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Diagnostic delay in psoriatic arthritis: insights from a nationwide multicenter study

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Abstract

This study aimed to investigate the duration of diagnostic delay in patients with psoriatic arthritis (PsA) and identify potential contributing factors using a comprehensive, population-based approach. Data were obtained from the Turkish League Against Rheumatism (TLAR)-Network, involving patients who met the CASPAR criteria. Diagnostic delay was defined as time interval from symptom onset to PsA diagnosis, categorized as ≤ 2 years and > 2 years. Temporal trends were assessed by grouping patients based on the year of diagnosis. Various factors including demographics, clinical characteristics, disease activity, quality of life, physical function, disability, fatigue, and well-being were examined. Logistic regression models were used to identify factors associated with diagnostic delay. Among 1,134 PsA patients, mean diagnostic delay was 35.1 months (median: 12). Approximately 39.15% were diagnosed within 3 months, and 67.02% were diagnosed within 24 months. Patients experiencing longer delays had higher scores in Psoriatic Arthritis Quality of Life Questionnaire (PsAQoL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), patient's global assessment (PtGA) and physician's global assessment (PhGA). Diagnostic delay has decreased over time, with median delay falling from 60 to 24 months throughout pre-2010 and 2015–2019 terms. Several factors were identified as significant contributors to delayed diagnosis, including lower levels of education (OR = 2.63), arthritis symptoms preceding skin manifestations (OR = 1.72), low back pain at first visit (OR = 1.60), symptom onset age (OR = 0.96), and psoriasis subtype (OR = 0.25). Timely diagnosis of PsA is crucial for effective management and improved outcomes. Despite recent improvements, about one-third of PsA patients still experience delays exceeding 2 years. By identifying influential factors such as education level, arthritis symptoms preceding skin manifestations, initial visit symptoms, age of symptom onset, and psoriasis subtype, healthcare practitioners may create specific techniques to help in early detection and intervention.

Keywords Arthritis · Psoriatic · Delayed diagnosis · Incidental findings

Introduction

Psoriatic arthritis (PsA) is a clinically diverse and progressive form of inflammatory arthritis. Its prevalence varies among populations and regions. According to recent publications, PsA affects between 3.6 and 7.2 individuals per 100,000 person-years [1]. It can affect other regions of the body in addition to the joints, including the eyes, gastrointestinal tract, cardiovascular system, skin, and nails. The presence and severity of disease manifestations can vary among individuals [2].

The persistent inflammation associated with PsA can lead to the erosion and/or osteolysis within the affected joints, resulting in joint deformity and damage [3]. Moreover, this destructive nature of PsA can cause functional loss and significantly diminish the quality of life [4]. As a result, it

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becomes essential to act quickly by assuring early diagnosis and implementing proper therapies. This timely intervention plays a pivotal role in effectively controlling inflammation, preserving joint integrity, and relieving the associated symptoms.

Based on real-life experiences and supported by the literature, it is commonly observed that the process of identifying and confirming a diagnosis of PsA often exceeds the desired timeframe [1, 5]. Mease et al. discovered that more than one-third of PsA patients had previously gone undiagnosed [6]. This delay can be attributed to the unique challenges associated with early diagnosis of PsA, including the absence of specific diagnostic tests, its diverse clinical presentation, and its potential overlap with other conditions (i.e., fibromyalgia, gout, osteoarthritis) [1, 7–9]. Therefore, further research and implementation of targeted strategies are essential to improve early detection and timely management of PsA.

Until now, limited research has focused on the diagnostic delay in patients with PsA. A study carried out in Europe revealed a positive trend of improved time to diagnose PsA, indicating a reduction in the duration between the onset of symptoms and obtaining a definitive diagnosis. In contrast, a study conducted in the United States during the period from 2000 to 2011 did not find a significant difference in the time to diagnosis PsA. These findings underscore the importance of considering regional and temporal variations when investigating diagnostic delays in PsA. Understanding the variability in delay times across different regions and identifying factors linked with diagnostic delay in PsA might provide significant information for aimed improvements. Therefore, the primary objectives of our study were to investigate the diagnostic delay among PsA patients based on the year of diagnosis and identify potential demographic and clinical factors associated with this delay in a large population-based cohort.

Material method

Study design and data source

This cross-sectional study utilized data obtained from the Turkish League Against Rheumatism (TLAR)-Network, which is a comprehensive web-based multicenter registry covering a significant portion of the Turkey. The TLAR-Network provided a diverse dataset for conducting research in the field of PsA [10–13]. Data were collected from 25 secondary or tertiary referral centers specializing in rheumatology. The study protocol received approval from the Sakarya University Ethics Committee on January 25, 2018, with the protocol number of 42. Additionally, written informed consent was obtained from all participants involved in the study.

Inclusion and exclusion criteria

In this study, participants who met the following inclusion criteria were enrolled: being 18 years of age or older and fulfilling the ClASsification criteria for Psoriatic ARthritis (CASPAR) for PsA [14], as well as willingness to participate in the study. Exclusion criteria encompassed individuals with comorbidities that could significantly impact the assessment of outcomes, such as mental health disorders, malignancies, and other rheumatic diseases. Additionally, patients who were pregnant or lactating were also excluded from participation.

Outcome measures and assessments

In addition to demographic characterization, clinical features of PsA patients were recorded, including the presence of psoriasis, joint involvement, enthesitis, dactylitis, and extra-articular manifestations.

Multiple outcome measures were assessed during routine visits for patients with PsA. Disease activity was evaluated using standardized measures such as the Disease Activity in Psoriatic Arthritis (DAPSA), Minimal Disease Activity (MDA), Disease Activity Score-28—C-reactive protein (DAS28-CRP) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [15–17]. DAPSA is a well-established tool for assessing disease activity in PsA, taking into account the swollen/tender joint count, patient pain, patient global assessments, and CRP levels. The DAS28-CRP is a widely utilized composite measure for evaluating disease activity, comprising counts of 28 tender and swollen joints, CRP levels, and the patient's overall health assessment [18]. The MDA is another recognized measure to assess disease activity across multiple domains, including the swollen/tender joint count, skin involvement, physical function, pain, enthesis, and a general patient-based evaluation. The BASDAI, although primarily developed for ankylosing spondylitis, has also been utilized to assess disease activity in PsA, especially in cases with axial involvement. It consists of a questionnaire that evaluates several aspects of disease activity, including fatigue, spinal pain, joint pain/swelling, areas of localized tenderness, and the intensity and duration of morning stiffness. The Psoriasis Area Severity Index (PASI) was utilized to assess the severity and extent of skin involvement [19]. Functional impairment and quality of life were evaluated using the Health Assessment Questionnaire (HAQ) and Psoriatic Arthritis Quality of Life Questionnaire (PsAQoL), respectively [20, 21]. The Fibromyalgia Rapid Screening Tool (FiRST) was utilized to screen for fibromyalgia-related symptoms, including pain, fatigue,

and sleep disturbances [22]. The Visual Analog Scale (VAS) was used to assess pain and fatigue experienced by the PsA patients. The patient's global assessment (PtGA) and physician's global assessment (PhGA) were recorded to capture the overall assessment of disease activity and impact from both patient and physician perspectives [23]. Furthermore, psychological stress was assessed using the Hospital Anxiety and Depression Scale (HADS), which consists of two subscales: anxiety and depression. In the present study, predefined cutoff points were used to define the anxiety and depression subgroups (10 or above for anxiety and 7 or above for depression) [24]. Furthermore, the severity of fatigue and its impact on daily life were assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale [25].

Definition and categorization of diagnostic delay

Diagnostic delay is defined as the time interval between the onset of the first PsA-related symptoms and the diagnosis of PsA. To evaluate its impact on disease outcomes, the delay was classified into two predefined intervals based on clinical relevance: a delay of over 2 years and a delay of less than 2 years [5]. In addition, to investigate the temporal trends of diagnostic delay among PsA patients, the PsA patients were categorized into four groups based on the year of diagnosis: pre-2005, 2005–2009, 2010–2014, and 2015–2019.

Statistical analysis

The statistical analyses were conducted using the SPSS (Statistical Package for the Social Sciences) software package (version 23.0, IBM Corporation, Armonk, NY, USA). The normality of the data distribution was assessed using the Kolmogorov–Smirnov test. Descriptive statistics were employed to summarize the demographic and clinical characteristics of the patients. Variables were reported as *n* (%) for categorical data, mean ± standard deviation (SD) for normally distributed continuous data, and median (interquartile range [IQR]) for skewed continuous data for relevant cases. Differences between groups were evaluated using appropriate statistical tests including Pearson's Chi-square for categorical variables, *t* test for normally distributed continuous variables, Kruskal–Wallis for non-normally distributed continuous variables. Binary logistic regression analysis was employed to identify factors associated with diagnostic delay. First, univariate analysis was conducted to identify potential factors that may be associated with the outcome variable. Subsequently, these factors were included in a multivariate logistic regression analysis. The dependent variable in this analysis was diagnostic delay exceeding 2 years from symptom onset to diagnosis. The independent variables were considered as presence of low back pain, dactylitis, skin and nail symptoms at the first visit, age at symptom onset, level of the healthcare center of diagnosis (tertiary or secondary), educational status of the patients, family history of psoriasis and psoriatic arthritis, development of arthritis before skin manifestation and type of psoriasis. The results of the regression analysis are reported with odds ratios (OR) and confidence intervals (CI). A significance level of $p < 0.05$ was applied to establish statistical significance for all analyses.

Results

Demographic and clinical characteristics

A total of 1,134 patients with PsA participated in the analysis. In terms of gender distribution, 408 individuals (36.0%) were men, and 726 individuals (64.0%) were women. The mean (SD) age of the patients was 47.0 (12.3) years. The mean (SD) age at PsA symptom onset was 37.6 (12.9) years.

Diagnostic delay within various time frames

The mean (SD) diagnostic delay among patients with PsA was found to be 35.1(55.4) months, with a median (IQR) delay of 12 (48) months. Among these patients, 39.15% received their diagnosis within 3 months of symptom onset, and 43.30% within 6 months. The majority, constituting 56.7%, were diagnosed within 12 months from the onset of symptoms. Furthermore, out of the total patient population, 760 individuals (67.02%) experienced a diagnostic delay of 24 months or less, while 374 individuals (32.98%) encountered a delay exceeding 24 months. When comparing the two groups, patients with a diagnostic delay 24 months or less had a mean delay of 6.24 (8.41) months, whereas patients with a diagnostic delay exceeding 24 months had a mean delay of 93.84 (63.49) months which was noticeable longer.

Comparison of diagnostic delay of less or more than 24 months PsA

No significant differences were observed in gender, body mass index (BMI), educational level, acute phase reactions, history of extra-articular manifestations, PASI total scores, and disease activity measures, including DAPSA, between patients with PsA and a diagnostic delay of ≤ 24 months, compared to > 24 months. However, a history of IBD, PsAQoL, FACIT, BASDAI, PtGA, and PhGA scores were significantly higher in the group with a diagnostic delay > 24 months (Table 1).

Table 1 Comparison of clinical features, disease activity, and quality of life in patients with diagnostic delay ≤ 24 months and > 24 months

	Diagnostic delay ≤ 24 months ($n = 760$)	Diagnostic delay > 24 months ($n = 374$)	p
Patient characteristics			
Age, years	46.38 ± 12.51	48.13 ± 11.63	0.021
BMI, kg/m^2	28.67 ± 5.08	29.03 ± 4.92	0.253
Gender, male *n* (%)	275 (36.2)	133 (35.6)	0.837
Diagnostic delay, months	6.24 ± 8.41	93.84 ± 63.49	< 0.001
Education level, *n* (%)			0.077
Primary school or below	349 (45.9)	187 (50.0)	
Middle/high school	281 (37.0)	142 (38.0)	
Higher education	130 (17.1)	45 (12.0)	
Enthesitis current/past *n* (%), ($n = 1130$)	355 (47.0)	198 (52.9)	0.058
Dactylitis current/past *n* (%), ($n = 1130$)	219 (29.0)	106 (28.3)	0.823
IBD current/past *n* (%), ($n = 1130$)	11 (1.5)	12 (3.2)	0.049
Disease activity measures			
VAS pain score	4.61 ± 2.67	4.88 ± 2.5	0.093
Patient's global assessment	4.42 ± 2.56	4.75 ± 2.42	0.036
Physician's global assessment	3.82 ± 2.25	4.14 ± 2.16	0.023
CRP mg/L, ($n = 1085$)	8.2 ± 12.24	8.28 ± 12.64	0.916
DAS28, ($n = 1056$)	3.36 (1.25)	3.49 (1.17)	0.101
BASDAI total, ($n = 1019$)	3.84 ± 2.33	4.15 ± 2.23	0.043
DAPSA, $n = 1034$	16,69 ± 12.4	17.74 ± 13.08	0.22
DAPSA high disease activity, *n* (%)	96 (13.8)	57 ± 16.8)	0.212
MDA, *n* (%), ($n = 1060$)	140 (19.80)	56 (15.80)	0.113
PASI total score, ($n = 1027$)	3.1 ± 5.04	2.78 ± 4.22	0.262
Emotional well-being and quality of life			
HADS-A ≥ 10, *n* (%), ($n = 1128$)	174 (23.0)	96 (25.7)	0.319
HADS-D ≥ 7, *n* (%), ($n = 1128$)	372 (49.30)	202 (54.20)	0.123
HAQ	0.41 ± 0.45	0.45 ± 0.49	0.155
FiRST	2.41 ± 2.18	2.55 ± 2.21	0.322
FACIT score	18.69 ± 10.55	20.49 ± 10.97	0.009
PsAQoL score	6.58 ± 6.24	7.37 ± 6.38	0.048

n, sample size (number of participants); BMI, body mass index; VAS, Visual Analog Scale; CRP, C-reactive protein; DAS28, BASDAI, Disease Activity Score-28; Bath Ankylosing Spondylitis Disease Activity Index; DAPSA, Disease Activity in Psoriatic Arthritis; MDA, Minimal Disease Activity; PASI, Psoriasis Area and Severity Index; IBD, inflammatory bowel disease; HADS, Hospital Anxiety and Depression Scale; HAQ, Health Assessment Questionnaire; FiRST, Fibromyalgia Rapid Screening Tool; FACIT, Functional Assessment of Chronic Illness Therapy; PsAQoL, Psoriatic Arthritis Quality of Life Questionnaire. Data in the table are presented as mean ± SD or as n (%)

Temporal trends in diagnostic delays for PsA patients

The diagnostic delay duration was zero months for 417 (36.8%) patients, and the median diagnostic delay was determined for the remaining patients (Fig. 1). After categorizing the patients based on the year of diagnosis, it was found that patients diagnosed before the year 2010 experienced a median (IQR) diagnostic delay of 60 (96) months. Subsequently, for the period 2010–2014, the median (IQR) diagnostic delay decreased to 36.0 (72) months. Finally, between 2015 and 2019, the median (IQR) diagnostic delay further reduced to 24 (38.1) months. The median diagnostic delay for the period 2015–2019 was statistically lower than the median delays observed in the earlier periods ($p = 0.004$). Figure 2 illustrates the distribution of diagnostic delay and symptom duration among all PsA patients over time.

Factors associated with diagnostic delay in PsA

In the univariate logistic regression analysis, variables that were deemed significant and potentially associated with diagnostic delay were entered into the multivariate logistic regression analysis. These variables included: low back pain

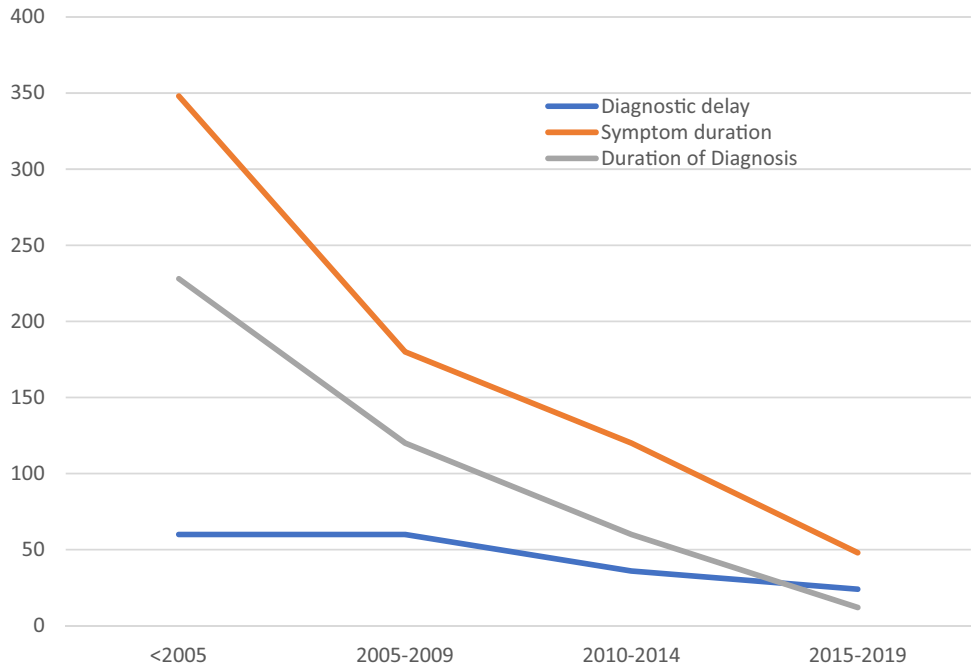

Fig. 1 The trends of median diagnostic delay, symptom duration, and duration of diagnosis over the years (date of diagnosis, < 2005 to 2019) among PsA cases with diagnostic delay > 0

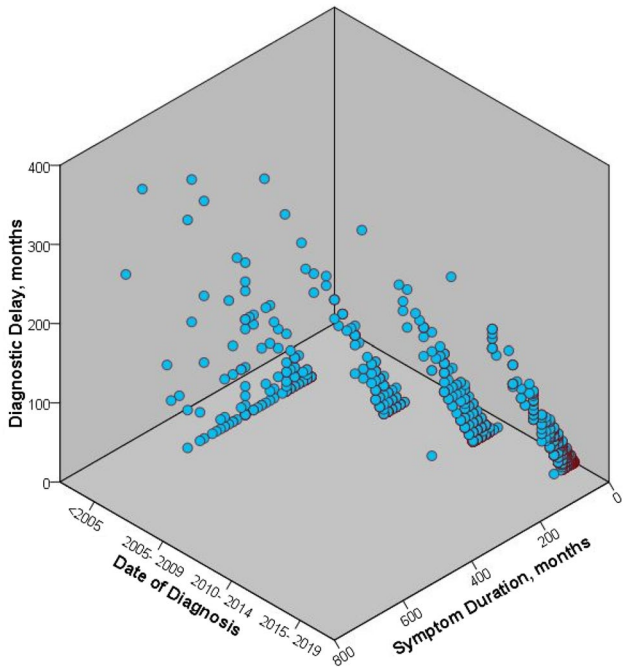

Fig. 2 Distribution of diagnostic delay and symptom duration among all PsA cases over time periods (date of diagnosis, < 2005 to 2019)

at first visit, dactylitis at first visit, skin and nail symptoms at first visit, age at symptom onset, tertiary or secondary center of diagnosis, educational status, family history of psoriasis and psoriatic arthritis, development of arthritis before skin manifestation, and type of psoriasis. The multivariate logistic regression analysis provided valuable insights into

Table 2 Factors associated with diagnostic delay in PsA

	Exp(B)	95% CI	*p*
Age of symptoms onset	0.956	0.945–0.967	< 0.001
Low back pain at first visit	1.597	1.209–2.111	0.004
Dactylitis at first visit	0.605	0.357–1.026	0.062
Generalized type psoriasis	0.253	0.065–0.977	0.046
Educational status			
Primary school or low	2.629	1.716–4.026	< 0.001
Middle/ high school	1.775	1.165–2.703	0.008
Arthritis before skin manifestation	1.717	1.198–2.462	0.003

the predictors of diagnostic delay in PsA (Table 2). Lower levels of education, specifically primary school education or less (OR 2.63, 95% CI 1.72–4.03), arthritis symptoms before skin manifestations (OR 1.72, 95% CI 1.20–2.46), and low back pain at first visit (OR 1.60, 95% CI 1.21–2.11) were associated with a diagnostic delay more than 2 years. Conversely, symptom onset age (OR 0.96% CI 0.95–0.97) and type of psoriasis particularly generalized psoriasis (OR 0.25, 95% CI 0.07–0.98) were negatively associated with a diagnostic delay in patients with PsA.

Discussion

In this study, we investigated diagnostic delay among PsA patients and identified potential factors associated with this delay in a large population-based cohort. Our findings carry significant implications for the field of PsA. Notably, we

pinpointed key factors associated with diagnostic delays, aiding clinicians in identifying high-risk patients and devising focused strategies to expedite diagnoses. In addition, our study highlights the need to account for regional and temporal variations when investigating PsA diagnostic delays, considering how healthcare systems, resources, awareness, and practices can influence timely diagnoses. Despite recent improvements in diagnostic timeliness, about one-third of PsA patients experienced delays exceeding 2 years. Furthermore, patients with prolonged diagnostic delays had higher levels of fatigue, lower quality of life, and increased disease activity, according to BASDAI, PtGA, and PhGA measurements.

In 2015, the nationwide Danish DANBIO registry conducted a comprehensive investigation, revealing a median diagnostic delay of 4.4 years (53 months) in patients with PsA [26]. In the following year, the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey reported an extended diagnostic delay of 5 years for PsA patients in North America and Europe [27]. In 2021, a systematic review and meta-analysis involving a wide range of 69 to 1970 individuals with PsA showed a mean diagnostic delay of approximately 2.6 years [28]. In addition, a small, retrospective, population-based cohort study conducted in Minnesota from 2000 to 2017 found a median time of 2.5 years from symptom onset to diagnosis in patients with PsA [5]. In our study, the mean diagnostic delay was found to be 35.1 months (median delay 12 months). However, it is noteworthy that a higher percentage of patients in our study received a diagnosis at 6 months, 1 year, and 2 years, compared to the other studies [5]. Overall, these findings show that diagnosis delay in PsA cases is still a major concern in many geographical regions and healthcare settings, highlighting the importance of better methods and tools for prediction to speed up the diagnosis process.

Early recognition and timely diagnosis of PsA play a crucial role in initiating appropriate treatment, preventing potential disease progression, and improving long-term outcomes [29, 30]. A noteworthy study involving 283 PsA patients made a significant observation: even a relatively short delay of 6 months in diagnosis resulted in more pronounced joint destruction and impaired long-term physical well-being [31]. Similarly, within our study, a comparison between patient with a diagnostic delay of 2 years or less and those with a delay exceeding 2 years in PsA revealed that the latter group experienced a higher level of fatigue, lower quality of life, and higher disease activity, as indicated by BASDAI, PtGA, and PhGA assessments. These data emphasize the negative consequences of a prolonged diagnosis delay in PsA and underline the importance of early detection and intervention. By addressing this delay, patient outcomes can be substantially improved.

Previous clinical trials investigated diagnostic delay in various rheumatic diseases and identified the multifaceted nature of this delay, involving patient, healthcare provider, and system-related factors [32–34]. However, within the context of PsA, it remains uncertain whether specific patient-related factors and disease characteristics significantly influence the extent of delay experienced by affected individuals. In 2015 and 2021, two separate population-based studies shed light on this matter, revealing insights into potential factors contributing to diagnostic delay. They found that an earlier age at the onset of PsA symptoms, higher BMI, low education level, and the presence of enthesitis were associated with a diagnostic delay of more than 2 years [5, 31]. In addition, our study further contributes to this topic by exploring factors that also contributed to diagnostic delays of more than 2 years in a comprehensive PsA population.

The study conducted by Haroon et al. in PsA patients confirms our finding of a significant association between lower levels of education and diagnostic delay in PsA [31]. This observation suggests that PsA patients with lower educational attainment may encounter challenges in recognizing early symptoms and seeking timely medical attention, resulting in delays in receiving a proper PsA diagnosis. Understanding this association highlights the importance of targeted educational interventions and public awareness programs to address diagnostic delays and improve overall disease management in PsA patients [35]. Moreover, our investigation has identified the presence of arthritis symptoms before skin manifestations as a potential factor associated with diagnostic delays in PsA. The resemblance of inflammatory arthritis symptoms in PsA with those present in other rheumatic diseases, such as spondyloarthritis (SpA) and rheumatoid arthritis (RA), may contribute to diagnostic delays, especially in PsA cases that skin manifestations are absent in the outset. Notably, PsA patients who presented with low back pain as their first symptom also experienced a diagnostic delay of more than 2 years. This finding aligns with a previous study and indicates that low back pain is often inadequately recognized as a symptom of PsA, leading to its attribution to more common non-inflammatory back pain conditions, such as degenerative diseases or fibromyalgia [36]. This delayed recognition and misattribution could potentially hinder timely diagnosis in PsA.

Conversely, our analysis revealed specific factors that were negatively associated with diagnostic delay in PsA patients. At younger age, the onset of PsA symptoms was linked to an increased probability of diagnostic delay in PsA. This observation was also confirmed by another population-based study in Olmsted County, Minnesota [5]. Younger patients might exhibit a tendency to overlook or underestimate symptoms related to PsA, potentially contributing to the delay in diagnosis. Additionally, certain psoriasis subtypes, particularly generalized psoriasis, were found to

be negatively associated with diagnostic delay. This finding implies that patients with this specific psoriasis subtype might be more likely to receive an earlier diagnosis of PsA.

The exploration of trends in diagnostic delay of PsA has been limited. The Danish nationwide DANBIO registry demonstrated a significant improvement in PsA diagnosis time from 2000 to 2011, with a notable reduction from 42 months (2000–2002) to 7 months (2009–2011). Conversely, a small population study in the US did not find any significant change in time to PsA diagnosis between 2000 and 2017 [5]. Our study examined diagnostic delay across four time periods: pre-2005, 2005–2009, 2010–2014, and 2015–2019. A remarkable reduction in PsA diagnosis time was observed, decreasing from median 60 months (pre-2005, 2005–2009) to 24 months (2015–2019). Notable improvement in diagnostic delay in the most recent year could potentially be associated with increased awareness of PsA, improvements in the healthcare system, and advancements in diagnostic tools. Moreover, our findings highlight the importance of considering regional and temporal variations when studying diagnostic delays in PsA, as different healthcare systems, resources, and strategies may contribute to differing outcomes in various countries or regions. Further research is needed to better understand the factors contributing to these variations and to design targeted approaches for addressing diagnostic delays in PsA.

The strength of our study lies in its utilization of data from a large nationwide registry, which allowed for a comprehensive analysis of diagnostic delay trends in PsA, providing robust and real-life experience. On the other hand, this study has some limitations. Given its cross-sectional study design, the results may not fully generalize to the entire PsA population and may restrict the establishment of causal relationships. The retrospective nature of the study may introduce uncertainty regarding recall bias when determining the exact onset of symptoms particularly in patients with longer disease duration. Moreover, it is important to acknowledge that diagnostic delay can be influenced by a range of factors, including healthcare accessibility, socioeconomic status, and patient-specific characteristics, which were not exhaustively explored in this study. Future research in this area should consider prospective longitudinal studies with larger and more diverse patient populations to validate these findings and explore potential predictors of diagnostic delay. These prospective studies may establish a strong contribution for developing highly targeted and personalized interventions.

In conclusion, notwithstanding recent improvements in diagnosis time, approximately one-third of PsA patients still experience diagnostic delays exceeding 2 years. Several factors, including education level, arthritis symptoms preceding skin manifestations, first visit symptoms, particularly low back pain, age of symptom onset, and psoriasis subtype were identified as significant factors associated with delayed diagnosis. By addressing these factors and enhancing early detection, healthcare professionals can significantly improve patient outcomes and patient well-being in PsA.

Author contributions Substantial contributions to the conception and design of the study: EK, GK, KN, İT. Acquisition of data and interpretation: all authors. Participation in data analysis: EK and GK. Drafting the manuscript: GK and EK. Critical revision for important intellectual content: all authors. Final approval of the version to be published: all authors. All authors take full responsibility for the integrity and accuracy of all aspects of the work.

Data availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no competing interest.

Ethical approval The protocols of this study were approved by local ethics committee (25.01.2018/42), and written informed consent was obtained from each participant. No part of this manuscript is copied or published elsewhere in whole or in part.

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