TREATING PSORIATIC ARTHRITIS TO TARGET: DEFINING PSORIATIC ARTHRITIS DISEASE ACTIVITY SCORE (PASDAS) THAT REFLECTS STATE OF MINIMAL DISEASE ACTIVITY (MDA)

Running Head: **PASDAS and Minimal Disease Activity in PsA**

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ABSTRACT

Objective: PASDAS is a composite disease activity measure (range 0–10) for psoriatic arthritis (PsA). We aimed to validate a cutoff value of PsA Disease Activity Score (PASDAS) that defines minimal disease activity (MDA) state, as well as validate previously defined PASDAS cutoffs for low and high disease activity.

Methods: Patients were prospectively recruited from the University of Toronto PsA clinic according to a standard protocol and variables necessary to complete the PASDAS and the MDA were collected. ROC curve analysis determined the optimal PASDAS cutoff discriminating patients in MDA state from those not in MDA. Previously proposed PASDAS disease activity cutoff scores were validated by determining the proportion of patients requiring treatment escalation, a surrogate of active disease, in each of low, moderate, and high disease activity groups.

Results: 178 patients [53.9% male, mean (sd) PASDAS 3.29 (1.29), 48.9% in MDA] were recruited. ROC curve analysis identified a PASDAS score of 3.2 as the point that maximized the sensitivity and specificity for MDA based on 5 of 7 criteria (sensitivity 88%, specificity 92%, AUC 0.96). For MDA based on meeting 6 of 7 and 7 of 7 criteria, PASDAS scores of 2.6 and 2.1 maximized sensitivity and specificity, respectively. An increasing proportion of patients from low to high disease activity groups required treatment escalation, increasing from 8.1% to 42% to 67%.

Conclusion: A PASDAS score <3.2 reflects MDA. This study has externally validated PASDAS cutoff scores previously proposed to differentiate between low, moderate and high disease activity.

Key Words: Spondyloarthritis, disease activity, psoriasis, outcome measure

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INTRODUCTION

Psoriatic arthritis (PsA) is a systemic chronic inflammatory musculoskeletal disease associated with psoriasis[1]. It is a disease that mainly affects the skin and the peripheral joints. Other common features include spondylitis, enthesitis, dactylitis, nail changes, and extra-articular features associated with spondyloarthritis (SpA)[1]. The disease has a significant impact on quality of life and function[2,3]. Assessment of PsA disease activity is challenging due to its variable manifestations. Moreover, levels of traditional acute phase reactants such as erythrocyte sedimentation rate (ESR) or C reactive protein (CRP) are within the normal range in half of PsA patients in spite of active disease[4]. The presence and severity of the various clinical features associated with PsA vary among patients and within each patient over time[5]. Therefore, instruments that measure the individual domains of this heterogeneous disease are essential for gauging the impact of the disease on the patient[6]. However, the use of multiple such measures for individual domains within the clinical setting may place undue burden on patients and clinicians. Therefore, the availability of a composite measure for the clinical setting, and research, is essential[6].

Until recently, clinical outcome measures used to assess the disease activity of PsA patients were mainly borrowed from rheumatoid arthritis (RA)[7]. These included the American College of Rheumatology (ACR) response criteria and the Disease Activity Score for 28 joints (DAS28)[7]. Both of these measures focus on peripheral joint activity and evaluate the other domains of PsA indirectly with the patient global assessment (PGA) of disease[8]. The recently developed composite disease activity measures specific for PsA include the Composite Psoriatic Disease Activity Index (CPDAI), the Disease Activity index for Psoriatic Arthritis (DAPSA), the Psoriatic Arthritis

Disease Activity Score (PASDAS), and the Arithmetic Mean of Desirability Function (AMDF-the GRACE index)[6,9,10]. The CPDAI has been criticized for the empiric nature of selection of its cutoffs of disease severity within the individual domains[10]. On the other hand, DAPSA has been criticized for its focus on articular disease[11,12].

The PASDAS incorporates assessment of joints, dactylitis, enthesitis, physical function, quality of life, acute-phase response, and both patient and physician global ratings of disease. A PASDAS score between 0-10 is calculated using a weighted formula (0= no disease, 10= severe disease). When tested against other composite outcome measures using the GO-REVEAL dataset, PASDAS outperformed the other measures by being the most responsive[13]. Moreover, the proportion of subjects without radiographic progression in the 'good' outcome group was highest for PASDAS compared to GRACE index and DAPSA[14]. From the GRACE dataset, using input from physicians and patients, it was proposed that a PASDAS score of 3.2 differentiates those with low from moderate disease activity and a score of 5.4 those with moderate from high disease activity[15]. However, no studies have externally validated these proposed PASDAS thresholds[7].

In addition to the composite disease activity measures described above, a state of Minimal Disease Activity (MDA) for PsA was proposed by Coates *et al*. as the target for treatment since patients in this state either have an absence of or a mild level of disease activity[16]. The state of MDA is defined as having achieved at least 5 of the following 7 criteria: tender joint count ≤1, swollen joint count ≤1, Psoriasis Area Severity Index (PASI) score ≤1 or Body Surface Area (BSA) ≤3, patient pain visual analog scale (VAS) ≤15, patient global activity VAS ≤20, Health Assessment Questionnaire (HAQ) ≤0.5 and tender entheseal points ≤1[16]. It is generally considered an acceptable level of

disease even though patients may still have active disease in 1 or 2 domains of PsA. MDA as a treatment target has been validated in subsequent studies that showed reduced radiographic progression of joint damage in those who achieved MDA[17,18]. While PASDAS generates a continuous score that reflects a patient's level of disease, patients either meet or do not meet the MDA criteria. Using the GRACE study dataset (the dataset originally used to develop PASDAS), it was shown that the median score for the PASDAS where the physician judged the patient to be in a state of minimal disease activity (i.e. not based on patients satisfying the MDA criteria) was 2.93[19]. While a PASDAS score that differentiates low, moderate, and high disease activity has been proposed, a cutoff score differentiating patients in a state of MDA from those not in such a state has not yet been established in an independent study. Therefore, it is of interest to find a point on the PASDAS scale that reflects MDA state, the target for treatment in PsA. Recent work by Coates *et al*. also suggested that tighter criteria for MDA (i.e. achieving 6 or all 7 of the criteria) may be needed to reflect patients who are truly in a low disease activity or remission state[19]. Hence, determining cut-offs of PASDAS for stricter definitions of low disease activity states are also of interest.

The first objective of the current study was to define a cutoff score of PASDAS that discriminates between patients in MDA from those not in MDA, as currently defined, in a routine care setting. We further aimed to define PASDAS cutoff scores for the stricter definitions of low disease activity states (i.e., meeting 6 of 7 criteria, and 7 of 7 criteria). The second objective was to validate the PASDAS thresholds differentiating low, moderate and high disease activity initially proposed by the GRACE project, using our cohort of PsA patients.

PATIENTS AND METHODS

Patients

One hundred and seventy-eight PsA patients were consecutively recruited and assessed at the University of Toronto PsA clinic from June to September 2015, similar to the design followed in the multicentre GRACE project[10]. Patients consented to this study which was ethically approved by the University Health Network Research Ethics Board (REB No. 08-0630-AE), and agreed to publication of the material. Patients satisfied classification criteria for PsA (CASPAR). The patients' disease activity was assessed using a standard protocol that includes all elements required to calculate PASDAS and MDA. This included sex, date of birth, date of PsA diagnosis, disease duration, comorbidities, medications, actively inflamed (tender of 68, and swollen of 66) joints, PASI score and BSA, enthesitis count, dactylitis count, CRP, and physician global disease activity rating (VAS) from 0-100mm. At their visit, patients completed the Health Assessment Questionnaire (HAQ), the Medical Outcomes Study Short Form – 36 measure (SF-36), and were asked to rate their global disease activity and pain over the past week using a visual analogue scale (VAS) from 0-100mm. In addition, the treating physician was asked whether or not treatment was escalated or if they had the intent to escalate treatment, and if so, whether this was for active disease in the skin, joints, or both. Treatment escalations included intra-articular injections, addition of medications(s), increase of doses of current medication(s), and/or changes to different medications for reasons other than adverse effects or patient preference.

The PASDAS is calculated using the following formula[10]:

PASDAS = (((0.18 x √Physician global VAS) + (0.159 x √Patient global VAS) – (0.253 x √SF36 – PCS) + (0.101 x LN (Swollen joint count + 1)) + (0.048 x LN (Tender joint count + 1)) + (0.23 x LN (Leeds Enthesitis Count + 1)) + (0.377 x LN (Dactylitis count + 1)) + (0.102 x LN (CRP +

1)) +2)*1.5 where all VAS scores are from 0-100mm; PCS = Physical Component Summary Scale of the SF-36; LN = natural logarithm; swollen and tender joint counts can range from 0 to 66 and 68 joints, respectively; and CRP = C-reactive protein measured in mg/l. The PASDAS score ranges from 0-10 with higher scores indicating worse disease activity.

Identifying PASDAS cutoff score for MDA state

Each patient was placed into one of two groups for analysis defined by either fulfilling or not fulfilling MDA criteria. Patients meeting at least 5 of the 7 criteria for MDA were considered to be in a state of MDA. A receiver-operating characteristic (ROC) curve for PASDAS with MDA state as the discriminator was produced. The optimal cutoff for PASDAS was determined using the Youden index to maximize the sum of the sensitivity and specificity[20]. The same analysis was undertaken to identify the PASDAS cutoff for patients meeting 6 of 7 MDA criteria as well as meeting all 7 of the MDA criteria (very low disease activity [VLDA])[19].

Validation of PASDAS cutoff scores differentiating low, moderate and high disease activity

PASDAS disease activity cutoff scores proposed by Helliwell *et al*. (low/moderate disease = 3.2 and moderate/high disease = 5.4)[15] were validated by determining the proportion of patients requiring treatment escalation, a surrogate of active disease, in each of low, moderate, and high disease activity groups.

RESULTS

Patients

Demographic and clinical characteristics for the 178 PsA patients are shown in Table 1. Patient's characteristics reflected routine practice, as indicated by low mean swollen and tender joint counts, low mean PASI score, and other clinical measures. The mean (standard deviation [s.d.]) age at assessment was 56.8 (12.8) years and patients had mean disease duration from diagnosis of 17.6 (12.7) years; 36 (20.2%) had PsA duration of less than 5 years. Overall, patients had good functional status as reflected in a mean Health Assessment Questionnaire score of 0.53 (0.59) and good self-reported quality of life with mean SF-36 – PCS and SF-36 – MCS scores within one standard deviation of the general population. The mean (s.d.) PASDAS was 3.29 (1.29); 47.8% of patients were deemed to be in a state that reflected the target for treatment (MDA state: 5 of 7 criteria met).

Table 2 presents a breakdown of the number of patients that met each individual criterion used to classify patients into an MDA state. The two criteria that were least achieved were patient's pain and patient's global disease activity VAS scores. The proportion of patients meeting 6/7 and 7/7 criteria were 28.1% and 11.8%, respectively (Table 2). Treating physician's escalated treatment or intended to escalate treatment for 47 of the 178 patients; some required more than one type of treatment escalation. Table 3 presents a breakdown of the type of treatment escalation that was initiated or intended for these patients with active disease, along with whether this was for disease activity in the joints or skin or both. Patients predominantly required an increase in dosage or frequency of their current medication and adding or switching to another drug class(es). Most patients required treatment escalation due to activity in the joints.

Identifying PASDAS cutoff score for MDA state

ROC curve analysis identified a PASDAS score of 3.2 as the point that maximized the sensitivity and specificity for differentiating MDA based on 5/7 criteria (Figure 1A). At this value, the sensitivity was 88% (95% CI: 80-93), the specificity was 92% (95% CI: 84-96) and the area under the curve (AUC) was 0.96 (95% CI: 0.94-0.99). For MDA 6/7, the equivalent score was 2.6 (Figure 1B). At this value, sensitivity was 88% (95% CI: 82-93), specificity was 86% (95% CI: 74-93) and the AUC was 0.92 (95% CI: 0.88-0.96). For VLDA (MDA 7/7), a PASDAS score of 2.1 was deemed optimal (Figure 1C). At this value, sensitivity was 89% (95% CI: 83-93), specificity was 81% (95% CI: 60-92) and the AUC was 0.91 (95% CI: 0.86-0.96).

Validation of PASDAS cutoff scores for differentiating low, moderate and high disease activity:

The total number and proportion of patients in each of low, moderate, and high disease activity groups, based on the published PASDAS cutoffs[15], that had their treatment escalated due to increased disease activity as determined by the treating physician (without knowledge of the PASDAS score) are shown in Table 4. An increasing proportion of patients from low to high disease activity groups required treatment escalation, increasing from 8.1% to 42% to 67%. Exact Cochran-Armitage trend test demonstrated a statistically significant increasing trend of treatment escalation with increasing PASDAS cutoffs ($p<0.001$). While the mean disease duration for the overall sample was 17.6 years, one-fifth of the sample had disease duration of <5 years. Even within this subgroup, the expected pattern of increasing proportion requiring treatment escalation from low to moderate to high PASDAS score was found (Cochran-Armitage Trend Test, p-value=0.0025).

Of note, the treating rheumatologist did not recommend treatment escalation in 52 patients with moderate or high disease activity according to PASDAS. Compared to the 40 patients with moderate to high disease activity according to PASDAS for whom treatment escalation was recommended, these 52 patients had lower mean CRP, lower Physicians Global Assessment VAS, were less likely to be on DMARDs and there was a trend towards lower swollen joint count and lower prevalence of dactylitis.

DISCUSSION

There has long been a need for a PsA-specific instrument to measure disease activity. Prior to the development of PASDAS, disease activity was measured by instruments borrowed from RA, such as the DAS28, which were considered one-dimensional because these focused mainly on peripheral joints. Composite measures, such as the CPDAI, reflect the entire spectrum of manifestations of PsA and have been previously validated[6,10]. Recently, Helliwell *et al* proposed the PASDAS disease activity cut-offs for measuring activity of PsA based on data from the GRACE study[15]. The purpose of the present study was twofold. The first was to define cutoff scores of PASDAS that discriminate patients meeting criteria for MDA state, as well as the alternative definitions of MDA state, and the second was to validate Helliwell *et al*'s disease activity cutoffs scores.

A state of MDA is achieved by meeting 5 of 7 criteria and is defined as a state of minimal disease or remission that should be the target of treatment[21]. We found that a PASDAS score of 3.2 was the cutoff that best differentiated patients in MDA from those that were not, with an AUC of 0.96. When looking at the alternative definitions of MDA, MDA- 6/7 and MDA- 7/7 (VLDA/remission),

lower cutoff scores of 2.6 and 2.1, respectively, reflected the fact that these criteria by definition require stricter control of disease activity.

This study has also validated the cutoff scores proposed by Helliwell *et al*. for differentiating between low, moderate and high disease activity, by using physician determined treatment escalation as an external standard from the clinical and laboratory parameters that are captured by the PASDAS composite measure to reflect active disease. In doing so, there was a more than eight-fold difference in the proportion of patients needing escalation of therapy between those deemed to have low versus high disease activity. Compared to the low disease activity group, there was more than a five-fold need for escalation of therapy in the moderate disease activity group. This trend suggests that the disease activity cutoff values proposed by Helliwell *et al*. are able to discriminate patients who have active disease requiring treatment escalation.

Defining MDA state accurately is important as tight-control of disease activity using a treat-to-target approach based on meeting MDA state improves joint outcomes for patients. MDA state by definition is a state of low or very low disease activity. The results from this study suggest that the proposed cutoff for PASDAS low disease activity (3.2), defined by Helliwell *et al*. based on a combination of patient and physician's perspective of disease activity, match well with low disease based on the MDA state (3.2). Coates *et al*. recently explored alternative criteria for the MDA state including meeting 5 of 7 criteria while mandating the criteria related to the joints be met, meeting 6 of 7 criteria, and meeting 7 of 7 criteria. They proposed a new definition for MDA state whereby meeting 7 of 7 criteria should be considered very low disease activity. Based on the original GRACE dataset, the associated cutoff of PASDAS for this MDA 7/7 state was 1.9. Using an independent cohort, we found a PASDAS score of 2.1 best differentiated between those meeting

and not meeting a 7 of 7 criteria, an estimate quite similar to that derived from the GRACE dataset[19].

Our study is the first to validate the PASDAS cutoff scores that were proposed to differentiate between low, moderate and high disease activity in an independent and external dataset. To date, there has been no knowledge about how PASDAS would perform within other datasets. As well, our results regarding MDA cutoffs for PASDAS support the work Coates *et al* have undertaken in defining a very low disease activity state using MDA criteria. Unlike the GRACE dataset, our cohort of patients come from a single centre. Thus, there is likely more consistency in how patients are evaluated and managed.

The inability to achieve a target based on a composite outcome measure like the MDA is often driven by high (i.e. worse) scores on the patient-reported components of the composite measure. We have previously demonstrated in a cohort of patients treated with methotrexate that only 17% achieve MDA[22]. The most common criteria not met were specific to the patient reported outcome measures (patient pain score $\leq$ 15; patient global disease activity $\leq$ 20; HAQ score $\leq$ 0.5). The presence of low back pain was also associated with a lower probability of achieving MDA. Consistent with this findings, the current study also showed that the two most difficult criteria to satisfy were patient pain and patient global disease activity. Back pain could also be a contributing factor. We however did not formally investigate the association between these features and MDA in this cross-sectional study.

There are certain limitations in this study. The current study only captured patients' disease activity at a single visit. While we are able to determine cutoffs for disease activity, no analyses regarding

the ability of PASDAS to measure response to therapies was made. A responder index that is able to classify a response as good, moderate or poor given an initial PASDAS score is lacking, and for this reason follow-up data is currently being collected. There is room for improvement in our current standards for assessing disease activity; we used the intention to intensify treatment as the measure reflecting active disease, which has its drawbacks and is not objective or independent of other measures. Patients included in this study had a mean disease duration of 17.6 years; therefore, lack of representation of patients with early disease may be of concern. However, one-fifth of the study participants had disease duration of <5 years. Even within this subgroup, we found the expected pattern of increasing proportion requiring treatment escalation from low to moderate to high PASDAS score. Thus, the study reflects the mix of patients typically seen in PsA clinics, and we believe the results are therefore generalizable across the disease duration spectrum. Lastly, it has already been noted that PASDAS requires a fairly comprehensive clinical assessment of the patient to obtain the information necessary to calculate the score[10]. The MDA is easier to score and complete and since the PASDAS cut-off reflecting MDA reflects low disease activity based on published PASDAS cut-offs, it may be more feasible to use MDA rather than PASDAS within a busy clinical setting. PASDAS may be more valuable as a response measure in clinical trials, as well as a measure of disease activity in research studies.

PsA is a chronic autoimmune disease with heterogeneous manifestations best assessed by a composite disease activity measure like PASDAS. In this study, we have validated the cutoff scores for differentiating low, moderate and high disease activity for PASDAS derived from the GRACE dataset. Further, we have used data from the University of Toronto PsA observational

cohort to derive the cutoff representing MDA state. The cutoff for MDA may represent the target score for treatment.

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DISCLOSURE STATEMENT

The authors declare that they do not have any potential conflicts of interests

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FIGURE LEGEND

Figure 1A: ROC curve for PASDAS with MDA state (5/7) as the discriminator. The value of PASDAS when Youden index was maximized (0.80) was 3.2. At this point, the sensitivity (%) was 88 (95% CI: 80-93), the specificity (%) was 92 (95% CI: 84-96) and the area under the curve (AUC) was 0.96 (95% CI: 0.94-0.99). **1B**: ROC curve for PASDAS with MDA-6/7 state as the discriminator. The value of PASDAS when Youden index was maximized (0.74) was 2.6. At this point, the sensitivity (%) was 88 (95% CI: 82-93), the specificity (%) was 86 (95% CI: 74-93) and the area under the curve (AUC) was 0.92 (95% CI: 0.88-0.96). **1C**: ROC curve for PASDAS with MDA-7/7 state as the discriminator. The value of PASDAS when Youden index was maximized (0.70) was 2.1. At this point, the sensitivity (%) was 89 (95% CI: 83-93), the specificity (%) was 81 (95% CI: 60-92) and the area under the curve (AUC) was 0.91 (95% CI: 0.86-0.96).

***Table 1*. Demographic and clinical characteristics of PsA patient sample.**

Characteristic	PsA, n = 178
Sex	
Female	82 (46.1%)
Male	96 (53.9%)
Age, years*	56.8 (12.8)
Age at PsA diagnosis, years*	39.1 (13.6)
Disease duration from PsA diagnosis, years*	17.6 (12.7)
Swollen Joint Count (0-66)*	0.71 (2.03)
Swollen Joint Count, median (range)	0 (0-19)
Tender Joint Count (0-68)*	2.21 (4.88)
Tender Joint Count, median (range)	0 (0-31)
Patients with oligoarticular PsA	28 (15.73%)
Patients with axial disease (NY criteria)	67 (37.64%)
Psoriasis Area Severity Index [PASI (0-72)]*	1.64 (3.95)
Leeds Enthesitis Index (0-6)*	0.13 (0.49)
CRP (mg/L)*	5.08 (6.88)
Health Assessment Questionnaire Disability Index (0-3)*	0.53 (0.59)
SF-36 – PCS (0-100)*	40.10 (12.39)
SF-36 – MCS (0-100)*	48.93 (10.75)
No. of digits with dactylitis *	0.03 (0.22)

Patient Pain VAS (0-100mm)*	37.81 (27.02)
Patient Global Disease Activity VAS (0-100mm)*	34.97 (25.57)
Physician Global Disease Activity VAS (0-100mm)*	18.93 (14.00)
PASDAS*	3.29 (1.29)
MDA (5 of 7)	85 (47.8%)
Patients treated with conventional DMARDs	114 (64.04%)
Patients treated with methotrexate	87 (8.88%)
Patients treated with Biologic agents	89 (50.0%)

*mean (stand deviation); SF-36 – PCS- Physical component summary score of the Medical Outcomes Survey- Short Form 36; SF-36 – MCS- Mental component summary score of the Medical Outcomes Survey- Short Form 36; VAS- Visual Analogue Score; PASDAS- Psoriatic Arthritis Disease Activity Score; MDA- Minimal Disease Activity

Table 2: **Breakdown of the individual criterion of MDA status**

Criterion	n (of 178) (%)
Composite criteria	
MDA-5/7	85 (47.8)
MDA-6/7	50 (28.1)
MDA-7/7	21 (11.8)
Individual criteria	
Tender Joint Count ≤ 1	125 (70.2)
Swollen Joint count ≤ 1	151 (84.8)
PASI ≤ 1	97 (54.5)
Patient pain VAS ≤ 15	46 (25.8)
Patient global activity VAS ≤ 20	75 (42.1)
HAQ ≤ 0.5	112 (62.9)
Tender entheseal points ≤ 1	166 (93.2)

MDA- Minimal Disease Activity; HAQ- Health Assessment Questionnaire; VAS- Visual Analogue Score

Table 3: **Treatment escalation, reflecting changes or intent to escalate, for 47 patients**

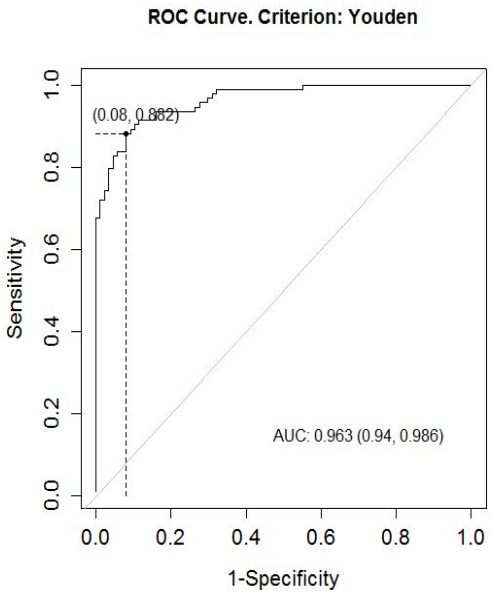
Escalation Type/Reason	**n**
Type of Treatment Escalation	
Increase in dosage or frequency	21
Switch medications within same drug class	8
Adding or switching to another drug class(es)	17
Intra articular steroid injection	8
Reason for Escalation	
Skin Disease	5
Joint Disease	38
Skin and Joint Disease	4

47 patients required escalation of treatment in total with some requiring more than one type of treatment escalation.

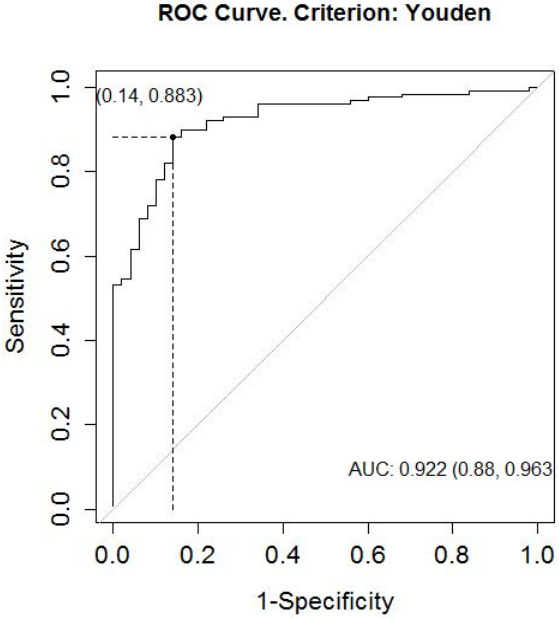
Table 4: **Proportion of patients requiring treatment escalation by disease activity category as defined by published PASDAS cut-offs.**

	PASDAS low disease activity	**PASDAS mod. disease activity**	**PASDAS high disease activity**
Number of patients	86	86	6
Number requiring treatment escalation	7	36	4
Proportion	0.081	0.42	0.67

A



B



C