Original Article

Polypharmacy and Potential Drug–Drug Interactions in Patients with Rheumatoid Arthritis

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Abstract

Background: Rheumatoid arthritis (RA) is a systemic autoimmune disease with protean manifestations. It is characterized by symmetric polyarticular inflammation, which can lead to progressive joint damage. As a result, RA is associated with substantial functional disability, morbidity, and accelerated mortality, which pose an enormous and growing societal burden. Polypharmacy is a major public health concern, which is growing worldwide. Polypharmacy is associated with adverse outcomes including mortality, falls, adverse drug reactions, increased length of stay in hospital and readmission to hospital soon after discharge. **Objectives:** The aim of this study was to quantify polypharmacy in a group of patients with RA, its relationship with patients' characteristics and to assess the risk of potential undesirable interactions between medications used for managing RA and those used for chronic and non-chronic diseases. **Materials and Methods:** A cross-sectional study was conducted at Baghdad Teaching Hospital, Rheumatology Unit during the period from December 2019 to December 2020. A total of 188 adult patients, previously diagnosed with RA according to the 2010 American College of Rheumatology/European League against Rheumatism rheumatoid arthritis classification criteria, were included in the study. Data were collected using a pre-constructed data collection sheet. Questionnaires included demographic and clinical data of the patients. In this study, polypharmacy was defined as the association of five or more medications, regardless of the duration. Drug interactions were identified by use of the Medscape's drug interaction checker® database. **Results:** Among 188 RA patients in this study, polypharmacy was found in 71.8% of the patients and there were 331 potential drug–drug interactions (1.77 ± 2.52 DDIs/patient). Most of the potential drug–drug interactions were related to the use of methotrexate, with nonsteroidal anti-inflammatory drugs being the major representative of these drug–drug interactions with methotrexate. **Conclusion:** High prevalence of polypharmacy was found in RA patients. Positive correlation between polypharmacy and patient's age, disease activity and the presence of other comorbid conditions. Polypharmacy was associated with increased incidence of potential drug–drug interactions in RA patients. Methotrexate was involved in most drug–drug interactions.

Keywords: Drug–drug interactions and methotrexate, polypharmacy, rheumatoid arthritisdrug–drug

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune condition with protean manifestations. The primary expression of disease occurs in the synovial tissues and is characterized by symmetric polyarticular inflammation, which can lead to progressive joint damage.[1]

The prevalence of RA is estimated at 1% in most developed countries, with a frequency ranging from less than or equal to 0.1%–1.9% in surveys from different parts of the world.[2] In Iraq, the prevalence of RA is 1%.[3]

Polypharmacy is considered as the administration of many drugs. It is a major public health concern, which is growing worldwide. The identification of Polypharmacy relies on drug count on a given time window.[4] Polypharmacy exists if this count exceeds a predefined threshold. Although there is no consensus among scientists, five is the most frequently used number.[5]

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A well-known aspect of RA is the high prevalence of comorbidities, especially cardiovascular and metabolic, which can be explained by the pathophysiological mechanisms of the disease and/or complications of the drugs used.[6] Therefore, an RA patient would require the concomitant use of several drugs, often leading to polypharmacy. The occurrence and consequences of polypharmacy have been studied extensively in the elderly and in patients with other chronic diseases, such as heart disease or cancer.[7] In rheumatology, to our knowledge, there is a shortage of studies on polypharmacy and its consequences.

Materials and Methods

This is a cross sectional study conducted at the Rheumatology Unit of Baghdad Teaching Hospital/ Medical City over a period from December 2019 to December 2020.

Patients

A total of 188 adult patients, previously diagnosed with RA according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA, were included in the study.[8] Patients with mental illnesses and psychiatric disorders were excluded from the study.

Methods

The following variables were collected: sex, age, disease duration, employment, educational level, smoking, alcohol use, medications used for RA treatment, and other medications used at time of the study with or without medical prescription. Disease activity is assessed using CDAI including the number of swollen and tender joints, patient global assessment of disease activity and physician global assessment of disease activity.[9] The scoring for patients was graded as follows:

1. Remission CDAI ≤ 2.8
2. Low disease activity CDAI >2.8 and ≤ 10
3. Moderate disease activity CDAI >10 and ≤ 22
4. Severe disease activity CDAI >22

Considering the maximum number of drug used, the patients will be classified according to the presence or absence of polypharmacy. In this study, polypharmacy was defined as the association of five or more medications, regardless of the duration.[4,5] Topical medications, domestic formulations, and eye solutions were not included in the evaluation. The study assessed the existence of possible interactions between the medications used for treating RA and those used for treating other chronic diseases and non-chronic affections. The medications used for treating non-chronic affections are those used by patients at any time of the study and that have no indication to be used in chronic diseases. The drugs used in the symptomatic RA treatment are included in the group of drugs for non-chronic affections.

The Medscape's drug interaction checker® database[10] will be used to assess reports of possible interactions between the drugs previously cited. Drug interaction will be classified as contraindicated in which this combination should never be used because of high risk for dangerous interaction, serious interaction in which it is better to use other medications, significant interaction in which close monitoring is needed and minor interaction in which interaction is not significant and regular monitoring may be required.

Informed consent was obtained from each of the study participants, and the study was approved by the supervising committee of the Iraqi Board of Medical Specializations.

Statistical analysis

Statistical Package for Social Sciences (SPSS®) Software (version 25.0) was used to perform the statistical analysis for this study. Qualitative data were represented as numbers and percentages, while continuous numerical data were represented as mean ± standard deviation. Categorical variables were compared using chi-square test. Pearson's rho correlation coefficient was calculated in order to assess the correlation between discrete numerical variables. A value of $P < 0.05$ was considered statistically significant.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before being included in the study. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 35 in 12/1/2021.

Results

This study included 188 adult patients with RA. The mean age of patients was 49.85 ± 11.62 years ranged from 19 to 78 years. Out of the 188 RA patients, 156 were females (83%) and 32 were males (17%) with a male to female ratio of 1:5.

The mean disease duration was 10.6 ± 10.1 years (range: 3 months to 35 years). The mean disease activity measured by CDAI was 16.75 ± 9.8 and the median was 14 (range from 3 to 53).

Disease activity varied between patients in the study sample with 45 patients (23.93%) had high disease activity, 86(45.74%) moderate disease activity and 57(30.31%) had low disease activity [Figure 1].

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In addition to RA, other chronic diseases were present in 84 patients (44.7%) 60 of them having one additional disease (71.43%) while the remaining 24 patients (28.57%) having 2 or more additional diseases [Figure 2].

The presence of polypharmacy was observed in 71.8% of the patients. The mean number of medications used was 5.96 ± 2.53 with a median of 6 drugs ranging from 1–15 drugs [Figure 3].

Spearman's rho correlation analysis showed that the prevalence of polypharmacy increased significantly with increasing patients' age (P = 0.010). Significant positive correlation was also observed between disease activity measured by CDAI and the number of medications used (P < 0.001). Similarly, there was also an increase in the prevalence of polypharmacy with the presence of chronic diseases other than RA (P < 0.001). No significant correlation was observed between the presence of polypharmacy and patients' gender (P = 0.993), [Table 1], [Figure 4].

The total number of medications used was 1120 with MTX being the most commonly used sDMARDs 111 patients (59.04%) and the etanercept being the most common bDMARDs used in 140 patients (74.46%).

Steroids were the most common non-DMARDs medication used by the study population (100 patients,53.19%), followed by paracetamol in 80 patients (42.55%), followed by NSAIDs in 77 patients (40.95%) and proton pump inhibitors(PPIs) in 65 patients (34.57%) [Figure 5].

There were 331 drug interactions, of these 62(18.73%) were serious, 188(56.79%) were significant and 81(24.47%) were minor.

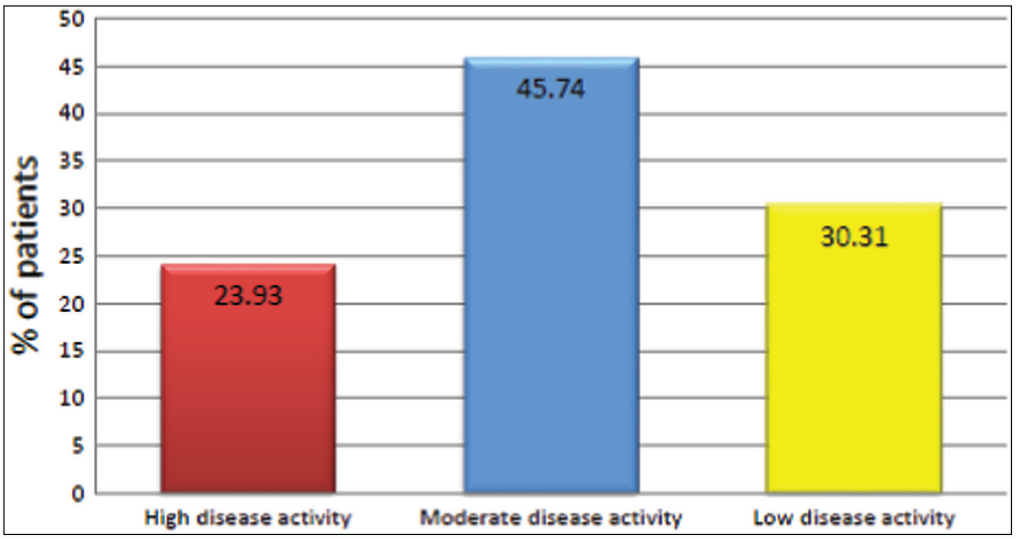

Figure 1: Patients distribution according to disease activity

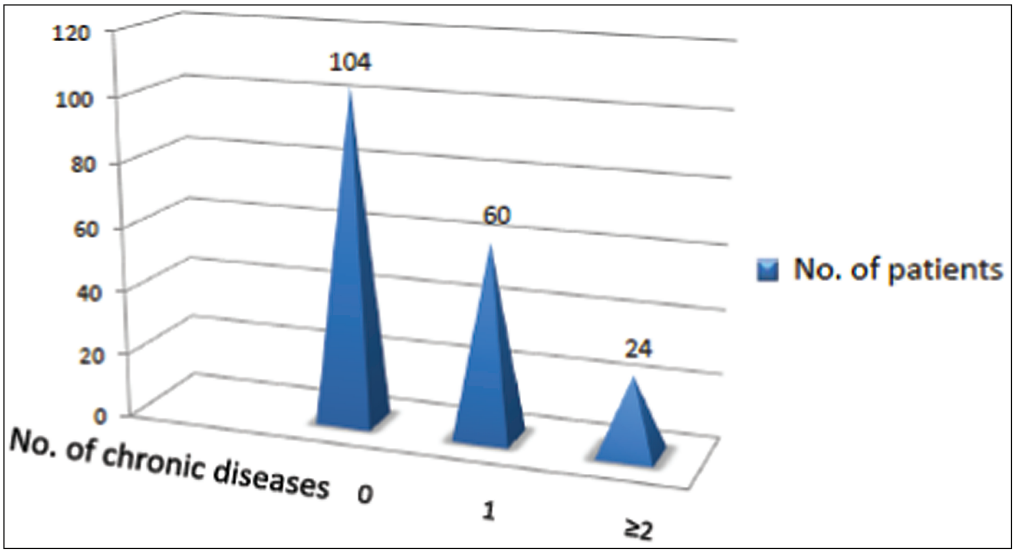

Figure 2: Patients distribution according to the number of chronic diseases other than RA

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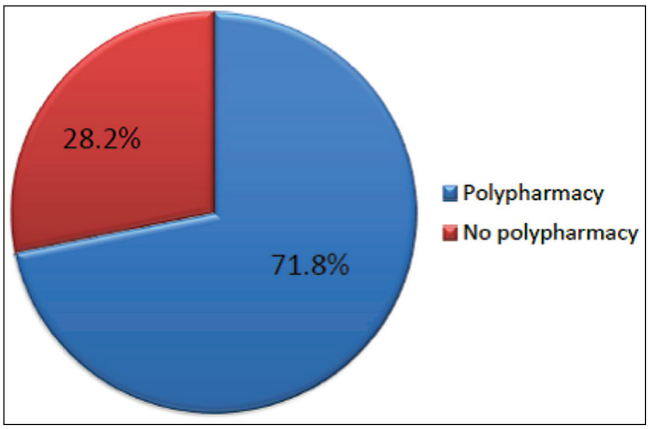

Figure 3: Patients distribution according to the presence of polypharmacy

Table 1: Polypharmacy relations with demographic and clinical variables

Variables	With polypharmacy no. (%)	Without polypharmacy no. (%)	Total no. (%)	*P*-value*
Gender				
Male	23(71.9%)	9(28.1%)	32(100%)	0.993
Female	112(71.8%)	44(28.2%)	156(100%)	
Age				
Mean ± SD	51.21 ± 11.16	46.40 ± 12.16	49.85 ± 11.62	0.010
CDAI				
High disease activity	38(84.4%)	7(15.6%)	45(100%)	<0.001
Moderate disease activity	60(69.8%)	26(30.2%)	86(100%)	
Low disease activity	37(64.9%)	20(35.1%)	57(100%)	
Presence of chronic diseases				
0	63(60.6%)	41(39.4%)	104(100%)	<0.001
1	49(81.7%)	11(18.3%)	60(100%)	
≥2	23(95.8%)	1(4.2%)	24(100%)	

*significant at $P < 0.05$

The mean, median and range of DDI were 1.77 ± 2.52, 1 and 0–14, respectively. Most of the DDIs were related to the use of MTX with NSAIDs (mostly diclofenac sodium) in 77 patients (40.95% of patients) and PPIs (mostly omeprazole) in 65 patients (34.57% of patients) [Figure 6].

While other sDMARDs related DDIs were reported less frequently and no DDIs were reported with the use of antiTNFs [Table 2].

Spearman's rho correlation showed a significant positive correlation between the number of drug interaction and number of medications used (correlation coefficient = 0.581, $P < 0.001$).

Also the number of DDIs increased markedly with increasing number of comorbidities other than RA (correlation coefficient = 0.400, $P < 0.001$). Furthermore positive correlation was found between number of DDIs and patients' age as (correlation coefficient = 0.231, $P = 0.01$), [Figure 7].

Discussion

To the best of our knowledge there was no previous local study discussing polypharmacy in RA patients. In this study, prevalence of polypharmacy in RA patients, its relationship with disease activity, the presence of other comorbid diseases and patients' age and gender were assessed.

In this study, the mean age of the RA patients was 49.85 ± 11.62 years which was comparable to that found by previous local Iraqi studies done by Saleh *et al*.[11] and Jassim *et al*.,[12] who found a mean age of 48.55 ± 11.81 years and 47.43 ± 11.9 years, respectively. However, the mean age was higher than that found by Shakerdi *et al*.[13] of 33.1 ± 6.1 years and lower than that found by Bagatini *et al*.[14] with mean age of 56.9 ± 13.1 years. This may be explained by differences in sample sizes between the studies.

There was marked female predominance with a female:male ratio of 5:1 which is similar to that reported by Jassim *et al*.[12] but lower than what had been found by Al-Bedri *et al.* with a ratio of 7.6:1.[15]

It was found that 71.8% of RA patients were using five or more medications, satisfying the definition of polypharmacy, a finding that was comparable to that found by Brazilian study done by Gomides *et al.* in which polypharmacy prevalence was 67% in 792 RA patients,[16] while it was lower than the Brazilian cohort study of Bagatini *et al.* with a prevalence of 95.1%, the possible elucidation for this difference is the higher mean age of the patients included in their study.[14]

The mean number of medications used by patients included in this study was 5.96 ± 2.53 that was similar to other studies done by Treharne *et al.* and Filkova *et al.* in which the mean number of medications used were 5.39 and 5.43, respectively.[17,18]

There was a positive correlation between the presence of polypharmacy and the patients' age, which was consistent with the study of Treharne *et al*.,[17] Gomides *et al*.,[16] Filkova *et al*.[18] and Morin *et al.*[19]

Another positive correlation was found between polypharmacy and RA disease activity, measured by CDAI, which was also consistent with the finding of Treharne *et al*.,[17] Gomides *et al*.[16] and Filkova *et al*.[18]

The presence of chronic diseases other than RA was also positively correlated with the prevalence of polypharmacy which was also documented by Treharne *et al*.,[17] Gomides *et al*.[16] and Filkova *et al*.[18]

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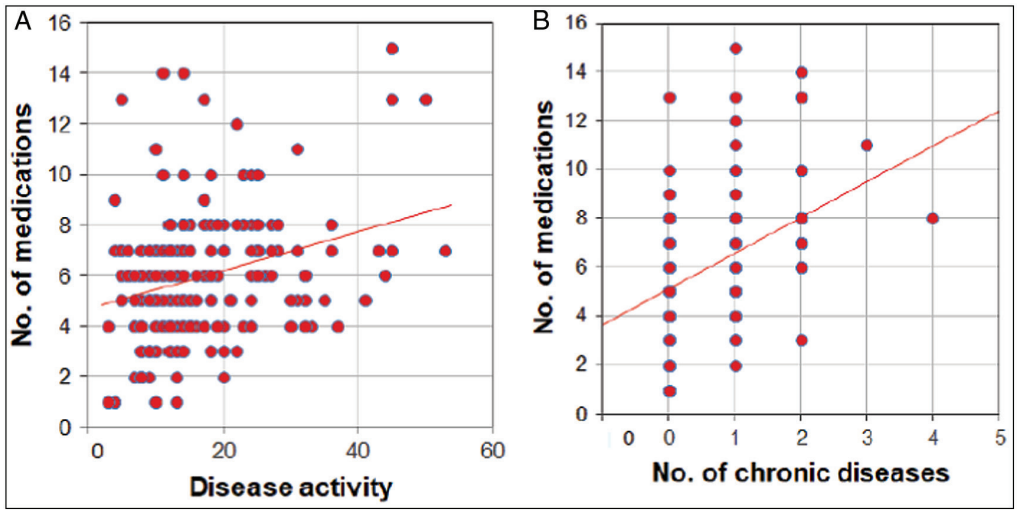

Figure 4: Correlation between number of medications used and (A) disease activity (B) number of chronic diseases

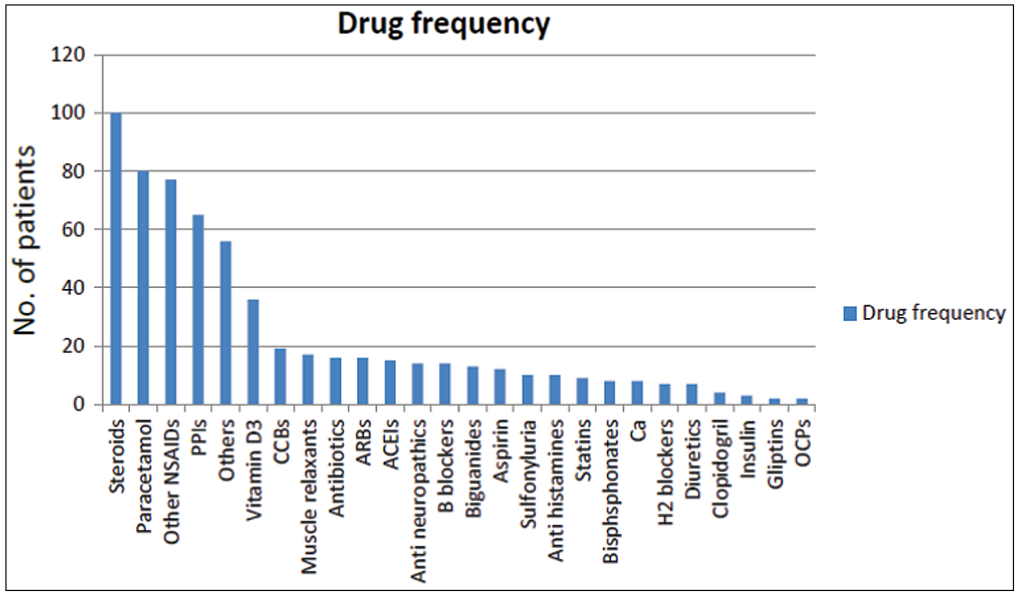

Figure 5: Frequency of medications used other than DMARDs

No correlation was found between patients' gender and number of medications used, a finding consistent with that found by Treharne *et al*.[17] and Gallego *et al*.[20] In contrast to Meraya *et al.* and Filkova *et al.* which showed a higher incidence of polypharmacy in females that might be due to the differences in population characteristics.[18,21]

Most of drug interactions found in this study were associated with MTX use, six possible DDIs were observed, two of which were classified as serious, three as significant and one as minor, together these have accounted for a total of 163 DDIs. This emphasizes the need for being cautious when prescribing and dispensing other medications to patients already using methotrexate in their treatment regimens, as well as the need for instructing patients regarding self-medication.

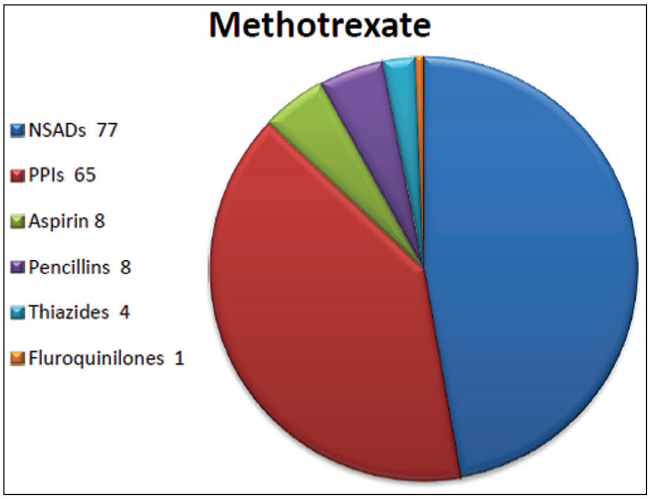

Figure 6: Drugs interacting with MTX

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The association of MTX and NSAIDs can cause several complications, such as severe hematologic and gastrointestinal toxicities. In addition, preexisting renal dysfunctions (or NSAID-induced renal dysfunctions) potentiate the risk for adverse reactions.[10,22]

Although the concomitant administration of NSAIDs and MTX can potentially cause severe toxicity, low doses of that association are considered well tolerated, but the appearance of severe adverse effects should always be cautiously monitored.[10,22]

Table 2: Other DMARDs related DDIs

DMARDs	Interacting drugs	Degree of DDI
Leflunomide	Diclofenac	Minor
Sulfasalazine	Amoxicillin	Significant
	Aspirin	Significant/minor
	Diclofenac	Significant/minor
	Prednisolone	Significant/minor
	Glimepiride	Significant
Hydroxychloroquine	Azithromycin	Serious
Azathioprine	Captopril	Significant
TNFis	No interacctions	

Evidence for a potential interaction between NSAID and MTX first emerged when the use of aspirin during oncological high-dose MTX therapy resulted in a 54% decrease in white cell count, where 50 mg per day of MTX was given for 10 days.[23]

Proton pump inhibitors interactions were classified as significant. The concomitant use of MTX and omeprazole can increase the risk of toxicity of the former,[10,24] because, according to Suzuki *et al*.,[25] the coadministration of PPIs can delay the excretion of MTX and potentiate its adverse effects. Thus, patients receiving that association should be strictly monitored to avoid possible damage resulting from the high concentration of MTX in their bodies.[10,26]

Because of the structural similarity between penicillin and MTX, a competitive inhibition of MTX tubular secretion can occur, increasing its half-life.[27]

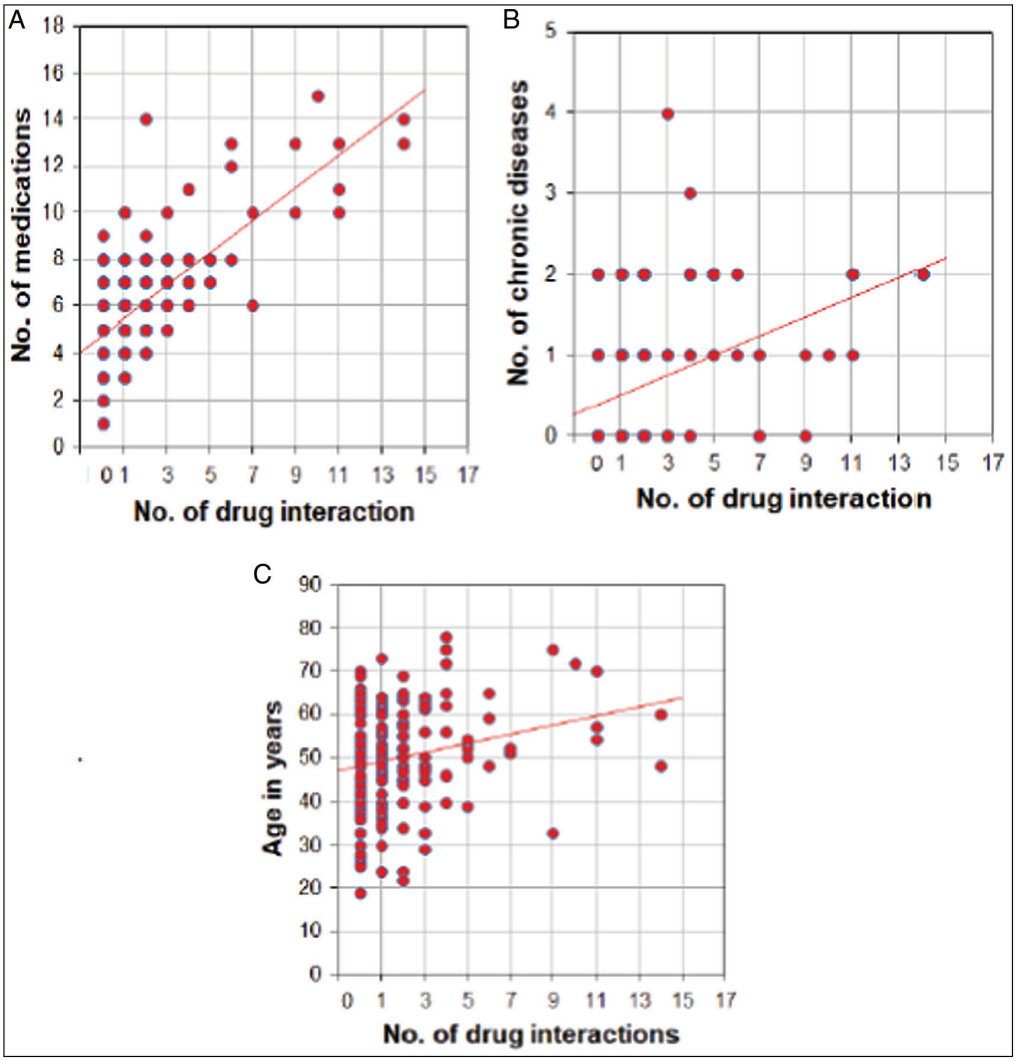

Figure 7: Correlation between number of DDIs and (A) no. of medications, (B) no. of chronic diseases, and (C) age of the patients

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Thiazide diuretics increase the toxicity of MTX by decreasing the elimination of MTX at the renal tubules.[10] Antineoplastic doses of MTX may cause prolonged bone marrow suppression with concomitant thiazide administration.[28]

Other interactions were also found in this study but these had occurred less frequently than those related to MTX but still worth noting.

Regarding TNF inhibitors, no DDIs were found in this study that was consistent with what was found by Zhou H. 2009.[29]

As all possible DDIs evaluated in this study refer to standard dosage schemes, thus the interaction(s) may be significantly more distinct or only present in higher therapeutic drug concentrations. For the anchor drug MTX the interaction potential may well be overestimated due to a reduced dosage in rheumatology as opposed to high dose administration in oncology.

In this study the number of DDIs were significantly correlated with patients' age, presence of comorbid conditions and the number of medications taken by the patients and this was consistent with most of studies regarding DDI.[14,18]

It was not surprising that polypharmacy was found to be significantly associated with the occurrence of drug related problems. This was strongly supported by other studies which found that an increase in medications prescribed posed an elevated risk of medication errors, which in turn lead to DDIs.[30]

This study had some limitations. The participating center was a tertiary/university hospital, and therefore, the patients are probably in a more serious condition. There were also limitations inherent to the design of the study. As it was a cross-sectional study, cause–effect relationships such as the consequences of polypharmacy could not be evaluated. However, the results were important because they bring awareness to a problem that has not been adequately addressed in the literatures.

It is worth noting that, in this study, the detection of potential drug interactions was based on an information technology tool included in The Medscape's drug interaction checker® database,[10] which cannot consider aspects related to patients, dosages, and sequence and time of medication administration. This, thus, may overestimate the incidence and risk of potential drug interactions.

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Conflicts of interest
There are no conflicts of interest.

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