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Original Research Article

A clinical study on the risk and safety profiles of NSAIDs used for osteoporotic fractures in Chinese patients with rheumatoid arthritis

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Abstract

Purpose: *To investigate the risk and safety profile of non-steroidal anti-inflammatory drugs (NSAIDs) for osteoporotic fractures in patients with rheumatoid arthritis (RA).*
Methods: *298 RA patients admitted to The First People's Hospital of Huzhou, Huzhou, China from August 2020 to September 2022, were investigated. Patients were assigned to groups based on drugs used viz: control group received anti-rheumatic drugs other than NSAIDs; corticosteroid group received dexamethasone, disease-modifying anti-rheumatic drugs (DMARDs) groups received sulfasalazine, NSAID group received either diclofenac or ibuprofen etc. Each group of patients received the respective treatment frequently for at least 3 years. The primary outcome in this study was the incidence of osteoporotic fracture resulting from fragile bone and deterioration of bone mass.*
Results: *The incidence of osteoporotic fracture was highest in NSAID group (11.58 %) when compared to 5.44, 4.96, and 2.36 % in the corticosteroid, DMARD and control groups, respectively ($p < 0.05$). This shows that users of NSAIDs had a 5-fold higher risk of osteoporotic fracture than patients in control group (OR = 1.26 (95 % CI: 1.22 - 1.81)) and 2-fold possibility of osteoporotic fracture when compared to corticosteroid users ((OR = 1.46 (95 % CI: 1.57 - 2.32)) and DMARD users (1.83 (95 % CI: 1.26 - 1.67)).*
Conclusion: *Rheumatoid arthritis patients on NSAIDs such as celecoxib, diclofenac, ibuprofen, indomethacin, and oxaprozin are at risk of developing osteoporotic fracture. Therefore, NSAIDs must be used with proper counseling in RA patients to minimize the risk of osteoporotic fracture. In future, the study duration will need to be extended to determine the long-term effects and potential changes in bone properties.*

Keywords: *Rheumatoid arthritis, Osteoporotic fractures, NSAIDs, Corticosteroids, DMARDs*

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INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic autoimmune disease that primarily attacks synovial joints [1]. Various inflammatory cells such as innate immune cells (e.g. mast cells, macrophages, dendritic cells, and natural killer (NK) cells); adaptive immune cells (T- and B-

cells), and fibroblast-like synoviocytes (FLS), are activated in the joints of RA patients [2]. These cells interact with each other via an array of cytokines and/or cell-to-cell contacts, leading to prolonged inflammation, abnormal proliferation of FLS, and the destruction of cartilage and bone [2].

Rheumatoid arthritis (RA) is a persistent inflammatory disease with various co-morbidities [3]. The job of caring is fundamental in the early diagnosis and treatment of this crippling illness [3]. Non-steroidal anti-inflammatory drugs (NSAIDs) are effective pain-relieving medications [4]. It is of particular importance to recognize co-existing conditions and related treatments that could heighten the risk of NSAIDs in certain patients [4].

It has been reported that globally, the prevalence of RA is 0.8 %, with the chances of having the disease being twice in females than in males [5]. Rheumatoid arthritis (RA) occurs at any time in life. Therefore, prompt attention to all sets of experiences, as well as actual assessment, are the best methods for early diagnosis of the disease [5,6]. As a rule, patients who experience rheumatoid joint pain require pain-relieving and calming medications to control the symptoms of the illness [6]. Non-steroidal anti-inflammatory drugs (NSAIDs), as well as corticosteroids (adrenal cortical steroidal calming medications), are regularly utilized as adjuncts in the treatment of rheumatic joint inflammation, due to their advantages in decreasing the agonizing pain usually associated with the illness [7,8].

A person suffering from osteoporotic arthritis or RA, customarily requires NSAIDs, for example, diclofenac and naproxen which ease pain by inhibiting the enzymes cyclo-oxygenase (COX) 1 and COX 2 [9]. In contrast, other COX enzyme inhibitors, including etoricoxib, serve as reliable drugs used for management of pain aggravation related to two types of arthritis namely, osteoporotic arthritis and RA [10,11].

In the present study, the risk and safety profile of NSAIDs were investigated among Chinese RA patients. The study was also an attempt to assess the risk of osteoporotic fractures among RA patients on NSAIDs, relative to those on other classes of drugs such as DMARDs and corticosteroids. The DMARDS are a group of drugs used for the treatment of patients with RA. These drugs slow down or control RA. The DMARDs include methotrexate, sulfasalazine, hydroxychloroquine and leflunomide, amongst others.

METHODS

Study design and population

A total of 298 RA patients who received treatment at The First People's Hospital of Huzhou, Huzhou, Zhejiang Province, China from August 2020 to September 2022, were enrolled in the study. The subjects were patients who were exposed to NSAIDs, corticosteroids, DMARDs and other anti-rheumatic drugs for more than three years from the date of enrollment.

Ethical statement

All procedures used in this study were performed in line with the guidelines of the 1964 Declaration of Helsinki and its later amendments [12]. Written consent was obtained from all participants. All procedures used in the study were approved by the Hospital Medical Ethical Board vide approval no. S32414A/32.

Inclusion criteria

Patients in the following categories were enrolled in the study: those who were diagnosed with rheumatoid arthritis (RA; patients within the age range of 55 and 80 years; patients exposed to NSAIDs, corticosteroids, DMARDs, and other anti-rheumatic medications for a minimum duration of three years from the date of enrollment, and those who were willing to participate in the study and provided informed consent.

Exclusion criteria

Patients diagnosed with joint pain, and those who were not exposed to NSAIDs, corticosteroids, DMARDs, or other anti-rheumatic medications, for at least three years, were excluded from the study. Moreover, patients who had contraindications or allergies to the specified medications, and those who were unable or unwilling to provide informed consent, were excluded.

Impact of NSAIDs, corticosteroids, DMARDs, and control drugs on risk of osteoporotic fracture

The enrolled patients were those who were administered doses of NSAIDs, corticosteroids, DMARDs and other anti-rheumatic drugs. The patients were divided into four different groups *viz* NSAID group (n = 97; 32.62 %), corticosteroid group (n = 80; 26.8 %), DMARD group (n = 72; 24.2 %), and control group (n =

49; 16.4 %). Patients in NSAID group were given 100 mg of celecoxib (Pfizer Inc., NY 10017, USA); 50 mg of diclofenac, (GlaxoSmithKline, Bretford, UK); 200 mg of ibuprofen (Pfizer Inc., NY 10017, USA); 25 mg of indomethacin (Takeda Pharmaceuticals, Tokyo, Japan) and 600 mg of oxaprozin (Pfizer Inc., NY 10017, USA). All treatments were given orally twice a day, except diclofenac and ibuprofen which were administered thrice daily. Patients in the corticosteroid group were given 1 mg of dexamethasone (Sandoz, Novartis AG, Basel, Switzerland) twice daily; 10 mg of hydrocortisone (Pfizer Inc., NY 10017, USA) thrice daily; 20 mg of prednisone (Takeda Pharmaceuticals, Tokyo, Japan) thrice daily, and 20 mg methylprednisolone (Pfizer Inc., NY 10017, USA) twice daily. All treatments were administered orally. In DMARD group, patients were given 0.5 mg of methotrexate (Pfizer Inc., NY 10017, USA) once daily; 500 mg of sulfasalazine (Pfizer Inc., NY 10017, USA) once daily; 200 mg of hydroxychloroquine (Sandoz, Novartis AG, Basel, Switzerland) once daily, and 50 mg of leflunomide (Sanofi Pharmaceuticals, Paris, France) once daily. Patients in control group were given anti-rheumatic drugs other than NSAIDs: 10 mg of tofacitinib (Pfizer Inc., NY 10017, USA) twice daily; 2 mg of baricitinib (Eli Lily, IN 46285, USA) once daily; 1 mg of dexamethasone twice daily, and combination of 0.5 mg of methotrexate plus 500 mg of sulfasalazine once daily. All treatments were given orally. All observations and information about drug effects and osteoporotic fracture related to the administration of each drug were recorded during the study period. NSAID group comprised patients who were given celecoxib (100 mg twice day), diclofenac (50 mg thrice daily), ibuprofen (200 mg thrice daily), indomethacin (25 mg twice daily), and oxaprozin (600 mg twice daily) via the oral route, or any other NSAIDs, e.g., naproxen (250 mg twice daily) given orally. The corticosteroid users were defined as those treated with dexamethasone (1 mg twice daily), hydrocortisone (10 mg thrice daily), prednisone (20 mg thrice daily) and methylprednisolone (20 mg twice daily) via the oral route. The DMARD users group comprised patients given methotrexate (0.5 mg daily), sulfasalazine (500 mg daily), hydroxychloroquine (200 mg daily) and leflunomide (50 mg daily) through the oral route. Control group was defined as those who received anti-rheumatic drugs other than NSAIDs or in combination with any corticosteroids or any DMARDs such as tofacitinib (10 mg twice daily), baricitinib (2 mg daily), dexamethasone (1 mg twice daily) and methotrexate (0.5 mg daily) plus sulfasalazine (500 mg daily) combination therapy, via the oral route. Follow-up continued till the end of the study period. The major outcome in this study was osteoporotic fracture resulting from fragile bone and deterioration of bone mass.

Evaluation of parameters/indices

Determination of bone mineral density (BMD)

For the determination of BMD, patients were suited with sterile clothing without metal accessories and metallic objects, such as jewelry, were removed before the scan.

DEXA scanning

Dual Energy X-ray absorptiometry (DEXA) scans were carried out and the spine, hip, wrist, forearm and pelvis were scanned. Clinical evaluation was measured based on bone mineral density (BMD) analysis. The DEXA scores are reported as *T*- and *Z*-scores which were evaluated based on recommendations of the International Society for Clinical Densitometry (ISCD).

Determination of risk assessment and incidence rate for OF

The risk assessment and incidence rate of osteoporotic fracture were determined by dividing the number of fractures during the study period by the total years of observation by each individual. The years of observation per individual account for the time each participant contributed to the study.

Logistic regression analysis

Multiple linear regression analysis was conducted to examine the association between independent variables which include asthma, cardiovascular, chronic obstructive pulmonary disorder (COPD), diabetes, gastroesophageal reflux disease (GERD), hepatobiliary, hypothyroidism, major infections and renal disease against dependent variables including NSAID, corticosteroids and DMARDs users. Odds ratio, *p*-values, and 95 % confidence intervals were determined to assess the significance of the relationships.

Determination of smoking status and alcohol use on OF

The determination of smoking status and alcohol use were evaluated based on patient's smoking history and alcohol consumption habits associated with OF during initial interviews and questionnaires. Information such as current

smoking status and alcohol use, history of smoking and alcohol use, duration of smoking, number of cigarettes per day, frequency and quantity of alcohol consumption were recorded. Multivariable logistic regression analyses was performed to determine associations between these lifestyle factors and the occurrence of osteoporotic fractures.

Risk assessment and incidence rate for OF

The risk assessment and incidence rate of osteoporotic fracture were evaluated by identifying the potential risk factors for osteoporotic fractures in RA patients, which may include age, gender, duration of medication exposure, and specific medications used such as NSAIDs, corticosteroids and DMARD. Multivariable logistic regression was carried out to assess the relationship between these risk factors and the occurrence of osteoporotic fractures.

Statistical analysis

The SPSS 18.0 statistical package was used for analysis (SPSS Inc, USA). The risks for osteoporotic fractures and their association with NSAIDs and other drugs were evaluated. The statistical significance was evaluated based on factors such as co-morbidities, co-medications, smoking status, alcohol use, and severity of disease. Non-users of NSAIDs were used as controls. Multivariable logistic regression was carried out to understand the strength of the association, and it was estimated using odds ratio at 95 % confidence interval.

RESULTS

A total of 298 RA patients were enrolled in this study. The mean age of the patients was 67.04 years. The total number of patients on NSAIDs, corticosteroids, DMARDs and control drugs were 97 (32.62 %), 80 (26.8 %), 72 (24.2 %), and 49 (16.4 %), respectively (Table 1). Among the 298 patients with RA, there were 176 female patients, while the total number of males was 122. The number of female RA patients was higher in the NSAIDs group, with 59 females (F) and 38 males (M). Similarly, there were higher numbers of female RA patients than males in the corticosteroid group (44 F and 36 M), DMARD group (43 F and 29 M), and control group (30 F and 19 M). The results of body mass index (BMI) measurements indicated that majority of the patients were overweight (n = 155). The highest number of overweight RA patients was observed in the NSAIDs group (57 patients; 32.6 %), whereas the highest number of obese RA patients (13; 4.4 %) was observed in the corticosteroid group. There were no significant differences in smoking status and alcohol intake amongst the studied groups.

A box plot highlighting smoking status and alcohol use is presented in Figure 1. There were no marked differences in co-morbidities and co-medications amongst the groups. However, disease severity was highest in the NSAIDs group, with 33 (11.1 %) severe cases, relative to 20 (6.7 %), 17 (5.7 %), and 10 (3.4 %) severe cases in the corticosteroid, DMARD, and control groups, respectively.

Figure 1: Box-plot highlighting smoking status and alcohol use based on the type of drug administration viz. control, corticosteroids, DMARDs and NSAIDs

During the study period, a total of 103 patients with RA had osteoporotic fractures, details and types of which are presented in Table 2. The highest incidence of osteoporotic fracture (11.58 %) occurred in NSAID group (p = 0.045), while the corresponding incidence values in the corticosteroid group, DMARD group and control group were 5.44, 4.96 and 2.36 %, respectively (Table 2). This shows that users of NSAIDs had a 5-fold higher risk of developing osteoporotic fractures than patients in control group (OR = 1.26 (95 % CI: 1.22 - 1.81)) and 2-fold higher possibility of developing osteoporotic fractures when compared to the users of corticosteroids ((OR = 1.46 (95 % CI: 1.57 - 2.32)) and users of DMARDs ((1.83 (95% CI: 1.26 - 1.67)).

Concerning the type of fracture, most of the RA patients had spine fractures (n = 39), with 20 cases in NSAID group, 8 cases each in the corticosteroid and DMARD groups, and 3 cases in control group (Table 3). This was followed by Hip fracture with a total of 24 cases, forearm fracture (17 cases), wrist fracture (16 cases), and pelvic fracture (7 cases).

Table 1: Characteristics of patients with rheumatoid arthritis

Characteristic	Control n, (%)	Corticosteroids n, (%)	DMARDs n, (%)	NSAIDs n, (%)
N	49 (16.4)	80 (26.8)	72 (24.2)	97 (32.6)
Age, Mean SD	68.81	65.53	67.87	66.55
Male (N=122)	19 (6.4)	36 (12.1)	29 (9.7)	38 (12.8)
Female, (N=176)	30 (10.1)	44 (14.8)	43 (14.4)	59 (19.8)
BMI				
Normal (18.5-24.9) N=108	22 (7.4)	30 (10.1)	25 (8.4)	31 (10.4)
Overweight (25.0-29.9) N=155	23 (7.7)	36 (26.8)	39 (24.2)	57 (32.6)
Obesity (<30) N=35	4 (1.3)	13 (4.4)	8 (2.7)	10 (3.4)
Smoking status				
No (N=130)	24 (8.1)	37 (12.4)	30 (10.1)	39 (13.1)
Yes (N=168)	25 (8.4)	43 (14.4)	42 (14.1)	58 (19.5)
Alcohol use				
No (N=111)	19 (6.4)	22 (7.4)	26 (8.7)	44 (14.8)
Yes (N=187)	30 (10.1)	53 (17.8)	46 (15.4)	58 (19.5)
Comorbidities				
Characteristic	**Control n, (%)**	**Corticosteroids n, (%)**	**DMARDs n, (%)**	**NSAIDs n, (%)**
Asthma	8 (2.7)	7 (2.3)	9 (3.0)	7 (2.3)
Cardiovascular disease	2 (0.7)	9 (3.0)	5 (1.7)	12 (4.0)
COPD	4 (1.3)	12 (4.0)	5 (1.7)	7 (2.3)
Diabetes	2 (0.7)	5 (1.7)	7 (2.3)	6 (2.0)
GERD	9 (3.0)	13 (4.4)	14 (4.7)	4 (1.3)
Hepatobiliary	4 (1.3)	5 (1.7)	10 (3.4)	7 (2.3)
Hypothyroidism	5 (1.7)	8 (2.7)	10 (3.4)	24 (8.1)
Major infections	4 (1.3)	14 (4.7)	8 (2.7)	13 (4.4)
Renal disease	11 (3.7)	7 (2.3)	4 (1.3)	17 (5.7)
Comedications				
Characteristic	**Control n, (%)**	**Corticosteroids n, (%)**	**DMARDs n, (%)**	**NSAIDs n, (%)**
Anticoagulants	1 (0.3)	3 (1.0)	7 (2.3)	3 (1.0)
ACE inhibitors	2 (0.7)	4 (1.3)	5 (1.7)	9 (3.0)
Antacids	7 (2.3)	10 (3.4)	17 (5.7)	15 (5.0)
Anti-diabetic	9 (3.0)	12 (4.0)	10 (3.4)	16 (5.4)
Calcium	6 (2.0)	18 (6.0)	10 (3.4)	16 (5.4)
Laxatives	9 (3.0)	9 (3.0)	5 (1.7)	15 (5.0)
Statins	3 (1.0)	4 (1.3)	7 (2.3)	2 (0.7)
Thyroid medication	5 (1.7)	7 (2.3)	8 (2.7)	8 (2.7)
Vitamin D	7 (2.3)	13 (4.4)	13 (4.4)	13 (4.4)
Severity of diseases				
Characteristic	**Control n, (%)**	**Corticosteroids n, (%)**	**DMARDs n, (%)**	**NSAIDs n, (%)**
Mild	26 (8.7)	42 (14.1)	39 (13.1)	37 (12.4)
Normal	13 (4.4)	18 (6.0)	16 (5.4)	27 (9.1)
Severe	10 (3.4)	20 (6.7)	17 (5.7)	33 (11.1)

COPD: Chronic obstructive pulmonary disease; GERD: Gastroesophageal reflux disease

Table 2: Risk assessment and incidence rate for OF

User	Osteoporotic Fractures (N=103)	Incidence Rate per 100 persons	Adjusted Odds Ratio	*P*-value
Control	10	2.36	Reference	Reference
NSAIDs	49	11.58	1.26 (1.22-1.81)	0.045
Corticosteroids	23	5.44	1.46 (1.57-2.32)	0.312
DMARDs	21	4.96	1.83 (1.26-1.67)	0.063

These data are shown in Table 3. The results of logistic regression analysis of the association of NSAID, corticosteroid and DMARD with co-morbidities (with control group as reference), are presented in Table 4. NSAID group was significantly associated with cardiovascular diseases (p = 0.05 (OR = 3.92; 95 % CI: 0.97 - 15.91)) and hepatobiliary diseases (p = 0.02 (OR = 5.63; 95 % CI: 1.37-23.17)). In addition, the DMARD group was significantly associated with hepatobiliary diseases (p = 0.04 (OR = 5.78; 95 % CI: 1.12 - 29.85)).

Table 3: Risk assessment based on type of fracture

Item	Spine (N=39)		Hip (N=24)		Wrist (N=16)		Forearm (N=17)		Pelvis (N=7)	
Drug Class (Total no of OF)	Cases	frequency	Cases	frequency	Cases	frequency	Cases	frequency	Cases	frequency
Control (N=10)	3	30.0	2	20.0	2	20.0	1	10.0	2	20.0
NSAIDs (N=49)	20	40.82	11	22.45	8	16.33	7	14.29	3	6.12
Corticosteroids (N=23)	8	34.78	6	26.09	4	17.39	4	17.39	1	4.35
DMARDs (N=21)	8	38.10	5	23.81	2	9.52	5	23.81	1	4.76

Note: OF: Osteoporotic fracture

Table 4: Logistic regression analysis on the association of NSAID and co-morbidities with control group as the reference

Intercept	NSAID		Corticosteroids		DMARDs	
	Odds ratio	*P*-value	Odds ratio	*P*-value	Odds ratio	*P*-value
Asthma	0.69 (0.22-2.14)	0.52	1.71 (0.53-5.51)	0.37	3.13 (0.86-11.34)	0.08
Cardiovascular	3.92 (0.97-15.91)	0.05	3.94 (0.86-18.01)	0.08	5.78 (1.12-29.85)	0.04
COPD	0.82 (0.23-2.92)	0.77	2.56 (0.73-9.01)	0.14	2.17 (0.49-9.6)	0.31
Diabetes	1.55 (0.40-5.97)	0.53	2.66 (0.64-11.06)	0.18	1.91 (1.23-2.34)	0.69
GERD	0.39 (0.12-1.27)	0.12	1.72 (0.57-5.22)	0.34	2.76 (.79-9.61)	0.11
Hepatobiliary	5.63 (1.37-23.17)	0.02	2.89 (0.95-8.82)	0.06	2.83 (0.85-9.47)	0.09
Hypothyroidism	1.62 (0.63-4.15)	0.32	0.82 (0.25-2.63)	0.74	8.67 (2.01-17.38)	0.07
Major infections	1.24 (0.43-3.56)	0.69	1.82 (0.67-3.12)	0.43	2.41 (0.64-9.03)	0.19
Renal Diseases	1.11 (0.31-4.06)	0.87	1.9 (0.48-7.47)	0.36	1.31 (0.92-3.78)	0.71

DISCUSSION

In the present investigation, users of NSAIDs had a 5-fold possibility of developing osteoporotic fracture, when compared to control group, and 2-fold possibility of developing the disease, when compared to the users of corticosteroids and DMARDs. Many RA patients receiving NSAIDs for a year or longer had serious health-threatening issues related to osteoporotic fractures, as well as upper gastrointestinal medical occasions such as tumors, ulcers, diverticula and strictures [13]. In terms of mechanism of action, COX-2 inhibitors are the most specific NSAIDs that are essentially effective in suppressing pain aggravation, which makes them viable candidates in the development of drugs for joint pain [14]. The study also observed that the use of NSAIDs was associated with a higher risk for fractures of the spine, hip, wrist, and forearms, especially the use of COX-2 inhibitors. Selective COX-2 inhibitors also serve as NSAIDs which effectively target COX-2, resulting in mild irritation and pain that ultimately reduce the likelihood of developing peptic ulcers [15].

It has been reported that randomized controlled trials (RCTs) zeroing in on the safety of other NSAIDs (e.g., etoricoxib) resulted in poor outcomes regarding gastrointestinal and cardiovascular effects [15]. Despite their ideal gastrointestinal after-effects, cyclooxygenase (COX)-2 inhibitors (COXIBs) are still inadequate in the treatment of RA, chiefly due to their cardiovascular (CV) secondary properties and high cost [16]. The pathogenesis of RA is determined through continuous tests which, by and large, depict an interplay of hereditary factors and atherogenic antigens which enhance bone and joint destruction [17]. The occurrence of gastrointestinal events related to NSAIDs significantly rises in the presence of risk factors such as previous incidents or advanced age. This is because treating severe patients through a protective mechanism such as the use of a specific COX-2 inhibitor rofecoxib, averts clinical gastrointestinal incidents [18]. In a published study, NSAIDs were used along with other anti-inflammatory agents, anti-platelets, anticoagulants, misoprostol, sucralfate and proton pump inhibitors [19]. This is important in limiting the gastrointestinal risk associated with using NSAIDs in the general populace [19]. In another study, it was observed that RA patients aged 65 - 74 years who were on NSAIDs were seriously incapacitated due to rheumatoid joint pain, and they were prone to moderate physical handicaps [20]. Moreover, incapacitation due to RA is linked to a high incidence of mortality.

The Wellbeing Evaluation Poll, specifically the Health Assessment Questionnaire (HAQ) record for individuals with RA, has identified variations in standard deviation in HAQ scores correlating proportionally with the likelihood of mortality among users of NSAIDs [20]. Patients with rheumatic ailments such as rheumatoid joint inflammation and osteoarthritis, present with agony and joint stiffness which are significant

pointers of decreased well-being [21]. In another study, a wide overview of the treatment of 253 RA patients was presented, with a total of 143 patients on NSAIDs [22]. Sick people have serious issues regarding the adverse effects of NSAIDs [23]. Moreover, RA patients are of great concern because they are viewed as ongoing users of NSAIDs [24].

However, there was no significant difference in the adverse side effects and osteoporotic fracture between users of NSAIDs and patients on co-medications such as anticoagulants, angiotensin-converting enzyme (ACE) inhibitors, anti-diabetics and thyroid medications. It has been hypothesized that the adverse side effects of NSAIDs may be linked to the harmful impacts of the medications on platelets and endothelial cells [25]. On the other hand, corticosteroids are considered unfriendly to the gastrointestinal environment, and on many occasions, methotrexate, a DMARD drug, is utilized in the treatment of RA. Thus, the adverse effects are considered to arise from the antagonistic impacts of joint treatment [26].

However, in the present study, the use of corticosteroids and DMARDs resulted in a lower risk of osteoporotic fracture than the use of NSAIDs. In addition, the risk of osteoporotic fracture was neither associated with drinking alcohol nor tobacco smoking status, a clear indication that osteoporotic fracture was due to the side effects of NSAIDs. Thus, it is plausible to infer that the osteoporotic fracture could be mainly due to the individual effect of NSAIDs, rather than other factors.

Limitations of this study

The study has several limitations. Firstly, the study population is relatively small and specific to a particular geographical region. Secondly, it predominantly focuses on the Han Chinese population, making the results less directly applicable to other ethnic groups. Thirdly, the study covers only a short period, lacking insights into long-term effects and potential changes over extended periods. Nevertheless, the study introduces various possibilities for future research, providing avenues to enhance the understanding of the correlation between non-steroidal anti-inflammatory drugs (NSAIDs) and osteoporotic fractures in individuals with rheumatoid arthritis. This investigation is positioned to assist scientists and clinicians in refining their understanding of the relationship between NSAID utilization and osteoporotic fractures, ultimately guiding more informed treatment decisions and leading to improved patient outcomes.

CONCLUSION

This study has demonstrated that the use of NSAIDs such as celecoxib, diclofenac, ibuprofen, indomethacin, and oxaprozin in RA patients increases the risk of osteoporotic fracture. The study rules out any association between the risk of osteoporotic fracture and drinking and smoking status. Osteoporotic fracture was neither associated with other co-medications nor with comorbidities such as cardiovascular disease, diabetes, hepatobiliary, and renal diseases. Thus, osteoporotic fractures seen in this investigation might be due to the individual effects of the NSAIDs. Therefore, it may be reasonably advised that NSAIDs should be used with proper counseling in RA patients to prevent the risk of osteoporotic fracture. Since NSAIDs are used over longer periods, there is the need in future to extend the study duration to determine the long-term effects and potential changes in the bones.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Jianxiang Zhu, Zengbing Xia, Jikang Min, Wenlin Hu, Heng Li and Chao Mei conceived and designed the

study, collected, analyzed and interpreted the experimental data, drafted the manuscript and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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