Development and Internal Validation of a Multivariable Risk Prediction Model for Serious Infection in Patients With Psoriasis

A Prospective Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR)

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SUMMARY

We developed a clinical multivariable risk prediction model that provides an absolute risk for serious infections occurring within one year of initiating systemic therapies for psoriasis.

This model will help patients and dermatologists in the United Kingdom and the Republic of Ireland to identify modifiable risk factors and to enable identification of patients who may need closer monitoring and intervention.

BACKGROUND

1. Systemic therapies for psoriasis depress the immune system, leading to patient and clinician concerns over the associated risk of serious infection.
2. Patients with psoriasis have a higher baseline risk of serious infection due to their condition, associated comorbidities, and lifestyle factors[1].
3. Patient concerns over potential adverse events associated with therapy such as serious infections may lead to intentional non-adherence[2].
4. Currently, there are no risk models available to help patients and their clinicians estimate a personal risk of infection upon initiation of a systemic therapy for psoriasis.

AIM

To develop and internally validate a personalised prognostic multivariable prediction model for serious infection occurring within one year of initiating systemic therapy in patients with psoriasis

METHODS

British Association of Dermatologists Biologic Interventions Register (BADBIR) - prospective safety registry of patients with psoriasis on systemic therapies established in 2007 in the UK and the Republic of Ireland[3].

Data collected 6 monthly for first 3 years, annually thereafter.
Inclusion criteria: patients with chronic plaque psoriasis, with follow-up data for 1 year or had a serious infection within 1 year, data lock February 2017. Patients starting a biologic therapy (etanercept, infliximab, adalimumab, ustekinumab) or a systemic non-biologic therapy (methotrexate, ciclosporin, psoralen-UVA, acitretin, hydroxycarbamide, fumaric acid esters)
Serious infection defined by hospitalisation and/or; intravenous antimicrobial therapy and/or; death

***A priori* chosen co-variates**
Variables chosen to be included in the model: age, gender, body mass index, psoriasis area and severity index (PASI), starting therapy

Variables assessed for inclusion in backward elimination logistic regression (p = 0.1): alcohol intake, smoking status, diabetes, chronic obstructive pulmonary disease (COPD), asthma, number of co-morbidities, psoriatic arthritis, depression, hypertension, employment status, total number of previous biologic therapies, total number of previous systemic therapies

Continuous predictors tested for non-linearity with fractional polynomial transformations; missing data accounted for using 20 imputed datasets

Model performance assessed by:

C-statistic (discrimination)

Probability model would identify patients who had a serious infection as having higher risk

Calibration slope (C-slope) (calibration)

Measures overfitting or underfitting

Calibration-in-the-large (CITL) (calibration)

Measures whether predictions are systematically too low or too high

Internal validation:

1. Produce 200 bootstrap samples.
2. Model development process repeated in each bootstrap sample.
3. Developed model applied to original and bootstrap data, average measures of optimism for the model performance statistics calculated through the difference between the two datasets.
4. Uniform shrinkage factor was applied to the original β coefficients with re-estimation of the intercept to adjust for overfitting.

RESULTS

N=10033
Serious infections within 1 year = 175 (1.7%)

Variable	Odds Ratio (95% confidence interval)
Age	1.00 (0.98, 1.01)
Female gender	1.35 (1.13, 1.95)
PASI	1.01 (0.99, 1.02)
Alcohol (units per week)	1.01 (1.00, 1.02)
Number of comorbidities	1.08 (1.04, 1.13)
COPD	1.78 (1.01, 3.11)
BMI	1.01 (0.99, 1.03)
Employment status	
Working / studying	Ref
Unemployed	1.42 (0.99, 2.04)
Retired	2.05 (1.28, 3.31)
Initiation therapy	
Non-biologics	Ref
Etanercept	0.87 (0.54, 1.40)
Infliximab	3.55 (2.03, 6.21)
Adalimumab	1.10 (0.77, 1.54)
Ustekinumab	1.30 (0.87, 1.93)

Table 1: Final multivariable prediction model for risk of serious infection one year after initiation of therapy in BADBIR. Odds ratios are derived after application of uniform shrinkage factor to adjust for overfitting.

Performance statistic	Apparent performance	Internal validation test performance	Average optimism	Optimism corrected performance
C-statistic	0.68 (0.63, 0.72)	0.66 (0.61, 0.70)	+0.033	0.64 (0.60, 0.69)
CITL	0.01 (-0.15, 0.16)	0.01 (-0.14, 0.16)	-0.009	0.02 (-0.14, 0.17)
C-slope	1.02 (0.84, 1.20)	0.87 (0.69, 1.04)	+0.134	0.88 (0.70, 1.07)

Table 2: Internal validation model diagnostics (95% confidence intervals)
Apparent performance - estimated directly from original dataset used to develop model
Test performance - estimated by developing model in bootstrap sample + applying to original dataset
Average optimism - difference between model performance in bootstrap data and test performance in original dataset
Optimism correct performance - subtracting average optimism from apparent performance

Box 1: Risk score equation and case study
The risk score to predict serious infection within one year of initiating systemic therapy for psoriasis:

Log Odds = -4.985 -0.004 x Age + 0.304 x Female gender + 0.006 x PASI + 0.008 x Units of alcohol / week + 0.081 x Number of comorbidities + 0.574 x COPD + 0.010 x BMI + 0.354 x Unemployed/Not currently working + 0.720 x Retired – 0.140 x Etanercept + 1.267 x Infliximab + 0.098 x Adalimumab + 0.260 x Ustekinumab

- 50 year old unemployed man with severe psoriasis (PASI 20) attends clinic
- Background: 25 units alcohol/week; 4 comorbidities; BMI 36
- Considering the use of adalimumab
- Predicted risk = 2.3% (95% CI 0.9% to 6.1%).
- Physician illustrates that if he takes 5 units of alcohol, loses weight to a BMI of 25, and improves his diet and restrict his salt intake - predicted risk drops to 1.6% (95% CI 0.7% to 3.9%).
- The choice of initiation of biologic therapy is also important: for the same patient, initiating infliximab instead of adalimumab = increased risk 5.0% (95% CI 2.0% to 11.9%).

DISCUSSION

1. This is the first study to utilise a large psoriasis treatment registry to develop a prediction model for serious infection in patients with psoriasis receiving systemic therapy.
2. The risk score algorithm uses variables that are readily available within the routine clinical care of patients.
3. The model highlights modifiable lifestyle factors and can facilitate discussions and motivational interviewing for better holistic care of patients with psoriasis. This has the potential to decrease intentional non-adherence to therapy[2].

Strengths and weaknesses of the study

✓ Real-world data
✓ Large sample size
✓ Detailed data capture
✓ Involvement of 153 UK and ROI dermatology centres
✓ Fully industry independent data analysis
✘ Non-randomisation
✘ Residual confounding
✘ Moderate model performance

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