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Clinical Research Article

Development and Validation of a Prediction Model for Incident Hypothyroidism in a National Chronic Kidney Disease Cohort

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Abstract

Context: Hypothyroidism is a common yet under-recognized condition in patients with chronic kidney disease (CKD), which may lead to end-organ complications if left untreated.

Objective: We developed a prediction tool to identify CKD patients at risk for incident hypothyroidism.

Methods: Among 15 642 patients with stages 4 to 5 CKD without evidence of pre-existing thyroid disease, we developed and validated a risk prediction tool for the development of incident hypothyroidism (defined as thyrotropin [TSH] > 5.0 mIU/L) using the Optum Labs Data Warehouse, which contains de-identified administrative claims, including medical and pharmacy claims and enrollment records for commercial and Medicare Advantage enrollees as well as electronic health record data. Patients were divided into a two-thirds development set and a one-third validation set. Prediction models were developed using Cox models to estimate probability of incident hypothyroidism.

Results: There were 1650 (11%) cases of incident hypothyroidism during a median follow-up of 3.4 years. Characteristics associated with hypothyroidism included older age, White race, higher body mass index, low serum albumin, higher baseline TSH, hypertension, congestive heart failure, exposure to iodinated contrast via angiogram or computed tomography scan, and amiodarone use. Model discrimination was good with similar C-statistics in the development and validation datasets: 0.77 (95% CI 0.75-0.78) and 0.76 (95% CI 0.74-0.78), respectively. Model goodness-of-fit tests showed adequate fit in the overall cohort ($P = .47$) as well as in a subcohort of patients with stage 5 CKD ($P = .33$).

Conclusion: In a national cohort of CKD patients, we developed a clinical prediction tool identifying those at risk for incident hypothyroidism to inform prioritized screening, monitoring, and treatment in this population.

Key Words: prediction scores, thyroid status, hypothyroidism, thyrotropin, chronic kidney disease

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; CT, computed tomography; eGFR, estimated glomerular filtration rate; FT4, free thyroxine; GOF, goodness-of-fit; EHR, electronic health record; IQR, interquartile range; PS, prognostic score; TSH, thyrotropin.

Patients with chronic kidney disease (CKD) have a disproportionately higher prevalence of hypothyroidism compared with their non-CKD counterparts (ie, 25% vs 5%, respectively) (1-4). Early or subclinical hypothyroidism is defined as an elevated thyrotropin [TSH] and a free thyroxine (FT4) measurement in the reference range and overt hypothyroidism when the FT4 falls below the reference range. While thyroid dysfunction is common in the general population (ie, 20 million US adults affected (5)), this endocrine disorder, both subclinical and overt, is substantially more prevalent in those with kidney disease (1-4). For example, data from the National Health and Nutritional Examination Survey (NHANES) have shown an increasingly higher prevalence of hypothyroidism with incrementally worse kidney function (ie, 5%, 11%, 20%, and 23% of participants with estimated glomerular filtration rates [eGFRs] ≥90, 60-89, 45-59, and <45 mL/min/1.73 m^2, respectively) (6). In the largest cohort examined to date, among 461 607 US veterans with stages 3 to 5 CKD who underwent simultaneous serum TSH and creatinine testing, each 10 mL/min/1.73 m^2 decrement in eGFR was associated with an 18% higher risk of hypothyroidism (4).

Thyroid hormone has actions in nearly all tissues, and, if left untreated, hypothyroidism may lead to multiple end-organ

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sequelae, including cardiovascular, reproductive, hematologic, and neuropsychiatric complications (2, 3, 7-9). While the adverse effects of thyroid dysfunction across the spectrum of subclinical and overt hypothyroidism have been well described in the non-CKD population (10-14), a growing body of evidence has demonstrated the adverse impact of hypothyroidism on health-related quality of life (15), cardiovascular health (16-20), kidney function (21-24), and survival of patients with CKD (25-30). Given the vast number of CKD patients (31), heterogeneity of potential risk factors for thyroid dysfunction (ie, underlying socio-demographics (5, 32, 33), exposure to iodinated contrast (34-36), obesity (37, 38), etc.), and paucity of screening recommendations in this population, there is compelling need for clinical tools that can identify which CKD patients are at high risk of developing hypothyroidism and its ensuing complications. A risk prediction model to predict hypothyroidism in CKD patients could inform prioritized screening, monitoring, and potential treatment for those who are at greatest risk for hypothyroidism.

Thus, to address this clinical gap, we sought to develop, rigorously validate, and calculate risk scores to predict the development of incident hypothyroidism among a large, national cohort of US adults with moderate to advanced kidney disease (ie, stages 4-5 CKD) from the Optum Labs Data Warehouse (39, 40). Given the availability of longitudinal patient-level information in this cohort, including detailed socio-demographic, comorbidity, procedure, medication, and laboratory result data, we hypothesized that clinical characteristics can be used to develop and validate prediction models that can identify which CKD patients will develop de novo thyroid disease over time.

Materials and Methods

Source Population

The study cohort was derived from patients from the Optum Labs Data Warehouse data source (39, 40). This study used de-identified administrative claims and electronic health record (EHR) data with linked laboratory results, socioeconomic status information, and death information from the Optum Labs Data Warehouse. The database contains longitudinal health information on enrollees and patients, representing a mixture of ages and geographical regions across the United States. The claims data in the Optum Labs Data Warehouse includes medical and pharmacy claims, laboratory results, and enrollment records for over 200 million commercial and Medicare Advantage enrollees. The EHR-derived data include a subset of EHR data that has been normalized and standardized into a single database.

Adults with moderate to advanced kidney dysfunction were included in the study cohort provided that they (1) had at least 1 eGFR value measured over the period of January 1, 2010, to December 31, 2018, that was <30 mL/min/1.73 m^2 (the first of which was designated as the index eGFR value), (2) were ≥18 years of age or older at the time of study entry (defined as the time of the index eGFR measurement), (3) had at least 1 TSH measurement within 1 year on or prior to the index eGFR measurement that was within the reference range of 0.5 to 5.0 mIU/L (designated as the baseline TSH), as well as 1 or more TSH measurement after the index eGFR (to ascertain the development of incident hypothyroidism), and (4) had both medical and pharmacy coverage as well as a minimum period of continuous enrollment of 1 year following the index eGFR measurement and a minimum period of continuous enrollment of 1 day before the index eGFR date for claims data only (Fig. S1 (41)). Patients were excluded if at study entry they (5) had evidence of a prior diagnosis of hypothyroidism or hyperthyroidism ascertained by diagnostic/procedural codes, (6) had prior use of thyroid hormone supplementation or antithyroid medication, (7) had prior radioactive iodine or surgical thyroid ablation, (8) were missing core socio-demographic variables (ie, age, sex), or (9) were missing core covariates in the prediction model (ie, FT4, eGFR slope, body mass index [BMI], or serum albumin) within 2 years on or before the index eGFR date. Criteria 3 and 5 through 7 were implemented to ensure consideration of incident thyroid functional disease. Since this study involved analysis of pre-existing, de-identified data, it was exempt from Institutional Review Board approval.

Ascertainment of Incident Hypothyroidism

We aimed to develop prediction models for the development of incident hypothyroidism among patients with stages 4 to 5 CKD. Given that all patients were required to have a baseline (first) TSH level within reference range (TSH 0.5-5.0 mIU/L), incident hypothyroid cases were defined as those whose subsequent (second) TSH level following the index eGFR were >5.0 mIU/L (7). This cutoff was selected based on increasing evidence showing that TSH levels exceeding 5.0 mIU/L and even below this threshold are associated with adverse outcomes, including higher mortality risk (25, 26, 28, 29), cardiovascular disease (20, 42), and patient-reported outcomes (15) in patients with moderate to advanced CKD. Since subsequent FT4 levels following the index eGFR were not available for the majority of patients, hypothyroidism was defined based on an elevation in serum TSH above the reference range. Follow-up started at the date of index eGFR (January 1, 2010) and continued until occurrence of the event of developing de novo hypothyroidism or until the end of the study period (March 31, 2019).

Socio-demographic, Comorbidity, Medication, and Laboratory Data

Optum Labs Data Warehouse data were used to determine patients' baseline socio-demographic information (ie, age, sex, etc.), comorbid conditions (ascertained from International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification diagnostic and procedural codes and Current Procedural Terminology codes), receipt of procedures (ie, angiogram and/or computed tomography [CT] scan with iodinated contrast using Current Procedural Terminology codes), laboratory data, and medications (39, 40). Optum Labs derives ethnicity by assigning 1 of 5 race/ethnicity codes: W (non-Hispanic White), B (non-Hispanic Black), H (Hispanic), A (Asian), and U (Unknown), based on data licensed from an external vendor who employs a rule-based system that uses names, geography, and other data to determine ethnicity. Charlson Comorbidity Index (CCI) scores were estimated using the Deyo modification for administrative datasets (43).

Statistical Methods

Baseline characteristics of the study cohort, including all predictors, were summarized as means ± SD or interquartile

range (IQR) for continuous variables and proportions for categorical variables.

Prediction models were developed for incident hypothyroidism using Cox proportional hazards models. The primary cohort was comprised 15 642 patients (Fig. S1 (41)) with complete data (ie, complete case analysis) and was randomly divided into a two-thirds training/development set ($n_d = 10\,428$) and a one-third test/validation set ($n_v = 5124$). This included patients in the "Other/Missing" category for race/ethnicity, which was not considered missing for prediction purposes. A secondary cohort included (n = 21 604) patients with missing BMI (23%) and missing albumin (8%) data. These missing covariates were addressed with imputation using mean values. Candidate predictors for incident hypothyroidism were a priori selected based on preliminary studies and the scientific literature according to clinical considerations for hypothyroidism (Table 1).

The final model was obtained using backward selection based on Akaike's information criterion, since it has better statistical properties in variable selection than selection procedures based on *P* value (44) and it avoids arbitrary and ineffective selection rules based on *P* values. To address potential model overfitting (optimism) and also for model calibration, we estimated a linear shrinkage factor γ ($0 \leq \gamma \leq 1$) based on 100 bootstrap samples of the development dataset. This estimated shrinkage factor, γ, was used to adjust the final Cox prediction models to correct for model overoptimism (44-47). We noted that overfitting, a concern typically in small datasets, results in regression coefficients being overestimated (overfitted) for prediction. For this reason, a shrinkage factor ($0 \leq \gamma \leq 1$) was estimated and applied to the risk score to shrink the regression coefficients so that predictions will more likely show better calibration on new patients (ie, validation data).

Furthermore, model calibration was assessed by a group-based goodness-of-fit (GOF) test developed for survival models (48). Briefly, the population was divided into deciles (groups) of the risk score, and the group-based GOF test provided an overall assessment of model calibration as well as for each group. Calibration plots for 1-year to 5-year event probabilities were also assessed.

Model predictive performance or discrimination were assessed using internal validation on the one-third validation dataset, not used in the model development process. Model discrimination was assessed using the index of concordance, or C-statistic, which accounts for censoring in time to event models (49) and is equivalent to the area under the receiver operating characteristic curve for binary outcomes (logistic regression) (46, 49).

Estimated probabilities of incident hypothyroidism at a given time *t* (ie, *t* year) were based on the final prediction model via the shrunken prognostic score (PS). That is, the shrunken PS is $PS^* = \gamma X\beta$, where β is collection of estimated coefficients corresponding to predictor variables set *X* in the final prediction model. The predicted survival at time *t* for a new patient can then be obtained as $S_0(t)^{\exp(PS^*)}$, where $S_0(t)$ is the baseline survival estimate from the final model. Analyses were performed in Stata version 13 and R version 3.6.1 using libraries RMS and SURVIVAL.

Results

Baseline Characteristics of the Study Cohort

Details of the overall cohort characteristics are provided in Table 1, along with the two-thirds and one-third randomly sampled development and internal validation/test cohorts, respectively. The primary overall study cohort consisted of 15 642 patients with stages 4 to 5 CKD (eGFR < 30 mL/min/1.73 m^2), among whom the mean ± SD age was 60 ± 18 years old; 67% were female; 67%, 19%, and 8% were non-Hispanic White, non-Hispanic Black, and Hispanic, respectively. Among these patients, the mean ± SD index (baseline) eGFR level was 16.8 ± 1.69 mL/min/1.73 m^2, with 59% and 41% of the cohort having index eGFR levels 15 to <30 mL/min/1.73 m^2 (stage 4 CKD) and <15 mL/min/1.73 m^2 (stage 5 CKD), respectively. In the overall cohort, 92% of patients had baseline CCI scores ≥2, and 42%, 66%, and 23% of patients had underlying diabetes, hypertension, and heart failure, respectively. Prior to the index eGFR date, 28% of patients received an angiogram and/or CT scan with iodinated contrast, and 6% were prescribed amiodarone. With respect to baseline body anthropometry and laboratory data, 41% of patients have BMI levels >30 kg/m^2; 67% of patients had serum albumin levels <4.0 g/dL; and the median (IQR) baseline TSH and FT4 levels were 1.70 (1.10, 2.58) mIU/L and 1.04 (0.90, 1.20) ng/dL, respectively.

Development of the Prediction Score for Incident Hypothyroidism

In the primary cohort, after a median (IQR) follow-up time of 3.4 (1.6, 5.3) years, we observed 1650 (10.6%) cases of the outcome of interest, incident hypothyroidism, during the study follow-up period. We developed the prediction risk score for incident hypothyroidism using the development set (n = 10 428, Table 1). The final prediction model coefficients are presented in Table 2. Patient characteristics including older age (≥60 years), non-Hispanic White race/ethnicity, higher baseline TSH, hypertension, congestive heart failure, receipt of angiogram and/or CT scan with iodinated contrast, and amiodarone use were each associated with higher risk of incident hypothyroidism, whereas non-Hispanic Black race/ethnicity, higher BMI (≤30 kg/m^2), and higher serum albumin (≥4.0 g/dL) were each associated with lower risk (effect estimates shown in Table 2). Among these predictors, higher baseline TSH level (by +Δ1.0 mIU/L: HR 2.04, 95% CI 1.95-2.15) and amiodarone use (HR 1.64, 95% CI 1.36-1.98) were associated with the largest increases in the hazard of incident hypothyroidism. Figure 1 displays the distribution of the risk score and the corresponding predicted 3-year event probabilities, where the predicted probabilities (percentage) at the 25th, 50th and 75th percentiles of the risk level for incident hypothyroidism are 3.2%, 6.0%, and 11.6%, respectively.

As a sensitivity analysis, a second prediction score was developed based on a secondary cohort (n = 21 604) that included patients with missing BMI (23%) and serum albumin (8%) data. Overall, the secondary prediction score, performance, and calibration results were similar to the main prediction score for incident hypothyroidism, and these results are provided elsewhere (Table S1 and Table S2 (41)). Also, with the exception of BMI, the standardized mean differences for all candidate predictor variables between the primary cohort (n = 15 642) and the excluded patients due to missing BMI and serum albumin (n = 5962) were small to moderate (all observed absolute standardized mean difference values <0.49, Table S3 (41)).

Table 1. Baseline characteristics of the primary study cohort (overall cohort), the two-thirds development set, and the one-third validation set

Candidate predictors	Total n (%)	Development n (%)	Validation n (%)
Total n	15 642	10 428	5214
Age, years	60 ± 18	60 ± 18	59 ± 18
Age <60	6887 (44)	4559 (44)	2328 (45)
Age ≥60	8755 (56)	5869 (56)	2886 (55)
Female	10 550 (67)	6988 (67)	3562 (68)
Male	5092 (33)	3440 (33)	1652 (32)
Race			
Non-Hispanic White	10 428 (67)	6986 (67)	3442 (66)
Non-Hispanic Black	3000 (19)	1978 (19)	1022 (20)
Hispanic	1281 (8)	849 (8)	432 (8)
Other/Missing	933 (6)	615 (6)	318 (6)
eGFR, mL/min/1.73 m^2	18 (9, 25)	18 (9, 25)	18 (9, 25)
eGFR <15	6472 (41)	4316 (41)	2156 (41)
eGFR 15-<30	9170 (59)	6112 (59)	3058 (59)
CCI	0 (0, 0)	0 (0, 0)	0 (0, 0)
CCI ≤2	14 427 (92)	9608 (92)	4819 (92)
CCI >2	1215 (8)	820 (8)	395 (8)
Diabetes	6494 (42)	4324 (41)	2170 (42)
Hypertension	10 365 (66)	6880 (66)	3485 (67)
Heart failure	3670 (23)	2461 (24)	1209 (23)
Receipt of contrast-enhanced angiogram or CT scan	4386 (28)	2918 (28)	1468 (28)
Amiodarone use	984 (6)	670 (6)	314 (6)
BMI, kg/m^2	28.1 (23.7, 33.9)	28.1 (23.7, 33.9)	28.3 (23.6, 33.9)
BMI ≤30	9274 (59)	6195 (59)	3079 (59)
BMI >30	6368 (41)	4233 (41)	2135 (41)
Baseline TSH, mIU/L	1.70 (1.10, 2.58)	1.70 (1.10, 2.58)	1.69 (1.11, 2.59)
FT4, ng/dL	1.04 (0.90, 1.20)	1.04 (0.90, 1.20)	1.04 (0.90, 1.20)
eGFR slope	−3.7 (−4.5, −2.9)	−3.7 (−4.5, −2.9)	−3.7 (−4.5, −2.9)
Albumin, g/dL	3.7 (3.1, 4.1)	3.7 (3.1, 4.1)	3.7 (3.1, 4.1)
Albumin <4.0	10 528 (67)	7023 (67)	3505 (67)
Albumin ≥4.0	5114 (33)	3405 (33)	1709 (33)

Abbreviations: eGFR, estimated glomerular filtration rate; CCI, Charlson Comorbidity Index; CT, computed tomography; BMI, body mass index; FT4, free thyroxine.

Internal Validation of the Prediction Score

The prediction performance of the prediction score was assessed in the development dataset (n = 10 428) using 100 bootstrap samples as well as in the independent validation dataset (n = 5214). The model discrimination was good with similar C-statistics in both the development dataset (0.77, 95% CI 0.75-0.78) and validation dataset (0.76, 95% CI: 0.74-0.78). Similar predictive performance was observed for the secondary cohort (Table S2 (41)).

Model fit was assessed using group-based GOF tests, which showed no significant overall difference between observed and predicted hypothyroidism events (overall $P = .47$, Table 3). Acceptable model GOF test results were also found when assessed on a subset of patients with stage 5 CKD (ie, eGFR <15 mL/min/1.73 m^2) ($P = .33$, Table 4). Similarly, model GOF was acceptable in the secondary cohort (all $P > .15$; results not shown). Calibration plots were examined for 1-year to 5-year event/incident hypothyroidism probabilities (observed vs predicted probabilities), and calibration plots for 3-year hypothyroidism probabilities are illustrated elsewhere (Fig. S2 (41)), where results that are graphically consistent with the group-based GOF tests are shown. As is typical, calibration was slightly better in the development data than in the validation dataset.

Illustration of Model Prediction

Using scores from our main model, we presented the estimated probabilities of hypothyroidism at 1, 2, 3, 4, and 5 years from baseline for 4 hypothetical clinical scenarios (ie, defined as Patients A-D) with an "average" baseline TSH level of 1.96 mIU/L and a "higher" baseline TSH level of 4.0 mIU/L (Table 5). For a hypothetical Patient A with an average baseline TSH level and who is of younger age (<60 years old); is relatively healthier at baseline (ie, no underlying hypertension nor heart failure and serum albumin >4.0 g/dL); did not

Table 2. Cox regression model for predicting incident hypothyroidism

	Parameter	HR (95% CI)	*P*
Age, years			
Age <60	Ref.		
Age ≥60	0.1935	1.21 (1.06-1.39)	.005
Race/ethnicity			
Non-Hispanic White	Ref.		
Non-Hispanic Black	−0.3427	0.71 (0.59-0.85)	<.001
Hispanic	−0.0921	0.91 (0.72-1.15)	.44
Other/Missing	−0.0148	0.99 (0.76-1.28)	.91
Baseline TSH	0.715	2.04 (1.95-2.15)	<.001
Albumin, g/dL			
Albumin <4.0	Ref.		
Albumin ≥4.0	−0.2422	0.78 (0.69-0.90)	<.001
BMI, kg/m^2			
BMI ≤30	Ref.		
BMI >30	−0.1559	0.86 (0.76-0.97)	.01
Hypertension	0.181	1.20 (1.03-1.39)	.02
Heart failure	0.371	1.45 (1.26-1.67)	<.001
Angiogram, CT scan with iodinated contrast	0.1733	1.19 (1.04-1.35)	.009
Medication: amiodarone	0.4957	1.64 (1.36-1.98)	<.001

Model parameter estimates before application of shrinkage factor of 0.9847. Final coefficients are multiplied by this shrinkage parameter. The estimated event (hypothyroidism) probability at time t can be obtained as: $1\text{-}S_0(t)^{\exp(PS^*)}$, where $PS^*=\gamma\times LP$, γ is the shrinkage factor, and LP is the linear predictor using the given parameter estimates. $S_0(t)$ at $t = 1, 2, 3, 4$, and 5 year is 0.9689, 0.9507, 0.9355, 0.9259, and 0.9137, respectively.
Abbreviations: BMI, body mass index; CT, computed tomography; PS, prognostic score.

receive an angiogram or CT scan with iodinated contrast; and was not prescribed amiodarone, the estimated probability of incident hypothyroidism at 3-year follow-up from the index eGFR (ie, postbaseline) is low at 4.7% (Patient A: Scenario 1, Table 5). However, as might be expected, this risk increases to 18.2% if Patient A's baseline TSH is higher at 4.0 mIU/L (Patient A: Scenario 2, Table 5).

For a hypothetical Patient B with the same characteristics as Patient A, except for having previously received an angiogram and/or CT scan with iodinated contrast and prescription of amiodarone, the risk of developing de novo hypothyroidism is substantially elevated to 8.8% and 32.1% when the baseline TSH is 1.96 mIU/L and 4.0 mIU/L, respectively (Patient B: Scenarios 1 and 2, Table 5). For Patient C, who has the same characteristics as Patient A, except for being of older age (≥60 years), the estimated risk of incident hypothyroidism is also higher at 5.6% and 21.6% when the baseline TSH is 1.96 mIU/L and 4.0 mIU/L, respectively (Patient C: Scenarios 1 and 2, Table 5). Finally, for Patient D, who has the same characteristics as Patient B, except for being of older age (≥60 years), the estimated risk of incident hypothyroidism is as high as 10.5% and 37.4% when the baseline TSH is 1.96 mIU/L and 4.0 mIU/L, respectively (Patient D: Scenarios 1 and 2, Table 5).

Discussion

In this study, we developed and validated a prediction tool for estimating the risk of de novo hypothyroidism in a national contemporary cohort of US adults with moderate to advanced CKD. Using detailed longitudinal de-identified data from the national Optum Labs Data Warehouse, we identified combinations of clinical characteristics, including socio-demographics, comorbidities, receipt of procedures/medications, and laboratory test patterns that predicted the risk of developing incident hypothyroidism among patients with stages 4 to 5 CKD. In the primary prediction model that was developed from our main cohort's development set with complete clinical data, the risk prediction tool demonstrated good performance with respect to model discrimination and calibration. Similar predictive discrimination and calibration performance was observed for the secondary cohort that included patients with missing BMI and serum albumin data, as well as in sensitivity analyses of a subset of patients with stage 5 CKD.

While epidemiologic studies have uncovered a high burden of hypothyroidism across multiple diverse CKD cohorts (4, 6, 27, 28, 50-53), thyroid dysfunction remains an underrecognized endocrine disorder in CKD patients (3). Although the mechanistic link between thyroid dysfunction in kidney disease has not been fully elucidated (1-3), various risk factors have been implicated in the development of hypothyroidism (ie, contrast-enhanced procedures (34-36), medications (54-57)), some of which are commonly observed in CKD patients (1-3). However, in current clinical practice, there remains substantial uncertainty of whether thyroid function should be screened and monitored in the vast numbers of CKD patients; even in the non-CKD population, there are widely varying screening recommendations across clinical practice guidelines (58-65). Despite growing data demonstrating the adverse impact of hypothyroidism on the cardiovascular health (16-20), patient-reported outcomes (15), and survival of CKD patients (25-30), many cases remain under-detected and untreated. Hence, convenient and practical clinical tools are needed to identify CKD patients at heightened risk for thyroid disease and its related end-organ complications.

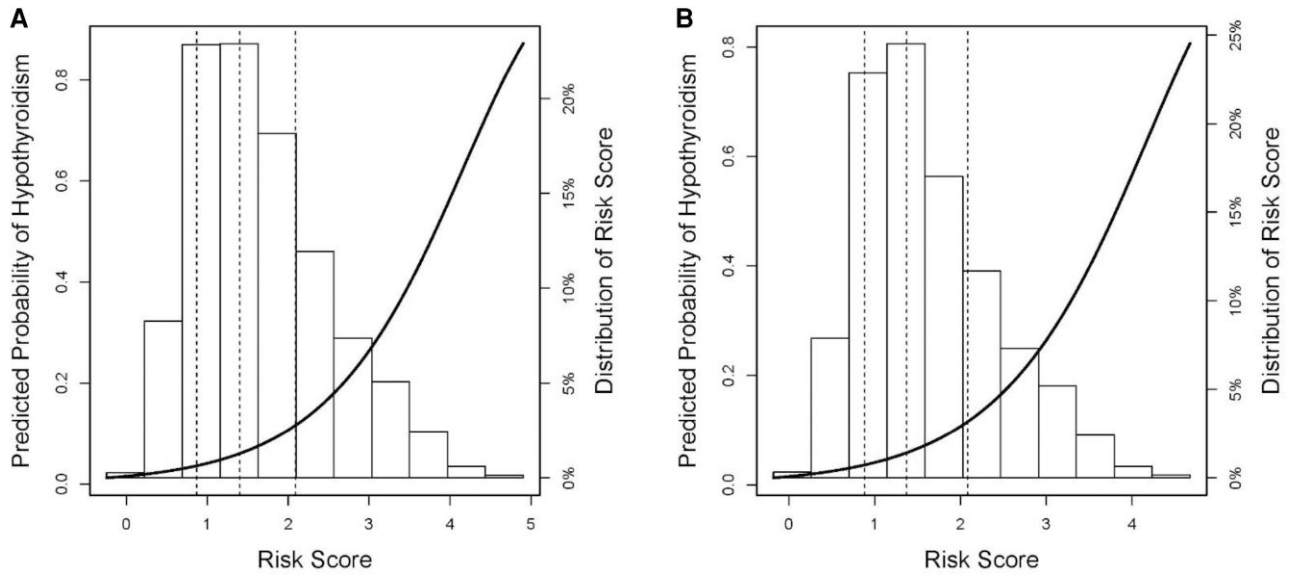

Figure 1. Distribution of the risk score and 3-year predicted event probability of incident hypothyroidism (solid curve). Dashed vertical lines indicates the 25th, 50th and 75th percentiles of the risk score. (A) Development dataset and (B) validation dataset.

Table 3. Group-based goodness-of-fit test results for hypothyroidism for all patients

Deciles	All patients					
	Risk score	n	Observed (O)	Expected (E)	O/E	*P*
1	≤−1.03	1043	21	27.0	0.78	.25
2	>−1.03 to −0.795	1043	32	36.2	0.89	.49
3	>−0.795 to 0.594	1044	41	43.1	0.95	.75
4	>−0.594 to −0.376	1041	45	51.7	0.87	.35
5	>−0.376 to −0.152	1043	64	63.4	1.01	.94
6	>−0.152 to 0.0804	1043	75	78.2	0.96	.72
7	>0.0804 to 0.368	1042	99	97.1	1.02	.85
8	>0.368 to 0.75	1043	150	132.3	1.13	.12
9	>0.75 to 1.32	1043	215	193.9	1.11	.13
10	>1.32	1043	356	375.3	0.95	.32
Total		10 428	1098	1098.2	1.00	

Over all $\chi^2 = 8.63$, df = 9, *P* for goodness-of-fit test = 0.47.

As the first study to develop a prediction tool that systematically estimates the risk of incident hypothyroidism in CKD patients, our findings address a major unmet need in the management of this population. By leveraging clinical data easily accessible in claims data and/or EHRs, we were able to estimate the predicted probabilities of developing incident hypothyroidism at various time courses. Notably, in the hypothetical scenario of a relatively healthy patient (ie, no underlying hypertension, heart failure, nor overweight status, and with adequate nutritional status) with a high-normal baseline TSH who received a prior contrast-enhanced angiogram and/or CT scan and amiodarone, the 3-year probability of developing hypothyroidism was estimated to be as high as ~25% to 30% (depending on age). In a similar hypothetical patient with the same clinical characteristics except for not having receipt of a prior contrast-enhanced angiogram and/or CT scan nor amiodarone, we found that the 2-year estimated probability remained as high as ~14% to 17%. Given the lack of screening recommendations for thyroid dysfunction specific to the CKD population, our convenient risk prediction tool can inform the clinical management of these patients by identifying those who warrant prioritized screening, serial monitoring, and long-term treatment. Furthermore, by using clinical data readily available in medical records, our score lends itself to automated implementation in the EHR. Future corollary studies are needed to determine the performance of this prediction model in other CKD cohorts, as well as how to effectively implement and disseminate this prediction tool throughout other health care systems.

Another noteworthy finding of our study was the identification of several modifiable risk factors associated with developing hypothyroidism in CKD. We observed that receipt of a prior angiogram and/or CT scan with iodinated contrast, as well as prescription of amiodarone were each potent

Table 4. Group-based goodness-of-fit test results for hypothyroidism for patients with estimated glomerular filtrate rate (eGFR) <15 mL/min/1.73 m^2

Deciles	Patients with eGFR <15 mL/min/1.73 m^2					
	Risk score	n	Observed (O)	Expected (E)	O/E	*P*
1	≤−1.07	432	11	10.9	1.01	.97
2	>−1.07 to −0.832	433	14	14.3	0.98	.93
3	>−0.832 to −0.638	430	15	17.1	0.88	.61
4	>−0.638 to −0.431	432	25	20.4	1.22	.31
5	>−0.431 to −0.226	431	26	24.7	1.05	.80
6	>−0.226 to 0.0116	432	34	29.8	1.14	.44
7	>0.0116 to 0.3	431	44	37.3	1.18	.28
8	>0.3 to 0.692	432	63	47.2	1.33	.02
9	>0.692 to 1.22	431	79	74.8	1.06	.63
10	>1.22	432	132	151.9	0.87	.11
Total		4316	443	428.5	1.03	

Over all $\chi^2 = 10.25$, df = 9, *P* for goodness-of-fit test = 0.33.

Table 5. Predicted probabilities for incident hypothyroidism at 1, 2, 3, 4, and 5 years with 95% CI for 4 patients/clinical scenarios (Patients A-D) with an average baseline thyrotropin (TSH) of 1.96 mIU/L (Scenario 1) and higher TSH of 4.0 mIU/L (Scenario 2) using the prediction model for some typical clinical scenarios

Probability (%) of hypothyroidism	Our new model with all variables									
	1 year		2 year		3 year		4 year		5 year	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Patient A1-TSH 1.96	2.2	1.8-2.7	3.6	2.9-4.2	4.7	3.8-5.5	5.4	4.4-6.3	6.3	5.2-7.3
Patient A2-TSH 4.0	9.1	7.4-10.8	14.2	11.6-16.6	18.2	15.1-21.2	20.8	17.3-24.1	23.8	19.9-27.5
Patient B1-TSH 1.96	4.3	3.1-5.4	6.8	5.0-8.5	8.8	6.5-11.0	10.1	7.5-12.6	11.7	8.7-14.6
Patient B2-TSH 4.0	16.8	12.5-20.9	25.5	19.3-31.2	32.1	24.6-38.8	36.1	27.9-43.4	40.8	31.8-48.6
Patient C1-TSH 1.96	2.7	2.2-3.2	4.3	3.5-5.0	5.6	4.6-6.6	6.5	5.4-7.6	7.5	6.2-8.8
Patient C2-TSH 4.0	10.9	8.9-12.8	16.9	14.0-19.6	21.6	18.0-25.0	24.5	20.6-28.3	28.0	23.6-32.2
Patient D1-TSH 1.96	5.2	3.8-6.5	8.1	6.0-10.1	10.5	7.9-13.1	12.1	9.1-15.0	14.0	10.5-17.3
Patient D2-TSH 4.0	19.9	15.0-24.6	29.9	23.1-36.2	37.4	29.2-44.6	41.9	33.0-49.6	46.9	37.3-55.1

Patient A1-A2: Patient age <60, White race, no heart failure and hypertension, did not have an angiogram/CT with iodinated contrast, not on amiodarone, albumin ≥4.0 g/dL, body mass index ≤30 kg/m^2 and with (A1) average baseline TSH of 1.96 mIU/L and (A2) baseline TSH of 4.0 mIU/L.
Patient B1-B2: Patient with the same characteristics as A, except have had a prior angiogram/CT with iodinated contrast and on amiodarone for (B1) average baseline TSH of 1.9 mIU/L and (B2) baseline TSH of 4.0 mIU/L.
Patients C1-C2: Patient with the same characteristics as A, except age ≥60 years for (C1) average baseline TSH of 1.96 mIU/L and (C2) baseline TSH of 4.0 mIU/L.
Patients D1-D2: Patients with the same characteristics as B, except age ≥ 60 years for (D1) average baseline TSH of 1.96 mIU/L and (D2) baseline TSH of 4.0 mIU/L.

predictors of incident hypothyroidism, and amiodarone use was in fact found to be among the strongest factors linked with the largest increase in the risk of developing de novo hypothyroidism. It bears mention that, in the general population, exposure to iodinated contrast media has been associated with incident hypothyroidism and hyperthyroidism in various adult (34, 36) and pediatric cohorts (35). Notably, CKD patients are frequently exposed to iodine from contrast-enhanced imaging studies (eg, fistulograms, cardiac catheterizations, peripheral angiograms, CT scans) which may confer 90 to 400 000 times the daily recommended intake (34, 36), and it has been suggested that impaired iodine clearance and retention in kidney dysfunction may lead to hypothyroidism via the Wolff–Chaikoff effect (1-3, 66). Furthermore, CKD patients have a disproportionately higher burden of atrial fibrillation vs their non-CKD counterparts (67, 68), and consequently are more likely to receive amiodarone (69). In light of the potential direct toxicity of amiodarone on the thyroid (70) and guideline-based recommendations to monitor thyroid function with receipt of this antiarrhythmia agent (71, 72), it is possible that thyroid exposure to excess iodine in the context of reduced GFR may exacerbate the profound thyroid-related sequelae of this medication. Given the high utilization of these procedures and medications in CKD patients, our findings suggest that closer monitoring of thyroid function is particularly warranted in those with underlying kidney dysfunction following exposure to iodinated contrast media and/or amiodarone.

While the discriminatory performance of our risk score may be improved by adding other factors such as dietary intake (ie,

consumption of iodine-rich foods (73, 74)) and/or other laboratory test results (ie, autoimmune thyroid disease markers (75)), these potential predictors are difficult to capture because they are not consistently assessed in the clinical setting and/or required trained specialists for their collection and/or interpretation. Future studies may be needed to further develop and refine comprehensive risk models that account for additional measures specific to the CKD population that may help predict the development of thyroid disease more precisely. Nonetheless, our study shows that clinical characteristics readily available in claims data and the EHR can be used to conveniently risk stratify CKD patients in measuring their hypothyroid-related risk.

The strengths of our study include its examination of a large national contemporary cohort of US adults with extended follow-up; detailed availability of longitudinal data on sociodemographics, comorbidities, procedures, medications, laboratory results, and clinical events; and rigorous ascertainment of incident thyroid status. However, several limitations of our study bear mention. First, our cohort consisted of patients with moderate to advanced CKD, and this model should be used with caution in patients with milder degrees of kidney dysfunction. Hence, future study of model refinements is needed that include a mixture of cohorts more representative of earlier-stage CKD patients. Second, the performance of the prediction model performance may depend on the accuracy of data on comorbidities, procedures, and laboratory results. While we used specific diagnostic codes from the claims and EHR data, we were not able to confirm their accuracy. Third, ascertainment of incident hypothyroidism relied solely on serum TSH levels. Given the sparsity of repeated FT4 and free triiodothyronine measurements and their unclear accuracy in kidney disease (ie, peripheral conversion of T4 to triiodothyronine is sensitive to nonthyroidal illness; routinely used FT4 assays are dependent upon protein–hormone binding, and the presence of uremic toxins that interfere with protein–hormone binding may lead to spurious levels (1-3, 8, 9, 76-78)), we utilized serum TSH levels as the most sensitive and specific single biochemical metric of thyroid status to identify incident hypothyroid cases (7). Although some aberrations of TSH have been described in the context of CKD, it remains a more robust metric of thyroid status particularly in the setting of underlying illness (ie, TSH levels typically remain normal in mild–moderate nonthyroidal illness, and become suppressed only in severe critical illness states) (1-3, 8, 9). Fourth, in our ascertainment of incident hypothyroid cases, we did not take into consideration subsequent TSH measurements, and it is possible that a proportion of patients with modestly aberrant TSH levels may have later reverted to reference ranges (79). While there is the possibility of outcome misclassification on the basis of using 1 TSH measurement to define incident hypothyroidism, the prevalence of hypothyroidism observed in our cohort is similar to lower than other epidemiologic studies of hypothyroidism in moderate to advanced CKD patients (25, 27-29). Although a growing number of population-based studies show a robust association between even lower TSH thresholds (ie, >2.5 or 3.0 mIU/L) and adverse clinical outcomes (15, 25-29, 42, 45), we selected a higher and more conservative TSH threshold of >5.0 mIU/L in order to mitigate capture of modest TSH elevations that may be transient and/or not associated with worse outcomes. While the major objective of the prediction model is to inform prioritized screening among CKD patients who are at higher risk of hypothyroidism, the implementation of this model in the real-world setting should be followed by confirmatory testing. Fifth, given that our cohort was derived from retrospective claims and EHR data, we were not able to ascertain the indications for TSH testing. It is possible that these patients may have had a higher than average perceived risk of thyroid disease, and while this may affect influence generalizability, given that these criteria applied equally to patients included in the cohort irrespective of exposure to predictor variables, this should not affect internal validity (ie, bias). Sixth, while thyroid autoimmunity is a known risk factor for hypothyroidism in the general population, due to the sparse measurement of antithyroid peroxidase antibodies within the cohort, we were not able to include this covariate within the prediction models. Finally, we cannot exclude the possibility of noncapture of clinical data including thyroid functional tests where claims are not part of Optum Labs Data Warehouse. However, our eligibility criterion requiring a minimum period of continuous enrollment of 1 year following the index eGFR measurement within the claims dataset mitigates this potential risk.

In conclusion, we developed and validated an innovative prediction tool for hypothyroidism among a national cohort of US adults with CKD that can be broadly applied in the clinical setting. Our tool addresses a previously unmet need in CKD patients by identifying those who warrant prioritized screening, serial monitoring, and potential long-term treatment for thyroid dysfunction. Additionally, these findings have the potential to improve the quality of care of CKD patients by bringing attention to hypothyroidism as a highly prevalent yet under-recognized endocrine complication of kidney disease.

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Disclosures

None of the authors have any relevant conflicts of interest to report.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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