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Impact of disease duration on systemic clinical profile in Sjogren's syndrome

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Abstract

Background Primary Sjogren's Syndrome (pSS) is a systemic autoimmune disorder characterized by lymphocyte infiltration of the exocrine glands. Disease duration plays a pivotal role in evaluating the development of SS. In this study, we aimed to clarify the clinical manifestations of pSS across various stages of its progression, thereby offering critical insights for early diagnosis and targeted management strategies for Sjogren's Syndrome.

Methods We conducted a retrospective analysis involving 3,978 patients with primary Sjogren's Syndrome (mean [SD] age: 53.1[24] years) from Peking University People's Hospital between January 2015 and December 2022. We classified patients into five distinct groups based on the duration of the syndrome: T0 (≤ 1 year), T1 (> 1 year, ≤ 5 years), T2 (> 5 years, ≤ 10 years), T3 (> 10 years, ≤ 20 years), and T4 (> 20 years).

Results We observed a statistically significant increase in the percentage of pSS patients with white blood cell (WBC) decrease, specifically: T0 (9.23%), T1 (15.40%), T2 (22.62%), T3 (20.22%), T4 (26.45%). The decreases in hemoglobin (HGB) and platelet (PLT) were also robustly associated with extended disease duration ($p < 0.0001$). Simultaneously, systemic involvements aggravated with disease progression as incidence rates of skin, joint, lung, and nervous system were strikingly increased in each group. The findings also indicated that patients with long-term pSS exhibit a higher likelihood of developing comorbid conditions, such as diabetes and tumors. In summary, disease duration serves as a crucial determinant for the prognosis of patients with pSS.

Conclusions Therefore, early identification of symptoms and initiation of therapies are imperative for mitigating the risk of significant complications in pSS patients.

Keywords Sjogren's syndrome(SS), Disease duration, Systemic involvement

Background

Primary Sjogren's Syndrome (pSS) is a chronic inflammatory autoimmune disease, characterized by lymphocytic infiltration in exocrine glands, including lacrimal and salivary glands [1]. The hallmark clinical manifestations are dryness of the eyes and mouth, along with abnormal fatigue [2]. Approximately 30–40% of patients experience systemic manifestations, which can affect multiple organs, such as joints, lungs, nervous system, kidneys, and non-exocrine glands [3]. pSS predominantly affects middle-aged females, with a peak incidence occurring around the age of 50 [4].

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The underlying mechanisms of pSS remains not yet fully understood; however, recent research revealed critical insights into its pathogenesis. Epithelial cells plays a pivotal in disease development. These cells are not only targets of immune attacks, but also triggers of immune responses. Through interactions with immune cells, epithelial cells promote inflammatory responses mediated by cytokines and chemokines, which further exacerbate local inflammation [5]. The abnormal activation of the interferon (IFN) signaling pathway is particularly significant in SS. Overexpression of type I interferon is considered a key factor in promoting B cell activation, the activation of B cells produces autoantibodies including anti-Ro/SSA and anti-La/SSB antibodies which was associated with an earlier disease onset [6]. Additionally, epigenetic factors and environmental factors also contributes to pathogenesis of SS, influencing the immune system and potentially leading to immune dysregulation [5].

Numerous lines of evidence highlighted that various factors contribute to the progression of SS, including genetic background, environmental risks, and demographic characteristics. Previous studies have attempted to explore the potential correlation between age of onset and specific disease manifestations in pSS [7], suggesting that patients with early-onset pSS often exhibit higher disease activity and an unfavorable prognosis, which may be associated with a longer disease duration and potentially more rapid disease progression. Therefore, investigating disease duration is of paramount clinical importance, as understanding how prolonged disease exposure influences SS patients may enhance our knowledge of the disease's progression and inform more effective management strategies.

Despite the known impact of pSS on multiple organ systems, there is limited information regarding clinical phenotypes across different stages of the disease. Our study aimed to fill this gap by assessing the impact of disease duration on clinical and immunological parameters in a cohort of 3978 SS patients, providing critical insights for accurate diagnosis and the development of targeted therapeutic strategies in the management of Sjögren's Syndrome.

Materials and methods

Patients

A retrospective study was carried out and a total of 3978 pSS patients from Peking University People's Hospital between January 2015 and December 2022 were included. We determine the time when a patient was first diagnosed with Sjogren's syndrome as the onset time of the disease. The diagnosis of SS in our institution was based on the 2002 American European Consensus Group (AECG) criteria [8] or the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria [9], while the onset time of patients diagnosed in other institutions was accessed by reviewing their medical history and was re-evaluated to meet the 2016 ACR criteria. Patients were divided into 5 independent groups according to the duration of their disease: T0 (≤ 1 year), T1 (> 1 year, ≤ 5 years), T2 (> 5 years, ≤ 10 years), T3 (> 10 years, ≤ 20 years), and T4 (> 20 years) The distribution of patients across these groups was as follows: 390(9.8%), 2072(34.2%), 725(52.1%), 549(13.8%) and 242(6.1%), respectively. This study was approved by the Ethics Committee of Peking University People's Hospital.

Data collection

Basic clinical manifestations such as dry mouth, dry eyes, parotitis, and dental caries were extracted from the medical records of eligible patients and the hospital information system. Blood samples were collected from pSS patients for laboratory analysis, and flow cytometry was employed to detect immune cell subsets. As for the diagnostic criteria of systemic diseases, we define a patient as having leukopenia when their white blood cell count is below 3.5*10^9/L, anemia when their hemoglobin level is below 115 g/L, and thrombocytopenia when their platelet count is below 125*10^9/L. PAH was evaluated according to echocardiography and Interstitial lung disease (ILD), a group of pulmonary disorders characterized by diffuse parenchymal lung infiltration [10], was detected using Pulmonary Function Tests (PFTs) and high-resolution computed tomography (HRCT). The results were evaluated by two experienced radiologists, with diagnoses confirmed by clinical physicians.

Statistical analysis

Descriptive variables are presented as the percentage (%), mean with standard deviation (SD), or median with interquartile range (IQR). Statistical analysis was performed using SPSS R27.0.1.0 (SPSS Inc, Chicago, IL, USA). Comparisons among continuous values were assessed using analysis of variance (ANOVA), while Chi-square test was employed to examine the association between systemic involvement and SS duration. Both the ANOVA tests and Chi-square tests were performed on GraphPad Prism 10 (GraphPad Software, La Jolla, CA, USA). Additionally, Python language was used to create figures illustrating immune cell subpopulations. Statistical significance was determined as a two-tailed p-value of less than 0.05.

Results

Demographic characteristics of pSS patients

A total of 3978 patients with pSS (mean [SD] age, 53.1[24] years) were included in this study, there were 3715 (93.4%) females and 263 (6.6%) males across

various stages of disease. At the time of data collection, the median disease duration was 6.8 (0–71) years. The baseline demographic and clinical characteristics of the patients are presented in Table 1.

Laboratory characteristics in pSS patients

Laboratory analysis revealed a progressive increase in the prevalence of leukopenia, rising from 9.23% in patients with a disease duration of ≤ 1 year (T0) to 26.45% in those with a duration of > 20 years (T4) (Fig. 1A and Table 2; $p < 0.0001$). A similar trend is observed for decreased hemoglobin levels, with rates increasing from 13.85% in the T0 group to 35.54% in the T4 group. Thrombocytopenia follows the same tendency, with an incidence rising from 7.69 to 18.60% across the same duration spectrum (Fig. 1B and C; Table 2; $p < 0.0001$). These findings collectively suggest that longer disease duration in pSS is associated with a higher prevalence of both hematological abnormalities.

Clinical manifestations in pSS patients with different diseases duration

The frequency of interstitial lung disease (ILD) shows a remarkable escalation, from 3.33% in T0 to 10.74% in T4 (Fig. 1D and Table 3; $p < 0.0001$). Similarly, the occurrence of pulmonary arterial hypertension (PAH) increases with disease duration, ranging from 3.59% in the T0 group to 7.85% in the T4 group (Fig. 1E and Table 3; $p < 0.0001$). However, Chronic Obstructive Pulmonary Disease (COPD) reached no significant relationship among these groups (Table 3; $p = 0.3374$).

Data also reveals a progressive increase in the incidence of renal tubular acidosis (RTA), with the rate rising from 7.69% in patients with a disease duration of ≤ 1 year (T0) to 22.31% in those with a duration of > 20 years (T4) (Fig. 1F and Table 3; $p < 0.0001$).

Furthermore, central nervous system (CNS) involvement, including diseases such as cerebrovascular disease and cognitive dysfunction, shows an increasing trend, starting at 0.26% in the T0 group and reaching 2.48% in the T4 group (Fig. 1G and Table 3; $p < 0.0001$). Similarly, peripheral nervous system (PNS) disorders, such as neuropathy, also increase, with the incidence rising from 1.02 to 5.79% across the same duration stages (Fig. 1and Table 3; $p < 0.0001$).

The analysis further indicated a growing prevalence of diabetes, malignancies, and other conditions involving the skin, joints, and muscles as disease duration extends (Table 3). These trends collectively suggested that prolonged duration of pSS is associated with an increased burden of systemic complications, highlighting the exacerbation of the disease).

Immunological responses with diseases progression

To explore the immune phenotyping with disease progression in pSS patients, flow cytometry was conducted to investigate their immunological profiling. Total lymphocytes were comparable among these groups but total T cells presented a significant increase (Figure S1 A and B); Total lymphocytes: $p = 0.858$; Total T cells: $p = 0.033$). It is noted that B cells and NK cells failed to exhibit significant variation with disease progression (Figure S1 C and D). Since lymphopenia primarily results from T cell deficiency, we conducted a detailed sub-analysis of T cell subsets. Our findings revealed that the ratio of CD4 + T cells remained relatively constant compared to CD8 + T cells over time. Additionally, the ratio of CD4 + T cells to T regulatory cells showed no significant variation with disease duration (Figure S1 E and F). These findings suggest that while the proportion of total T cells increases with disease duration, other immune cell subsets do not show significant changes, indicating a selective alteration in immune cell dynamics in pSS patients.

Discussion

Primary Sjögren's Syndrome (pSS) is a heterogeneous autoimmune disorder primarily affecting the lacrimal and salivary glands, but its progression can lead to systemic involvement and multi-organ dysfunction. Although the pathogenesis of pSS is still unclear, it is hypothesized that aberrant immune cells play pivotal roles in disease progression [11–13]. As the disease develops, patients with pSS are more likely to induce systemic manifestations like pulmonary fibrosis, central neuropathy, hematological

Table 1 Clinical characteristics of the groups according to disease duration. Table depicting baseline demographic characteristics of 3978 SS patients enrolled in this experiment. The patients were divided into 5 cohorts due to SS duration (T0-T5), and relevant symptoms and indicators were recorded. ****$P \leq 0.0001$;<0.0001***$P \leq 0.001$;0.001 < **$P \leq 0.01$; 0.01< *$P \leq 0.05$

	T0($n = 390$)	T1($n = 2072$)	T2($n = 725$)	T3($n = 549$)	T4($n = 242$)	Total($n = 3978$)	P Value
Female (%)	89.2	93.3	94.0	95.0	95.0	93.4	0.1536
Age, mean(SD)	50.65(15.43)	51.63(15.18)	53.43(13.89)	56.68(12.57)	60.48(11.59)	53.09(14.67)	< 0.0001
Disease duration, mean(SD)	0.98(0.14)	3.36(1.11)	7.46(1.35)	13.69(2.66)	27.45(7.35)	6.77(6.88)	< 0.0001
Dry mouth, n(%)	225 (57.69%)	1348 (65.06%)	558 (76.97%)	423 (77.05%)	209 (86.36%)	2763 (69.45%)	< 0.0001
Dry eyes, n(%)	197 (50.51%)	1262 (60.91%)	526 (72.55%)	392 (71.40%)	197 (81.40%)	574 (64.71%)	< 0.0001
Parotid disease, n(%)	89 (22.82%)	618 (29.83%)	289 (39.86%)	225 (40.98%)	97 (40.08%)	1318 (33.13%)	< 0.0001
Caries, n(%)	39 (10.00%)	280 (13.51%)	138 (19.03%)	120 (21.86%)	49 (20.24%)	626 (15.74%)	< 0.0001

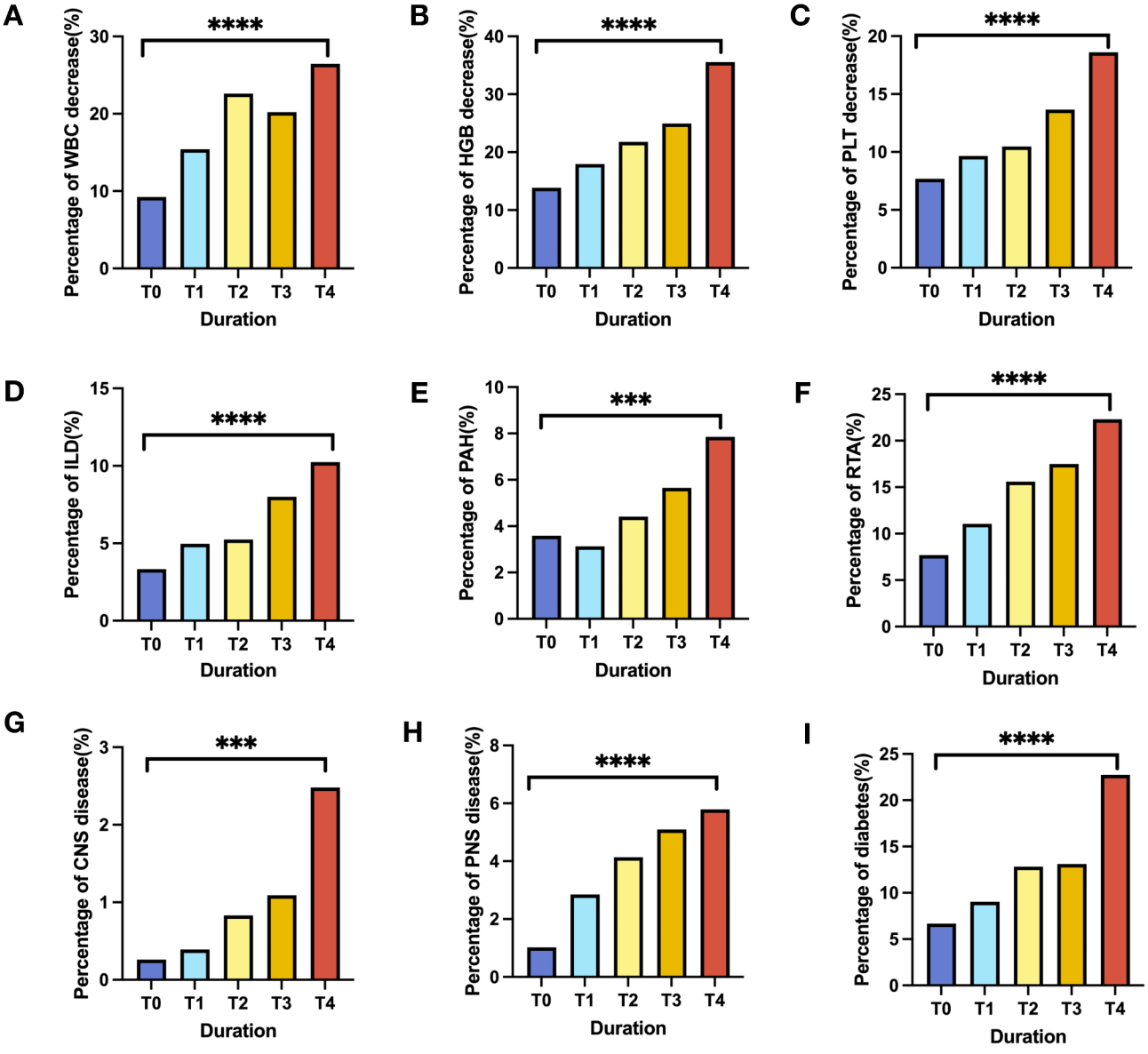

Fig. 1 Systemic involvement in pSS according to disease duration. To explore the effect of disease duration on systemic manifestation of pSS patients. Patients are divided into 4 groups according to SS duration: T0 (≤ 1 year), T1 (> 1 year, ≤ 5 years), T2 (> 5 years, ≤ 10 years), T3 (> 10 years, ≤ 20 years), and T4 (> 20 years). (**A**-**C**) Hematological involvement indicated that the percentage of leukopenia, anemia and thrombocytopenia significantly differed among groups. (**D**-**I**) Other organ involvements showed a significant association with the disease duration, including interstitial lung disease, pulmonary arterial hypertension, renal tubular acidosis, CNS disease, PNS disease and diabetes. ****$P \leq 0.0001$;<0.0001***$P \leq 0.001$;0.001 < **$P \leq 0.01$; 0.01< *$P \leq 0.05$

Table 2 Laboratory findings of the groups according to disease duration. Table depicting laboratory findings of 3978 SS patients enrolled in this experiment. The patients were divided into 5 cohorts due to SS duration (T0-T5), and relevant symptoms and indicators were recorded

	T0($n=390$)	T1($n=2072$)	T2($n=725$)	T3($n=549$)	T4($n=242$)	Total($n=3978$)	*P*Value
Ro/SSA positive, n(%)	92 (23.59%)	655 (31.61%)	299 (41.24%)	230 (41.89%)	93 (38.43%)	1369 (34.41%)	< 0.0001
La/SSB positive, n(%)	34 (8.71%)	233 (11.25%)	114 (15.72%)	73 (13.30%)	23 (9.50%)	477 (11.99%)	0.0906
Rheumatoid factor, average(min-max)	65.04(8-488)	172.47(3-4320)	248.67(2-4680)	171.40(4-2500)	256.85(10-2680)	188.28(2-4680)	0.406
WBC decrease, n(%)	36 (9.23%)	319 (15.40%)	164 (22.62%)	111 (20.22%)	64 (26.45%)	694 (17.44%)	< 0.0001
HGB decrease, n(%)	54 (13.85%)	372 (17.95%)	158 (21.79%)	137 (24,95%)	86 (35.54%)	807 (20.29%)	< 0.0001
PLT decrease, n(%)	30 (7.69%)	200 (9.65%)	76 (10.48%)	75 (13.66%)	45 (18.60%)	426 (10.71%)	< 0.0001

Table 3 Clinical characteristics of the groups according to disease duration. Table depicting clinical characteristics of 3978 SS patients enrolled in this experiment. The patients were divided into 5 cohorts due to SS duration (T0-T5), and relevant symptoms and indicators were recorded. The table was also presented in the form of graph in the next figures

	T0(*n* = 390)	T1(*n* = 2072)	T2(*n* = 725)	T3(*n* = 549)	T4(*n* = 242)	Total(*n* = 3978)	*P* Value
ILD, n(%)	13 (3.33%)	103 (4.97%)	38 (5.24%)	44 (8.01%)	26 (10.74%)	224 (5.63%)	< 0.0001
PAH, n(%)	14 (3.59%)	65 (3.13%)	32 (4.41%)	31 (5.65%)	19 (7.85%)	161 (4.05%)	0.0001
COPD, n(%)	0 (0%)	10 (0.05%)	5 (0.007%)	0 (0%)	3 (1.24%)	18 (0.45%)	0.3374
Other chronic lung diseases, n(%)	9 (2.31%)	33 (1.59%)	21 (2.90%)	22 (4.01%)	16 (6.61%)	101 (2.54%)	< 0.0001
RTA, n(%)	30 (7.69%)	229 (11.05%)	113 (15.59%)	96 (17.49%)	54 (22.31%)	522 (13.12%)	< 0.0001
Other chronic kidney diseases, n(%)	3 (0.77%)	15 (0.72%)	8 (1.10%)	10 (1.82%)	6 (2.48%)	42 (1.06%)	0.0026
CNS disease, n(%)	1 (0.26%)	8 (0.39%)	6 (0.83%)	6 (1.09%)	6 (2.48%)	27 (0.68%)	0.0002
PNS disease, n(%)	4 (1.02%)	59 (2.85%)	30 (4.14%)	28 (5.10%)	14 (5.79%)	135 (3.39%)	< 0.0001
Skin disease, n(%)	61 (15.64%)	455 (21.96%)	204 (28.14%)	160 (29.14%)	110 (45.45%)	990 (24.8%)	<0.0001
Joint disease, n(%)	156 (40.00%)	1054 (50.87%)	448 (61.79%)	354 (64.48%)	173 (71.49%)	2185 (54.93%)	< 0.0001
Muscle disease, n(%)	18 (4.62%)	121 (5.84%)	63 (8.69%)	51 (9.29%)	31 (12.81%)	284 (7.13%)	< 0.0001
Diabetes, n(%)	26 (6.67%)	187 (9.03%)	93 (12.83%)	72 (13.11%)	55 (22.73%)	433 (10.88%)	< 0.0001
Tumor, n(%)	5 (1.28%)	27 (1.30%)	11 (1.52%)	8 (1.46%)	10 (4.13%)	61 (1.53%)	0.0193

abnormalities, and dysfunction of the renal, liver, and thyroid [14]. However, most of the pSS symptoms can be atypical and often overlap with other conditions, resulting in the difficulties of diagnosis as well as treatment. Therefore, identifying the clinical and immune profile throughout the progression of pSS is essential for enabling clinicians to better predict recognize clinical signs of disease progression, ultimately supporting efforts to mitigate the risk of multi-organ damage in pSS patients.

In our study, we explored the clinical manifestations of pSS across various stages of the disease. Our findings revealed that hematological abnormalities, such as leukopenia, anemia, and thrombocytopenia, increased with disease duration. This could be attributed to the suppression of hematopoiesis due to prolonged immune system activation, leading to an abnormal hematological profile in pSS patients.

Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are common and significant complications in pSS, associated with a poor prognosis. A systemic review reported that the prevalence of pulmonary involvement in pSS increases to between 43% and 75% following systematic investigation [15]. Our study found that patients with longer disease duration were more likely to develop chronic lung diseases, emphasizing the importance of disease duration as a prognostic factor in pSS. The findings suggest that clinicians should closely monitor pulmonary function in patients with long-term pSS to improve early detection and intervention.

Kidney involvement, particularly renal tubular acidosis (RTA), was another important clinical manifestation that worsened with the duration of pSS. Previous research indicated that renal complications are present in approximately 12.34% of pSS patients [16]. Our study supports these findings and underscores the need for ongoing renal assessment in pSS patients, particularly those with prolonged disease courses.

Neurological involvement is also frequently observed in Sjogren's syndrome. Central nervous system disorders, such as cerebrovascular disease and cognitive dysfunction, and peripheral nervous system disorders, such as limb numbness and muscle weakness, can both result in irreversible damage to the patient. As previously described, the incidence of CNS involvement in pSS patients ranges from 9.8-13% [17–19]. In our study, the incidence of CNS complications was relatively lower, and patients with longer disease duration were more susceptible to resulting in central nervous system complications while peripheral nervous system diseases also showed a significant rise. These results align with Tishler et al.'s findings, who observed more frequent CNS involvement in early-onset pSS than patients with shorter disease duration, but these results were not statistically significant [20].

Long-term pSS patients also exhibit a higher prevalence of conditions such as diabetes and tumors, potentially due to immune system dysfunction.

Peripheral lymphopenia was associated with higher disease activity and mortality in pSS patients [21]. In the present study, we compared the distribution of lymphocyte subsets in pSS patients across different disease duration. We found a significant positive correlation between the percentage of total T cells and disease duration. However, the total lymphocyte count, as well as B cell and NK cell levels, remained stable, indicating a nuanced dysfunction of the immune system.

The ratio of CD4/CD8 did not change significantly, but this differs from Loureiro's study which suggests a diminished CD4/CD8 ratio in patients suffering from SS [22]. This discrepancy may partly shed light on further research concerning characteristics of immune cells in SS

patients and how they vary while disease develops. These findings may also provide a new potential perspective on the pathogenesis of SS.

The age distribution within our cohort reveals significant variation, suggesting that chronological age may influence the manifestation of the disease in patients. Therefore, this factor warrants careful consideration in our analysis. However, a recent study published in June found that, aside from fatigue, the presence of anti-SSA antibodies, and the use of antimalarial agents, there were no statistically significant differences in other clinical features, laboratory findings, treatment approaches, or outcomes between elderly and younger patients with Sjögren's syndrome [23]. This research provides evidence that the systemic involvement observed in our findings is more likely associated with the duration of SS rather than age itself.

Here are some certain limitations of the study. Firstly, all the data on the prevalence of SS-related diseases were collected from a single center, which may have genetic and environmental factors, so further research based on multiple centers and larger cohort could be carried out to verify our conclusion. Second of all, our experimental results offer a deeper understanding of the disease manifestations in Sjögren's syndrome but have not delved into the specific mechanisms by which the disease course affects these manifestations, so future research should focus on the contribution of disease duration on the pathogenesis of SS.

Additionally, we have yet to study the exact connection between SS duration and clinical diagnosis, suggesting clinicians to confirm and extend the present findings toward the ultimate goal of more effective evaluation and management of pSS.

Conclusions

In conclusion, our study demonstrates that disease duration is a key determinant in the progression and severity of Primary Sjögren's Syndrome. As the disease duration increases, there is a noticeable escalation in systemic involvement, including hematological abnormalities, lung and kidney dysfunction, and neurological complications. These findings highlight the importance of early diagnosis, ongoing monitoring, and timely interventions to prevent or minimize multi-organ damage in pSS patients. Future research should focus on expanding these insights to develop tailored therapeutic strategies that address the specific needs of patients at various stages of the disease. By further investigating the immune profiles and clinical trajectories of pSS patients across different disease duration, we can optimize patient care and improve long-term outcomes.

Abbreviations

pSS	Primary Sjogren's syndrome
WBC	White blood cell
HGB	Hemoglobin
PLT	Platelet
IFN	Interferon
ILD	Interstitial lung disease
PAH	Pulmonary arterial hypertension
COPD	Chronic obstructive pulmonary disease
RTA	Renal tubular acidosis
CNS	Central nervous system
PNS	Peripheral nervous system

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13075-025-03490-2.

Supplementary Material 1

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Author contributions

J.H. conceived and designed the project. J.W and R.F contributed equally to this article, they conducted data acquisition, drafted and revised the first manuscript. J.W. and R.W. performed data analysis. All the authors have revised and approved the manuscript submission.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the ethical committee of Peking University People's Hospital (approval number 2020PHB359-01) and informed consent was obtained from all subjects involved in the study.

Consent for publication

Written informed consent for publication was obtained from all participants.

Competing interests

The authors declare no competing interests.

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References

1. Mariette X, Criswell LA. Primary Sjögren's syndrome. N Engl J Med. 2018;378(10):931–9.
2. Zhang X, Miao M, Zhang R, et al. Efficacy and safety of low-dose interleukin-2 in combination with methotrexate in patients with active rheumatoid arthritis: a randomized, double-blind, placebo-controlled phase 2 trial. Signal Transduct Target Ther. 2022;7(1):67.
3. Berman N, Vivino F, Baker J, Dunham J, Pinto A. Risk factors for caries development in primary Sjogren syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019;128(2):117–22.
4. Qin B, Wang J, Yang Z, et al. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. Ann Rheum Dis. 2015;74(11):1983–9.
5. Negrini S, Emmi G, Greco M, et al. Sjögren's syndrome: a systemic autoimmune disease. Clin Exp Med. 2022;22:9–25.

6. Hernández-Molina G, Leal-Alegre G, Michel-Peregrina M. The meaning of anti-ro and anti-la antibodies in primary Sjögren's syndrome. Autoimmun Rev. 2011;10(3):123–5. https://doi.org/10.1016/j.autrev.2010.09.001. Epub 2010 Sep 15. PMID: 20833272.
7. Wei L, Zhifei X, Xiaoran N, et al. Patients with early-onset primary Sjögren's syndrome have distinctive clinical manifestations and circulating lymphocyte profiles. Rheumatology (Oxford). 2022;61(2):597–605.
8. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002;61(6):554–8.
9. Shiboski CH, Shiboski SC, Seror R, et al. 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. Ann Rheum Dis. 2017;76(1):9–16.
10. Olson A, Hartmann N, Patnaik P, et al. Estimation of the prevalence of Progressive Fibrosing interstitial lung diseases: systematic literature review and data from a Physician Survey. Adv Ther. 2021;38(2):854–67.
11. Yoon J, Lee M, Ali AA, et al. Mitochondrial double-stranded RNAs as a pivotal mediator in the pathogenesis of Sjögren's syndrome. Mol Ther Nucleic Acids. 2022;30:257–69.
12. An Q, Zhao J, Zhu X, et al. Exploiting the role of T cells in the pathogenesis of Sjögren's syndrome for therapeutic treatment. Front Immunol. 2022;13:995895.
13. Shimizu T, Nakamura H, Kawakami A. Role of the Innate Immunity Signaling Pathway in the Pathogenesis of Sjögren's Syndrome. Int J Mol Sci 2021;22(6).
14. Dai X, Sui X, Chen S, Zhao B, Liu Z, Wang X. The diagnostic performance of salivary gland ultrasound elastography in Sjögren's syndrome and sicca symptoms: a systematic review and meta-analysis. Eur Radiol. 2024;34(3):1545–55.
15. Flament T, Bigot A, Chaigne B, Henique H, Diot E, Marchand-Adam S. Pulmonary manifestations of Sjögren's syndrome. Eur Respir Rev. 2016;25(140):110–23.
16. Duan N, Li Z, Fan Y, et al. Related factors of renal injury in primary Sjögren's syndrome. Immun Ageing. 2023;20:48.
17. Fan G, Dai F, Chen S, et al. Neurological involvement in patients with primary Sjögren's syndrome. J Clin Rheumatol. 2021;27(2):50–5.
18. Flores-Chávez A, Kostov B, Solans R, et al. Severe, life-threatening phenotype of primary Sjögren's syndrome: clinical characterisation and outcomes in 1580 patients (GEAS-SS Registry). Clin Exp Rheumatol. 2018;36(3):121–9.
19. Fan W, Par-Young J, Li K, et al. Clinical features and high-risk indicators of central nervous system involvement in primary Sjögren's syndrome. Clin Rheumatol. 2023;42(2):443–51.
20. Tishler M, Yaron I, Shirazi I, Yaron M. Clinical and immunological characteristics of elderly onset Sjögren's syndrome: a comparison with younger onset disease. J Rheumatol. 2001;28(4):795–7.
21. Brito-Zerón P, Kostov B, Solans R, et al. Systemic activity and mortality in primary Sjögren syndrome: predicting survival using the EULAR-SS Disease Activity Index (ESSDAI) in 1045 patients. Ann Rheum Dis. 2016;75(2):348–55.
22. Loureiro-Amigo J, Palacio-García C, Martínez-Gallo M, Martínez-Valle F, Ramentol-Sintas M, Soláns-Laqué R. Utility of lymphocyte phenotype profile to differentiate primary Sjögren's syndrome from Sicca syndrome. Rheumatology (Oxford). 2021;60(12):5647–58.
23. Said F, Naceur I, Ben Achour T, Jeridi M, Ben Ghorbel I, Smiti M. Particularities of Sjögren Syndrome in elderly. Tunis Med. 2024;102(7):419–22. https://doi.org/10.62438/tunismed.v102i7.4876. French.

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