Title: A nationwide questionnaire survey on the prevalence of ankylosing spondylitis and non-radiographic axial spondyloarthritis in Japan

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The number of text pages: 12, The numbers of table: 2, The number of figures: 4

Keywords: Ankylosing spondylitis, nationwide survey, non-radiographic axial spondyloarthritis, the prevalence
Abstract

Objective: This nationwide study aimed to reveal the prevalence of ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-ax SpA), and the positive rate of human leukocyte antigen (HLA) among these patients in Japan.

Methods: The first survey was conducted in 2221 randomly selected facilities (26.3%) in September, 2018, where the patients with AS/nr-ax SpA were taken care of from January to December, 2017. We estimated the total number of these patients using response and extraction rate. A second survey was conducted in 147 facilities (49.8%) to assess for HLA-B 27 positivity rate and clinical features.

Results: The estimated total number of the patients with AS and nr-ax SpA were 3200 (95% confidence interval [CI]: 2400–3900) and 800 (530–1100), suggesting that the prevalence of AS and nr-ax SpA in general population were 2.6/100,000 (0.0026%) and 0.6/100,000 (0.0006%), respectively. Although 55.5 % (76/137) of patients with AS were HLA-B27 positive, those whose age of onset was estimated to be over 50 years tended to undergo less HLA-B27 testing.

Conclusion: This study revealed the lower prevalence of AS/nr-ax SpA in Japan, compared to those in other countries. Further studies are required to reveal the association of HLA-B27 with the clinical features.

Keywords: Ankylosing spondylitis, non-radiographic axial spondyloarthritis, nationwide survey, the prevalence
Introduction

Ankylosing spondylitis (AS) is a major cause of axial spondyloarthritis (SpA) that results in chronic inflammation of the spine and sacroiliac joints [1]. AS predominantly occurs in men aged < 45 years, some of whom may become bedridden due to long-lasting bone rigidity. AS was included on the list of intractable diseases in 2015 in Japan, with a focus on its epidemiology and future treatment strategies. On the other hand, non-radiographic axial SpA (nr-ax SpA) is a newly categorized disease in SpA that shows SpA without definite radiographic findings in sacroiliac joint, according to the Assessment of Spondyloarthritis International Society (ASAS) classification criteria in 2009 [1]. Some patients with nr-ax SpA can progress to AS over time [2]. Recently, in 2020, guidelines for the diagnosis of nr-ax SpA were published in Japan [3].

Globally, the prevalence of AS and nr-ax SpA varies by region. This trend may be mostly attributed to the varying rates of leukocyte antigen B27 positivity (HLA-B27) in regional populations [4-7]. In the 1990’s, a nationwide survey in Japan was conducted to determine the prevalence of AS [8]. However, little is known about the prevalence of nr-ax SpA in Japan because this is a newly categorized disease. In addition, literature is lacking regarding the positive rate of HLA-B27 in both diseases in the Japanese population. Therefore, in this study, we aimed to reveal the prevalence and incidence of AS and nr-ax SpA, and their positive rate of HLA, using a systematic nationwide survey in Japan.

Materials and Methods

We conducted a nationwide survey in Japan in September 2018, based on the Nationwide Epidemiologic Survey Manual issued by the Research Committee on Epidemiology of Intractable Disease [9-11]. Target sample facilities were selected randomly based on the stratified number of beds as follows: 1) the stratification and extraction rate was defined based on the number of beds in the facilities: university hospitals (100%), > 500 beds (100%), 400–499 beds (80%), 300–399 beds (40%), 200–299 beds (20%), 100–199 beds (10%), and < 99 beds (5%), 2) 2221/8456 facilities (26.3%) were randomly selected as a target sample, comprised of three departments: orthopedics, pediatrics, and rheumatology, and 3) after stratification, the actual number of facilities for orthopedics, pediatrics, and rheumatology was 1108, 824, and 289, respectively.

The first survey was conducted by using questionnaires to target facilities (26.3%, 2221/8456), where the patients with AS or nr-ax SpA were taken care of from January to December 2017. We classified patients as AS positive if they met the modified New York criteria [6], including patients with not only definite cases (one more clinical symptoms and radiographic change) but also possible cases (three specific clinical symptoms or
radiographic changes without clinical features). We defined nr-ax SpA if they met the ASAS criteria for axial SpA without the radiographic criteria for AS [1, 3]. We excluded comorbid cases, such as psoriasis, inflammatory bowel disease, reactive arthritis, osteitis condensans illii, synovitis–acne–pustulosis–hyperostosis–osteitis syndrome, diffuse idiopathic skeletal hyperostosis, fibromyalgia and osteoarthritis, according to the diagnostic guidelines for AS and nr-ax SpA [3]. The second survey was focused on the facilities that responded to the first survey where patients with AS or nr-ax SpA were diagnosed within the last 3 years (49.8%, 117/235). Questionnaires in the second survey comprised the detailed clinical characteristics, including age, sex, the results of the HLA-B27 test, the estimated age of disease onset, the severity of the disease, and the effectiveness of the biopharmaceutical products. The current study, however, focused on the prevalence of AS and nr-ax SpA and the HLA-B27 positive rate.

We calculated the estimated number of patients with AS and nr-ax SpA using the response rate and reported numbers of each disease as follows:

\[ \text{The estimated number of patients} = \frac{\text{the reported number of patients}}{\text{extraction rate} \times \text{response rate}} \]

We calculated the 95% confidence interval (CI) and standard error (SE) based on the multinomial hypergeometric distributions [9]. We calculated the incidence per 100,000 persons according to the calendar year by dividing the estimated number of patients in each calendar year by the total number of population in that year using vital statistical data based on the second survey. We expected that the distribution of the number of patients would be the same in each calendar year, and the incidence was calculated as follows:

\[ \text{The incidence of calendar year } i = \frac{\text{the estimated number of patients diagnosed in calendar } i}{\text{total number of population in calendar } i} \times 100,000 \]

Ethics approval number

This study was approved by the Jichi Medical University (17-148) and Osaka University (18055).

Results

The prevalence and the incidence of AS and nr-ax SpA

In the first survey, the response rate was 62.8% (1395/2221 facilities), including 56% in the department of orthopedics (620/1108 facilities), 76.7% in pediatrics (632/824 facilities), and 49.5% in
rheumatology (143/289 facilities). The response rate classified by the number of beds was highest in the university hospital/hospitals with over 500 beds (71.5%/58.0% in orthopedics, 59.3%/48.7% in rheumatology, 79.5%/83.9% in pediatrics). The reported number of patients with AS and nr-ax SpA was 1173 and 333, respectively (Table 1). The estimated number of patients with AS and nr-ax SpA was 3200 (95% CI: 2400–3900) and 800 (95% CI: 530–1100), respectively. In 2017, the estimated prevalence of AS and nr-ax SpA in the overall general population using Japanese vital statistics (n=124,648,471) was 2.6/100,000 (0.0026%) and 0.6/100,000 (0.0006%), respectively. The incidence increased slightly from 2015 to 2017 in both diseases (AS: from 0.50 to 0.62 (per 100,000 person-years), nr-ax SpA: from 0.13 to 0.23 (per 100,000 person-years)) (Figure 1).

Age- and sex-specific prevalence of AS and nr-ax SpA

Of the 235 facilities, 117 (49.8%) responded to the second survey, which included 20% (230/1173) of patients with AS and 25% (84/333) of patients with nr-ax SpA who responded to the first survey. Males were dominant in AS (70.9% vs 29.1%), but not in nr-ax SpA (51.2% vs.48.8%). The age distribution by sex is shown in Table 2. Patients with AS were most commonly distributed in the middle age (40–49 years), both in males (23.8%) and females (26.3%). Although males with nr-ax SpA were evenly distributed in middle-aged (40–49 years, 23.3%) or younger groups, females with nr-ax SpA had two peaks at 30–39 years (29.7%) and 50-59 years (24.3%). Age- and sex-specific prevalence of AS and nr-ax SpA in the general population are shown in Figure 2.

The prevalence of AS in the general population was 4.06 per 100,000 in males, which was three times higher than that in females (1.36 per 100,000). The peak age- and sex-specific prevalence of AS was 40–49 years in both males and females (Figure 2). In contrast, there was no difference in the prevalence of nr-ax SpA in the general population between males and females (0.74 per 100,000 and 0.60 per 100,000, respectively). The peak age- and sex-specific prevalence of nr-ax SpA was younger than that of AS (males: 10–19 years, females: 30–39 years) (Figure 2).

HLA-B27 testing and the estimated age of onset

HLA-B27 testing was performed in 60% (137/230) of patients with AS, 55.5 % (76/137) of which were HLA-B27 positive. Males showed a higher HLA-B27 positive rate (66%, 64/97) than females (26.5%, 9/34). The estimated age of onset of AS, in addition to relevant HLA-B27 testing, is shown in Figure 3. The estimated age of onset in males peaked during 20–29 years, and the positive rate of HLA-B27 was highest at a younger age (10–19 years) (72.2%). Additionally, the positive rate of HLA-B27 decreased over 50 years (Figure 3).
Similarly, in females, the estimated age of onset of AS peaked during 40–49 years and the positive rate of HLA-B27 was the highest in younger age (20–29 years) (Figure 3).

In the same way, HLA-B27 testing was performed in 70.2% (59/84) of patients with nr-ax SpA, 23.7% (14/59) of which were HLA-B27 positive. Males showed a higher HLA-B27 positive rate (32.3%, 11/34) than females (8.3%, 2/24). The estimated age of onset in males had two peaks in 10–19 years and 30–39 years. However, the majority of positive HLA-B27 was found in patients aged < 30 years (Figure 4). Similarly, the estimated age of onset in females peaked between 30 and 39 years. Although some female patients with nr-ax SpA were not tested for HLA-B27, approximately 50% of patients aged 10-19 years were HLA-B27 positive (Figure 4).

Discussion

This is the first nationwide study to reveal the prevalence and the incidence of AS and nr-ax SpA in the general population in Japan. The estimated prevalence of AS and nr-ax SpA among the general population in Japan was 2.6/10,0000 (0.0026%) and 0.6/10,0000 (0.0006%), respectively, both of which were significantly lower than those reported in other countries. The incidence of AS and nr-ax SpA increased slightly. The age- and sex-specific prevalence of AS peaked in middle-aged patients, and males had a higher prevalence than females. In contrast, the age- and sex-specific prevalence of nr-ax SpA were evenly distributed in ages under 40–49 in males; however, females had two peaks in ages 30-39 and 50-59. Approximately 50% of patients with AS were HLA-B27 positive; however, patients with late-onset AS had a lower HLA-B27 positivity rate.

The prevalence and the incidence of AS and nr-ax SpA

The prevalence of AS and nr-ax SpA in Japan is significantly lower than those reported in other countries. The reported prevalence of AS varies in regions as follows: 0.02% in Sub-Saharan Africa, 0.16% in East Asia, 0.2% in North America, 0.25% in Europe, and 0.35% in Northern Arctic communities [4]. Even in East Asia, the prevalence of AS varies in 0.25% in China, 0.24% in Malaysia, 0.05% in South Korea, and 0.03% in Philippines [5, 6]. This variation in the prevalence of AS may be mostly attributed to a varying frequency of HLA-B27 positivity rate in these regions, in addition to some methodological differences in each study, such as study design, data source, and case definition. Some theories on the mechanisms behind the relationship between HLA-B27 and AS have been described, and HLA-B27 is considered to be a fundamental factor [12]. The positive rate of HLA-B27 varies regionally, such as 6.1% in the United States, 1.8% in China, and 0.3% in Japan.
Additionally, we must consider how frequently people with HLA-B27 will eventually present with AS. In general, < 10% of patients with HLA-B27 are likely to develop AS; however, the precise rate of development in the Japanese population has not been reported [7]. Dividing the estimated prevalence of AS (0.0026%) by the positive rate of HLA-B27 in the general population (0.3%), we expect that only 1% of Japanese patients with HLA-B27 may develop AS. However, there may still be many undiagnosed patients with HLA-B27 in Japan due to difficulties in diagnosis.

Similarly, the prevalence of nr-ax SpA in Japan is lower (0.0006%) than that of other countries. Although a large epidemiological study on nr-ax SpA has not been conducted in any region, the reason for the low prevalence found in Japan may be explained by the lower HLA-B27 positive rate in Japan as well as AS [14]. Another reason for the low prevalence of nr-ax SpA in Japan may be a lack of recognition of this newly established concept. The previous study, conducted across 19 countries, showed that 38.7% of the patients with chronic low back pain met the criteria for inflammatory back pain, wherein 53.7% were diagnosed as AS and 29.1% as nr-ax SpA [15]. As there have been few reports regarding epidemiological studies on nr-ax SpA in Japan, we speculate that a substantial number of patients are underdiagnosed/misdiagnosed with nr-ax SpA in Japan due to the lack of information on this disease. We believe this current nationwide study, along with the 2020 diagnostic guidelines for nr-ax SpA, may lead to a greater recognition of these diseases among physicians and the general community in Japan.

The incidence of AS also varies globally: 0.4 per 100,000 persons in Iceland to 15.0 per 100,000 persons in Canada [16, 17]. Our current study revealed a slight increase in the incidence of AS in Japan from 0.50 per 100,000 person-years in 2015 to 0.62 per 100,000 person-years in 2017. Although the incidence of AS is similar between Japan and Iceland, the prevalence of AS in Iceland was higher than that in Japan (101 per 100,000 persons vs 2.6 per 100,000 persons). These differences may be influenced by population size. Additionally, the increase in the incidence of AS in Japan may be attributed to the fact that AS was included in the list of intractable diseases in Japan in 2015, which could have led to increased recognition of these diseases among physicians.

The age- and sex-specific prevalence of AS and nr-ax SpA

The age- and sex-specific prevalence of AS in our survey peaked in the middle-aged (40-49 years) in both males and females. This finding is inconsistent with the previous studies in other countries [6, 18]. A study from South Korea showed a higher number and a younger age in the prevalence of AS: 155.3 per 100,000 in
males and 38.8 per 100,000 in females, both in individuals aged 30–39 years [6]. Another study from northwest Greece showed a higher prevalence of AS and a younger age in females (100 per 100,000 in males aged 45–54 years and 30 per 100,000 in females aged 35–44 years) [18]. It is noteworthy that these studies suggested other possible factors relevant to the difference in the prevalence of AS, which included socioeconomic status, racial difference, and other environmental factors. They mentioned the high prevalence of AS among those who received financial support from the government due to low income. This may be partially explained by poor work activity due to the severe symptoms of AS. As a precise mechanism of the onset of the AS is still unknown, these factors, along with HLA-B27, should be the subject of future research on these diseases.

In contrast, the age- and sex-specific prevalence of nr-ax SpA was evenly distributed in those aged under 40–49 years in males; however, females had two peaks at ages 30–39 years and 50–59 years. This may be because of the differences in clinical features among the sexes.

### HLA-B27 testing and the estimated age of onset

Our present study showed the difference between the age at disease onset and HLA-B27 testing, where some patients with late-onset AS had a lower HLA-B27 positive rate (Figure 3). This finding is supported by other clinical reports showing that patients with late-onset (over 50 years) AS had a lower HLA-B27 positive rate, less inflammatory sign, and delayed diagnosis [19]. We speculate that HLA-B27 may have a potential impact on not only the disease onset but other clinical characteristics, such as severity of disease and effectiveness of biopharmaceutical product, which must be addressed by future studies.

The estimated age of onset in males with nr-ax SpA had two peaks at 10–19 years and 30–39 years. The HLA-B27 positivity rate in males was lower in those over 30–39 years compared to that in those of other ages. These differences in HLA-B27 positivity suggest the presence of different subtypes among males with nr-ax SpA as well as AS. Similarly, the estimated age of onset in females with nr-ax SpA peaked between 30 and 39 years. Future studies are required to examine the differences in the clinical features of female patients with nr-ax SpA, whether they are HLA-B27 positive or not.

### Previous survey in Japan

According to a survey conducted in the 1990s in Japan, the estimated prevalence of AS was 6.5 per 100,000 (0.0065%) [8], which was two times higher than that in our present study. We have speculated as to several reasons that may explain this difference, including the difference in target institutions, the difference in...
diagnostic criteria, and the inclusion criteria. The previous survey used the Rome criteria or New York criteria for AS, and the target institutions for the survey were selected by the survey supervisor assigned to each district in Japan where at least one licensed orthopedic rheumatologist was posted. Our current survey used modified New York criteria, and the target institution was selected randomly according to the stratified number of beds. Additionally, the current study excluded comorbid cases. Therefore, these differences may have influenced the results.

**Limitation**

The present study has several limitations. First, not all patients with AS were tested for HLA-B27 in the current study, as there were no standard indications for testing. In particular, patients whose age of onset was over 50 years old tended to be clinically diagnosed without the HLA-B27 test. Furthermore, the HLA-B27 test has not yet been covered by Japanese health insurance. To more accurately assess the number of patients that develop AS among general population who were positive in HLA-B27, consistent future studies are needed to reveal more detailed epidemiological characteristics of these patients. Second, we limited our second survey to patients with AS/nr-ax SpA who were diagnosed within last three years, which may lead to an underestimation in the total number of AS/nr-ax SpA patients. Although we excluded comorbid cases for our survey, it would still be difficult to clearly distinguish them from other inflammatory diseases, such as fibromyalgia. Lastly, ongoing examination of epidemiological factors is needed to better characterize the prevalence of AS and nr-ax SpA.

**Conclusion**

Our nationwide survey showed a lower prevalence and incidence of AS and nr-ax SpA in Japan than those described in other countries. The positive rate of HLA-B27 was higher in the young-age-of-onset group than in the old-age-of-onset group. However, the latter underwent fewer HLA-B27 tests. Further studies will be required to reveal the precise proportion of the positive rate of HLA-B27 and its association with disease severity in clinical images.

**Acknowledgments**

We appreciate all medical doctors who participated in this survey. This survey was conducted as a collaborative research project of the Research Committee on Epidemiology of Intractable Disease (Chairman: Yosikazu Nakamura), and a large-scale multi-institutional research committee aiming at an epidemiological
survey of spondyloarthritis, creation of diagnostic criteria, and development of clinical guidelines (Chairman: Tetsuya Tomita) sponsored by the Ministry of Health and Welfare of the Japanese government.

We also appreciate Hunter L. Kauffman, BS, and the Drs. Daisuke Matsubara, Kurisu Tada, Hidetoshi Shuto, Yoshinori Taniguchi, Yoshifuji Matsumoto, Yoko Ishihara, Yasuhiko Yoshinaga, Masashi Tamaki.

Conflict of interest:

NT (N Tamura) has received speaker fees and/or consulting fees from AbbVie, Astellas, Bristol-Myers Squibb, Eisai, Eli Lilly, Janssen, Kyowa Kirin, Mitsubishi-Tanabe, and Novartis.

HK has received research grants from AbbVie, Asahi-Kasei, Astellas, Behringer, Chugai, Eli Lilly Mitsubishi-Tanabe and Novartis, and received consultancy and speaker fees from AbbVie, Asahi-Kasei, Astellas, Bristol-Myers Squibb, Chugai, Eisai, Eli Lilly, Gilead Sciences, Janssen, Kyowa Kirin, Mitsubishi-Tanabe, Novartis, Pfizer and UCB. KO has received speaker fees from AbbVie, Asahi Kasei, Astellas, Bristol-Myers Squibb, Chugai, Eli Lilly, Glaxo SmithKline, Jansen, Novartis, Pfizer, Sanofi, Tanabe-Mitsubishi, and UCB. MK has received consultancy and speaker fees from AbbVie, Amgen-Astellas BioPharma, Astellas, Ayumi Pharma, Bristol-Myers Squibb, Celgene, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly and Company, Gilead, Janssen, Kyowa Kirin, Mitsubishi-Tanabe, Novartis, Pfizer, and UCB Pharma. YK has received speaker fees from AbbVie, Eli Lilly, Novartis. ST has received research grants and speaker and/or consulting fees from AbbVie, Eli Lilly, Janssen, Novartis, and UCB. TA has accepted research grants and/or honoraria for meetings from Gilead Sciences Inc., Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Pfizer Inc., AbbVie Inc., Eisai Co.Ltd., Daiichi Sankyo Co. Ltd., Bristol-Myers Squibb Co., UCB Japan Co. Ltd. Eli Lilly Japan K.K. Otsuka Pharmaceutical Co., Ltd., Boehringer Ingelheim Co., Ltd. and Alexion Inc. HM has received speaker fees from Mochida, Chugai, Daiichi Sankyo, Eli Lilly. SK receives personal fees from Kyowa Kirin, Novartis Pharma K.K., Eli Lilly Japan K.K., Chugai Pharma, Asahi Kasei Pharma, Gilead Sciences and Janssen Pharma K.K. outside the submitted work. KF has received speaking fees, and/or honoraria from Tanabe Mitsubishi, Bristol Myers, Eli Lilly, Chugai, Jansen, Pfizer, Ono, AbbVie, Ayumi, Astellas, Sanofi, Novartis, Daiichi Sankyo, Eisai, Asahi Kasei, Japan Blood Products Organization, and Kowa, and has received research grants from Tanabe Mitsubishi, Bristol Myers, Eli Lilly, Chugai, AbbVie, Ayumi, Astellas, Sanofi, Eisai, Tsumura & Co., and Asahi Kasei. NN has received grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan, Chugai, and Eisai, and consultancy and speaker fees from Chugai, AbbVie, Eisai, Eli Lilly, Novartis, Mitsubishi-Tanabe, Astellas. AN has received research...
grants from Chugai, Mitsubishi Tanabe, Pfizer Japan and speaker’s fees from AbbVie, Actelion Pharmaceuticals Japan, Asahi Kasei, Astellas, Ayumi, Bristol Myers Squibb, Chugai, Eisai, Eli Lilly Japan, GlaxoSmithKline, Hisamitsu, Kyorin, Mitsubishi Tanabe, Otsuka, Pfizer Japan, and Teijin. KM has received research grants from Chugai and Asahi Kasei. Y.N. received speaking fees or research grants from Chugai Pharmaceutical, Mitsubishi-Tanabe Pharma, Pfizer, Eisai, AbbVie, Bristol-Myers Squibb, Astellas, AYUMI, Hisamitsu, Taisho Toyama Pharmaceutical, Dai-ichi Sankyo. AK has received grants from AbbVie, Actelion, Asahi Kasei, Astellas, AYUMI, Boehringer Ingelheim, Bristol-Myers Squibb, Celltrion, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Kyowa Hakko Kirin, MSD, Neopharma, Novartis, ONO, Sanofi, Taisho, Takeda Science Foundation, and Teijin and speakers’ fee from AbbVie, Actelion, Asahi Kasei, Astellas, Boehringer Ingelheim, Celltrion, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, GSK, Janssen, Kowa, MedPeer, Mitsubishi Tanabe, Novartis, ONO, Pfizer, Taisho, and Takeda. MM has received grants from Chugai, UCB Japan, CSL Behring, AbbVie, Japan Blood Products Organization, Ayumi, Nippon Kayaku and Asahi-Kasei, and consultancy and speaker fees from MSD K.K., Taisho, and Daiichi Sankyo. TT has received consultancy and speaker fees from AbbVie, Astellas, Bristol-Myers Squibb, Eisai, Eli Lilly and Company, Janssen, Kyowa Kirin, Mitsubishi-Tanabe, Novartis, and Pfizer.

Funding

This work was supported by a grant from the development of the diagnostic guidance for nr-axSpA in Japan is a collaborative work by Research On Rare and Intractable Diseases, Health and Labour Sciences Research Grant: a Large-scale multi-institutional research committee aiming at an epidemiological survey of spondyloarthritis, creation of diagnostic criteria, and development of clinical guidelines.

References

spondyloarthritis. Mod Rheumatol 2021;31:277-82.


Figure Legends

Figure 1. Crude annual incidence of AS and nr-ax SpA in general population.
Figure 2. The prevalence of AS and nr-ax SpA in general population in 2017.
Figure 3. The estimated age of onset of AS and the proportion of HLA-B27 positive number in male and female.
Figure 4. The estimated age of onset of nr-ax SpA and the proportion of HLA-B 27 positive number in male and female.

Table 1. The reported and estimated number of patients with AS and nr-ax SpA

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<td>1700</td>
<td>210</td>
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<td>25</td>
<td>0-90</td>
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SE: Standard error  
CI: Confidence interval
Table 2. Age distribution by sex, of AS and nr-ax SpA

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<td>female(%)</td>
<td>total(%)</td>
<td>male(%)</td>
<td>female(%)</td>
<td>total(%)</td>
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</tr>
<tr>
<td>10-19</td>
<td>8(5.0)</td>
<td>1(1.8)</td>
<td>10(4.4)</td>
<td>8(18.6)</td>
<td>2(5.4)</td>
<td>11(13.3)</td>
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</tr>
<tr>
<td>20-29</td>
<td>19(11.9)</td>
<td>5(8.8)</td>
<td>25(11.0)</td>
<td>8(18.6)</td>
<td>6(16.2)</td>
<td>14(16.9)</td>
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</tr>
<tr>
<td>30-39</td>
<td>27(16.9)</td>
<td>9(15.8)</td>
<td>37(16.3)</td>
<td>8(18.6)</td>
<td>11(29.7)</td>
<td>19(22.9)</td>
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<tr>
<td>40-49</td>
<td>38(23.8)</td>
<td>15(26.3)</td>
<td>55(24.2)</td>
<td>10(23.3)</td>
<td>7(18.9)</td>
<td>17(20.5)</td>
<td></td>
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<tr>
<td>50-59</td>
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<td>10(17.5)</td>
<td>36(15.9)</td>
<td>2(4.7)</td>
<td>9(24.3)</td>
<td>11(13.3)</td>
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<tr>
<td>60-69</td>
<td>24(15.0)</td>
<td>8(14.0)</td>
<td>34(15.0)</td>
<td>3(7.0)</td>
<td>1(2.7)</td>
<td>6(7.2)</td>
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<tr>
<td>70-79</td>
<td>15(9.4)</td>
<td>8(14.0)</td>
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<td>3(7.0)</td>
<td>1(2.7)</td>
<td>4(4.8)</td>
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<tr>
<td>80+</td>
<td>4(2.5)</td>
<td>1(1.8)</td>
<td>5(2.2)</td>
<td>1(2.3)</td>
<td>0(0.0)</td>
<td>1(1.2)</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>160(100.0)</td>
<td>57(100.0)</td>
<td>227(100.0)</td>
<td>43(100.0)</td>
<td>37(100.0)</td>
<td>83(100.0)</td>
<td></td>
</tr>
</tbody>
</table>

Some patients are lack of information about sex, therefore the total number is not the equal of sum of each sex.