR 0–<15	11	4.0 (2.0–7.1)	182	59.1 (50.8–68.3)	232	95.4 (83.5–108.5)
Overall	6828	18.2 (17.8–18.6)	6521	44.5 (43.4–45.6)	3809	67.6 (65.5–69.8)
Emergency room visit (*N* = 18,327)						
	(*n* = 11,423)		(*n* = 4995)		(*n* = 1909)	
eGFR 60–75	3090	13.1 (12.6–13.6)	1207	17.2 (16.2–18.2)	301	15.1 (13.5–16.9)
eGFR 45–<60	1754	17.5 (16.7–18.3)	690	16.0 (14.8–17.2)	335	23.1 (20.7–25.7)
eGFR 30–<45	520	17.5 (16.0–19.0)	737	31.9 (29.6–34.3)	139	11.5 (9.7–13.6)
eGFR 15–<30	205	32.0 (27.7–36.6)	214	30.9 (26.9–35.3)	178	24.0 (20.6–27.8)
eGFR 0–<15	100	36.3 (29.5–44.1)	91	29.6 (23.8–36.3)	39	16.0 (11.4–21.9)
Overall	5669	15.1 (14.7–15.5)	2939	20.1 (19.3–20.8)	992	17.6 (16.5–18.7)

CI: confidence interval; eGFR: estimated glomerular filtration rate; UACR: urine-albumin creatinine ratio

is likely that there is a difference between the charges incurred for the same health care services between payer types, with higher charges expected for commercially insured patients. Nonetheless, data show that there could be a significant cost saving for commercial and federal health care providers alike if patients can be prevented from progressing to the later stages of kidney disease, such as through earlier CKD detection and the adoption of new and effective interventions that can substantially delay the progression of CKD to the more costly advanced stages.

As shown by this study, costs associated with CKD are high even without considering the requirements for chronic and acute dialysis in the more advanced stages of the disease (G5: kidney failure), with 2019 estimates of the annual cost of dialysis that ranged from $76,159 for peritoneal dialysis to $91,795 for hemodialysis.[21] Furthermore, contemporary modeling predictions project a substantial increase in US CKD-associated health care costs from 2020 to 2025, with an overall increase from $232 billion to $376 billion, with a particular elevation in the later stages of the disease (3-fold increase in costs for stage 4 CKD).[22] In addition to the cost burden of CKD, declining kidney function imposes a large burden on patients because of worsening of symptoms and comorbidities, and on caregivers, resulting in mental health decline and a decrease in paid employment.[23] These high costs of therapy and substantial patient morbidity further emphasize the benefits of early CKD detection and the prevention of disease progression through proactive management.

TriNetX captured patient data from across US health care organizations in the secondary care setting, primarily consisting of large academic medical institutions that provide inpatient care. LCED, captured claims data

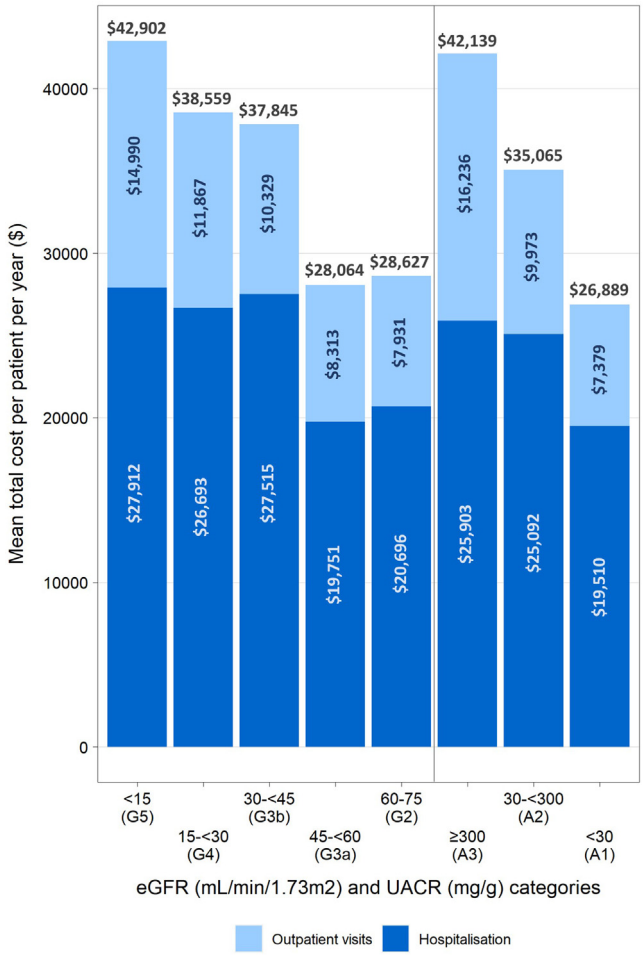

Figure 1. Mean annual per patient health care costs for overall LCED cohort, stratified by eGFR and UACR. Total costs presented above bars; resource category costs presented within bars. Granular KDIGO stratified costs presented in Table 4. eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

from patients in both primary and secondary care settings, covering both hospitals and general practitioners that provide outpatient care only. Data captured from the LCED and TriNetX databases showed similar trends of increasing hospitalization and outpatient visit utilization as CKD severity worsened. However, the rates of hospitalization were substantially greater from TriNetX and outpatient visit rates were greater from LCED, which may be as expected because of the differences in care settings captured by each database.

Even though there were fewer patients with advanced CKD compared to those with mildly reduced kidney function (G2 and A1), they accounted for the largest per patient costs and resource utilization. Mean annual costs increased substantially as severity increased in line with UACR (A3: $42,139) and eGFR (G5: $42,902) across the cohort. Though annual costs are higher in the later stages of CKD, they are still considerable (more than $25,000 PPPY) in the early stages, including for patients with reduced kidney function without CKD (eGFR 60–75 and UACR <30), regardless of payer type. These findings are in agreement with other contemporary real-world evidence studies in the US.[13,14]

Our study showed that the cost and resource burden is not only imbalanced across severity groups, but across patient groups stratified by underlying comorbidities, in particular HF. Patients with HF and CKD were associated with substantially elevated costs and HCRU compared to patients without HF. These findings highlight the need for effective early diagnosis and management of not only CKD but also its associated comorbidities to avoid progression to the more costly later stages of disease.

Limitations

This study is based on real-world observational data collected in the usual clinical setting through electronic medical records or administrative claims. Although the data captured from LCED and TriNetX were considered robust, the data reflect routine care and were not collected for research purposes. Consequently, data are prone to missingness and are subject to potential coding error.

The additional UACR requirements applied to this study were beyond those of the broader DISCOVER CKD inclusion criteria, and this greatly limited the number of patients eligible for analysis. As a selection criterion, UACR measurement may have enriched the study population with a higher burden of comorbidities because of the increased likelihood of UACR monitoring at baseline. The lack of available UACR data highlights the wider need for more frequent and thorough UACR recording across electronic health records to aid in the prognosis and management of CKD. This represents a limitation of effective CKD staging which is well recognized.[24] The limited number of patients was particularly relevant when evaluating those with G5 CKD; <11 patients with HCRU events were available for this subgroup when stratifying by payer type and comorbidity, thus limiting the validity of the mean cost calculations.

TriNetX and LCED captured patient data only when the patient received care at the participating health care organization, care received in other settings was not available for inclusion in this analysis. This analysis did not capture the specific costs of dialysis or transplant. However, patients initiating dialysis or transplant during the study period were not censored, therefore, a very small number of hospital or outpatient visits attributable to dialysis and transplant may have been captured for patients with kidney failure (<20 patients in the LCED cohort with stage 5 CKD). The costs of dialysis and transplant should be considered in

Table 4. Health care costs per resource category from LCED cohort, stratified by UACR and eGFR

	UACR 0–<30 mg/g	UACR 30–<300 mg/g	UACR ≥300 mg/g	Overall (per eGFR category)
	Total mean (SD) cost per patient per yr			
Hospitalizations				
eGFR 60–75	$18,111 (29,581)	$27,621 (77,873)	$33,423 (75,863)	$20,696 (46,086)
eGFR 45–<60	$17,964 (42,836)	$23,394 (49,619)	$19,903 (37,572)	$19,751 (44,520)
eGFR 30–<45	$31,782 (97,277)	$26,092 (58,462)	$18,559 (19,341)	$27,516 (76,547)
eGFR 15–<30	$31,026 (46,715)	$13,075 (9,409)	$35,784 (41,436)	$26,693 (37,882)
eGFR 0–<15	$54,923 (97,463)	$12,055 (9,972)	$13,530 (7,113)	$27,912 (57,909)
Overall (per UACR category)	$19,510 (42,845)	$25,092 (64,053)	$25,903 (51,687)	-
Outpatient visits				
eGFR 60–75	$7266 (16,122)	$9600 (19,346)	$18,459 (61,179)	$7,931 (19,386)
eGFR 45–<60	$7502 (14,998)	$10,334 (20,599)	$11,303 (22,462)	$8,313 (16,855)
eGFR 30–<45	$7947 (12,818)	$9,772 (13,538)	$19,863 (53,627)	$10,329 (24,635)
eGFR 15–<30	$8773 (10,718)	$13,562 (16,668)	$14,822 (18,860)	$11,867 (15,260)
eGFR 0–<15	$14,487 (12,793)	$14,870 (19,844)	$16,480 (20,906)	$14,990 (16,848)
Overall (per UACR category)	$7379 (15,651)	$9973 (19,093)	$16,236 (46,908)	-

eGFR, estimated glomerular filtration rate; UACR, urine albumin creatinine ratio.

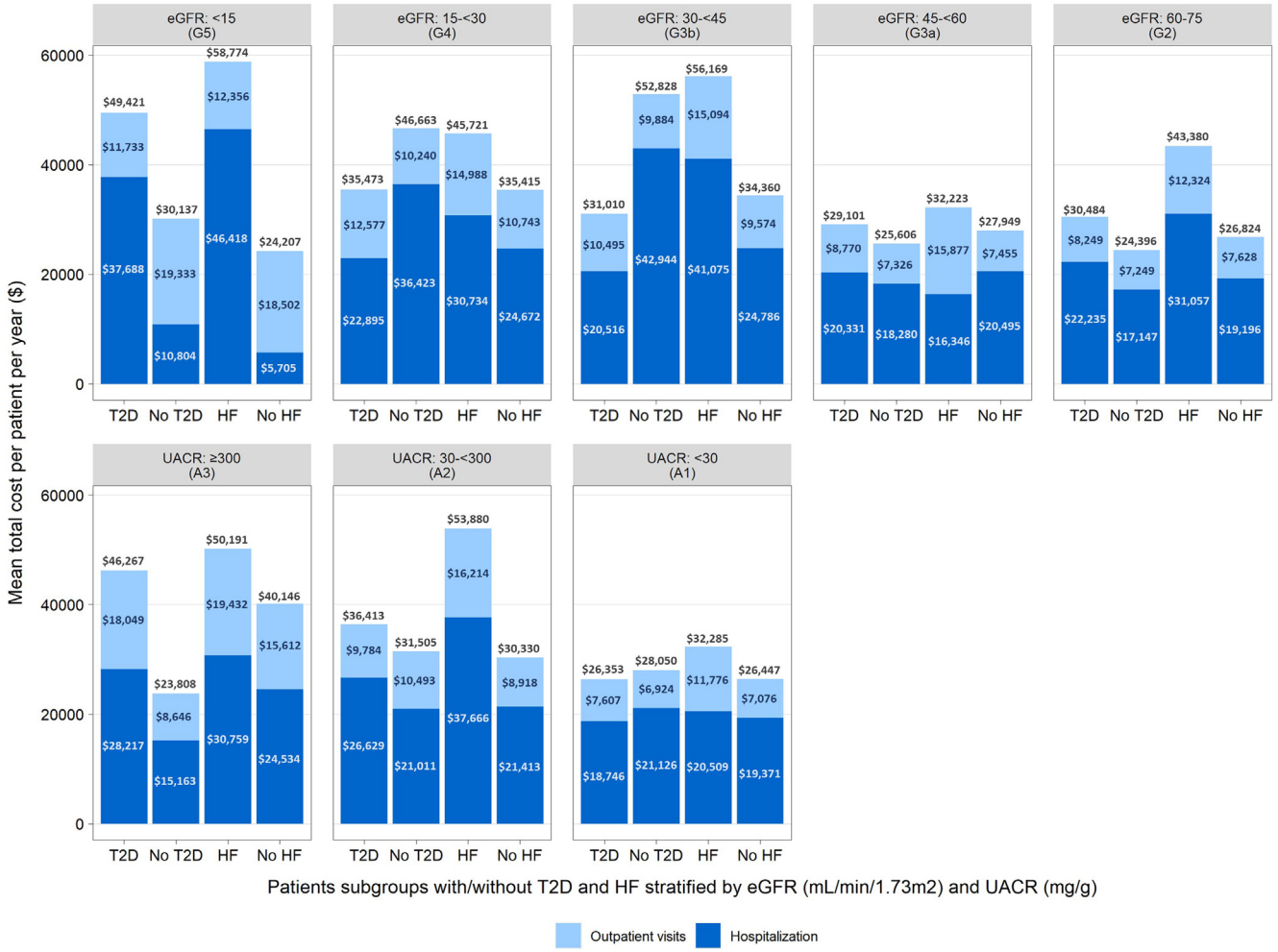

Figure 2. Mean annual per patient health care costs for patient subgroups with/without T2D and HF, stratified by eGFR and UACR. Data from LCED cohort. Total costs presented above bars; resource category costs presented within bars. eGFR, estimated glomerular filtration rate; HF, heart failure; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

Figure 3. Mean annual per patient health care costs covered by commercial payers and Medicare, stratified by eGFR and UACR. Total costs presented above bars; resource category costs presented within bars. eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

addition to those reported in this study. The exclusion of patients undergoing dialysis or transplant at index resulted in a slight underrepresentation of patients with kidney failure compared to the overall real-world CKD population.

Reflecting the inclusion criteria of part of the DAPA-CKD trial population, an eGFR range of 60 to 75 ml/min per1.73 m^2 was applied to define G2. Therefore, HCRU and costs will be an overestimate if modeled using an eGFR range of 60 to 89 ml/min per 1.73 m^2, which defines the G2 group according to KDIGO guidelines.[10,11] The long-term implications of preventing or delaying CKD progression are not directly addressed in this analysis, only postulated based on HCRU trends. Any conclusions based on the causal mechanisms of CKD in relation to HCRU outcomes should be treated with caution, resource use is assumed to relate to CKD but in a cohort greatly affected by comorbidities and other underlying conditions this cannot be concluded with certainty.

Finally, results from this analysis are only reflective of the US and may have limited generalizability to other settings. The results are, however, based on multiple health care systems and payers, and may be considered as generalizable throughout the US.

Conclusions

Health care costs and resource use associated with CKD and reduced kidney function more broadly were shown to pose a substantial burden across health care systems and payers, increasing in line with CKD severity. Early identification and proactive management of CKD may not only improve patients' length and quality of life but could provide a significant per patient resource and cost saving to health care providers. The detailed reporting of HCRU provided by this study will be highly valuable in supporting the evaluation of novel therapies for CKD, and to help health care systems understand the true burden of CKD.

DISCLOSURE

The results presented in this paper have not been published previously in whole or part, except in abstract format. JJGS, MA, TC, and SN are employees and stockholders of AstraZeneca. CP has received consulting fees from AstraZeneca, Eli Lilly/ Boehringer Ingelheim, Merck Sharp, and Dohme, Novartis, Vifor, Amgen, Otsuka, Sanofi and Janssen and has received speaker fees from Novartis, Janssen Cilag, Otsuka, and Vifor. JJC has received institutional grants from AstraZeneca, Vifor and Astellas, speaker fees from AstraZeneca, Abbott and Nutricia, and consultancy fees from AstraZeneca, Baxter Healthcare and Bayer. RPF is an employee of Arbor Research Collaborative for Health, which receives global support for the ongoing DOPPS Programs (provided without restriction on publications by a variety of funders - for details see https://www.dopps.org/AboutUs/Support.aspx) and has received research grants from Fresenius Medical Care, consulting fees from AstraZeneca, Akebia, Novo Nordisk and Fresenius, nonfinancial support from AstraZeneca, Bayer, Boehringer, Novo Nordisk, Akebia, and personal fees from Retrophin outside the submitted work. CL is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore and has received research support from Bayer and Roche Diagnostics, and has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Abbott, Actelion, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc., EchoNous Inc, Impulse Dynamics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Radcliffe Group Ltd., Roche Diagnostics, Sanofi and Us2.ai, and serves as cofounder and nonexecutive director of Us2.ai Pte Ltd. DCW has received consulting fees from Akebia, Bayer, Baxter, GlaxoSmithKline, Gilead, Janssen and Zydus, and reports personal fees and nonfinancial support from AstraZeneca, as well as personal fees from Bayer, Boehringer Ingelheim, Astellas, GlaxoSmithKline, Janssen, Napp, Mundipharma, Reata, Vifor Fresenius, and Tricida, and participates in Data Safety and Monitoring Boards for Gilead and Zydus. GJ has nothing to declare.

ACKNOWLEDGMENTS

The authors thank Alyshah Abdul Sultan for input into the study design and interpretation of results, and Ben Wilding of Health Economics and Outcomes Research Ltd. for providing medical writing support/editorial support, which was funded by AstraZeneca in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). This work was supported by AstraZeneca who provided support for the analysis and medical writing for this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the study design, interpretation of results, and review and approval of this manuscript.

SUPPLEMENTARY MATERIAL

Supplementry File (PDF)

Supplementary Methods.

Figure S1. KDIGO classification groups aligned with the DISCOVER CKD eligible population.

Table S1. Number of patients in each KDIGO category at baseline from LCED cohort.

Table S2. Number of patients in each KDIGO category at baseline from TriNetX cohort.

Table S3. Health care resource utilization and costs of the overall LCED cohort, stratified by UACR.

Table S4. Health care resource utilization and costs of the overall LCED cohort, stratified by eGFR.

Table S5. Health care resource utilization and costs from overall LCED cohort.

Table S6. Health care resource utilization and costs of the LCED cohort covered by commercial payers, stratified by UACR.

Table S7. Health care resource utilization and costs of the LCED cohort covered by commercial payers, stratified by eGFR.

Table S8. Health care resource utilization and costs of the LCED cohort covered by Medicare, stratified by UACR.

Table S9. Health care resource utilization and costs of the LCED cohort covered by Medicare, stratified by eGFR.

Table S10. Health care resource utilization from LCED cohort covered by commercial payers, stratified by eGFR and UACR.

Table S11. Health care resource utilization from LCED cohort covered by Medicare, stratified by eGFR and UACR.

REFERENCES

1. Braun L, Sood V, Hogue S, Lieberman B, Copley-Merriman C. High burden and unmet patient needs in chronic kidney disease. *Int J Nephrol Renovasc Dis*. 2012;5:151–163. https://doi.org/10.2147/IJNRD.S37766
2. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298:2038–2047. https://doi.org/10.1001/jama.298.17.2038
3. Stevens LA, Li S, Wang C, et al. Prevalence of CKD and comorbid illness in elderly patients in the United States: results from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis*. 2010;55(Suppl 2):S23–S33. https://doi.org/10.1053/j.ajkd.2009.09.035
4. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events,

and hospitalization. *N Engl J Med*. 2004;351:1296–1305. https://doi.org/10.1056/NEJMoa041031

5. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation*. 2003;108: 2154–2169. https://doi.org/10.1161/01.CIR.0000095676.90936.80
6. Seidel UK, Gronewold J, Volsek M, et al. Physical, cognitive and emotional factors contributing to quality of life, functional health and participation in community dwelling in chronic kidney disease. *PLoS One*. 2014;9:e91176. https://doi.org/10.1371/journal.pone.0091176
7. United States renal data system, Healthcare expenditures for persons with CKD: 2017 Annual Data Report, Volume 1 – CKD in the United States, Accessed February 22, 2023. https://www.niddk.nih.gov/about-niddk/strategic-plans-reports/usrds/prior-data-reports/2017.
8. Hoerger TJ, Simpson SA, Yarnoff BO, et al. The future burden of CKD in the United States: a simulation model for the CDC CKD Initiative. *Am J Kidney Dis*. 2015;65:403–411. https://doi.org/10.1053/j.ajkd.2014.09.023
9. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*. 2013;3:1–150.
10. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int*. 2011;80:17–28. https://doi.org/10.1038/ki.2010.483
11. Levey AS, Eckardt K-U, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: A position statement from Kidney Disease: improving Global Outcomes (KDIGO). *Kidney Int*. 2005;67:2089–2100. https://doi.org/10.1111/j.1523-1755.2005.00365.x
12. Garcia Sanchez JJ, Abdul Sultan A, Batista MC, et al. MO486 inside CKD: modelling the impact of improved screening for chronic kidney disease in the Americas and Asia-pacific region. *Nephrol Dial Transplant*. 2021;36:gfab087. https://doi.org/10.1093/ndt/gfab087.006
13. Olufade T, Lamerato L, Sánchez JJG, et al. Clinical outcomes and healthcare resource utilization in a real-world population reflecting the DAPA-CKD trial participants. *Adv Ther*. 2021;38:1352–1363. https://doi.org/10.1007/s12325-020-01609-2
14. Folkerts K, Petruski-Ivleva N, Kelly A, et al. Annual health care resource utilization and cost among type 2 diabetes patients with newly recognized chronic kidney disease within a large U.S. administrative claims database. *J Manag Care Spec Pharm*. 2020;26:1506–1516. https://doi.org/10.18553/jmcp.2020.26.12.1506
15. Astor BC, Matsushita K, Gansevoort RT, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int*. 2011;79:133–1340. https://doi.org/10.1038/ki.2010.550
16. Gansevoort RT, Matsushita K, Van Der Velde M, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int*. 2011;80: 93–104. https://doi.org/10.1038/ki.2010.531
17. Van Der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int*. 2011;79:1341–1352. https://doi.org/10.1038/ki.2010.536
18. Pecoits-Filho R, James G, Carrero JJ, et al. Methods and rationale of the DISCover CKD global observational study. *Clin Kidney J*. 2021;14:1570–1578. https://doi.org/10.1093/ckj/sfab046
19. The medicare current beneficiary survey 2018 chartbook-characteristics and perceptions of the medicare population. Centers for Medicare & Medicaid Services. Published 2018. Accessed February 22, 2023. https://www.cms.gov/research-statistics-data-and-systemsresearchmcbsdata-tables/2018-medicare-current-beneficiary-survey-annual-chartbook-and-slides
20. Kidney disease statistics for the United States. National Institute of Diabetes and Digestive and Kidney Diseases. Published 2016. Accessed February 22, 2023. https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease
21. Saran R, Robinson B, Abbott KC, et al. US renal data system 2019 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2020;75(suppl 1):A6–A7. https://doi.org/10.1053/j.ajkd.2019.09.003
22. Abdul Sultan A, Batista MC, Cabrera C, et al. MO518 inside CKD: modelling the economic burden of chronic kidney disease in the Americas and the Asia-Pacific region using patient-level microsimulation. *Nephrol Dial Transplant*. 2021;36. ;0038: gfab087.
23. Michalopoulos SN, Gauthier-Loiselle M, Sanon M, Serra E. *PO0272 - Reported Caregiver Burden in CKD With and Without Anemia: a US-Based Survey*. American Society of Nephrology; 2020. Accessed February 22, 2023. https://www.asn-online.org/education/kidneyweek/2020/program-abstract.aspx?controlId=3439120
24. Sanchez JG, Carrero J, Arnold M, et al. POS-319 Emergency and critical healthcare resource utilisation of patients with chronic kidney disease according to severity of albuminuria: a report from the discover CKD retrospective cohort. *Kidney Int Rep*. 2021;6:S137.