

Referral to nephrologists is associated with the slow progression of kidney dysfunction in patients with type 2 diabetes mellitus

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Background: Although treatment guidelines exist, referrals and discussions among clinicians about the disease can lead to more appropriate treatment for the patient. This study evaluated the effects of referrals from diabetes clinics to nephrologists on kidney function in type 2 diabetic patients through causal inference analysis.

Methods: Patients with type 2 diabetes mellitus (DM) who initially visited the diabetes clinic were either referred to nephrologists (referral group) or continued under the care of diabetologists at the diabetes clinic (non-referral group). The slope of the estimated glomerular filtration rate (eGFR) per year was calculated based on the annual median difference in yearly eGFR values. We applied a difference-in-differences model to this time-series dataset with an inverse propensity weighting estimator to evaluate the effect of referral to nephrologists.

Results: Among the 30,160 patients who initially visited the diabetes clinic, 3,885 (12.9%) were referred to nephrologists during follow-up. At the time of referral, the median (interquartile range) values of the eGFR and random urine albumin-to-creatinine ratio were 55.0 mL/min/1.73 m² (40.3–76.8 mL/min/1.73 m²) and 107 mg/g (20–846 mg/g), respectively. The average treatment effect of referral to nephrologists was an improvement in the eGFR slope, with an increase of 5.8 mL/min/1.73 m² (95% confidence interval, 4.8–6.8 mL/min/1.73 m²) per year. The effect of referral was greater in patients with a high risk of progression than in those with a low risk.

Conclusion: Referral to nephrologists is associated with slow progression of kidney dysfunction in patients with type 2 DM, supporting the need to evaluate how to facilitate timely referral for each patient as a next step.

Keywords: Chronic renal insufficiency, Diabetes complications, Diabetes mellitus, Diabetic nephropathies, Referral and consultation

Introduction

Chronic kidney disease (CKD) is a major complication of type 2 diabetes mellitus (DM), contributing substantially to morbidity and health care costs. Approximately one-

third of individuals with type 2 DM develop CKD, which can progress to end-stage kidney disease (ESKD) if not effectively managed [1]. The progression of CKD in diabetic patients is influenced by various factors, including uncontrolled hyperglycemia, hypertension, and albumin-

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uria [2,3]. The effective management of these risk factors is crucial for slowing the progression of kidney dysfunction and improving patient outcomes. Recent guidelines from the Kidney Disease Improving Global Outcomes (KDIGO) and American Diabetes Association (ADA) propose evidence-based strategies for managing risk factors in patients with diabetic kidney disease (DKD), including renin-angiotensin system (RAS) blockers, sodium-glucose cotransporter inhibitors, and glucagon-like peptide-1 receptor agonists [4,5].

Although comprehensive guidelines for the management of DM are available, they emphasize the importance of setting individualized targets for each patient rather than adopting a universal treatment approach [6,7]. With respect to blood pressure targets, optimal and tolerable levels can differ for each patient [8,9]. Similarly, for glycemic control, individualized targets of glucose and hemoglobin A1c are advised based on the risk of hypoglycemia [4,5]. The perspective and treatment of such patients can vary depending on their condition and comorbidities. Therefore, experts in each field may have different approaches to treating the same patient, which can create synergy in treatment or lead to debates that require discussion. The ADA guidelines suggest referring the patients to a nephrologist when the estimated glomerular filtration rate (eGFR) is less than 30 mL/min/1.73 m² or when persistent worsening of albuminuria and eGFR are observed, but the evidence for this recommendation of referral or its timing is not definitive [4]. Referring to nephrologists could aid in the preservation of kidney function and recovery from acute kidney dysfunction if it exists [10–12], but further exploration and research are needed to understand how such referrals can truly lead to better patient outcomes.

We aimed to evaluate the effects of referrals from diabetologists to nephrologists on the progression of kidney dysfunction in patients with type 2 DM. Conducting a randomized controlled trial on the effect of referral to nephrologists may pose ethical and research limitations. Therefore, we addressed this issue via causal inference analysis with a large cohort of patients with type 2 DM who initially visited the diabetic clinic. We also explored the differences in management, such as medications and the frequency of kidney biopsy, between diabetologists and nephrologists. These findings may provide valuable insights into the importance of referral to nephrologists in managing patients

with DKD.

Methods

Ethical considerations

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The research protocol was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (No. H-2307-104-1449). To ensure patient data confidentiality, all patient information was anonymized and securely stored, with access restricted to authorized researchers only.

Study patients

A total of 52,625 patients who visited the diabetes clinic at a tertiary hospital between July 2004 and November 2023 due to a diagnosis of type 2 DM were included. Patients were excluded if they were under the age of 18 years, had DM other than type 2 DM (e.g., suspected steroid-induced or postpancreatectomy DM), had underlying stage 5 CKD or ESKD (e.g., dialysis and kidney transplantation), had a follow-up duration of less than 2 years, or if laboratory tests necessary to calculate changes in eGFR were unavailable. Additionally, patients who visited the nephrology clinic before the diabetes clinic were excluded. After applying these criteria, 30,160 patients were included in the final analysis. A detailed flow chart of the patient selection process is provided in [Supplementary Fig. 1](#) (available online).

Data collection and study variables

We collected a comprehensive set of variables for each patient, including demographic information such as age, sex, body mass index, systolic and diastolic blood pressures, and comorbidities (e.g., hypertension, malignancy, ischemic heart disease, and cerebrovascular disease). The following laboratory findings were retrieved: serum creatinine, hemoglobin A1c, hemoglobin, protein, albumin, cholesterol, and random urine albumin-to-creatinine ratio (ACR). The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [13]. When the protein-to-creatinine ratio was measured without

measuring the ACR value, this value was converted to the ACR according to a previously proposed formula [14]. The patients were categorized into subgroups based on the risk of CKD progression, as described in the KDIGO guideline [5]. We also calculated the 2-year and 5-year risks of ESKD progression suggested by the KDIGO guidelines [5]. Data on medication prescriptions were collected, and a detailed list of medications is provided in [Supplementary Table 1](#) (available online). The rates of kidney biopsies and the corresponding diagnoses were documented.

To quantify the degree of kidney function decline, we calculated the slope of the eGFR. This slope represents the change in the median eGFR, estimated as the representative value for each calendar year, over the following year. If the eGFR dropped below 10 mL/min/1.73 m², an indication of irreversible or severe kidney dysfunction, all subsequent eGFR values were censored and excluded from the slope calculation. The eGFR slope was computed for the study period, provided that more than two sequential eGFR values were available for accurate calculation. Years lacking adequate data were excluded from the analysis.

Definition of nephrology referral and timing

In this study, we categorized patients with type 2 DM who regularly attended a diabetic clinic into two groups based on their nephrology referral status. Patients without any record of visiting the nephrology department were classified as the “non-referral” group, while those with at least one nephrology visit were classified as the “referral” group. The timing of referral was defined as the date of the patient’s first nephrology outpatient visit. For each patient in the referral group, we calculated the 2-year ESKD risk at the time of this initial nephrology visit, using the KDIGO guideline’s risk formula [5,15]. Patients with a 2-year risk greater than 10% were classified as “late referral,” while those with a risk lower than 10% were classified as “early referral.” The risk was calculated as follows:

$$\begin{aligned} \text{exponent} &= -0.2201 \times \left(\frac{\text{age}}{10} - 7.036 \right) + 0.2467 \times (\text{male} - 0.5642) \\ &\quad - 0.5567 \times \left(\frac{\text{eGFR}}{5} - 7.222 \right) + 0.4510 \times (\log \text{ACR} - 5.137) \\ \text{2 year risk} &= 1 - 0.9832^{\text{exp}(\text{exponent})} \end{aligned}$$

Statistical analysis

The variables were organized according to the calendar year, with the number of prescribed days for the medication variable and the median values for the other variables. In cases with missing data, the forward filling method was applied to fill in the gaps. If the initial value of a variable was missing, it was imputed using the median value of the initial non-missing data points. Serum creatinine and eGFR values, which represent kidney function, were not imputed and were left as missing values if not available.

Descriptive statistical analyses were performed to summarize the patient information. Continuous variables with a normal distribution are presented as the means \pm standard deviations, whereas those without a normal distribution are presented as medians with interquartile ranges (IQRs). Categorical variables are shown as percentages. Categorical variables were compared using either the chi-square test or Fisher exact test, whereas continuous variables were compared using either the Student t test or the Mann-Whitney U test, depending on their distribution. Penalized spline regression was used to smooth and visualize changes in values over time. To quantify the differences in medication prescription rates between the referral group and the non-referral group, negative binomial regression was used. These analyses were conducted for each year and each medication, with Bonferroni correction applied for multiple testing. All the statistical analyses were conducted using R version 4.2.2 (R Foundation for Statistical Computing) and Python version 3.11.5. A two-sided p-value of less than 0.05 was considered statistically significant.

Causal inference analysis

To assess the effect of referral to nephrologists on kidney function in patients with type 2 DM, we employed the difference-in-differences (DiD) model using the *did* package [16], which demonstrated its utility in previous studies [17,18]. This approach enhances causal interpretation by using a difference-in-differences of variables before and after the referral to control baseline differences between referral and non-referral groups. By comparing outcome changes over time within each group, the method isolates the referral effect while accounting for differences in patient complexity, initial kidney function, and shared trends

that might otherwise confound results. Examining how trends diverge post-intervention allows for a more accurate estimate of the referral's causal impact, distinguishing it from other time-related factors. The *did* package further allows for multiple time periods and variations in treatment timing, ensuring that the parallel trends assumption conditionally holds on adjusted variables. Unlike traditional two-way fixed effects regressions, the *did* package mitigates common drawbacks by providing more accurate treatment effect estimates.

The analysis utilized an inverse probability weighting estimator, allowing for an unbalanced panel. The treated group consisted of patients who were referred to nephrologists, whereas the untreated group consisted of patients who were not referred. We calculated the average treatment effect of the treatment group (ATT) based on the relative time to the referral point, adjusting for sex, age, body mass index, eGFR, ACR, hemoglobin A1c, albumin, and comorbidities, including hypertension, any cancer, ischemic heart disease, and cerebrovascular disease. This approach enabled us to precisely measure the impact of referrals on the annual change in eGFR, considering variations in referral timing.

We conducted a sensitivity analysis using the *HonestDiD* package [19], which provides robust inference and sensitivity tools for difference-in-differences and event study designs. This package allows for a formalization of the hypothesis that pretreatment trends can inform potential violations of parallel trends in the posttreatment period. The relative magnitudes of these violations were bound, ensuring that posttreatment violations were no more than a constant \bar{M} times larger than the maximum pretreatment violations. For example, setting $\bar{M}=1$ implies that posttreatment violations are no worse than the worst pretreatment violations.

Results

Baseline characteristics of patients visiting the diabetes clinic

The baseline characteristics of the study patients are summarized in [Table 1](#). This cohort consisted of 30,160 patients, with a mean age of 59.1 ± 12.3 years, and 43.4% of patients were female. Among these patients, 3,885 were referred to

nephrologists during follow-up. The median time from the initial visit to the diabetes clinic to referral was 4 years (IQR, 2–8 years). When baseline characteristics were compared between the two groups, the referral group had higher rates of comorbidities such as hypertension, ischemic heart disease, and cardiovascular disease than the non-referral group. The referral group had worse baseline kidney function, with a low eGFR and a high ACR. Medication usage at baseline differed between the groups; the referral group had lower usage rates of metformin, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter-2 inhibitors, but higher usage rates of secretagogues, thiazolidinediones, and insulin than the non-referral group. The prescription rates for all the medications are listed in [Supplementary Table 1](#) (available online).

Trends in referrals and laboratory findings

[Fig. 1](#) shows the changes in patient numbers over time. The number of patients who visited the diabetes clinic remained constant over the years, with a median number of 1,592 patients (IQR, 1,554–1,653 patients) per year. The number of patients referred to nephrologists gradually increased over time ([Fig. 1A](#)). The total number of patients who visited the diabetes clinic at least once per year steadily increased, peaking at 16,951 in 2022, while the number of patients who visited nephrologists at least once per year was highest in 2023, at 2,214 ([Fig. 1B](#)).

Changes in laboratory findings and estimated ESKD risk between the referral and non-referral groups over time are depicted in [Fig. 2](#). At the start of the observation period, the eGFR trends significantly differed between the two groups, with the referral group having markedly low eGFR levels ([Fig. 2A](#)). The eGFR slope highlights these differences, with the referral group exhibiting a steeper decline of -2.121 mL/min/1.73 m² per year than -0.849 mL/min/1.73 m² per year in the non-referral group ([Fig. 2B](#)). These differences in baseline kidney function between the two groups indicate that patients with kidney dysfunction were referred primarily to nephrologists throughout the study period. The hemoglobin A1c levels were similar between the two groups, with a similar trend as the study time progressed ([Fig. 2C](#)). The ACR values continuously increased in the referral group, whereas the non-referral group had con-

Table 1. Baseline characteristics of patients visiting the diabetes clinic

Characteristic	Total	Non-referral group	Referral group	p-value
No. of patients	30,160	26,275	3,885	
Age (yr)	59.1 ± 12.3	58.8 ± 12.3	60.8 ± 11.9	<0.001
Female sex (%)	43.4	43.7	41.8	0.03
Body mass index (kg/m ²)	24.8 ± 4.3	24.8 ± 4.3	24.9 ± 4.3	0.26
Systolic blood pressure (mmHg)	131.3 ± 15.8	131.2 ± 15.7	132.2 ± 17.5	0.40
Diastolic blood pressure (mmHg)	77.1 ± 10.8	77.1 ± 10.7	76.6 ± 11.9	0.53
Hypertension (%)	9.6	9.0	13.7	<0.001
Malignancy (%)	11.3	11.4	10.9	0.34
Ischemic heart disease (%)	5.3	4.9	7.8	<0.001
Cerebrovascular disease (%)	4.8	4.3	7.8	<0.001
Laboratory finding				
Serum creatinine (mg/dL)	0.87 (0.74–1.00)	0.85 (0.73–1.00)	1.00 (0.83–1.20)	<0.001
eGFR (mL/min/1.73 m ²)	86.7 (73.1–97.2)	88.0 (75.6–97.9)	72.6 (58.6–87.9)	<0.001
Hemoglobin A1c (%)	7.1 (6.5–8.1)	7.1 (6.5–8.1)	7.2 (6.5–8.3)	<0.001
Hemoglobin (g/dL)	13.6 (12.2–14.8)	13.6 (12.3–14.9)	13.2 (11.8–14.5)	<0.001
Protein (mg/dL)	7.2 (6.8–7.5)	7.2 (6.8–7.5)	7.1 (6.7–7.5)	<0.001
Albumin (g/dL)	4.3 (4.0–4.5)	4.3 (4.0–4.5)	4.2 (3.8–4.4)	<0.001
Cholesterol (mg/dL)	168 (142–196)	168 (142–196)	168 (142–196)	0.33
ACR (mg/g)	14.0 (8.0–39.0)	13.0 (7.0–31.0)	38.0 (12.0–199.0)	<0.001
Medication prescription (%)				
Metformin	62.7	63.8	55.5	<0.001
Dipeptidyl peptidase-4 inhibitor	28.8	29.9	21.6	<0.001
Glucagon-like peptide-1 receptor agonist	0.9	0.9	0.5	0.006
Sodium-glucose cotransporter-2 inhibitor	4.2	4.7	1.2	<0.001
Secretagogues	41.1	40.3	46.3	<0.001
Thiazolidinedione	5.4	5.1	7.5	<0.001
Insulin	27.7	26.7	34.6	<0.001
Calcium channel blocker	20.3	19.1	28.4	<0.001
ACEi or ARB	31.7	29.5	46.9	<0.001
β-Blocker	12.1	11.3	17.7	<0.001
Diuretics	14.4	13.1	22.9	<0.001
Kidney biopsy (%)	0.5	0.02	3.8	<0.001

Data are expressed as number only, mean ± standard deviation, percentage only, or median (interquartile range).

ACEi, angiotensin-converting enzyme inhibitor; ACR, random urine albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate.

sistently low ACR levels (Fig. 2D). The 2-year and 5-year risks of progression to ESKD increased over time, whereas the degree of increase was more pronounced in the referral group than in the non-referral group (Fig. 2E, F). This change was prominent during the first 5-year period, where it accelerated more rapidly than it did in the subsequent years.

Treatment effect of referral to nephrologists

We analyzed the treatment effect of referral to nephrologists based on the slope of the eGFRs. The DiD model was applied after adjusting for variables, such as age, sex, body mass index, eGFR, ACR, hemoglobin A1c, serum albumin, and comorbidities. Accordingly, ATTs were estimated over time, with the overall ATT for the entire period being 5.8 mL/min/1.73 m² per year (95% confidence interval [CI], 4.8–6.8 mL/min/1.73 m² per year). The ATT after referral to

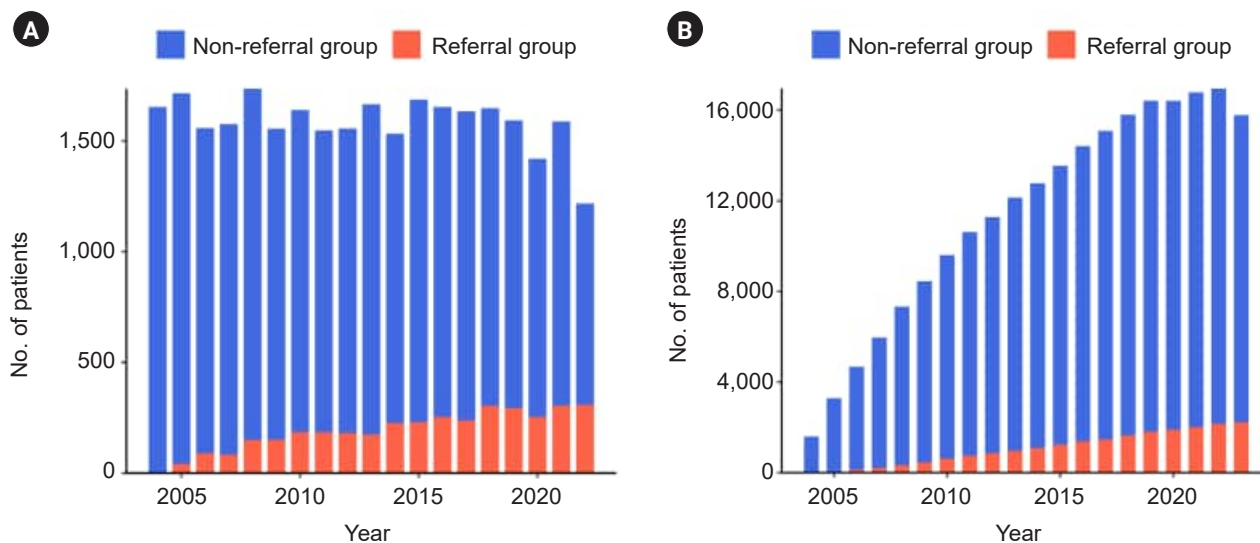


Figure 1. Trends in the number of patients over time and by referral status. (A) The number of new patients visiting the diabetes clinic each calendar year. (B) The number of patients followed up in the diabetes clinic or the department of nephrology each calendar year.

nephrologists remained consistently greater than zero, indicating a beneficial effect of referral on preserving kidney function (Fig. 3). The estimated confidence intervals of ATT remained above zero for \bar{M} values up to 0.4 (Supplementary Fig. 2, available online). The deviation from parallel trends after referral was no more than 0.4 times the maximum deviation observed before referral. These results indicate that the DiD model was reliable after the basic assumption was considered.

Given that ACR is also an indicator of kidney status, we performed a DiD analysis on ACR changes. However, the results were not statistically significant (ATT value, 0.02 mg/g; 95% CI, -0.537 to 0.577 mg/g), suggesting that nephrology referral did not lead to substantial improvement in albuminuria. Additionally, we conducted a DiD analysis on hospitalization rates (events per year) and found that nephrology referral significantly reduced the hospitalization rate, with an ATT of -0.247 events per year (95% CI, -0.376 to -0.117) (Supplementary Fig. 3, available online). However, when limited to cardiovascular events, the ATT value was not significant (-0.003 events per year; 95% CI, -0.048 to 0.041).

We conducted a subgroup analysis to explore how ATT values for referrals varied according to the risk of CKD progression. The CKD risk categories are defined based on the KDIGO guidelines [5], using a combination of glomer-

ular filtration rate and albuminuria levels to assess CKD risk, classifying patients into low, moderate, high, and very high-risk groups. The referral group was categorized into groups at low risk ($n = 928$), moderate risk ($n = 778$), high risk ($n = 901$), and very high risk ($n = 1,278$) at the time of referral to nephrologists (Supplementary Fig. 4, available online). As the risk level increased, the ATT values also increased: 0.9 mL/min/1.73 m² per year (95% CI, 0.1–1.8) for low risk, 3.5 mL/min/1.73 m² per year (95% CI, 2.4–4.6) for moderate risk, 4.8 mL/min/1.73 m² per year (95% CI, 2.9–6.8) for high risk, and 10.4 mL/min/1.73 m² per year (95% CI, 8.6–12.3) for very high risk. Subgroup analysis was performed according to the time point at which the 2-year ESKD risk reached 3%. The patients who were referred earlier and later than this time point were categorized into the early referral group ($n = 2,553$) and the late referral group ($n = 1,332$), respectively. The ATT values for the early and late referral groups were 3.1 mL/min/1.73 m² per year (95% CI, 2.4–3.7) and 9.9 mL/min/1.73 m² per year (95% CI, 8.1–11.8), respectively. These results suggest that referral has a positive effect on kidney function regardless of whether it is early or late, with the effect appearing to align with higher CKD progression risk.

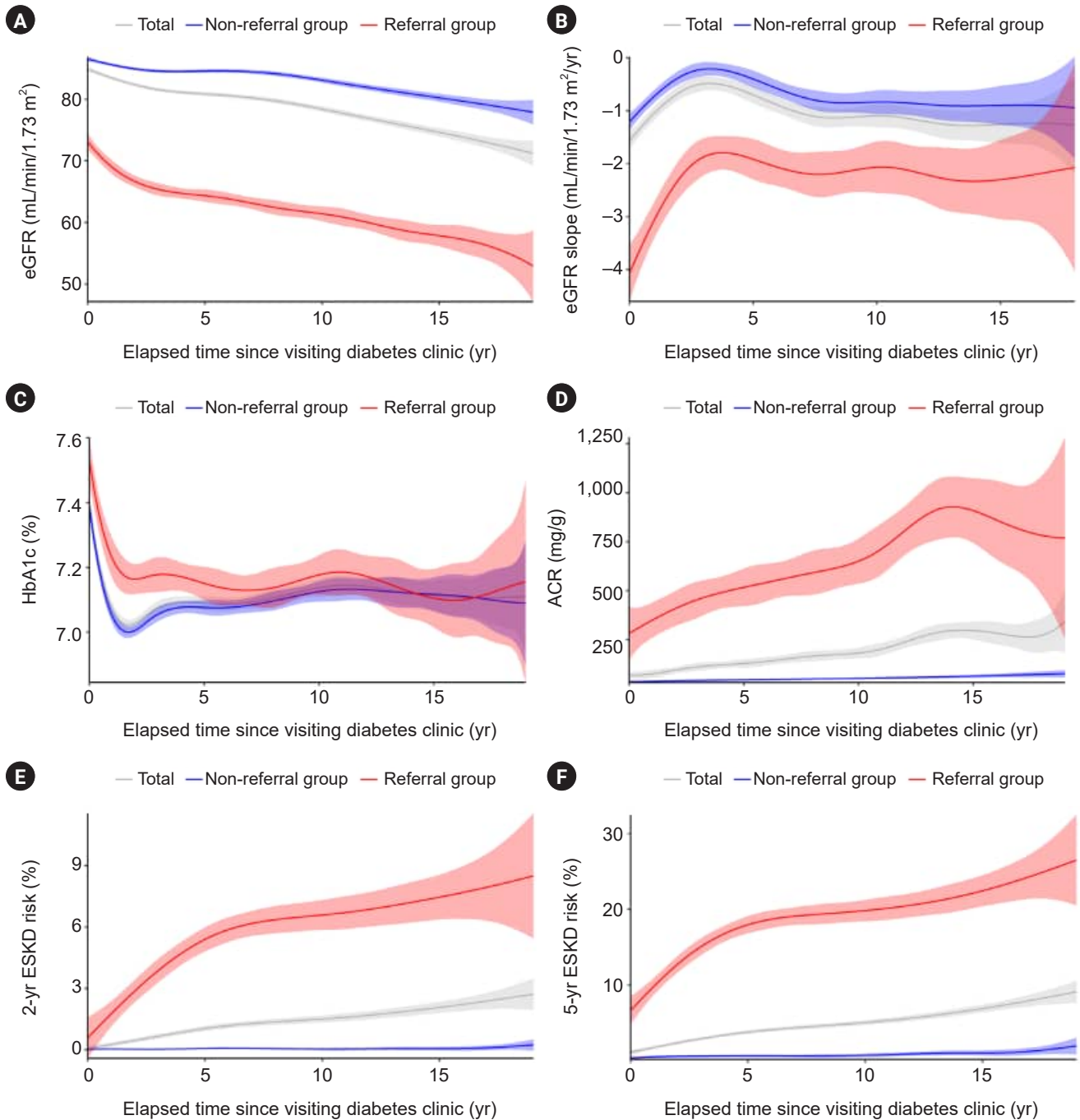


Figure 2. Trends in laboratory findings from the initial visit to the diabetes clinic. (A) Estimated glomerular filtration rate (eGFR). (B) Slope of the eGFR. (C) Hemoglobin A1c (HbA1c). (D) Random urine albumin-to-creatinine ratio (ACR). (E) Two-year and (F) 5-year risk of progression to end-stage kidney disease (ESKD).

Trends in medication prescriptions over time

The median, maximum, and minimum prescription rates of medications per calendar year are described in [Sup-](#)

[plementary Table 2](#) (available online). Metformin was the most commonly prescribed antidiabetic medication, with a median prescription rate of 56.8% (IQR, 48.7%–60.6%), followed by secretagogues at 31.6% (IQR, 28.6%–43.1%).

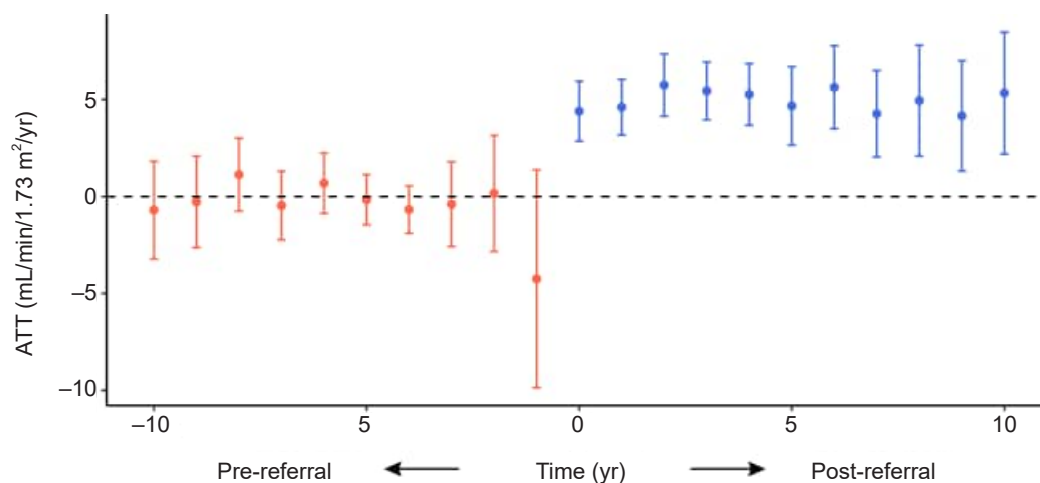


Figure 3. Changes in the average treatment effect of the treatment group (ATT) based on the relative time to referral according to the difference-in-differences model.

The ATT was estimated as the annual slope of estimated glomerular rates.

Among antihypertensive medications, RAS blockers were the most frequently prescribed, with a median rate of 34.6% (IQR, 34.0%–35.8%), followed by calcium channel blockers at 20.4% (IQR, 19.8%–20.9%) and diuretics at 12.8% (IQR, 10.8%–15.5%).

To visualize differences in prescription rates between the referral and non-referral groups, we rescaled the minimum and maximum prescription rates for each medication to a range between 0 and 1 and presented the results as a heatmap (Fig. 4A). Over the years, the prescription rates of medications, such as metformin, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter-2 inhibitors, increased, while the prescription of nonsteroidal anti-inflammatory drugs decreased over time.

To compare the prescription patterns between the referral and non-referral groups, we accounted for temporal and patient-specific differences with a negative binomial regression. The multivariate-adjusted coefficients are shown as a heatmap (Fig. 4B). The prescription trends for glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors initially showed a tendency toward fewer prescriptions in the referral group, but this reversed over time, resulting in more prescriptions in the referral group by 2023. Antihypertensive medications, such as RAS blockers, were increasingly prescribed in the referral group over time. The prescription of acetaminophen or

tramadol was more common, while nonsteroidal anti-inflammatory drugs were less frequently prescribed in the referral group than in the non-referral group. Febuxostat and allopurinol were frequently prescribed in the referral group for most of the study period. Fibrates were prescribed less frequently in the referral group than in the non-referral group. Overall, prescription patterns for certain medications changed following referral to nephrologists.

Differences in kidney biopsies between the referral and non-referral groups

Among all patients, 152 kidney biopsies (0.5%) were performed. Kidney biopsy was performed more frequently in the referral group than in the non-referral group, with 148 (3.8%) and four cases (0.02%), respectively. Among the biopsied patients, 80 (52.6%) were diagnosed with diabetic nephropathy, 52 (34.2%) with glomerulonephritis, 15 (9.9%) with tubular disorders, two (1.3%) with thrombotic microangiopathy, and three (2.0%) with no specific lesions on histology (Fig. 5). For the four patients in the non-referral group who underwent kidney biopsy, the results revealed glomerulonephritis.

Within the glomerulonephritis category, the most common diagnosis was immunoglobulin A nephropathy in 17 patients, followed by membranous nephropathy in nine patients. Among the patients with tubular disorders, 11 had

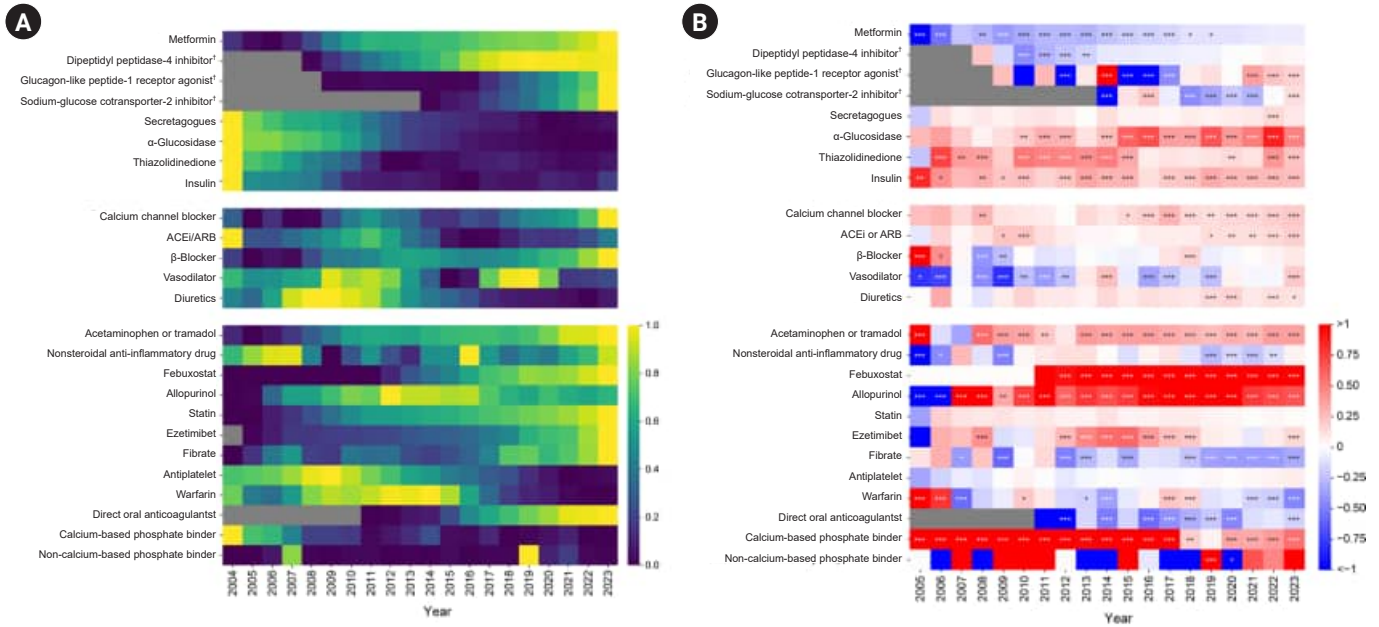


Figure 4. Heatmap showing the medications used according to calendar year. (A) Scaled prescription ratios according to calendar year. The prescription ratio represents the proportion of days within a year that a particular medication was prescribed. Each prescription ratio is scaled between a minimum value of 0 and a maximum value of 1 across the entire period, visualizing changes in prescriptions over time. (B) The differences in the patterns of medication prescription between the referral and non-referral groups. The negative binomial regression coefficients of medication prescription days according to the referral are visualized as natural logarithms. Values of >0 indicate more prescriptions (a coefficient of 1 means 2.718 times more prescriptions) in the referral group than in the non-referral group. The analysis was adjusted for age, sex, estimated glomerular filtration rate, random urine albumin-to-creatinine ratio, hemoglobin A1c, and comorbidities. Bonferroni correction was applied to p-values for multiple testing. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. †Periods when these drugs were not introduced in the hospital are represented in gray. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

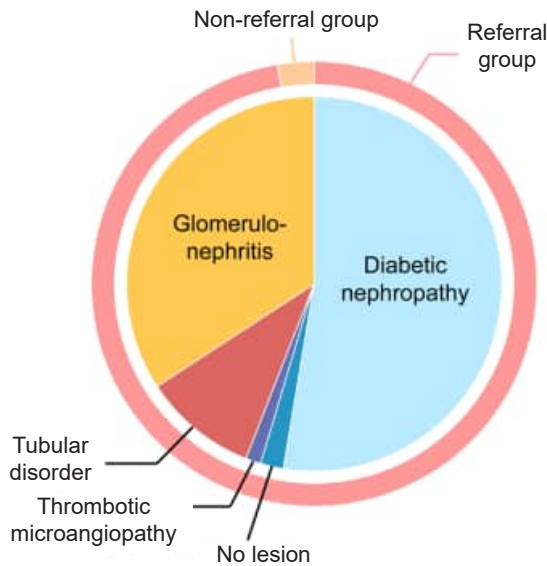


Figure 5. Histopathologic results in the referral and non-referral groups.

chronic tubulointerstitial nephritis, three had acute tubulointerstitial nephritis, and one had acute tubular necrosis. For patients who underwent kidney biopsy, only one patient developed post-biopsy bleeding requiring transarterial embolization. The findings highlight the significant diagnostic yield of kidney biopsies, predominantly in the referral group, emphasizing the role of nephrologists in addressing complex kidney conditions or other combined disorders in patients with type 2 DM.

Discussion

Appropriate referrals and subsequent discussions between clinicians can help improve patient outcomes. However, direct evidence to show that referral to nephrologists is beneficial for type 2 diabetic patients is lacking. The DiD model, adjusting for baseline differences, demonstrated

that referral to nephrologists was associated with a low rate of decline in yearly eGFR values. Compared with the non-referral group, the rate of prescription of renoprotective hypoglycemic and antihypertensive medications increased, whereas the rate of prescription of medications that may negatively affect kidney function decreased. Additionally, kidney biopsies were frequently performed in the referral group, which revealed kidney diseases other than diabetic nephropathy. These factors, such as differences in medication use and biopsy frequency, might affect the treatment approach. These findings underscore the importance of referral to nephrologists to enhance kidney care for type 2 diabetic patients with CKD.

Several studies have shown that the involvement of nephrologists in multidisciplinary care significantly improves outcomes in patients with kidney diseases [12]. These studies employed statistical methods to compare eGFR values before and after the referrals [11,20] or between the referral and the non-referral groups [21,22]. Randomized controlled trials on referrals have not been conducted, partially because conducting such trials may not be feasible. Accordingly, we employed a causal inference model to estimate and validate the effect of nephrology referral. The estimated ATT of referral on the eGFR slope was 5.8 mL/min/1.73 m² per year after accounting for confounding variables and biases. These findings support previous study results, which revealed a difference in the eGFR slopes before and after referral ranging from 1 to 5 mL/min/1.73 m² per year [11,20]. We also found that nephrology referral reduces hospitalizations, thereby potentially improving patients' overall health outcomes and reducing the burden on healthcare resources. The present model further revealed that the beneficial effect of referral was evident even in patients with preserved kidney function, suggesting that early referral may be the optimal timing for some patients. Although the nephrology referral did not show a beneficial effect on ACR reduction, this result may reflect the preexisting use of RAS inhibitors by diabetologists prior to referral, which could have already optimized ACR levels, thereby limiting the potential for further improvement after referral.

The medication usage trends differed before and after referrals. Although guidelines for managing diabetic patients have been established, these guidelines emphasize the setting of individual targets. Medication choices may

vary depending on the clinician's perspective. The use of hypoglycemic medications known for renoprotective effects, such as sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists [23–26], markedly increased over time. Furthermore, the use of antihypertensive medication became more aggressive over time, with a notable difference between the referral and non-referral groups. The findings underscore the need to establish individual treatment targets and select suitable medications through referrals and discussions between clinicians. The differences in the use of other medications that can provoke kidney injuries are noteworthy. Despite the well-known nephrotoxicity of nonsteroidal anti-inflammatory drugs [27], a significant reduction in their use was observed after referral, indicating increased awareness among nephrologists. Similarly, the high usage rates of allopurinol and febuxostat for uric acid control suggest a focused interest from nephrologists and may contribute to kidney function preservation [28]. With respect to lipid-lowering agents, a trend toward less frequent use of fibrates was observed, likely due to concerns about the initial increase in creatinine levels associated with their use [29,30]. These patterns indicate that concerted efforts were undertaken to preserve kidney function in the referral group through careful medication selection.

Almost half of the patients who underwent kidney biopsy were diagnosed with other kidney diseases, not diabetic nephropathy. This finding is consistent with a previous study, which reported a 64% rate of nondiabetic etiologies [31]. This significant proportion emphasizes the importance of distinguishing between diabetic nephropathy and other kidney diseases because of their unique pathophysiology, which sometimes requires different treatment approaches. Histopathologic confirmation is especially crucial in DKD patients with unusual or exceptional clinical signs, as biopsy complications are very rare, occurring in less than 0.5% of patients [32]. Although a small proportion of referred patients underwent kidney biopsy, the presence of patients with nondiabetic kidney diseases underscores the diagnostic value of nephrology referral in identifying and managing these cases.

Despite the strengths of our study, certain limitations must be acknowledged. Although we conducted a causal analysis by adjusting for multiple variables, we did not establish the optimum timing of referral. To determine the

precise timing, randomized controlled trials or meta-analyses on various criteria are needed. Because this study was conducted in a single center within the Korean medical system, factors such as physician preferences, insurance coverage, and lack of data on medications prescribed at other hospitals may limit the generalizability of our findings to other settings or healthcare systems. Additionally, due to the limitations of our outpatient data collection nature, we were unable to distinguish between acute kidney injury and CKD or obtain patient outcomes such as mortality and dialysis initiation, and serum creatinine was measured using different methods over time, with the Jaffe method used before 2009 and the enzymatic method thereafter.

In conclusion, the present study demonstrated that referral to nephrologists is associated with the slow progression of kidney dysfunction in patients with type 2 DM. Although a causal inference model was used for the study, the results provide evidence that appropriate referrals and discussions between clinicians should be applied to this patient subset, particularly those with kidney dysfunction or potential for worse outcomes. Clinical trials involving DKD patients should consider or incorporate these findings, as the presence of referrals may affect overall outcomes.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Data sharing statement

The datasets generated during and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

Conceptualization, Project administration, Supervision, Funding acquisition: SSH
Data curation: SB

Formal analysis, Investigation, Software: DY

Methodology: DY, SSH

Writing—original draft: DY, SSH

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References

1. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (CDC). Chronic kidney disease in the United States, 2021. U.S. Department of Health and Human Services, CDC; 2021.
2. Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol* 2013;24:302–308.
3. de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care* 2022;45:3075–3090.
4. ElSayed NA, Aleppo G, Aroda VR, et al. 11. Chronic kidney disease and risk management: standards of care in diabetes-2023. *Diabetes Care* 2023;46(Suppl 1):S191–S202.
5. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2024;105(4S):S117–S314.
6. Whelton PK, Carey RM, Mancia G, Kreutz R, Bundy JD, Williams B. Harmonization of the American College of Cardiology/American Heart Association and European Society of Cardiology/European Society of Hypertension Blood Pressure/Hypertension Guidelines. *Eur Heart J* 2022;43:3302–3311.
7. Williams DM, Jones H, Stephens JW. Personalized type 2 diabetes management: an update on recent advances and recom-

- mendations. *Diabetes Metab Syndr Obes* 2022;15:281–295.
8. Mancia G, Kreutz R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens* 2023;41:1874–2071.
 9. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;71:e127–e248.
 10. Boulware LE, Troll MU, Jaar BG, Myers DI, Powe NR. Identification and referral of patients with progressive CKD: a national study. *Am J Kidney Dis* 2006;48:192–204.
 11. Jones C, Roderick P, Harris S, Rogerson M. Decline in kidney function before and after nephrology referral and the effect on survival in moderate to advanced chronic kidney disease. *Nephrol Dial Transplant* 2006;21:2133–2143.
 12. Wavamunno MD, Harris DC. The need for early nephrology referral. *Kidney Int Suppl* 2005;(94):S128–S132.
 13. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–612.
 14. Weaver RG, James MT, Ravani P, et al. Estimating urine albumin-to-creatinine ratio from protein-to-creatinine ratio: development of equations using same-day measurements. *J Am Soc Nephrol* 2020;31:591–601.
 15. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *JAMA* 2016;315:164–174.
 16. Callaway B, Sant’Anna PH. Difference-in-differences with multiple time periods. *J Econom* 2021;225:200–230.
 17. Duan KI, Obara E, Wong ES, et al. Supplemental oxygen use, outcomes, and spending in patients with COPD in the medicare competitive bidding program. *JAMA Intern Med* 2024;184:1457–1465.
 18. Kannan S, Bruch JD, Song Z. Changes in hospital adverse events and patient outcomes associated with private equity acquisition. *JAMA* 2023;330:2365–2375.
 19. Rambachan A, Roth J. A more credible approach to parallel trends. *Rev Econ Stud* 2023;90:2555–2591.
 20. Ide A, Ota K, Murashima M, et al. Nephrology referral slows the progression of chronic kidney disease, especially among patients with anaemia, diabetes mellitus, or hypoalbuminemia: a single-centre, retrospective cohort study. *Nephrology (Carlton)* 2024;29:510–518.
 21. Duggal V, Montez-Rath ME, Thomas IC, Goldstein MK, Tamura MK. Nephrology referral based on laboratory values, kidney failure risk, or both: a study using veterans affairs health system data. *Am J Kidney Dis* 2022;79:347–353.
 22. Siew ED, Peterson JF, Eden SK, et al. Outpatient nephrology referral rates after acute kidney injury. *J Am Soc Nephrol* 2012;23:305–312.
 23. Alicic RZ, Johnson EJ, Tuttle KR. SGLT2 inhibition for the prevention and treatment of diabetic kidney disease: a review. *Am J Kidney Dis* 2018;72:267–277.
 24. Dieter BP, Alicic RZ, Tuttle KR. GLP-1 receptor agonists in diabetic kidney disease: from the patient-side to the bench-side. *Am J Physiol Renal Physiol* 2018;315:F1519–F1525.
 25. Heerspink HJ, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;383:1436–1446.
 26. Shaman AM, Bain SC, Bakris GL, et al. Effect of the glucagon-like peptide-1 receptor agonists semaglutide and liraglutide on kidney outcomes in patients with type 2 diabetes: pooled analysis of SUSTAIN 6 and LEADER. *Circulation* 2022;145:575–585.
 27. Baker M, Perazella MA. NSAIDs in CKD: are they safe? *Am J Kidney Dis* 2020;76:546–557.
 28. Bose B, Badve SV, Hiremath SS, et al. Effects of uric acid-lowering therapy on renal outcomes: a systematic review and meta-analysis. *Nephrol Dial Transplant* 2014;29:406–413.
 29. ACCORD Study Group; Ginsberg HN, Elam MB, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1563–1574.
 30. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005;366:1849–1861.
 31. Sharma SG, Bomback AS, Radhakrishnan J, et al. The modern spectrum of renal biopsy findings in patients with diabetes. *Clin J Am Soc Nephrol* 2013;8:1718–1724.
 32. Luciano RL, Moeckel GW. Update on the native kidney biopsy: core curriculum 2019. *Am J Kidney Dis* 2019;73:404–415.