Clinical Rheumatology (2023) 42:385–390
https://doi.org/10.1007/s10067-022-06492-6

ORIGINAL ARTICLE

Mortality in psoriatic arthritis patients, changes over time, and the impact of COVID-19: results from a multicenter Psoriatic Arthritis Registry (PsART-ID)

Abdulsamet Erden[1] · Gizem Ayan[2] · Levent Kilic[2] · Dilek Solmaz[3] · Sibel Bakirci[4] · Gezmis Kimyon[5] · Esen Kasapoglu Günal[6] · Atalay Dogru[7] · Ozun Bayindir[8] · Ediz Dalkilic[9] · Cem Özisler[10] · Servet Akar[3] · Gözde Yildirim Cetin[11] · Emine Figen Tarhan[12] · Orhan Küçüksahin[13] · Ahmet Omma[14] · Emel Gonullu[15] · Fatih Yildiz[16] · Emine Duygu Ersozlu[17] · Muhammed Cinar[18] · Abdurrahman Tufan[19] · Seval Pehlevan[20] · Serpil Ergulu Esmen[21] · Sema Yilmaz[22] · Tuncay Duruoz[23] · Timucin Kasifoglu[24] · Veli Yazısız[25] · Kenan Aksu[8] · Sibel Zehra Aydin[26,27] · Umut Kalyoncu[2]

Received: 7 November 2022 / Revised: 19 December 2022 / Accepted: 21 December 2022 / Published online: 13 January 2023
© The Author(s), under exclusive licence to International League of Associations for Rheumatology (ILAR) 2023

Abstract

Background This study aimed to assess the mortality of PsA before and during the COVID-19 pandemic.

Methods From the prospective, multicenter PsART-ID (Psoriatic Arthritis Registry-International Database), patients from Turkey were analyzed by linking the registry to the Turkish Cause of Death Registry. The outcome of interest was death from any cause, pre-pandemic (since the onset of registry—March 2014–March 2020), and during the pandemic (March 2020–May 2021). The crude mortality rate and standardized mortality ratio (SMR) were determined.

Results There were 1216 PsA patients with a follow-up of 7500 patient-years. Overall, 46 deaths (26 males) were observed. In the pre-pandemic period, SMR for PsA vs the general population was 0.95 (0.61–1.49), being higher in males [1.56 (0.92–2.63)] than females [0.62 (0.33–1.17)]. The crude mortality rate in PsA doubled during the pandemic (pre-pandemic crude mortality rate: 5.07 vs 10.76 during the pandemic) with a higher increase in females (2.9 vs 8.72) than males (9.07 vs 14.73).

Conclusion The mortality in PsA was found similar to the general population in the pre-pandemic era. The mortality rates in PsA doubled during the pandemic. Whether PsA patients have more risk of mortality than the general population due to COVID-19 needs further studies.

Key Points

- *Decrease in mortality in PsA might be expected with the more effective treatment options and better disease control.*
- *A crude mortality rate is comparable to the general population and not increased until the pandemic.*
- *Currently, there is a 2-fold increase in crude mortality rate possibly due to the COVID-19.*

Keywords Mortality · Pandemic · Psoriatic arthritis · COVID-19

Introduction

Psoriatic arthritis (PsA) is associated with several co-morbidities, including cardiovascular disease, diabetes, and obesity [1]. With the improved health care for PsA patients, more effective treatment options, and better disease control, decrease in mortality rates might be expected. Supporting that, Ali et al. demonstrated that the standardized mortality ratios (SMR) in PsA was reduced by 0.56 (0.14–2.25) in the last decade [2].

In addition to the expected changes in mortality due to therapeutic advances over time, the SARS-CoV-2 pandemic was another major factor recently that may influence mortality rates. Within an inflammatory joint disease population, the absolute all-cause mortality during the first 6-month period of the pandemic was found higher than a period of 2015–2019, while the relative risks compared to the general population

✉ Umut Kalyoncu
umut.kalyoncu@yahoo.com

Extended author information available on the last page of the article

remained similar within the same periods [3]. The change in mortality rate in PsA with the COVID-19 is scarce.

The objective of this study was (a) to compare the rate of all-cause mortality of PsA patients during the pandemic and pre-pandemic period, (b) to explore the rate of all-cause mortality among patients with PsA in comparison to the general population, and (c) explore the reasons of death including COVID-19.

Materials and methods

Patients selection

PsART-ID (Psoriatic Arthritis-International Database) is an international multicenter registry that was initiated in Turkey in 2014, and was extended to Canada in 2015 and Italy in 2018 [4, 5]. From the PsART-ID registry, only patients from Turkey were included for this analysis by linking the registry with the administrative database (Turkish Cause of Death Registry).

Data collected within the registry included demographic data, clinical features, treatments, co-morbidities (hypertension, diabetes mellitus [DM], metabolic syndrome, hyperuricemia, coronary artery disease (CAD), depression), and smoking status. Disease activity parameters are collected including patient global disease activity visual analog scale (VAS), physician global disease activity VAS, pain VAS, fatigue VAS, swollen joint count (66 joints), and tender joint count (68 joints). Patient-reported composite indices such as BASDAI, BASFI, and HAQ-DI scores were also assessed.

This registry was conducted in accordance with the Declaration of Helsinki and approved by the local ethics board [Hacettepe University Ethics Board, Ankara (GO 14/578)] and informed consent was obtained from all patients before data collection.

Mortality causes and rates/ratios

The outcome of interest was death from any cause within the patients that were recruited to the registry was obtained from the "Turkish Cause of Death Registry (https://obs.saglik.gov.tr)." This is a central registry within the Ministry of Health where all deaths are recorded including the mortality as reported by the physicians.

Statistical analysis

The mortality rates were analyzed by crude mortality rate and SMR:

The crude mortality rate was calculated as the number of deaths in a specified period divided by the number of people exposed to the risk of death during that time given as per 1000 person-years. The crude mortality rate was assessed in three different periods, until May 2021 (whole period), between March 2020 and May 2021 (during pandemic), and until March 2020 (pre-pandemic).

SMRs (95% CI) was calculated as the ratio of deaths observed in a cohort to those expected in a group of the same size from the general population in the same area and standardized for age and sex of the individuals [6]. The mortality rate of the general population was retrieved from the data reported by Turkish Statistical Institute (TUIK) (https://data.tuik.gov.tr). The expected number of deaths was calculated as the total number of person-years contributed by the study population multiplied by the mortality rate of the general population. Since the mortality rate within TUIK is only available until the pandemic, therefore the SMR could only be calculated until March 2020 (pre-pandemic). The analysis was also provided by stratifying according to sex. All statistical analyses were performed using SPSS software, version 21 (IBM Corporation, Armonk, NY, USA), which was used to conduct all analyses.

Results

There were 1216 PsA patients recruited to the registry between 31 March 2014 and 7 May 2021. Demographics and disease characteristics are provided in Table 1. Total follow-up duration was calculated as 7500 patients-year (2577 patients-year for males, and 4923 patients-year for females).

All-cause mortality of PsA patients pre and during-pandemic period

Within the whole period, 46 deaths (3.9%) were observed with an overall crude mortality rate of 6.13. Thirty-one deaths occurred before the pandemic with an overall crude mortality rate of 5.07. There were 15 deaths during the pandemic, crude mortality rates reaching to 10.76. Therefore, there was an overall 2.12 fold increase in mortality rates with the pandemic (10.76 vs 5.07).

Regarding the change in the mortality with pandemic, crude mortality rates increased, 1.62 (14.73 vs 9.07) in males and 2.91 (8.72 vs 2.9) fold in females with COVID-19 (Table 2, Fig. 1).

Rate of all-cause mortality among patients with PsA in comparison to the general population

According to TUIK, the crude mortality rate within the general population was 5.3 [5.8 (male), 4.8 (female)] in

Table 1 Clinical features and outcome measures according to the survival status

	Whole group *n*:1216	Survival group *n*:1170	Non-survival group *n*: 46
Male, *n* (%)	424 (34.8)	398 (34)	26 (56.5)
Age, mean (SD), years	51.7 (12.6)	51.4 (12.5)	59.6 (12.5)
Age at PsA diagnosis, mean (SD), years	40.4 (13.1)	40 (12.9)	49.3 (12.9)
Age at psoriasis diagnosis, mean (SD), years	30.8 (14.8)	30.5 (14.7)	37.2 (16.2)
Follow-up duration at PsART-ID (year)	6.4 (0.6)	6.4 (0.5)	3.92 (3.8)
PsA duration, years	9.3 (6.4)	9.3 (6.5)	8.2 (9.2)
Psoriasis duration, years	18.3 (15.5)	18.3 (15.4)	18.7 (22.1)
Duration of education, years	8 (6)	8 (7)	5 (3)
Body Mass Index	27.6 (6.3)	27.7 (6.3)	29.3 (6.1)
Swollen joint counts (0–66),	1 (3)	1 (3)	2 (4)
Tender joints count (0–68)	2 (6)	2 (6)	3 (5)
BASFI (0–100)	16 (40)	15 (40)	26.5 (44)
Patient global assessment (VAS) (0–100)	40 (50)	40 (50)	50 (70)
Physician global assessment (VAS) (0–100)	30 (50)	30 (50)	30 (50)
Fatigue (VAS) (0–100)	40 (55)	40 (52)	40 (70)
Pain (VAS), (0–100)	50 (50)	50 (50)	50 (40)
HAQ-DI, (0–3)	0.75 (1)	0.75 (1)	1 (1.1)
ESR mm/h	21 (26)	20 (26)	34 (22)
CRP mg/l	4 (11.3)	4 (10.3)	8.5 (17)
At least one comorbidity *n* (%)	584 (48)	543 (46.3)	41 (89.1)
Presence of Hypertension, *n* (%)	264 (21.7)	239 (20.5)	25 (54.3)
Presence of metabolic syndrome, *n* (%)	138 (11.3)	125 (10.7)	13 (28.3)
Presence of coronary artery disease, *n* (%)	45 (3.7)	32 (2.7)	13 (28.3)
Presence of diabetes mellitus, *n* (%)	170 (13.9)	153 (13.1)	17 (37)
Presence of depression, *n* (%)	204 (16.8)	192 (16.5)	12 (26.1)
Presence of hyperlipidemia, *n* (%)	215 (17.6)	196 (16.8)	19 (41.3)
Presence of hyperuricemia, *n* (%)	79 (6.5)	71 (6.1)	8 (17.4)
Presence of cerebrovascular disease, *n* (%)	14 (1.2)	13 (1.1)	1 (2.2)

VAS, visual analog scale; *BASFI*, Bath Ankylosing Spondylitis Functional Index; *ESR*, erythrocyte sedimentation rate; CRP, C-reactive protein; *SD*, standard deviation; *IQR*, interquartile range

Values are given in median (IQR) unless otherwise stated

Table 2 Numbers of death within psoriatic arthritis patients stratified by dates

	March 2014–May 2021 (whole period)			March 2020–May 2021 (during pandemic)			March 2014–March 2020 (pre-pandemic)		
	Overall	Male	Female	Overall	Male	Female	Overall	Male	Female
Patients number	1216	424	792	1185	405	780	1216	424	792
Follow-up duration (person × year)	7500	2577	4923	1393	476	918	6107	2102	4006
Death number	46	26	20	15	7	8	31	19	12

PsART-ID: Psoriatic arthritis registry international database: NA: Not available

the pre-pandemic period. Overall SMR for PsA vs the general population was 0.95 (0.61–1.49), being higher in males [male: 1.56 (0.92–2.63)] than females [female: 0.62 (0.33–1.17)].

Causes of death in PsA and risk factors

The most common reasons were cardiac ($n=23$) and infections ($n=23$). With decreasing order, the cause of death was

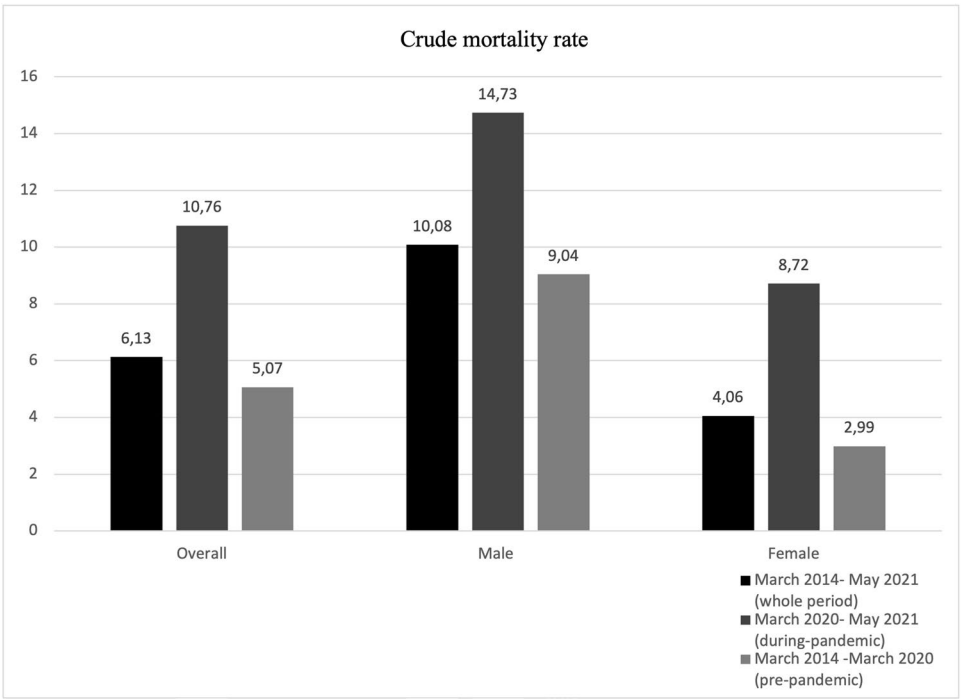

Fig. 1 Change in crude mortality rate over time

pulmonary ($n=12$), malignancy ($n=11$), renal ($n=6$), hepatobiliary ($n=5$), and other causes ($n=5$). Interestingly, 6% of the deaths were caused by pulmonary reasons in the pre-pandemic period, while it was 66% during the pandemic. In six patients, the underlying reason was COVID-19. The details of mortality causes and medications that the patients were on in pre- and during pandemic are given in Supplementary Table 1.

Death occurred more often in male patients (56.5% vs 34%, $p=0.002$) with higher crude mortality rate in each period compared to females. Mortality was linked to older age ($p=<0.0001$), being less educated ($p=0.004$), and higher acute phase reactants ($p=0.002$ for erythrocyte sedimentation rate; $p=0.018$ for C-reactive protein). Moreover, significantly higher metabolic comorbidities ($p=<0.0001$ for hypertension, DM, CAD metabolic syndrome, hyperlipidemia; $p=0.002$ for hyperuricemia) were seen in the non-survival group (Table 1).

Six patients (F: M = 3:3) died from COVID-19 during pandemic. Patients were aged between 39 and 73.8 years and three of them were never smokers. Five patients had at least one metabolic comorbidity and one patient had an additional malignancy. At the time of death, two patients were treated with biologics (both infliximab) (Supplementary Table 2).

Discussion

This large multicentric PsA cohort showed that the crude mortality rate has doubled during the pandemic. This study added important information about the impact of COVID-19, on the mortality of PsA patients.

Global results showed approximately 15–20% increased mortality in general population during the COVID-19 era [7]. Similar to these observations, significantly increased SMRs were observed in several regions of the world related to the COVID-19 [8]. A current report showed similar results with higher absolute all-cause mortality in inflammatory rheumatic diseases in the pandemic, but relative risks remained similar compared to the general population.[3] Our PsA population showed an approximate of 100% of increased crude mortality, which suggests that PsA patients may be at increased risk of mortality compared to general population. The increased mortality during the pandemic in PsA can be explained by the nature of the disease itself or medications used. In general, mortality during the COVID-19 infection is also more commonly observed in patients with pre-existing comorbidities [9]. Since patients with PsA have higher risk of metabolic comorbidities, this may also be an important factor to increase the risk of mortality in PsA. Moreover, the global efforts to restrict the pandemic may have prevented these patients from attending regular follow-up visits with their either rheumatologist or specialists taking care of their other comorbidities, which may have prevented timely recognition of potential complications. Whether PsA patients have a specific risk for mortality due to COVID-19 can only be understood by doing a direct comparison with the general population. Unfortunately, mortality rates during the pandemic in the Turkish general population have not been declared yet and we could not calculate the SMR in PsA patients in this period.

Our limitations are the lack of data for mortality in the Turkish population during the pandemic and low overall mortality rates that does not allow us to analyze the risk factors of death. Another limitation is the lack of the comorbidity assessment using a specific index, however we could provide the comparison of metabolic comorbidities which is strongly related to COVID-19-related mortality. In addition, the causes of mortality have been collected from the administrative database which can be subject to reporting bias. However, the administrative database, Turkish Cause of Death Registry, has been capturing the mortality data in the same way from its initiation; therefore, the comparison mortality rates before and during the pandemic is not expected to be affected with any biases.

As a result, mortality in PsA showed that there was a crude mortality rate comparable to the population and not increased until the pandemic. However, there is a twofold increase in crude mortality rate compared to the pre-pandemic period in PsA, possibly due to the COVID-19. Our assessment period within pandemic includes the time which the vaccination is not widely accessible. Whether PsA patients have an excess risk of death during the pandemic, what is the impact of vaccination requires a further study that compares mortality rates in PsA vs the general population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10067-022-06492-6.

Acknowledgements We would like to thank all collaborators for their participation. Collaborators: All authors contributed to data collection only. Soner Senel, Senol Kobak, Salim Donmez, Ridvan Mercan. Muge Aydin Tufan, Meryem Can, Lutfi Akyol, Ismail Dogan. Hamide Kart Koseoglu, Funda Erbasan, Bunyamin Kisacik, Baris Yilmazer, Ayse Balkarli, Ali Sahin, Ahmet Mesut Onat, Adem Kucuk, Sukran Erten

Author contribution Abdulsamet Erden, Gizem Ayan, Sibel Zehra Aydin, and Umut Kalyoncu have made substantial contributions to the conception and design of the work and the acquisition, analysis, and interpretation of data for the work; have drafted the work and revised it critically for important intellectual content; and approved the final version to be published.

Levent Kilic, Dilek Solmaz, Sibel Bakirci, Gezmis Kimyon, Esen Kasapoglu Günal, Atalay Dogru, Özün Bayindir, Ediz Dalkilic, Cem Özisler, Servet Akar, Gözde Yildirim Cetin, Emine Figen Tarhan, Orhan Küçüksahin, Ahmet Omma, Emel Gonullu, Fatih Yildiz, Emine Duygu Ersozlu, Muhammed Cinar, Abdurrahman Tufan, Seval Pehlevan, Serpil Ergulu Esmen, Sema Yilmaz, Tuncay Duruoz, Timucin Kasifoglu, Veli Yazısız, and Kenan Aksu have made substantial contributions to the acquisition, and interpretation of data for the work; have drafted the work and revised it critically for important intellectual content; and approved the final version to be published.

Data Availability Data are available upon reasonable request.

Compliance with ethical standards

Ethical approval This study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics board [Hacettepe University Ethics Board, Ankara (GO 14/578)] and informed consent was obtained from all patients before data collection.

Competing interests Sibel Zehra Aydin received honoraria from Abbvie, Celgene, UCB, Novartis, Jannsen, Pfizer, Eli Lilly and Sanofi, research grants from Abbvie, Jannsen, Novartis, Eli Lilly, UCB, Pfizer, Sanofi. Emine Duygu Ersozlu received honoraria from Abbvie, Pfizer, Amgen, MSD and Veli Yazisiz received honoraria from Abbvie, Pfizer, UCB, Novartis, MSD. The other authors declared no competing interests.

References

1. Gupta S, Syrimi Z, Hughes DM, Zhao SS (2021) Comorbidities in psoriatic arthritis: a systematic review and meta-analysis. Rheumatol Int 41:275–284. https://doi.org/10.1007/s00296-020-04775-2
2. Ali Y, Tom BD, Schentag CT, Farewell VT, Gladman D (2007) Improved survival in psoriatic arthritis with calendar time. Arthritis Rheum 56:2708–2714. https://doi.org/10.1002/art.22800
3. Bower H, Frisell T, Di Giuseppe D et al (2021) Impact of the COVID-19 pandemic on morbidity and mortality in patients with inflammatory joint diseases and in the general population: a nationwide Swedish cohort study. Ann Rheum Dis 80:1086–1093. https://doi.org/10.1136/annrheumdis-2021-219845
4. Kalyoncu U, Bayindir Ö, Ferhat Öksüz M et al (2017) The Psoriatic Arthritis Registry of Turkey: results of a multicentre registry on 1081 patients. Rheumatology (Oxford) 56:279–286. https://doi.org/10.1093/rheumatology/kew375
5. Bakirci S, Ayan G, Gazel U, Tinazzi I, Solmaz D, Kasapoglu E, Kalyoncu U, Aydin SZ (2021) Patient characteristics and minimal disease activity in psoriatic arthritis: a transcontinental comparison. Clin Rheumatol 40:3169–3174. https://doi.org/10.1007/s10067-021-05648-0
6. Mok CC, Kwok CL, Ho LY, Chan PT, Yip SF (2011) Life expectancy, standardized mortality ratios, and causes of death in six rheumatic diseases in Hong Kong, China. Arthritis Rheum 63:1182–1189. https://doi.org/10.1002/art.30277
7. Aron JM, J (2020) Transatlantic excess mortality comparisons in the pandemic. INET Oxford Working Paper No-18 https://ourworldindata.org/covid.excess.mortality. Accessed 9 Jan 2023
8. Morfeld P, Timmermann B, Groß JV, Lewis P, Cocco P, Erren TC (2021) COVID-19: heterogeneous excess mortality and "burden of disease" in Germany and Italy and their states and regions, January–June 2020. Front Public Health 9:663259. https://doi.org/10.3389/fpubh.2021.663259
9. Khan MMA, Khan MN, Mustagir MG, Rana J, Islam S, Kabir I (2020) Effects of underlying morbidities on the occurrence of deaths in COVID-19 patients: a systematic review and meta-analysis. J Glob Health 10:020503. https://doi.org/10.7189/jogh.10.020503

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

Authors and Affiliations

Abdulsamet Erden[1] · Gizem Ayan[2] · Levent Kilic[2] · Dilek Solmaz[3] · Sibel Bakirci[4] · Gezmis Kimyon[5] · Esen Kasapoglu Günal[6] · Atalay Dogru[7] · Ozun Bayindir[8] · Ediz Dalkilic[9] · Cem Özisler[10] · Servet Akar[3] · Gözde Yildirim Cetin[11] · Emine Figen Tarhan[12] · Orhan Küçüksahin[13] · Ahmet Omma[14] · Emel Gonullu[15] · Fatih Yildiz[16] · Emine Duygu Ersozlu[17] · Muhammed Cinar[18] · Abdurrahman Tufan[19] · Seval Pehlevan[20] · Serpil Ergulu Esmen[21] · Sema Yilmaz[22] · Tuncay Duruoz[23] · Timucin Kasifoglu[24] · Veli Yazısız[25] · Kenan Aksu[8] · Sibel Zehra Aydin[26,27] · Umut Kalyoncu[2]

1 Department of Internal Medicine, Division of Rheumatology, Ministry of Health Ankara City Hospital, Ankara 06800, Turkey

2 Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Hacettepe University Medical School, Sihhiye, Ankara 06100, Turkey

3 Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Izmir Katip Celebi University, Izmir, Turkey

4 Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Antalya Training and Research Hospital, Antalya, Turkey

5 Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Mustafa Kemal University, Antakya, Hatay, Turkey

6 Medeniyet University, Goztepe Research and Training Hospital, Istanbul, Turkey

7 Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Suleyman Demirel University, Isparta, Turkey

8 Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ege University, Izmir, Turkey

9 Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Uludag University, Bursa, Turkey

10 Department of Internal Medicine, Division of Rheumatology, Diskapi Yildirim Beyazit Education and Research Hospital, Ankara, Turkey

11 Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey

12 Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Mugla Sitki Kocman University, Mugla, Turkey

13 Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara Yildirim Beyazit University, Ankara, Turkey

14 Department of Internal Medicine, Division of Rheumatology, Ankara Numune Education and Research Hospital, Ankara, Turkey

15 Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Sakarya University, Sakarya, Turkey

16 Department of Internal Medicine, Division of Rheumatology, University of Health Sciences, Van Training and Research Hospital, Van, Turkey

17 Department of Internal Medicine, Division of Rheumatology, Adana Numune Training and Research Hospital, Adana, Turkey

18 Department of Internal Medicine, Division of Rheumatology, Gülhane Training and Research Hospital, Ankara, Turkey

19 Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Gazi University, Ankara, Turkey

20 Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Fatih University, Istanbul, Turkey

21 Department of Internal Medicine, Division of Rheumatology, Konya Education and Research Hospital, Konya, Turkey

22 Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Selcuk University, Konya, Turkey

23 Faculty of Medicine, Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Marmara University, Istanbul, Turkey

24 Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Eskisehir Osmangazi University, Eskisehir, Turkey

25 Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology,, Akdeniz University, Antalya, Turkey

26 Faculty of Medicine, Division of Rheumatology, University of Ottawa, Ottawa, ON, Canada

27 The Ottawa Hospital Research Institute, 1967 Riverside Drive, Ottawa, ON K1H 7W9, Canada