

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

Ankara City Hospital

Gizem Ayan

Hacettepe University

Levent Kilic

Hacettepe University

Dilek Solmaz

Izmir Katip Celebi University

Sibel Bakirci

Antalya Training and Research Hospital

Gezmiş Kimyon

Mustafa Kemal University

Esen Kasapoglu Günel

Medeniyet University Goztepe Research and Training Hospital

Atalay Dogru

Suleyman Demirel University

Özün Bayindir

Ege University

Ediz Dalkilic

Uludag University

Cem Özisler

Diskapi Yildirim Beyazit Education and Research Hospital

Servet Akar

Izmir Katip Celebi University

Gözde Yildirim Cetin

Kahramanmaraş Sutcu Imam University

Emine Figen Tarhan

Mugla Sitki Kocman University

Orhan Küçüksahin

Ankara Yildirim Beyazit University

Ahmet Omma

Ankara Numune Education and Research Hospital

Emel Gonullu

Sakarya University

Fatih Yildiz

University of Health Sciences, Van Training and Research Hospital

Emine Duygu Ersozlu

Adana Numune Training and Research Hospital

Muhammed Cinar

Gülhane Training and Research Hospital

Abdurrahman Tufan

Gazi University

Seval Pehlevan

Fatih University

Serpil Ergulu Esmen

Konya Education and Research Hospital

Sema Yilmaz

Selcuk University

Tuncay Duruoç

Marmara University

Timucin Kasifoglu

Osmangazi University

Veli Yazısız

Akdeniz University

Kenan Aksu

Ege University

Sibel Zehra Aydın

University of Ottawa Faculty of Medicine

Umut Kalyoncu (✉ umut.kalyoncu@yahoo.com)

Hacettepe University

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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.

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 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, 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 includes demographic data, clinical features, treatments, co-morbidities (hypertension, diabetes mellitus [DM], metabolic syndrome, hyperuricemia, coronary artery disease (CAD), depression), 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 are 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 for 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-May 2021 (during-pandemic), until March 2020 (pre-pandemic).

SMRs (95% CI) is 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, 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 was 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) 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, 2.91(8.72 vs 2.9) folds in females with COVID-19 (Table-2, Figure).

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 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 pulmonary (n = 12), malignancy (n = 11), renal (n = 6), hepatobiliary (n = 5), other causes (n = 5). Interestingly 6% of the deaths 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 detail of mortality causes and medications that the patients were on in pre and during-pandemic 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), 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 39-73.8 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. 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. In addition, since the causes of mortality have been collected from the administrative database, it is subject to reporting bias. However, the Turkish Cause of Death Registry captures all the mortality data, 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 2-fold increase in crude mortality rate compared to the pre-pandemic period in PsA, possibly due to the COVID-19. Whether PsA patients have an excess risk of death during the pandemic, requires a further study that compares mortality rates in PsA vs the general population.

Declarations

Acknowledgments: We would like to thank all collaborators for their participation. Collaborators: All authors contributed to data collection only.

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Competing interests: Sibel Zehra Aydin received honoraria from Abbvie, Celgene, UCB, Novartis, Janssen, Pfizer, Eli Lilly and Sanofi, research grants from Abbvie, Janssen, 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.

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Author contributions: 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; approved the final version to be published.

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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.

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Tables

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/hour	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)
<p>VAS; visual analog scale, BASFI: Bath ankylosing spondylitis functional index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, SD: Standard deviation, IQR: Interquartile range</p> <p>• Values are given in median (IQR) unless otherwise stated</p>			

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 (personxyear)	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									

Figures

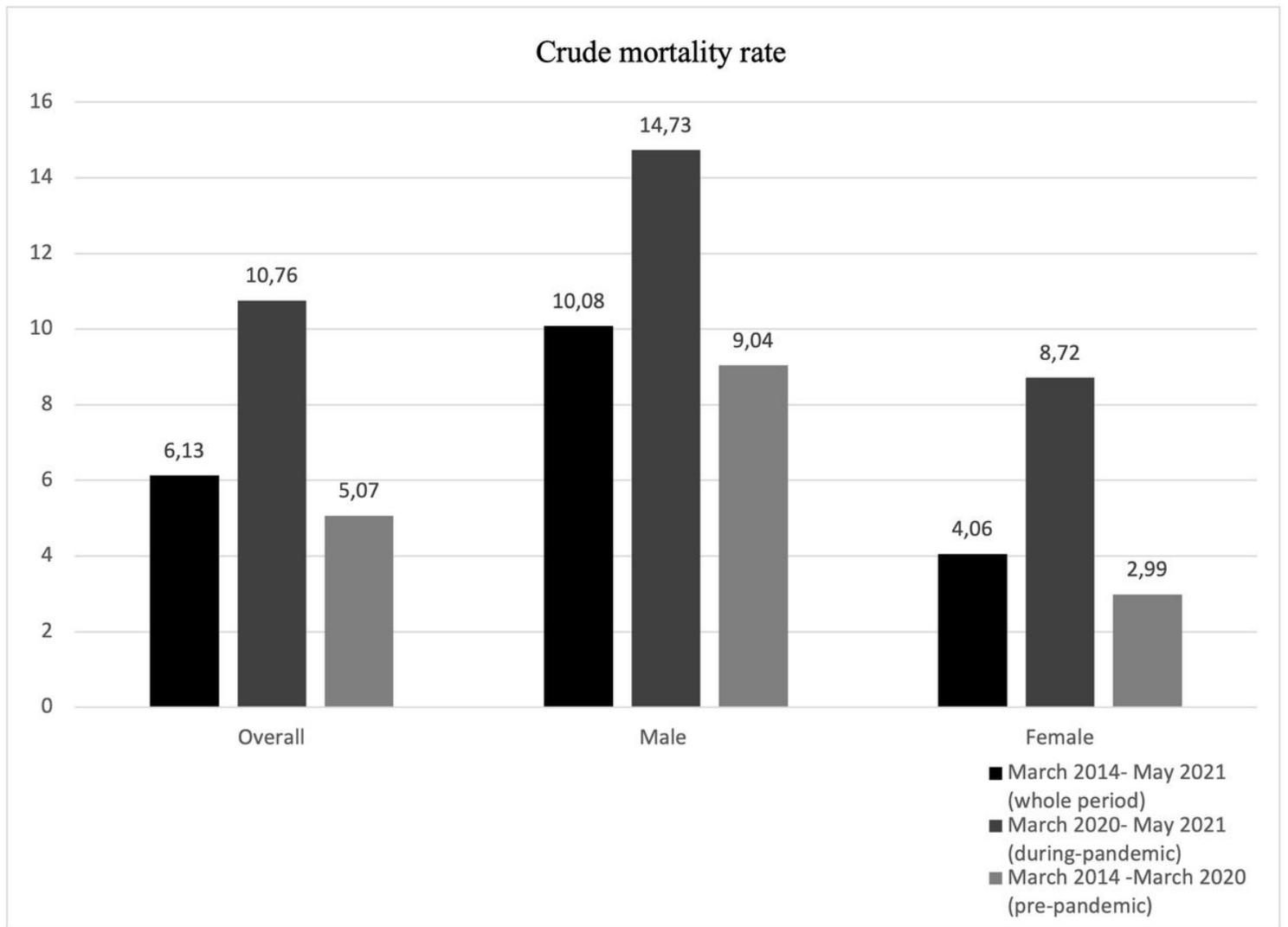


Figure 1

Change in crude mortality rate over time

Supplementary Files

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- [SupplementaryMaterial.docx](#)