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CLINICAL EVOLUTION OF PATIENTS WITH NEW-ONSET INFLAMMATORY BACK PAIN: A POPULATION-BASED COHORT STUDY

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Abstract

Objective—Inflammatory back pain (IBP) is often an early manifestation of spondyloarthritis (SpA), but the prognosis of patients with incident IBP is unknown. We investigated the long-term outcomes of patients with IBP, and predictors of progression to SpA, in a retrospective longitudinal study of a population-based cohort.

Methods—We used the Rochester Epidemiology Project, a longstanding population-based study of residents of Olmsted County, Minnesota, USA, to identify patients aged 16 to 35 with clinical visits for back pain from 1999 to 2003. We screened these patients for the presence of new-onset IBP, and performed medical record reviews to collect data on clinical, laboratory, and imaging features of SpA. We followed their outcomes until July 2016. We used survival analysis for competing risks to examine their progression either to SpA, a non-SpA diagnosis, or resolution of back pain. We used recursive partitioning to identify predictors of progression to SpA.

Results—Among 5304 patients with back pain, we identified 124 patients with new-onset IBP. After a median follow-up of 13.2 years, 39 patients progressed to SpA, 15 developed a non-SpA diagnosis, and 58 had resolution of IBP. At 10 years, the probability of having SpA was 30%,

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while the probability of resolution of IBP was 43%. The most important predictors for progression to SpA included uveitis, male sex, and family history of SpA.

Conclusion—A minority of patients with new-onset IBP progress to SpA, while many resolve. That IBP often resolves may explain the difference between the prevalence of IBP (3-6%) and prevalence of SpA (0.5-1%).

Keywords

inflammatory back pain; ankylosing spondylitis; spondyloarthritis; long-term outcomes

Inflammatory back pain (IBP) is a form of chronic low back pain, typically with gradual onset in young adulthood, characterized by improvement with exercise, worsening with inactivity, and associated with morning stiffness. IBP is commonly considered a *sine qua non* of spondyloarthritis (SpA), and its presence is considered an indication to refer patients to appropriate specialists for further evaluation (1). It is an important component of the modified New York criteria for ankylosing spondylitis (AS), as well as the recent Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial SpA (2,3).

The importance of distinguishing IBP from other more common forms of low back pain is evidenced by attempts to codify the unique features of this symptom. The Calin, Berlin, and ASAS criteria for IBP have specificities for a diagnosis of SpA that range from 72% to 91.7% (4–8). With this high specificity, it has been assumed that most patients with IBP either have, or will later develop, SpA.

The prevalence of IBP among adults aged 20-69 in the United States is 5.0% to 6.0%, based on data from the 2009–2010 National Health and Nutrition Examination Survey (NHANES) (9). In contrast, the prevalence of SpA is estimated to range from 0.4 – 1.3% (10,11). This gap between the prevalence of IBP (the symptom) and the prevalence of SpA (the disease) is unexplained. It could mean that IBP features are common components of back pain due to many different disorders, and that the IBP criteria are less specific when applied to the general population. Alternatively, it could indicate that a substantial number of patients with IBP have inflammatory symptoms but do not evolve to AS or SpA. Although several studies have reported the clinical evolution of patients with possible AS or undifferentiated SpA, no studies have specifically examined the long-term outcomes of patients with IBP who do not necessarily have other SpA features (12–14).

To address these questions, study of an inception cohort of patients with IBP with a long follow-up is needed, given that it may take up to 10 years from symptom onset to diagnosis of SpA (15). In addition, the study should include patients who present to primary care as well as many diverse specialties, given that many types of providers care for patients with back pain. Therefore, we conducted a retrospective longitudinal study of a population-based cohort based in the Rochester Epidemiology Project (REP). Our goal was to determine the long-term clinical outcomes of patients with new-onset IBP, and specifically to determine the proportion that progressed to a clinical diagnosis of SpA. Finding that a large proportion of patients progressed to SpA would support the notion that IBP and SpA are tightly linked

processes. Alternatively, finding that many patients progressed to conditions other than SpA would suggest limited specificity of IBP symptoms for a diagnosis of SpA. Finding that IBP in many patients resolved would indicate that IBP can be a self-limited problem. We also sought to identify whether there were subgroups of patients who, based on their demographic or clinical characteristics, were more likely to progress to SpA.

PATIENTS AND METHODS

Data Source and Patient Inclusion

The REP is a medical record-linkage system with longitudinal medical data of the complete population of Olmsted County, Minnesota (108,095 persons in 2000), with a 98% participation rate in 2000 (16). REP includes medical records from all subspecialties, which is particularly important in a retrospective study of IBP. Diagnoses and symptoms present at each visit are extensively coded using both International Classification of Diseases, ninth edition (ICD-9) and Hospital International Classification of Diseases Adaptation (HICDA) codes. This study was approved by the institutional review boards of the Mayo Clinic and Olmsted Medical Center, Rochester MN.

We included Olmsted County residents who had newly identified IBP at an age of 16 to 35 years between January 1st, 1999 and December 31st, 2003. These years were chosen because electronic medical records (EMRs) were adopted in 1999, and to allow for at least 12 years of follow up. Our operational definition of IBP was fulfillment of any one of the three IBP criteria sets (Calin, Berlin, or ASAS) based on medical record review, or notation of the presence of IBP by a treating rheumatologist (even if the patient did not fulfill of one of the three criteria sets) (4–6).

Case Ascertainment and Data Collection

We used three steps to identify patients with new-onset IBP: 1. electronic searches of medical records for relevant diagnosis and procedure codes; 2. screening of EMRs of potentially-eligible back pain visits for implicit diagnosis of IBP; 3. detailed chart review of those who screened positive for IBP on implicit review to apply explicit IBP criteria. The process is illustrated in Supplemental Figure 1.

Specifically, we started with a search for patients aged 16 to 35 with a diagnosis of back pain in 2000–2003, using ICD-9 codes and HICDA codes for back pain. A complete list of codes is provided in Supplemental Table 1. We excluded patients who had a back pain visit and a diagnosis code of external causes of injury and poisoning (E-code) on the same day, patients who had a back pain visit and a code for pregnancy on the same day, and patients with diagnosis codes of sciatica (ICD9 724.3) or lumbosacral neuritis (ICD9 724.4) and a procedure code of laminectomy/discectomy within one year of either of these diagnoses. These exclusions were based on preliminary chart reviews that showed these patients had very low likelihoods of having IBP. Additionally, in preliminary work, the yield of cases of incident IBP was much lower among patients older than 35, so we set this as the maximum age of onset for this study.

The initial search identified 5304 patients who had a medical visit for back pain (not necessary new onset back pain) in 2000 - 2003, at age 16 to 35. Two rheumatologists (RW and MMW) reviewed medical records of these back pain visits, and each patient was labeled as “No IBP,” “possible IBP,” or “definite IBP” based on the reviewers’ impression of back pain descriptions. Charts of all patients with “possible IBP” or “definite IBP” were reviewed and confirmed by both reviewers. To ensure the specificity of our cohort, a third rheumatologist (KW) not involved in the initial screening also reviewed the records of patients who had determinations of “possible IBP” and “definite IBP” to confirm or refute the presence of IBP. Patients who had “possible IBP” and “definite IBP” underwent detailed chart review (RW).

To identify incident cases, we then identified those who had no back pain visits before January 1st, 1999, and who fulfilled our operational definition of IBP, as the inception cohort of patients with IBP. The date that the patient first fulfilled the IBP definition was defined as the IBP incidence date. We also collected demographic information, data on SpA-related clinical features, clinical diagnosis and laboratory results, including inflammatory markers and HLA-B27 status, through follow-up until the end of data collection on July 31st, 2016. Clinical SpA features included a past history of uveitis, peripheral arthritis, psoriasis, dactylitis, enthesitis, inflammatory bowel disease, reactive arthritis, good response to NSAIDs, and family history of SpA, as recorded in the medical records. Clinical features that were not described or documented in the medical records were considered absent. HLA-B27 was not tested in all patients, and was categorized as HLA-B27-positive, negative, or unknown.

The primary outcome was the development of SpA, including either AS by modified NY criteria or a clinical diagnosis of spondyloarthritis, psoriatic arthritis, inflammatory bowel disease-associated arthritis, or reactive arthritis by the treating rheumatologist. Given that all patients satisfied the clinical criterion of IBP, AS was defined as the presence of bilateral grade 2, or unilateral grade 3 or 4 sacroiliitis based on review of all available pelvis, hip, lumbar spine, or abdominal radiographs by one reader (MMW) (2). Diagnoses other than SpA that explained the patient’s back pain symptoms, such as degenerative spine conditions and fibromyalgia, were recorded as well.

For patients who developed SpA, the outcome date was defined as the date of a clinical diagnosis of SpA, or the date of the first radiographs that showed sacroiliitis, whichever occurred first. For patients diagnosed with non-SpA conditions, the outcome date was the date of non-SpA diagnosis. Patients who received no specific diagnosis for their back pain during follow-up were categorized into one of two outcome groups: 1) those who continued to report back pain on visits within one year of their last recorded medical visit were defined as persistent IBP without a SpA diagnosis; 2) those whose back pain was recorded as resolved at a medical visit and did not later recur, or whose last medical visit on which back pain was reported was more than one year prior to their last recorded medical visit were defined as IBP resolved. For those whose back pain resolved, the outcome date was the date of the visit documenting resolution of back pain; when this was not recorded, the mid-point between the date of the last medical visit with back pain and the date of last medical visit was used. The remaining patients, whose IBP was persistent without a specific diagnosis

throughout follow-up, were censored at their last medical visit. If a patient had both SpA and a non-SpA diagnosis, we designated SpA as the outcome, regardless of whether the non-SpA diagnosis preceded the SpA diagnosis.

Statistical Analysis

Descriptive statistics were used to summarize the data. Aalen-Johansen methods, a multistate generalization of cumulative incidence with adjustment for competing risks, were used to examine the progression to three outcomes: SpA, a specific non-SpA diagnosis, or resolution of IBP (17).

We performed two sensitivity analyses. The first sensitivity analysis included patients who were considered as having “possible IBP” or “definite IBP” by all three reviewers and fulfilled the explicit IBP definition. The second sensitivity analysis used the date of back pain onset, rather than the date of fulfillment of IBP criteria, as the start date for the analysis. In some patients, the reported onset of back pain was months, or occasionally years, earlier than the time when IBP was documented in the medical records, and the time of back pain onset may reflect the true start of IBP.

We used recursive partitioning methods and Cox proportional hazards models with a time-to-event outcome to identify predictors of progression to SpA. Recursive partitioning identifies predictors that best segregate subgroups with different prognoses. By its hierarchical tree structure, the method also identifies interactions between predictors that are prognostically influential. Demographic features, clinical SpA features, inflammatory markers, and HLA-B27 status were used as potential predictors in these analyses. Ten-fold cross-validation was used to prune the tree by applying a 1 minus standard error rule to the complexity parameter to avoid overfitting. Analyses were performed using R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Cohort

Of 5304 Olmsted County residents who had clinical visits for back pain at ages 16–35 years, 172 patients had “possible IBP” or “definite IBP” on implicit review (Supplemental Figure 1). After detailed medical record review, 124 patients with new-onset IBP were identified (2.3% of all with visits for new back pain) (Table 1). There were 82 men and 42 women in the cohort. The mean ± standard deviation (SD) age of inclusion was 27.8 ± 5.0 years. The mean ± SD age of back pain onset was 25.0 ± 5.5 years. Ninety-two percent of the cohort fulfilled the Calin criteria, 28% fulfilled the Berlin criteria, and 48% fulfilled the ASAS criteria for IBP. Twenty-nine patients (23%) were evaluated at least once by a rheumatologist. In fourteen patients (11%), IBP was explicitly documented by their treating rheumatologists, one of whom did not fulfill any of the IBP criteria sets. The median (IQR) follow-up of the cohort was 13.2 (8.9, 14.6) years. The median number of follow-up pelvis or spine radiographs was 2 (range 1 to 6).

Progression to SpA

At the end of follow-up, 39 patients with IBP had progressed to SpA, including 33 patients with AS based on radiographic sacroiliitis and 6 with SpA based on clinical diagnosis by treating rheumatologists. Fifteen patients evolved to non-SpA conditions: degenerative disk conditions in 9, fibromyalgia in 3, mechanical back pain in 2, and systemic lupus erythematosus in one patient. In 58 patients, IBP resolved during the follow up period. Five patients were censored because of loss to follow-up.

The cumulative probabilities that patients with IBP evolved to SpA at 5, 10, and 15 years were 24% (95% confidence interval [95% CI] 16–31), 30% (95% CI 21–37), and 33% (95% CI 24–42), respectively (Figure 1A, 1B). The cumulative probabilities that patients with IBP evolved to a specific non-SpA diagnosis at 5, 10, and 15 years were 11% (95% CI 5–16), 11% (95% CI 5–16), and 13% (95% CI 6–19), respectively. The cumulative probabilities that symptoms of IBP resolved at 5, 10, and 15 years were 19% (95% CI 12–26), 43% (95% CI 34–52), and 49% (95% CI 39–57), respectively. Of note, within the first year of inclusion, the probability of evolving to SpA was 24% (95% CI: 16-31%), and the probability of evolving to non-SpA diagnosis was 6% (95% CI: 2-11%). Results were similar in the sensitivity analysis that included patients who were determined to have IBP by all three reviewers (Supplemental Figure 2). In the sensitivity analysis that started follow-up from the time of back pain onset, the cumulative probability that patients with IBP evolved to SpA at 5, 10, and 15 years was 20% (95% CI 12–26), 27% (95% CI 19–35), and 31% (95% CI 22–38), respectively (Figure 2A, 2B). The cumulative probabilities that patients with IBP evolved to a specific non-SpA diagnosis at 5, 10, and 15 years were 7% (95% CI 2–11), 11% (95% CI 5–16), and 12% (95% CI 6–17), respectively. The cumulative probabilities that IBP resolved at 5, 10, and 15 years were 15% (95% CI 8–21), 36% (95% CI 27–44), and 43% (95% CI 33–51), respectively.

Predictors of progression to SpA

Recursive partitioning identified a history of uveitis, male sex, and family history of SpA as the most important predictors for developing SpA (Figure 3). Patients with history of uveitis had a 5-fold higher risk of developing SpA compared to those without a history of uveitis (HR: 5.0; 95% CI: 2.5, 10.2). Among those without a history of uveitis, men had a 2.7-fold higher risk of SpA compared to women (HR: 2.7; 95% CI: 1.0, 7.1). Among men with no personal history of uveitis, a family history of SpA increased the risk of developing SpA by 3.2 fold compared to men without a family history (HR: 3.2; 95% CI: 1.3, 8.1). Among men with no personal history of uveitis or family history of SpA, whether a HLA-B27 test was performed predicted the risk of progression to SpA with a 3-fold risk compared to those who were not tested (HR: 3.1; 95% CI: 1.2; 8.1).

The absolute risk of developing SpA at 5 years of IBP ranged from 69% for those with a past history of uveitis to 8% for women with no history of uveitis. Risks in other subgroups were intermediate. Other clinical features, such as peripheral arthritis, enthesitis, dactylitis, inflammatory bowel disease, were not identified as prognostically important.

DISCUSSION

Despite the widespread use of IBP in the diagnosis of SpA, little is known about the long-term outcomes of patients with IBP. In this population-based study, we found that less than one-third of patients with IBP progressed to SpA during a follow-up period of over 13 years. IBP symptoms resolved in almost one-half of patients. In our cohort, a history of uveitis was the most important predictor of whether a patient was likely to progress to SpA.

The finding that IBP resolved without progression in a large proportion of patients suggests that the symptom complex described by IBP may often reflect a self-limited process. This could represent inflammation that is either not intense enough or sustained enough to result in established SpA. In this way, IBP should be considered analogous to arthralgia, which may not always be associated with objective arthritis. It could also suggest that IBP may be associated with a broader differential diagnosis than solely SpA. In many patients, IBP persisted for several years before resolving, suggesting that inflammation was not always transient.

Alternatively, patients without a true inflammatory cause of back pain may have also reported symptoms of IBP, in part because the language describing morning stiffness and changes with activity or rest can be imprecise (18) Clinicians and patients may interpret and discuss these concepts differently. These patients may have either gone on to be diagnosed with a specific non-SpA diagnosis or have their back pain resolve. Some misclassification could occur due to the limited specificity of the construct or the words used to describe IBP.

Several surveys have reported the prevalence of IBP in general populations. In a study conducted in the United Kingdom, 20% patients with back pain fulfilled the Calin criteria for IBP; among them, only 5% had radiographic sacroiliitis (19). In another UK population-based survey, the prevalence of IBP in patients who had a back pain visit with their primary care providers were from 7.7% to 15.4%, depending on the criteria used (20). The prevalence of IBP in Mexico was estimated at 3.0% (21). In the 2009–2010 NHANES, the prevalence of IBP ranged from 5.0% to 6.0%, depending on the criteria used (9), while the estimated prevalence of SpA in the US is 1.0% (10). Our finding that the majority of patients with IBP do not progress to SpA explains this gap between the prevalence of IBP and that of SpA.

Uveitis was the most important predictor for the development of SpA in this cohort, a finding consistent with a previous study(8). Up to 50% of patients with AS have at least one episode of uveitis during the course of their disease (22). Genetic studies of AS and uveitis have shown shared associations with HLA-B27, as well as *IL23R*, *ERAP1*, and the intergenic locus *2p15* (23). In addition, sex and family history also had a role in predicting progression to SpA in patients with IBP. These findings are consistent with the notion that the risk for developing SpA is largely genetically determined. These results also indicate that all SpA-associated features are not equally predictive of progression, and weighting of different features may be useful for this purpose.

In our main analysis, there was a steep increase in SpA at the time patients met the IBP criteria. It is likely that patients had some IBP symptoms for years, and at the time of their

initial visit, both IBP and a diagnosis of SpA were identified simultaneously. Because of the design of this study, in which patients were assessed only when they presented for a medical visit rather than at pre-specified time intervals, this analysis may have misspecified the true onset of IBP. We addressed this issue in a sensitivity analysis that used the onset of back pain as Time 0, which showed a more gradual progression to SpA.

Several limitations are present due to the retrospective nature of the study. We emphasized specificity in the patients who were included, and likely omitted some cases in which the treating physicians failed to recognize or document the presence of IBP features. Misclassification of these patients may have occurred because these patients had less typical or prominent IBP symptoms, and may have been even less likely to progress to SpA than patients with typical or prominent IBP symptoms. Patient follow-up was based on clinical need, so those with milder symptoms may not have been re-evaluated as frequently. This could have resulted in an underestimation of the progression to SpA. In addition, over time, patients may accommodate to their back pain symptoms, and it may have not remained an active issue during clinical encounters. This could lead to over-estimate of resolution. In the analysis of predictors for progression, we considered any undocumented clinical feature as not present, which could lead to under-appreciation of some risk factors. Only 31% of patients were tested for HLA-B27, and diagnostic suspicion bias likely contributed to the prognostic importance of the results related to HLA testing. If HLA testing had been done universally, the predictors for progression might be different. We did not find peripheral arthritis, enthesitis, dactylitis, or inflammatory bowel disease to be prognostically important, however, the sample size of our study may not be large enough to examine these conditions. Medication history was not included in our analysis. These limitations are balanced by the strengths of the study, which is the first population-based study of outcomes in patients with IBP. We also had the advantage of accessing complete medical records over an extended time, which allowed tracking of clinical outcomes.

Our findings indicate that while IBP can be a precursor of SpA, the presence of IBP is not a predestination to SpA. IBP is more accurately considered a symptom complex of a specific type of arthralgia that may or may not be associated with SpA and may be self-limited. Therefore, caution should be taken to not over-interpret the implications of IBP for diagnosis, and seek objective findings and other aspects of the medical history when counseling patients regarding their prognosis for progression to SpA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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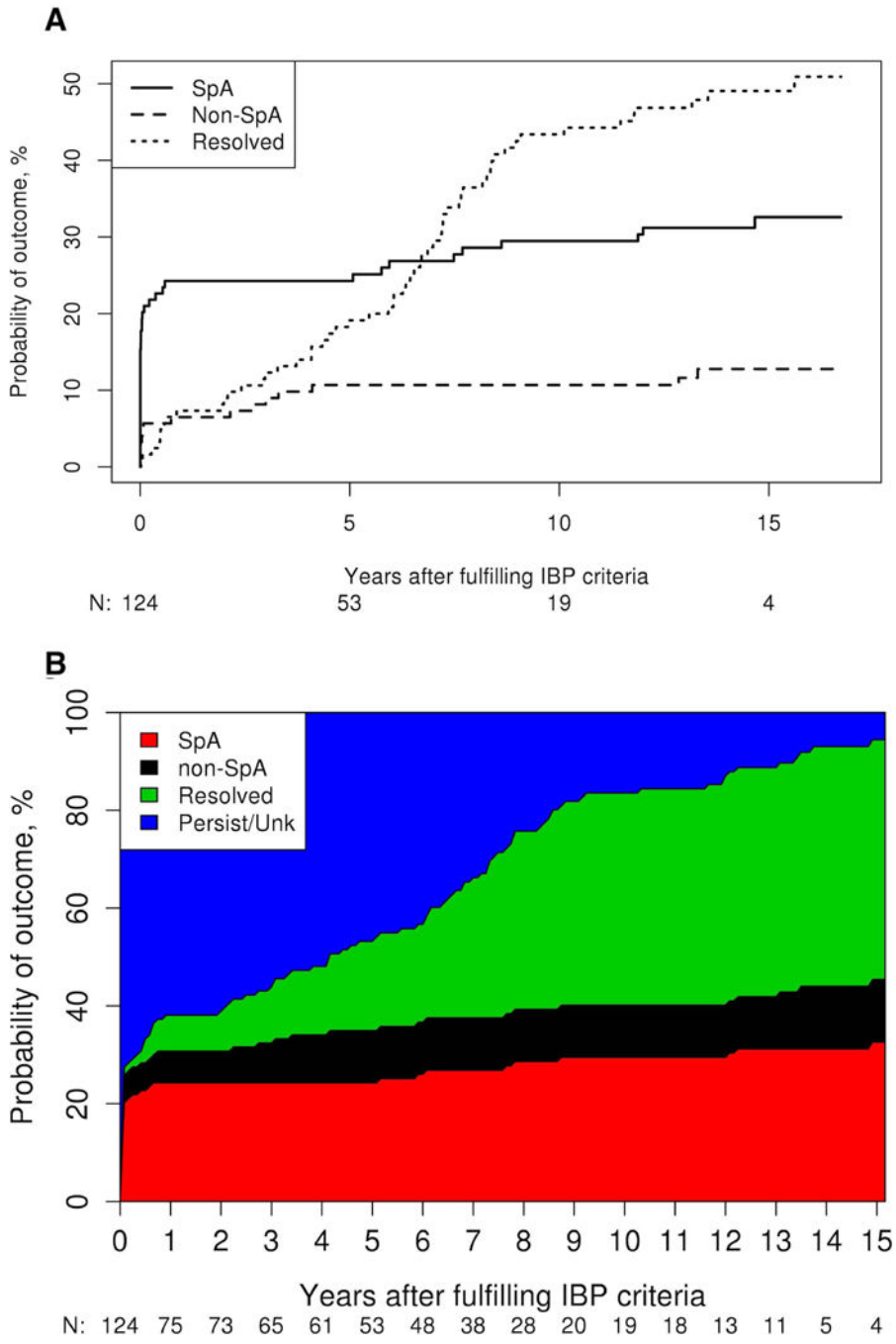

Figure 1.

Progression from inflammatory back pain (IBP) to spondyloarthritis (SpA), non-SpA diagnosis, and resolution of back pain beginning from the time of fulfilment of IBP criteria. A. Cumulative incidence curves for the progression to each outcome. B. Area graph for proportion of each outcome over time. The numbers across the bottom are the number of patients at risk at each time point.

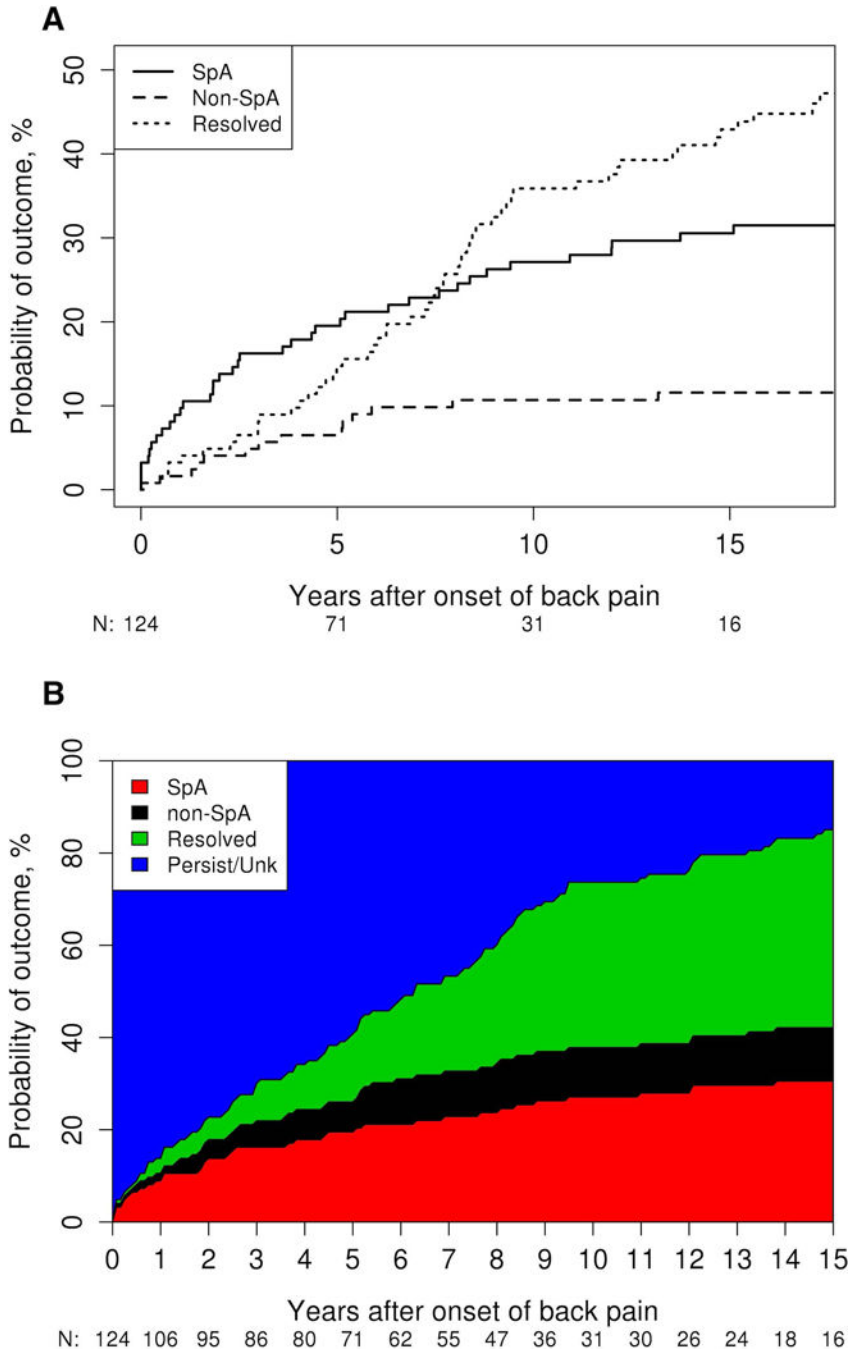

Figure 2.

Progression from inflammatory back pain (IBP) to spondyloarthritis (SpA), non-SpA diagnosis, and resolution of back pain beginning with time of back pain onset. A. Cumulative incidence curves for the progression to each outcome. B. Area graph for proportion of each outcome over time. The numbers across the bottom are the number of patients at risk at each time point.

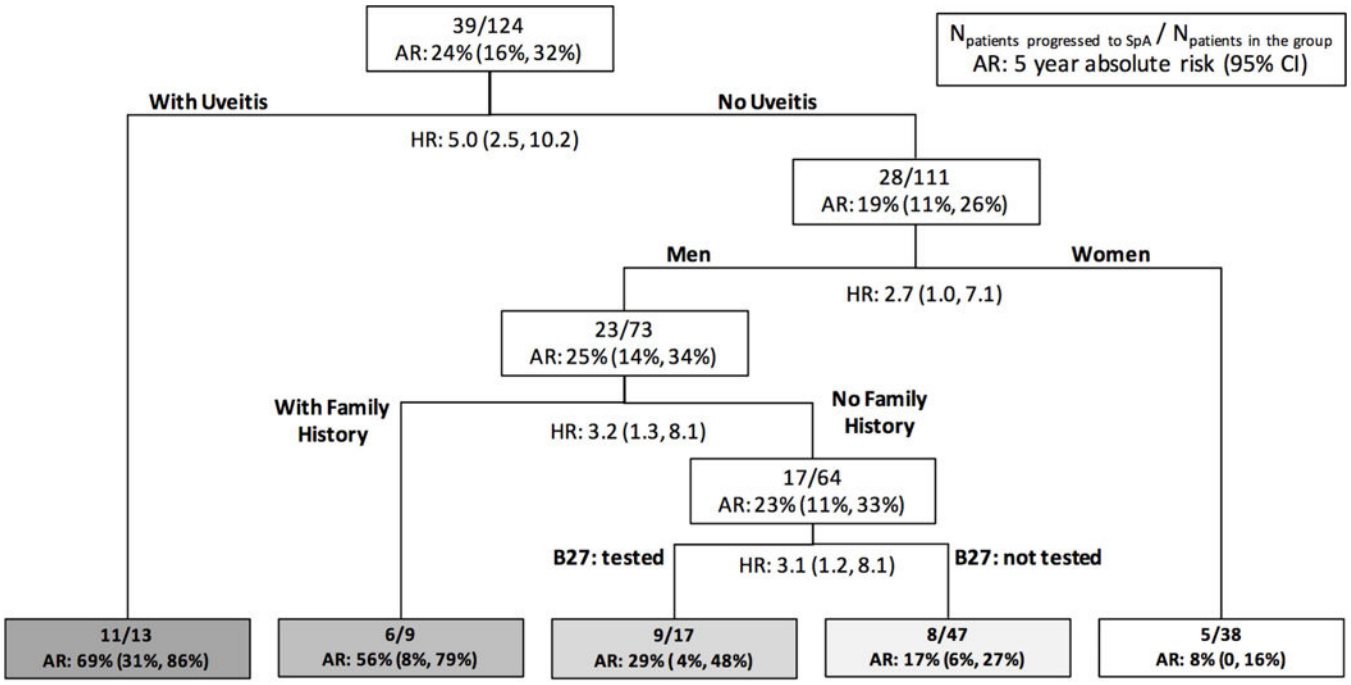

Figure 3.

Recursive partitioning model for progression to spondyloarthritis (SpA), developed using all predictors. The variable on the top of the tree, history of uveitis, resulted in the best separation of the risk for developing SpA. The hazard ratio for progression to SpA is 5.0 for the group with a history of uveitis, compared to the group without a history of uveitis. These subgroups were then repeatedly split, based on the presence or absence of other clinical features, until the final groups that were most homogenous for their risk of progression to SpA were obtained. $N_{\text{patients progressed to SpA}}$: number of patients who progressed to spondyloarthritis; $N_{\text{patients in the group}}$: total number of patients in the group; AR: 5-year absolute risk of progression to SpA; HR: hazard ratio.

Table 1

Demographic and clinical features of 124 patients included in the cohort of patients with inflammatory back pain (IBP).

		Main Analysis (N = 124)	Sensitivity Analysis 1 (N=113)
Age at inclusion, mean ± SD, years		27.8±5.0	28.0±4.8
Age at back pain onset, mean ± SD, years		25.0±5.5	25.0±5.4
Duration of follow-up, median (IQR) years		13.2 (8.9, 14.6)	13.3 (9.2, 14.6)
Male, n (%)		82 (66%)	76 (67%)
Uveitis, n (%)		13 (10%)	13 (12%)
Dactylitis, n (%)		5 (4%)	5 (4%)
Enthesitis, n (%)		18 (15%)	17 (15%)
Arthritis, n (%)		8 (6%)	8 (7%)
IBD, n (%)		4 (3%)	4 (4%)
Psoriasis, n (%)		8 (6%)	8 (7%)
Reactive arthritis, n (%)		1 (1%)	1 (1%)
Family history of SpA, n (%)		17 (14%)	17 (15%)
HLA – B27	Positive, n (%)	20 (16%)	20 (16%)
	Negative, n (%)	19 (15%)	19 (15%)
	Not tested, n (%)	85 (69%)	85 (69%)
History of smoking, n (%)		46 (38%)	42 (38%)
Good response to NSAIDs, n (%)		51 (41%)	49 (43%)
Elevated inflammatory markers, n (%)		16 (13%)	16 (14%)
Rheumatologist visit, n (%)		29 (23%)	29 (26%)
Loss to follow-up, n		5	5
Number of follow-up X rays, median (range)		2 (1, 6)	2 (1.6)

IBD: inflammatory bowel disease; SpA: spondyloarthritis; NSAID: nonsteroidal anti-inflammatory drugs. SD: standard deviation. IQR: interquartile range. Sensitivity analysis 1: included patients who were considered as having “possible IBP” or “definite IBP” by all three reviewers and fulfilled the explicit IBP definition.