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FIELD OF STUDY: MEDICINE

# CORRELATIONS BETWEEN WORK DISABILITY AND INFLAMMATORY MUSCULOSKELETAL DISORDERS-ANKYLOSING SPONDYLITIS IN CONSTANŢA COUNTY POPULATION

# THESIS SYNOPSIS

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## CONTENT

## ABBREVIATIONS

| | |
|---|---|
| **AS** | = Ankylosing Spondylitis |
| **SpA** | = SpondyloArthritis |
| **ASAS** | = Assessment of SpondyloArthritis international Society |
| **ASAS-HI** | = ASAS Health Index |
| **ASDAS** | =Ankylosing Spondylitis Disease Activity Score |
| **BASDAI** | =B ath ankylosing spondylitis disease activity index |
| **BASFI** | = Bath Ankylosing Spondylitis Functional Index |
| **BASMI** | = Bath Ankylosing Spondylitis Metrology Index |
| **ICF** | = International Classification of Functioning, Disability and Health |
| **WHO** | =World Health Organization |
| **ESR** | =Erythrocyte Sedimentation Rate |
| **CRP** | = C reactive Protein |
| **VAS** | = Visual analogue scale |
| **NSAID** | =Non steroidal Antiinflamatory Drug |
| **BMI** | =Body Mass Index |
| **CBC** | =Complete Blood Count |
| **HLA** | =Human Leukocyte Antigen |
| **TNF** | =Tumor necrosis factor |
| **RA** | =Rheumatoid Arthritis |
| **DFI** | =Dougados Funcţional Index |
| **HAQ-S** | =Health Assessment Questionnaire modified for the spondylarthropathies |
| **RLDQ** | =Revised Leeds Disability Questionnaire |
| **ASQoL** | =The Ankylosing Spondylitis Quality of Life |
| **OR** | =Odds Ratio |

**KEY WORDS**: Ankylosing Spondylitis , Socio-Demographic and Clinical Features, Work Capacity Assessment, Work Disability, ICF, ICF Core Set

# INTRODUCTION

Temporary or permanent work disability is a state with repercussions on the individual, the employing company and society. Assessing the work capacity of sick person is different from country to country, often lacking transparency and virtually lacking international evidence-based guidelines for quantifying the remaining functionality of the patients affected by somatic or psychological conditions. In the past 10 years the use and implementation of International Classification of Functioning, Disability and Health - ICF (International Classification of Functioning, Disability and Health – ICF has started. This classification provides the framework and language necessary to build a universal model for the classification of the "components" of health and its "consequences", a model that can be applied in medicine to assess the impact of various diseases on a global and complex level. The disease/state of illness affects the body both structurally and functionally (in a mild or severe, temporary or permanent, progressive, regressive or stationary; intermittent or continuous manner) followed by disability which can be influenced (attenuated or aggravated) by contextual factors, particularly the contextual factors of the environment (the physical, social and attitudinal) in which the ill individual takes their existence. ICF allows an assessment of the damage suffered by the individual throughout the disease not only form a biological standpoint but also from a social, highlighting the importance of the health policies in disability management.

The idea of using ICF in assessing work capacity stands as a basis of this PhD thesis started approximately 10 years ago .At that point, it seemed necessary the use of the validated measurement instruments combined with this WHO classification of functionality and disability in order to perform an unitary and complex assessment of the consequences of the illness.

We oriented on AS due to its being a chronic rheumatic disorder, an inflammatory condition that affects the young adult, able to work and employed most of the times. AS leads to structural and functional involvement of the musculoskeletal system, thus limiting the individual's activity and participation in various life areas or domains. The decrease of work capacity due to disease frequently imposes changing the place of employment, a reduction in work time or work disability pension, with economic consequences not only for the patient and his/her family but also for the society. The pain, the Stiffness, the limited mobility, the sleep disorders, depression and discouragement, the changes in the physical appearance affect the interpersonal relationships whether we're talking about family life or society and impose participation restrictions in certain life situations. To all these aspects are added the adverse reactions due to prolonged NSAID use, with cardiovascular or gastrointestinal effects more or less severe. AS is a condition that affects the quality of life and changes the patient's life as it'd slowly progressing towards disability and handicap.
Therefore, AS, through its clinical manifestations, its complications or the medication adverse effects is responsible of activity and participation limitation in numerous domains (education, family life, interactions and personal relationships, self-care) including work and employment .Implementing ICF criteria in assessing the work capacity of the AS patient represents one of the objectives of this thesis.

Throughout realizing this paper we confronted with numerous difficulties in ICF criteria usage when assessing the disease consequences on the health status and therefore work and work employment. We confronted the following problems:

1. The absence of questionnaires to clear out the ICF code content to the physician and patient (Eg: b130 Energy and drive functions d845 Acquiring, keeping and terminating a job. D845 Seeking, finding and choosing employment, being hired and accepting employment, d850 Remunerative employment)
2. The absence of ICF code sets associated with work disability in different disorders including AS (other than the basic ICF codes that assess AS impact on function and health focused on physical and motor disability)

3. Establishing some standards/instruments regarding the value of the given qualifiers
4. The absence of a composite index to assess the disease impact upon the work capacity that takes into account the disease impact on various ICF components: the severe impact on the ICF components from the core set associated with AS, including the criteria focused on physical and motor disability in rheumatic disease did not have the expected weight in the group with AS and work disability retirement.

Prior to 2000 ASAS/OMERACT has selected for AS nine domains that were assessed through validated measurement instruments (BASDAI, BASFI etc.). These domains represented by pain, stiffness, physical function, fatigability, spinal mobility, peripheral joint involvement entheseal involvement, spinal radiological changes and inflammatory markers assess primarily the functional status and mobility in the AS patient. They fail to show the disease impact in all its dimensions , neglecting psychosocial aspects such as work participation, , welfare, family and social relationships, and also neglecting the intervention of contextual factors on functionality and disability in the AS patient. In order to design a bio0psycho-social model with the purpose of assessing AS consequences upon participation and activity based on the ICF model, ASAS Assessment of SpondyloArthritis international Society) through 19 experts in AS from 12 countries in a consensus conference selected 2 criteria sets for AS Comprehensive Core Set" (80 de criteria) and „Brief Core Set" (19 criteria) including components from Body Functions and Structures, Activity and Participation and Environmental Factors. These criteria were published in the EULAR magazine, Annals of the Rheumatic diseases. Later, from the core ICF set assigned to AS, ASAS finalized in 2015 an instrument designed to quantify the health status of the AS patient called ASAS HI (health index), a composite index that includes 15 of the categories of the comprehensive ICF set. Developing ASAS HI as an assessment instrument also included a questionnaire explaining the ICF categories used in this composite index. We must mention that both the AS criteria set (be it comprehensive or concise) and ASAS HI are not dedicated to work capacity expertise.

Appling the ICF core set in assessing disability in AS patients by the expert physician is a recent and unstandardized experience. In what measure the ICF set can be used in a correct assessment of work disability is a question for which the experts in rehabilitation are still looking for answers.. In Romania, the introduction of ICF in the actual work capacity expertise system is one of the objectives of the ongoing Governmental Social Care Modernization Project . From this standpoint this paper represents probably the first finalized attempt to assess work capacity through the ICF set applied to an AS patient lot.

## THE PURPOSE AND THE OBJECTIVES OF THE THESIS\

### THE IMPORTANCE OF THE PROBLEM

Even though there are numerous instruments measuring the disease activity and the functional status, assessing the activity limitations and participation restrictions and therefore the invalidity classification is made on criteria (different from country to country) based on structural consequences of the disorder and objectifying them through imaging investigations (radiological investigations especially in AS) is mandatory determining the degree of disability and handicap. These criteria are insufficient in showing the disease impact of AS upon function and disability in all its dimensions, neglecting the psycho-social aspects of the disease related to the contextual factors (both personal and environmental). In order to create a bio-psycho-social model designed to assess AS impact on activity and participation under the influence of contextual factors 19 experts in AS from 12 countries, gathered in a consensus conference selected 2 criteria sets for AS: Comprehensive Core Set" (80 criteria) and „Brief Core Set" (19 criteria). These sets are a part of ICF and allow assessing the disease impact on an individual from both a biological and social point of view underlining the importance of health policies in disability management. ICF promotes standardized reports of disability allowing an unitary system of assessment in different parts of the world. Implementing ICF in assessing disability is recent, the classification criteria for disease impact in various musculoskeletal conditions upon the functional status being established by the experts starting of 2000: For rheumatoid arthritis, osteoarthritis and osteoporosis in 2004, for chronic lumbar pain and diffuse pain syndrome in 2008 and for ankylosing spondylitis in 2010.

Besides, the definition of invalidity/disability and its measurement is an ongoing process on which is working since 2001 an international group of experts *The Washington Group" under the aegis of UN , a group that also has the duty to monitor the recommendations of UN Convention on the Rights of Persons with Disabilities: the right to equal opportunities in the society and the need to identify the disabled people in each nation.

### OBJECTIVES

The paper is made up out of three cross sectional studies regarding the AS patient:

**Study 1 Objective:** describing the demographical and clinical features of the AS patients.

**Study 2 Objective**: Identifying the main causes that lead to disability and medical retirement in the AS patients from Constanta County

**Study 3 Objective** : Assessing the work disability retired AS patients (according to the current Romanian legislation ) using the Brief Core set for AS.

### MATERIAL AND METHOD:

We enrolled 213 AS patients (diagnosis based on the NY criteria) who accepted the study participation after signing an informed consent.

**Inclusion criteria**

- Positive AS diagnosis according to the NY 1984 criteria
- Age≥18 years
- The signing of an informed consent

**Exclusion criteria**

- Uncertain diagnosis
- The work disability retired patients with AS as a secondary diagnosis
- The patient's refusal
- Old age retirement

We enrolled the following categories of patients:

- AS patients in the evidence of the Medical Expertise and Work Capacity Recovery Service Constanta
- AS patients in the evidence of the Rheumatology Department of The "Sfântul Apostol Andrei" Constanta Emergency County Hospital admitted between January 2012-january 2015
- AS patients newly diagnosed in Rheumatology Department of The "Sfântul Apostol Andrei" Constanta Emergency County Hospital admitted between January 2012-january 2015

We collected the following types of data:

1. Demographical data: sex, age, ethnic group, place of living, educational level, profession (including the occupation classification) occupational status (ever employed, currently employed, retired, housewife, student, no occupation) recreational or professional sportive activities, marital status, economical status (average family member income)
2. Clinical Data: age at the onset and the moment of AS diagnosis, the length of the disease at retirement and assessment , the onset type (juvenile /adult) the disease form (axial/peripheral) history of peripheral arthritis, history of extraarticular manifestations (uveitis), treatment, disease complications (hip replacement) or treatment complication (NSAID gastropathy), comorbidities, we determined the disease activity according to BASDAI and ASDAS.
3. The clinical examination of the spine, girdles, and peripheral joints (peripheral arthritis, ankylosis in flexed position), entheses (achillean enthesitis), muscles (atrophies or contractures); we determined the metrological indices (occiput-wall, chest expansion index, Schober test, fingertip to ground distance intermaleolar distance) and the BASMI index.
4. Biological data CBC, ESR, CRP, glycaemia, serum creatinine, lipid profile, liver function test, HLA-B27
5. Data regarding retirement: age, length of the disease an work seniority at the moment of the retirement.
6. Radiological data: sacroiliac, hip and spine x-rays
7. Assessment according the Brief ICF Core set for AS
8.

The brief ICF set for AS includes components from the following domains: functions (code b), structures (code s), activities and participation (code d) and environment (code e). In this paper we analyzed the involvement using the codes b, s, and d. Identifying the involvement in various ICF fields is made by talking with the patient (clinical anamnesis) and clinical examination.

The assessment of the involvement type of different components is expressed through digits added after the component's code letter. The first digit following the code letter corresponds to the chapter and represents the hierarchy level 1. In the brief ICF set for AS in the mentioned codes corresponding to the described components are included the following chapters (level 1):

Code B includes functions from chapter 1 (mental functions-b1) Chapter 2 (sensorial functions and pain-b2) chapter 4 (Functions of the cardiovascular, hematological, immunological and respiratory systems-b4) and chapter 7 (Neuromusculoskeletal and movement related functions -b7)

Code s includes structures from chapter 7 (structures related to movement-s7)

Code d includes activities an participations from chapter 2 (General tasks and demands-d2), chapter 4 (mobility d4), chapter 7 (interpersonal interactions and relationships-d7)chapter 8 (major life areas-d8) and chapter 9 (community, social and civic life). The following 2 digits are used for a deeper assessment and represent the second lever of the hierarchy

In the AS core set the second level is represented as following

- b1: includes energy level and impulse functions (b130), sleep functions (b134) and emotional functions (b152) (1);
- b2: includes pain sensations (b280) (1);
- b4: includes effort tolerance functions (b455) (1);
- b7: includes jointmobility and (b710) and sensations associated with the muscles or muscle groups of the body and their movement (b780) (1);
- s7: includes pelvic structure, (s740), inferior extremity structure (s750), trunk structure (s760) and additional musculoskeletal structures related to movement. (s770) (1);
- d2: includes carrying out daily routine (d230) (1);
- d4: includes changing basic body position (d410), walking (d450) and driving a vehicle (d475due to the small number of the patients who drove we did not asses this code(1);
- d7: includes family relations(d760) (1);
- d8: includes acquiring, keeping and terminating a job (d845 Remunerative employment (d850) (1);
- d9: includes Recreation and leisure (d920) (1);

The AS ICF core set tops at the second level of the classification and contains one letter and 3 digits. Besides, in real life there are commonly used second level classifications (3 digits), with detailed versions being used in special services (4 or 5 digits).The components expressed through these codes are assessed through "califications) that appreciate the degree of functional and structural involvement. We must mention that for medical users these involvements are not identified by the underlying condition but are mere manifestations of it. (1)

The procedure used in our paper addressed to the brief set of ICF criteria for AS, using a level 2 classification (1 letter and 3 digits) and it established the involvement dimension and subsequently the disability degree using a one digit scale (first qualifier) ranging from 0 to 4 (0=no problem, 1-slight problem, 2-moderate problem, 3 severe problem and 4-complete problem) which allows a quantification of the involvement, capacity/performance limitation within a 5% margin as following 0 – 4 % marked as 0, 5 - 24% marked as 1, 25 - 49% marked as 2, 50 - 95% marked as 3, 96 – 100% marked as 4. (1)

The first calificative is an performance one, describing what an individual does in a social context. In order to interpret the notions from the core set we used details from the core AS set ( which includes also level 3 and 4 classifications) and the definitions and classification of these notions as presented in the Romanian translation of the ICF(1).

## STATISTICAL ANALYSIS

In order to collect the data we used Microsoft Office 2010-EXCEL and for statistical analysis SPSS, 20.0.

For nominal variables we designed the frequency tables and we graphically represented the data through bar charts

For score variables we used the following central tendency indicators the average value, standard deviation (for normal distribution data) and the median value and standard deviation for the data with an abnormal distribution.

In order to asses the differences between the groups we used the z test ant t test for the variables with a normal distribution and the l Mann-Whitney U test (for the difference between the arithmetic means in various groups( for the data with an abnormal distribution. (47)

In order to assess the differences between nominal variables we have used Pearson Chi square test (47)

For the variables with a very low frequency we have used Fisher exact test processed for 2x2 tables)

In order to identify the predictors of patient distribution in certain categories we used binomial logistic regression and Wald test

The predictors used in the binomial logistic regression were both dichotomic and score variables

In establishing the statistical significance limit we used $p<0,05$(47).

Both the tables and the charts used in this paper were designed using SPSS.

## STUDY I-THE SOCIODEMOGRAPHIC AND CLINICAL FEATURESOF THE AS PATIENT

### RESULTS

We included 213 patients : 183 men (85,9%) and 30 women(14,1%). The sex ratio M:F for the whole group is 6:1with variations depending on current age and the age at the onset of the disease, ethnic group, living in an urban or rural area and HLA B27

**Table 1.**Demographic features of AS patients

| Variable | Number (%) | Mean and standard deviation |
|---|---|---|
| Age (years() | | 47,94±12,04 (19 -76) |
| Age at onset *years) | | 27,95±10,10 (9 – 59 |
| Disease duration (years)) | | 19,96±11,10 (1 -52) |
| Men (%) | 183 (85,9%) | |
| Caucasian (%) | 200 (93,9%) | |
| Urban (%) | 171 (80,3%) | |
| Marital status (married) (%) | 155 (72,8%) | |
| Education level (%)<br>Higher education<br>Secondary education<br>Primary and gymnasial education | <br>45 (21,1%)<br>95 (44,6%)<br>73 (34,3%) | |
| History of employment(%) | 193 (90,6%) | |
| Work disability (%) | 96 (45,1%) | |
| Satisfactory income(%) | 82 (32,5%) | |
| Sporting activity | 59 (27,7%) | |
| History of smoking(%) | 123 (57,7%) | |
| BMI (Kg/m²) | | 26,79±5,27 (14,83 – 47,02) |
| Family history of AS | 65 (30,5%) | |
| HLA-B27 (+)(%) | 101 out of 109 tested (92,7%) | |

The patients included in our study have an average age of 47,94±12,04 (ranging between 19 and 76 years, with a median of 50 years. The average age for women is 48,8±12,50 years (23 - 72 years) and 47,80±11,99 years for men (19 -76 years( with no significant statistical differences between the two sexes

The disease onset is at a mean age of 27,95±10,10 years (between 9 and 59 years). In our cohort, AS debuts earlier in men than women (27,4±10.0 vs. 31,13±9,73 years ) (p=0,062), in Caucasians than Tatars (27,53±10,0 vs. 34,46±9,40 years) (p=0,016in HLA-B27(+) men (25,46±9,39 vs. 33,50±9,24 years) (p=0,023) and in those with a family history of AS (25,11±8,26 vs. 29,20±10,60 years) ( p=0,006)

Most patients live in an urban environment (80,3%); out of those , 87,7% are men. The sex ratio is larger in an urban setting (7:1) than in a rural one (3,7:1), but the differences regarding the sex distribution depending on the dwelling environment have no statistically significant differences (p=0,127)

More than half of the patients (65,7%) au have either secondary or higher education: 44,6% respectively 21,1%. There are no illiterate patients in our cohort. The male patients have more frequently higher education than AS females. (23,5% compared with 6,7%). Secondary education was registered in 53,3 % of the women and 43,2% of the men in our study group

Out of the 213 AS patients in our cohort, 193 (90,6%) either have or had a contract for full time employment: 171 (88,6%) men and 22 (11,2%) women with a ratio M:F of 7,7:1 and performed

a qualified labor. Out of the patients with history of employment, 97 ( 50,3%) are still employed and r 96 (49,7%) have retired due to work disability with no significant differences between the sexes (p=0,498).

Professional Qualification and the history of employment are strongly correlated. Thus, 97,6% of the patients with a professional qualifications were employed at some point, compared with 67,34% of the unqualified patients (p<0,001). More than two thirds of the patients in our study performed manual labor, (69,48%), with statistically significant differences between qualified patients (61,58% performed manual labor) and the unqualified patients (95,91% performed manual labor) (p<0,001).

The employment is highly correlated with the educational level 90% of the patients with secondary education or higher having a history of employment (93,8% respectively 93,3%) (p=0,038).

We notice statistically significant differences between the sexes regarding employment: in our cohort : 93,4% of men and 73,3% of women have ever been employed (p =0,002). Also, 81,42% men versus 50% women performed a qualified work, a statistically significant difference (p<0,001; OR M/F=4,38).

With or without a qualification, the labor performed was manual in 69,5% of the cases and required in 91,1% of the cases at most a medium energy use (including the housewives) , just 19 patients, all men had jobs/professions requiring a high energy use; (16 patients) or very high (3 patients).

The analysis of the work disability group (96 patients)depending on the age at the retirement shows that 26^ had work disability at the age of 40, and that 65,6% at the age of 50. Analyzing the same group depending on disease duration shows that 25% were retired after 7 years since the disease onset and around 50 % (53,1%) after 15 years

Out of the 213 patients in our study , 131 patients (61,5%) report an insufficient income. The most important influences regarding the income belong to the educational level and employment status. 80% of the patients with a higher education report a satisfactory income (p<0,001)
More than half of the patients (57,7%). were smokers (61,7% men).(p =0,005)

Disease duration was established depending on the onset of first symptoms, thus the average disease duration was 19,96 years ±11,10 (1 – 52 years), without statistically significant differences between AS men (20,27±10,82 years) and AS women (18,10 ±12,73 years).

The case distribution according to its length is the following: : 9,4% cases with a ≤ 5 year duration, 23,9% with ≤ 10years, 38,5% with a disease duration≤ 15 years, 51,6% with a disease duration≤ 20 years, 69% with a disease duration ≤ 25 years, 80,3% ≤ 30 years, 91,1% ≤ 35 years, and the remaining with a disease duration between 36 and 52 years

One third of the patients (30,5%) had a family history of AS and HLA - B27 was present in 92,6% out of 119 patients that were tested for it.

HLA-B27 presence is not correlated with demographical features such as the sex of the ethnic group, but it determines a significant drop of the age at the disease onset in men. HLA B27 positivity is not correlated with disease clinical manifestations such as juvenile onset, disease form (axial or peripheral), hip involvement or severe radiological changes

We registered 29 cases (13,6%) with juvenile onset (onset ≤ 16 years of age) and 16 cases (7,4%) with a late onset debut ( > 45 years). The juvenile onset was similarly represented in both sex groups : 14,2% of the men vs 10% of the women. Similarly, the late onset is present in almost equal proportions in both: 7,85%of the AS men vs 6,6% of the AS women in our cohort

The juvenile AS cases have a mean disease duration . of 27,34±11,58 years. Most of the cases with a juvenile onset (89,7%) were identified in male patients with a sex ratio M:F of 8,6:1. In 58,6% of the cases, the juvenile onset disease also had peripheral involvement.

The clinical presentation is dominated by axial involvement, with severe impairment in lumbar spine mobility in 50,7% of the cases and moderate/severe impairment in cervical spine mobility in 45% of the patients. Coxo-femural girdle involvement led to hip replacement surgery in 7,5% of the patients. Peripheral arthritis was identified in 42,7% of the patients throughout the disease ant calcaneal enthesitis was identified when evaluating the patients in 26,3% of the patients. Extra articular manifestations were exclusively ocular and were present in the medical history of 21,6% of the patients. (Table 2)

More than half of the patients need continuous NSAID use (>20 days/month) and about 1/3 receive biological therapies with anti TNF alpha agents

**Table 2**. The clinical and radiological manifestations in AS patients

| **Variable** | **Number (%)** | **Average and standard deviation** |
|---|---|---|
| Current age (Years) | | 47,94±12,04 (19 -76) |
| Disease duration (Years) | | 19,96±11,10 (1 -52) |
| Juvenile onset (%) | 29 (13,42%) | |
| Men (%) | 183 (85,9%) | |
| Dorsolumbar syndesmophytes (%) | 166 (77,9%) | |
| Lumbar and thoracic bridges(%) | 144 (67,6%) | |
| Generalized syndesmophytes (%) | 111 (52,1%) | |
| Severe impairment of lumbar spine mobility (%) | 108 (50,7%) | |
| Cervical spine involvement (%) | 111 (52,1%) | |
| Impaired cervical spine mobility (moderate and severe) (%) | 96 (45%) | |
| Peripheral arthritis history (%) | 91 (42,7%) | |
| Hip prosthesis (%) | 16 (7,5%) | |
| Current calcaneal enthesitis%) | 56 (26,3%) | |
| Ocular manifestations (%) | 46 (21,6%) | |
| Continuous NSAID use (%) | 112 (52,6%) | |
| Anti TNF medication (%) | 74 (34,7%) | |
| Comorbidities (%)<br>Hypertension<br>Diabetes mellitus<br>Major cardiovascular events(MI, stroke) | 78 (36,6%)<br>24 (11,3%)<br>13 (6,1%) | |

Most of the patients (62,9%) had stage 4 sacroiliitis (66,1% of the men and 43,3% of the women) followed by 31,5% with stage 3 sacroiliitis (29% of the men and 46,7% of the women) and 5,6% with stage 2 sacroiliitis (4,9% of the men and 10% of the women) (p =0,018). Stage 2 sacroiliitit was identified only in patients with a disease duration of less than 3 years (Table 2)

Dorso-lumbar syndesmophytes, thoracic and lumbar bridges and generalized syndesmophytes are present in a large number of patients (table 2) and generally occur in patients with a disease duration of >20 yers. There is a highly significant correlation between syndesmophyte presence and disease duration.($p<0,001$).

The functional assessment included determining the metrological indexes for vertebral segments mobility (lumbar, thoracic, cervical ) and of the hip girdle, determining the respiratory dysfunction due to extrapulmonary causes and the functional self assessment index BASFI) (Table 3)

**Table 3** The functional assessment of AS patients

| Variable | Average and standard deviation |
|---|---|
| Schober index (cm) | 12,12±1,63 |
| Fingertip-ground distance (cm) | 31,50±1,60 |
| Chest expansion (cm) | 2,49±1,60 |
| Occiput to wall distance (cm) | 9,98±10,14 |
| Ventilatory dysfunction (%) | 95 (44,6%) |
| BASFI | 5,88±2,71 |

Even though our cohort has a small number of women, the differences between AS men and women (Table 4) are similar with those from other studies both from a demographical and from a clinical standpoint (77, 35).

**Table 4**: Disease features depending on the patient's sex

| Variable | Men (n= 183) | Women (n = 30) | P |
|---|---|---|---|
| Current age (years)) | 47,80±11,99 | 48,80±12,50 | ns |
| Age at the disease onset (years) | 27,43±10,0 | 31,13±9,733 | ns |
| Disease duration (years)) | 20,27±10,828 | 18,10±12,732 | ns |
| HLA –B27 (+) | 81/89 | 20/20 | ns |
| Family history (%) | 30,1 | 33,3 | ns |
| Stage 4 sacroiliitis (%) | 66,1 | 43,3 | 0,053 |
| Generalized syndemophytes (%) | 55,7 | 30 | 0,010 |
| Hip involvement (%) | 46,4 | 30 | ns |
| Hip prosthesis (%) | 8,2 | 3,3 | ns |
| Peripheral arthritis (%) | 27,3 | 43,3 | ns |
| Eye involvement (%) | 23 | 13,3 | ns |
| Continuous NSAID(%) | 53,6 | 46,7 | ns |
| Anti TNF (%) | 38,2 | 46,7 | ns |
| BASDAI | 5,17±,2,58 | 5,92±1,94 | ns |
| BASFI | 5,83±2,70 | 6,16±2,80 | ns |
| ESR (mm/h) | 29,48±24,79 | 37,90±29,76 | ns |
| CRP (mg/dl) | 1,73±2,66 | 1,88±4,02 | ns |
| ASDAS CRP | 2,98±1,34 | 3,26±1,36 | ns |
| ASDAS ESR | 3,01±1,26 | 3,57±1,17 | 0,026 |

Hip involvement is common in our study: 39,9% of the patients had at one point clinical involvement of the hip joint , 41,3% have radiological changes (unscored) and 7,5% have hip prosthesis, results similar to those published in other studies (105)

HLA-B27 positivity may change the clinical and radiological manifestations in spondyloarthritis, as demonstrated by the DESIR cohort (Devenir des Spondylarthropathies Indifférenciées Récentes) which included 708 patients with early axial spondyloarthritis. HLA-B27 presence is associated with a younger age at the onset of the disease, radiological sacroiliitis, a low activity and a low psoriasis prevalence. The functional status was not influenced by . HLA-B27 presence(38)

In our study cohort, HLA-B27 was determined in 109 patients, with only 8 patients being HLA-B27 (-).. The disease debuts earlier in HLA-B27 (+) patients, who associate more frequently a family history and ocular involvement. The hip prosthesis were present only in HLA-B27 (+) patients. However, AS patients with HLA-B27 (-) have more often severe radiological changes and a more altered functional status (Table 5).

**Tabel 5:** Disease features of AS patients and HLA-B27

| Variable | HLA-B27 (+) (n=101) | HLA-B27(-) (n=8) | P |
|---|---|---|---|
| Men (%) | 81/89 | 20/20 | ns |
| Caucasian(%) | 95/102 | 6/7 | ns |
| Current age (years) | 42,74±12,45 | 53,38±3,99 | 0,018 |
| Age at the disease onset (years) | 26,70±9,81 | 33,50±9,24 | 0,061 |
| Disease duration (years) | 16,23±9,57 | 19,88±7,64 | ns |
| Juvenile onset (%) | 14,9 % | 12,5% | ns |
| Family history(%) | 35,6% | 12,5% | ns |
| Stage IV sacroiliitis (%) | 44,6% | 62,5% | ns |
| Generalized syndesmophytes (%) | 29,7% | 62,5% | ns |
| Hip prosthesis (%) | 7,9% | 0% | ns |
| Peripheral arthritis | 27/101 | 3/8 | ns |
| Ocular involvement (%) | 21,85% | 12,5% | ns |
| Enthesitis (%) | 28,7% | 50% | ns |
| Psoriazis (%) | 5% | 0% | ns |
| Schober Index (cm) | 13±1,64 | 11,13±0,91 | 0,02 |
| Occiput to wall distance (cm) | 5,28±8,15 | 11,25±11,57 | 0,057 |
| Chest expansion (cm) | 3,09±1,69 | 1,88±1,30 | 0,051 |
| Fingertip to ground distance (cm) | 25,48±17,57 | 38,38±18,70 | 0,049 |
| ESR (mm/h) | 25,67±23,43 | 26,25±23,28 | ns |
| CRP (mg/dl) | 1,37±2,29 | 2,91±5,26 | ns |
| BASDAI | 4,65±2,74 | 5,23±1,56 | ns |
| BASFI | 4,74±2,64 | 5,14±3,21 | ns |
| Continuous NSAID | 46/101 | 3/8 | ns |
| Anti TNF alpha | 49/101 | 2/8 | ns |

## STUDY I CONCLUSIONS

1 The sex ratio M:F is 6:1, double than the values reported in the literature. It is influenced by the ethnicity and the age at the onset. Among the Mongolian patients and among the cases in which the disease began at a young age (<30 years ) we registered a sex ratio M:F of 12:1 respectively 10:1

2.The patients in our study cohort have a long disease duration (19,96±11,10 years) with more than 90% of them having an advanced , longstanding disease (stage III and IV sacroiliitis)

3. The age at the onset is decreased in HLA B 27 (+) patients and in the men with a positive family history

4. Over 90% of patients with AS benefited from a remunerated contract of employment. High education level (secondary and higher education) and professional qualification, significantly increase the chance of employment of patients with AS. The most important factor in gaining a presence in paid employment is professional qualification.

5. The lack of professional employment significantly decreases the income of AS patients.

6.The disease does not influence family relations, Most of the AS patients are married with children.

7. More than half of the patients (69,5%) have an active disease, with a BASDAI >4. The disease activity is significantly influenced by the presence of enthesitis, a high functional impairment, (BASFI) and ESR

8. Clinical hip involvement occurs in an important proportion of patients (46.9%)

9. An important percentage of patients (34.7%) receive biological therapy.

## STUDY II: EMPLOYMENT AND DISABILITY RETIREMENT IN PATIENTS WITH SA

The studied cohort of patients with AS is comprised of 97 patients with full-time employee status (45.4%), 96 disabled pensioners (45.1%), 4 students (1.9%) 8 housewives (3, 8%) and 8 patients (3.8%) who have never had an employment contract.

Of the 213 patients with AS included in the study group, 193 (90.6%) had or have a contract for full-time paid employment: 171 (88.6%) men and 22 (11.2%) women with a M : W ratio of 7.7: 1. We notice statistically significant differences between the sexes on the employment contract: In the study group, 93.4% of men and 73.3% of women were employed at least at one point ($p = 0.002$)

Of these 193 patients who were employed at a point, 82.9% performed/ are performing a qualified labor: 81.42% of men versus 50% of women have performed skilled labor, the difference being statistically significant ($p < 0.001$; OR M / W = 4.38).

Qualifications and history of paid employment (employment contract) are highly correlated. Thus, 97.6% of patients who have qualifications were employed at some point, compared to 67.34% of unskilled workers ($p < 0.001$).

With or without qualification, labor was done manually in 69.5% of cases and in 73.5% of the cases it required an average energy consumption; just 19 patients, all male, had professions / occupations involving high energy consumption (16 patients) or very high (3 patients).

Manual labor is associated with an average energy consumption compared to non-manual professional activities, energy consumption is decreased in 98% of these cases ($p < 0.001$)

Employment is strongly correlated with the level of training, more than 90% of those with secondary and higher education are the beneficiaries of an employment contract (93.8% and 93.3%) ($p = 0.038$). Training level correlates with low energy consumption at the work place: 90% of those with higher education and 10% of those with primary and secondary schools have activities that require low energy consumption ($p < 0.001$)

Logistic regression analysis identified the presence of professional qualification (<0.001) as the most important factor in the acquisition of paid employment.

Lack of employment correlates with lack of qualifications ($p < 0.001$) and educational level ($p = 0.025$)

The analysis of the cohort study, in terms of incapacity, shows that half of those who were employed benefit disability pension when assessed. Evaluation of the clinical characteristics of disability pensioners was made at the time of the trial and not at retirement.

90.6% of the disability pensioners are males, with an average age of 55.21 ± 8.45 years. At retirement, AS patients had a mean age of 46.18 ± 9.29 years, mean disease duration of 15.90 ± 10.07 years and an employment record of 15.90 ± 10.07 years (2-44 years) (Table 6)

Further analysis by age reveals the following distribution of medical retirees: 3.1% were retired before 25 years, 7.3% between 25-34 years old, 24.6% between 35-44 years old, 44, 4% between 45-54 years, 14.6% between 55-64 years. Retirement largest contingent was between 45 and 54 years.

Subgroup analysis of patients who had paid employment (193 patients) establishes the following relationship between duration of disease and medical retirement: 9.4% retired after the first 10 years of disease, 29.2% after 20 years of disease; 50% of patients (53.1%) retired after 25 years of disease and after 30 years of work 67.7% of the patients from the group with disability pension were retired.

Subgroup analysis of patients with disability pension (96 patients) highlights the following distribution of retirement be disease duration cases: 18.8% in the first 5 years of disease, 28.7% from 6 -10 years, 15 6% between 11-15 years, 14% between 16-20 years, 21.5% between 21 -25 years, 13.5% between 26 -30 years and 7.2% after 30 years.

**Table 6**. Demographic characteristics of patients with AS, disability pensioners

| Variable | Retirees N= 96 | Employees N=97 | P |
|---|---|---|---|
| Men | 90,6% (87) | 86,6% (84) | Ns |
| Caucasians | 93,8% (90) | 92,8% (90) | Ns |
| Urban | 83,3% (80) | 80,4% (78) | Ns |
| With partner | 77,1% (74) | 73,2% (71) | Ns |
| Children | 82,3% (79) | 72,2 (70) | Ns |
| Satisfactory standard of living | 13,5% (13) | 63,9% (62) | <0,001 OR=11,31 |
| Sporting activity | 30,2% (29) | 26,8% (26) | Ns |
| Current age (years) | 55.21±8,45 | 42.15±10.42 | <0,001 |
| Retirement age (years) | 46,18±9,29 | - | |
| Age at onset (years) | 29.99±10,13 | 27.16±9.83 | 0,048 |
| Disease duration (years) | 24.88±9,82 | 15.26±10.47 | <0,001 |
| Disease duration at retirement (years) | 15,90±10,07 | - | |
| Length of employment at retirement (years) | 24,92±9,47 | - | |
| BMI (kg/m²) | 28.11±6,03 | 25.84±3,90 | 0,002 |
| Smokers (%) | 68,8% (66) | 54,2% (52) | 0,054 OR=1,82 |
| Higher education (%) | 8,3% (8) | 35,1% (34) | <0,001 |
| Secondary education (%) | 57,3% (55) | 36,1% (35) | Ns |
| Primary and secondary education (%) | 34,4% (33) | 28,9% (28) | Ns |
| Qualified labor (%) | 85,4% (82) | 80,4(78) | Ns |
| Manual labor (%) | 84,4% (81) | 52,6 (51) | <0,001 OR=4,87 |
| Low energy consumption (%) | 25% (24) | 53,6 (52) | 0.001 |
| Average energy consumption (%) | 62,5% (60) | 39,2% (38) | 0,001 |

Of the 96 patients with AS and invalidity pension did manual labor ( 84.4% ) and the occupations required an average energy consumption in 62.5% of cases (Table 6)

Higher education, non – manual work and a low energy consumption activity characterizes the employee status. Disability retirement is associated with lower living standards.

Logistic regression analysis shows that the level of training differentiates a disability pensioner status vs an employee ($p = 0.046$).

Clinical characteristics of the disease such as spinal pain, morning stiffness, impaired hip movement (pain and limitation of movement measured by the intermalleolar distance), presence of peripheral arthritis are significantly associated with disability pensioner status. There is no correlation with statistical significance between disease retirement and hip prosthesis, enthesitis damage or ocular manifestations. Pharmacological treatment, appreciated through continuous NSAID consumption (> 20days / month) and biological medication agents such as anti-TNF-alpha did not differ between the two compared subgroups. (Table 7).

Functional status, expressed by the BASFI index, reduced mobility of the spine (lumbar and cervical), reduced chest expansion and presence restrictive ventilatory dysfunction are significantly correlated with medical retirement. (Table 7).

**Table 7**. Clinical features of patients with AS and disease retirement

| Variable | Retirees (n= 96) | Employees (n=97) | P |
|---|---|---|---|
| Juvenile onset (%) | 9,4% (9) | 13,4% (13) | Ns |
| Spinal pain VAS | 6,76±2,37 | 5,38±2,88 | <0,001 |
| VAS stiffness | 5,60±2,47 | 4,30±2,82 | 0,001 |
| Sacroiliitis gr III (%) | 14,6% (14) | 47,9% (46) | <0,001 |
| Sacroiliitis gr IV (%) | 85,4% (82) | 41,2 (40) | <0,001 |

| Variable | Retirees (n= 96) | Employees (n=97) | P |
|---|---|---|---|
| Lumbar spine sindesmophyte (%) | 94,8% (91) | 62,9% (61) | <0,001 OR=10,74 |
| Vertebral bridges(%) | 88,5% (85) | 48,5% (47) | <0,001 OR=8,221 |
| Generalized sindesmophytes(%) | 78,1% (75) | 27,8% (27) | <0,001 OR=9,259 |
| Severe limitation of cervical spine movements (%) | 27,1% (26) | 5,2% (5) | <0,001 |
| Moderate limitation of cervical spine movements (%) | 42,7% (41) | 16,5% (16) | <0,001 |
| Normal mobility of the cervical spine (Nr) | 9 | 50 | <0,001 |
| Severe lumbar flexion limitation (%) | 72,9% (70) | 29,9% (29) | <0,001 |
| Schober (cm) | 11.29±1,23 | 12.88±1.67 | <0,001 |
| Restrictive ventilatory dysfunction (%) | 65,6% (63) | 27,8% (27) | <0,001 |
| Cirtometric index [cm] | 1.80±1,25 | 3.08±1,63 | <0,001 |
| Occiput-wall index [cm] | 14.94±10,25 | 5.07±7,16 | <0,001 |
| Finger-floor index [cm] | 38.23±13,61 | 24.37±16,90 | <0,001 |
| Peripheral arthritis (n) | 36,5% (35) | 22,7% (22) | 0,041 OR=1,95 |
| Hip pain (%) | 63,5% (61) | 26,8% (26) | <0,001 OR=4,75 |
| Hip mobility reduction (moderate / severe) (No.) | 20/96 | 4/97 | <0,001 |
| Hip prosthesis (%) | 10,8% (10) | 3,1% (3) | ns |
| Enthesitis (%) | 28,1% (27) | 26,8% (26) | ns |
| Iridocyclitis (%) | 20,8% (20) | 21.9% (21) | ns |
| Anemia (%) | 25% (24) | 24% (23) | ns |
| BASFI | 7.29±1,81 | 4.57±2.74 | <0,001 |
| NSAIDs / month (days / month) | 18.22±10,11 | 18.04±10,81 | ns |
| Continuous NSAID (%) | 53,1% (51) | 54,6% (53) | ns |
| Biological therapy (%) | 31,3% (30) | 35,1% (34) | ns |
| Comorbidities (hypertension) (%) | 55, 7% (53/95) | 20,6% (20/97) | <0,001 |

Binary logistic regression analysis nominates advanced sacroiliitis, the presence of peripheral arthritis, cervical spine damage and increasing BASFI score (0.036) as variables that characterize significant disability pensioner status.

Radiographic changes and their severity establish statistically significant correlations with the status of pensioner, many of which are criteria for admission to various degrees of disability. Most of the retired patients have sacroiliitis grade IV, syndesmophytes and damaged cervical spine. (Table 7). The degree of disease activity, expressed by scores BASDAI, ASDAS - ESR, ASDAS - PCR is significantly increased in patients with a disability pension, but the reactants of the acute phase (ESR and CRP) don't register any significant differences between the two analyzed subgroups (Table 8).

**Table 8**. The degree of disease activity in patients with AS and care retirement

| Variabiles | Retirees (n = 96) | Employees (n=97) | p |
|---|---|---|---|
| ESR [mm / h] | 31.49±24,71 | 28.99±24.60 | ns |
| CRP [mg/dl] | 1.61±2,52 | 1.77±2.69 | ns |
| BASDAI | 5.99±2,19 | 4.77±2.62 | 0,001 |
| BASDAI>4 | 82,3% (79) | 59,8% (58) | 0,001 OR=3,12 |
| ASDAS/ESR | 3.39±1,12 | 2.85±1,27 | 0,003 |
| ASDAS very high and high | 44,8% (43)<br>41,7% (40) | 39,2% (38)<br>30,9% (30) | 0,044 |
| ASDAS/CRP | 3.29±1,21 | 2,80±1,38 | 0,011 |

**Special cases identified among disability pensioners**:

• disability retirement after 5 years of disease (18 patients) (Table 9)

• disability retirement age (≤ 45 years) (13 patients) (Table 9)

• disability retirement after 30 years of disease (36 patients) (Table 10)

• disability retirement for women with AS (9 patients)

**Table 9**. Special situations: disability retirement at a young age

| Variable | Retirees (n= 96) | Retirees with ≤ 5 years of disease (n=18) | Current retirees aged ≤ 45 years (n=13) |
|---|---|---|---|
| Men (%) | 90,6% (87) | 100% (18) | 92,3% (12) |
| Current age (years) | 55.21±8,45 | 51,06±9,68 | 40,69±4,36 |
| Retirement age (years) | 46,18±9,29 | 41,11±10,87 | 33,23±6,48 |
| Age at onset (years) | 29.99±10,13 | 36,67±11,79 | 22,46±5,66 |
| Disease duration at retirement(years) | 15,90±10,07 | 2,89±1,67 | 9,54±6,50 |
| Retirement seniority (years) | 24,92±9,47 | 21,6±11,68 | 12,15±6,53 |
| Organized sport (%) | 30,2% (29) | 33,3% (6) | 53,8% (7) |
| Smokers (%) | 68,8% (66) | 83,3% (15) | 76,9% (10) |
| Secondary education (%) | 57,3% (55) | 66,7% (12) | 61,5% (8) |
| Manual labor (%) | 84,4% (81) | 94,4% (17) | 76,9% (10) |
| HLA –B27 (+)* (%) | 81,3% | 62,5% | 100% |
| Unsatisfactory standard of living (%) | 86,5% (83) | 88,9% (11) | 100% (13) |
| Family history (%) | 32,3% (31) | 38,9% (7) | 30,8% (4) |
| Sacroiliitis gr IV (%) | 85,4% (82) | 66,7% (12) | 92,3% (12) |
| Generalized syndesmophytes (%) | 78,1% (75) | 55,6% (10) | 69,2% (9) |
| TMD (%) | 44,8% (43) | 61,6% (11) | 46,2% (6) |
| Hip prosthesis (%) | 10,4% (10) | 5,6% (1) | 15,4% (2) |
| Iridocyclitis (%) | 20,8% (20) | 11,1% (2) | 30,8% (4) |
| ESR (mm / h | 31.49±24,71 | 32,06±26,76 | 34,15±21,76 |
| CRP (mg/dl) | 1.61±2,52 | 1,85 ±2,69 | 1,46±1,15 |
| BASDAI | 5.99±2,19 | 6,26±2,25 | 5,55±2,64 |
| BASFI | 7.29±1,81 | 7,17±1,65 | 7,51±1,54 |
| Psoriasis (%) | 9,4% (9) | 22,2% (4) | 23,3% (3) |
| HBP (%) | 55, 2% (53) | 22,2% (4) | 23,3% (3) |
| Anti TNF alfa (%) | 31,3% (30) | 22,2% (4) | 38,5% (5) |

**Table 10** Professional status of patients with AS and long disease duration (n = 46)

| **variable** | **Retire patients with ≥ 30 years disease (N = 36)** | Emplayed patients with ≥ 30 years of disease (n = 10) | **p** |
|---|---|---|---|
| Men(%) | 94,4% (34) | 90% (9) | ns |
| Current age (years) | 52,28±7,30 | 55,40±5,85 | ns |
| Age at onset (years) | 22,92±6,55 | 18,40±4,37 | 0,047 |
| Retirement age (years) | 47,94±9,50 | - | |
| Current disease duration (years) | 34,92±4,35 | 36,90±7,03 | ns |
| Disease duration at retirement (years) | 25,0±7,70 | - | |
| Smokers (%) | 55,6% (20) | 60% (6) | ns |
| Studies | | | |
| Higher (%) | 11,1% (4) | 30% (30) | ns |
| Medii (%) | 52,8% (19) | 40% (4) | |
| Primary and secondary (%) | 36,1% (13) | 30% (3) | |
| Qualified labor (%) | 86,1% (31) | 100% (10) | ns |
| Manual work (%) | 83,35% (30) | 60% (6) | ns |
| Energy consumption | | | |
| Low (%) | 25% (9) | 50% (5) | ns |
| Medium (%) | 66,7% (24) | 20% (2) | |
| High and very high (%) | 8,4% (3) | 30% (3) | |
| Sacroiliitis gr IV (%) | 91,7% (33) | 80% (8) | ns |
| Generalized syndesmophytes (%) | 88,9% (32) | 50% (5) | 0,015 |
| TMD (%) | 41,7% (15) | 50% (5) | ns |
| Hip prosthesis (%) | 13,9% (5) | 0% | |
| I. Schober (cm) | 10,85±0,75 | 12,00±1,65 | 0,003 |
| I. cirtometric (cm) | 1,48±0,90 | 2,40±1,02 | 0,013 |
| Fingers - ground distance (cm) | 40,67±14,98 | 27,10±17,99 | 0,019 |
| Occiput-wall distance (cm) | 18,19±9,16 | 8,90±10,81 | 0,009 |
| Restrictive respiratory dysfunction (%) | 80,35% (30) | 60% (6) | |
| ESR (mm / h) | 28,58±21,72 | 32,50±21,18 | ns |
| CRP (mg/dl) | 1,20±1,25 (0,53)* | 4,11±6,18 (1,44)* | 0,010 |
| BASFI | 7,43±1,93 | 4,81±3,34 | 0,003 |
| Psoriasis (%) | 8,3% (3) | 0 | |
| HBP (%) | 58,3% (21) | 50% (50) | ns |
| Anti TNF alfa (%) | 33% (12) | 20% (2) | ns |

Decrease or loss of working capacity is one of the consequences of AS, risk of disability, temporary or permanent, is three times higher among patient with SA to the general population (19). Older patients, longer duration of disease, poor training and manual labor are recognized risk factors involved in decreased ability to work and professional ceasing (18).

Specialized studies assessing patients' ability to work with AS, use the term "work status" in literature, defined as the ability or inability to paid employment. This term has many nuances, especially in terms of the degree of incapacity to provide a paid work ("work disability, disability pension, inability to work, withdrawn from work"), and the terminology used to define the objectives in studies aimed fir objective "work status" of patients with AS is also different from study to study. Therefore, the results provided by these studies vary within wide limits.

Most studies are longitudinal, demographic and clinical characteristics of patients being assessed at the time of the trial and not at retirement in patients with AS and invalidity.

In our cohort, 193 patients with AS (90.6%) have had the status of full-time employee. Analysis of 96 patients with disability pension shows a smaller percentage of employees after 5 years of disease and a higher percentage of retirement after 20 years of disease, compared with Boonen) meta-analysis. (21 These results are biases determined by the composition of study group, which have

a surprisingly important percentage of patients who maintain their employment status after 45 years of disease (Table 11).

**Table 11.** Professional status and disability retirement according to disease onset

| Variable | Boonen meta-analysis | Constanţa (n=96)* | Constanţa (n=213)** |
|---|---|---|---|
| Employed after 5 years of disease | 96% | 81,2% | 41,5% |
| Employed after 45 years of disease | 34% | 0 | 0,5% |
| Retired after 20 years of disease | 36% | 32% | 66% |
| Retired after 45 years of disease | 50% | 100% | 99,5% |

*After Boonen 2002*
**pensioner; ** Whole cohort*

A comparison of disability pensioners and full-time employees, present and Barlow et al in 2001. Older age, longer duration of disease, low education level, presence of comorbidities, a functional deficit higher and higher levels of pain and stiffness, characterize the group of patients with AS and disability retirement (14) (Table 12).

**Table 12:** Comparison between full-time employees and retirees disability AS patients

| Variable | Employed Constanţa (n=97) | Retired Constanţa (n=96) | p | Employed UK ( n=33) | Retired UK (n=53) | P |
|---|---|---|---|---|---|---|
| Men (%) | 86,6 | 90,6% | ns | 89% | 70% | 0,044 |
| Education ≤ 12 years (%)<br>Education> 12 years (%) | 65%<br>35% | 91,7<br>0,3% | 0,001 | 93% | 63% | 0,001 |
| With partner (%) | 73,2% | 77,1% | ns | 81% | 73% | Ns |
| Comorbidities (hypertension) (%) | 20,6%* | 55,7%* | <0,001 | 48% | 82% | 0,001 |
| Current age (years) | 42.15±10.42 | 55.2±8,45 | <0,001 | 42.1± 9.1 | 52.8± 13.0 | <0.001 |
| Age at diagnosis / onset * (years) | 27.16±9.8* | 30,0±10,0* | ns | 26.0±6.0 | 28.0±5.2 | Ns |
| Retirement age (years) | - | 46,18±9,29 | - | - | - | - |
| Disease duration (years) | 15.26±10.4 | 24.88±9,8 | <0,001 | 21.8± 10.9 | 31.6± 14.1 | <0.001 |
| Disease duration at retirement(years) | - | 15,9±10,0 | - | - | - | - |
| VAS pain (mm) | 5,38±2,88 | 6,76±2,37 | <0,001 | 4.40±2.93 | 6.30±2.38 | 0.003 |
| VAS stiffness (mm) | 4,30±2,82 | 5,60±2,47 | 0,001 | 5.19± 2.71 | 7.23± 2.26 | 0.001 |

*After Barlow, 2001*

Rafael Ariza-Ariza and his collaborators identify predisposing factors of incapacity for work in a study that includes a large number of participants (9) (Rafael Ariza-Ariza, 2009). Like the Spanish study, age, disease duration, physical function and radiological changes are determinants of permanent incapacity to work. In addition, patients with AS and employment in our group have a functional impairment similar to Spanish patients receiving invalidity pension (Table 13)

**Table 13:** Predisposing factor for work disability for AS patients

| Variable | Retired Constanţa (n= 96) | Employed Constanţa (n=97) | p | Retired* Spain (n= 179) | Employed Spain (n= 520) | p |
|---|---|---|---|---|---|---|
| Meni (%) | 90,6% | 86,6% | Ns | 87% | 73% | < 0.001 |
| Current age (years) | 55,2±8,45 | 42.15±10.42 | <0,001 | 56.4 ± 10.0 | 46.1 ± 12.5 | <0,001 |

| Variable | Retired Constanța (n= 96) | Employed Constanța (n=97) | p | Retired* Spain (n= 179) | Employed Spain (n= 520) | p |
|---|---|---|---|---|---|---|
| Disease duration (years) | 24.88±9,8 | 15.26±10.4 | <0,001 | 19.7 ± 9.7 | 12.1 ± 9.5 | <0,001 |
| HLA - B27 (+)(%) | 80% | 96,8% | 0,016 | 81% | 82% | 0,7 |
| VAS pain (mm) | 6,76±2,37 | 5,38±2,88 | <0,001 | 4.5 ± 2.8 | 4.2 ± 2.7 | 0,2 |
| BASDAI | 5.99±2,19 | 4.77±2.62 | 0,001 | 4.7 ± 2.2 | 4.0 ± 2.4 | <0,001 |
| BASFI | 7.29±1,81 | 4.57±2.74 | <0,001 | 5.3 ± 2.4 | 3.3 ± 2.6 | <0,001 |
| BASRI | - | - | - | 8.6 ± 3.2 | 5.7 ± 3.1 | <0,001 |
| Cirtometric index (cm) | 1.80±1,25 | 3.08±1,63 | <0,001 | 2.6 ± 1.8 | 3.9 ± 2.0 | <0,001 |
| Schober index (cm) | 1,12±0, 12 | 1,28±0, 16 | <0,001 | 2.2 ± 2.2 | 3.2 ± 1.9 | < 0.001 |
| Occiput-wall index (cm) | 14.94±10,25 | 5.07±7,16 | <0,001 | 8.2 + 7.1 | 3.8 ± 5.4 | < 0.001 |
| Fingers-ground index (cm) | 38.23±13,61 | 24.37±16,90 | <0,001 | 26.5 ± 13.0 | 17.2 ± 14.7 | < 0.001 |
| CRP(mg/dl) | 16,1±25,2 | 17,7±26,9 | ns | 8.6 ± 11.7 | 9.2 ± 15.0 | 0,6 |

*After Rafael Ariza-Ariza 2009*

The issue of disability retirement has been studied in patients with AS and in Romania. Thus, a study conducted at the Hospital Dr Ion Cantacuzino in collaboration with the National Institute of Medical and Rehabilitation of Work Capacity that aimed to develop a prognostic score for retirement, identified disease duration, manual professional activity, ventilatory dysfunction of restrictive type, important functional deficit (BASF) and the active disease (BASDAI) as predictors of retirement age. We note the similarities between the two groups explained by the fact that patients in both studies retired according to the retirement criteria defined in the social Insurance (Table 14) (83).

**Table 14**: Comparison of employed and the disability retired patients with AS (Constanta / Bucharest)

| Variable | Retired Constanta (n= 96) | Employed Constanta (n=97) | p | Retired Bucharest (n=120) | Employed Bucharest (n=50) | p |
|---|---|---|---|---|---|---|
| Men (%) | 90,6% | 86,6 % | ns | 85% | 76% | ns |
| Urban | 83,3% (80) | 80,4% (78) | ns | 63,8% | 88% | 0,007 |
| Current age (years) | 55.21±8,45 (46,18±9,29) | 42.15±10.42 | <0,001 | 48,4±6,6 | 32,8±5,6 | <0.001 |
| Disease duration (years) | 24.88±9,82 | 15.26±10.47 | ns | 20,5±9,6 | 9,6± 6,5 | <0,001 |
| Education ≤ 12 years (%) | 91,7% | 65% | 0,001 | 98,3% | 48.0% | <0,001 |
| Manual work (%) | 84,4% | 52,6 | <0,001 | 80% | 36% | 0,002 |
| Ventilatory dysfunction (%) | 65,6% (63) | 27,8% (27) | <0,001 | 82,6% | 6,3% | <0,001 |
| BASFI | 7.29±1,81 | 4.57±2.74 | <0,001 | 6.2± 2.1 | 2.1±2.0 | <0,001 |
| BASDAI | 5.99±2,19 | 4.77±2.62 | <0,001 | 6,1±1,8 | 3.7± 2,0 | <0,001 |

*C. Oancea 2015*

## STUDY II CONCLUSIONS

1. The number of patients which continue their activity decreases with disease duration. From the group, 90% of the patience keep working after 5 years and 65.3% after 25 years of disease.
2. The rate of disability pensioners increases with age: up to 11.7% at the age of 50 years and 35.2% at the age of 60 years.
3. The training level is the strongest predictor of the employee status.
4. Binary logistic regression analysis nominates advanced sacroiliitis, presence of peripheral arthritis, cervical spine damage and increased BASFI index as variables that significantly characterize the disability pensioner status.
5. The onset at a young age, hip impairment, ocular manifestations are associated with the retirement at young age (<50 years)
6. Late-onset arthritis and peripheral presence is correlated with retirement after a low disease duration (≤5 years)

## STUDY III: ICF AND ITS RELATIONSHIP WITH DISABILITY RETIREMENT

### RESULTS

Since one of the objectives is to use ICF assessment for the work capacity of patients with AS, ICF codes were analyzed in relationship with the medical retiree or employee status of patients with AS from our cohort study. The utilized ICF codes were included in a restricted set of criteria proposed in 2010 to assess the consequences of AS on body functions and structures, on activities and participation of the patient. Since disability retirement requires a functional deficit of at least 50%, retiree medical status was correlated with associated marks of severely reduced ICF components (≥ grade 3). The relationships of the ICF codes, with demographics and clinical features of patients with AS included in the study group, was also analyzed.

**Code b: functions**

Disability retirement of patients with AS is significantly associated with severe pain functions (b280), mobility (b710), stiffness (b780) and exercise tolerance (b455). Statistical analysis through binary regression shows that the statistical predictor value for retiree status of patients with AS is the severe mobility problems (b710) ($p = 0.006$).

The codes b134 (sleep quality) and b152 (emotional status) functions are affected by a minority of cases (<10%) with no significant differences between the two analyzed subgroups (Table 15). b130 functions, energy and impulse functions, assimilated in our study with fatigue, were severely affected in less than 20% of the analyzed subgroups, about equally in patients with disease retirement of employee status.

**Table 15.** Severe impairment of function in patients with AS and disability retirement

| **Code b (≥ grade 3)** | **Retired (n=96)** | **Employed (n=97)** | **p** | **P*** |
|---|---|---|---|---|
| b280 (pain) | 61 (63,5%) | 45 (46,4%) | 0,012 | ns |
| b710 (mobility) | 31 (32,3%) | 10 (10,3%) | <0,001 | 0,001 |
| b780 (sensations related to muscles and movement functions) | 43 (44,8%) | 29 (29,9%) | 0,038 | ns |
| b130 (energy and impulse) | 16 (16,7%) | 14 (14,4%) | ns | - |
| b134 (sleep) | 4 (4,2%) | 7 (7,2%) | ns | - |
| b152 (emotions) | 5 (5,2%) | 1 (1,0%) | ns | - |
| b455 (exercise tolerance) | 25 (26%) | 12 (12,4%) | 0,018 | ns |

** Binomial logistic regression*

**Code b280 Sensation of pain**

It was taken into consideration the level of pain in one part of the body (b2801), the patient was questioned about head and neck pain(b28010), chest pain (b28011) back pain (pain in the dorsal and lumbar spine) (b28012), leg pain (b28015) and joint pain (including thigh and shoulder pain) (b28016). Although the patient's sensation of pain assessment was done in detail (up to level 4), the information was processed by the classification level 2 (b280) which included the sensation of pain in all of the mentioned locations.

In the entire study cohort ($n = 213$), the severe pain is present in 52.6% of cases. It is statistically significantly correlated with low level of education ($p = 0.035$), with manual labor ($p = 0.017$), with professional activities involving high energy consumption ($p = 0.009$) and with the status of disability retirement ($p = 0.004$).

Increased energy consumption of the professional activity is a significant predictor factor for severe damage to the b280 function.

The clinical characteristics of the disease significantly associated with severe pain are represented by the presence of peripheral arthritis (p = 0.039), hip impairment (radiological and clinical) (p = 0.054) and the presence of ventilator dysfunction, restrictive type (p = 0.007). Severe pain is less frequent in patients treated with anti-TNF alpha (p <0.001), but more frequent in those reporting continued consumption of NSAIDs (> 20days / month) (p <0.001). The severe modification of the pain function (ICF b280) is associated with very high averages for VAS spinal pain, VAS stiffness. It is also associated with elevated activity of all scores (BASDAI, ASDAS - ESR, ASDAS - PCR) and elevated acute phase reactants (ESR and CRP).

Although the correlation of the pain function with the measured BASFI functional status index is highly significant, the pain function is not influenced by severe radiological changes (grade IV sacroiliitis and generalized syndesmophytes) which have an important contribution to functional deficit. These are identified as significant predictors for severe pain (via binary regression method), presence of peripheral arthritis, elevated ESR (> 30mm / h) and increased disease activity assessed by BASDAI and ASDAS -ESR.

A significant proportion of the patients with AS and severe pain have the full-time employee status. These patients are younger (average age 41.96 years) a mean disease duration of 15 years, most often are educated and have a non-manual occupation. Keeping a job for most patients ensures a satisfactory level of living that gives them economic independence (Table 4). Young age is the only significant predictor factor (p <0.001) associated with maintaining employee status of patients with AS and severe impairment if the b28 function.

Patients with AS, disability retirement and severe pain, often show hip impairment, restrictive ventilatory dysfunction, increased functional impairment (BASFI), mobility reduction in lumbar and cervical spine (Schober's test), reduced chest expansion (cyrtometric measurements) and severe radiographic changes (grade IV sacroiliitis and generalized syndesmophytes). Binary regression analysis of predictive factors for retired patients with severe impairment of b280 function, identified grade IV sacroiliitis (p = 0.002), impaired hip (p = 0.044) and increased BASFI score value (p = 0.001) as significant predictors.

There is also a proportion of patients with AS, disability pension and mild or moderate pain. They have an average age of 55 years, disease duration of over 20 years with onset after the age of 30, few have a higher education and usually perform manual labor with a average energy consumption (Table 4). Physical labor and old age are the most important predictors of disability retirement in patients with AS and mild/moderate impairment of b280 function (p = 0.005 and p <0.001 respectively).

These patients often exhibit retirement predictors such as hip impairment (p=0,049), restrictive pulmonary dysfunction, increased functional deficits (BASFI p=0,038), decreased cyrtometric index (p=0,04), severe radiographic changes and associations with other disorders (Arterial hypertension).

**Code b710: Mobility of joint functions**

In order to assess the diversity and ease of movement, two-level classification of function and joint mobility was used. It includes studying the mobility of one or more joints, vertebrae mobility, shoulder, hip, knees, ankles, specific joints affected in ankylosing spondylitis.

Even if mentioned only in 32,3 % of cases, severe decrease in joint mobility (≥ 3 score for b710) highly statistically correlates with the disabled retiree status of the AS patient (p <0,001) and remains the only function whose severely impaired status represents a significant predictor for it.

The demographic factors that influence the reduction of joint mobility are: old age, long disease duration, smoker status and physical labor. The majority of AS patients that have severe reduction of joint mobility are disabled retirees. The predictive score of factors like smoker status and

old age (with an average above 50 years old) for the impairment of the b710 function are p=0,036 and p=0,024 respectively.

Severe reduction in mobility is associated with peripheral joint impairment, impaired hip, increased acute phase reactants and high degree of disease activity (BASDAI, ASDAS - ESR, ASDAS - CRP) with functional impairment expressed by BASFI index, severe radiological impairment ( sacroiliitis grade IV and presence of generalized syndesmophytes) with elevated metrology index and ventilatory dysfunction presence of the restrictive type.

Among these clinical features, the conditional regression model of elimination, we can see that following are statistically significant predictors for severe impaired b710 function: the presence of peripheral arthritis, hip prosthesis, severe reduction of cervical spine mobility, and elevated CRP, BASFI score.

Patients with AS and mild / moderate function b710 problems, with disability retirement status are characterized demographically by age, duration of disease over 20 years and low levels of education. They usually performed manual labor with an average energy consumption (Table 8). Manual labor is indeed a statistically significant predictive factor associated with the retiree status in these patients ($p < 0.001$). HLA - B27 is associated with improved functional status, the percentage of HLA B27 (+) is higher among those who maintain full-time employment status

**Code b780-Sensations associated with the muscles or muscle groups of the body and their movement**

The B780 code represents the sensations which are related to muscles and movement functions and sensations include stiffening and muscle tension, muscle spasm or tightness of muscles and sensation of heaviness, pain sensation is excluded. In our study we associated this code with a feeling of stiffness, in the Romanian variant BASDAI form. After the b280 code (sensation of pain), the b780 code with a grade $\geq 3$ is present in 44.4% of cases of disability retirement and is significantly associated with this status.

Demographic factors related to sex, patient age, disease duration or type of professional activity does not correlate significantly with severe stiffness. Patients with AS and disability retirement status had more frequently severe stiffness than those who keep their jobs ($p = 0.022$)
Severe impairment of muscle function and movement associated stiffness is significantly corelated with impairment of peripheral joint impairment (presence of arthritis at the time of assessment), with axial and lumbar damage, reduced mobility indices at this level, with indicators of disease activity (acute phase reactants of BASDAI, ASDAS - ESR, ASDAS - PCR) with the respective type of ventilatory dysfunction and elevated functional index (BASFI).

The movement function is significantly influenced by increased acute phase reactants and the type of medication, level of activity is positively correlated with anti-TNF alpha agents and negatively with continuous use of NSAIDs.

Correlation analysis between b780 (functions of muscles and movement) and the clinical characteristics associated with the employee or the disability retirement status, highlights the relations with statistical significance between the muscles and movement functions and presence of peripheral arthritis, disease activity (VAS, BASDAI, ASDAS), functional index ( BASFI), increased acute phase reactants and the presence of the restrictive type dysfunction.

Patients with AS and severe impairment of the b 780 function is characterized clinically by the presence of peripheral arthritis damage to the hip, a significant drop in the mobility of the spine and thoracic expansion, an important functional impairment with elevated levels of the BASFI index, severe radiological manifestations of cardiovascular disease.

Factors with significant predictive value for the retiree status, highlighted through the binary regression, are increased BASFI score (p = 0.016), a significant drop in chest circumference (p = 0.026) and presence of peripheral arthritis (p = 0.032).

**Code b455-Exercise tolerance functions**

The ICF, the b455 code is included in the additional functions and sensations of the cardiovascular and respiratory system. Exercise tolerance functions are functions related to respiratory and cardiovascular capacity, necessary to withstand a sustained physical effort. Functions include physical endurance, aerobic capacity and fatigue. Severely reduced exercise tolerance in patients with AS and retirement disability is present in 26% of the patients in this subset, a significantly higher rate than those with AS and employment status (12.4%). But to what extent are fatigue and decreased exercise tolerance related to the respiratory and the cardiovascular system, is hard to say. Age, employment status, qualified work, with a manual labor, increased energy consumption and comorbidities affect exercise tolerance in patients with AS.

Predictive factors for the severe impairment of the b455 function are low energy consumption, presence of comorbidities (Table 14), presence of peripheral arthritis, increased CRP and severe functional impairment assessed by the BASFI index.

People with AS and disability retiree status, associate the severely reduced exercise tolerance with the presence of restrictive ventilatory dysfunction, with reduced chest mobility (measured by cytometric index) and severe radiographic changes.

## S structure codes

ICF association with the structures involved in AS is represented by the thoracic structure ratings (S760), pelvic structure (S740), musculoskeletal structures related to movement (S770) and the lower extremity structure (S750). Severe damage (grade 3) or complete (grade 4) means a deterioration of these structures with a magnitude between 50-100%.

Severe or complete structural lesions, for the entire group, are as follows: 21.6% (46 patients) for S760, 6.1% (13 patients) for S740, 2.3% (5 patients) for the S770 and 14, 6% (31 patients) for S750. In the disability retirees subgroup (96 patients), the severe structural changes have following distribution: 36.5% (35 patients) for S760, 10.4% (10 patients) for S740, 5.2% (5 patients) for S770 and 25% (24 patients) for S750 (Table 16).

**Table 16.** Severe thoracical structural damage in patients with AS and disability retirement

| **s code(≥ grade 3)** | **Retired (n=96)** | **Employed (n=97)** | **p** | **P*** |
|---|---|---|---|---|
| s760 (thoracic structure) (%) | 35 (36,5%) | 7 (7,2%) | <0,001 | <0,001 |
| s740 (pelvic structure) (%) | 10 (10,4%) | 2 (2,1%) | 0,018 | ns |
| s770 (adjacent musculoskeletal structures related to movement) (%) | 5 (5,2%) | - | 0,029 | ns |
| s750 (lower extremity structure) (%) | 24 (25%) | 5 (5,2%) | <0,001 | 0,046 |

**Code s760 Structure of trunk**

The most common structural changes in the thoracic area (s760). According to comprehensive criteria, the fallowing were taken in consideration: structural changes present in the cervical spine, the thoracic spine and lumbar spine. The fallowing structural changes have been recorded and: the previous protrusion of the head, thoracic kyphosis, thorax flattening, removal / disappearance of lumbar lordosis, scoliosis. They were assigned grades between 0 and 4 for the damage, established by

clinical examination (medical structural changes observed on physical examination) and self-assessment (structural changes observed by the patient).

Severe impairment of thoracic structures correlates statistically significant with the mean patient age, disease duration, employment or disability retirement status, with smoking status and the number of packages per year. Type of profession (skilled labor, manual labor, rendered energy consumption) influences the onset of severe structural changes, but it doesn't reach the threshold of statistical significance. Patients with higher education, non-manual jobs and low energy consumption present low/medium structural changes. Patients with severe structural deterioration of the thoracic area declare an unsatisfactory lifestyle rating (84.8%), the obvious presence of these changes affect family life of patients with AS. The presence of HLA-B 27 is negatively correlated with severe torso structural changes, which are present in a higher ratio in patients with AS and HLA - B 27 negative.

From the clinical point of view, the situation of patients with AS and severe structural manifestations of the torso are characterized by clinically impaired hip (presence of pain but no limitation of motion, expressed by the intermalleolar distance) and a significant drop in the mobility of the cervical spine (occiput – wall distance), lumbar spine (unchanged Schober index and finger-floor distance) and chest expansion (cyrtometric index). Restrictive ventilatory dysfunction is present in a proportion of 82.6% among patients with severe torso structural changes (Table 2). These patients associate advanced radiological changes, grade IV sacroiliitis, present in 97.8% of patients, while the presence of generalized syndesmophytes is 93.5% in this subset of patients.

Altered functional status, expressed through an increased value of the BASFI index, is significantly associated with the severe torso structural changes. Acute phase reactants, the degree of disease activity, treatment with anti-TNF alpha agents do not establish significant correlations with severe structural damage to the torso, expressed through s760 code scores.

In the cohort of analyzed patients, 193 patients have or had a remunerated job. Structural impairment of the torso ( s760 code) is present in 21.8% of patients (42 patients) and establishes a statistically significant relationship with disability retirement: 35 patients out of 96 with retiree status have a grade $\geq 3$ for s760 (36.4%) while only 7 of the 97 patients with employee status have the same code S760 grade(7.2%).

There are patients with severe structural damage who still have employee status (7 of 42) and patients with moderate structural damage and AS have retired due to incapacity (61 of 151).
Patients with severe structural damage and the status of employee are all male and have a higher level of education (either primary or secondary). Slightly less than half (43%) live in rural areas and have never smoked.

From a clinical point of view, it is considered that they have a functional status (assessed by BASFI) and have a better chest expansion. Maintaining a higher income may be an explanation for continuing work for these patients.

**Code s750: Lower extremity structure**

This code includes hip joint prostheses, contracture of the hip during flexion, knee flexion contracture, muscular atrophies, arthritis, knee and ankle bursitis and Achilles enthesitis.
Old age, disease duration and energy consumption of professional activity statistically significantly influence the degree of impairment of the lower extremities structures. Analysis though binary regression highlights lengthy illness period as a significant predictor for severe damage to the structures of the lower extremities.

The presence of peripheral arthritis, impaired hip, spinal pain, morning stiffness, the degree of activity (including acute phase reactants) malfunction disease and severe radiological changes significantly influence the occurrence of severe problems with the s750 code. Binary regression analysis reveals disease activity (as measured by ASDAS-CRP) and damage to the cervical spine

(occiput-wall index) as significant predictors for severe damage to the structures of the lower extremities.

The s750 component is one of the predictors with statistical significance for appartenance to the disability retirement group (Table 17).

Most patients with AS and disability retirement (%) show mild / moderate damage to the lower extremity structures. These patients are characterized, demographically, by age, disease onset after 30 years, low education level, predominantly manual labor, with at least average energy consumption. Patients in this subset are often smokers and the presence of HLA-B27 is less frequent. Binary logistic regression analysis highlights as predictors with statistical significance associated disability retirees, old age ($p < 0.001$) and educational level ($p = 0.001$).

Most patients with AS and disability retirement status present impairment mild / moderate impairment of the s750 component. Retiree status is significantly correlated with impaired hip, spinal pain and morning stiffness, reducing the mobility of the spine and chest expansion, severe radiographic changes and important functional deficit. Predictors of disability retirement that have a statistical significance are represented by occiput – wall index ($p = 0.005$), reduced mobility of the lumbar spine and impaired hip (finger – hip index) ($p = 0.005$), HBP ($p = 0.01$) and the grade of the radiological sacroiliitis($p = 0.047$).

A small percentage of patients with AS and severe structural damage to the lower extremity are employed full time. All of these patients are men, doing qualified labor which often involves a low energy consumption. They are younger and have a shorter duration of. From a clinical point of view, they have a less affected mobility and functional status.

Predictive factors, statistically associated with disability retirement in patients with severely affected s750 component, are represented by: older age ($p < 0.001$), impaired hip ($p < 0.001$), a significant drop in functional status ($p < 0.001$), reduced mobility of the spine ($p < 0.001$) and chest expansion ($p = 0.026$). Increasing living standards represent a significant motivation for keeping the employee status ($p < 0.001$).

**Code d: activities and participation**

The ICF established set of criteria, for assessing disability in patients with AS, includes the areas of activities and participation component (d code). Being significantly associated with the disability retirement status, there are severe problems related to walking (D450) and family relationships (d760). Mobility, represented by a severely D450 code, is the significant predictive factor of disability retirement in patients with AS analyzed in relation to this component (activities and participation) (Table 17).

**Table 17.** Severe impairment of the activities and participation component in patients with AS

| ICF d ≥ 3 | Retired (%) | Employed (%) | p | P* |
|---|---|---|---|---|
| d230 (n= 36) | 20,8 | 14,4 | ns | - |
| d410 (n=. 36) | 24 | 10,3 | ns | - |
| d450 (nr. ) | 17,7 | 4,1 | 0,003 | 0,002 |
| d760 (nr. ) | 9,4 | 3,1 | 0.018 | ns |

* Binomial logistic regression

**Code d230: Daily programme**

For the entire group, the demographics factors (gender, age, disease duration, education level) or work-related factors (unqualified, manual labor, mean energy consumption) do not correlate significantly with severe problems in implementing the daily program management. Many patients with AS and disability retirement status say they organize their daily schedule and adapt according to

the lack of functionality. It is important to analyze the problems that patients with SA and remunerated employment contract in carrying out the daily schedule, including work tasks.

Severe problems regarding the fulfillment of the daily program relate particularly significant to the manifestations of acute inflammatory type, both clinical (peripheral arthritis, clinical hip damage, enthesitis, pain and stiffness) and biological (increased acute phase reactants), implicitly scores activity.

Code d230 does not achieve significant correlations with severe radiological manifestations, spinne mobility reduction or chest expansion. Severe problems in fulfilling the daily schedule does not correlate with structural changes (codes s).

**Code d450: walking**

Only 22 patients (%) present severe problems related to walking. Of these, 21 have or have had a full time job, at the time of analysis 17 patients (81%) had the disability retirement status. Most patients (172 patients) who have concluded an employment contract, don't have severely impaired walking, a percentage of 45.9% are retired when assessing disability.

Severe impairment of walking is significantly influenced by age and average energy consumption, age is still a statistically significant predictive factor of severe problems related to walking. The other demographic features, related to gender, level of education or professional activity doez not influence the occurrence of the severe walking problems in patients with AS.

In terms of clinical features, severe problems of patients related to walking are significantly correlated with impaired peripheral joint, of leg enthesis, of the hip (including hip joint) with a high degree of disease activity (including high acute phase reactants) and high degree of disability expressed by the BASFI index.

Heel enthesis, hip prosthesis and the high degree of failure assessed by BASFI index, represent significant predictor factors of severe disorders of peripheral arthritis.

Qualifications and history of paid employment (employment contract) are highly correlated. Thus, 97.6% of patients who have qualifications were employed at some point, compared to 67.34% of unskilled workers ($p < 0.001$). Logistic regression analysis identified qualification as the most important factor in gaining a employment status($<0.001$)

Education level, type of working conditions and level of energy consumption is significantly related to employee or retiree status of patients.

Logistic regression analysis shows that the level of training differs best the disability retirement status ($p = 0.046$).

## DISCUSSIONS

The International Classification of Functioning, Disability and Health (ICF), developed by the World Health Organization (WHO), is an accepted model for the classification of health "components" and "consequences", model which can be applied in medicine to assess the consistent and complex consequences of various diseases (ICF) (1).

The work capacity evaluation , for patients with various diseases, varies from country to country and criticisable in terms of quality and transparency, which is why over the past 10 years, work has started towards implementing and using the International Classification of Functioning, Disability and Health - ICF (International Classification of Functioning, disability and Health - ICF) to assess the degree of incapacity for work caused by illness (7).

ICF wasn't designed to assess the working capacity. In 2004, at the 15th EUMASS congress at Lille, the EUMASS (European Union of Medicine in Assurance and Social Security) has recognized the potential usefulness of ICF in social security. A working group was assembled, in

which Romania was a member. The main focus of this working group was the development of a set of basic criteria to assess functional disability, to grant benefits under schemes of European social security.

Romania, as a member of EUMASS, participated in the decision involving thee creation and validation of the core set. (100, 4.5)

This project was materialized in 2008 when EUMASS published a list of 20 categories selected for the basic set: 5 for body functions and 15 for activities and participation. This "core set" is generic, enumerating a list of categories that regardless of diagnosis, should be evaluated by a doctor.

This basic set was tested in several countries, and was later validated currently, being used in the UK, Netherlands (4), Sweden, Iceland, and most recently in Cyprus (101)

The particularity in the ICF-based assessment of the Disability Assessment Centers in Cyprus is the existence of two committees composed of doctors and rehabilitation specialists. A committee that sets the degree of disability and one that quantifies the restrictions in participation and environmental factors influencing functionality. The person with disability can choose either or both the first committee. (53)

The ICF model reflects the modern tendency of disability evaluation in a bio - psycho – social concept and allows experts and doctors to identify which components are important in assessing disability, but the definitions provided by this model are limited in regard to the assessment of work capacity. In Romania, the introduction of ICF in the existing expertise of working capacity is one of the objectives of the government is to modernize the social assistance system (53)

The application of the ICF set, to assess disability of people with ankylosing spondylitis by the medic, objective of this thesis, is a recent and non-standard procedure. To what extent are the ICF criteria selective for specific sets of various diseases and can be used in the correct assessment, is still a debatable question (73). Moreover, even health evaluation of the patient with AS in relation to the ICF is an ongoing process validation. From basic ICF set of associated with AS, ASAS recently completed a criteria for quantifying the health of the patient, called ASAS HI (health index) which is a composite index that includes 15 categories of the ICF comprehensive set.ASAS HI has three levels of severity, an average of 8.37 ± 3.9 (0-17), significantly correlated with BASDAI, spinal pain and BASFI (Table 18).

**Table 18**. Distribution of ASAS HI according to disease activity and functional level

| | **Group I (0 – 3,9)*** **BASDAI (n=146** | **Group II (4 – 6)*** **BASDAI (n=166)** | **Group III (6,1-10)*** **BASDAI (n=293)** |
|---|---|---|---|
| | 5,0±3,2 | 7,4±3,1 | 10,6±3,0 |
| ASAS HI mean e± SD | Group I (0-3,9)* | Group II (4-6)* | Group III (6,1-10)* |
| | BASFI (n=256) | BASFI (n=152) | (BASFI (n=195) |
| | 5,7±3,0 | 8,5±2,8* | 11,7±2,8 |
| ASAS HI mean ± SD | Group I (0-3,9)* | Group II (4-7)* | Group III (7,1-10)* |
| | Total spinal pain (n=205) | Total spinal pain (n=264) | Total spinal pain (n=131) |
| ASAS HI mean ± SD | 5,6±3,4 | 9,0±3,1 | 11,4±2,9 |

*After Boonen 2015*
*On a scale from 0-10*

ASAS HI includes 15 categories in the ICF comprehensive set ICF as follows: b280 (pain), d415 (maintaining body position), d455 (moving impairment - moving through means other than walking - running - down the street, through obstacles, jumps - forward with a dive, jump over a rock), d530 (toilet – urination hygiene, defecation, menstruation), b130 (function of energy and momentum), b1301 (motivation - mental function that generates the incentive to act), b640 (sexual functions), d475 (driving ), d910 (social life), d240 (ability to cope with stress and other

psychological stress), d920 (recreation and leisure), b152 (emotional functions), d510 (washing), d870 (economic independence), b134 (sleep function) (72).

**Table 19:** Explanatory ASAS-HI legend

| Item | Categories | ICF code |
|---|---|---|
| Pain interrupts my normal work | Pain | b280 |
| I have difficulty standing on my feet for long periods of time | Maintaining body position | d415 |
| I am having trouble running | Movement | d455 |
| I have problems with using the toilet | Toilet | d530 |
| I am often exhausted | Energy and momentum | b130 |
| I am less motivated to do something that requires physical effort | Motivation | b1301 |
| I have lost interest in sex | Sexual function | b640 |
| I have difficulty using the car pedals | Driving | d475 |
| I'm having trouble connecting with other people | Social life | d910 |
| I cannot move on flat surfaces | Walking | d455 |
| I have trouble concentrating | Stress management | d240 |
| I have travel restrictions due to mobility | Recreation and leisure | d290 |
| I often feel frustrated | Emotional function | b152 |
| I wash my hair with difficulty | Washing / Hygiene | d510 |
| I went through financial / economic changes due to my rheumatic disease | Eonomic independence | d870 |
| I have bad night sleep | Sleep | b134 |
| I cannot overcome my problems | Stress management | d240 |

*After Kiltz 2015*

The development of ASAS HI as a tool for assessing the health of patients with AS included a questionnaire explaining the ICF categories used in this composite index (Table 19) (71).

The ICF categories included in ASAS HI belong to the function component (code b), shares and participation (code d). In this study, these codes were used were only those included in the concise set of criteria, namely: b280, b130, b134, d920. Code d475 was not used because a small number of patients with AS and medical retirement owned vehicles. Codes b134, d920 weren't used either due to severe problems of these categories, either they were not present (d920) or were found in a small a percentage of cases (b134) hence with no significant correlations regarding work disability. Code b130 (energy levels and motivation) was not analyzed either because the purposes of the code was difficult to discern. Correlated with fatigue, for this code, severe problems were reported n 14.6% of the 213 cases. Severe impairment was present in approximately equal proportions retirees (16.7%) and employees (14.4%).

ASAS HI does not include mobility (b710) nor ICF categories related to structures (code s). In our study, severe impairment of these codes was significantly correlated with work disability and disability retirement.

The assessment of functional impairment in patients with AS, according to the ICF core set applied in the expertise of work capacity, has proved to be disappointing. Severe structural and functional impairment, as they were valued in this study, are present in a small percentage of patients with AS and work disability (Table 20).

Pain function (b280) and stiffness (b780) are most commonly affected, severe problems of these functions being present in 63.5 respectively 44.8% of patients with AS and disability retirement (Table 3). The only function with predictive value for retiree status is mobility (b710), whose severe impairment is found only in 1/3 of patients with AS and disability retirement (Table 3).

**Table 20.** The structural and functional impairment in patients with AS (retirees vs employees)

| **Code (grade ≥ 3) (%)** | **Retired (n=96)** | **Employed (n=97)** | **p** | **P*** |
|---|---|---|---|---|
| b710 (mobility) | 31 (32,3%) | 10 (10,3%) | <0,001 | 0,006 |
| b280 (pain) | 61 (63,5%) | 45 (46,4%) | 0,021 | ns |
| b780 (Sensations related to muscles and movement functions) | 43 (44,8%) | 29 (29,9%) | 0,038 | ns |
| b455 (exercise tolerance) | 25 (26%) | 12 (12,4%) | 0,018 | ns |
| s760 (trunk structure) | 35 (36,5%) | 7 (7,2%) | <0,001 | <0,001 |
| s740 (pelvic structure) | 10 (10,4%) | 2 (2,1%) | 0,018 | ns |
| s770 (adjacent musculoskeletal structures related to movement) | 5 (5,2%) | - | 0,029 | ns |
| s750 (lower extremity structure) | 24 (25%) | 5 (5,2%) | > 0,001 | 0,046 |
| d450 | 17,7% | 4,1 | 0,003 | 0,002 |
| d760 | 9,4 | 3,1 | 0.018 | ns |

** Binomial logistic regression*

The severe problems of structures were present in a small number of patients with work disability and AS. Significantly correlated with the status of retiree and predictive value for membership in this subgroup, severe problems of the torso structure (b760) and lower extremities structures (b750) are present in only 25% respectively 36.5% of patients with AS and disability retirement (Table 21).

**Table 21** Relationship between ICF severe problem - level of education and type of work performed (retired)

| **Variable** | **b280** | **b710** | **b780** | **b455** | **s760** | **s740** | **s770*** | **s750** | **d410** | **d450** |
|---|---|---|---|---|---|---|---|---|---|---|
| Retirees (No.) (%) | 61 (63,5%) | 31 (32,3%) | 43 (44,8%) | 25 (26%) | 35 (36,5%) | 10 (10,4%) | 5 (5,2%) | 24 (25%) | 23 | 17 |
| current age | <0,001 | 0,007 | <0,001 | 0,022 | ns | ns | | 0,01 | ns | ns |
| Age of onset | ns | ns | ns | ns | ns | ns | | ns | ns | ns |
| disease duration | <0,001 | <0,001 | <0,001 | 0,001 | ns | ns | | 0,01 | 0,003 | ns |
| HLA-B27 | ns | ns | ns | ns | ns | ns | | ns | ns | ns |
| Education level | 0,023 | ns | 0,01 | ns | 0,01 | ns | | ns | ns | ns |
| Manual labor | 0,011 | ns | 0,01 | ns | ns | ns | | ns | 0,036 | ns |
| Energy consumption | ns | ns | ns | ns | ns | ns | | ns | ns | ns |
| Smoking | ns | ns | ns | ns | ns | ns | | ns | ns | ns |

**without comparison group*

A number of significant demographic factors associated with severely reduced function in patients with AS and medical retirement have been identified. Instructional level and manual labor can significantly influence the emergence of severe functional problems (pain and stiffness) (Table 3).

Severe impairment of function and structure in patients with AS and disability retirement is consistently associated with hip involvement (clinical and / or radiological), with restrictive ventilatory dysfunction and the presence of generalized syndesmophytes (Table 22). These changes (clinical, functional, radiological ) are among the Romanian criteria for work capacity expertise

**Table 22.** The relationship between severe ICF problems and clinical features (retiree vs employees)

| **Variable** | **b280 n*=61** | **b710 n=31** | **b780 n=43** | **b455 n=25** | **s760 n=35** | **s740 n=10** | **s770 n=5 *** | **s750 n=24** | **d410 n=23** | **d450 n=17** |
|---|---|---|---|---|---|---|---|---|---|---|
| Axial form | ns | Ns | 0,055 | ns | ns | ns | - | ns | ns | ns |
| Peripheral arthritis | ns | Ns | 0,028 OR=3,29 | ns | ns | ns | - | ns | ns | ns |
| Enthesitis | ns | Ns | Ns | ns | ns | ns | - | ns | ns | ns |
| Hip impairment | > 0,001 OR=4,77 | Ns | 0,003 OR=4,9 | ns | ns | ns | - | 0,046 OR=10,5 | 0,032 OR=7,0 | ns |
| Hip prosthesis | ns | Ns | Ns | ns | ns | ns | - | ns | ns | ns |
| Ventilatory dysfunction | <0,001 | 0,003 OR=12,13 | 0,006 | 0,006 OR=10,2 | ns | ns | - | ns | 0,001 OR=24,5 | 0,006 |
| Iridocyclitis | ns | Ns | Ns | ns | ns | ns | - | ns | ns | ns |
| Generalized syndesmophytes | > 0,001 OR=10,05 | <0,001 OR=21,75 | <0,001 OR=8,41 | <0,001 OR=35,5 | ns | ns | - | ns | 0,004 OR=15,75 | 0,022 OR= |
| Anti TNF | ns | Ns | Ns | ns | ns | ns | - | ns | ns | ns |

** Number of pensioners*

The analysis of the AS patients with work disability group shows that the severe problems of functions and structures are significantly correlated with the functional index (BASFI), with impaired mobility of the spine and reduced expansion of the chest, but not with the degree of activity (BASDAI, ASDAS or the values of acute phase reactants (Table 23)

**Table 23**. The relationship between severe ICF problem - functional status and disease activity ( retired vs employees)

| **Variable** | **b280 (n=61)** | **b710 (n=31)** | **b780 (n=43)** | **b455 (n=25)** | **s760 (n=35)** | **s740 (n=10)** | **s770* (n=5)** | **s750 (n=24)** | **d410 (n=23)** | **d450 (n=17)** |
|---|---|---|---|---|---|---|---|---|---|---|
| BASFI | <0,001 | 0,002 | 0,001 | 0,005 | 0,007 | ns | - | 0,001 | 0,05 | ns |
| Schober index | <0,001 | <0,001 | 0,001 | <0,001 | ns | ns | - | 0,032 | 0,002 | ns |
| I. finger-ground | <0,001 | 0,011 | 0,001 | <0,001 | 0,013 | ns | - | 0,027 | 0,001 | 0,017 |
| Chest expansion | <0,001 | <0,001 | <0,001 | <0,001 | 0,005 | ns | - | <0,001 | <0,001 | 0,28 |
| I. occiput wall | <0,001 | 0,002 | 0,002 | <0,001 | ns | ns | - | ns | 0,007 | ns |
| BASDAI | ns | ns | Ns | ns | ns | ns | - | ns | ns | ns |
| ESR | ns | ns | Ns | ns | ns | ns | - | ns | ns | ns |
| CRP | ns | ns | Ns | ns | ns | ns | - | ns | ns | ns |
| ASDAS CRP | ns | ns | Ns | ns | ns | ns | - | ns | ns | ns |

Smoking history and increased cigarettes consumption have been identified as predictors of severe reduction of mobility (b710) and severe torso structural problems (s760) (Table 23). Our results are in agreement with the results of other clinical trials that incriminate smoking as a risk factor for the decrease in the functional index in patients with AS (112), predictor factor of severe radiologic changes (113) and reduced mobility (114), quitting smoking being recommended and reducing alcohol consumption as a non-pharmacological measure in AS patient management (114).

Binary regression analysis showed functional impairment and / or severe structural and retiree status as predictors with statistical value between the following categories of demographic variables: age, disease duration, low energy consumption and presence of comorbidities (Table 24).

**Table 24**. The relationship between ICF severe problems - demographic factors (retiree vs employees)

| **Variable** | **b280 n=112 (52,65)** | **b780 n=77 (36,2%)** | **b710 n=42 (20,2%)** | **b455 (n=39) (18,3%)** | **s760 (n=46) (21,6%)** | **s750 n=31 (14,6%)** | **d230 n=36 (16,9%)** | **d410 n=36 (16,9%)** | **d450 n=22 (10,3%)** |
|---|---|---|---|---|---|---|---|---|---|
| Current age | 0,029 | ns | 0,002* | ns | <0,001 | 0,016 | ns | 0,013* | 0,026 |
| Onset age | ns | ns | ns | ns | ns | ns | ns | ns | ns |
| Disease duration | ns | ns | 0,003 | ns | <0,001* | <0,001* | ns | ns | ns |
| HLA-B27 | ns | ns | ns | ns | 0,012 | ns | ns | ns | ns |
| Instructional level | 0,035 | ns | ns | ns | ns | ns | ns | ns | ns |
| Manual labor | 0,017 | ns | ns | 0,007 | ns | ns | ns | ns | ns |
| Energy consumption | 0,009* | ns | ns | 0,006* | ns | 0,012 | ns | ns | ns |
| smoking | ns | ns | 0,038* | ns | 0,042 | ns | ns | ns | ns |
| No. packs / year | ns | ns | ns | ns | 0,027* | ns | ns | ns | ns |
| Comorbidities | ns | ns | ns | 0,001* | ns | ns | ns | ns | ns |

** Statistically predictive value for disability retirement*

** Binomial logistic regression*

## STUDY III CONCLUSIONS

1. Severe structural and functional impairment, as they were valued in this paper, are present in a minority of patients with AS and disability retirement.
2. Disability retirement for patients with AS is significantly associated with reduced mobility (B710), severe torso structure damage (S760), to the legs (S750) and severe walking problems and (D450 - walking).
4. Patient age, disease duration, level of education and manual labor can significantly influence the occurrence of severe functional problems (pain and stiffness).
5. Severe function and structure impairment in patients with AS and disability retirement are consistently associated with impaired hip (clinical and / or radiological) with ventilatory dysfunction restrictive type and presence of generalized syndesmophytes. These changes (clinical, functional and radiological) are found in other retirement criteria of the Romanian expertise of working capacity.
6. Functional Index (BASF) is significantly correlated with severe problems of functions and structure in patients with AS and disability retirement. On the other hand, extent of activity (BASDAI, ASDAS or values of acute phase reactants) are not.

## GENERAL CONCLUSIONS

1. Work disability in AS patients depends on the person's age, disease duration and modifiable factors such as level of education, professional qualifications, type of work performed. To help patients with AS keep their jobs, the Ministry of Labor and Social Insurance Medicine must consider a number of issues such as:

- educational and vocational guidance (increasing training)
- availability of part time or home jobs
- educational programs for training / retraining

2. The severe problems in the functional, structural, activities and participation areas from the ICF criteria have been identified in a small number of patients with AS and disability retirement. We believe that the ICF addition to the existing expertise of working capacity involves:

- creating a ICF index (explanatory questionnaires used for the ICF categories) relevant to the expertise of working capacity domain
- adaptation to the disease and performed work type
- establishment of multidisciplinary assessment teams (medical expert, rheumatologist specialist, PRM specialist, psychologist, social worker, etc.)

3. Involvement of patients in the process of creating a ICF index to asses work capacity and developing employment and social programs.

## BIBLIOGRAFIE


1. Clasificarea internaţională a funcţionării, dizabilităţii şi sănătăţii OM a Sănătăţii - 2004 - Editura MarLink, Bucureşti
2. **Adomaviciute D. et al.** Prevalence survey of rheumatoid arthritis and spondyloarthropathy in Lithuania, *Scand J Rheumatol*. 2008 Mar-Apr;37(2):113-90
3. **Alamanos Y, Papadopoulos NG, Voulgari PV, Karakatsanis A, Siozos C, Drosos AA**. Epidemiology of ankylosing spondylitis in Northwest Greece, 1983–2002. *Rheumatology*. 2004 May 1;43(5):615-8.
4. **Amor B, Dougados M, Mijiyawa M.** [Criteria of the classification of spondylarthropathies]. *Revue Du Rhumatisme Et Des Maladies Osteo-Articulaires*. 1990 Feb;57(2):85-9.
5. **Anagnostopoulos I, Zinzaras E, Alexiou I, Papathanasiou AA, Davas E, Koutroumpas A, Barouta G, Sakkas LI.** The prevalence of rheumatic diseases in central Greece: a population survey. *BMC Musculoskeletal Disorders*. 2010 May 26;11(1):1.
6. **Ancuţa I.** Dinamica şi aderenţa la terapie biologică pentru poliartrita reumatoidă, spondilita anchilozantă şi artropatia psoriazică în România în perioada 2009-2013. *Revista Română de Reumatologie*. 2014;23(2):70-86.
7. **Anner J, Schwegler U, Kunz R, Trezzini B, de Boer W.** Evaluation of work disability and the international classification of functioning, disability and health: what to expect and what not. *BMC Public Health*. 2012 Jun 21;12(1):1.
8. **Ariza-Ariza R, Hernández-Cruz B, Collantes E, Batlle E, Fernández-Sueiro JL, Gratacós J, Juanola X, Linares LF, Mulero J, Zarco P**. Work disability in patients with ankylosing spondylitis. *The Journal of Rheumatology*. 2009 Nov 1;36(11):2512-6.
9. **Ariza-Ariza R, Hernández-Cruz B, Collantes E. et al**. Work Disability in Patients with Ankylosing Spondylitis. *The Journal of Rheumatology* 2009; 36:11).
10. **Bakland G, Gran JT, Becker-Merok A, Nordvåg BY, Nossent JC.** Work disability in patients with ankylosing spondylitis in Norway. *The Journal of Rheumatology*. 2011 Mar 1;38(3):479-84.
11. **Bakland G, Gran JT, Becker-Merok A, Nordvåg BY, Nossent JC.** Work disability in patients with ankylosing spondylitis in Norway. *The Journal of Rheumatology*. 2011 Mar 1;38(3):479-84.)
12. **Bakland G, Nossent HC, Gran JT**. Incidence and prevalence of ankylosing spondylitis in Northern Norway. *Arthritis Care & Research*. 2005 Dec 15;53(6):850-5.
13. **Baraliakos X, Braun J.** Spondyloarthritides. Best Practice & Research Clinical *Rheumatology*. 2011 Dec 31;25(6):825-42.
14. **Barlow JH, Wright CC, Williams B, Keat A.** Work disability among people with ankylosing spondylitis. *Arthritis Care & Research*. 2001 Oct 1;45(5):424-9.
15. **Bolosiu H.** Spondilita anchilozantă. *Ghid de reumatologie*. Ed. Dacia, Cluj-Napoca, 1989
16. **Boonen A, Braun J, van der Horst Bruinsma IE, Huang F, Maksymowych W, Kostanjsek N, Cieza A, Stucki G, van der Heijde D**. ASAS/WHO ICF Core Sets for ankylosing spondylitis (AS): how to classify the impact of AS on functioning and health. *Annals of the Rheumatic Diseases*. 2010 Jan 1;69(01):102-7.2
17. **Boonen A, Brinkhuizen T, Landewé R, van der Heijde D, Severens JL.** Impact of ankylosing spondylitis on sick leave, presenteeism and unpaid productivity, and estimation of the societal cost. *Annals Of The Rheumatic Diseases*. 2010 May 3:annrheumdis116764.
18. **Boonen A, Chorus A, Miedema H, van der Heijde D, Landewe R, Schouten H, Van Der Tempel H, Van Der Linden S.** Withdrawal from labour force due to work disability in patients with ankylosing spondylitis. *Annals of the Rheumatic Diseases.* 2001 Nov 1;60(11):1033-9.
19. **Boonen A, Chorus A, Miedema H, van Der Heijde D, van Der Tempel H, Van der Linden SJ.** Employment, work disability, and work days lost in patients with ankylosing spondylitis: a

cross sectional study of Dutch patients. *Annals of the Rheumatic Diseases*. 2001 Apr 1;60(4):353-8.

20. **Boonen A, de Vet H, van der Heijde D, van der Linden SJ**. Work status and its determinants among patients with ankylosing spondylitis. A systematic literature review. *The Journal of Rheumatology*. 2001 May 1;28(5):1056-62.
21. **Boonen A, van Der Heijde D, Landewe R, Spoorenberg A, Schouten H, Rutten-van Mölken M, Guillemin F, Dougados M, Mielants H, De Vlam K, van Der Tempel H**. Work status and productivity costs due to ankylosing spondylitis: comparison of three European countries. *Annals of the Rheumatic Diseases*. 2002 May 1;61(5):429-37.
22. **Boonen A, van Der Heijde D, Landewe R, Spoorenberg A, Schouten H, Rutten-van Mölken M, Guillemin F, Dougados M, Mielants H, De Vlam K, van Der Tempel H.** Work status and productivity costs due to ankylosing spondylitis: comparison of three European countries. *Annals of the Rheumatic Diseases.* 2002 May 1;61(5):429-37..
23. **Boonen A.** A review of work-participation, cost-of-illness and cost-effectiveness studies in ankylosing spondylitis. *Nature Clinical Practice Rheumatology.* 2006 Oct 1;2(10):546-53.
24. **Braun J, Bollow M, Remlinger G, Eggens U, Rudwaleit M, Distler A, Sieper J.** Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. *Arthritis & Rheumatism*. 1998 Jan 1;41(1):58-67.
25. **Bruges-Armas J, Lima C, Peixoto MJ, Santos P, Mendonca D, Da Silva BM, Herrero-Beaumont G, Calin A.** Prevalence of spondyloarthritis in Terceira, Azores: a population based study. *Annals of the Rheumatic Diseases*. 2002 Jun 1;61(6):551-3.
26. **Brunner R, Kissling RO, Auckenthaler C, Fortin J**. Clinical evaluation of ankylosing spondylitis in Switzerland. *Pain Physician.* 2002 Jan;5(1):49-56.
27. **Cakar E, Taskaynatan MA, Dincer U, Kiralp MZ, Durmus O, Ozgül A**. Work disability in ankylosing spondylitis: differences among working and work-disabled patients. *Clinical Rheumatology*. 2009 Nov 1;28(11):1309-14.
28. **Calin A, Brophy S, Blake D**. Impact of sex on inheritance of ankylosing spondylitis: a cohort study. *The Lancet*. 1999 Nov 13;354(9191):1687-90.
29. **Calin A, Garrett S, Whitelock H, Kennedy LG, O'hea J, Mallorie P, Jenkinson T.** A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *The Journal of Rheumatology.* 1994 Dec;21(12):2281-5.
30. **Calin A, Porta J, Fries JF, Schurman DJ**. Clinical history as a screening test for ankylosing spondylitis. *JAMA*. 1977 Jun 13;237(24):2613-4
31. **Calin, A**. The spodylarthritides. *Revista de Reumatologie*, vol. IV (supliment), 36-39
32. **Cansu DÜ, Çalışır C, Yavaş US, Kaşifoğlu T, Korkmaz C.** Predictors of radiographic severity and functional disability in Turkish patients with ankylosing spondylitis. *Clinical Rheumatology*. 2011 Apr 1;30(4):557-62.
33. **Carmona L, Ballina J, Gabriel R, Laffon A**. The burden of musculoskeletal diseases in the general population of Spain: results from a national survey. *Annals of the Rheumatic Diseases*. 2001 Nov 1;60(11):1040-5.
34. **Carter ET, Mckenna CH, Brian DD, Kurland LT**. Epidemiology of ankylosing spondylitis in Rochester, Minnesota, 1935–1973. *Arthritis & Rheumatism*. 1979 Apr 1;22(4):365-70.
35. **Castro RO, Ugalde PF, Villegas MC, Gutiérrez JC, Gomariz EM, Montejo PZ, Almodóvar R, Mendoza JM, Torre-Alonso JC, Masmitjá JG, Roura XJ**. Diferente expresión clínica de los pacientes con espondilitis anquilosante según el sexo en función del tiempo de evolución. Datos de REGISPONSER. *Reumatología Clínica.* 2013 Aug 31;9(4):221-5.

36. **Chen CH, Chen HA, Lu CL, Liao HT, Liu CH, Tsai CY, Chou CT**. Association of cigarette smoking with Chinese ankylosing spondylitis patients in Taiwan: a poor disease outcome in systemic inflammation, functional ability, and physical mobility. *Clinical Rheumatology*. 2013 May 1;32(5):659-63.
37. **Chorus AM, Boonen A, Miedema HS, Van der Linden SJ.** Employment perspectives of patients with ankylosing spondylitis. *Annals of the Rheumatic Diseases.* 2002 Aug 1;61(8):693-9.
38. **Chung HY, Machado P, Van Der Heijde D, D'Agostino MA, Dougados M.** HLA-B27 positive patients differ from HLA-B27 negative patients in clinical presentation and imaging: results from the DESIR cohort of patients with recent onset axial spondyloarthritis. *Annals Of The Rheumatic Diseases*. 2011 Nov 1;70(11):1930-6.
39. **Cieza A, Schwarzkopf S, Sigl T, Stucki G, Melvin J, Stoll T, Woolf A, Kostanjsek N, Walsh N**. ICF Core Sets for osteoporosis *J Rehabil Med*. 2004 Jul;(44 Suppl):81-6),
40. Clasificarea internaţională a funcţionării, dizabilităţii şi sănătăţii Organizatiei Mondiale a Sănătăţii - 2004 - Editura MarLink, Bucureşti
41. **Collantes E, Zarco P, Munoz E, Juanola X, Mulero J, Fernández-Sueiro JL, Torre-Alonso JC, Gratacós J, González C, Batlle E, Fernández P.** Disease pattern of spondyloarthropathies in Spain: description of the first national registry (REGISPONSER)—extended report. **Rheumatology.** 2007 Aug 1;46(8):1309-15.
42. **Copeman W. S. C.** *Copeman's Textbook of Rheumatic Disease*. Edited by J.T. Scott, 6th edition. Churchil Livingstone, Edinburg .
43. **de Angelis R., Salaffi F, Grassi W. on behalf of the MArche Pain Prevalence INvestigation Group (MAPPING) study,** Prevalence of spondyloarthropathies in an Italian population sample: a regional community based study. *Scand J Rheumatol*. 2007 Jan-Feb;36(1):14-21.
44. **Dougados M, Linden SV, Juhlin R, Huitfeldt B, Amor B, Calin A, Cats A, Dijkmans B, Olivieri I, Pasero G, Veys E.** The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis & Rheumatism.* 1991 Oct 10;34(10):1218-27.
45. **Dougados M**. Diagnostic features of ankylosing spondylitis. *Rheumatology*. 1995 Apr 1;34(4):301-3.
46. **Dreinhöfer K, Stucki G, Ewert T, Huber E, Ebenbichler G, Gutenbrunner C, Kostanjsek N, Cieza A.** ICF Core Sets for osteoarthritis. *J Rehabil Med*. 2004 Jul;(44 Suppl):75-80,
47. **E. Collantes et al.** Disease pattern of spondyloarthropathies in Spain: description of the first national registry (REGISPONSER)—extended report. *Rheumatology* 2007;46:1309–1315
48. **Eyres S, Tennant A, Kay L, Waxman R, Helliwell PS**. Measuring disability in ankylosing spondylitis: comparison of bath ankylosing spondylitis functional index with revised Leeds Disability Questionnaire. *The Journal of Rheumatology.* 2002 May 1;29(5):979-86.
49. **Fallahi S, Jamshidi AR, Mahmoudi M, Qorbani M**. Are clinical measures influenced by various ethnic origins in Iranian patients with ankylosing spondylitis? A pilot study. *Caspian Journal Of Internal Medicine*. 2014;5(2):59..
50. **Feldtkeller E, Khan M, van der Heijde D, van der Linden S, Braun J**. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatology International*. 2003 Mar 1;23(2):61-6.
51. **Forejtová Š, Mann H, Štolfa J, Vedral K, Fenclová I, Némethová D, Pavelka K**. Factors influencing health status and disability of patients with ankylosing spondylitis in the Czech Republic. *Clinical Rheumatology*. 2008 Aug 1;27(8):1005-13.
52. **Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, Watson KD, Lunt M, Symmons DP, BSRBR Control Centre Consortium**. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6

months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology*. 2011 Jan 1;50(1):124-31.

53. **Gherman D,.** Clasificarea internationala a funcționarii, dizabilitatii și sanătății (CIF) și expertiza medicala a capacității de muncă. *Revista Romana de Expertiza Medicala și Reabilitare a Capacitatii de Muncă* **vol 21 nr 1/2015 9-17**
54. **Gömör B, Gyodi E, Bakos L.** Distribution of HLA B27 and ankylosing spondylitis in the Hungarian population. *The Journal of Rheumatology*. Supplement. 1976 Dec;3:33-5.
55. **Gordeev VS, Maksymowych WP, Evers SM, Ament A, Schachna L, Boonen A**. Role of contextual factors in health-related quality of life in ankylosing spondylitis. *Annals of the Rheumatic Diseases*. 2010 Jan 1;69(01):108-12.
56. **Gran JT, Husby G, Hordvik M.** Prevalence of ankylosing spondylitis in males and females in a young middle-aged population of Tromsø, northern Norway. *Annals of the Rheumatic Diseases.* 1985 Jun 1;44(6):359-67.
57. **Gran JT, Husby G.** Ankylosing spondylitis in women. *Semin Arthritis Rheum.* 1990 Apr;19(5):303-12).
58. **Haglund E, Bremander AB, Petersson IF, Strömbeck B, Bergman S, Jacobsson LT, Turkiewicz A, Geborek P, Englund M**. Prevalence of spondyloarthritis and its subtypes in southern Sweden. *Annals of the Rheumatic Diseases*. 2011 Jun 1;70(6):943-8.
59. **Hanova P, Pavelka K, Holcatova I, Pikhart H**. Incidence and prevalence of psoriatic arthritis, ankylosing spondylitis, and reactive arthritis in the first descriptive population-based study in the Czech Republic. *Scandinavian Journal of Rheumatology.* 2010 Aug 1;39(4):310-7.
60. **Haroon NN, Paterson JM, Li P, Haroon N**. Increasing proportion of female patients with ankylosing spondylitis: a population-based study of trends in the incidence and prevalence of AS. *BMJ open.* 2014 Dec 1;4(12):e006634.
61. **Healey EL, Haywood KL, Jordan KP, Garratt A, Packham JC.** Impact of ankylosing spondylitis on work in patients across the UK. *Scandinavian Journal of Rheumatology.* 2011 Jan 1;40(1):34-40.
62. **Healey EL, Haywood KL, Jordan KP, Garratt AM, Ryan S, Packham JC**. Ankylosing spondylitis and its impact on sexual relationships. *Rheumatology*. 2009 Nov 1;48(11):1378-81.
63. **Holst H, Iversen PF.** On the incidence of spondylarthritis ankylopoetica in a Norwegian county. *Acta Medica Scandinavica*. 1952 Jan 12;142(5):333-8.
64. **Johnsen K, Gran T, Dale K, Husby G.** The prevalence of ankylosing spondylitis among Norwegian Samis (Lapps). *The Journal of Rheumatology*. 1992 Oct;19(10):1591-4.
65. **Kaarela K, Lehtinen K, Luukkainen R.** Work capacity of patients with inflammatory joint diseases: an eight-year follow-up study. Scandinavian Journal of *Rheumatology*. 1987 Jan 1;16(6):403-6.
66. **Kaipiainen-Seppanen O, Aho K, Heliovaara** *M.* Incidence and prevalence of ankylosing spondylitis in Finland. *The Journal of Rheumatology*. 1997 Mar;24(3):496-9.
67. **Karaarslan A, Yilmaz H, Aycan H, Orman M, Kobak S**. Demographic, clinical, and laboratory features of Turkish patients with late onset ankylosing spondylitis. *Bosnian Journal of Basic Medical Sciences.* 2015 Aug;15(3):64.
68. **Kennedy LG, Edmunds L, Calin A**. The natural history of ankylosing spondylitis. Does it burn out?. *The Journal of Rheumatology.* 1993 Apr;20(4):688-92.
69. **Khan MA**. A worldwide overview: the epidemiology of HLA-B27 and associated spondyloarthritides. *The Spondyloarthritides*. Oxford University Press, Oxford. 1998:17-26.
70. **Khan MA**. An overview of clinical spectrum and heterogeneity of spondyloarthropathies. *Rheumatic Diseases Clinics of North America*. 1992 Feb;18(1):1-0.

71. **Kiltz U, van der Heijde D, Boonen A, Braun J.** The ASAS Health Index (ASAS HI)–a new tool to assess the health status of patients with spondyloarthritis. *Clin Exp Rheumatol*. 2014 Sep 1;32(Suppl 85):105-8.
72. **Kiltz U, Van Der Heijde D, Boonen A, Cieza A, Stucki G, Khan MA, Maksymowych WP, Marzo-Ortega H, Reveille J, Stebbings S, Bostan C.** Development of a health index in patients with ankylosing spondylitis (ASAS HI): final result of a global initiative based on the ICF guided by ASAS. *Annals of the Rheumatic Diseases*. 2015 May 1;74(5):830-5.
73. **Kirschneck M, Legner R, Armbrust W, Nowak D, Cieza A.** [Can ICF core sets be helpful in preparing a social-medical expert report due to incapacity to work?--a first proposal]. *Die Rehabilitation*. 2015 Apr;54(2):92-101..
74. **Kirschneck M, Winkelmann A, Kirchberger I, Glassel A, Ewert T, Stucki G, Cieza A**: Use of ICF Core Sets for medical reports concerning patients with low back pain and chronic widespread pain syndrome. *Gesundheitswesen* 2008, 70:674–678)
75. **Koko V, Ndrepepa A, Skënderaj S, Ploumis A, Backa T, Tafaj A.** An epidemiological study on ankylosing spondylitis in southern Albania. *Materia Socio-medica*. 2014 Jan 1;26(1):26.
76. **Lee JH, Jun JB, Jung S, Bae SC, Yoo DH, Kim TY, Kim SY, Kim TH**. Higher prevalence of peripheral arthritis among ankylosing spondylitis patients. *Journal of Korean Medical Science.* 2002 Oct;17(5):669.
77. **Lee W, Reveille JD, Davis JC, Learch TJ, Ward MM, Weisman MH.** Are there gender differences in severity of ankylosing spondylitis? Results from the PSOAS cohort. *Annals of the Rheumatic Diseases*. 2007 May 1;66(5):633-8.
78. **Lehtinen K**. Working ability of 76 patients with ankylosing spondylitis. *Scandinavian Journal Of Rheumatology*. 1981 Jan 1;10(4):263-5.
79. **M. Rudwaleit, Désirée M.F.M. van der Heijde, R. Landewé**, ACR 2009, 20 oct
80. **Madans JH, Loeb ME, Altman BM**. Measuring disability and monitoring the UN Convention on the Rights of Persons with Disabilities: the work of the Washington Group on Disability Statistics. *BMC Public Health*. 2011 May 31;11(4):1.
81. **McCarthy,DJ.** *Arthritis and allied conditions*. 11th Edition.Les Febiger, Philadelphia, 1989
82. **Monjardino T, Lucas R, Barros H**. Frequency of rheumatic diseases in Portugal: a systematic review. *Acta Reumatológica Portuguesa*. 2011 Oct 1;36(4).
83. **Oancea C, Mihai C, Gherman D, Milicescu M, Ancuta I, Martin A, Bojinca M, Stoica V, Ciuvica MM.** Development of a prognostic score for work disability in Romanian patients with ankylosing spondylitis. *Disability and rehabilitation*. 2015 Mar 13;37(6):506-11.
84. **Onen F, Akar S, Birlik M, Sari I, Khan MA, Gurler O, Ergor A, Manisali M, Akkoc N.** Prevalence of ankylosing spondylitis and related spondyloarthritides in an urban area of Izmir, Turkey. *The Journal Of Rheumatology*. 2008 Feb 1;35(2):305-9.
85. **Popa OM et al**. Distribution of HLA-B27 in Romanian spondyloarthritides patients. *Int J Immunogenet*. 2010 Dec;37(6):513-6
86. **Raevschi E**. Clasificarea internaţională a funcţionării, dizabilităţii şi sănătăţii (OMS)-un nou cadru conceptual al reabilitării medicale. *Acta Medica Transilvanica*. 2011 Sep 1;16(3)
87. **Reveille JD.** Epidemiology of spondyloarthritis in North America. *The American Journal of the Medical Sciences.* 2011 Apr;341(4):284.
88. **Rudwaleit M, Jurik AG, Hermann KA, Landewé R, van der Heijde D, Baraliakos X, Marzo-Ortega H, Østergaard M, Braun J, Sieper J.** Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. *Annals of the Rheumatic Diseases.* 2009 Oct 1;68(10):1520-7.
89. **Rudwaleit M, Landewe R, Van der Heijde D, Listing J, Brandt J, Braun JV, Burgos-Vargas R, Collantes-Estevez E, Davis J, Dijkmans B, Dougados M.** The development of Assessment

of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Annals of the Rheumatic Diseases*. 2009 Jun 1;68(6):770-6.

90. **Rudwaleit M, Metter A, Listing J, Sieper J, Braun J**. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. *Arthritis & Rheumatism*. 2006 Feb 1;54(2):569-78.
91. **Saraux A, Guillemin F, Guggenbuhl P, Roux CH, Fardellone P, Le Bihan E, Cantagrel A, Chary-Valckenaere I, Euller-Ziegler L, Flipo RM, Juvin R.** Prevalence of spondyloarthropathies in France: 2001. *Annals of the Rheumatic Disease*s. 2005 Oct 1;64(10):1431-5.
92. **Sieper J, Rudwaleit M, Khan MA, Braun J.** Concepts and epidemiology of spondyloarthritis. *Best Practice & Research Clinical Rheumatology*. 2006 Jun 30;20(3):401-17.
93. **Sigl T, Cieza A, van der Heijde D, Stucki G**. ICF based comparison of disease specific instruments measuring physical functional ability in ankylosing spondylitis. *Annals of the Rheumatic Diseases*. 2005 Nov 1;64(11):1576-81.
94. **Sirjita N.** *Elemente de expertiză medicală şi recuperarea capacităţii de muncă*. Editura TipArg, 2004 pp 112-118
95. **Spoorenberg A, Van der Heijde DM, De Klerk E, Dougados M, De Vlam K, Mielants H, Van der Tempel H, Van der Linden S.** A comparative study of the usefulness of the Bath Ankylosing Spondylitis Functional Index and the Dougados Functional Index in the assessment of ankylosing spondylitis. *The Journal of Rheumatology*. 1999 Apr;26(4):961-5.
96. **Stucki G, Cieza A, Geyh S, Battistella L, Lloyd J, Symmons D, Kostanjsek N, Schouten J.** ICF Core Sets for rheumatoid arthritis. *Rehabil Med*. 2004 Jul;(44 Suppl):87-93
97. **Stucki G, Ewert T.** How to assess the impact of arthritis on the individual patient: the WHO ICF. *Annals of the Rheumatic Diseases*. 2005 May 1;64(5):664-8.
98. **Şuţa M**. *Actualităţi in spondilita anchilozantă şi artritele reactive*. Editura Comandor. 2000
99. **Trontzas P, Andrianakos A, Miyakis S, Pantelidou K, Vafiadou E, Garantziotou V, Voudouris C.** Seronegative spondyloarthropathies in Greece: a population-based study of prevalence, clinical pattern, and management. The ESORDIG study. *Clinical Rheumatology*. 2005 Dec 1;24(6):583-9.
100. **Tudorache D. L. , Grigoriu S. Dumitru M, Calota M** Elaborarea şi monitorizarea unui program de reabilitare intr-un caz cu deficienţă locomotorie utilizând ca instrument de lucru clasificarea internaţională a funcţionării, dizabilităţii şi sănătăţii (CIF) **Revista Română de Expertiză Medicală şi Reabilitare a Capacităţii de Muncă* 2014, nr 2, vol 20 pag 45=55
101. **Tudorache D.T, Amarasteanu S,** Evaluarea dizabilitatii pe baza Clasificarii CIF intr-un stat din UE (Cipru) *Revista Romana de Expertiza Medicala şi Reabilitare a Capacitatii de Muncă* Vol 20 nr 2/2014 pag 50-51
102. **Van der Heijde D, Bellamy N, Calin A, et al**. Preliminary core sets for endpoints in ankylosing spondylitis. Assessments in Ankylosing Spondylitis Working Group**. J Rheumatol** 1997;24:2225–9
103. **Van Der Horst-Bruinsma IE, Zack DJ, Szumski A, Koenig AS**. Female patients with ankylosing spondylitis: analysis of the impact of gender across treatment studies. *Annals of the Rheumatic Diseases*. 2013 Jul 1;72(7):1221-4.
104. **Van der Linden SM, Valkenburg HA, de Jongh BM, Cats A.** The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. A comparison of relatives of spondylitis patients with the general population. *Arthritis Rheum* 1984;27:241–9
105. **Vander Cruyssen B, Muñoz-Gomariz E, Font P, Mulero J, De Vlam K, Boonen A, Vazquez-Mellado J, Flores D, Vastesaeger N, Collantes E.** Hip involvement in ankylosing

spondylitis: epidemiology and risk factors associated with hip replacement surgery. *Rheumatology*. 2010 Jan 1;49(1):73-81.

**106. Vătafu C, Şuţa M.** Prevalenţa spondilitei anchilozante la populaţia caucaziană. *Revista Română de Reumatologie*, ISSN: 1843-0791 Volumul XXI Nr. 2, An 2012 pg: 93-97

**107. Vătafu C, Lilios G, Şuţa C, Bratu I Work Disability in Ankylosing Spondylitis** *Archives of the Balkan Medical Union***,** Celsius Publishing House, ISSN 0041-6940 Nr 3 An 2012 pg 262

**108. Verstappen SM, Watson KD, Lunt M, McGrother K, Symmons DP, Hyrich KL.** Working status in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology*. 2010 Aug 1;49(8):1570-7.

**109. Ward MM, Hendrey MR, Malley JD, Learch TJ, Davis JC, Reveille JD, Weisman MH**. Clinical and immunogenetic prognostic factors for radiographic severity in ankylosing spondylitis. *Arthritis Care & Research*. 2009 Jul 15;61(7):859-66.

**110. Ward MM, Kuzis SU**. Risk factors for work disability in patients with ankylosing spondylitis. *The Journal of Rheumatology*. 2001 Feb 1;28(2):315-21.

**111. Ward MM, Reveille JD, Learch TJ, Davis JC, Weisman MH**. Impact of ankylosing spondylitis on work and family life: comparisons with the US population. *Arthritis Care & Research*. 2008 Apr 15;59(4):497-503.

**112. Ward MM, Weisman MH, Davis JC, Reveille JD**. Risk factors for functional limitations in patients with long-standing ankylosing spondylitis. *Arthritis Care & Research*. 2005 Oct 15;53(5):710-7.

**113. Yenal O, Usman ON, Yassa K, Uyar A, Agbaba S**. Epidemiology of rheumatic syndromes in Turkey. III. Incidence of rheumatic sacro-iliitis in men of 20-22 years. *Zeitschrift fur Rheumatologie*. 1976 Dec;36(9-10):294-8.

**114. Zhang S, Li Y, Xu X, Feng X, Yang D, Lin G**. Effect of cigarette smoking and alcohol consumption on disease activity and physical functioning in ankylosing spondylitis: a cross-sectional study. *International Journal of Clinical and Experimental Medicine*. 2015;8(8):13919.

**115. Zink A, Listing J, Klindworth C, Zeidler H**. The national database of the German Collaborative Arthritis Centres: I. Structure, aims, and patients. *Annals of the Rheumatic Diseases*. 2001 Mar 1;60(3):199-206.

**116. Zlatkovic-Svenda MI, Stojanovic RM, Sipetic-Grujicic SB, Radak-Perovic MM, Damjanov NS, Guillemin F.** Prevalence of spondyloarthritis in Serbia: a EULAR endorsed study. *Annals of the Rheumatic Diseases*. 2015 Oct 1;74(10):1940-2.

**117. Zochling J, Smith EU** Seronegative spondyloarthritis. *Best Pract Res Clin Rheumatol*. 2010 Dec;24(6):747-56.

**118. Zochling J**. Measures of symptoms and disease status in ankylosing spondylitis: Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), and Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S). *Arthritis Care & Research.* 2011 Nov 1;63(S11):S47-58.