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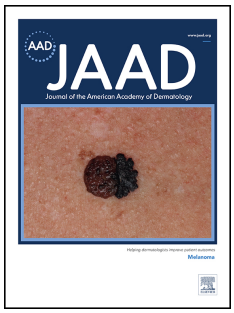

Variables associated with joint involvement and development of a prediction rule for arthritis in psoriasis patients. An analysis of the Italian PsoReal database

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Variables associated with joint involvement and development of a prediction rule for arthritis in psoriasis patients. An analysis of the Italian PsoReal database

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Capsule summary

- Limited data are available concerning the prediction of arthritis in psoriasis patients.

- We developed and validated a prediction model for incident arthritis in psoriasis patients, which could be used in clinical practice to improve early detection of arthritis. The restricted model may assist when planning health interventions at population level.

Abstract

Background: Limited data exist to predict the development of psoriatic arthritis (PsA) in psoriasis (PsO) patients

Objective: To analyze factors associated with incident PsA in PsO patients, and to develop a predictive algorithm for progression to arthritis using a full set of variables and a restricted one applicable to administrative data.

Methods: Cohort study within the PsoReal registry in Italy. Multivariable generalized linear models were used to assess factors associated with PsA and to derive a predictive model.

Results: Among 8895 patients, 226 PsA cases were identified (incidence 1.9 per 100 patient-years). Independent predictors in the full model were: female sex, age 40-59 years, BMI≥25, chronic-plaque PsO features, presence of palmoplantar pustulosis, hospitalization for PsO in the last 5 years, and previous use of systemic PsO therapy, area under the curve of Receiver Operating Characteristics curve (AUC-ROC) = 0.74. Female sex, age 40-59 years, hospitalization for PsO, previous use of systemic PsO therapy were independent predictors in the restricted model, AUC-ROC = 0.72.

Limitations: Lack of other potential predictors for PsA.

Conclusion: Our models could be used by clinicians and health authorities when planning intervention and population surveillance. Future studies should confirm our models using larger datasets and additional variables.

Introduction

Psoriasis (PsO) is a chronic inflammatory disease of the skin that affects about 2% to 3% of the general population.[1,2] Several comorbidities have been linked with PsO, including particularly psoriatic arthritis (PsA).

PsA follows the diagnosis of PsO in the large majority of patients. Although many studies have highlighted potential risk factors for PsA development, no predictive algorithm has been developed so far to identify PsO patients at risk of progressing to PsA as confirmed by a rheumatologist. A predictive model for the development of PsA in PsO patients, based on measures that are regularly captured in dermatological settings, could enable dermatologists to stratify patients appropriately and intervene early, if necessary, to prevent PsA progression.

This study aimed at analyzing variables associated with incident PsA and at building a prediction model for PSO progression to PsA by using data of a large PsO registry in Italy. Further validation of the model relying on a restricted set of variables which could be obtained from administrative datasets was also performed.

Methods

This was a cohort study using data collected within the previous PsoCare and the on-going PsoReal registry in Italy, involving a network of the main hospital-based Dermatological Departments in Italy.

The PsoReal registry continues the activities of the former PsoCare registry.[3-5] Both registries gather prospective information on patients initiating a new systemic treatment for PsO. For simplicity, we refer here to the two registries by using the single term PsoReal registry. The registries were approved by the ethics committees of the participating centers.

In addition, record linkage of Italian health care datasets was used to validate a restricted model for PsA progression to be applied to administrative datasets or claim data. More information on record linkage is included in the **Suppl. materials**.

Inclusion criteria

All patients included in the registry had a definite PsO diagnosis confirmed by a dermatologist. Patients with history of PsA or without information on basic demographics or comorbidities at baseline as well as patients without any follow-up data were excluded from the analysis.

Data collection

Data were collected through a remote electronic data capture system, and stored in the central database of the PsoReal registry.

For study purposes, all clinical and personal data available in the registry were considered, including age, sex, years of education, body mass index [BMI, smoking and drinking habits, main comorbidities, and clinical characteristics of psoriasis, including age at first PsO diagnosis, age at PsO onset, main PsO locations, type of PsO lesions, severity as assessed by the Psoriasis Area and Severity Index (PASI), pruritus assessed by use of a 0- to 10-point visual analogue scale [VAS]), number of hospitalizations for PsO in the last 5 years, and previous systemic therapies for PsO,

PsA ascertainment

At every scheduled follow-up visit (at 6-month intervals), an accurate screening for PsA was made by dermatologists. Items of the Psoriasis Epidemiology Screening Tool

(PEST) questionnaire and clinical symptoms of PsA were systematically collected. When PsA was suspected, a rheumatologist was consulted. The final diagnosis of PsA was always made by a rheumatologist.

Statistical analysis

Continuous variables were presented as means with standard deviations (SD) or as medians with interquartile ranges (IQRs), and nominal variables as numbers with percentages.

Factors associated with PsA occurrence were first assessed by using uni- and multivariable generalized linear models (GLMs) with Poisson distribution, including age and sex as adjustment factors and reported as incidence rate ratios (IRRs) with their 95% confidence intervals (CIs) and p-values.

For predictive purposes, the full dataset was randomly partitioned into training and test sets using a 70/30 split, with a similar proportion of PsA cases in both groups. The training set was used to develop the predictive model and select variables, while the “real-world” model performance was determined on the test set.

More specifically, all variables with p-value <0.20 in the age- and sex-adjusted analysis were assessed for inclusion in a multivariable Poisson GLM with a stepwise forward selection algorithm using the Akaike information criterion. Time (on both linear and natural logarithmic scales) was also evaluated for inclusion in the model. An alternative model restricted to a 2-year follow-up period was also assessed.

Furthermore, a separate model for predicting progression from PsO to PsA in the context of administrative datasets, focusing on the first 2 years of follow-up, was developed with the same procedure, based on a reduced set of predictors. This model was also independently validated on data extracted from record linkage of health care datasets in Italy.

Measures of predictive accuracy, including model R^2, area under receiver operating characteristic curve (AUC), accuracy, specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and F1 score, were produced.

A full description of the statistical methods is reported in the **Suppl. materials**. All tests were considered statistically significant at p-value <0.05. Analyses were performed with MATLAB software v.9.1 (The MathWorks Inc., Natick, Massachusetts, USA).

Results

Of a total of 17 598 patients registered between January 2005 and October 2021, there were 17 177 (mean age ± SD: 48.8 ± 14.4; 66.4% males) adult subjects with available demographics and comorbidity information at baseline. Among these, 3890 had a prevalent PsA at baseline and were therefore excluded from the analysis. A total of 4392 patients had limited information at follow-up and were also excluded from the analysis.
Finally, 8895 adult patients with available follow-up information were included in the study.

The distribution of variables in the study cohort are reported in **Table 1**.

PsA incidence

Patients were followed up for a median of 12.5 months (IQR: 5.5-23.9). Overall, 226 cases of PsA were identified at follow-up, with an incidence of 1.9 cases per 100 patient-years (95% CI: 1.7-2.2), with 1.7 (95% CI: 1.5-2.1) in males and 2.2 (95% CI: 1.8-2.8) in females. The incidence peaked between 40 and 59 years in females and between 50 and 59 years in males (**Figure 1**). Most events (95.1%) were recorded in the first 3 years of follow-up, with an overall cumulative incidence of 5.2% (95% CI: 4.3-6.1) at the third year. The cumulative incidence increased almost linearly in this period and then started to taper slightly off at 5 (8.6%; 95% CI: 5.6-11.6) and 10 years (13.5%; 95% CI: 7.3-19.7) (**Suppl. Figure S1**, **Table S1**).

Factors associated with PsA occurrence

Univariable and age- and sex-adjusted analysis of factors associated to PsA occurrence is reported in **Suppl. Table 2.** Statistically significant factors identified in the adjusted analysis were age between 40 and 59 years, being overweight or obese (BMI ≥25), genital PsO involvement, nail involvement, presence of classic chronic-plaque PSO, being hospitalized for PsO in the last 5 years, previous use of systemic therapy for PsO and, in particular, use of conventional nonbiologic agents. Other candidate factors for the subsequent predictive analysis ($p<0.2$) included sex, smoking and drinking habits, presence of heart disease, hyperlipidemia and overall number of comorbidities, age at PsO diagnosis, age at PsO onset, disease duration, presence of palmoplantar PsO, and palmoplantar pustulosis.

Predictive model

The following variables were selected as independent predictors by using a GLM with Poisson distribution (**Table 2**): female sex, age between 40 and 59 years, BMI ≥25, presence of classic chronic-plaque PsO, presence of palmoplantar pustulosis, hospitalization for PsO in the last 5 years, previous use of systemic therapy for PsO, and logarithm of time. Internal and external model validation measures are reported in **Suppl. Table S3**. The overall AUC of the model was 0.69 on the training set and 0.66 on the separate test set (**Figure 2a)**. The following final formula was derived on the full dataset in order to calculate the probability (P) of PsA occurrence at a certain time (T):

$$\mathrm{P}(\mathrm{T}_{\mathrm{mths}}) = \exp(-4.2970 + .2838 * \mathrm{Sex}_{\mathrm{F}} + .5520 * \mathrm{Age}_{40-59} + .4158 * \mathrm{BMI}_{25+} + .4385 * \mathrm{Chr\_plaq} + .8053 * \mathrm{Palm\_pust} + .5071 * \mathrm{Hosp\_pre} + .3093 * \mathrm{Sys\_pre} - .3654 * \mathrm{Ln}(\mathrm{T}))$$

where each factor is a variable indicator, with value 1.0 if the factor is present, or zero otherwise, and Ln is the natural logarithm of time in months. An optimal cutoff of 0.025, which

optimizes both sensitivity and specificity, was found for this model, giving an overall accuracy of 61.7% in the test set.

A better fit of the model was achieved by limiting the observation period to 2 years, truncating cases that occurred after this period. Predictors selected during the training stage were the same as those of the model on the whole period (**Table 2**), but with the addition of a linear time effect. The AUC of this model was 0.75 on the training set and 0.74 on the separate test set **(Figure 2b, Suppl. Table S3**). The following final formula was derived on the full dataset in order to calculate the probability (P) of PsA occurrence at a certain time (T) in the first 24 months:

$$\mathrm{P}(\mathrm{T}_{\mathrm{mths}}) = \exp(-4.7247 + .3395 * \mathrm{Sex}_{\mathrm{F}} + .5460 * \mathrm{Age}_{40-59} + .4313 * \mathrm{BMI}_{25+} + .6932 * \mathrm{Chr\_plaq} + .6652 * \mathrm{Palm\_pust} + .5070 * \mathrm{Hosp\_pre} + .3381 * \mathrm{Sys\_pre} + .2667 * \mathrm{Ln(T)} - .1242 * \mathrm{T})$$

An optimal cutoff of 0.023 was found for this model, giving an overall accuracy of 66.2% in the test set.

Predictive reduced model using administrative data

A reduced model was trained on a set of variables available in the context of administrative datasets (i.e., age, sex, main comorbidities, previous hospitalizations for PsO, and previous use of systemic therapies for PsO), considering only the first 2 years of follow-up, as the overall model accuracy was higher and the available data for external validation were also limited to this period. The following variables were finally selected in the model (**Table 2**): female sex, age between 40 and 59 years, hospitalization for PsO in the last 5 years, previous use of systemic therapy for PsO, time, and logarithm of time. The overall AUC of the model was 0.73 on the training set and 0.72 on the test set (**Figure 2c, Suppl. Table**

S3). The following final formula was derived on the full dataset in order to calculate the probability (P) of PsA occurrence at a certain time (T):

$$P(T_{mths}) = \exp(-3.8363 + .2742 * Sex_F + .5864 * Age_{40-59} + .5671 * Hosp\_pre + .3720 * Sys\_pre + .2582 * Ln(T) - .1230 * T)$$

An optimal cutoff of 0.023 was found for this model, giving an overall accuracy of 65.1% in the test set.

The performance of the model was then assessed on an independent dataset extracted from record linkage of health care datasets in Italy. The dataset comprised 34 724 PsO patients without PsA diagnosis in the last 5 years and with a follow-up period up to 2 years. A total of 328 PsA cases were detected, with an incidence rate of 0.49 per 100 patient-years (95% CI: 0.44-0.54). Our model predicted PsA onset with an AUC of 0.96 and an overall accuracy of 98.7% based on the previously cutoff of 0.023 found **(Figure 3c, Suppl**. **Table S3)**. However, as the PsA incidence was different between the registry and the record-linkage data, the optimal cutoff was calibrated again on the latter dataset, obtaining a value of 0.007, which increased sensitivity from 38.7% to 91.5% at the cost of a slightly lower specificity and overall accuracy (94.0%).

Accuracy of other predictive models

The accuracy of other algorithms, including elastic-net GLMs and boosting-based machine learning models, is reported in the **Suppl. Table S4**. However, these models did not show superior performance on the test set in comparison with standard GLM regression.

Discussion

Scant data exist regarding PsA incidence in PsO patients, with recent figures ranging from 0.27 to 2.7 cases per 100 patient-years.[6-9] In our cohort we found an incidence of 1.9 PsA cases per 100 patient-years, which is very close to the estimates of Eder et al.[7,8]

Female sex was a predictor for the development of PsA. To our knowledge only one previous study detected an increased risk of PsA in women,[10,11]

The incidence of PsA peaked between 40 and 59 years in both sexes, which is in line with a previous report.[12] This age range was a predictor for developing PsA in the multivariable analysis.[13]

A BMI ≥25 was an additional independent predictor in our analysis, confirming data from previous reports.[10,14,15,16] In some of these reports an increased trend of risk according to body weight was also found.[14,15]

Classic chronic plaque PsO and palmoplantar pustulosis were both significant predictors in our analysis. To the best of our knowledge, the association of palmoplantar pustulosis with PsA has been never explored in previous studies. In our cohort the majority of patients with palmoplantar pustulosis had concomitant plaque psoriasis or guttate psoriasis (87/155). Previous studies have shown that the prevalence of PsA in palmoplantar pustulosis is higher in cases of coexistent plaque psoriasis.[17] Other types of joint complaints such as pustulotic arthro-osteitis or inflammatory synovitis have been described as associated with palmoplantar pustulosis [16,17], so it cannot be excluded that, in some cases, there was a misclassification of arthritis in favor of PsA.

Nail PsO, which was found to be a risk factor by others,[8,10,18-20] was associated with PsA in our age- and sex-adjusted analysis, although it was not retained as a predictor in the model. Notably, in a recent systematic review, nail disorders in general did not show strong evidence for association with PsA.[11] It should be noted that CASPAR criteria include nail involvement

as a diagnostic feature for PsA, hence possibly inflating the association of PsA with such a feature.

Previous hospitalizations for PsO in the last 5 years and previous use of systemic therapies were all significant predictors in our analysis. Although these were a proxy for the complexity and severity of PsO patients, our analysis was unable to find a direct association of PsA with PASI at baseline. PASI has been detected as a potential risk factor in other studies.[8,19,20] Hospitalization included hospital daycare and overnight hospital stay.

We also developed a separate predictive model on a restricted number of predictors that are usually available in the context of health care datasets. This model was of similar accuracy compared with the full model.

So far, we found only two studies presenting models for predicting the risk of PsA in PsO patients.[21,16] One of the studies was focused on the risk of detecting PsA at baseline and did not use prospective information.[22] The other recent study had a design very similar to ours, but the diagnosis of PsA was made by dermatologists; in this study, a parsimonious model including PEST and BMI had good performance in predicting PsA over 2 years.[22]

Our study has some limitations, including the lack of additional potential predictors for PsA development, such as genetic data, imaging, serum biomarkers, or family history of PsA, which were not captured in our registry, as well as the presence of missing or incomplete information. As the model was trained on rare events, it might need calibration on datasets of other populations of interest. There is a small risk, that PsA at baseline was underestimated in patients with previous systemic therapy.

All in all, this study confirmed some previous factors' association with PsA occurrence and enabled us to develop a predictive rule for the development of PsA in PsO patients. Our predictive models could be used in clinical practice by physicians to identify patients at risk for PsA and so enhance the detection and treatment of PsA. They may also be used by

health authorities when planning health interventions and surveillance at the population level. Further studies should confirm or refine our models by using larger health care datasets.

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Figure 1. Incidence of PsA in the study cohort according to sex and age groups

Figure 2. Receiver operating characteristic (ROC) curves on training and test sets a) of the full predictive model in the overall study b) of the full predictive model limited to the first two years, c) of the model in the first two years of follow-up considering a reduced set of variables available in the context of administrative health care datasets and on an independent dataset extracted from record-linkage of health care datasets in Italy

Table 1 - Demographics and baseline clinical characteristics of patients included in the study

		N=8895*	%
Sex	Male	6072	68.3%
	Female	2823	31.7%
Age (years)	*Mean, SD*	*48.1*	*14.7*
BMI (kg/m^2)	*Mean, SD*	*27.0*	*5.0*
Educational attainment	Elementary/lower secondary	4373	49.2%
	Upper secondary	3448	38.8%
	University	1063	12.0%
Smoking habits	Never	3320	38.8%
	Yes	3558	41.6%
	Ex-smoker	1672	19.6%
Alcohol consumption	Never	4998	59.9%
	Regular drinker	3159	37.9%
	Ex-drinker	185	2.2%
Comorbidities**	Type II diabetes	603	6.8%
	Tuberculosis (including latent)	394	4.4%
	Hypertension	2093	23.5%
	Heart disease†	299	3.4%
	Hyperlipidemia	1058	11.9%
	Liver disease	325	3.7%
	Kidney disease	132	1.5%
	Lung disease	134	1.5%
	Neoplasm^	125	1.4%
	Gastro-intestinal diseases°	85	1.0%
Age at first PsO diagnosis (years)	*Mean, SD*	*31.3*	*16.3*
Age at PsO onset (years)	*Mean, SD*	*30.1*	*16.3*
PsO duration§ (years)	*Mean, SD*	*16.8*	*12.7*
Diagnostic delay (years)	*Mean, SD*	*1.2*	*3.9*
Main PsO locations**	Head	6359	73.8%
	Face	2364	27.4%
	Trunk	7021	81.5%
	Upper/lower limbs	7513	87.2%
	Folds	2100	24.4%
	Genitalia	1455	16.9%
PsO types**	Chronic-plaque PsO	7450	83.8%
	Palmoplantar PsO	1989	22.4%
	Palmoplantar pustulosis	155	1.7%
	Nail PsO	3143	35.3%
	Guttate PsO	425	4.8%
	Erythrodermic PsO	247	2.8%
PASI	*Mean, SD*	*17.8*	*10.6*
	Median, IQR	*15.0*	*10.2-22.6*
	<10	1115	17.1%
	10 - 20	3079	47.3%
	20+	2312	35.5%
Pruritus intensity (VAS)	*Mean, SD*	*4.7*	*3.2*
Hospitalization for PsO in the last 5 years	No	6445	76.5%
	Yes	1982	23.5%
Previous systemic therapy for PsO	0	3550	39.9%
	1	2424	27.3%
	2	1875	21.1%
	3+	1046	11.8%
Type**	Conventional	5303	59.6%
	Biological	380	4.3%

BMI: body mass index, IQR: interquartile range, PASI: psoriasis area severity index, PsO: psoriasis, SD: standard deviation, TBC: tuberculosis, VAS: 0-10 visual analogue scale

* Numbers may not add up to the total due to missing data
** More than one category per patient is possible
^ Excluding non-melanoma skin cancer
° Including: gastritis, ulcer, Crohn's disease, colitis of various kinds

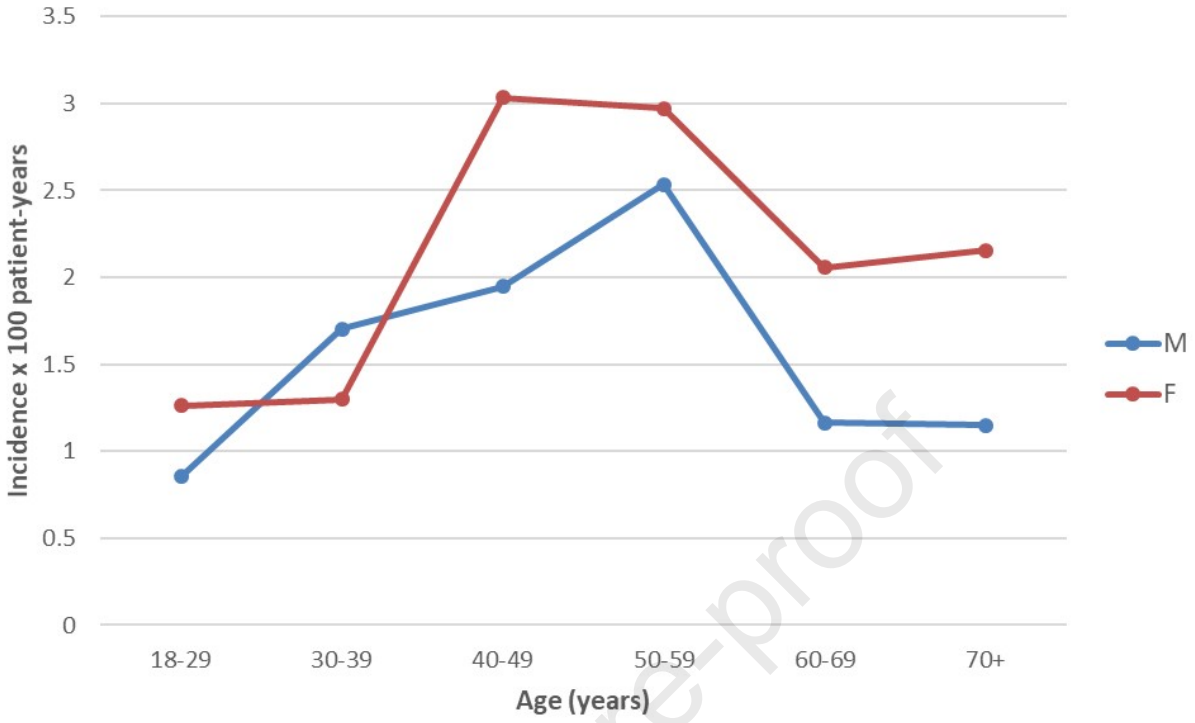
374 † Including: coronary artery disease, heart failure and cerebrovascular accidents
375 § PsO duration since diagnosis

Table 2 - Predictive factors for PsA occurrence in the full model based on cohort data and in the model using a reduced set of variables available in the context of administrative health care datasets

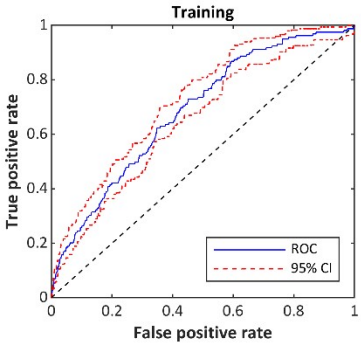
		Full model				**Reduced model**	
		Overall period		**2 years limited**			
		IRR (95% CI)*	**P**	**IRR (95% CI)***	**P**	**IRR (95% CI)***	**P**
Sex	Male	1		1		1	
	Female	1.33 (1.01-1.75)	0.044	1.40 (1.05-1.88)	0.024	1.32 (0.98-1.76)	0.065
Age (years)	<40 / 60+	1		1		1	
	40 - 59	1.74 (1.33-2.27)	<0.001	1.73 (1.29-2.30)	<0.001	1.80 (1.35-2.39)	<0.001
BMI (kg/m2)	<25.0	1		1		-	-
	25.0+	1.52 (1.12-2.05)	0.007	1.54 (1.12-2.12)	0.009		
Chronic-plaque PsO	No	1		1		-	-
	Yes	1.55 (1.00, 2.39)	0.048	2.00 (1.20-3.32)	0.007		
Palmoplantar pustulosis	No	1		1		-	-
	Yes	2.24 (1.09, 4.57)	0.027	1.94 (0.86-4.42)	0.112		
Hospitalization for PsO in the last 5 years	No	1		1		1	
	Yes	1.66 (1.26-2.19)	<0.001	1.66 (1.23-2.24)	0.001	1.76 (1.31-2.38)	<0.001
Previous systemic therapy for PsO	No	1		1		1	
	Yes	1.36 (1.02-1.82)	0.035	1.40 (1.03-1.90)	0.03	1.45 (1.07-1.97)	0.017

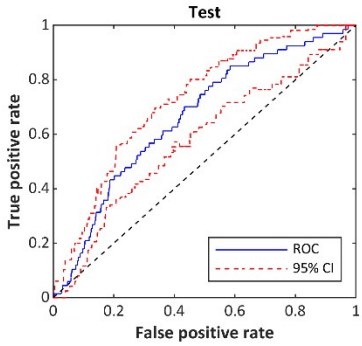
CI: confidence interval, IRR: incidence rate ratio, PsO: psoriasis

* Estimates based of multivariable Poisson regression with stepwise forward selection algorithm (AIC criterion)



a)





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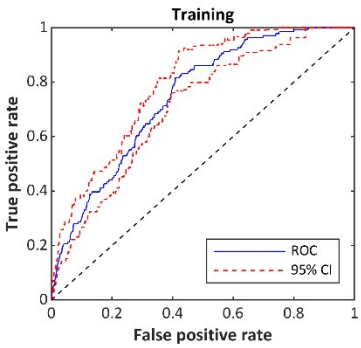

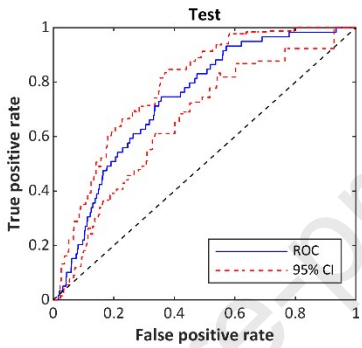

c)