Development and validation of a prognostic model for predicting the risk of allopurinol-induced severe cutaneous adverse reactions: a retrospective new-user cohort study using linked primary care, hospitalisation, and mortality data

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See Comment page e826

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Summary

Background Allopurinol, the most prescribed urate-lowering drug, is a known cause of severe cutaneous adverse reactions. We aimed to develop and validate a model to assess the risk of allopurinol-induced severe cutaneous adverse reactions in adults newly prescribed allopurinol.

Methods In this retrospective new-user cohort study, we developed and validated a prognostic model using primary care, hospitalisation, and mortality data extracted from the UK Clinical Practice Research Datalink (CPRD) primary care database, for the period Jan 1, 2001, to March 29, 2021. Data from CPRD Aurum was used for model development and data from and CPRD GOLD was used for model validation. Adults (aged ≥18 years) residing in England who were newly prescribed allopurinol were followed up for 100 days to assess whether a severe cutaneous adverse reaction was recorded in hospitalisation or mortality records. Risk predictors included in the model were age, sex, ethnicity, chronic kidney disease stage, initial allopurinol dose, ischaemic heart disease, and heart failure. The primary outcome was to predict the 100-day risk of allopurinol-induced severe cutaneous adverse reactions in people newly prescribed allopurinol. We developed the model using multivariable Cox regression and pseudo-values, followed by penalisation and external validation. We assessed calibration, discrimination, and clinical utility in the risk range of 0·0001 to 0·003. People with lived experience of allopurinol use or gout were not involved in developing this research question, but will be involved in the dissemination of results.

Findings 225 761 patients newly prescribed allopurinol were registered in the CPRD Aurum database (development cohort) and 173 812 were included in the study. 44 630 (25·7%) of 173 812 patients were female, 129 182 (74·3%) were male, 154 323 (88·8%) were White, and the mean age was 63·9 years (SD 15·0). Of the patients newly prescribed allopurinol with data in the CPRD GOLD database (validation cohort), 55 395 patients were screened and 41 610 were included in the study. 10 829 (26·0%) of 41 610 patients were female, 30 781 (74·0%) were male, 37 242 (89·5%) were White and the mean age was 64·4 years (SD 14·9). 63 (0·04%) severe cutaneous adverse events occurred in 173 812 patients in the development cohort and 16 (0·04%) occurred in 41 610 patients in the validation cohort. Age (adjusted hazard ratio 1·03 [95% CI 1·01–1·06]), chronic kidney disease stages 3, 4, and 5 (2·24 [1·20–4·17] for stage 3; 6·65 [2·90–15·23] for stage 4; 18·85 [6·32–56·19] for stage 5), initial allopurinol dose of 300 mg or higher (5·99 [3·56–0·08]), South Asian ethnicity (5·35 [2·37–12·07]), and other Asian ethnicity (5·63 [1·34–23·61]) were associated with the 100-day risk of allopurinol-induced severe cutaneous adverse reactions. In the development dataset, after optimism-adjustment, the model's explained variation (Royston and Sauerbrei's R^2_D) was 0·50 and Harrell's C was 0·82. In the validation dataset, the calibration slope was 0·93 (95% CI 0·18–1·68), the R^2_D was 0·44 (95% CI 0·20–0·62), and Harrell's C was 0·79 (95% CI 0·71–0·88). The model had clinical utility across the prespecified risk range.

Interpretation We developed and validated a prognostic model for the 100-day risk of an allopurinol-induced severe cutaneous adverse reaction with good predictive performance and clinical utility. This model could be used to inform the choice of urate-lowering drugs.

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Introduction

Gout is the most common type of inflammatory arthritis worldwide. Globally, 91% of patients with gout prescribed urate-lowering drugs were prescribed allopurinol.[1] Allopurinol is a known cause of severe cutaneous adverse reactions, including Stevens–Johnson syndrome, toxic

Research in context

Evidence before this study

Allopurinol, the most prescribed urate-lowering drug, is a cause of severe cutaneous adverse reactions. Allopurinol-induced severe cutaneous adverse reactions have a mortality rate of up to 26%, incur considerable health-care costs, and have long-term sequelae. Allopurinol-induced severe cutaneous adverse reactions are associated with the *HLA-B*58:01* allele. Due to the low prevalence of this risk allele, genetic screening before allopurinol initiation is not cost-effective and is not recommended in most countries. Approximately one in two people with an allopurinol-induced severe cutaneous adverse reaction do not carry the *HLA-B*58:01* allele in ethnicities with a low prevalence of this polymorphism (eg, White and Hispanic individuals). There are several established risk factors for allopurinol-induced severe cutaneous adverse reactions that can be used to develop a risk prediction model to aid in the safer choice between different urate-lowering drugs. We searched Medline and the Cochrane Central Register of Controlled Trials databases for randomised controlled trials, cohort studies, case-control studies, and cross-sectional studies published in English from database inception to May 31, 2024, using the search terms "[(Stevens-Johnson OR toxic epidermal necrolysis OR cutaneous reactions" OR "acute generalised exanthematous pustulosis" OR "drug rash with eosinophilia and systemic symptoms OR skin reactions)" AND allopurinol]". We included studies of clinical risk prediction models for allopurinol-induced severe cutaneous adverse reaction. Reference lists were searched to identify other relevant articles. The search yielded no studies of prognostic models for the prediction of the risk of allopurinol-induced severe cutaneous adverse reactions. We identified 12 studies reporting risk factors for allopurinol-induced severe cutaneous adverse reactions. The risk factors associated with allopurinol-induced severe cutaneous adverse reactions were initial allopurinol dose, age, sex, chronic kidney disease, ischaemic heart disease, heart failure, presence of the *HLA-B*58:01* allele, and ethnicity.

Added value of this study

Using data on established clinical predictors, this study developed and externally validated a prognostic model to predict the risk of an allopurinol-induced severe cutaneous adverse reaction in people newly prescribed allopurinol. The use of linked primary care, hospitalisation, and mortality data allowed for comprehensive ascertainment of exposure and outcomes. The model included easy-to-ascertain clinical predictors and had good calibration, discrimination, and clinical utility across a range of clinically relevant risk thresholds (0·0001–0·003). According to the model, allopurinol-induced severe cutaneous adverse reaction was a very rare event (defined as ≤1 case per 10 000 individuals) for approximately 65% of the population, while it was a rare event (defined as between 1 case in 10 000 individuals to ≤1 cases in 1000 individuals) for approximately 30% of the population. Most of the parameters included in the prognostic model (age, sex, ethnicity, chronic kidney disease, ischaemic heart disease, and heart failure) are not modifiable. Allopurinol starting dose was the only modifiable risk factor included and was a strong predictor of severe cutaneous adverse reactions. Therefore, to minimise the risk of severe cutaneous adverse reactions, it is essential that allopurinol is initiated at a daily dose of ≤100 mg per day. Lower starting doses (eg, 50 mg per day) might be used in the presence of chronic kidney disease as recommended in the American College of Rheumatology and the European Alliance of Associations for Rheumatology guidelines.

Implications of all the available evidence

This prognostic model provides individual estimates of the 100-day risk of an allopurinol-induced severe cutaneous adverse reaction. The model had good predictive performance and clinical utility and can be used to better inform an individual's choice between alternate urate-lowering drugs based on individual risk compared with the current practice of using population level risk. Knowledge about individual risk might minimise concerns about an allopurinol-induced severe cutaneous adverse reaction when this is predicted to be very rare or rare and improve the uptake of urate-lowering treatment. Avoiding allopurinol in individuals for whom the risk of allopurinol induced severe cutaneous adverse reactions is considerable will reduce the potential for serious harm in people at greater risk.

epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms syndrome.[2,3] Stevens–Johnson syndrome and toxic epidermal necrolysis present with skin and mucosal blistering and extensive epidermal detachment, whereas drug reaction with eosinophilia and systemic symptoms is characterised by widespread rash, eosinophilia, and involvement of internal organs such as the liver, kidneys, and lungs.[3]

These conditions together have an annual hospitalisation rate of 0·7–2·0 per 1000 new allopurinol initiators.[4–6] Allopurinol-induced severe cutaneous adverse reactions have a high mortality rate of up to 26%[4–6] and incur considerable health-care costs. The direct health-care costs of managing the acute phase of severe cutaneous adverse reactions in hospital were £11 209–£31 232 in Europe before 2015 and US$45 661 in the USA between 2009 and 2013.[7,8] Severe cutaneous adverse reactions are associated with mucocutaneous, ocular, and renal complications, and psychological sequelae including post-traumatic stress disorder.[9] Early recognition and immediate withdrawal of the culprit drugs is crucial to minimise the severity and consequences of severe cutaneous adverse reactions.[3]

Allopurinol-induced severe cutaneous adverse reactions are associated with the *HLA-B*58:01* allele.[10] However, pretreatment genetic testing is only recommended in people with a high prevalence of this allele (ie, those from Han Chinese, Korean, Thai, and

African ethnicities[11,12]) although between 30%[6] and 90%[13] of allopurinol-induced severe cutaneous adverse reactions occur in people from other ethnicities (eg,White and Hispanic people) in whom the prevalence of this allele is often less than 1%. Therefore, pre-treatment genetic testing is not deemed cost-effective.[7,8] Universal genetic testing is also not recommended as approximately one in two people with allopurinol-induced severe cutaneous adverse reactions do not carry the *HLA-B*58:01* allele in countries with low prevalence of this polymorphism.[10]

Currently, there are no mechanisms to predict the risk of severe cutaneous adverse reactions or to guide treatment decisions in patients for whom pre-treatment genetic testing is either not recommended or unavailable. The established associations between several demographic and clinical predictors (ie, increasing age, female sex, chronic kidney disease, congestive cardiac failure, ischaemic heart disease, and initial allopurinol dose) and allopurinol-induced severe cutaneous adverse reactions highlight the need for the development of a risk prediction model to aid safer prescribing of urate-lowering drugs. Developing mechanisms to predict and minimise these life-threatening side-effects of allopurinol are important research priorities as per the US Agency for Healthcare Research and Quality[14] and the Gout, Hyperuricemia and Crystal-Associated Disease Network.[15]

To address this important gap in patient care, we developed and externally validated a prognostic model to predict the 100-day risk of allopurinol-induced severe cutaneous adverse reactions in people newly prescribed allopurinol.

Methods

Study design and participants

We used data from the Clinical Practice Research Datalink (CPRD) Aurum and GOLD databases to develop (Aurum) and externally validate (GOLD) a prognostic model. The CPRD is an anonymised prospective database of electronic health records originating during routine clinical care in the primary care of the National Health Service in the UK. In England, CPRD data are also linked to hospitalisation (hospital episode statistics) and mortality (Office for National Statistics) databases.[16,17] Both CPRD Aurum and GOLD databases have comparable data structure with information on demographic and lifestyle factors, diagnoses, primary care prescriptions, and laboratory results. The differences between the two relies on the software used to input data. General practices that contribute data to CPRD Aurum use EMIS software whereas those that contribute data to CPRD GOLD use VISION software. To avoid overlap between model development and validation datasets, we used a bridging file provided by the CPRD to identify general practices that contributed data to both databases. Such general practices were excluded from the model development cohort (ie, CPRD Aurum) due to the large sample size (38 million *vs* 9 million in CPRD GOLD). The CPRD has been widely used for epidemiological research across a broad range of health outcomes. Participants in the CPRD are representative of the UK population in terms of age, sex, and ethnicity.[16,17]

This was a new-user study which included patients who had been newly prescribed allopurinol in primary care. We believed that this criterion would capture almost all patients who were prescribed allopurinol for the first time as gout is predominantly managed in primary care in the UK.[18] Patients newly prescribed allopurinol in England between Jan 1, 2001, and March 29, 2021, were included. Participants were required to be at least 18 years on the date of first allopurinol prescription, had their primary care data linked with the hospital episode statistics and Office for National Statistics databases, and be registered in their current general practice for at least 3 years before the first allopurinol prescription to be considered for inclusion. The registration history criterion minimised the chance of patients who were previously prescribed allopurinol being misclassified as new users. Typically, a 1-year drug-free registration is considered sufficient to ascertain people newly prescribed a drug. However, since gout is an intermittent illness, and patients might consult their general practitioners infrequently, a 3-year prescription free-registration period was used as in previous studies.[4] Eligible patients were also required to have had no previous record of a severe cutaneous adverse reaction due to any drug in either their primary or secondary care records. This ensured that any record of a severe cutaneous adverse reaction during follow-up was truly an incident event and not due to long-term complications of a previous event. The study setting, eligibility criteria, and ascertainment of outcome and predictors were the same in development and validation cohorts.

This study was approved by CPRD's Research Data Governance (protocol 24_003915), which has overarching research ethics committee approval for research studies using anonymised data (reference 05/MRE04/87). Practices that contribute data to the CPRD agreed on using anonymised patient data for approved research projects. Additional patient consent was not required. This study followed the recommendations of the Reporting of Studies Conducted using Observational Routinely Collected Data statement. Patients with lived experience of allopurinol use or gout were not involved in this study, however members of the the UK Gout Society will be involved in disseminating the study findings.

Procedures

Patients newly prescribed allopurinol were followed up from the date of first prescription until the earliest date of the outcome, 100 days, death, patient leaving the practice, last data collection, or study end (March 29, 2021),

whichever occurred first. A 100-day follow-up period was chosen since similar duration of follow-up (90–100 days) has been used in previous epidemiological studies.[4–6]

We selected candidate predictors based on the results of a scoping literature review (appendix pp 4–9). We included seven predictors in the model that are readily available in practice: age (years) on the date of the first allopurinol prescription; sex (male or female); ethnicity (White or Hispanic, Black, Chinese, South Asian [Indian, Pakistani, or Bangladeshi], other Asian [ie, Korean, Thai, Malay, Sinhalese, Javanese, Arab, Asian, Caribbean Asian, Filipino, other Asian, or southeast Asian], and other or unknown ethnicity [ie, Jewish, Turkish, Romani people and Travellers, Japanese, or unspecified mixed background]); allopurinol starting dose (≤100, 101–299, or ≥300 mg per day); chronic kidney disease stage (0–2, 3, 4, or stage 5 or dialysis); and ischaemic heart disease and heart failure (present or absent). By contrast, other factors such as diuretic use, diabetes, cancer, comorbidity index, and use of antibiotics or angiotensin-converting enzyme inhibitors did not consistently show an association with allopurinol-induced severe cutaneous adverse reactions across studies and were therefore not included as candidate predictors in our prognostic model (appendix pp 4–9).

We categorised ethnicities according to the prevalence of *HLA-B*58:01* polymorphism and potential for different risk of allopurinol-induced severe cutaneous adverse reactions.[6,10] Ethnicity data were obtained from hospital episode statistics (appendix p 10). For those participants with missing or unknown ethnicity in the hospital episode statistics dataset, information on ethnicity was extracted from the primary care records. In England, 94% of patients have complete ethnicity information when linked hospital episode statistics and primary care data are used and the concordance between these sources has been shown to be greater than 90%.[19]

The chronic kidney disease stages were defined according to the 2012 Kidney Disease Improving Global Outcomes recommendations[20] and using the most recent estimated glomerular filtration rate or serum creatinine result or primary care recording of the chronic kidney disease stage before the date of first allopurinol prescription. To obtain an estimated glomerular filtration rate from creatinine, we used the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[21]

Data were missing for ethnicity and allopurinol dose. We handled missing data in the same way in both model development and validation datasets, as recommended.[22] When ethnicity information was missing or unknown, patients were assigned to the category other or unknown to be consistent with how it would be assigned if unknown on model deployment. When data on the daily dose of allopurinol was not provided by the CPRD, we estimated the daily allopurinol dose by multiplying the allopurinol tablet strength (100 mg or 300 mg) provided by the CPRD with the mode of the daily dosing instruction for that tablet strength for all new allopurinol prescriptions with information on number of tablets to take each day provided. The modal dose was one tablet per day for both allopurinol 100 mg and 300 mg tablets, consistent with our clinical experience that most new allopurinol prescriptions are one tablet per day. This approach to estimating missing dose data was preferred over multiple imputation because we did not think the predictors included in the model could be used to impute missing allopurinol dose, and it would be incorrect to include other variables that predict the allopurinol dose in the model as they are not candidate predictors of allopurinol-induced severe cutaneous adverse reactions.

See Online for appendix

We reviewed patient data from the 5 years preceding the start of follow-up to identify comorbidities. We developed search strategies and applied them to generate code lists for both CPRD Aurum and GOLD databases to build comparable code lists (appendix pp 30–73). Code lists were updated using a 2023 publication.[19]

Outcomes

The primary outcome was to predict the 100-day risk of allopurinol-induced severe cutaneous adverse reactions in people newly prescribed allopurinol. Severe cutaneous adverse reactions (Stevens–Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms syndrome) were defined using a previously validated definition with a positive predictive value of 100%.[4] This definition required the main reason for hospitalisation or the primary cause of death to be generalised skin eruption due to drugs and medicaments (ICD-10 diagnosis code L27.0), bullous erythema multiforme or Stevens–Johnson syndrome (L51.1), toxic epidermal necrolysis or Lyell syndrome (L51.2), other erythema multiforme (L51.8), or unspecified erythema multiforme (L51.9) within 100 days of the first allopurinol prescription, without any subsequent primary care prescription of allopurinol after the hospitalisation episode.[4] Other medications associated with a high risk of severe cutaneous adverse reactions[23] (appendix p 3) were excluded as the culprit drug if they had been prescribed for more than 100 days before the event or continued to be prescribed after the event.[4]

Statistical analysis

We included all seven candidate predictors (14 parameters) in a Cox regression model without variable selection using data from CPRD Aurum. We checked Cox's proportional hazards assumptions and found no evidence for non-proportional hazards (all $p>0·05$; appendix p 14).

To allow for a potential non-linear association between age and the outcome, we modelled age using second-order fractional polynomial terms with functional forms chosen in the presence of all predictors. Since there was no clear evidence that the non-linear function would have a better fit than a linear function ($p=0·67$ for

comparing the model with age as a linear term with the model with age modelled as the best fitting second-order polynomials), age was not transformed.

The baseline survival function at 100 days (S_0[100]) was estimated using the Nelsen-Aalen approach.[24] The S_0(100) was combined with the Cox regression coefficients (β) to estimate a patient's cumulative risk at 100 days (F[100]) of a severe cutaneous adverse reaction by 100 days after allopurinol initiation using the following formula:

$$F(100)=1-S_0(100)^{\exp(\beta X)}$$

where βX is the estimated linear predictor (ie, $\beta_1x_1+\ldots+\beta_{14}x_{14}$) from the Cox model.

The Cox model is fitted across all timepoints, but our focus was the risk prediction at 100 days. The apparent calibration plots at 100 days showed significant miscalibration in the model development data. Therefore, still using the development dataset, we recalibrated the original F(100) equation by fitting a generalised linear equation with a complementary loglog link function directly to observed pseudo-values[25] (ie, jack-knife estimators representing an individual's contribution to the cumulative incidence function for the outcome), to give an updated equation:

$$F_{recal}(100)=1-\exp(-\exp(\alpha+\gamma(\beta X^{\varepsilon}))).$$

The linear predictor from the original model (βX) was the only variable included in the recalibration model, which allowed for a non-linear recalibration effect using fractional polynomials. Observed event probabilities were defined using pseudo values.

To examine and correct the F_{recal}(100) recalibrated generalised linear model and its performance estimates for optimism due to overfitting, we did bootstrap sampling with replacement of 500 samples from the model development population.[26]

To adjust the F_{recal}(100) recalibrated model for overfitting, we quantified a uniform shrinkage factor as the average of calibration slopes at 100 days from each of the bootstrap samples tested in the original sample. The intercept (α) was then re-estimated after penalisation to ensure that the calibration-in-the-large was correct (ie, that the sum of predicted probabilities equals the overall proportion of observed events by 100 days).

Ten anonymised patient profiles, one from the middle of each of the 10 groups defined by tenths of predicted risk were selected from the development cohort and their clinical characteristics and risk scores were displayed for illustrative purposes.

The distribution of each parameter included in the prognostic model (mean [SD] for continuous variables and n [%] for categorical variables) was stratified according to predicted risk categories as per the British National Formulary: very rare side-effect (predicted risk <1 event in 10 000 individuals), rare side-effect (between 1 event in 10 000 and 1 event in 1000 individuals), and uncommon side-effect (>1 event in 1000 individuals) using data from the development cohort.

The developed model equation was applied to data in the validation dataset. The model's predictive performance was assessed in terms of calibration, discrimination, and overall model fit (Royston and Sauerbrei R^2_D; appendix pp 15–16).

Model calibration was assessed through comparison of predicted probabilities with observed pseudo-values at 100 days. We also produced calibration plots at 100 days using observed pseudo-values (observed risk, y-axis) with a smooth calibration curve to show the calibration across the spectrum of predicted risks (x-axis) with 95% CIs. We used calibration-in-the-large and calibration slope to summarise the overall calibration at 100 days. We assessed discrimination using the Harrell's C statistic.

	Development cohort (n=173 812)	Validation cohort (n=41 610)
Age, years	63·9 (15·0)	64·4 (14·9)
Sex		
Male	129 182 (74·3%)	30 781 (74·0%)
Female	44 630 (25·7%)	10 829 (26·0%)
Ethnicity		
White or Hispanic	154 323 (88·8%)	37 242 (89·5%)
Black	4818 (2·8%)	490 (1·2%)
Chinese	778 (0·4%)	106 (0·3%)
South Asian (Indian, Pakistani, or Bangladeshi)	5685 (3·3%)	675 (1·6%)
Other Asian ethnicities*	1942 (1·1%)	268 (0·6%)
Other or unknown†	6266 (3·6%)	2829 (6·8%)
Diagnosed with gout‡	146 499 (84·3%)	35 454 (85·2%)
Subcutaneous tophi	2493 (1·4%)	578 (1·4%)
Last serum urate measurement, μmol/L	504·4 (93·1)	508·5 (94·2)
Individuals with missing data	42 428 (24·4%)	8699 (20·9%)
Allopurinol starting dose, mg per day		
≤100	129 992 (74·8%)	28 910 (69·5%)
101–299	3400 (2·0%)	1330 (3·2%)
≥300	40 420 (23·3%)	11 370 (27·3%)
Chronic kidney disease stage		
0–2	126 442 (72·7%)	29 167 (70·1%)
3	40 423 (23·3%)	10 609 (25·5%)
4	5643 (3·2%)	1514 (3·6%)
5 or dialysis	1304 (0·8%)	320 (0·8%)
Glomerular filtration rate, mL per min§	77·9 (22·8)	74·3 (23·5)
Ischaemic heart disease	32 483 (18·7%)	8860 (21·3%)
Heart failure	19 049 (11·0%)	4791 (11·5%)
Number of outcomes	63 (0·04%)	16 (0·04%)
Follow-up time, days	98·1 (11·0)	97·7 (12·0)

Data are n (%) or mean (SD). *Other Asian ethnicities included Korean, Thai, Malay, Sinhalese, Javanese, Arab, Asian, Caribbean Asian, Filipino, other Asian, and southeast Asian. †Jewish, Turkish, Romani people and Travellers, Japanese, or unspecified mixed background. ‡Gout was defined as a primary care consultation for gout, a hospitalisation with gout among the diagnoses in the discharge summary, or a primary care prescription for colchicine. §Glomerular filtration rate was estimated from creatinine levels using the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[29]

Table 1: **Characteristics of patients in the development and validation cohorts**

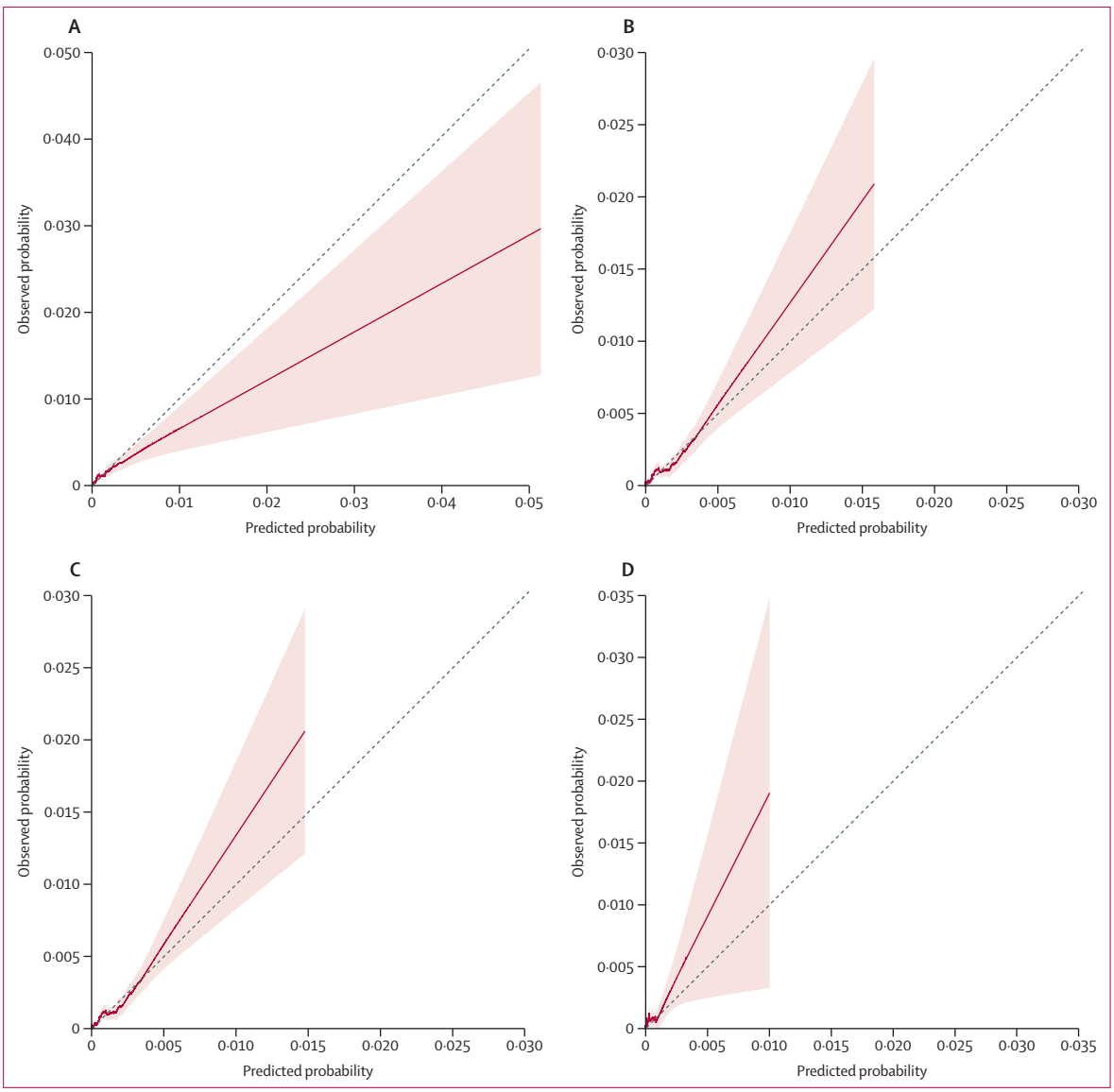

Figure 1: **Calibration curves of the prognostic model for severe cutaneous adverse reactions within 100 days of allopurinol initiation**
Before (A) and after (B) model recalibration in the development cohort. After model recalibration and penalisation in the development dataset (C) and the validation dataset (D). The black dashed lines represent the ideal calibration performance. The red lines show the model calibration and the red shaded area shows the 95% CIs. Further details about performance metrics of the prognostic models are provided in the appendix (pp 15–16).

The clinical utility of the model was evaluated with decision curve analysis in both datasets. Decision curve analysis provides a measure of the net benefit of an intervention (ie, to decide who to treat with allopurinol based on the newly developed prognostic model) across a range of relevant risk thresholds to define high risk, compared with two alternative strategies (ie, treating all patients with allopurinol or treating none, regardless of their severe cutaneous adverse reactions risk). Since severe cutaneous adverse reactions are a rare-to-very-rare side-effect of allopurinol, with a cumulative rate of 0·001–0·0001 as per the British National Formulary, and the historical rate of severe cutaneous adverse reactions due to allopurinol in a population at high-risk from Taiwan before genetic testing was 0·003,[27] we defined a priori that risk thresholds between 0·0001 and 0·003 would be of clinical interest, since above that risk genetic testing would be indicated. The sample size and number of predictor parameters for model development was suitable for estimating the overall risk and minimising overfitting (appendix p 29). As a sensitivity analysis, we evaluated the performance of the model in people diagnosed with gout in the validation dataset.

All statistical analyses were done using Stata (version 18). The model was developed and validated

	Initial model*		Final model†	
	Apparent performance in development dataset (95% CI)	Mean bootstrap estimate of optimism	Performance in development dataset	Performance in the validation dataset (95% CI)
Calibration slope	1·0 (0·63 to 1·37)	0·04	1·04	0·93 (0·18 to 1·68)
Calibration-in-the-large	0 (–0·37 to 0·37)	..	0	0·39 (–0·42 to 1·20)
Harrell's C statistic	0·84 (0·80 to 0·89)	0·02	0·82	0·79 (0·71 to 0·88)
R^2_D	0·53 (0·42 to 0·61)	0·03	0·50	0·44 (0·20 to 0·62)

*Cox model followed by generalised linear model recalibration at 100 days. †Initial model followed by penalisation and re-estimation of the intercept.

Table 2: **Model performance measures in development and validation cohorts**

adhering to the PROGnosis RESearch Strategy framework[28] and is reported according to TRIPOD+AI guidelines (appendix pp 11–13).[29]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

225 761 patients newly prescribed allopurinol were registered in the CPRD Aurum database (development cohort), of whom 173 812 were included in the study (appendix p 17). 44 630 (25·7%) of 173 812 patients were female, 129 182 (74·3%) were male, 154 323 (88·8%) were White and the mean age was 63·9 years (SD 15·0). 146 499 (84·3%) had a diagnosis of gout and the mean pre-treatment serum urate was 504·4 µmol/L (SD 93·1; table 1). The mean follow-up duration was 98·1 days (SD 11·0).

Of the patients newly prescribed allopurinol with data in the CPRD GOLD database (validation cohort), 55 395 patients were screened and 41 610 were included in the study (appendix p 18). 10 829 (26·0%) of 41 610 patients were female, 30 781 (74·0%) were male, 37 242 (89·5%) were White and the mean age was 64·4 years (SD 14·9). 35 454 (85·2%) had a diagnosis of gout and the mean pre-treatment serum urate was 508·5 µmol/L (SD 94·2; table 1). The mean follow-up duration was 97·7 days (SD 12·0).

The median interval between the first allopurinol prescription and hospitalisation or death due to an allopurinol-induced severe cutaneous adverse reaction was 34·0 days (IQR 23·0–49·0) in the CPRD Aurum database and 35·0 days (12·0–51·5) in CPRD GOLD database (appendix p 19). Most allopurinol-induced severe cutaneous adverse reactions occurred within 8 weeks of the first allopurinol prescription in CPRD Aurum database (52 [82·5%] of 63 reactions) and CPRD GOLD database (13 [81·3%] of 16 reactions).

In the development cohort, there were 63 (0·04%) allopurinol-induced severe cutaneous adverse reactions in 173 812 patients (1·35 events per 1000 person-years [95% CI 1·05–1·73]). 43 (68·3%) of 63 events were generalised skin reactions due to drugs, 14 (22·2%) events were Stevens-Johnson syndrome, and six (9·5%) events were either toxic epidermal necrolysis, or other or unspecified erythema multiforme (<5 events in each category therefore data not shown).

Age, chronic kidney disease stages 3, 4, or 5, an allopurinol starting dose greater than 300 mg per day, and South Asian ethnicity (Indian, Pakistani, or Bangladeshi) and Other Asian ethnicity (Korean, Thai, Malay, Sinhalese, Javanese, Arab, Asian, Caribbean Asian, Filipino, other Asian, or southeast Asian) were predictors of allopurinol-induced severe cutaneous adverse reactions (appendix p 20).

Since the Cox model showed large miscalibration with a calibration slope at 100 days of 0·79 (95% CI 0·58–1·00; figure 1A), we recalibrated the original (initial) model to the observed pseudo-values to improve the calibration of estimated risks at 100 days (figure 1B).

From the bootstrap internal validation of this recalibrated model, a uniform shrinkage factor of 0·96 was obtained and used to shrink predictor coefficients to produce a final model adjusted for optimism. After model recalibration and penalisation (figure 1C), average model predictions matched the average observed outcome probabilities with 95% CIs overlapping the 45° line (where predicted risks exactly match observed ones). The final model had a good overall fit (R^2_D=0·50) and discrimination (Harrell's C=0·82) after penalisation (table 2).

Since most patients had a low risk of the outcome (appendix pp 21–22), most groups were clustered at the bottom left of the calibration plot, because the range of predictions was narrow (0–0·015). Calibration was closest in the range of 0 to 0·005. The final equation to predict the 100-day risk of allopurinol-induced severe cutaneous adverse reactions is shown in the appendix (appendix p 23).

Ten anonymised patient profiles, one from the middle of each of the 10 groups defined by tenths of predicted risk were selected from the development cohort (appendix p 24). The cumulative 100-day risk of allopurinol-induced severe cutaneous adverse reactions ranged from 0·15 events per 1 000 000 individuals in the middle of the first group to 100 events per 1 000 000 individuals in the middle of the sixth group, and 1600 events per 1 000 000 individuals in the middle of the tenth group (appendix p 24).

The distribution of each parameter included in the prognostic model according to the predicted risk (ie, predicted risk <1 event in 10 000 individuals, between 1 event in 10 000 individuals and 1 event in 1000 individuals, and >1 event in 1000 individuals) in the development cohort is shown in the appendix (p 25).

In the validation cohort, there were 16 (0·04%) allopurinol-induced severe cutaneous adverse reactions in 41 610 patients (1·44 events per 1000 person-years [95% CI 0·88–2·35]). Data for different allopurinol-induced severe cutaneous adverse reactions were suppressed due to the occurrence of fewer than five events for several events, as per CPRD policy.

Due to the rarity of events, predictive performance of the final model was measured with large uncertainty, but observed estimates showed a good overall fit (R^2_D=0·44 [95% CI 0·20 to 0·62]) and discrimination (Harrell's C=0·79 [95% CI 0·71 to 0·88). The observed calibration curve showed excellent calibration in those with estimated risks between 0 and 0·002 (where the majority of the predefined risk threshold range lies), but increasing underestimation of risks in those with the highest estimated risks (>0·002); this is reflected by the corresponding calibration slope of 0·93 (95% CI 0·18 to 1·68; figure 1D) and a calibration-in-the-large of 0·39 (95% CI –0·42 to 1·20). Most groups clustered at the bottom left of the calibration plot due to the low estimated risk for most patients (range 0–0·010; appendix pp 26–27).

The model had comparable performance in people diagnosed with gout compared to the overall population of allopurinol initiators (appendix p 28).

Decision curve analysis examining the final model's net benefit across risk thresholds between 0·0001 and 0·003 suggests that the model had clinical utility over treat-all with allopurinol and treat-none with allopurinol to prevent allopurinol-induced severe cutaneous adverse reactions in both development and validation cohorts in the risk range that would be of clinical interest (figure 2).

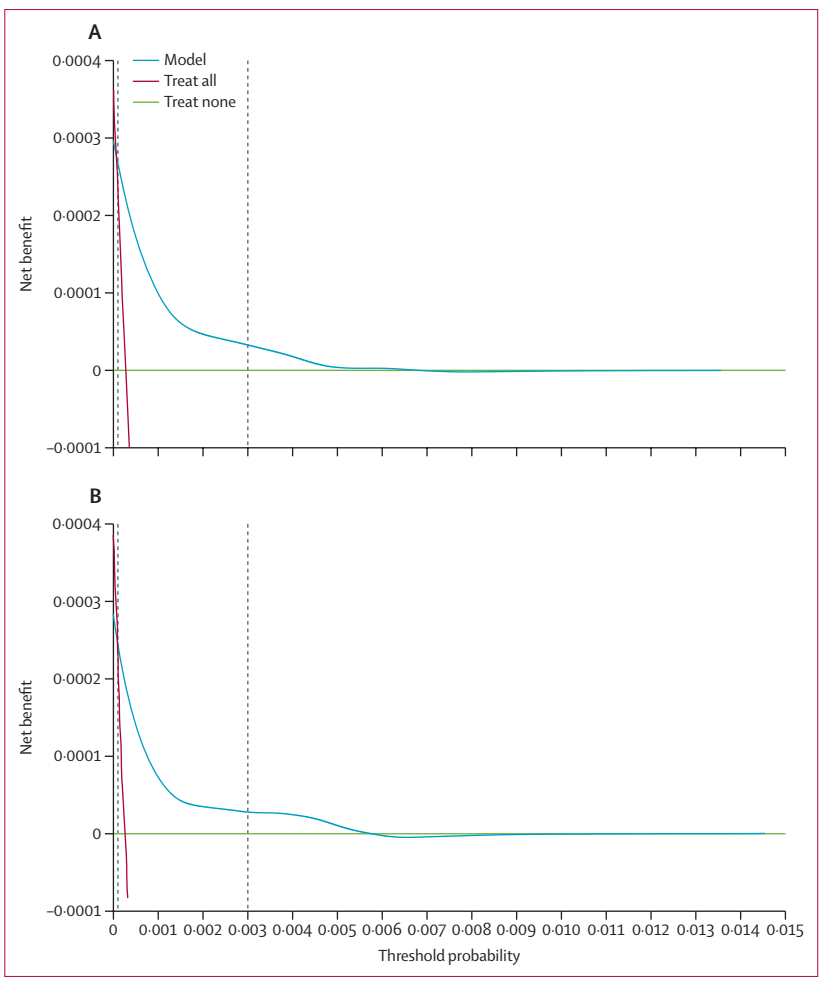

Figure 2: **Decision curve analysis**
Decision curve analysis for the development (A) and validation (B) cohorts. The dashed lines represent the pre-defined risk range of clinical interest (lower limit of 0·0001 and upper limit of 0·003).

Discussion

In this retrospective new-use cohort, we developed and externally validated a prognostic model for the 100-day risk of an allopurinol-induced severe cutaneous adverse reaction that used demographic and clinical data. The model had promising performance and clinical utility.

We found increasing age, an allopurinol starting dose of 300 mg per day or higher, and Asian ethnicities to be predictors of allopurinol-induced severe cutaneous adverse reactions as reported previously (appendix pp 4–9). Multiple studies have reported higher risk associated with initiating allopurinol at doses of 300 mg per day or higher and female sex. An age-related increase in allopurinol-induced severe cutaneous adverse reactions risk has been consistently observed. The elevated risk in individuals of Asian ethnicity has also been documented, with no difference identified between people of Chinese, Malay, and Indian ethnicities. Additionally, previous studies have suggested that cardiovascular diseases such as ischaemic heart disease and heart failure might increase the risk of allopurinol-induced severe cutaneous adverse reactions. This study also showed a dose-response effect between the stage of chronic kidney disease and the development of allopurinol-induced severe cutaneous adverse reactions. This is a novel finding since the majority of previous studies considered chronic kidney disease as present or absent.

At present, the British National Formulary describes the population level risk of allopurinol-induced severe cutaneous adverse reactions as ranging from 1 in 10 000 to 1 in 1000, which is a wide range that makes individualised shared decision making difficult. Our prognostic model provides estimates of individual risk that ranges from less than 1 in 1 000 000 to more than 1 in 100. This represents a substantial improvement compared with the information currently available and can result in safer urate-lowering drug prescription

especially in individuals unable to access testing for the *HLA-B*58:01* polymorphism.

We anticipate this prognostic model will allow better informed decision making about the choice of urate-lowering drug and safer prescribing in individuals for whom testing for *HLA-B*58:01* polymorphism is not currently recommended. The risk prediction tool should not be used to avoid screening for the *HLA-B*58:01* polymorphism in ethnicities that are at high risk of allopurinol-induced severe cutaneous adverse reactions. Estimating the individual risk will aid decision making with regard to the use of allopurinol or febuxostat as first-line urate-lowering drug, since febuxostat has a 16-fold lower risk of severe cutaneous adverse reactions than allopurinol.[30] However, it is beyond the scope of this study to recommend specific risk thresholds at which alternate drugs should be offered as an alternative to allopurinol. Such risk thresholds are best ascertained by national and international specialist societies.

Additionally, these findings highlight the crucial importance of appropriate allopurinol dosing to minimise the risk of allopurinol-induced severe cutaneous adverse reactions, particularly in older individuals (eg, ≥70 years old) and those with chronic kidney disease. Current guidelines, including those from the American College of Rheumatology and the European Alliance of Associations for Rheumatology, recommend initiating allopurinol at low doses (eg, ≤100 mg per day), with gradual dose escalation.[11,12] Although our model reflects risk patterns observed in routine practice where some patients were prescribed allopurinol 300 mg per day, adherence to the above-mentioned dosing recommendations will reduce the risk of allopurinol-induced severe cutaneous adverse reactions. In addition to considering the individual risk of severe cutaneous adverse reactions, health professionals should advise patients to discontinue allopurinol and seek health-care contact immediately if they experience symptoms of a severe cutaneous adverse reaction.[23]

While the model estimates the risk of a rare but serious side-effects, it is important to emphasise that long-term urate-lowering therapy is essential for the effective management of gout, and efforts to support safe prescribing and long-term adherence remain a clinical priority.

This study had several strengths. We used real-world and nationally representative datasets. The study population included all individuals who were newly prescribed allopurinol in primary care and the results are generalisable across indications for allopurinol—eg, gout and uric acid nephrolithiasis. We minimised the chances of intermittent allopurinol users entering the cohort as new users by requiring eligible patients to have a 3-year registration before cohort entry without any allopurinol prescription. The definition used to ascertain outcomes has 100% positive predictive value.[4] Similar to the validation study,[4] allopurinol-induced severe cutaneous adverse reactions were ascertained using data on cause of hospitalisation or death. In the UK, this information is recorded by administrative staff trained in the use of ICD system using discharge summaries and death certificates written by hospital doctors. We excluded individuals with a previous record of a severe cutaneous adverse reaction in primary or secondary care. This minimised potential bias from consultations for sequelae of previous severe cutaneous adverse reactions. Data about the parameters included in this model are easily ascertainable during routine clinical care, making the model simple to use.

However, this study also had several limitations. First, some people that were prescribed allopurinol in a hospital clinic or inpatient setting and had a severe cutaneous adverse reaction before allopurinol could be prescribed in primary care were excluded as prescriptions issued in secondary care are not available in CPRD. However, in the UK gout is primarily managed in primary care[18] and this limitation should not cause a major bias. Second, although the definition of allopurinol-induced severe cutaneous adverse reactions had 100% positive predictive value, there might be bias from under ascertainment of outcome—eg, if an allopurinol-induced severe cutaneous adverse reaction was not recorded in the discharge letter. We believe this is extremely unlikely because there is a high risk of recurrence of allopurinol-induced severe cutaneous adverse reactions, and we anticipate hospital specialists will take extra care to communicate with the general practitioner to prevent future harm. Third, due to the rarity of the outcome, there were only 16 events in the validation dataset and thus confidence intervals of model performance were wide. Since the development dataset met sample size guidance to precisely estimate the overall risk and minimise overfitting, this facilitates robustness of predictions in new data, but further evaluations in independent datasets are important. Fourth, we were unable to include the *HLA-B*58:01* status in the model. We included ethnicity as a proxy for *HLA-B*58:01* status, as guided by previous studies.[10] Fifth, the calibration-in-the-large value indicates that the model under-predicted the risk of allopurinol-induced severe cutaneous adverse reactions at external validation. However, the calibration curve indicates this is an issue for people with highest predicted risk (ie, around 5% of people who had a risk threshold of >0·001). In these people, under-prediction might be less relevant as a risk of less than 1 in 1000 might be sufficient to mandate the use of alternate urate-lowering drugs. We suggest that this limitation is recognised by any specialist society that formulates risk threshold to aid individual decision making. Sixth, in people without available information about daily allopurinol dose we assumed that the allopurinol starting dose was one tablet of the dose strength prescribed per day instead of using more advanced methods for imputing missing data, such as multiple imputation by chained equations. However,

considering that missing data are likely to be missing at random, we hypothesise that the differences between the two methods would be negligible. Furthermore, any potential issue from this is minimised by the fact that we were aware of the tablet strength (100 mg or 300 mg for all prescriptions) and any new prescription would be likely to be one tablet daily. Although this might have introduced some uncertainty, we observed a dose–response effect with increasing allopurinol starting dose showing stronger association with allopurinol-induced severe cutaneous adverse reactions as described in previous studies (appendix pp 4–9).

Future research is needed to identify the risk thresholds at which alternate urate-lowering drugs should be considered and to validate the prognostic model in data from other countries. Future studies could also evaluate whether replacing ethnic categories with the *HLA-B*58:01* status would improve model performance, whether the model could be used to guide screening for the *HLA-B*58:01* allele, and the side-effect profile of febuxostat and uricosurics in patients at high risk of allopurinol-induced severe cutaneous adverse reactions.

In conclusion, we have developed and externally validated an easy-to-use prognostic model for estimating the 100-day risk of an allopurinol-induced severe cutaneous adverse reaction in patients newly prescribed allopurinol. This model has promising calibration and discrimination and has clinical utility. It could be used to support an individualised risk-based choice between different urate-lowering drugs in patients for whom genetic screening for the *HLA B*58:01* polymorphism is not indicated.

Contributors

AA conceived the idea for the study and contributed to the study design; supervised data analysis and interpreted the results; critically reviewed the manuscript. CS provided clinical dermatology input; interpreted the results; critically reviewed the manuscript. EC conceived the idea for the study and contributed to the study design, did data management and analysis, wrote the first draft of the manuscript and critically reviewed the manuscript. DR advised on data analysis for fitting a generalised linear equation with a complementary loglog link function; interpreted the results; critically reviewed the manuscript. GN contributed to the study design; did data analysis; supervised data analysis and interpreted the results; critically reviewed the manuscript. RR contributed to the study design; supervised data analysis and interpreted the results; critically reviewed the manuscript. SM provided clinical dermatology input; interpreted the results; critically reviewed the manuscript. All authors affiliated with the University of Nottingham had full access to all the data in the study since due to Clinical Practice Research Datalink (CPRD) licencing requirements, CPRD data cannot be shared outside of the licence institution. All authors had final responsibility for the decision to submit for publication. EC, GN, and AA directly accessed and verified the underlying data reported in the manuscript.

Declaration of interests

AA reports personal fees from UpToDate, Eli Lilly, Novartis, and SOBI outside the submitted work. EC is funded by the Foundation for Research in Rheumatology and European Alliance of Associations for Rheumatology; and reports personal fees from Novartis, IBSA, and Horizon Therapeutics outside the submitted work. RR receives royalties for two academic textbooks: *Individual Participant Data Meta-Analysis: A Handbook for Healthcare Research* and *Prognosis Research in Healthcare Concepts, Methods, and Impact*; and is funded by the National Institute for Health and Care Research Birmingham Biomedical Research Centre at the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham; and is a National Institute for Health and Care Research Senior Investigator. All other authors declare no competing interests.

Data sharing

This study used data from the CPRD. These data were provided under a licence that does not permit data sharing with third parties. Data can be obtained from the CPRD (https://www.cprd.com/data-access). EC, GN and AA took responsibility for the integrity of the data and the accuracy of the data analysis. STATA codes are available on reasonable request from the corresponding author. The study's protocol is available on the CPRD website (https://www.cprd.com/approved-studies/predicting-serious-cutaneous-adverse-reaction-due-allopurinol-people-gout) or from the corresponding author on reasonable request.

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