



Research Paper

The mental health impact of primary Sjögren Syndrome among Italian women

Eleonora Prina^{*}, Federico Tedeschi, Laura Rabbi, Francesco Amaddeo

Section of Psychiatry, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy

ARTICLE INFO

Keywords:

Anxiety
Depression
Mental health
Primary Sjögren's Syndrome
Quality of life
Women

ABSTRACT

Background: This cross-sectional online survey aims to investigate the impact of Primary Sjögren's Syndrome (pSS) on mental health by measuring anxiety, depressive symptoms and health-related quality of life (HR-QoL) in the Italian context.

Methods: Participants diagnosed with pSS were recruited via the National Association of Sjögren's Syndrome Patients (A.N.I.Ma.S.S.), composed by members across Italy, and completed an online survey using the Lime-Survey platform. Data collected encompassed demographic, clinical information (e.g., age, gender, disease duration), diagnostic details (suspecting and diagnosing specialists), and mental health assessments (HADS for depressive and anxiety symptoms, SF-36 for HR-QoL). Descriptive analyses were conducted, including frequencies for binary variables, mean and standard deviations for interval-level variables, alongside correlation assessments between clinical scales.

Results: The study included 216 women with pSS who completed the survey (average age: 54 years). Mental health symptoms evaluated by the HADS subscales revealed a clinical level of anxiety in 50 % and depression in 41 % of the respondents. Patients with pSS had a low score in all eight domains of the SF-36.

Limitations: The study has limitations, including its focus on female pSS patients due to limited male participants, potential biases in self-reported survey data, and the lack of certain demographic and clinical variables.

Conclusion: Our results emphasize the critical role of emotional distress in the progression of pSS, highlighting the need for its proper management. This insight contributes to the development of a rational therapeutic approach to pSS patients useful for all the healthcare professionals, pharmaceutical industry, and drug regulatory organizations.

1. Introduction

Primary Sjögren's Syndrome (pSS) is a chronic systemic autoimmune disease characterized by inflammation and lymphocytic infiltration of the exocrine glands, namely the salivary and lachrymal glands. This scenario results in slow progressive functional impairment, with oral, ocular dryness and possible systemic manifestations (Fox, 2005; Shibuski et al., 2017; Vitali and Del Papa, 2017).

As synthesized by the only systematic review and meta-analysis on the epidemiology of pSS (Qin et al., 2015) and in line with the incidence and prevalence rates regarding autoimmune diseases (Kouranloo et al., 2023), most of the patients are women. Of these, the majority are in their mid-50s, in their postmenopausal period, with onset occurring at around 40 years of age (Shahane and Patel, 2014).

The heterogeneous presentations of patients with pSS (e.g. symptoms

related to glandular involvement, extraglandular manifestations, widespread pain, depressive state) can make the disease difficult to diagnose and treat (Brito-Zerón et al., 2016). Actually, the majority of patients do not receive a diagnosis in the first period of illness (Chou et al., 2017; Jones et al., 2010), and many of them felt that physicians lacked understanding of pSS (Gairy et al., 2020), increasing the level of emotional distress. Since pSS is a slowly progressive disease, common classification criteria (Del Papa and Vitali, 2018) might be unable to capture patients in the early stage of disease, in which a therapeutic intervention may have good possibilities to improve the natural history and the Health related Quality of Life (HRQoL) of the patients (Giacomelli et al., 2017). Moreover, there are no available therapies that have been effective in targeting the pSS (Vitali et al., 2021) and the current COVID-19 pandemic dramatically affected the management of people with chronic diseases, including pSS (Brito-Zerón et al., 2021; Carubbi et al.,

^{*} Corresponding author.

E-mail address: eleonora.prina@univr.it (E. Prina).

2020; Prina et al., 2023).

Notably, as other chronic diseases, the pSS is also associated with emotional overload and a lower HRQoL in patients with a formal diagnosis (Al-Ezzi et al., 2023; Dias et al., 2021; Tarn et al., 2022). There is increasing evidence that emotional distress may not only be the expression of adjustment to life with a chronic disorder and its consequence or limitations but could be directly related to the pathophysiology of the autoimmune diseases (Pisetsky, 2023). Patients with pSS have reported several limitations during daily life due to a mismatch between their functional capabilities and the demands of the environment (Unger et al., 2021). Adding to this, an online qualitative study aiming to explore the symptoms experience of patients with pSS highlights how these symptoms place a high burden on physical, emotional and social aspects of patients' lives (Gairy et al., 2020).

Currently, available data on mental health outcomes in this population have increased significantly over the last decade, showing a higher prevalence of anxiety (33.8 %) and depression (36.9 %) and a strong association between pSS and impaired HR-QoL (Cui et al., 2018a, 2018b; Dias et al., 2021; Priori et al., 2015). However, despite the recent recommendations suggests advocating for mental health (Ramos-Casals et al., 2020), screening for mental health problems (e.g. depression and anxiety) (Vitali et al., 2021) is not done routinely during the clinic visits for this type of population.

Together these evidence go in the same direction in showing the relevance onto promote, prevent, and treat the mental health conditions in people living with pSS. For the above reasons, this cross-sectional online survey aims to investigate the impact of pSS on mental health by measuring anxiety, depressive symptoms and the HR-QoL in the Italian context. This will help to better inform policymakers aiming at improving a multidimensional approach to manage this type of syndrome, ensuring that care provision is biopsychosocial-oriented to optimize effectiveness.

2. Methods

The present cross-sectional online survey was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement of cross-sectional studies (Supplementary material) (Von Elm et al., 2008).

2.1. Setting

The study was conducted in Italy, where there is a National Health Service (NHS) that provides public health care also with dedicated centers for autoimmune rheumatic diseases, tertiary rheumatologic centers, some outpatient services, and where the National Association of Sjögren's Syndrome Patients (A.N.I.Ma.S.S.) is active ("A.N.I.Ma.S.S. ODV," 2023).

2.2. Sample

The participants were recruited through the A.N.I.Ma.S.S., composed by members from all over Italy with a diagnosis of pSS. Selected participants were informed that the research study was being carried out to investigate the mental health of people living with pSS and were invited to participate in the study via an invitation email addressed to them.

The inclusion criteria for individuals to participate in the study were: (1) being members of A.N.I.Ma.S.S., (2) being 18 years or older, (3) giving consent to participate in the study. The exclusion criterion was: (1) miss responses in the survey.

A sample size was calculated considering 45.8 % expected prevalence of the primary outcome (depressive symptoms) (Morreale et al., 2014), a confidence level of 95 %, a confidence interval width of 2 %, and a retention rate of 30 %. Therefore, a minimum sample size of 149 participants was estimated to obtain the necessary statistical significance. Finally, the final sample consisted of 216 participants. The Stata

17 software was used for all statistical analyses (Stata Statistical Software, 2019).

2.3. Procedure

This study was conducted through the LimeSurvey online platform ("LimeSurvey," 2023), from the University of Verona, which ensures the protection of confidential data in agreement with the General data protection regulation (GDPR) and European Union (EU) law. Participants were given adequate information regarding the aims of the study, the processing and confidentiality of personal data (as established by the Italian Legislation - DL 196/2003, art.13). Then each was free to give an informed consent before answering the questionnaires, through online flags. The data was collected for three months. Coordination of data collection and analysis was carried out by the Research Unit "Register of Psychiatry, Economics and Geography of Mental Health", of the Department of Neuroscience, Biomedicine and Movement Science at the University of Verona.

2.4. Variables

Demographic and clinical data collected included age, gender, disease length, professional background or medical specialty of the healthcare providers involved in the diagnostic process (i.e., specialist who first had the diagnostic suspect, and specialist who first diagnosed the syndrome).

The screening tools used for the data collection about mental health and QoL are reliable and valid instruments that have been used widely among adults with pSS (Del Papa et al., 2021).

The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) is a self-assessment questionnaire composed of seven items to evaluate the level of anxiety symptoms and seven items to measure the level of depressive symptoms. We have considered the two HADS subscales both as scores and as categorical variables, by grouping the participants according to the following criteria: absent depression/anxiety (score below eight), borderline depression/anxiety (score between eight and ten), clinical depression/anxiety (score between 11 and 21). The presence of depression and anxiety was thus indicated by a score of at least eight of the related subscales. The Italian version of the HADS was validated by Annunziata and colleagues (Annunziata et al., 2011).

The Short Form-36 Health Survey (SF-36) (Ware and Sherbourne, 1992) was used to evaluate the HR-QoL. It has 36 items grouped into the following eight domains: 1) Physical Functioning, 2) Role-Physical, 3) Bodily Pain, 4) General Health, 5) Vitality, 6) Social Functioning, 7) Role-Emotional, and 8) Mental Health. For each domain, a standardized total score was obtained, ranging from 0 (worst QoL) to 100 (best QoL). The Italian version was validated by Apolone & Mosconi (Apolone and Mosconi, n.d.). We have used the SF-36 manual score as the interval variable (Ware et al., 1993). Each survey session lasted 20 min.

2.5. Statistical methods

Descriptive analyses were carried out for all variables considered (absolute and relative frequencies for binary variables, mean and standard deviations for interval-level variables), and the correlation between clinical scale was calculated.

The comparison of the distributions of the two HADS subscales scores between the two-disease length groups i.e., short illness duration (<10 years), long illness duration (≥10 years), was carried out through the Mann-U Whitney test. The association of the two disease-length groups with the two HADS subscales was also assessed through a Chi-square test, by using the three disease categories defined above.

2.6. Ethical consideration

The data were processed in accordance with Reg (EU) 2016/679 and collected exclusively for the purposes of the study. This study has been conducted in accordance with the ethical principles contained in the Helsinki Declaration (2000) for medical research involving human subjects. The protocol for this study was approved by the Local Ethics Committee (3404 CESC. Prot. 46581, 9 June 2021). The generated database does not contain personal data that would allow for the identification of the respondents, and the respondents appear in the database using a user code.

3. Results

3.1. Characteristics of study sample

A total of 338 A.N.I.Ma.S.S. members were assessed for enrollment, 219 of which fulfilled the eligibility criteria. Only three male participants replied to the survey, and then they were excluded from the analysis. A total of 216 women with pSS who completed the survey were included in the study. Of these, only about 22 % had less than 45 years (mean age: 54 years, SD 11.5), and about 52 % have been diagnosed less than 10 years before filling the questionnaire (average course of disease: 14.5 years). Globally, rheumatologists, immunologists, or internists diagnosed the pSS (82 %), but less frequently have been the first who had the diagnostic suspect (40 %) (Table 1).

3.2. Anxiety, depression and health-related quality of life

Mental health symptoms evaluated by the HADS subscales revealed a clinical level of anxiety in 50 % and depression in 41 % of the respondents with pSS; and respectively 29 % and 32 % of women in a

Table 1

Sociodemographic and clinical characteristics of women with primary Sjögren's Syndrome (pSS) ($n = 216$).

	N	%
Age (years)		
18–24	1	0.46
25–44	47	21.76
45–64	128	59.26
65+	40	18.52
Disease length (years with pSS)		
< 10	113	52.31
≥10	103	47.69
Specialist who diagnosed the pSS (8 missing)		
Rheumatologist, Immunologist, Internist	170	81.73
Other ^a	29	13.94
Ophthalmologist	8	3.85
Patient	1	0.48
Person who first had the diagnostic suspect (3 missing)		
Rheumatologist, Immunologist, Internist	86	40.38
Other ^b	52	24.41
Ophthalmologist	29	13.62
General practitioner	16	7.51
Otolaryngologist	10	4.69
Hematologist	9	4.23
Patient	8	3.76
Non-healthcare professional ^c	3	1.41

^a Hematologist, endocrinologist, otolaryngologist, allergist, maxillofacial surgeon, hepatologist, gastroenterologist, neurologist, cardiologist, physiatrist, primary physician, infectious, traumatologist.

^b Echographer, endocrinologist, neurologist, gastroenterologist, orthopedist, allergist, angiologist, cardiologist, hepatologist, physiatrist, gynecologist, odontostomatologist, anesthesiologist, maxillofacial surgeon, internal medicine surgeon, vascular surgeon, immunologist, dermatologist, physiotherapist, osteopath, optician, pediatrician, pulmonologist, radiologist, traumatologist, oncologist.

^c Shiatsu operator, patient's mother, mason, none, colleague.

borderline condition (Table 2). The overall mean was 10.6 (SD 3.8) for anxiety and 9.6 (SD 3.8) for depression, with a positive correlation between the two subscales of 0.571 ($p < 0.001$) and a negative correlation between the eight domains of the SF-36 ($p < 0.001$ in all cases) (Table 3). Broadly, correlations are increasingly stronger for depression compared to anxiety, except for the one with mental health domain which is slightly stronger for anxiety (-0.717 vs -0.674). The latter subscale has the strongest correlation for both anxiety and depression (both around -0.7).

Finally, anxiety and depression did not show any significant association with disease length, either through the Chi-square test (p -value 0.824 for anxiety groups and 0.573 for depression groups) or through the Mann U -Whitney test (p -value 0.921 for anxiety groups and 0.523 for depression groups).

Patients with pSS have a low score in all eight domains of the SF-36 (Table 2) which overall measured HR-QoL. The highest values are those related to Physical functioning (55.32 ± 24.86), followed by Mental Health (49.06 ± 18.71) and Social Functioning (45.43 ± 22.97), while the lowest ones are those related to the limitations due to physical problems (21.76 ± 33.25), followed by the General Health domain (27.17 ± 15.82). These results when compared with the Italian normative sample by Apolone & Mosconi (Apolone and Mosconi, n.d.) showed a relevant reduction in HR-QoL among women with pSS. The correlations between the eight domains that measure HR-QoL are always relevant (between 0.3 and 0.6).

4. Discussion

This study aimed to evaluate the impact of mental health on patients with pSS by assessing anxiety, depressive symptoms and the HR-QoL through an online cross-sectional study design. It contributes to gathering insights into the role of mental health in the progression of pSS.

Two-hundred sixteen women with pSS participated in the online survey, reflecting the epidemiology of pSS. Rheumatologists, immunologists, internists diagnosed and / or had the diagnostic suspect of pSS for the majority of the cases, even so a varied and wide range of specialists was mentioned. This may be due to the syndrome's complexity and the heterogeneity in its presentation, course and outcome (Lee et al., 2021; Vivino et al., 2019). Additionally, this is related to and explains why the specialists refer to the pSS as a spectrum in all the clinical presentations of the symptoms (Vivino et al., 2019).

Regarding the mental health impact, the present study found a high

Table 2

Anxiety, depression and health-related quality of life among women with pSS ($n = 216$).

	Mean (SD)	N (%)
HADS^a, anxiety	10.63 (3.80)	216
Clinical		109 (50.46)
Borderline		63 (29.17)
Absent		44 (20.37)
HADS, depression	9.63 (3.83)	216
Clinical		89 (41.20)
Borderline		70 (32.41)
Absent		57 (26.39)
SF-36^b domains	Study sample	Italian normative sample *
General Health	27.17 (15.82)	65.22
Physical Functioning	55.32 (24.86)	84.46
Role-Physical	21.76 (33.25)	78.21
Role-Emotional	30.40 (36.75)	76.16
Social Functioning	45.43 (22.97)	77.43
Vitality	29.63 (17.49)	61.89
Mental Health	49.06 (18.71)	66.59
Bodily Pain	37.29 (19.31)	73.67

^a HADS: Hospital Anxiety and Depression Scale.

^b SF-36: Short Form-36 Health Survey.

* Apolone & Mosconi, 1998.

Table 3

Pearson correlations among the 8 domains of SF-36 (health-related quality of life) and the HADS (depression, anxiety) in 216 pSS women.

	HADS anxiety	HADS depression	General Health	Physical Functioning	Role-Physical	Role-Emotional	Social Functioning	Vitality	Mental Health	Bodily Pain
HADS anxiety	1									
HADS depression	<i>0.571*</i>	1								
General Health	<i>-0.344*</i>	<i>-0.472*</i>	1							
Physical Functioning	<i>-0.269*</i>	<i>-0.482*</i>	0.415*	1						
Role-Physical	<i>-0.289*</i>	<i>-0.406*</i>	0.435*	0.479*	1					
Role-Emotional	<i>-0.388*</i>	<i>-0.508*</i>	0.392*	0.345*	0.623*	1				
Social Functioning	<i>-0.508*</i>	<i>-0.575*</i>	0.450*	0.472*	0.529*	0.480*	1			
Vitality	<i>-0.382*</i>	<i>-0.637*</i>	0.523*	0.553*	0.461*	0.336*	0.543*	1		
Mental Health	<i>-0.717*</i>	<i>-0.674*</i>	0.436*	0.300**	0.344*	0.500*	0.558*	0.565*	1	
Bodily Pain	<i>-0.352*</i>	<i>-0.553*</i>	0.532*	0.612*	0.552*	0.393*	0.558*	0.585*	0.396*	1

Correlations above 0.6 in absolute value are marked in bold.

Correlations involving HADS scales are marked in italics.

* $p < 0.001$.

** Lowest correlation in absolute value.

level of anxiety and depressive symptoms and low HR-QoL among participants. Additionally, a negative correlation between HR-QoL and depression and anxiety was observed.

The findings about mental health impact on women living with pSS are consistent with those of an Italian report (Morreale et al., 2014) and a recent systematic review and meta-analysis by Cui and colleagues (Cui et al., 2018a). This review included 12 studies with 1917 participants, reporting on the prevalence of pSS with depression. Among these included studies, nine specifically focused on women with pSS, and results revealed that the depression score in pSS patients was higher than in the healthy controls across Germany, Netherlands, Italy, Türkiye, U.S.A., Brazil, and Australia.

Another important finding of the present study relates to the role of anxiety in women with pSS. Half of our sample (50.46 %) have a clinical status of this condition, highlighting the significant psychological burden of pSS among women. A recent review and a cross-sectional study collecting 160 pSS patients (95 % women) adds into this, highlighting the greater prevalence of depression and anxiety among women living with pSS (Cui et al., 2018b). Moreover, the syndrome uses to occur during the perimenopausal period for most female pSS patients, when women inevitably are living new psychological, social and biological changes (Flores-Ramos et al., 2018; Kanadys et al., 2016). The quality of life of women in this period may be conditioned by many factors, and this could be one of the possible explanations of this psychological trend according to the current evidence in Europe (Seghieri et al., 2021).

The finding that the level of HR-QoL is reduced among women with pSS and it is negatively associated with the depression and anxiety symptoms expands previous data collected in this type of population (Al-Ezzi et al., 2023, 2017; Zhang et al., 2017). Taking care of Italian context, Priori and colleagues (Priori et al., 2015) remark on the relationship between resilience, quality of life, and mental health. Resilient people could have a different perception of their disease and therefore can better cope with chronic illness, improve their quality of life and reduce the health cost of the syndrome (Vitali et al., 2021).

5. Limitations and strengths

Results from this study should be considered in light of several limitations. First, the results were limited to female pSS patients due to the low number of male patients among the survey's responders, and thus, the findings cannot be generalized to the entire pSS population. Second, response biases, which can often be difficult to eliminate in self-reported survey research like this one, may have influenced respondents' opinions. Third, we did not include other useful demographic and clinical

variables in the sociodemographic survey, thus limiting the results of this study, that we will consider in a future and separate study to provide a more comprehensive understanding of the factors influencing mental health in this type of population. Fourth, recruiting within the A.N.I.Ma.S.S., though very powerful and promising, may lead to exclude patients with pSS that do not want to be involved with patient's associations or support groups, maybe also because of mental symptoms.

Notwithstanding these limitations, to the best of our knowledge, this was the first cross-sectional online survey assessing the mental health impact on women living with pSS across a whole European country. Strengths of the present study included the close cooperation with the national non-governmental nonprofit organization (A.N.I.Ma.S.S.), key reference point for patients with primary Sjögren Syndrome, family members, physicians and all others who express their interest in this syndrome.

6. Conclusion and future avenue

Mental health evaluation, diagnosis' recognition, prevention and treatment decisions remain challenging in clinical practice for pSS patients, without a specific therapeutic target beyond the relief of symptoms as the most important goal (Pezoulas et al., 2022). Consistently with an extensive literature showing the need for psychiatric evaluation, early diagnosis, and treatment for patients with pSS (Shen et al., 2015; Wang et al., 2021), our findings point out the need for action. There is the demand to widely use common classification criteria to identify patients in need of care pathways, in which a therapeutic multidimensional intervention may have greater chances of modifying the natural history of this type of patients with such of psychiatric comorbidities (Vitali et al., 2021). This call is also promoted by the European League Against Rheumatic (EULAR) recommendations (Brito-Zerón et al., 2016; Ramos-Casals et al., 2020; Retamozo et al., 2021), aimed at developing evidence and consensus-based guidelines for the management of patients with Sjögren's syndrome. Our study is just a starting point, and we aspire to undertake further efforts to support more concrete clinical and organizational actions. Nevertheless, our results develop and support a rational therapeutic approach to pSS patients useful for all the health-care professionals, pharmaceutical industry, and drug regulatory organizations with the goal to become broadly applied in clinical practice and to serve as a template for local therapeutic adaptation across all countries (Ramos-Casals et al., 2020).

CRediT authorship contribution statement

Eleonora Prina: Conceptualization, Data curation, Methodology,

Visualization, Writing – original draft, Writing – review & editing. **Federico Tedeschi**: Data curation, Formal analysis, Investigation, Methodology, Software, Writing – review & editing. **Laura Rabbi**: Conceptualization, Resources, Validation, Visualization, Writing – review & editing. **Francesco Amaddeo**: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

All authors have no competing interest to report.

Acknowledgements

We would like to express our gratitude to the A.N.I.Ma.S.S. Association and to all the participants in our survey.

Funding

The Department of Neuroscience, Biomedicine and Movement Sciences of the University of Verona received a contribution of 4,000 € from the A.N.I.Ma.S.S. Association.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jadr.2024.100806](https://doi.org/10.1016/j.jadr.2024.100806).

References

- Al-Ezzi, M.Y., Khan, K.S., Tappuni, A.R., 2023. Smell dysfunction in patients with primary Sjögren's syndrome: impact on quality of life. *J. Clin. Med.* 12, 2724. <https://doi.org/10.3390/jcm12072724>.
- Al-Ezzi, M.Y., Pathak, N., Tappuni, A.R., Khan, K.S., 2017. Primary Sjögren's syndrome impact on smell, taste, sexuality and quality of life in female patients: a systematic review and meta-analysis. *Mod. Rheumatol.* 27, 623–629. <https://doi.org/10.1080/14397595.2016.1249538>.
- A.N.I.Ma.S.S. ODV, 2023. Assoc. Naz. Ital. Mal. Sindrome Sjogren. URL: <https://www.ani.mass.org/> (accessed 11.5.23).
- Annunziata, M.A., Muzzatti, B., Altoè, G., 2011. Defining Hospital Anxiety and Depression Scale (HADS) structure by confirmatory factor analysis: a contribution to validation for oncological settings. *Ann. Oncol.* 22, 2330–2333. <https://doi.org/10.1093/annonc/mdq750>.
- Apolone, G., Mosconi, P., n.d. The Italian SF-36 Health Survey: translation, Validation and Norming.
- Brito-Zerón, P., Melchor, S., Seror, R., Priori, R., Solans, R., Kostov, B., Baldini, C., Carubbi, F., Callejas, J.L., Guisado-Vasco, P., Hernández-Molina, G., Pasoto, S.G., Valim, V., Sisó-Almirall, A., Mariette, X., Carreira, P., Ramos-Casals, M., the Sjögren Big Data Consortium, Members of the EULAR-SS Task Force Big Data Consortium who contributed to this study, Brito-Zerón, P., Morcillo, C., Brito-Zerón, P., Flores-Chávez, A., Ramos-Casals, M., Acar-Denizli, N., Horvath, I.F., Szanto, A., Tarr, T., Seror, R., Mariette, X., Mandl, T., Olsson, P., Li, X., Xu, B., Baldini, C., Bombardieri, S., Gottenberg, J.E., Gandolfo, S., De Vita, S., Priori, R., Giardina, F., Hernandez-Molina, G., Sánchez-Guerrero, J., Kruize, A.A., Hinrichs, A., Valim, V., Isenberg, D., Solans, R., Rischmueller, M., Downie-Doyle, S., Kwok, S.-K., Park, S.-H., Nordmark, G., Suzuki, Y., Kawano, M., Giacomelli, R., Devauchelle-Pensec, V., Saraux, A., Hofauer, B., Knopf, A., Bootsma, H., Vissink, A., Morel, J., Vollenweider, C., Atzeni, F., Retamozo, S., Moça Trevisano, V., Armagan, B., Kilic, L., Kalyoncu, U., Pasoto, S.G., Kostov, B., Sisó-Almirall, A., Consani-Fernández, S., Carubbi, F., Callejas, J.L., López-Dupla, M., Pérez-Alvarez, R., Akasbi, M., Guisado-Vasco, P., Sánchez, I., 2021. SARS-CoV-2 infection in patients with primary Sjögren syndrome: characterization and outcomes of 51 patients. *Rheumatology* 60, 2946–2957. <https://doi.org/10.1093/rheumatology/keaa748>.
- Brito-Zerón, P., Theander, E., Baldini, C., Seror, R., Retamozo, S., Quartuccio, L., Bootsma, H., Bowman, S.J., Dörner, T., Gottenberg, J.-E., Mariette, X., Bombardieri, S., De Vita, S., Mandl, T., Ng, W.-F., Kruize, A.A., Tzioufas, A., Vitali, C., Buyon, J., Izmirly, P., Fox, R., Ramos-Casals, M., On Behalf Of The Eular Sjögren Synd, 2016. Early diagnosis of primary Sjögren's syndrome: EULAR-SS task force clinical recommendations. *Expert Rev. Clin. Immunol.* 12, 137–156. <https://doi.org/10.1586/1744666X.2016.1109449>.
- Carubbi, F., Alunno, A., Ferri, C., Gerli, R., Bartoloni, E., 2020. The Impact of SARS-CoV-2 outbreak on primary Sjögren's syndrome: an Italian experience. *Front. Med.* 7, 608728. <https://doi.org/10.3389/fmed.2020.608728>.
- Chou, A., Gonzales, J.A., Daniels, T.E., Criswell, L.A., Shiboski, S.C., Shiboski, C.H., 2017. Health-related quality of life and depression among participants in the Sjögren's International Collaborative Clinical Alliance registry. *RMD Open* 3, e000495. <https://doi.org/10.1136/rmdopen-2017-000495>.
- Cui, Y., Li, L., Yin, R., Zhao, Q., Chen, S., Zhang, Q., Shen, B., 2018a. Depression in primary Sjögren's syndrome: a systematic review and meta-analysis. *Psychol. Health Med.* 23, 198–209. <https://doi.org/10.1080/13548506.2017.1339895>.
- Cui, Y., Xia, L., Li, L., Zhao, Q., Chen, S., Gu, Z., 2018b. Anxiety and depression in primary Sjögren's syndrome: a cross-sectional study. *BMC Psychiatry* 18, 131. <https://doi.org/10.1186/s12888-018-1715-x>.
- Del Papa, N., Minniti, A., Maglione, W., Pignataro, F., Caporali, R., Vitali, C., 2021. Instruments for outcome evaluation of specific domains in primary Sjögren's syndrome. *Biomolecules* 11, 953. <https://doi.org/10.3390/biom11070953>.
- Del Papa, N., Vitali, C., 2018. Management of primary Sjögren's syndrome: recent developments and new classification criteria. *Ther. Adv. Musculoskelet. Dis.* 10, 39–54. <https://doi.org/10.1177/1759720x17746319>.
- Dias, L.H., Miyamoto, S.T., Giovelli, R.A., De Magalhães, C.I.M., Valim, V., 2021. Pain and fatigue are predictors of quality of life in primary Sjögren's syndrome. *Adv. Rheumatol.* 61, 28. <https://doi.org/10.1186/s42358-021-00181-9>.
- Flores-Ramos, M., Silvestri Tomassoni, R., Guerrero-López, J.B., Salinas, M., 2018. Evaluation of trait and state anxiety levels in a group of peri- and postmenopausal women. *Women Health* 58, 305–319. <https://doi.org/10.1080/03630242.2017.1296059>.
- Fox, R., 2005. Sjögren's syndrome. *Lancet* 321–332. [https://doi.org/10.1016/S0140-6736\(05\)66990-5](https://doi.org/10.1016/S0140-6736(05)66990-5).
- Gairy, K., Ruark, K., Sinclair, S.M., Brandwood, H., Nelsen, L., 2020. An innovative online qualitative study to explore the symptom experience of patients with primary Sjögren's syndrome. *Rheumatol. Ther.* 7, 601–615. <https://doi.org/10.1007/s40744-020-00220-9>.
- Giacomelli, R., Afeltra, A., Alunno, A., Baldini, C., Bartoloni-Bocci, E., Berardicurti, O., Carubbi, F., Cauli, A., Cervera, R., Ciccía, F., Cipriani, P., Conti, F., De Vita, S., Di Benedetto, P., Doria, A., Drosos, A.A., Favalli, E.G., Gandolfo, S., Gatto, M., Grembiale, R.D., Liakouli, V., Lories, R., Lubrano, E., Lunardi, C., Margiotta, D.P.E., Massaro, L., Meroni, P., Minniti, A., Navarin, L., Pendolino, M., Perosa, F., Pers, J.-O., Prete, M., Priori, R., Puppo, F., Quartuccio, L., Ruffatti, A., Ruscitti, P., Russo, B., Sarzi-Puttini, P., Shoenfeld, Y., Somarakis, G.A., Spinelli, F.R., Tinazzi, E., Triolo, G., Ursini, F., Valentini, G., Valesini, G., Vettori, S., Vitali, C., Tzioufas, A.G., 2017. International consensus: what else can we do to improve diagnosis and therapeutic strategies in patients affected by autoimmune rheumatic diseases (rheumatoid arthritis, spondyloarthritis, systemic sclerosis, systemic lupus erythematosus, antiphospholipid syndrome and Sjogren's syndrome)? *Autoimmun. Rev.* 16, 911–924. <https://doi.org/10.1016/j.autrev.2017.07.012>.
- Jones, R., Barraclough, K., Dowrick, C., 2010. When no diagnostic label is applied. *BMJ* 340. <https://doi.org/10.1136/bmj.c2683>.
- Kanady, K., Wiktor-Stoma, A., Lewicka, M., Sulima, M., Wiktor, H., 2016. Predictors of the quality of life of women in peri-menopausal period. *Ann. Agric. Environ. Med.* 23, 641–648. <https://doi.org/10.5604/12321966.1226860>.
- Kouranloo, K., Dey, M., Elwell, H., Nune, A., 2023. A systematic review of the incidence, management and prognosis of new-onset autoimmune connective tissue diseases after COVID-19. *Rheumatol. Int.* <https://doi.org/10.1007/s00296-023-05283-9>.
- Lee, J.J., Park, Y.J., Park, M., Yim, H.W., Park, S.H., Kwok, S.-K., 2021. Longitudinal analysis of symptom-based clustering in patients with primary Sjögren's syndrome: a prospective cohort study with a 5-year follow-up period. *J. Transl. Med.* 19, 394. <https://doi.org/10.1186/s12967-021-03051-6>.
- LimeSurvey [Internet], 2023. URL: <https://www.limesurvey.org/> (accessed 11.5.23).
- Morreale, M., Marchione, P., Giacomini, P., Pontecorvo, S., Marianetti, M., Vento, C., Tinelli, E., Francia, A., 2014. Neurological involvement in primary Sjögren syndrome: a focus on central nervous system. *PLoS ONE* 9, e84605. <https://doi.org/10.1371/journal.pone.0084605>.
- Pezoulas, V.C., Goules, A., Kalatzis, F., Chatzis, L., Kourou, K.D., Venetsanopoulou, A., Exarchos, T.P., Gandolfo, S., Votis, K., Zampeli, E., Burmeister, J., May, T., Marcelino Pérez, M., Lischuk, I., Chondrogiannis, T., Andronikou, V., Varvarigou, T., Filipovic, N., Tsiknakis, M., Baldini, C., Bombardieri, M., Bootsma, H., Bowman, S.J., Soyfo, M.S., Parisi, D., Delporte, C., Devauchelle-Pensec, V., Pers, J.-O., Dörner, T., Bartoloni, E., Gerli, R., Giacomelli, R., Jonsson, R., Ng, W.-F., Priori, R., Ramos-Casals, M., Sivils, K., Skopouli, F., Torsten, W., A G Van Roon, J., Xavier, M., De Vita, S., Tzioufas, A.G., Fotiadis, D.I., 2022. Addressing the clinical unmet needs in primary Sjögren's Syndrome through the sharing, harmonization and federated analysis of 21 European cohorts. *Comput. Struct. Biotechnol. J.* 20, 471–484. <https://doi.org/10.1016/j.csbj.2022.01.002>.
- Pisetsky, D.S., 2023. Pathogenesis of autoimmune disease. *Nat. Rev. Nephrol.* 19, 509–524. <https://doi.org/10.1038/s41581-023-00720-1>.
- Prina, E., Tedeschi, F., Salazzari, D., Botte, T., Ballarin, M., Rabbi, L., Imperadore, G., Rocco, S., Nicolaou, S., Ruggeri, M., Gomez, F., Lasalvia, A., Amaddeo, F., 2023. Effect of COVID-19 pandemic on utilisation of community-based mental health care in North-East of Italy: a psychiatric case register study. *Epidemiol. Psychiatr. Sci.* 32, e17. <https://doi.org/10.1017/S2045796023000100>.
- Priori, R., Minniti, A., Derme, M., Antonazzo, B., Brancatisano, F., Ghirini, S., Valesini, G., Framarino-dei-Malatesta, M., 2015. Quality of sexual life in women with primary Sjögren Syndrome. *J. Rheumatol.* 42, 1427–1431. <https://doi.org/10.3899/jrheum.141475>.
- Qin, B., Wang, J., Yang, Z., Yang, M., Ma, N., Huang, F., Zhong, R., 2015. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. *Ann. Rheum. Dis.* 74, 1983–1989. <https://doi.org/10.1136/annrheumdis-2014-205375>.
- Ramos-Casals, M., Brito-Zerón, P., Bombardieri, S., Bootsma, H., De Vita, S., Dörner, T., Fisher, B.A., Gottenberg, J.-E., Hernandez-Molina, G., Kocher, A., Kostov, B., Kruize, A.A., Mandl, T., Ng, W.-F., Retamozo, S., Seror, R., Shoenfeld, Y., Sisó-Almirall, A., Tzioufas, A.G., Vitali, C., Bowman, S., Mariette, X., 2020. EULAR

- recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Ann. Rheum. Dis.* 79, 3–18. <https://doi.org/10.1136/annrheumdis-2019-216114>.
- Retamozo, S., Baldini, C., Bootsma, H., De Vita, S., Dörner, T., Fisher, B.A., Gottenberg, J.-E., Hernández-Molina, G., Kocher, A., Kostov, B., Kruize, A.A., Mandl, T., Ng, W.-F., Seror, R., Shoenfeld, Y., Sisó-Almirall, A., Tzioufas, A.G., Vissink, A., Vitali, C., Bowman, S.J., Mariette, X., Ramos-Casals, M., Brito-Zerón, P., 2021. Therapeutic recommendations for the management of older adult patients with Sjögren's Syndrome. *Drugs Aging* 38, 265–284. <https://doi.org/10.1007/s40266-021-00838-6>.
- Seghier, C., Lupi, E., Tzioufas, A.G., De Vita, S., Baldini, C., 2021. Patient-reported experience and health-related quality of life in patients with primary Sjögren's syndrome in Europe. *Clin. Exp. Rheumatol.* 39, 123–130. <https://doi.org/10.55563/clinexprheumatol/vsv60z>.
- Shahane, A., Patel, R., 2014. The epidemiology of Sjögren's syndrome. *Clin. Epidemiol.* 247 <https://doi.org/10.2147/CLEP.S47399>.
- Shen, C.-C., Yang, A.C., Kuo, B.I.-T., Tsai, S.-J., 2015. Risk of psychiatric disorders following primary sjögren syndrome: a nationwide population-based retrospective cohort study. *J. Rheumatol.* 42, 1203–1208. <https://doi.org/10.3899/jrheum.141361>.
- Shiboski, C.H., Shiboski, S.C., Seror, R., Criswell, L.A., Labetoulle, M., Lietman, T.M., Rasmussen, A., Scofield, H., Vitali, C., Bowman, S.J., Mariette, X., the International Sjögren's Syndrome Criteria Working Group, Heidenreich, A.M., Lanfranchi, H., Vollenweider, C., Schiødt, M., Devauchelle, V., Gottenberg, J.E., Saraux, A., Pincemin, M., Dörner, T., Tzoufias, A., Baldini, C., Bombardieri, S., De Vita, S., Kitagawa, K., Sumida, T., Umehara, H., Bootsma, H., Kruize, A.A., Radstake, T.R., Vissink, A., Jonsson, R., Ramos-Casals, M., Theander, E., Challacombe, S., Fisher, B., Kirkham, B., Larkin, G., Ng, F., Rauz, S., Akpek, E., Atkinson, J., Baer, A.N., Carsons, S., Carteron, N., Daniels, T., Fox, B., Greenspan, J., Illei, G., Nelson, D., Parke, A., Pillemer, S., Segal, B., Sivils, K., St Clair, E.W., Stone, D., Vivino, F., Wu, A., 2017. 2016 American College of Rheumatology/European league against rheumatism classification criteria for primary Sjögren's Syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheumatol.* 69, 35–45. <https://doi.org/10.1002/art.39859>.
- Stata Statistical Software, 2019. StataCorp.
- Tarn, J., Lendrem, D., McMeekin, P., Lendrem, C., Hargreaves, B., Ng, W., 2022. Primary Sjögren's syndrome: longitudinal real-world, observational data on health-related quality of life. *J. Intern. Med.* 291, 849–855. <https://doi.org/10.1111/joim.13451>.
- Unger, J., Mattsson, M., Drăgoi, R.G., Avram, C., Boström, C., Buttgereit, F., Lackner, A., Witte, T., Raffener, B., Peichl, P., Durechova, M., Hermann, J., Stamm, T.A., Dejaco, C., 2021. The experiences of functioning and health of patients with primary Sjögren's Syndrome: a multicenter qualitative European study. *Front. Med.* 8, 770422 <https://doi.org/10.3389/fmed.2021.770422>.
- Vitali, C., Del Papa, N., 2017. Classification and diagnostic criteria in Sjögren's syndrome: a long-standing and still open controversy. *Ann. Rheum. Dis.* 76, 1953–1954. <https://doi.org/10.1136/annrheumdis-2017-211378>.
- Vitali, C., Minniti, A., Pignataro, F., Maglione, W., Del Papa, N., 2021. Management of Sjögren's Syndrome: present issues and future perspectives. *Front. Med.* 8, 676885 <https://doi.org/10.3389/fmed.2021.676885>.
- Vivino, F.B., Bunya, V.Y., Massaro-Giordano, G., Johr, C.R., Giattino, S.L., Schorpion, A., Shafer, B., Peck, A., Sivils, K., Rasmussen, A., Chiorini, J.A., He, J., Ambrus, J.L., 2019. Sjögren's syndrome: an update on disease pathogenesis, clinical manifestations and treatment. *Clin. Immunol.* 203, 81–121. <https://doi.org/10.1016/j.clim.2019.04.009>.
- Von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., Vandenbroucke, J.P., 2008. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J. Clin. Epidemiol.* 61, 344–349. <https://doi.org/10.1016/j.jclinepi.2007.11.008>.
- Wang, B., Chen, S., Zheng, Q., Li, Y., Zhang, X., Xuan, J., Liu, Y., Shi, G., 2021. Early diagnosis and treatment for Sjögren's syndrome: current challenges, redefined disease stages and future prospects. *J. Autoimmun.* 117, 102590 <https://doi.org/10.1016/j.jaut.2020.102590>.
- Ware, J., Sherbourne, C.D., 1992. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 30, 473–483.
- Ware, J.E., Snow, K.K., Kosinski, M., Gandek, B., 1993. *SF-36 Health Survey. Manual & Interpretation Guide*.
- Zhang, Q., Wang, X., Chen, H., Shen, B., 2017. Sjögren's syndrome is associated with negatively variable impacts on domains of health-related quality of life: evidence from Short Form 36 questionnaire and a meta-analysis. *Patient Prefer. Adherence* Vol. 11, 905–911. <https://doi.org/10.2147/PPA.S132751>.
- Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. *Acta Psychiatr. Scand.* 67, 361–370. <https://doi.org/10.1111/j.1600-0447.1983.tb09716.x>.