Progression of chronic kidney disease in individuals with and without type 2 diabetes with mortality as a competing risk

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BACKGROUND

- The Kidney Disease: Improving Global Outcomes (KDIGO) heat map is used for characterizing chronic kidney disease (CKD) risk and severity based on estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR) measurements and is an accepted tool for early CKD recognition and progression.[1]
  - KDIGO CKD staging is limited by the omission of diabetes diagnoses and inability to project timing of progression.[1]
- Real-world data on CKD progression in individuals with or without type 2 diabetes (T2D) is limited, particularly regarding the impact of acute events and predicting future risk while acknowledging mortality as a competing risk.

OBJECTIVE

- To identify and describe CKD progression patterns in individuals with CKD and evaluate the impact of prespecified acute events (i.e., congestive heart failure, acute kidney injury, myocardial infarction, and cerebrovascular accident) on the risk of CKD progression.

METHODS

Study design

- This was a 4-part, retrospective cohort study using Cleveland Clinic electronic health record data to analyze adult individuals from 12/1/11 to 8/1/24 with a CKD diagnosis, defined as 2 impaired eGFR (ie, <60 mL/min/1.73 m^2) or UACR (i.e., ≥30 mg/g) measurements taken 90 to 365 days apart. Eligible individuals were assigned an initial risk category (moderate or high) according to KDIGO heat map criteria.
- Individuals were followed from the index date (earliest record of 2 consecutive and consistent risk categories) to CKD progression (first transition from initial risk to any higher risk category), end of data availability, or death.
- Individuals were further compared based on baseline (6-month period before index date) T2D status (defined using the modified version of the EMERGE algorithm[2] based on the presence of diagnostic International Classification of Diseases [ICD] codes, abnormal glucose levels, T2D medication use).

Statistical analysis

- Cox proportional hazards regression models were used to analyze CKD progression, and time-to-event analyses were used to capture the impact of acute events.
- A multivariable predictive time-to-event model examined the effects of acute events on CKD progression considering T2D status and initial KDIGO risk category with death as a competing risk; predictors were created based on the presence of albuminuria and rapidly declining eGFR.

RESULTS

Population and baseline characteristics

- In total, 29,985 individuals were analyzed and divided into 2 cohorts (initial moderate risk: n=20,501; initial high risk: n=9,484).
- Demographics and baseline characteristics for the study population are described in **Table 1**.

Table 1. Baseline demographics stratified by initial CKD risk and T2D diagnosis

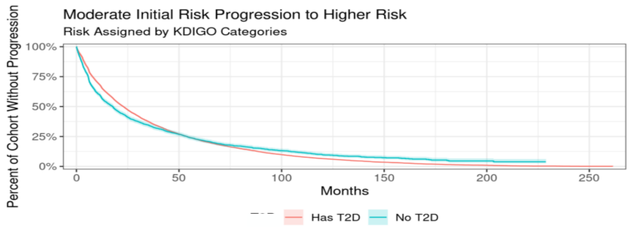
	Initial moderate risk			Initial high risk		
	CKD before T2D n=2,434	T2D before CKD n=15,581	No T2D n=2,486	CKD before T2D n=1,614	T2D before CKD n=6,268	No T2D n=1,602
Age at index date, years, median (IQR)	70 (64, 76)	70 (63, 77)	72 (65, 79)	72 (65, 79)	71 (63, 79)	75 (66, 82)
Female, n (%)	1,184 (49.0)	7,537 (48.0)	1,256 (51.0)	825 (51.0)	3,087 (49.0)	788 (49.0)
Died, n (%)	607 (25.0)	5,791 (37.0)	883 (36.0)	570 (35.0)	3,112 (50.0)	685 (43.0)
Race, n (%)						
American Indian or Alaska Native	1 (<0.1)	16 (0.1)	0 (0.0)	2 (0.1)	4 (0.1)	3 (0.2)
Asian	25 (1.0)	186 (1.2)	19 (0.8)	22 (1.4)	74 (1.2)	18 (1.1)
Black	405 (17.0)	3,070 (20.0)	372 (15.0)	297 (18.0)	1,447 (23.0)	290 (18.0)
Caucasian	1,868 (77.0)	11,582 (74.0)	2,006 (81.0)	1,188 (73.6)	4,437 (71.0)	1,232 (77.0)
Native Hawaiian or other Pacific Islander	1 (<0.1)	2 (<0.1)	0 (0.0)	1 (0.1)	2 (<0.1)	0 (0.0)
Other or not stated	134 (6.0)	725 (5.0)	89 (3.6)	104 (6.4)	304 (4.9)	59 (3.7)
Clinical characteristics, median (IQR)						
Systolic BP, mmHg	130 (120, 141)	130 (118, 141)	130 (118, 142)	130 (120, 144)	131 (120, 145)	130 (118, 142)
Diastolic BP, mmHg	71 (64, 80)	70 (61, 78)	71 (63, 80)	70 (62, 79)	70 (60, 78)	70 (62, 79)
HDL, mg/dL	46 (37, 55)	44 (36, 55)	51 (42, 64)	44 (36, 55)	43 (35, 54)	51 (41, 63)
LDL, mg/dL	72 (55, 93)	69 (52, 90)	82 (62, 104)	71 (53, 93)	69 (51, 90)	80 (61, 104)
Triglyceride, mg/dL	119 (86, 165)	116 (83, 166)	98 (73, 136)	121 (85, 168)	115 (81, 166)	99 (74, 138)
Total cholesterol, mg/dL	146 (124, 174)	143 (120, 170)	158 (133, 187)	146 (122, 172)	141 (118, 170)	158 (132, 187)
HbA1c, %	6.5 (6.0, 7.3)	6.9 (6.2, 7.8)	5.6 (5.4, 5.9)	6.5 (6.0, 7.4)	6.8 (6.1, 7.7)	5.6 (5.4, 5.9)
Potassium, mEq/L	4.3 (4.0, 4.7)	4.4 (4.0, 4.7)	4.3 (4.0, 4.6)	4.4 (4.0, 4.7)	4.4 (4.1, 4.8)	4.4 (4.0, 4.7)
eGFR, mL/min/1.73 m²	52 (42, 63)	51 (39, 65)	50 (42, 61)	40 (30, 50)	38 (26, 50)	38 (29, 49)
UACR, mg/g	27 (5, 85)	50 (14, 173)	17 (0.1, 62)	62 (20, 243)	105 (29, 476)	41 (11, 153)
Medication prescriptions by class, n (%)						
ACEis/ARBs	918 (38.0)	11,727 (75.0)	1,284 (52.0)	519 (32.0)	4,644 (74.0)	823 (51.0)
Antiplatelets	690 (28.0)	6,895 (44.0)	800 (32.0)	451 (28.0)	2,951 (47.0)	525 (33.0)
GLP-1RAs	3 (0.1)	1,021 (6.6)	1 (<0.1)	7 (0.4)	302 (4.8)	1 (0.1)
MRAs	98 (4.0)	1,022 (6.6)	107 (4.3)	65 (4.0)	416 (6.6)	78 (4.9)
SGLT2is	3 (0.1)	383 (2.5)	0 (0.0)	0 (0.0)	82 (1.3)	0 (0.0)
Statins	879 (36.0)	11,194 (72.0)	1,176 (47.0)	529 (33.0)	4,408 (70.0)	687 (43.0)

Key: ACEi – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker; BP – blood pressure; CKD – chronic kidney disease; eGFR – estimated glomerular filtration rate; GLP-1RA – glucagon-like peptide-1 receptor agonist; HbA1c – hemoglobin A1c; HDL – high-density lipoprotein; IQR – interquartile range; LDL – low-density lipoprotein; MRA – mineralocorticoid receptor antagonist; SGLT2i – sodium glucose cotransporter-2 inhibitor; T2D – type 2 diabetes; UACR – urine albumin-to-creatinine ratio.

CKD progression based on initial risk and order of CKD diagnosis

- Individuals with initial moderate risk CKD (n=20,501) had a similar likelihood of CKD progression, irrespective of T2D diagnosis (*P*=0.30) (**Figure 1**).
  - Individuals with a T2D diagnosis preceding their CKD diagnosis were significantly less likely to experience CKD progression compared to individuals who were diagnosed with CKD prior to T2D (*P*<0.0001).
  - The median time to CKD progression was longer for individuals with preceding T2D diagnoses (24.5 months [IQR: 23.9, 25.2]) vs those diagnosed with CKD prior to T2D (13.9 months [IQR: 12.9, 14.9]).
- Individuals with initial high risk (n=9,484) CKD also had a similar likelihood of progression, irrespective of T2D diagnosis, until month 25 when individuals with T2D were more likely to progress than individuals without T2D (*P*=0.003) (**Figure 2**).
  - Individuals with a T2D diagnosis preceding their CKD diagnosis were less likely to progress compared to individuals who were diagnosed with CKD prior to T2D (*P*<0.0001) and had a longer median time to CKD progression (18.9 [IQR: 18.2, 20.0] vs 12.2 [IQR: 11.3, 13.5] months, respectively).

Figure 1. CKD progression in individuals with initial moderate risk (individuals with T2D vs without T2D)



Key: CKD – chronic kidney disease; KDIGO – Kidney Disease: Improving Global Outcomes; T2D – type 2 diabetes.

Figure 2. CKD progression in individuals with initial high risk (individuals with T2D vs without T2D)

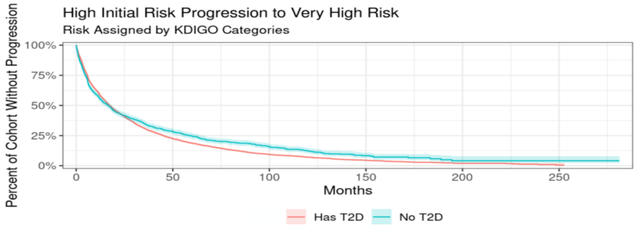


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Table 2. Effects of acute events on CKD progression

Acute events associated with progression for individuals with initial moderate risk						
Acute event	No T2D			T2D		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Any event	0.29	0.25, 0.35	<0.001	0.47	0.44, 0.50	<0.001
AKI	0.21	0.13, 0.34	<0.001	0.32	0.28, 0.37	<0.001
CHF	0.35	0.38, 0.43	<0.001	0.50	0.47, 0.55	<0.001
CVA	0.28	0.20, 0.39	<0.001	0.49	0.44, 0.54	<0.001
MI	0.13	0.05, 0.33	<0.001	0.45	0.38, 0.55	<0.001
Acute events associated with progression for individuals with initial high risk						
Acute event	No T2D			T2D		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Any event	0.29	0.23, 0.35	<0.001	0.40	0.37, 0.43	<0.001
AKI	0.16	0.09, 0.26	<0.001	0.27	0.22, 0.33	<0.001
CHF	0.36	0.28, 0.45	<0.001	0.44	0.39, 0.49	<0.001
CVA	0.27	0.17, 0.41	<0.001	0.40	0.34, 0.48	<0.001
MI	0.44	0.25, 0.77	0.004	0.47	0.38, 0.60	<0.001

Key: AKI – acute kidney injury; CHF – congestive heart failure; CI – confidence interval; CVA – cerebrovascular accident; HR – hazard ratio; MI – myocardial infarction; T2D – type 2 diabetes.

Occurrence of acute events based on initial CKD risk

- Regardless of T2D diagnosis, acute events were significantly associated with a reduced likelihood of CKD progression (all *P*<0.001) due to high mortality associated with acute events among all individuals included in the study (i.e., individuals with an acute event were more likely to die prior to progressing to the next CKD category) (**Table 2**).
- Occurrence of acute events in initial moderate risk individuals without T2D was 27.4%, 35.8% for individuals with T2D diagnosed before CKD, and 28.0% for individuals diagnosed with CKD before T2D.
- Occurrence of acute events in initial high risk individuals without T2D was 35.8%, 43.2% for individuals diagnosed with T2D before CKD, and 35.4% for individuals diagnosed with CKD before T2D.

Multivariable risk prediction model

- Incorporation of mortality as a competing factor minimized the association of acute events on CKD progression as individuals were more likely to experience mortality prior to progressing.
- Stratifying individuals by T2D and timing of T2D diagnosis relative to CKD improved model predictions.

STUDY LIMITATIONS

- Data source was a regional integrated delivery network, which may limit generalizability of findings to the broader population.
- The KDIGO heat map may not fully capture worsening kidney function in some individuals, especially those with incomplete or inaccurate UACR testing.

CONCLUSIONS

- **Individuals had a high risk of CKD progression, regardless of T2D diagnosis, but those with T2D and those diagnosed with CKD prior to T2D were at greater risk.**
- **Clinicians should prioritize and optimize goal-directed medical therapy for CVD and CKD risk reduction when treating individuals with CKD who have experienced an acute event to reduce mortality.**
- **Tailored approaches are warranted when managing individuals with CKD based on T2D status and chronological order of CKD and T2D diagnoses.**

REFERENCES

1. KDIGO. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. 2024. **2.** Kho AN, et al. *JAMIA*. 2012;19(2):212-218.

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