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ORIGINAL RESEARCH

Healthcare Resource Use, Costs, and Disease Progression Associated with Diabetic Nephropathy in Adults with Type 2 Diabetes: A Retrospective Observational Study

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ABSTRACT

Introduction: Diabetic nephropathy (DN) is a progressive kidney disease resulting as a complication of diabetes mellitus. This study evaluated the disease progression and economic burden of DN among commercially insured patients with type 2 diabetes in the USA.

Methods: The research design was a retrospective observational study based on healthcare claims data. The Truven MarketScan Databases (2004–2014) were queried for adults with type 2 diabetes with at least one urine albumin test (index, randomly selected) after diagnosis and at least one test after the index. On the basis of the index test, patients were classified into normoalbuminuria, microalbuminuria, or macroalbuminuria groups. Nephropathy-related treatment use was measured in the 6 months after the index, disease progression was assessed from the index to the end of data availability, and annual all-cause and nephropathy-related costs and healthcare resource use (HRU) were assessed up to 2 years from the index. Outcomes were compared between any two groups, controlling for baseline demographics.

Results: A total of 23,235 patients were identified and classified into normoalbuminuria ($N = 18{,}409$), microalbuminuria ($N = 3863$), or macroalbuminuria ($N = 963$) groups. Patients with albuminuria were more likely to be older, male, and have a higher burden of baseline comorbidities and HRU. Within 6 months following the index, 12–20% of patients with albuminuria were not treated with any relevant recommended treatment. Compared to the

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normoalbuminuria group, patients with macroalbuminuria had a significantly greater risk of disease progression (hazard ratio [HR] = 1.44), and both albuminuria groups were more likely to require dialysis (HR = 4.23 and 40.14 for micro- and macroalbuminuria, respectively; all $p < 0.05$). Annual all-cause (2016 US dollars, $3580 and $12,830 higher for micro- and macroalbuminuria vs. normoalbuminuria, respectively) and nephropathy-related ($362 and $3716) costs increased significantly with increasing nephropathy severity, consistent with the trend in increased HRU.

Conclusions: Diabetic nephropathy may be undertreated or inappropriately treated. It was also associated with significantly higher costs, HRU, and risk of disease progression among commercially insured patients with type 2 diabetes in the USA.

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Keywords: Albuminuria; Heath care costs; Microalbuminuria; Type 2 diabetes

INTRODUCTION

Diabetic nephropathy (DN) is a progressive kidney disease caused by damage to the small blood vessels in the kidney's glomeruli [1], resulting as a complication of diabetes mellitus (DM) [2]. DN affects up to 40% of patients with diabetes [3], with a total estimated prevalence of approximately 6.9 million people in the USA [4]. Diabetic nephropathy is a leading cause of end-stage renal disease (ESRD) and greatly increases the risk of all-cause mortality, cardiovascular-related morbidity and mortality, and kidney failure among patients with diabetes [5, 6]. This disease is usually detected by the presence of albuminuria, which is identified on the basis of urine albumin laboratory tests [3, 7, 8], e.g., urinary albumin excretion rate or albumin-to-creatinine ratio (ACR).

Treatment strategies for patients with mild to severe DN aim to prevent further renal function decline and delay disease progression via glycemic and blood pressure control, and through inhibition of the renin–angiotensin–aldosterone system (RAAS) [3, 7]. Treatment regimens commonly include RAAS-blocking agents such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB). However, these therapies are considered to be inadequate for the treatment of diabetic nephropathy, as they do not reverse the disease [9, 10]. Treatment combinations, such as dual-RAAS blockade with ACE inhibitors and ARBs, have been considered, but they are associated with adverse events (e.g., hyperkalemia and acute kidney injury); thus, these treatment combinations are not recommended, and are contraindicated in patients with renal impairment [8, 11]. Finally, even with treatment with currently available therapies, many patients with diabetic nephropathy nevertheless progress to ESRD, requiring dialysis while kidney transplant is considered [3].

As a result of the increased morbidity and mortality associated with diabetic nephropathy, patients with uncontrolled disease face severe economic burden, with estimated average annual healthcare costs ranging from $8000 to $43,000 [12]. Patients with diabetic nephropathy, especially those with severe stages of nephropathy such as chronic kidney disease and ESRD [12–15], incur higher economic burden compared to those without renal impairment [16–18]. In addition, patients who progress to severe stages of kidney disease experience higher rates of all-cause hospitalization and healthcare resource utilization (HRU) [13], and patients' incremental costs associated with the progression of chronic kidney disease are significantly higher than those of patients without renal impairment [12, 15].

Several prior studies have assessed the economic burden of diabetic nephropathy using various definitions of the condition. Nichols et al. assessed the incremental healthcare costs associated with progression to microalbuminuria, macroalbuminuria, and ESRD among patients enrolled in a US region-specific health maintenance organization with both type 2 diabetes mellitus (T2DM) and hypertension [18], which may not adequately represent the overall US patient population with DN. Further,

medical costs were estimated on the basis of the multiplicative product of "standard" visit costs and frequency of healthcare visits, rather than the observed reimbursement costs. Although there has been some evidence published on UK patients [19], there is currently limited US-specific information on disease progression and the economic burden associated with microalbuminuria or macroalbuminuria among patients with T2DM.

To address this knowledge gap, the current study evaluated real-world disease progression and the associated economic burden, including all-cause and nephropathy-related HRU and costs, among commercially insured USA-based patients with type 2 diabetes and diabetic nephropathy.

METHODS

Data Source

The data for this study were derived from the Truven Health Analytics MarketScan® Databases (Jan 1, 2004–Dec 31, 2014). The MarketScan Commercial and Medicare Supplemental claims databases represent approximately 25 million individuals (employees and their dependents, as well as Medicare-eligible retirees) annually covered by over 130 health plans and self-insured employers. The databases contain patient demographics, enrollment history, claims for inpatient and outpatient medical services, and claims for prescription pharmaceuticals. The MarketScan Lab Database contains laboratory test results for a subset of the individuals (approximately 1 million patients) covered in the Commercial and Medicare Supplemental databases, capturing lab tests ordered in office-based practices.

This article does not contain any new studies with human or animal subjects performed by any of the authors. All patient data were de-identified and complied with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act. No ethical approval was required.

Study Population and Subgroups

The study population included patients with type 2 diabetes who were at least 18 years old and had at least two urine albumin tests (24-h collection or ACR after the first observed type 2 diabetes diagnosis [International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes 250.x0 or 250.x2)]. From this population, a subset of patients with at least one eligible urine albumin test meeting the following criteria were identified: (1) at least one additional urine albumin test following the test date; and (2) continuous enrollment in a health plan for at least 12 months before the test date and at least 6 months following the test date and through at least one subsequent urine albumin test. Patients with ESRD (ICD-9-CM codes 403.x1, 404.x2, 404.x3, 585.5, or 585.6) during the 12-month period prior to the test date were excluded.

For each patient, the presence of microalbuminuria or macroalbuminuria was evaluated on the basis of a randomly selected eligible urine albumin test (index test) and used to classify the patient into one of three groups: (1) the normoalbuminuria group (urinary albumin excretion of less than 30 mg/24 h or an ACR of less than 30 μg/mg); (2) the microalbuminuria group (urinary albumin excretion of 30–300 mg/24 h or an ACR of 30–300 μg/mg); and (3) the macroalbuminuria group (urinary albumin excretion of greater than 300 mg/24 h or an ACR of greater than 300 μg/mg). The date of the index test was defined as the index date.

Study Measures and Outcomes

Patient demographics, disease characteristics, baseline nephropathy- and diabetes-related treatment use, and all-cause HRU and costs were measured during the 12-month period prior to the index date (baseline). The overall comorbidity burden during the baseline period was measured using the Charlson comorbidity index (CCI) [20].

Nephropathy-related treatment use was assessed in the 6 months following the index date, and included ACE inhibitors, ARBs,

diuretics, calcium channel blockers, and other antihypertensive agents, consistent with a prior publication [7]. Disease progression was assessed from the index date until the end of continuous eligibility, end of data availability, or inpatient mortality, whichever came first. Data captured included time to progression to a more severe stage of diabetic nephropathy and time to dialysis/hemodialysis. For the normoalbuminuria group, disease progression was defined as the presence of a urine albumin test indicating microalbuminuria or macroalbuminuria, a diagnosis of ESRD, or a dialysis or renal transplantation procedure. For the microalbuminuria group, disease progression was defined as the presence of a urine albumin test indicating macroalbuminuria, a diagnosis of ESRD, or a dialysis or renal transplantation procedure. For the macroalbuminuria group, disease progression was defined as the presence of a diagnosis of ESRD or a dialysis or renal transplantation procedure.

HRU and healthcare costs were assessed from the index date until 2 years from the index date, the end of continuous eligibility, end of data availability, or patient mortality, whichever occurred first. HRU included all-cause and nephropathy-related inpatient, emergency room (ER), outpatient, and other medical visits. Healthcare costs were evaluated from a third-party payer perspective and included all-cause and nephropathy-related healthcare costs resulting from medical services (inpatient, ER, outpatient, and other medical services) and pharmacy prescriptions. Nephropathy-related HRU and costs were defined as medical services and costs associated with a diagnosis of diabetic nephropathy or kidney disease (ICD-9-CM codes 249.4, 250.4, 583.81, 403.xx, 404.xx, or 585.xx), or a procedure for dialysis/hemodialysis or renal transplantation. Costs were converted to 2016 US dollars using the Consumer Price Index medical care component.

Statistical Analyses and Software

Baseline patient demographics and clinical characteristics were compared across groups using Wilcoxon rank-sum tests for continuous variables and Chi-square tests for categorical variables. Means and standard deviations were reported. Proportions of patients using nephropathy-related treatments during the 6 months following the index date were compared using multivariable logistic regression models, and adjusted odds ratios (ORs) with p values were reported. Time to progression to a more severe disease stage and time to dialysis/hemodialysis were evaluated using Kaplan–Meier analyses, and compared between study groups using log-rank tests. Cox proportional hazard models were used to further compare any two study groups with adjustment for baseline patient demographics, and adjusted hazard ratios (HRs) with 95% confidence intervals (CI) and p values were reported. Incidence rates of each type of healthcare visit per patient per year were described and compared using multivariable Poisson regression models, and the adjusted incidence rate ratios (IRRs) with 95% CIs and p values were reported. To account for over-dispersion, 95% CIs and p values were estimated using a nonparametric bootstrap resampling technique with 499 iterations. Annual costs in each cost category were described and compared using Wilcoxon rank-sum tests. Adjusted incremental cost differences were estimated using multivariable generalized linear models. For cost components with more than 5% zero values, a Tweedie distribution with an exponent of 1.67 was employed [21], and for all other components, a gamma distribution and a log link were used. All multivariable models were adjusted for baseline patient demographics, including age at index date, sex, region of residence, and insurance type. Baseline patient characteristics and outcomes were compared pairwise between any two of the three study groups.

Statistical analyses were performed using SAS, version 9.3 (Cary, NC, USA). A p value of 0.05 or less was considered to be significant.

RESULTS

Baseline Patient Demographic and Clinical Characteristics

A total of 23,235 patients met the sample selection criteria and were included in the

analysis. Of these, 18,409 (79%) patients were classified into the normoalbuminuria group, 3863 (17%) into the microalbuminuria group, and 963 (4%) into the macroalbuminuria group (Fig. 1). Baseline demographics such as age, sex, and residential region were different between the three groups (Table 1); patients with microalbuminuria or macroalbuminuria were slightly older (mean age [SD] = 54.9 [10.2] and 56 [10.3] years, respectively) and had more men (60% and 63%) than patients within the normoalbuminuria group (mean age [SD] = 54.3 [9.6] years, 53% male).

Patients with more severe nephropathy displayed exacerbated clinical characteristics and higher HRU and costs at baseline. The time from the first observed type 2 diabetes diagnosis in the database to the index date differed between groups, with the macroalbuminuria group having the longest time since diagnosis (mean [SD] = 44.0 [30.5] months), followed by the microalbuminuria (40.5 [27.9] months) and normoalbuminuria (37.8 [26.6] months; $p < 0.05$ all comparisons) groups (Table 1). A significantly higher comorbidity burden was also observed in patients with microalbuminuria (CCI [SD] = 1.9 [1.4]) and macroalbuminuria (2.5 [1.7]) compared with the normoalbuminuria group (1.6 [1.1]; all $p < 0.05$). With the exception of outpatient services, where 99% of patients in each group had at least one visit, patients with diabetic nephropathy experienced significantly higher rates of all-cause HRU during the baseline period compared to those with normoalbuminuria ($p < 0.05$ all comparisons), as well as higher

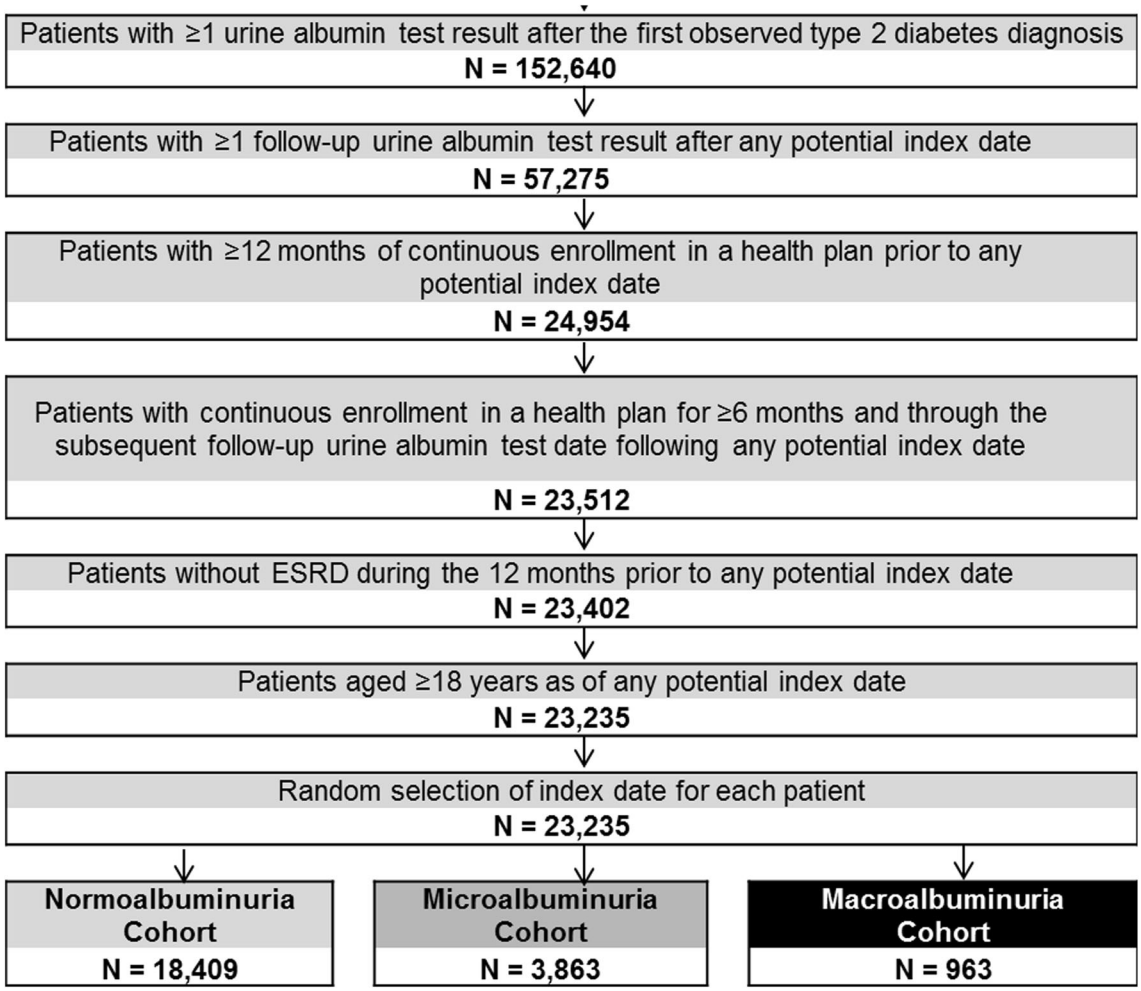

Fig. 1 Selection of study sample. *ESRD* end-stage renal disease, *N* number

Table 1 Patient baseline and clinical characteristics

	Normoalbuminuria [A] $N = 18,409$	**Microalbuminuria [B] $N = 3863$**	**Macroalbuminuria [C] $N = 963$**	**[A] vs. [B]**	**[A] vs. [C]**	**[B] vs. [C]**
Age at index date (years), mean ± SD	54.3 ± 9.6	54.9 ± 10.2	56.0 ± 10.3		§	‡
Male, *n* (%)	9836 (53%)	2310 (60%)	602 (63%)	*	§	
Region, *n* (%)						
Northeast	3577 (19%)	686 (18%)	180 (19%)	*		
North-Central	4687 (25%)	1029 (27%)	289 (30%)		§	‡
South	7666 (42%)	1687 (44%)	378 (39%)	*		‡
West	2475 (13%)	461 (12%)	116 (12%)	*		
Insurance plan type, *n* (%)						
Preferred provider organization	13,833 (75%)	2856 (74%)	711 (74%)			
Non-capitated point-of-service	1421 (8%)	250 (6%)	39 (4%)	*	§	‡
Exclusive provider organization	911 (5%)	191 (5%)	52 (5%)			
Comprehensive traditional plan	1597 (9%)	434 (11%)	136 (14%)	*	§	‡
Other plans	647 (4%)	132 (3%)	25 (3%)			
Time from first observed type 2 diabetes diagnosis in the database to the index date (months), mean ± SD	37.8 ± 26.6	40.5 ± 27.9	44.0 ± 30.5	*	§	‡
Index urine albumin test characteristics						
24-h urine albumin (mg)						
n (%)	208 (1%)	57 (1%)	24 (2%)			
Mean ± SD	7.5 ± 7.1	97.9 ± 73.5	2289.4 ± 2044.7	*	§	‡
Median [min, max]	7.2 [0.0, 29.1]	73.0 [30.0, 281.0]	1519.5 [315.0, 7140.2]			
Albumin/creatinine ratio (μg/mg)						
n (%)	18,201 (99%)	3806 (99%)	939 (98%)			
Mean ± SD	7.6 ± 6.5	88.6 ± 62.7	3439.6 ± 11,630.7	*	§	‡

Table 1 continued

	Normoalbuminuria [A] *N* = 18,409	**Microalbuminuria [B] *N* = 3863**	**Macroalbuminuria [C] *N* = 963**	**[A] vs. [B]**	**[A] vs. [C]**	**[B] vs. [C]**
Median [min, max]	6.0 [0.0, 29.8]	64.5 [30.0, 297.0]	734.0 [300.4, 90,000.0]			
CCI, mean ± SD	1.6 ± 1.1	1.9 ± 1.4	2.5 ± 1.7	*	§	‡
Disease-specific comorbidities, *n* (%)						
Neuropathy	2355 (13%)	618 (16%)	218 (23%)	*	§	‡
Ischemic heart disease	2191 (12%)	602 (16%)	192 (20%)	*	§	‡
Retinopathy	2004 (11%)	593 (15%)	251 (26%)	*	§	‡
Anemia	1358 (7%)	356 (9%)	155 (16%)	*	§	‡
Depression	1198 (7%)	219 (6%)	51 (5%)			
Cerebrovascular disease	852 (5%)	255 (7%)	102 (11%)	*	§	‡
Heart failure	370 (2%)	159 (4%)	60 (6%)	*	§	‡
Ketoacidosis	150 (1%)	37 (1%)	22 (2%)		§	‡
Hyperkalemia	111 (1%)	55 (1%)	23 (2%)	*	§	‡
High parathyroid hormone level	106 (1%)	33 (1%)	22 (2%)	*	§	‡
High phosphorus level	16 (<1%)	5 (<1%)	3 (<1%)			
Disease-specific treatments, *n* (%)						
Nephropathy-related treatments	12,726 (69%)	3032 (78%)	830 (86%)	*	§	‡
ACE inhibitor	6199 (34%)	1548 (40%)	427 (44%)	*	§	‡
Diuretic	3276 (18%)	850 (22%)	339 (35%)	*	§	‡
Calcium channel blocker	2330 (13%)	811 (21%)	296 (31%)	*	§	‡
ARB	2293 (12%)	654 (17%)	208 (22%)	*	§	‡
Other antihypertensive agents	4661 (25%)	1132 (29%)	369 (38%)	*	§	‡
Diabetic treatments, *n* (%)	15,177 (82%)	3363 (87%)	852 (88%)	*	§	
Metformin	11,548 (63%)	2532 (66%)	510 (53%)	*	§	‡
Sulfonylureas	4293 (23%)	1125 (29%)	314 (33%)	*	§	‡
Insulin	3915 (21%)	1179 (31%)	459 (48%)	*	§	‡

Table 1 continued

	Normoalbuminuria [A] $N = 18,409$	Microalbuminuria [B] $N = 3863$	Macroalbuminuria [C] $N = 963$	[A] vs. [B]	[A] vs. [C]	[B] vs. [C]
DPP4 inhibitor	1756 (10%)	438 (11%)	111 (12%)	*	§	
GLP1-based therapy	1279 (7%)	293 (8%)	72 (7%)			
SGLT2 inhibitor	3 (<1%)	0 (0%)	0 (0%)			
Other antidiabetic agents	3847 (21%)	911 (24%)	259 (27%)	*	§	‡
All-cause healthcare resource utilization						
Patients with ≥1 visit, *n* (%)						
Inpatient admissions	1490 (8%)	453 (12%)	169 (18%)	*	§	‡
ER services	4150 (23%)	984 (25%)	263 (27%)	*	§	
Outpatient services	18,226 (99%)	3817 (99%)	952 (99%)			
Other	10,073 (55%)	2186 (57%)	610 (63%)	*	§	‡
Number of visits per patient, mean ± SD						
Inpatient admissions	0.1 ± 0.4	0.2 ± 0.5	0.2 ± 0.6	*	§	‡
Inpatient days	0.5 ± 2.9	0.8 ± 3.4	1.4 ± 4.5	*	§	‡
ER services	0.4 ± 1.2	0.5 ± 1.4	0.6 ± 2.0	*	§	
Outpatient services	12.9 ± 12.6	12.9 ± 12.4	14.0 ± 12.4		§	‡
Other	2.0 ± 4.1	2.5 ± 4.9	3.5 ± 6.7	*	§	‡
All-cause healthcare costs (2016 USD), mean ± SD						
Total healthcare costs	10,602.7 ± 19,847.4	12,882.6 ± 25,539.6	15,849.0 ± 23,728.3	*	§	‡
Total medical costs	7108.4 ± 18,682.0	9018.6 ± 24,305.0	11,184.5 ± 21,995.8	*	§	‡
Total pharmaceutical costs	3494.3 ± 4869.1	3864.0 ± 5130.1	4664.5 ± 6426.0	*	§	‡

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *CCI* Charlson comorbidity index, *DPP4* dipeptidyl peptidase 4, *ER* emergency room, *GLP1* glucagon-like peptide-1, *N* number, *SD* standard deviation, *SGLT2* sodium-glucose cotransporter 2, *USD* United States dollars

* $p < 0.05$ for [A] vs. [B]; § $p < 0.05$ for [A] vs. [C]; ‡ $p < 0.05$ for [B] vs. [C]

all-cause healthcare costs ($p < 0.05$, all comparisons) (Table 1).

Nephropathy-Related Treatment Use and Disease Progression During the Follow-up Period

During the 6 months following the index date, nephropathy-related treatments were used by 68% with normal urine albumin levels, 81% of patients with microalbuminuria, and 88% of patients with macroalbuminuria (Table S1). ACE inhibitors were the most commonly used treatment for nephropathy (32%, 41%, and 43% for the normoalbuminuria, microalbuminuria, and macroalbuminuria groups, respectively). Both ACE inhibitors and ARBs were used by 3% of patients with

microalbuminuria and 6% of patients with macroalbuminuria.

During the follow-up period, patients with microalbuminuria or macroalbuminuria had a significantly greater risk of progression to a more severe disease stage compared to patients in the normoalbuminuria group (HRs [CI] = 1.31 [1.08, 1.60] and 1.44 [1.21, 1.72], respectively; both $p < 0.05$) (Fig. 2a). Specifically, the 5-year disease progression rates were 15%, 19%, and 31% for the normoalbuminuria, microalbuminuria, and macroalbuminuria groups, respectively. Patients with microalbuminuria and macroalbuminuria were at significantly higher risk of receiving dialysis/hemodialysis compared to patients with normoalbuminuria (HRs [CI] = 4.23 [2.45, 7.30] and 40.14 [25.33, 63.60], respectively; both $p < 0.001$) (Fig. 2b). The 5-year dialysis rates were 0.3% among patients with normal albumin levels, 2% among those with microalbuminuria, and 18% among those with macroalbuminuria.

Annual All-Cause and Nephropathy-Related HRU During the Follow-up Period

The annual frequency of all-cause healthcare visits rose significantly with the increasing severity of the patient's nephropathy, a trend that was consistent across inpatient, outpatient, ER, and other medical services visits ($p < 0.05$ in all pairwise adjusted IRR comparisons) (Table 2). The microalbuminuria group experienced significantly higher utilization rates of each type of all-cause medical service in comparison with the normoalbuminuria group, particularly inpatient admissions (adjusted IRR [CI] = 1.51 [1.37, 1.65]; $p < 0.05$ all adjusted IRR comparisons) (Table 2). Furthermore, the macroalbuminuria group experienced particularly heightened average annual incidence rates of all-cause inpatient admissions in comparison with the microalbuminuria and normoalbuminuria groups (adjusted IRRs [CI] of 1.78 [1.50, 2.09] and 2.70 [2.34, 3.16], respectively; both $p < 0.05$). A similar trend was observed in healthcare visits related to nephropathy, with an increased magnitude of difference between groups. In comparison with the normoalbuminuria group, the microalbuminuria group had significantly higher incidence rates of nephropathy-related inpatient (adjusted IRR [CI] = 2.94 [2.21, 3.88]), ER (4.70 [3.09, 7.76]), outpatient (3.77 [3.16, 4.48]), and other medical service visits (6.26 [2.43, 19.46], all $p < 0.05$) (Table 2). Additionally, in comparison with both the microalbuminuria and normoalbuminuria groups, patients with macroalbuminuria had significantly higher incidence rates of nephropathy-related inpatient (adjusted IRRs [CI] = 5.24 [3.91, 7.09] and 16.53 [12.14, 21.87], respectively), ER (4.03 [2.49, 6.46] and 18.96 [11.79, 29.88]), outpatient (4.83 [3.51, 6.30] and 18.25 [13.36, 24.86]), and other medical services visits (8.54 [3.87, 19.92] and 50.20 [16.45, 174.00]; all $p < 0.05$) during the follow-up period, after adjusting for baseline patient demographics (Table 2). For both all-cause and nephropathy-related HRU, the differences in adjusted annual HRU rates between the albuminuria and normoalbuminuria groups increased with disease severity, with the macroalbuminuria group exhibiting the highest HRU in all cases.

Annual All-Cause and Nephropathy-Related Healthcare Costs During the Follow-up Period

Patients with microalbuminuria or macroalbuminuria had significantly higher annual all-cause healthcare costs (2016 US dollars) compared to those in the normoalbuminuria group (mean [SD], normoalbuminuria = $12,353 [20,082], microalbuminuria = $15,893 [29,874], macroalbuminuria = $25,424 [47,844]), with adjusted cost differences of $3580 and $12,830 per year, respectively ($p < 0.05$, all comparisons) (Table 3). The microalbuminuria group had higher costs than those of the normoalbuminuria group ($p < 0.05$, all comparisons), and the macroalbuminuria group had significantly higher adjusted all-cause healthcare costs than either the normoalbuminuria or microalbuminuria groups in all categories (with the exception of

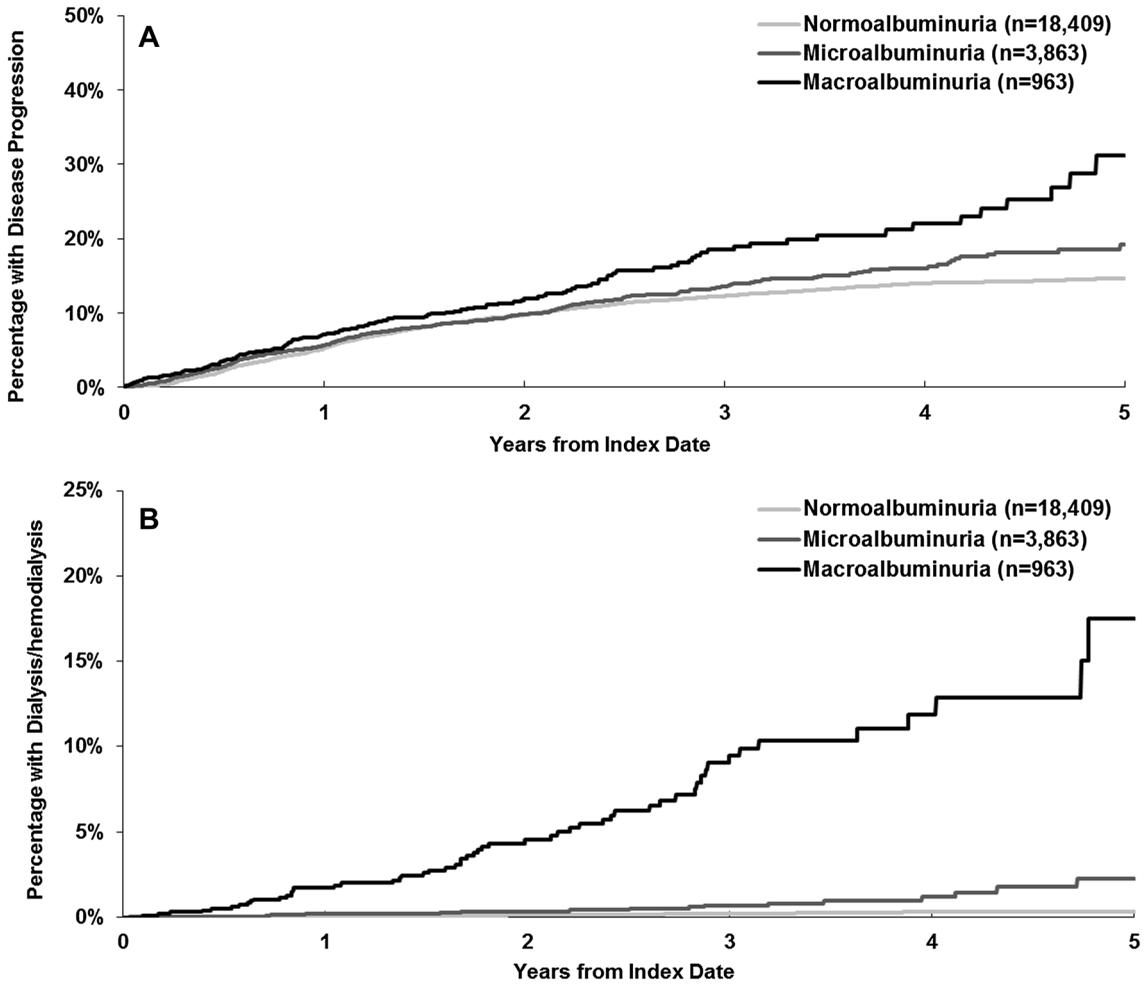

Fig. 2 Comparison of 1-, 3-, and 5-year clinical outcomes between groups. **a** Rates of disease progression: the median number of follow-up years for the macro-, micro-, and normoalbuminuria groups was 1.81, 1.93, and 1.95 years, respectively. The 1-, 3-, and 5-year progression rates for the macroalbuminuria group were 7.02%, 18.51%, and 31.19%, those for the microalbuminuria group were 5.64%, 13.49%, and 19.19%, and those for the normoalbuminuria group were 5.26%, 12.25%, and 14.68%. **b** Comparison of time to dialysis/hemodialysis: the median number of follow-up years for the macro-, micro-, and normoalbuminuria groups was 1.92, 2.06, and 2.13 years, respectively. The 1-, 3-, and 5-year dialysis rates for the macroalbuminuria group were 1.75%, 9.46%, and 17.52%, those for the microalbuminuria group were 0.19%, 0.71%, and 2.25%, and those for the normoalbuminuria group were 0.02%, 0.19%, and 0.33%. *n* number

ER visits in comparison with the microalbuminuria group) (Table 3). Inpatient admissions costs accounted for 45–51% of the adjusted cost differences between groups, followed by outpatient (20–24%) and pharmaceutical costs (10–15%). A similar trend was observed in adjusted nephropathy-related costs (Table 3). Compared to patients in the normoalbuminuria group, patients with microalbuminuria and macroalbuminuria incurred higher total nephropathy-related adjusted healthcare costs, with increases of $362 and $3716, respectively. The nephropathy-related total annual healthcare costs among patients with macroalbuminuria were $4427, driven by high inpatient (mean [SD] = $2048 [10,765]) and outpatient ($1526 [11,515]) medical costs.

Table 2 Comparison of health resource utilization during the follow-up period

Outcome measures	Annual incidence rate			Adjusted incidence rate ratio					
	Normoalbuminuria group [A] $N = 18,409$	Microalbuminuria group [B] $N = 3863$	Macroalbuminuria group [C] $N = 963$	[B] vs. [A]		[C] vs. [A]		[C] vs. [B]	
				IRR (95% CI)	*p* value	IRR (95% CI)	*p* value	IRR (95% CI)	*p* value
All-cause healthcare resource utilization									
Inpatient admissions	0.10	0.16	0.29	1.51 (1.37, 1.65)	0.004*	2.70 (2.34, 3.16)	0.004*	1.78 (1.50, 2.09)	0.004*
Inpatient days	0.56	0.94	2.26	1.63 (1.40, 1.84)	0.004*	3.82 (2.94, 4.84)	0.004*	2.31 (1.76, 2.85)	0.004*
Emergency room services	0.44	0.56	0.69	1.29 (1.16, 1.42)	0.004*	1.62 (1.39, 1.91)	0.004*	1.25 (1.04, 1.49)	0.016*
Other	2.26	2.97	5.05	1.29 (1.22, 1.37)	0.004*	2.11 (1.80, 2.51)	0.004*	1.61 (1.39, 1.88)	0.004*
DN-related healthcare resource utilization									
Inpatient admissions	0.01	0.02	0.12	2.94 (2.21, 3.88)	0.004*	16.53 (12.14, 21.87)	0.004*	5.24 (3.91, 7.09)	0.004*
Inpatient days	0.06	0.20	1.27	3.18 (2.13, 4.69)	0.004*	21.05 (13.38, 31.46)	0.004*	6.12 (4.00, 9.57)	0.004*
Emergency room services	0.00	0.02	0.07	4.70 (3.09, 7.76)	0.004*	18.96 (11.79, 29.88)	0.004*	4.03 (2.49, 6.46)	0.004*
Outpatient services	0.21	0.80	3.97	3.77 (3.16, 4.48)	0.004*	18.25 (13.36, 24.86)	0.004*	4.83 (3.51, 6.30)	0.004*
Other	0.01	0.08	0.68	6.26 (2.43, 19.46)	0.004*	50.20 (16.45, 174.00)	0.004*	8.54 (3.87, 19.92)	0.004*

The mean length of follow-up was 1.69 years for the normoalbuminuria group, 1.67 years for the microalbuminuria group, and 1.63 years for the macroalbuminuria group

IRR incidence rate ratio, *CI* confidence interval, *DN* diabetic nephropathy

* Denotes a significant difference

Table 3 Comparison of all-cause and diabetic nephrology-related annual healthcare costs during the follow-up period

Outcome measures	Annual healthcare cost (2016 USD)			Adjusted cost difference					
	Normoalbuminuria group [A] $N = 18,409$	Microalbuminuria group [B] $N = 3863$	Macroalbuminuria group [C] $N = 963$	[B] vs. [A]		[C] vs. [A]		[C] vs. [B]	
				Diff	*p* value	Diff	*p* value	Diff	*p* value
All-cause healthcare costs, mean ± SD									
Total healthcare costs	12,353 ± 20,082	15,893 ± 29,874	25,424 ± 47,844	3580	<0.0001*	12,830	<0.0001*	9250	<0.0001*
Total medical costs	8320 ± 18,382	11,313 ± 28,405	19,748 ± 45,864	3035	<0.0001*	11,404	<0.0001*	8369	<0.0001*
Inpatient admission costs	2731 ± 12,935	4445 ± 20,316	9509 ± 35,499	1625	<0.0001*	6385	<0.0001*	4760	<0.0001*
Emergency room service costs	715 ± 3509	1098 ± 7554	1229 ± 3581	362	<0.0001*	535	<0.0001*	173	0.2422
Outpatient service costs	4110 ± 7576	4716 ± 11,993	6985 ± 16,479	706	<0.0001*	2926	<0.0001*	2221	<0.0001*
Other medical service costs	764 ± 2644	1055 ± 3631	2024 ± 6447	288	<0.0001*	1278	<0.0001*	990	<0.0001*
Total pharmaceutical costs	4033 ± 5625	4581 ± 5440	5675 ± 9183	529	<0.0001*	1454	<0.0001*	925	<0.0001*
DN-related healthcare costs, mean ± SD									
Total healthcare costs	368 ± 1934	780 ± 3817	4427 ± 20,290	362	<0.0001*	3716	<0.0001*	3353	<0.0001*
Total medical costs	110 ± 1868	444 ± 3765	3920 ± 20,294	285	<0.0001*	3600	<0.0001*	3317	<0.0001*
Inpatient admission costs	63 ± 1322	256 ± 2807	2048 ± 10,765	156	<0.0001*	2019	<0.0001*	1862	<0.0001*
Emergency room service costs	3 ± 114	15 ± 226	68 ± 521	8	0.0018*	64	<0.0001*	55	0.0187*
Outpatient service costs	40 ± 889	147 ± 1274	1526 ± 11,515	103	<0.0001*	1444	<0.0001*	1342	<0.0001*
Other medical service costs	4 ± 245	26 ± 570	278 ± 3817	13	0.0053*	245	<0.0001*	231	0.0007*

Table 3 continued

Outcome measures	Annual healthcare cost (2016 USD)			Adjusted cost difference					
	Normoalbuminuria group [A] $N = 18,409$	Microalbuminuria group [B] $N = 3863$	Macroalbuminuria group [C] $N = 963$	[B] vs. [A]		[C] vs. [A]		[C] vs. [B]	
				Diff	*p* value	Diff	*p* value	Diff	*p* value
Total pharmaceutical costs	257 ± 482	337 ± 547	506 ± 751	75	<0.0001*	220	<0.0001*	145	<0.0001*

The mean length of follow-up was 1.69 years for the normoalbuminuria group, 1.67 years for the microalbuminuria group, and 1.63 years for the macroalbuminuria group

USD US dollars, *Diff* difference, *DN* diabetic nephropathy, *SD* standard deviation

* Denotes a significant difference

DISCUSSION

The current study quantifies and underscores the significant risk of disease progression and incremental economic burden associated with microalbuminuria and macroalbuminuria compared with no renal impairment, as well as the progressive nature of such outcomes.

The results suggest that the incremental benefit of treating early-stage diabetic nephropathy may be substantial. A nearly 50% increased risk of mortality associated with albuminuria has been observed with very low levels not previously believed to be impactful (15–29 mg/24 h), suggesting an expansion of the category of diabetic patients who may benefit from early intervention [22] or screening [23]. Given the significantly higher risk of requiring costly dialysis and renal transplantation procedures in patients with albuminuria, reducing disease progression rates would result in significant cost savings. Accordingly, the development of effective treatments and early intervention strategies could reduce the risk of adverse clinical outcomes and ultimately reduce HRU and costs.

Most importantly, the high disease progression rates observed in this study, despite the availability of treatments of diabetic nephropathy, highlight the inadequacy of current DN treatments and the need for treatments that can effectively delay disease progression. In 2002, Adler et al. estimated DN progression rates in a UK population; progression rates reported in the current study are higher than those reported by Adler et al. in particular among patients with macroalbuminuria [19]. However, our study is not directly comparable to Adler et al.'s study for several reasons. Adler et al. defined disease progression among patients with macroalbuminuria by elevated plasma creatinine or renal replacement therapy [19], and microalbuminuria was defined using the UK Prospective Diabetes Study standards (urinary albumin excretion of 50–299 mg/24 h) [24]. In the current study, microalbuminuria was defined as 30–300 mg/24 h or an ACR of 30–300 μg/mg, and macroalbuminuria was defined on the basis of 24 h albumin, namely greater than 300 mg/

24 h or ACR of greater than 300 μg/mg. Adler et al.'s study also classified the stages of diabetic nephropathy based on two consecutive annual visits while the current study used only one visit to define the stages of DN, which might have resulted in an overestimation of the rates of progression. Despite these differences, the current study provides clinical evidence more applicable to the US population than Adler et al.'s study as it was based on the US population and had more than four times the number of included patients. Among other studies conducted within the USA, disease progression rates are higher than those reported by Adler et al. in the UK, and more consistent with the findings of the present study; the Wisconsin Epidemiologic Study of Diabetic Retinopathy examined rates of disease progression among diabetic patients and reported that during the 15 years following a diagnosis of diabetes, 45.2% of patients developed either microalbuminuria or macroalbuminuria [5].

Disease progression in diabetic nephropathy has been previously reported to be accompanied by rising medical treatment costs. Nichols et al. found that patients with type 2 diabetes and hypertension who progressed from normal urine albumin levels to microalbuminuria or microalbuminuria to macroalbuminuria incurred higher incremental annual costs of $2764 and $3618 from pre-progression to post-progression, respectively [18]. However, that study focused on a type 2 diabetes population limited to those with hypertension, which may not be generalizable to the entire diabetic nephropathy population, and costs were imputed using "standard" unit costs for visit types and visits frequencies rather than actual costs incurred. Conversely, the current study included a broadly defined population—any patients with type 2 diabetes—and compared both the frequency of healthcare visits and actual incurred healthcare costs between patients with and without nephropathy, as well as between patients with macroalbuminuria versus microalbuminuria. We found that, consistent with worsening clinical outcomes, patients with microalbuminuria and macroalbuminuria had higher all-cause and nephrology-related HRU and a substantial economic burden. However, the adjusted incremental all-cause cost burdens associated with macroalbuminuria as compared to microalbuminuria (an adjusted difference of $9250) or patients without albuminuria ($12,830), as well as that of microalbuminuria compared with patients without albuminuria ($3580), were higher than those found by Nichols et al. This difference may be due to differing levels of disease progression during follow-up between the two studies; only 5% of patients with macroalbuminuria were observed to progress to ESRD in Nichols et al. [18] (over 6.5 years of follow-up), compared to the estimated 5-year progression rate of 31% in the current study. Additionally, the current study observed higher annual costs at baseline among the normoalbuminuria, microalbuminuria, and macroalbuminuria groups, which may be indicative of underlying differences in cost calculations compared to that study.

This study also demonstrated that despite abnormal urine albumin test results, many patients are not receiving treatment for diabetic nephropathy—between 12% and 20% remained untreated during the 6 months following an abnormal urine albumin test result. However, among those treated, less than half of patients used ACE inhibitors or ARBs, the current treatments recommended by the American Diabetes Association (ADA) for patients with elevated urinary albumin excretion [8]. The results of this study have additional important implications for physicians treating patients with type 2 diabetes as well as for payers as it demonstrates the possible undertreatment and inappropriate treatment of patients with DN. Given the incremental benefit of treating early-stage diabetic nephropathy, both DN diagnosis and appropriate treatment must be timely as they are critical for delaying disease progression and reducing healthcare costs.

This study was subject to certain limitations. Patients were required to be continuously enrolled for at least 6 months after the index date and until the follow-up urine albumin test, which may introduce immortal time bias. However, as the mean follow-up time was similar among groups (1.69 years for the normoalbuminuria group, 1.67 years for the microalbuminuria group, and 1.63 years for the

macroalbuminuria group) the impact of this bias is expected to be similar across groups; thus, the results would be expected to be qualitatively similar to the results if immortal time bias was completely eliminated. The use of a single urine albumin test to determine increased urinary albumin excretion rates may cause misclassification of disease progression; if the urine albumin was transiently elevated, an underestimation of the difference between groups may have occurred.

Although the database is geographically representative of the USA, the data included only commercially insured patients and those who have commercial insurance in supplement to Medicare. In addition, to evaluate disease progression of diabetic nephropathy, the current study sample was further restricted to the subset of patients who were also in the MarketScan Lab Database and who had two urine albumin tests results. Thus, the results may not be generalizable across all study populations.

The selection of patients with two urine albumin tests for inclusion in the study may bias the study population toward one at high risk for diabetic nephropathy, who requires frequent monitoring of urine albumin levels, thus potentially biasing the study results toward greater progression rates than those of the general type 2 diabetic population. However, because the study results are consistent with a US prospective study, the selection bias is minimized. Furthermore, the limited information available in the database prevented further analysis on important patient characteristics (e.g., diabetes disease duration since the initial diagnosis, race), indirect costs (e.g., lost productivity), and additional important clinical measures (e.g., HbA1c, eGFR).

CONCLUSION

Microalbuminuria and macroalbuminuria were associated with significantly higher risk of disease progression and substantially increased economic burden among commercially insured patients with type 2 diabetes in the USA. These results highlight the persisting unmet need for effective treatments and early intervention strategies for adult patients with diabetic nephropathy.

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All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

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