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Polypharmacy and Potential Drug-Drug Interactions in Patients with Psoriatic Arthritis

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ABSTRACT

Background: Psoriatic arthritis (PsA) is an inflammatory arthropathy linked to psoriasis and typically negative for rheumatoid factor. Patients with PsA are at a higher risk of polypharmacy due to comorbidities and widespread pain. This growing health problem leads to negative outcomes like increased mortality, falls, medication adverse effects, prolonged hospital stays, and re-admission after discharge.
Objectives: Assessment of polypharmacy in patients with PsA, its relation to patient characteristics, and the potential for undesirable interactions between drugs used to treat PsA and those used for other conditions.
Methods: A cross-sectional study was conducted at the Rheumatology Unit of Baghdad Teaching Hospital/Medical City Complex, during the period from January 2023 to January 2024. The study included 100 adult PsA patients diagnosed according to the Classification of Psoriatic ARthritis (CASPAR) criteria. The demographic and disease-related characteristics were collected using a pre-constructed data collection document. Polypharmacy was defined as the concurrent use of at least five drugs irrespective of their duration. The drug interaction checker® of Medscape's database was used to assess the drug-drug interactions.
Results: Sixty-three of the 100 PsA (63%) patients exhibited polypharmacy, and there were 236 potential drug-drug interactions. The majority of these interactions were due to the use of methotrexate with folic acid, NSAIDs, and PPIs. Drug interactions were less frequent with the tumor necrosis factor (TNF) inhibitor.
Conclusion: The prevalence of polypharmacy was elevated among PsA patients. Polypharmacy was significantly correlated with patient age, peripheral disease activity, and the existence of comorbidity. Polypharmacy was linked to an increased risk of possible drug-drug interactions.

Introduction

Psoriatic arthritis (PsA) is a type of inflammatory arthritis associated with skin psoriasis and is generally classified under the spondyloarthropathy (SpA) group. It is typically negative for rheumatoid factor [1]. The reported prevalence of PsA among patients with psoriasis is 23.8%. It is nearly equally distributed between males and females, typically affecting individuals aged 30 to 60 years [2]. In addition to joint and skin symptoms, many patients with PsA have multiple comorbid conditions, including cardiometabolic diseases, uveitis, inflammatory bowel disease (IBD), malignancies, infections, and fibromyalgia. Recognizing and properly managing these comorbidities is crucial, as they can significantly impact the overall prognosis and outcomes for patients with PsA [3].

Polypharmacy refers to the prescription of multiple medications for an individual. Fifty percent of people over the age of 65 are prescribed five or more drugs. This has increased four times in the previous twenty years [4]. Polypharmacy has been defined in a variety of ways,

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including absolute quantitative measurements (often five or more drugs) and outcome-based measures (mostly the appropriateness of the medications). A quantitative definition has been implemented because the investigator was unable to obtain access to the medical records of patients, and thus, a qualitative decision on the appropriateness of the used drugs was not possible [5].

Polypharmacy has been linked to negative consequences such as an increased risk of falls, prolonged hospital stay, higher healthcare costs, readmission after discharge, medication interactions, medication adverse effects, loss of medication adherence, reduced functional capacity, and higher mortality rates. [6] [7]. Patients with rheumatic conditions are at increased risk of polypharmacy and its consequences, like adverse effects, drug interactions, and poor outcomes. A drug-drug interaction (DDIs) happens when the combined effects of multiple drugs (two or more) differ from their individual effects. These effects can occur at any stage (absorption, distribution, metabolism, or excretion). Despite the potential harmful complications of drug interactions, they are commonly overlooked [8]. Almost 1/3 of older people have what is known as the "iatrogenic triad" of polypharmacy, the use of inappropriate medications, and medication interactions, highlighting the significant effect of this problem on public health [9]. A study done by Sherin *et al*. on 150 psoriatic patients showed that those patients with the associated comorbidities, including PsA, had an increased number of DDIs, which can affect the therapeutic response [10].

Psoriatic arthritis patients have a high risk of polypharmacy due to their associated comorbidities and widespread pain. A study that included 73 patients with PsA found that 83.6% of them had polypharmacy in the 6th month of treatment [11]. Other studies demonstrated that PsA patients had an increased prevalence of polypharmacy, which was associated with increased age and the number of associated comorbidities and had a negative impact on their quality of life [12] [13]. The aim of study is to quantify polypharmacy in a group of PsA patients and to evaluate its correlation with the characteristics of the patients, and to assess the risk of potential undesirable interactions between medications used for managing PsA and those used for chronic and non-chronic indications.

Methods

This is a cross-sectional study conducted at the Rheumatology Unit of Baghdad Teaching Hospital/Baghdad Medical City over the period from January 2023 to January 2024.

The study included a total of 100 patients with an age of ≥18 years previously diagnosed with PsA according to the Classification of Psoriatic Arthritis (CASPAR) criteria (inflammatory articular disease plus ≥3 points from features like psoriasis, nail dystrophy, negative RF, dactylitis, and juxta-articular new bone formation) and the diagnosis of PsA was confirmed by a rheumatologist. The study excluded patients who had difficulties with communication and those who refused to participate.

Sociodemographic variables such as age, gender, residency, marital status, level of education, employment, smoking status, and alcohol use were reported. Also, BMI, disease duration, comorbidities, drugs used to treat PsA, and other prescribed or nonprescribed drugs were considered at the time of the study. Patients were assessed in the rheumatology unit for domains of PsA (peripheral arthritis and its patterns, axial PsA, dactylitis, enthesitis, IBD confirmed by a gastroenterologist, and uveitis confirmed by an ophthalmologist) and disease activity using the Disease Activity in Psoriatic Arthritis (DAPSA) score. The score categorized the patients as follows:

1. Remission (DAPSA ≤ 4)
2. Low disease activity (DAPSA > 4 and ≤ 14)
3. Moderate disease activity (DAPSA > 14 and ≤ 28)

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4. High disease activity (DAPSA > 28)

Axial disease activity was measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), where scores less than 4 represent mild or inactive disease, while scores 4 or more represent active disease.

The patients will be categorized based on the presence or absence of polypharmacy, taking into account the maximum number of drugs utilized. In this study, polypharmacy was defined as the concurrent use of at least five medications, irrespective of the duration of their use [14]. Topical drugs, home remedies, and ophthalmic preparations were not considered in the assessment.

The study investigated the possibility of medication interactions between those used to treat PsA and those used to treat the associated chronic diseases and non-chronic conditions. The drugs used to treat non-chronic conditions are those that were used at any point during the study, but do not indicate use in chronic conditions.

The drug interaction checker® in Medscape's database [15] was used to assess the possible interactions between the medications. Drug interactions were categorized as "contraindicated," in which the combination should be avoided; "serious interaction," in which it is preferred to use alternative agents; "significant interaction," in which close monitoring is required; or "minor interaction," in which the interaction is not clinically significant and only regular monitoring may be needed.

Statistical analysis

Statistical Package for Social Science version 26 (SPSS 26) ® from IBM® was used for data entry and analysis. The Shapiro-Wilk test was used to assess the normality of data distribution. The categorical variables were represented as frequencies and percentages, whereas the numeric variables were represented as means. Pearson Chi-Square test (or Fisher's exact test when appropriate) was used to assess the significance of the association between categorical (qualitative) variables. Correlation between continuous variables was tested by the Pearson test (or Spearman's rank test when appropriate). Binary logistic regression analysis was performed to determine the variables associated with the increased prevalence of polypharmacy. *A p*-value less than 0.05 was considered significant**.**

Results

Demographic characteristics of patients

One hundred adult PsA patients were included in this study. The mean age of patients was 43.37±11.318 years, ranging from 21 to 74 years. The mean for BMI was 30.29±5.37 Kg/m^2 [table1].

Table 1: Demographic characteristics

	Variable	No.	%
Age (in years)	18-40	38	38.0
	>40	62	62.0
Gender	Female	49	49.0
	Male	51	51.0
Weight groups (BMI kg/ m^2)	< 18.5	1	1.0
	18.5-24.9	13	13.0
	25-29.9	38	38.0
	≥30	48	48.0
Marital status	Single	10	10.0
	Married	85	85.0
	Divorced	1	1.0
	Widowed	4	4.0

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Residency	Urban	92	92.0
	Rural	8	8.0
Employment	No	54	54.0
	Yes	46	46.0
Smoking	Smoker	26	26.0
	Ex-smoker	9	9.0
	Never smoked	65	65.0

PsA-related characteristics

Disease duration and disease activity

The mean disease duration was 8.6 years (range from 3 months to 37 years), the interquartile range was 8 years, and the median was 7 years. The mean, median, and interquartile range for disease activity measured by DAPSA were [17.64 (± 10.66), 15.21, and 12.35], respectively, and by BASDAI were [4.15 (1.66), 4.2, and 2.2], respectively.

Disease activity varied among patients with PsA. For those with peripheral activity measured by DAPSA, 4.3% were in remission, 40.9% had low disease activity, 37.6% had moderate disease activity, and 17.2% had high disease activity. Axial disease activity measured by BASDAI showed that 56.4% had an active disease while 43.6% had inactive or mild disease.

Comorbidities associated with PsA

Comorbidities were present in 66%, with 50% having one comorbidity and 50% having two or more comorbidities.

Domains and patterns of PsA

Twenty-three (23%) of patients had two affected domains, 38% had three affected domains, and 39% had more than three affected domains. Skin and/or nail and peripheral joints were the most commonly affected domains in 99% and 93% of patients, respectively. The least affected domains were the eyes (in the form of uveitis) and gastrointestinal tract (in the form of IBD) at percentages of 6% and 1%, respectively.

Polyarticular arthritis was the most common pattern, representing 54% of patients, while oligoarticular arthritis was present in 31% of patients. Thirty-nine percent of patients exhibited axial involvement, 32% had combined axial and peripheral involvement, and 7% had isolated axial involvement. Distal interphalangeal (DIP) joint involvement and arthritis mutilans patterns were the least common patterns at a percentage of 5% and 3%, respectively.

The mean number of medications used was 5.5± 2.92, with a median of 5 drugs ranging from 1–15 drugs, and the interquartile range was 4. Polypharmacy has been detected in 63% of patients [Figure 1].

A significant positive correlation between age (correlation coefficient = 0.380, *P*-value < 0.001), comorbidities (correlation coefficient = 0.606, *P*-value < 0.001), and disease activity measured by DAPSA score (correlation coefficient = 0.316, *P*-value 0.002) and the number of medications used [figure 2].

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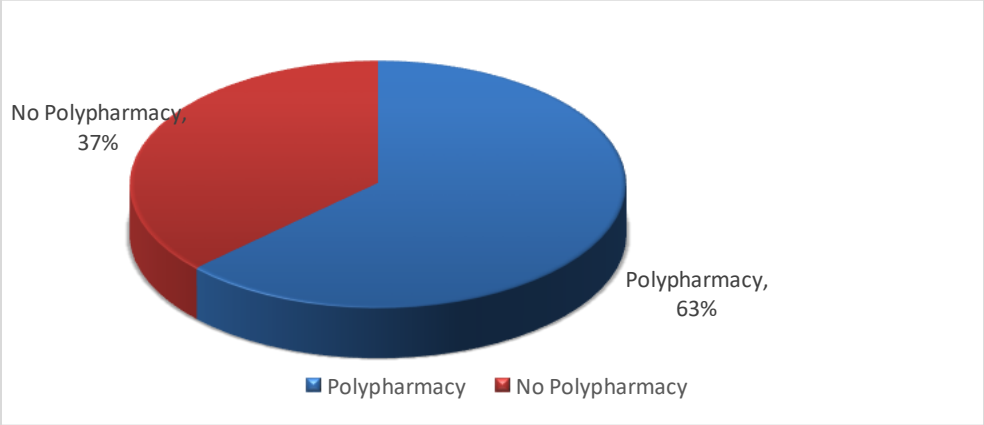

Figure 1: Distribution of patients according to the presence of polypharmacy

NO significant statistical association was found between polypharmacy and pattern of arthritis (*p*-value 0.644) or disease duration (*p*-value 0.281).

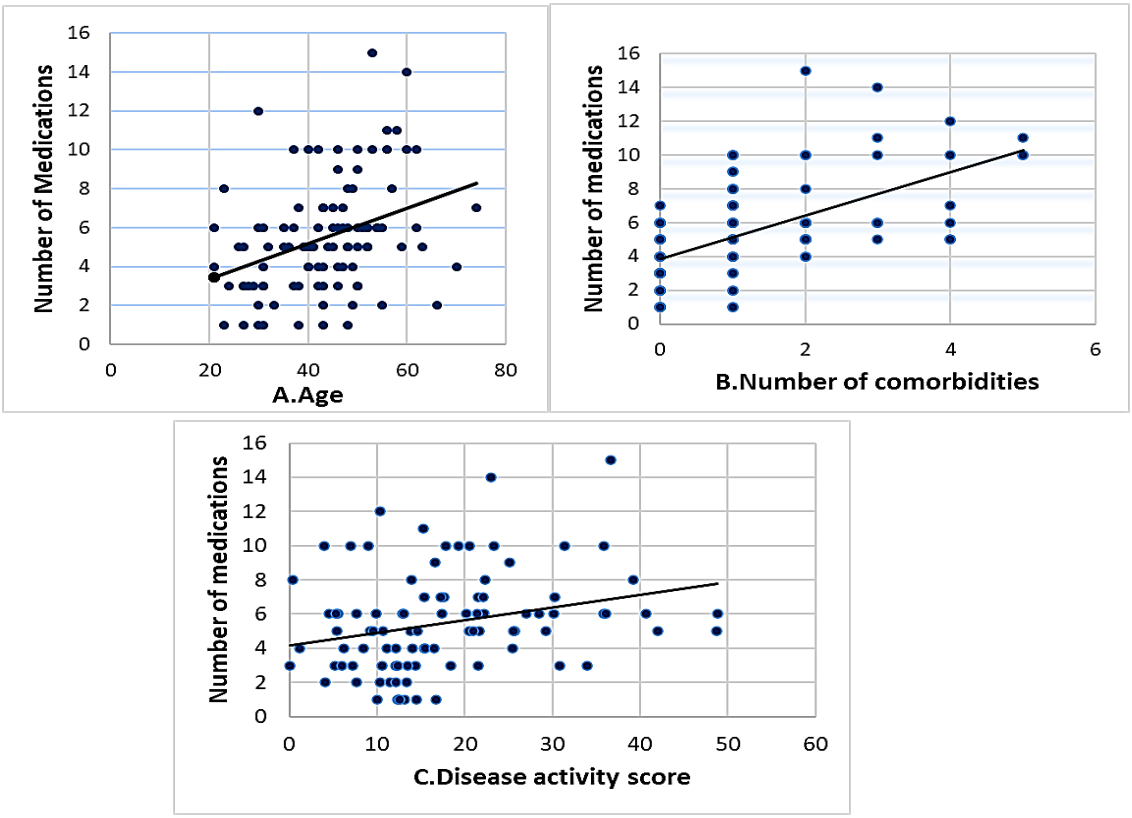

Figure 2: Correlation of the number of medications used with (A) age, (B) number of comorbidities, and (C) disease activity score.

Table 2: Polypharmacy relation with demographic and clinical variables

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Variable		Without polypharmacy, no. (%)	With polypharmacy No. (%)	Total No. (%)	p-value
Age In years	18-40	20 (52.6%)	18 (47.4%)	38 (100%)	< 0.001
	>40	17 (27.4%)	45 (72.6%)	62 (100%)	
Gender	Female	16 (32.7%)	33 (67.3%)	49 (100%)	0.377
	Male	21 (41.2%)	30 (58.8%)	51 (100%)	
Weight groups	Underweight	0 (0%)	1 (100%)	1 (100%)	0.065
	Normal	7 (53.8%)	6 (46.2%)	13 (100%)	
	Overweight	14 (36.8%)	24 (63.2%)	38 (100%)	
	Obese	16 (33.3%)	32 (66.7%)	48 (100%)	
Employment	No	16 (29.6%)	38 (70.4%)	54 (100%)	0.098
	Yes	21 (45.7%)	25 (54.3%)	46 (100%)	
Smoking	Smoker	12 (46.2%)	14 (53.8%)	26 (100%)	0.414
	ex-smoker	4 (44.4%)	5 (55.6%)	9 (100%)	
	Non-smoker	21 (32.3%)	44 (67.7%)	65 (100%)	
Comorbidity	No	25 (73.5%)	9 (26.5%)	34 (100%)	< 0.001
	One	10 (30.3%)	23 (69.7%)	33 (100%)	
	More than one	2 (6.1%)	31 (93.9%)	33 (100%)	
Number of domains	2 domains	9 (39.1%)	14 (60.9%)	23 (100%)	0.831
	3 domains	15 (39.5%)	23 (60.5%)	38 (100%)	
	> 3 domains	13 (33.3%)	26 (66.7%)	39 (100%)	
Peripheral disease activity	Remission	2 (50%)	2 (50%)	4 (100%)	0.002
	Low	22 (57.9%)	16 (42.1%)	38 (100%)	
	Moderate	10 (28.6%)	25 (71.4%)	35 (100%)	
	High	2 (12.5%)	14 (87.5%)	16 (100%)	
Axial disease activity	Active	6 (27.3%)	16 (72.7%)	22 (100%)	0.590
	Inactive/ mild	6 (35.3%)	11 (64.7%)	17 (100%)	

P-value less than 0.05 was considered significant.

Binary logistic regression

A significant positive correlation was observed between polypharmacy and peripheral disease activity as measured by DAPSA score and comorbidities, but this correlation was not significant with age [Table 3].

Table 3: Logistic regression to predict the correlation between polypharmacy and age of patient, peripheral disease activity, and comorbidities

Variable	*p*-value	Odd ratio	95% CI for the odds ratio
Age	0.588	1.014	0.964 -1.066
Disease activity	0.007	1.106	1.028 -1.190
Comorbidity	< 0.001	5.064	2.315 -11.077

CI: confidence interval.

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Drug frequencies and Drug-drug interactions (DDIs)

The total number of medications used was 550, with biologic disease-modifying antirheumatic drugs (bDMARDs), tumor necrosis factor inhibitors (TNFi) being the most frequently used medications (94%) in this study. Etanercept was the most frequently used bDMARD (66%), and methotrexate (MTX) was the most frequently used conventional synthetic DMARD (CsDMARD) (45%). Folic acid was the most frequent non-DMARD drug used by the study population (50% of patients), followed by non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and proton pump inhibitors (PPIs) at percentages of 44%, 36%, and 33%, respectively.

Drug-drug interactions were observed in 67%, with a total number of interactions of 236, of which 0.4% were contraindicated, 12.3% were serious, 44.9% were significant, and 42.2% were minor. The mean, median, interquartile range, and range of DDI were 2.36±3.54, 1, 3, and 0-27, respectively. The majority of interactions were due to the coadministration of MTX with other drugs; the total number of interactions was 90, of which 1.1% were contraindicated, 21.1% were serious, 22.2% were significant, and 55.6% were minor.

The study showed significant positive correlation between the number of DDIs and the age of patients (correlation coefficient = 0.343, *P*-value < 0.001), number of medications used (correlation coefficient = 0.734, *P*-value < 0.001), number of associated comorbidities (correlation coefficient = 0.42, *P*-value < 0.001), and peripheral disease activity (correlation coefficient = 0.372, *P*-value < 0.001) [Figure 4].

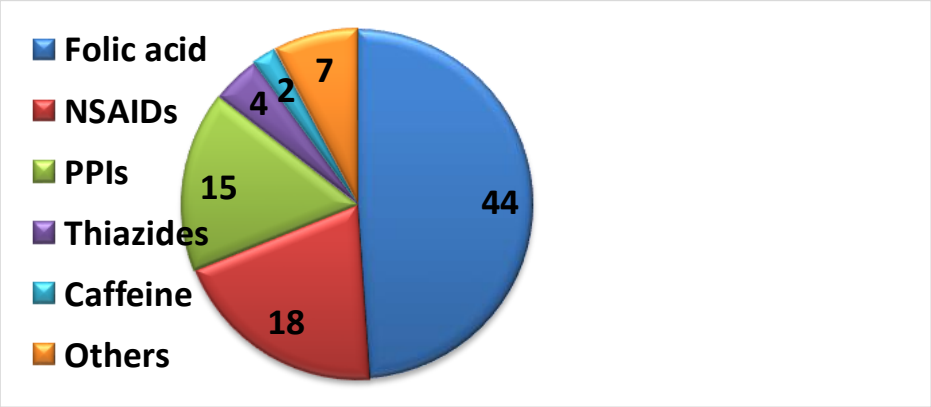

Figure 3: medications interacting with methotrexate.

Table 3: DDIs related to other DMARDs.

DMARDs	Interacting medication	Degree of DDI
Leflunomide	NSAIDs Methotrexate Etanercept Infliximab	Minor Serious Serious Serious
Sulfasalazine	Folic acid NSAIDs Escitalopram	Minor Significant/minor Significant
Azathioprine	Etanercept Infliximab	Serious Serious

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Etanercept	Leflunomide Azathioprine Denosumab	Serious Serious Significant
Infliximab	Leflunomide Azathioprine	Serious Serious
Adalimumab	Methotrexate	Minor
Golimumab	Methotrexate	Minor

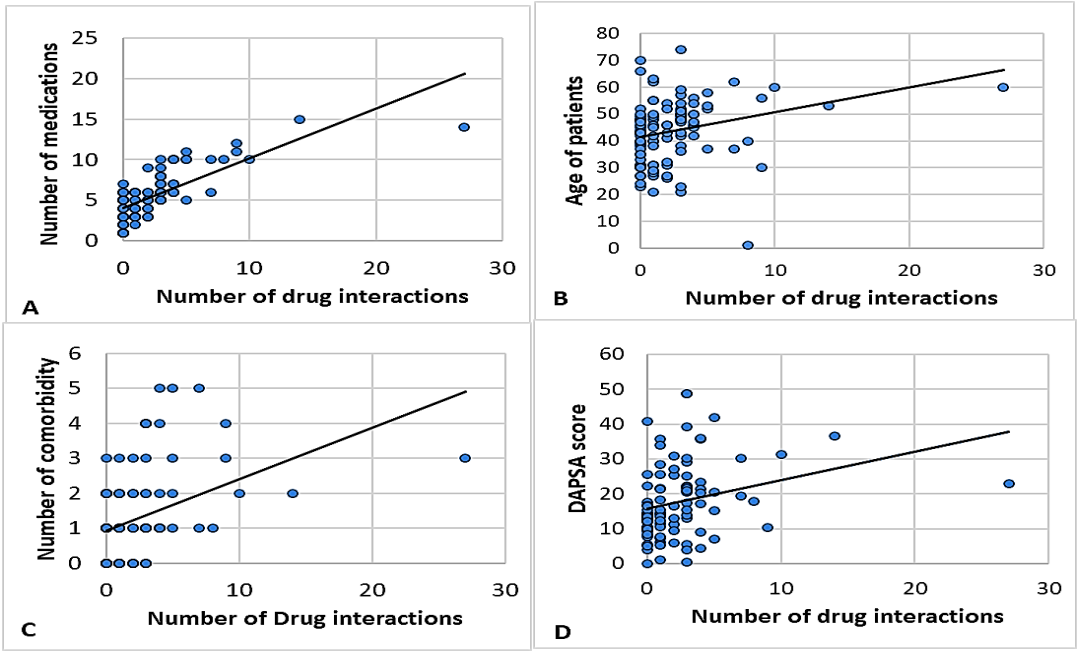

Figure 4: Correlation of drug interactions with (A) number of medications, (B) age, (C) number of comorbidities, and(D) dapsa score.

Discussion

In this study, the prevalence of polypharmacy and DDIs in PsA patients, their association with disease activity, affected domains, the presence of associated comorbid diseases, patients' age, gender, BMI, employment, smoking status, and education level were assessed.

The mean age of the PsA patients included in this study was 43.37 ± 11.318 years, which was comparable to that found by previous local Iraqi studies done by Mustafa *et al*., who found a mean age of 44.4±12.9 years [16].

Of the total sample of 100 patients with PsA, 51 (51%) were males, and 49 (49%) were females, which is comparable to that found by Delmás *et al.*, with females being 49.8% and males 50.2% [17].

This study showed an increased prevalence of polypharmacy among patients with PsA, a finding that is consistent with other studies done by Kara *et al*.[11], Albrecht *et al*.[12], and Gürsoy *et al.*[13]. This may be related to the complexity of PsA treatment, the coexistence of other comorbidities, and poor communication between health care providers.

It was found that 63% of PsA patients in this study were satisfying the definition of polypharmacy, a finding that was higher than the study by Albrecht *et al*. with a prevalence of

49% [12], the possible explanation for this difference is the inclusion of prescribed medications only with the exclusion of OTC medications in their study, in addition to the difference in sample sizes between studies; while it was lower than the Turkish cohort study by Kara *et al*. with a prevalence of 83.6%, the possible explanation for this difference is the exclusion of patients with axial involvement and the difference in sample sizes between studies [11].

In this study, the mean number of drugs used by patients was 5.5 ± 2.92, which was comparable to that found in the study by Albrecht *et al*. [12], in which the mean was 4.9 ± 2.8, but lower than that found in the study by Kara *et al*., where the mean number of drugs used after 6 months of treatment onset was 7.71 ± 3.3 [11].

This study showed positive correlations between the presence of polypharmacy and the age of patients and the number of comorbidities, which were in agreement with Kara *et al*., Albrecht *et al*., and Gürsoy *et al.* [11] [12] [13].

Also, there was a positive correlation between polypharmacy and peripheral disease activity of PsA measured by DAPSA score, which was consistent with the study by Kara *et al*. in which patients with polypharmacy had significantly high disease activity score (DAS-28 CRP) of peripheral arthritis [11].

There was no association between polypharmacy and gender, a finding which is in line with Albrecht *et al*. [12]. Also, there was no association between polypharmacy and the patient`s BMI, educational level, and smoking status, a finding which is in agreement with a Jordanian cross-sectional study done by Abu Farha *et al*. [18].

Etanercept was the most frequently used DMARD in 66% of patients, and MTX was the most frequently used CsDMARD in 45% of patients. Folic acid was the most frequent non-DMARD drug used by the study population (50% of patients), followed by NSAIDs, paracetamol, and PPI in percentages of 44%, 36%, and 33% respectively.

The majority of drug interactions reported in this study were associated with the use of MTX; 12 potential DDIs were identified, one of which was considered contraindicated, two as serious, five as significant, and four as minor; these interactions accounted for a total of 90 potential DDIs. This highlights the need to be cautious with the prescription of other medications to patients who are already using MTX as a part of their treatment regimens, in addition to the need for educating patients about self-medication.

Folic acid interaction with MTX was the most common, representing 48.9% of MTX interactions, and it is considered a minor interaction. A study of 184 patients with RA showed a significant reduction in the efficacy of MTX and increased need for steroids in patients using folic acid when compared to those who did not use folic acid [19]. Folic acid may decrease the efficacy and toxicity of MTX by competition for active transport into cells. MTX should be transported into cells to inhibit dihydrofolate reductase, in order to achieve its clinical effect [20].

Non-steroidal anti-inflammatory drugs (NSAIDs) were the second most common medications interacting with MTX, representing 20% of MTX interactions, and they were considered to be serious. NSAIDs have different effects on the pharmacokinetics of MTX, like increasing its concentration, increasing its half-life, or decreasing its clearance [21]. The recommendation is to avoid concurrent use of NSAIDs and high-dose MTX, like that used for malignant tumors, due to the risk of increased and prolonged MTX serum levels, which may lead to fatal hematological and gastrointestinal toxicity. NSAIDs must be used cautiously with lower doses of MTX, like those used for rheumatic diseases. RA trials have allowed concurrent use of MTX (7.5-15 mg/week) and NSAIDs without evidence of toxicity, but toxicity can occur if higher MTX doses are used with NSAIDs [20].

Proton pump inhibitors (PPIs) were the third most common medications interacting with MTX, representing 16.7% of MTX interactions, and they were classified as significant. It is important to temporarily interrupt PPIs in patients using high doses of MTX. If given

concurrently, MTX toxicity and/or delayed elimination should be monitored. MTX in low doses, as used in rheumatic disorders, is less likely to have significant toxicity than the high doses for oncologic indications. The exact mechanism for this interaction is uncertain but may be related to the inhibition of the renal hydrogen/potassium pump, leading to the reduction of MTX elimination [20].

Thiazide drug interactions with MTX were considered minor and represented 4.5% of MTX interactions in this study. They increase MTX toxicity by decreasing its elimination by the kidneys, resulting in an elevated risk of myelosuppression, particularly in oncologic doses [15]. In a study of 59 patients treated with high-dose MTX, the use of hydrochlorothiazide was associated with a significant risk of acute kidney injury, which necessitates frequent monitoring for nephrotoxicity [22].

Acitretin interaction with MTX is classified as contraindicated because it increases the risk of MTX-induced hepatotoxicity [15] [20].

Other medications interacting with MTX were also noticed in this study, but these had occurred less frequently than those previously mentioned, but still worth noting. Other CsDMARDs in this study were also noticed to have interactions, but less frequently than MTX. In this study, some interactions were observed with the use of TNFi, but far less common than MTX-related interactions. Of these was the interaction of CsDMARD (leflunomide) with TNFi (etanercept and infliximab), which was considered to be serious. Several studies on RA showed increased adverse effects and therapy discontinuation in patients who used leflunomide concomitantly with infliximab [23]. This may be related to the increased immunosuppressive effect; for this reason, it is important to monitor hemoglobin, platelet count, and white cell count every month rather than every 6-8 weeks when using this combination [20].

Another serious interaction noticed with TNFi in this study was the interaction with azathioprine. This may be related to the increased immunosuppressive effects and increased risk of infection [15]. A study done by Deepak *et al*. showed that the use of TNFi with azathioprine increased the risk of T-cell non-Hodgkin`s lymphoma, while the risk did not increase with TNFi alone [24].

A significant interaction was observed between etanercept and denosumab, which can alter lymphocyte function, leading to increased immunosuppressive effects and an increased risk of infection. For this reason, this combination should be used with caution [15] [20].

This study showed that the number of DDIs was significantly correlated with patients' age, the number of comorbid conditions, and the number of drugs used by the patients, and this was in line with several studies regarding DDIs [10] [25]. Also, a significant positive correlation was found between the number of DDIs and the disease activity score measured by DAPSA.

It was obvious that polypharmacy was significantly associated with drug-related problems. This was strongly supported by studies that found that an increased number of medications prescribed posed an increased risk of medication errors, which can lead to DDI [26].

To our knowledge, this is the first local study to assess polypharmacy and DDIs in patients with PsA. The biggest advantage of this study is the inclusion of all medications used by the patients (prescribed and OTC).

This study had some limitations. It was done in a Tertiary Center/University Hospital, and therefore, the patients are more likely to have a severe illness. There were additional limitations associated with the design of the study. Due to the cross-sectional design of the study, cause-effect relationships, including the outcomes of polypharmacy, could not be determined. Nonetheless, the findings were deemed significant because they shed light on a growing issue that hasn't been sufficiently explained in the literature. The comparison of results across different studies was challenging due to the limited number of published studies assessing polypharmacy in PsA.

It is important to note that the identification of drug interactions in this study was carried out by an application of technology included in Medscape's drug interaction checker® database, which does not take into account aspects that relate to patients, doses, administration time, and administration sequence. Therefore, this may lead to an overestimation of the prevalence and risk of potential drug interactions.

Conclusion

There was an increased frequency of polypharmacy among PsA patients. The correlation between polypharmacy and the age of the patient, peripheral disease activity of PsA, and the number of associated comorbidities was found to be statistically significant. There was a significant positive correlation between the number of potential DDIs and the age, number of comorbid conditions, polypharmacy, and peripheral disease activity of PsA. TNFi were the most frequently prescribed drugs, while MTX was the most common drug associated with possible DDIs. It is recommended to evaluate the risk-benefit ratio of each drug-drug interaction in PsA patients. Follow-up studies are needed to identify the consequences of polypharmacy and DDIs in PsA patients.

Conflicted interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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