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REVIEW ARTICLE

Performance and calibration of the algorithm ASSIGN in predicting cardiovascular disease in Italian patients with psoriatic arthritis

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Abstract

The increased cardiovascular (CV) risk is one of the major challenges in the management of patients with psoriatic arthritis (PsA). Recently, EULAR suggested to adapt the already available CV risk algorithms with a 1.5 multiplication factor in all the patients with rheumatoid arthritis (RA), but it is still uncertain if this adaptation could also be applied to patients with PsA. This study aims to evaluate the performance and calibration of the CV risk algorithm ASSIGN and its adaptations for RA (ASSIGN-RA) and according to EULAR recommendations in a cohort of patients with PsA (ASSIGN*1.5). Prospectively, collected data from two Italian cohorts has been analyzed. The discriminatory ability for CV risk prediction was assessed using the areas under the ROC curves. Calibration between predicted and observed events was assessed by Hosmer-Lemeshow (HL) test and calibration plots. For each algorithm, sensitivity and specificity were calculated for low- to high-risk cut-off (20%). One hundred fifty-five patients were enrolled with an observation of 1550 patient/years. Area under the ROC were 0.8179 (95% CI 0.72014 to 0.91558) for ASSIGN, 0.8160 (95% CI 0.71661 to 0.91529) for ASSIGN-RA, and 0.8179 (95% CI 0.72014 to 0.91558) for ASSIGN*1.5. HL tests did not demonstrate poor model fit for none of the algorithms. Discriminative ability and calibration were not improved by adaptation of the algorithms according to EULAR recommendations. Up to 20% of CV events occurred in patients at "low risk". No difference in performance has been observed between ASSIGN, Progetto CUORE, and QRISK2. ASSIGN could represent a useful tool in predicting CV risk in patients with PsA. Adaptation for RA or according to EULAR recommendations did not show any further improvement in performance and calibration.

Keywords ASSIGN · Cardiovascular disease · Cardiovascular risk · Psoriatic arthritis

Introduction

Patients with inflammatory arthritis, such as Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PsA), display an increased risk of cardiovascular disease (CVD) [1]. Specifically, in PsA, an increased risk of myocardial infarction, stroke, and cardiovascular mortality has been observed and CVD represents one of the most common comorbidities among patients with PsA [2–5].

The pathogenesis of CVD in patients with PsA is complex and involves different mechanisms. For instance, in PsA, a high prevalence of obesity and metabolic syndrome [6, 7] and subclinical atherosclerosis [8, 9] has been reported. Furthermore, many cytokines, which are highly produced in PsA, are also involved in plaque formation and pathology, such as interleukin (IL-1), IL-17, IL-23, and tumor necrosis factor (TNF)-alpha [10–12]. The forced reduction of physical activity and potential side effects of drugs can further explain increased cardiovascular (CV) risk in these patients [12].

The correct identification of high CV risk in patients with PsA is critical, in order to optimize preventive strategies, such as lifestyle changes and pharmacological interventions.

In general population, a large number of CV risk algorithms have been developed, but their performance and calibration in patients with inflammatory arthritis have not been

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fully evaluated yet. Arts and coauthors studied the performance and calibration of four CV risk algorithms in patients with RA, demonstrating that all the scores underestimated the actual CV risk [13].

Recently, the European League Against Rheumatism (EULAR) suggested to assess CV risk according to general population guidelines and to adapt the already available CV risk algorithms with a multiplication by the factor of 1.5 in patients with RA, except for QRISK2 in which the multiplication factor is intrinsic [1].

Only a few data evaluate the performance of different algorithms, both original and adapted according to EULAR indications, in predicting the CV risk in PsA. Recently, our group demonstrated fair to good discriminative ability for QRISK2, Framingham Risk Score (FRS), Reynold's Risk Score (RRS), Progetto CUORE, and Heart SCORE in patients with PsA and good calibration only for QRISK2 and FRS, without any further improvement using the multiplication factor according to EULAR recommendations [12].

The aim of this study is to assess in a bicentric cohort of patients with PsA the performance and calibration of the CV risk algorithm ASSIGN (a CV risk algorithm developed in Scotland by the SIGN group on risk estimation) [14] and its modifications, i.e., ASSIGN adapted for RA (ASSIGN-RA) and ASSIGN adapted with the 1.5 multiplication factor suggested by EULAR (ASSIGN*1.5).

Methods

A retrospective analysis of prospective collected data from PsA cohort of Unit of Immunorheumatology, Università Campus Bio-Medico di Roma, and Unit of Rheumatology, University of Naples "Federico II", has been made in

Table 1 Patients' characteristics at baseline (November 2007)

	Patients with PsA ($n = 155$)	Patients with PsA without CV event ($n = 140$)	Patients with PsA with CV event (n = 15)	p value (comparing patients with and without CV event)
Age (years), median (25th–75th Pctl)	48 (40–55)	47 (39–53.5)	56 (50–62)	0.0003
Female, *n* (%)	95 (61.3)	88 (62.86)	7 (46.67)	ns
Disease duration (months) at baseline, median (25th–75th Pctl)	50.47 (26.1–99.17)	50.47 (26.1–86.97)	62.63 (38.27–111.33)	ns
DAS28, median (25th–75th Pctl)	3.75 (2.42–4.705)	3.67 (2.33–4.72)	4.22 (2.6–4.4)	ns
Axial disease, *n* (%)	85 (54.83)	78 (55.71)	8 (53.33)	ns
Peripheral disease, *n* (%)	133 (85.81)	120 (85.71)	13 (86.67)	ns
Enthesitis, *n* (%)	80 (51.61)	71 (51.71)	9 (60)	ns
Dactylitis, *n* (%)	41 (26.45)	36 (25.71)	5 (33.33)	ns
PASI, median (25th–75th Pctl)	3.4 (1.575–5.6)	2.05 (1–4)	2 (1–3.6)	ns
IBD, *n* (%)	8 (5.16)	7 (5)	1 (6.67)	ns
Uveitis, *n* (%)	14 (9.03)	11 (7.86)	3 (20)	ns
Smokers, *n* (%)	52 (33.55)	47 (33.57)	5 (33.33)	ns
Atrial fibrillation, *n* (%)	6 (3.87)	4 (2.86)	2 (13.33)	ns
Total cholesterol (mg/dl), median (25th–75th Pctl)	187 (164–209)	188 (169–209)	162 (150–200)	ns
HDL cholesterol (mg/dl), median (25th–75th Pctl)	52 (43–65)	52 (43–63.5)	55 (44–77)	ns
Total cholesterol/HDL cholesterol ratio (*n*), median (25th–75th Pctl)	3.56 (2.80–4.36)	3.58 (2.81–4.50)	3.16 (2.69–4.19)	ns
Treatment with statins, *n* (%)	8 (5.16)	6 (4.29)	2 (13.33)	ns
Systolic blood pressure (mmHg), median (25th–75th Pctl)	125 (120–135)	120 (120–130)	140 (130–155)	0.0001
Antihypertensive treatment, *n* (%)	50 (32.26)	36 (25.71)	14 (93.33)	< 0.0001
BMI, median (25th–75th Pctl)	26.17 (23.67–29.21)	25.95 (23.53–28.9)	27.01 (24.22–30.48)	ns
Obesity (BMI ≥ 30), *n* (%)	30 (18.99)	23 (16.43)	4 (26.67)	ns
Type II diabetes, *n* (%)	12 (7.74)	9 (6.43)	3 (20)	ns
CRP (mg/l), median (25th–75th Pctl)	7 (1.6–25)	7 (1.6–26)	5 (1.8–20)	ns
ASSIGN, median (25th–75th Pctl)	13 (7–23)	12 (6–20)	25 (22–31)	0.0001
QRISK2, median (25th–75th Pctl)	4.5 (1.6–9.6)	3.85 (1.4–7.9	13.4 (11.5–21)	< 0.0001
Progetto CUORE, median (25th–75th Pctl)	1.8 (0.8–3.6)	1.5 (0.7–3)	5.4 (3.1–8)	< 0.0001

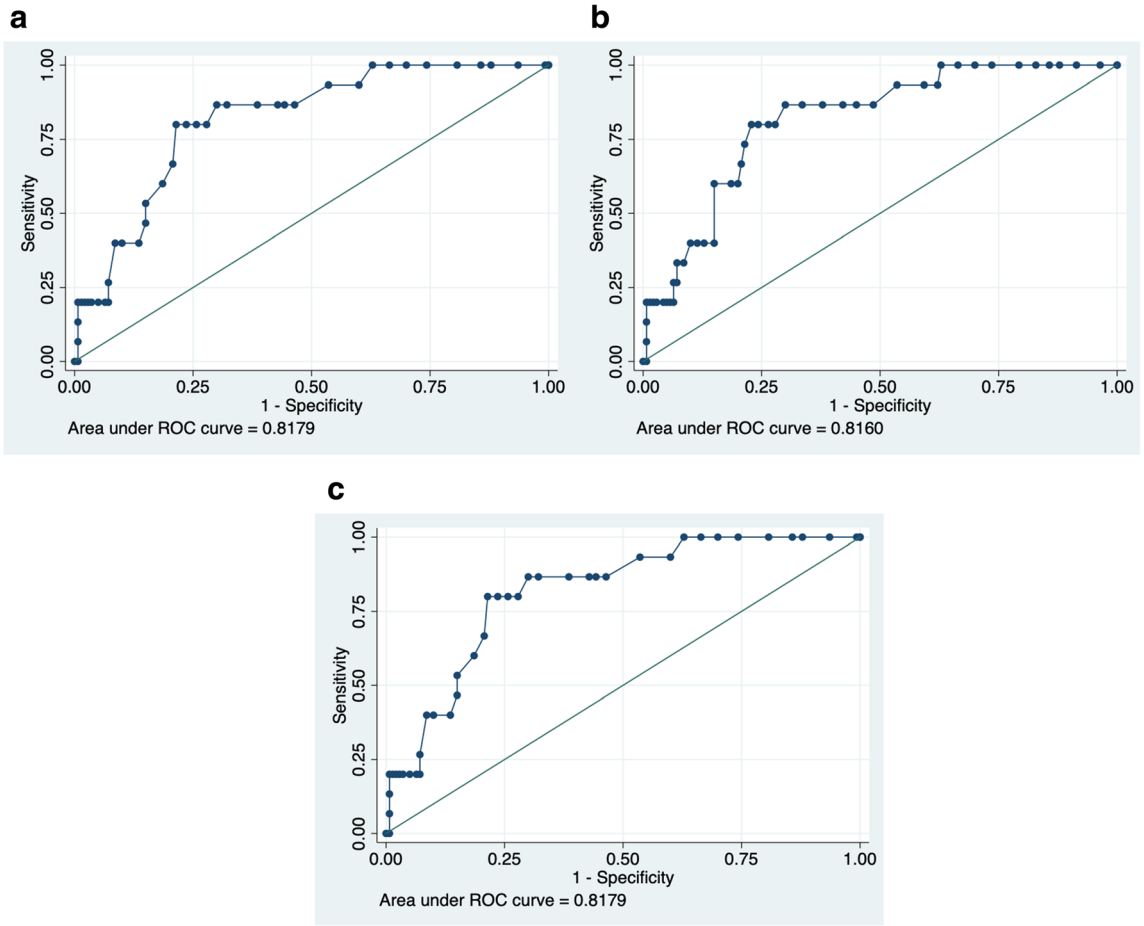

Fig. 1 ROC curves for ASSIGN, ASSIGN-RA, and ASSIGN*1.5. Areas under the curve (AUC)-values (95% CI) are 0.8179 (95% CI 0.72014 to 0.91558) for ASSIGN (A), 0.8160 (95% CI 0.71661 to 0.91529) for ASSIGN-RA (B), and 0.8179 (95% CI 0.72014 to 0.91558) for ASSIGN*1.5

November 2017. Only patients without a personal history of CV disease (CVD) at baseline (November 2007) were included in this study. At baseline, all the patients fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR). Baseline characteristics extracted from the cohort database were: age (years), gender (male/female), weight (kg), height (cm), CRP (mg/l), disease activity score (DAS) 28-joints, axial joint arthritis (Y/N), peripheral joint arthritis (Y/N), enthesitis (Y/N), dactylitis (Y/N), psoriasis area severity index (PASI), history of inflammatory bowel disease (Y/N), history of uveitis (Y/N), family history of CVD (Y/N), smoking status (Y/N/previous, and number of cigarettes smoked daily), hypertension (Y/N), systolic blood pressure (mmHg), total cholesterol (mg/dl), high-density-lipoprotein (HDL) cholesterol (mg/dl), use of statins (Y/N), use of antihypertensive medication (Y/N), diabetes mellitus (Y/N), atrial fibrillation (Y/N), chronic kidney disease stages IV–V (Y/N), angina, or heart attack in a first degree relative < 60 years (Y/N).

The primary outcome was the first CV event between sudden cardiac death, stable and unstable angina pectoris, myocardial infarction, cerebral vascular accident (CVA), and transient ischemic attack (TIA).

The 10-year general ASSIGN score was calculated using already published algorithm (Version 1.5.1). Items included are: age, sex, systolic blood pressure, total cholesterol, HDL cholesterol, number of cigarettes smoked daily, diabetes, family history of CV disease, and rheumatoid arthritis. As no patients residing in Scotland have been recruited, the default median value 15.89 for the Scottish Index of Multiple Deprivation (SIMD) has been used to calculate the ASSIGN score.

For every patient, three types of ASSIGN score have been calculated: the original one, the one adapted for patients with rheumatoid arthritis (ASSIGN-RA), and the one adapted using the multiplication factor according to EULAR recommendations (ASSIGN*1.5). The following CV risk algorithms have been also calculated: QRISK2 [15], QRISK2-RA, Progetto CUORE [16], and Progetto CUORE adapted according to EULAR recommendations (CUORE*1.5).

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy have been calculated for the cut-off value that marks the difference between low to high risk, which is 20%.

The discriminative ability of ASSIGN, ASSIGN-RA, and ASSIGN*1.5 algorithms was evaluated using the area under

the receiver operating characteristic (ROC) curve, which is similar to the concordance-statistic (*c*-statistic). Calibration was assessed by comparing the agreement between observed and predicted number of CV events in groups stratified in deciles of predicted risk using Hosmer-Lemeshow (HL) test and calibration plots. Fisher's exact test has been used for analysis of contingency table, while Mann-Whitney test has been used to compare ranks. The different ROC curves have been compared to test equality. Sample size calculated setting a type I error to 0.05, the test power to 0.8, the AUC of the adapted test to 0.7, was 143 patients. All statistical analysis was performed using STATA V.14.

Ethics committee of Università Campus Bio-Medico di Roma approved the study, which complied with the Declaration of Helsinki and its later amendments.

Results

In the present study, 155 patients (1550 patient-years) have been recruited. All the patients were Caucasic living in Center or South of Italy. During the 10-year follow-up, 15 patients showed a CV event predictable by the ASSIGN algorithm (0.97 events per 100 patient/years): eight patients with myocardial infarction or unstable angina pectoris, four patients with stable angina pectoris, and three patients with TIA. No cardiac deaths have been observed. Patients' characteristics are summarized in Table 1.

For ASSIGN, a *c*-statistic score of 0.8179 (95% CI 0.72014 to 0.91558) has been observed. No improvements in performances have been found using ASSIGN-RA (*c*-statistic score of 0.8160, 95% CI 0.71661 to 0.91529, p = ns vs ASSIGN) and ASSIGN*1.5 (*c*-statistic score of 0.8179, 95% CI 0.72014 to 0.91558, p = ns vs ASSIGN) (Fig. 1).

The HL test did not demonstrate a poor model fit for ASSIGN ($p = 0.42$), ASSIGN-RA ($p = 0.74$), and ASSIGN*1.5 ($p = 0.42$). Calibration plots are reported in Fig. 2.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the cut-off that marks the difference between low and high CV risk for ASSIGN, ASSIGN-RA, and ASSIGN*1.5 have been reported in Table 2. Among patients who developed CVD during follow-up, three of them (20%) were at "low risk" according

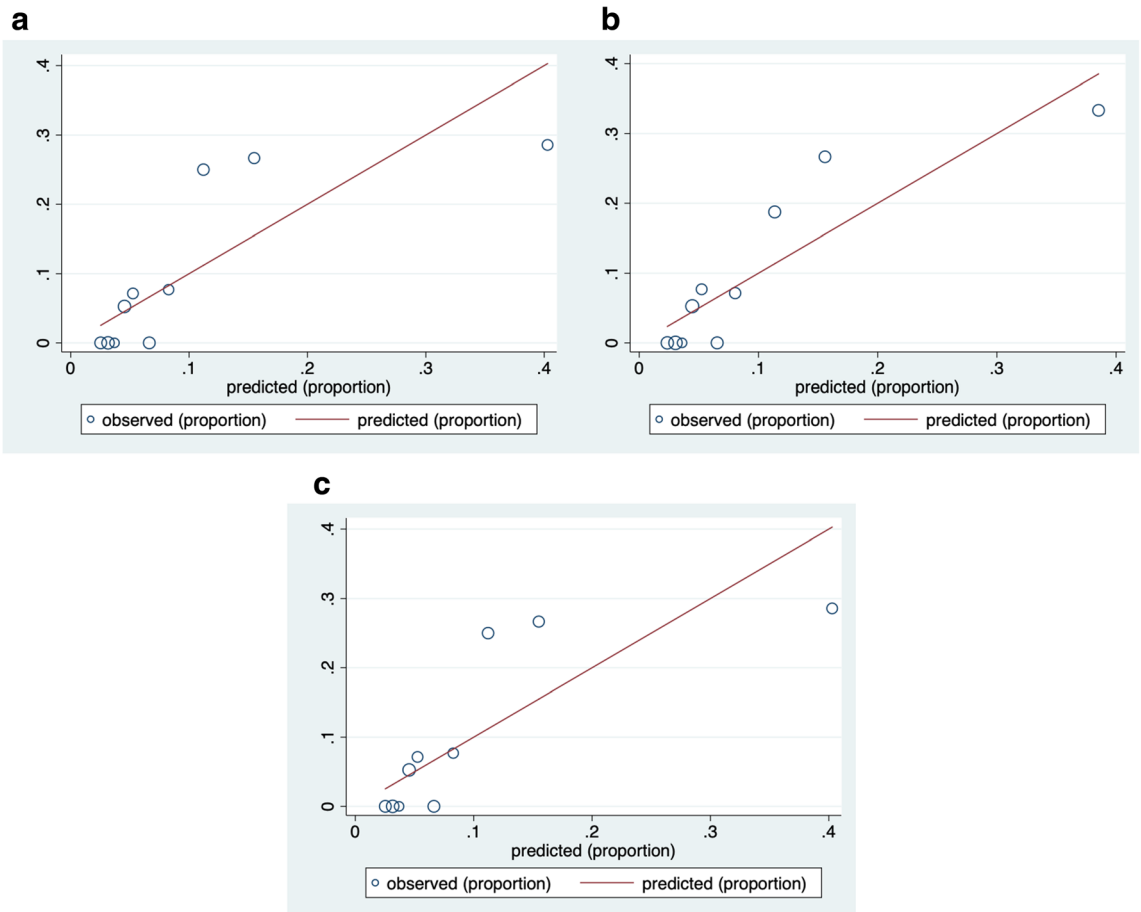

Fig. 2 Calibration plots for ASSIGN, ASSIGN-RA, and ASSIGN*1.5. Calibration plots for ASSIGN (A), ASSIGN-RA (B), and ASSIGN*1.5 (C)

Table 2 Sensitivity, specificity, and accuracy of cut-off value between low and high risk in ASSIGN

	True cases (n)	Pos tests (n)	True pos (n)	False pos (n)	False neg (n)	True neg (n)	Tot (n)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Accuracy (%)
ASSIGN > 20%	15	48	12	36	3	104	155	80	74.29	25	97.2	74.84
ASSIGN-RA > 20%	15	66	13	53	2	87	155	86.7	62.1	19.7	97.8	64.5
ASSIGN*1.5	15	78	13	65	2	75	155	86.7	53.6	16.7	97.4	56.77

Abbreviations: *pos* positive, *neg* negative, *tot* tale, *sens* sensitivity, *spec* specificity, *PPV* positive predictive value, *NPV* negative predictive value

to ASSIGN and two of them (13.3%) were at "low risk" according to ASSIGN-RA and ASSIGN*1.5. Overall, the best accuracy has been reported for ASSIGN.

When comparing the areas under the ROC, the performance of ASSIGN is not significantly different from QRISK2 ($p = 0.15$) and CUORE ($p = 0.23$); furthermore, the performance of ASSIGN-RA and ASSIGN*1.5 is not significantly different from QRISK2-RA () and CUORE*1.5 ($p = 0.23$).

Discussion

To date, the prevention of CVD in patients with PsA still remains an important unmet need [2, 4]. In these patients, a reliable use of the cardiovascular risk algorithms represents an important challenge which can lead to modifications of the lifestyle and preventive treatments. In this study, among the traditional risk factors [17], the two groups of patients differed in age, systolic blood pressure, and prevalence of antihypertensive treatment. A good discriminative ability of the ASSIGN algorithm has been reported, without any improvement using the adaptation for rheumatoid arthritis (ASSIGN-RA) or the multiplication factor suggested by EULAR recommendations (ASSIGN*1.5). Notably, the performance of ASSIGN is not inferior to QRISK2 and Progetto CUORE. Furthermore, the HL test yielded a good model fit for ASSIGN, ASSIGN-RA, and ASSIGN*1.5, demonstrating no significant difference in distribution of observed events compared to predicted ones. Despite this, still a relevant proportion of patients at low risk (20% for a ASSIGN and 13.3% for ASSIGN-RA and ASSIGN*1.5) developed CVD during the follow-up. A good sensitivity has been reported of all the three algorithms, while the original ASSIGN demonstrated the best specificity and accuracy.

Several weaknesses of this study should be taken into account. ASSIGN and its modifications have been developed for the Scottish population and studies about their performance in the Italian population are still lacking. Consequently, a personal SIMD could not be calculated, and a default median value has been used in the present study. Furthermore, we only recruited Caucasic patients with PsA from Center and South of Italy. Therefore, studies involving a larger number of patients and from other Countries or of other ethnicities are still required to confirm our results. Lastly, a low power of the HL test cannot be ruled out due to the small sample size.

Nevertheless, the present study systematically evaluated the performance and calibration of the CV risk algorithm ASSIGN and its modification in patients with PsA. Overall, ASSIGN demonstrated a good discriminative ability and calibration, without any improvement using the adaptation for patients with rheumatoid arthritis and according to EULAR recommendations. Therefore, ASSIGN could be considered for the CV risk assessment in patients with PsA. Despite a good accuracy for the cut-off point between low and high risk, a too high proportion of patients with PsA at low risk still develops CVD. Further studies are needed in order to improve CV risk prediction in PsA patients and to assess preventive strategies towards a CV-personalized medicine in patients with inflammatory arthritis.

Compliance with ethical standards

Conflict of interest The authors declare they have no conflicts of interest.

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