*Original Article*

**Development and Validation of a**

**Prediction Model for Incident Hypothyroidism in a National Chronic Kidney Disease Cohort**

(Running Head: Prediction of Hypothyroidism in CKD)

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None of the authors have any relevant disclosures to report.

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Prediction scores, thyroid status, hypothyroidism, thyrotropin, chronic kidney disease.

**ABSTRACT**

**Context:**

Hypothyroidism is a common yet under-recognized condition in chronic kidney disease (CKD) patients, 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 4-5 CKD without evidence of pre-existing thyroid disease, we developed and validated a risk prediction tool for the development of incident hypothyroidism (defined as TSH>5.0mIU/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 BMI, low serum albumin, higher baseline TSH, hypertension, congestive heart failure, exposure to iodinated contrast via angiogram or CT 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 (GOF) tests showed adequate fit in the overall cohort (p=0.47) as well as in a subcohort of stage 5 CKD patients (p=0.33).

**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.

**INTRODUCTION**

Patients with chronic kidney disease (CKD) have a disproportionately higher prevalence of hypothyroidism compared to their non-CKD counterparts (i.e., 25% vs. 5%, respectively).1-4 Early or subclinical hypothyroidism is defined as an elevated 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 (i.e., 20 million US adults affected5), 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 (i.e., 5%, 11%, 20%, and 23% of participants with estimated glomerular filtration rates[eGFRs] ≥90, 60-89, 45-59, and <45ml/min/1.73m2, respectively).6 In the largest cohort examined to date, among 461,607 US Veterans with stages 3-5 CKD who underwent simultaneous serum thyrotropin (TSH) and creatinine testing, each 10ml/min/1.73m2 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 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 the health-related quality of life (HRQOL),15 cardiovascular health,16-20 kidney function,21-24 and survival of CKD patients.25-30 Given the vast number of CKD patients,31 heterogeneity of potential risk factors for thyroid dysfunction (i.e., 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 (i.e., 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 includes 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 one or more eGFR values measured over the period of 1/1/2010 to 12/31/2018 that was <30ml/min/1.73m2 (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 one or more TSH measurements within one-year on or prior to the index eGFR measurement that was within the reference range of 0.5-5.0mIU/L (designated as the baseline TSH), as well as one or more TSH measurements 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 one-year following the index eGFR measurement and a minimum period of continuous enrollment of one-day before the index eGFR date for claims data only (**Supplementary Figure 1**). Patients were excluded if at study entry they 5) had evidence of a prior diagnosis of hypo- or hyperthyroidism ascertained by diagnostic/procedural codes, 6) had prior use of thyroid hormone supplementation or anti-thyroid medication, 7) had prior radioactive iodine or surgical thyroid ablation, 8) were missing core socio-demographic variables (i.e., age, sex), or 9) were missing core covariates in the prediction model (i.e., free thyroxine [FT4], eGFR slope, body mass index [BMI], or serum albumin) within two-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 4-5 CKD. Given that all patients were required to have a baseline (first) TSH level within reference range (TSH 0.5-5.0mIU/L), incident hypothyroid cases were defined as those whose subsequent (second) TSH level following the index eGFR were >5.0mIU/L.7 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 (1/1/2010) and continued until occurrence of the event of developing de novo hypothyroidism or until the end of the study period (3/31/2019).

***Socio-demographic, Comorbidity, Medication, and Laboratory Data***

Optum Labs Data Warehouse data were used to determine patients’ baseline socio-demographic information (i.e., 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 (i.e., 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 one of five 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.41

***Statistical Methods***

Baseline characteristics of the study cohort, including all predictors, were summarized as means  standard deviation (SD) or interquartile range (IQR) for continuous variables and or proportions for categorical variables.

Prediction models were developed for incident hypothyroidism using Cox proportional hazards models. The primary cohort was comprised of N=15,642 patients (**Supplementary Figure 1**) with complete data and was randomly divided into a two-thirds training/development set (Nd=10,428) and a one-third test/validation set (Nv=5124). A secondary cohort included (N=21,604) patients with missing BMI (23%) and missing albumin (8%) data. 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 (AIC) since it has better statistical properties in variable selection compared to selection procedures based on p-value42 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  (0  γ  1) based on 100 bootstrap samples of the development dataset. This estimated shrinkage factor, , was used to adjust the final Cox prediction models to correct for model over-optimism.42-45 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  γ  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 (i.e., validation data).

Furthermore, model calibration was assessed by a group-based goodness-of-fit (GOF) test developed for survival models.46 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 one-year to five-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 models47 and is equivalent to the area under the ROC curve for binary outcomes (logistic regression).44 47

Estimated probabilities of incident hypothyroidism at a given time *t* (i.e., *t* year) were based on the final prediction model via the shrunken prognostic score (PS). That is, the shrunken PS is PS\* =  *X*, where ** is collection of estimated coefficients corresponding to predictor variables set *X* in the final prediction model. The predicted survival at time *t* for new a patient can then be obtained as S0(*t*)exp(PS\*), where S0(*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 4-5 CKD (eGFR <30ml/min/1.73m2), 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/1.73m2, with 59% and 41% of the cohort having index eGFR levels 15-<30 ml/min/1.73m2 (stage 4 CKD) and <15 ml/min/1.73m2 (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 >30kg/m2; 67% of patients had serum albumin levels <4.0g/dl; and the median (interquartile range [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 BMI (>30kg/m2), lower serum albumin (<4.0g/dL), 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 (effect estimates shown in **Table 2**). Among these predictors, higher baseline TSH level (by +∆1.0mIU/L: HR [95%CI] 2.04 [1.95-2.15]) and amiodarone use (HR [95%CI] 1.64 [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 three-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 as supplementary materials (**Supplementary Table 1** and **Supplementary Table 2**). Also, with the exception of BMI, the standardized mean differences (SMDs) 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 SMD values <0.49, **Supplementary Table 3**).

***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 (**Supplementary Table 2**).

Model fit was assessed using group-based goodness-of-fit (GOF) tests, which showed no significant overall difference between observed and predicted hypothyroidism events (overall p=0.47, **Table 3A**). Acceptable model GOF test results were also found when assessed on a subset of patients with stage 5 CKD (i.e., eGFR <15 ml/min/1.73m2) (p=0.33, **Table 3B**). Similarly, model GOF was acceptable in the secondary cohort (all p>0.15; results not shown). Calibration plots were examined for one-year to five-year event/incident hypothyroidism probabilities (observed vs. predicted probabilities), and calibration plots for three-year hypothyroidism probabilities are illustrated in **Supplementary Figure 2**, which shows graphically consistent results as the group-based GOF tests. 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 one-, two-, three-, four-, and five-year from baseline for four hypothetical clinical scenarios (i.e., defined as “Patients A-D”) with an “average” baseline TSH level of 1.96mIU/L and a “higher” baseline TSH level of 4.0mIU/L (**Table 4**). 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 (i.e., no underlying hypertension nor heart failure and serum albumin >4.0g/dL); did not receive an angiogram nor CT scan with iodinated contrast; and was not prescribed amiodarone, the estimated probability of incident hypothyroidism at three-year follow-up from the index eGFR (i.e., post-baseline) is low at 4.7% (“Patient A: Scenario 1,” **Table 4**). However, as might be expected, this risk increases to 18.2% if Patient A’s baseline TSH is higher at 4.0mIU/L (“Patient A: Scenario 2,” **Table 4**).

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 as well as prescription of amiodarone, the risk of developing de novo hypothyroidism is substantially elevated to 8.8% and 32.1% when the baseline TSH is 1.96mIU/L and 4.0mIU/L, respectively (“Patient B: Scenarios 1 and 2,” **Table 4**). 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 1.96mIU/L and 4.0mIU/L, respectively (“Patient C: Scenarios 1 and 2,” **Table 4**). 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 1.96mIU/L and 4.0mIU/L, respectively (“Patient D: Scenarios 1 and 2,” **Table 4**).

**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 4-5 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 48-51 thyroid dysfunction remains an under-recognized 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 (i.e., contrast-enhanced procedures,34-36 medications52-55), some of which are commonly observed in CKD patients.1-3 However, in current clinical practice, there remains substantial uncertainty as to 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.56-63 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.

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 electronic health records, 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 (i.e., 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 three-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 two-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 electronic health record. 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 healthcare 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 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 adult34 36 and pediatric cohorts.35 Notably, CKD patients are frequently exposed to iodine from contrast-enhanced imaging studies (e.g., fistulograms, cardiac catheterizations, peripheral angiograms, CT scans) and medications (e.g., amiodarone64), in which the former 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 65 In light of the potential direct toxicity of amiodarone on the thyroid,66 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 may be rendered 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 (i.e., consumption of iodine-rich foods67 68) and/or other laboratory test results (i.e., autoimmune thyroid disease markers69), 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 electronic health record 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 socio-demographics, 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 predicted hypothyroidism should be interpreted 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 electronic health records 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 (i.e., peripheral conversion of T4- to-T3 is sensitive to non-thyroidal 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 levels1-3 8 9 70-72), 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 (i.e., TSH levels typically remain normal in mild-moderate non-thyroidal 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.73 Finally, we cannot exclude the possibility of non-capture of clinical data including thyroid functional tests where claims are not part of OLDW. However, our eligibility criterion requiring a minimum period of continuous enrollment of one-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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**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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**FIGURE LEGEND**

**Figure 1.** Distribution of the risk score and three-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 1.** Baseline characteristics of the primary study cohort (overall cohort), the two-thirds development set, and the one-third validation set.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Total** | **Development** | **Validation** |
| **Candidate predictors** | **N (%)** | **N (%)** | **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 | 10550 (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/1.73m2 | 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 ontrast-enhanced angiogram or CT scan | 4386 (28) | 2918 (28) | 1468 (28) |
| Amiodarone use | 984 (6) | 670 (6) | 314 (6) |
| BMI, kg/m2 | 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 | 10528 (67) | 7023 (67) | 3505 (67) |
| Albumin ≥4.0 | 5114 (33) | 3405 (33) | 1709 (33) |

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

**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) | 0.005 |
| **Race/ethnicity** |  |  |  |
| Non-Hispanic White | Ref. |  |  |
| Non-Hispanic Black | -0.3427 | 0.71 (0.59-0.85) | <0.001 |
| Hispanic | -0.0921 | 0.91 (0.72-1.15) | 0.44 |
| Other/Missing | -0.0148 | 0.99 (0.76-1.28) | 0.91 |
| Baseline TSH | 0.715 | 2.04 (1.95-2.15) | <0.001 |
| **Albumin, g/dL** |  |  |  |
| Albumin <4.0 | Ref. |  |  |
| Albumin ≥4.0 | -0.2422 | 0.78 (0.69-0.90) | <0.001 |
| **BMI, kg/m2** |  |  |  |
| BMI ≤30 | Ref. |  |  |
| BMI >30 | -0.1559 | 0.86 (0.76-0.97) | 0.01 |
| Hypertension | 0.181 | 1.20 (1.03-1.39) | 0.02 |
| Heart failure | 0.371 | 1.45 (1.26-1.67) | <0.001 |
| Angiogram, CT scan with iodinated contrast | 0.1733 | 1.19 (1.04-1.35) | 0.009 |
| Medication: Amiodarone | 0.4957 | 1.64 (1.36-1.98) | <0.001 |

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-S0(*t*)exp(PS\*), where PS\*=γ×LP, γ is the shrinkage factor, and LP is the linear predictor using the given parameter estimates. S0(*t*) at *t* = 1, 2, 3, 4, and 5 year is 0.9689, 0.9507, 0.9355, 0.9259, and 0.9137, respectively.

*Abbrev.: BMI, body mass index; CT, computed tomography.*

**Table 3.** Group-based goodness-of-fit test results for hypothyroidism for (A) all patients and (B) patients with estimated glomerular filtrate rate (eGFR) <15 ml/min/1.73m2.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Deciles** | 1. **All patients** | | | | | | 1. **Patients with eGFR <15 ml/min/1.73m2** | | | | | |
| **Risk score** | **N** | **Observed (O)** | **Expected (E)** | **O/E** | ***P*** | **Risk score** | **N** | **Observed (O)** | **Expected (E)** | **O/E** | ***P*** |
| 1 | ≤-1.03 | 1043 | 21 | 27.0 | 0.78 | 0.25 | ≤-1.07 | 432 | 11 | 10.9 | 1.01 | 0.97 |
| 2 | >-1.03 to -0.795 | 1043 | 32 | 36.2 | 0.89 | 0.49 | >-1.07 to -0.832 | 433 | 14 | 14.3 | 0.98 | 0.93 |
| 3 | >-0.795 to 0.594 | 1044 | 41 | 43.1 | 0.95 | 0.75 | >-0.832 to -0.638 | 430 | 15 | 17.1 | 0.88 | 0.61 |
| 4 | >-0.594 to -0.376 | 1041 | 45 | 51.7 | 0.87 | 0.35 | >-0.638 to -0.431 | 432 | 25 | 20.4 | 1.22 | 0.31 |
| 5 | >-0.376 to -0.152 | 1043 | 64 | 63.4 | 1.01 | 0.94 | >-0.431 to -0.226 | 431 | 26 | 24.7 | 1.05 | 0.80 |
| 6 | >-0.152 to 0.0804 | 1043 | 75 | 78.2 | 0.96 | 0.72 | >-0.226 to 0.0116 | 432 | 34 | 29.8 | 1.14 | 0.44 |
| 7 | >0.0804 to 0.368 | 1042 | 99 | 97.1 | 1.02 | 0.85 | >0.0116 to 0.3 | 431 | 44 | 37.3 | 1.18 | 0.28 |
| 8 | >0.368 to 0.75 | 1043 | 150 | 132.3 | 1.13 | 0.12 | >0.3 to 0.692 | 432 | 63 | 47.2 | 1.33 | 0.02 |
| 9 | >0.75 to 1.32 | 1043 | 215 | 193.9 | 1.11 | 0.13 | >0.692 to 1.22 | 431 | 79 | 74.8 | 1.06 | 0.63 |
| 10 | >1.32 | 1043 | 356 | 375.3 | 0.95 | 0.32 | >1.22 | 432 | 132 | 151.9 | 0.87 | 0.11 |
| Total |  | 10428 | 1098 | 1098.2 | 1.00 |  |  | 4316 | 443 | 428.5 | 1.03 |  |
|  | **Over all χ2 = 8.63, df = 9, *P* for goodness-of-fit test = 0.47** | | | | | | **Over all χ2 = 10.25, df = 9, *P* for goodness-of-fit test = 0.33** | | | | | |

**Table 4.** Predicted probabilities for incident hypothyroidism at 1-, 2-, 3-, 4-, and 5-years with 95% confidence intervals (CI) for four

patients/clinical scenarios (Patients A-D) with an average baseline thyrotropin (TSH) of 1.96mIU/L (Scenario 1) and higher TSH of 4.0mIU/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, Album 4.0 g/dL, BMI 30kg/m2 and with (A1) average baseline TSH of 1.96mIU/L and (A2) baseline TSH of 4.0mIU/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 4.0mIU/L.

**Patients C1-C2:** Patient with the same characteristics as A, except age 60 years for (C1) average baseline TSH of 1.96mIU/L and (C2) baseline TSH of 4.0mIU/L.

**Patients D1-D2:** Patients with the same characteristics as B, except age  60 years for (D1) average baseline TSH of 1.96mIU/L and (D2) baseline TSH of 4.0mIU/L.