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Acute kidney injury in gout: prevalence and risk factors through two decades

Nuria Perez-Herrero[1], Jose Manuel Urbizu-Gallardo[2,3], Fernando Perez-Ruiz[2,4]*

[1]Medicine and Nursery School, University of the Basque Country, 48903 Barakaldo, Spain
[2]Medicine Department, Medicine and Nursery School, University of the Basque Country, 48903 Barakaldo, Spain
[3]Osakidetza, OSI EEC, Cruces University Hospital, Nephrology Division, 48903 Barakaldo, Spain
[4]Osakidetza, OSI EEC, Cruces University Hospital, Rheumatology Division, 48903 Barakaldo, Spain

***Correspondence:** Fernando Perez-Ruiz, Osakidetza, OSI EEC, Cruces University Hospital, Rheumatology Division, Pza Cruces sn, 48903 Barakaldo, Spain. fperezruiz@telefonica.net
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Abstract

Aim: To compare the rate of acute kidney injury (AKI) associated with non-steroidal anti-inflammatory drugs (NSAIDs) through two consecutive decades in patients with gout and to study factors associated with AKI events.

Methods: Retrospective analysis of data from Jan 1994 to Dec 2024. Data on AKI and upper gastrointestinal bleeding (UGB) were collected during the same period (2005–2024), along with general (age, gender, time from onset), gout-related (tophi, imaging, clinical distribution, number of flares), treatment-related (diuretic and urate-lowering medications, exposure to the triple whammy), and comorbidities-related variables (hypertension, hyperlipidemia, diabetes, chronic kidney disease). Analysis was made for the whole cohort and comparing decades with each other. Survival analysis was performed to evaluate those variables independently associated with a higher risk of AKI.

Results: 1,207 cases were available for analysis. The overall cumulated rate of AKI was 13.3%, showing an increase from 9.9% to 16.1% from the first to the second decades, respectively, but no change in the severity of AKI was observed. In contrast, there was no change in the rate of UGB through the two decades (close to 2%). There was an increase in the frequency of gout severity variables, triple whammy exposure, and comorbid conditions through the two decades. Age, tophaceous gout, chronic kidney disease, triple whammy exposure, were variables independently associated with a higher risk of AKI, while urate-lowering prescription was associated with a lower risk.

Conclusions: An increase in the rate of AKI was observed through the two decades studied, associated with an increase in gout severity, comorbidity, and exposure to triple whammy. Chronic kidney disease and exposure to triple whammy in older patients with severe (tophaceous) gout seem to define the combination for the highest risk, in whom the avoidance of NSAIDs should be carefully considered.

Keywords

gout, kidney injury, chronic kidney disease, NSAIDs, triple whammy

Introduction

Gout is a disease caused by the inflammatory response, either acute (gout flares) or chronic (erosive gout), caused by monosodium urate crystals that nucleate, grow, and aggregate in the tissues, mainly in anatomical structures with synovial lining (joints, bursae, and tendons) [1].

Gout is the most common inflammatory arthritis in developed countries, and its prevalence in adult population in our setting is estimated to be 2.4% [2], similar to that of nearby European countries. Gout prevalence increases with aging and aging-associated comorbidities, such as renal and cardiovascular diseases, and diseases associated classically with renal and cardiovascular diseases, such as hypertension, diabetes, and hyperlipidemia [3].

Gout flares are the clinical hallmark of gout, and are mostly treated with non-steroidal anti-inflammatory drugs (NSAIDs) [4]. NSAID prescription is a well-recognized risk factor for acute kidney injury (AKI) [5], especially if they interact with medications prescribed for arterial hypertension, such as the angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor antagonists (ARA2), and diuretics, which is known as the "triple whammy (TW)" [6]. Chronic kidney disease (CKD) is also to be considered among those main risk factors associated with the risk of suffering AKI while on NSAIDs [7]. Gout patients are at heightened risk of AKI due to frequent NSAID use, pre-existing CKD, and concurrent TW exposure. However, longitudinal data on AKI trends in this population remain scarce.

In our clinical setting, the electronic prescription system for medications alerts through a "pop-up" message that the patient is subject to be exposed to the TW. The prescriber may consider an alternative prescription for NSAID, and therefore avoid the risk of AKI.

This study compares the last two decades, as the alert system was implemented during the second decade studied, the cumulated prevalence and risk factors for AKI, and we therefore expected that the alert on TW prescription would have reduced (or at least maintained stable) the rate of AKI. We have also studied the cumulative prevalence of upper gastrointestinal bleeding (UGB) in patients with gout exposed to NSAIDs, as the use of proton pump inhibitors (PPIs) to avoid NSAID-induced UGB in our clinical setting is universally implemented.

Materials and methods

We retrospectively analyzed data from a consecutively recruited nested cohort of patients with gout in a 4th level university hospital with a close to 400,000 referral population. This follow-up cohort was evaluated and approved by the Clinical Investigation Ethics Committee (code E03/45). All patients gave written consent, and the dataset was anonymized. The protocol was last amended to comply with the 2013 version of the Helsinki Declaration.

A pop-up alert on TW exposure was implemented in the electronic medication prescription, and therefore we compared the 2015–2024 decade to the 2005–2014 decade. Data gathered at entrance in the cohort include general variables (age, gender, time from the onset of the disease, either self-reported or retrieved from the date of diagnosis coding), variables specifically defining gout (self-reported number of flares in the previous year), presence of subcutaneous tophi in physical examination, observation of tophi during ultrasonographic examination in any of previously involved joints, radiographic structural joint damage (erosions and arthropathy), previous urate-lowering therapy (ULT), comorbid conditions such as hypertension and related treatments (ARA2, ACEi, diuretics), diabetes, hyperlipidemia, previous cardiovascular events, renal function evaluated as estimated glomerular filtration rate (eGFR). Blood biochemistry data were also available for glucose, urate, creatinine, total cholesterol, low-density lipoproteins, high density lipoproteins, and triglycerides.

Cases of AKI were defined according the "risk, injury, failure, loss, end stage (RIFLE)" criteria for AKI [8] from 2005 to 2013 and from 2014 onwards according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [9], as a sudden change in serum creatinine levels of at least 0.3 mg/dL in 48 h or an increase in 1.5 times the baseline creatinine levels in the previous week. AKI cases defined by the RIFLE criteria were reviewed and had to fit the new KDIGO definition to be considered as an AKI case.

AKI events were also graded (grades 1, 2, and 3) according to the referenced KDIGO guidelines [10]. Pre-renal AKI neatly associated with a clinically relevant UGB was not recorded as an AKI event, but as a UGB event.

UGB events were defined if hematemesis, bloody stools, or the endoscopy observation of a recent bleeding or an ulcer over the Treitz joint associated with a decrease of at least 2 g/dL of hemoglobin in the previous days was specifically recorded in the electronic file.

Comorbid conditions (hypertension, diabetes, hyperlipidemia) were codified according to varying international definitions at each period or by the presence of an active prescription of medications with specific indications. A previous vascular event was considered if angina, myocardial infarction, heart failure, cerebral vascular ischemia, or clinically relevant peripheric ischemia were recorded or coded in the electronic file.

eGFR was automatically calculated at each period by the software of the auto-analyzers. Different formulae were used consecutively according to international recommendations: Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). The TW was defined as concomitant ARA2 or ACEi with a diuretic and an NSAID [6].

We compared the rates of AKI and UGB in two decades: decade 1 from 2005 to 2014 (D1) and decade 2 from 2015 to 2024 (D2) in order to evaluate whether the rate of UGB would remain low, as expected, by the usual prescription PPIs [11]. In contrast, we cannot prescribe kidney-protective therapy to avoid the deleterious effects of NSAIDs, but we expected electronic alerts during prescription to reduce the risk of AKI.

Statistical analysis was made using an integrated statistical package with an institutional license, IBM SPSS V29.0. We performed a descriptive, exploratory bivariate analysis to find variables plausibly associated with AKI using Student's *T* test for continuous variables and Chi square for discrete variables. The results of continuous variables are shown as means ± standard deviation (SD; median, interquartile interval) and discrete variables as percentages. Missing data rate was null for all variables, except for ultrasound and X-ray, which did not reach 10%.

Kaplan-Meier survival analysis (Mantel-Cox log-rank test) was performed using time from onset of gout to AKI event as time exposed to NSAIDs. Those variables showing statistical significance < 0.2 in the Kaplan-Meier survival analysis were considered plausibly associated and selected for Cox proportional hazard survival analysis.

Results

Data from 1,207 patients were available for analysis; 544 from D1, and 663 from D2. There were 1,074 (89.0%) men and 133 (11.0%) women, mean age being 65.0 ± 13.9 years (66, 55–76), time from onset of gout to entrance in the cohort 6.5 ± 7.3 years (2, 2–4), and the number of flares in the year previous to first visit was 3.7 ± 6.6 (2, 1–6). The rates of discrete variables of the population sample are shown in Table 1.

Table 1. Frequency of discrete variables from available data.

Variable	*N*	%
Previous ULT prescription	568/1,207	47.1
Polyarticular involvement (> 4 joints ever)	417/1,207	34.5
Subcutaneous tophi	399/1,207	33.1

Table 1. Frequency of discrete variables from available data. (*continued*)

Variable	*N*	%
Ultrasonographic tophi	772/1,120	68.9
Joint damage in plain X-ray	684/1,207	56.7
Ethanol intake > 15 g/day	369/1,207	30.6
Arterial hypertension	815/1,207	67.5
Diabetes mellitus	333/1,207	27.6
Hyperlipidemia	719/1,207	59.6
Previous vascular event	404/1,207	33.5
CKD (eGFR < 60 mL/min)	480/1,207	39.8
Triple whammy	477/1,207	39.5

Ultrasonography was available for most, but not all patients. ULT: urate-lowering therapy; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

The overall cumulated rate of AKI was 13.3%, increasing from 9.9% to 16.1% from D1 to D2, whereas there was no increase, but a non-significant numerical decrease, in UGB (Table 2). There were 5 cases of AKI associated with UGB, and were codified as UGB.

Table 2. Rates of AKI and UGB globally and for each decade analyzed, shown as percentages and odds ratios with 95% confidence interval limits (95% CIL).

Event	Overall	D1	D2	Odds ratio (95% CIL)	*p*
AKI	161/1,207	54/544	107/663	1.746	0.002
	(13.3%)	(9.9%)	(16.1%)	(1.232–2.476)	
UGB	26/1,207	13/544	13/663	0.817	0.610
	(2.2%)	(2.4%)	(2.0%)	(0.376–1.777)	

AKI: acute kidney injury; UGB: upper gastrointestinal bleeding; D1: decade 1 from 2005 to 2014; D2: decade 2 from 2015 to 2024.

We did not observe a statistically significant relationship between AKI and UGB events, although the rate of UGB was higher in patients with AKI (Table 3).

Table 3. Relationship between AKI and UGB episodes.

	AKI (–)	AKI (+)	*N*
UGB (–)	1,025	156	1,181
UGB (+)	21	5	26
N	1,046	161	1,207

Chi square test, $p = 0.372$. Odds ratio 1.56 (95% CIL 0.58–4.21). AKI: acute kidney injury; UGB: upper gastrointestinal bleeding.

Although there was an increase in the frequency of AKI, we did not observe significant differences in AKI severity through the two decades, grade 3 cases comprising 9.3% and 15.9% for D1 and D2, respectively (Table 4).

Table 4. Severity of AKI, globally and in each decade studied.

AKI	Overall	D1	D2
Grade 1	62/161	24/54	38/107
	(38.5%)	(44.4%)	(35.5%)
Grade 2	77/161	25/54	52/107
	(47.8%)	(46.3%)	(48.6%)
Grade 3	22/161	5/54	17/107
	(13.7%)	(9.3%)	(15.9%)

Chi square test, $p = 0.380$. AKI: acute kidney injury; D1: decade 1 from 2005 to 2014; D2: decade 2 from 2015 to 2024.

In bivariate analysis, age, time from onset of gout, serum urate level, subcutaneous and ultrasonographic tophi, polyarticular involvement, presence of lesions in plain X-ray, hypertension, diabetes, previous vascular event, renal function impairment, and TW exposure were significantly associated with AKI (Table 5).

Table 5. Variables associated with AKI in bivariate analysis.

Variables	AKI (–)	AKI (+)	*p*
Age (years)	**63.9 ± 13.9**	**72.3 ± 11.8**	**< 0.001**
Time from onset of gout (years)	**6.3 ± 7.2**	**7.8 ± 7.9**	**0.026**
Serum urate at baseline (mg/dL)	**9.1 ± 1.5**	**9.6 ± 1.5**	**< 0.001**
Number of flares (previous year)	2.2 ± 2.3	2.4 ± 3.2	0.236
Gender (woman)	120/1,046 (11.5%)	13/161 (8.1%)	0.249
Subcutaneous tophi	**326/1,046 (31.2%)**	**73/161 (45.3%)**	**< 0.001**
Ultrasonographic tophi	**657/964 (68.2%)**	**115/156 (73.7%)**	**0.164**
Severe joint damage in plain X-ray	**189/1,046 (18.1%)**	**46/161 (28.6%)**	**0.002**
Polyarticular involvement (> 4 joints ever)	**335/1,046 (32.0%)**	**82/161 (50.9%)**	**< 0.001**
Ethanol intake (> 15 g/day)	321/1,046 (30.7%)	48/161 (29.8%)	0.832
Arterial hypertension	**675/1,046 (64.5%)**	**140/161 (87.0%)**	**< 0.001**
Previous ULT prescription	492/1,046 (47.0%)	76/161 (47.2%)	0.968
Triple whammy	**377/1,046 (36.0%)**	**100/161 (62.1%)**	**< 0.001**
Hyperlipidemia	622/1,046 (59.5%)	97/161 (60.2%)	0.861
Diabetes	**271/1,046 (25.9%)**	**62/161 (38.5%)**	**< 0.001**
Previous vascular event	**329/1,046 (31.5%)**	**75/161 (46.6%)**	**< 0.001**
CKD (eGFR < 60 mL/min)	**362/1,046 (34.6%)**	**118/161 (73.3%)**	**< 0.001**

Statistically significant variables are shown in bold. AKI: acute kidney injury; ULT: urate-lowering therapy; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

We further analyzed whether there were differences in the rates of the previous significant variables through both decades that could explain the increase in the rate of AKI in D2. In D2, patients were older, showed more severe gout, and increased frequency of comorbid conditions (Table 6).

Table 6. Differences in variables associated with AKI through the two decades studied.

Variables	D1	D2	*p*
Age (years)	**62.2 ± 13.3**	**67.3 ± 14.0**	**< 0.001**
Time from onset (years)	**7.0 ± 7.7**	**6.1 ± 6.9**	**0.016**
Serum urate at baseline (mg/dL)	**9.0 ± 1.4**	**9.3 ± 1.5**	**< 0.001**
Previous ULT prescription	245/544 (45.0%)	323/663 (48.7%)	0.202
Subcutaneous tophi	**199/544 (36.6%)**	**200/663 (30.2%)**	**0.018**
Polyarticular involvement (> 4 joints ever)	**169/544 (31.1%)**	**248/663 (37.4%)**	**0.021**
Joint damage in plain X-ray	**248/544 (45.6%)**	**436/663 (65.8%)**	**0.001**
Ultrasonographic tophi	324/460 (70.4%)	448/660 (67.9%)	0.363
Ethanol intake (> 15 g/day)	**191/544 (35.1%)**	**178/663 (26.8%)**	**0.002**
Arterial hypertension	**309/544 (56.8%)**	**506/663 (76.3%)**	**< 0.001**
Diuretic prescription	**193/544 (35.5%)**	**303/663 (45.7%)**	**< 0.001**
Triple whammy	**183/544 (33.6%)**	**294/663 (44.3%)**	**< 0.001**
Hyperlipidemia	**281/544 (51.7%)**	**438/663 (66.1%)**	**< 0.001**
Diabetes	**129/544 (23.7%)**	**204/663 (30.8%)**	**0.006**
Previous vascular event	**171/544 (31.4%)**	**233/663 (35.1%)**	**0.174**
CKD (eGFR < 60 mL/min)	**197/544 (36.2%)**	**283/663 (42.7%)**	**0.022**

Variables statistically significant are shown in bold. AKI: acute kidney injury; D1: decade 1 from 2005 to 2014; D2: decade 2 from 2015 to 2024; ULT: urate-lowering therapy; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

Afterwards, we performed Kaplan-Meier survival analysis with time from onset of gout as the time exposed to NSAIDs. Variables plausibly associated with AKI were the following: number of flares the previous year ($p = 0.018$), polyarticular involvement ($p = 0.086$), subcutaneous tophi ($p = 0.026$), X-ray damage ($p = 0.016$), exposure to TW ($p < 0.001$), diabetes ($p = 0.002$), eGFR < 60 mL/min ($p < 0.001$), previous vascular event ($p < 0.001$), and previous ULT ($p < 0.001$).

In Cox proportional hazard survival analysis, only age, eGFR < 60 mL/min, presence of subcutaneous tophi, and exposure to TW were independently associated with increased risk of AKI, whilst previous ULT was associated with a lower risk (Table 7).

Table 7. Variables independently associated with AKI in Cox proportional hazard survival analysis.

Variables	Risk	95% CIL	*p*
Age (per year exposed)	1.022	1.006–1.039	0.006
Triple whammy	1.754	1.240–2.482	0.001
Subcutaneous tophi	2.133	1.514–3.005	< 0.001
CKD (eGFR < 60 mL/min)	3.144	2.113–4.678	< 0.001
Previous ULT prescription	0.599	0.435–0.824	0.002

AKI: acute kidney injury; CIL: confidence interval limits; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ULT: urate-lowering therapy.

The presence of subcutaneous tophi was the only variable of gout severity associated independently with AKI events. We further analyzed the association of subcutaneous tophi with other gout severity related variables to ascertain whether tophaceous gout could be a surrogate of gout severity. The intimate relationship between tophaceous gout and other variables related to gout severity (ultrasound, X-ray, serum urate level, number of flares, polyarticular involvement) is shown in Table 8.

Table 8. Relationship between the presence of subcutaneous tophi and other gout severity related variables.

Variables	Without subcutaneous tophi	With subcutaneous tophi	*p*
Serum urate at baseline (mg/dL)	9.00 ± 1.33	9.58 ± 1.66	< 0.001
Number of flares in the previous year	2.6 ± 2.30	5.87 ± 6.81	< 0.001
Ultrasonographic tophi	398/742 (53.6%)	374/378 (98.9%)	< 0.001
Severe joint damage in plain X-ray	39/808 (4.8%)	196/399 (49.1%)	< 0.001
Polyarticular involvement	130/808 (16.1%)	287/399 (71.9%)	< 0.001

Discussion

The overall cumulated rate of AKI in our series exceeds 10%. This could be explained somehow because the population analyzed is referred to a fourth level hospital, therefore selecting the most severe cases in patients with the highest rate of comorbid conditions. Indeed, close to one third of the patients showed clinically relevant CKD, diabetes, a previous vascular event, polyarticular joint involvement, and tophaceous gout. Even more, two thirds suffered from hypertension, hyperlipidemia, and showed joint damage in plain X-ray. AKI has been reported to be more frequent in patients with comorbid conditions, mostly related to cardiovascular and renal risk factors [12], although others have reported AKI not to be associated with previous ischemic heart disease [7]. This could be due to the common use of anticoagulants, therefore limiting the prescription of NSAIDs.

We have observed a neat increase in the rate of AKI through the two decades analyzed, from 9.9% to 16.1%, although severity grading has not changed, fortunately being mild to moderate in close to 90%. We assume that the increase may be related to aging, more frequent comorbidities, such as hypertension, hyperlipidemia, and CKD, and more frequent exposure to diuretic medications, and therefore to TW. The increase in comorbidities such as hypertension, hyperlipidemia, and diabetes could be partially explained by changes in the international cut-off points for definitions, but does not explain the increase in clinically

significant CKD, as the cut-off point was calculated as eGFR < 60 mL/min, and both formulae used (MDRD and CKD-EPI) perform similarly in the lowest range of renal function [13].

Aldosterone inhibitors in monotherapy and prescription of thiazide diuretics concomitantly with ACEi have been reported to be more commonly associated with AKI, but no differences were observed between different NSAIDs [7].

Exposure to the TW has been reported overall to be associated with a 0.66 increase in the risk of developing AKI [14], while in our series, the risk was independently increased by 1.75 times. Once again, it could be explained by differences in the high rate of comorbid conditions present in our hospital-based population.

The rate of exposure to TW in the general population has been reported to range from 8% to 14% [15], while in our gout population was overall 39.5%, once again probably related to the high frequency of hypertension, CKD, and cardiovascular disease. Interestingly, the rate of exposure to TW increased from 34 to 44% through the two decades studied. The increase in exposure to TW from the D1 to D2 was observed even despite that a software alarm system was implemented during the second decade, alerting physicians with a pop-up message while prescribing the risk of exposure to TW, although this kind of alerts have been considered to be useful in preventing TW exposure [15].

The presence of tophi, associated as it was with other variables of gout severity (number of flares, joint structural damage, polyarticular involvement), could be considered as a surrogate of gout severity and therefore of the likelihood of more frequent use of NSAIDs. Aging has been considered, associated with other factors, to be associated with AKI, probably by changes in pharmacokinetics related to physiological aging [16].

The mechanisms for the TW effect are complex, mainly explained by changes induced by medications in the regulation of blood supply to the kidney [17]. In addition to the TW combination, other drugs have been reported, although not as consistently, to be associated with increased risk of AKI, such as PPIs [18], sodium-glucose transporter-2 inhibitors [19], and even allopurinol [20]. The effect of allopurinol on renal disease was shown to be neutral in the CKD-FIX clinical trial [21]. Nevertheless, we have found the allopurinol prescription was associated with a lower risk of AKI in our cohort. We are more prone to hypothesize, despite that different mechanisms have been claimed for this controversial effect, and that we lack data to support it, that physicians prescribing ULT for gout may be more prone to be closer to strict control of comorbidities.

Other factors also associated with increased risk of AKI include in-hospital admission [22], as acute clinical situations may derive on hypoperfusion, including diuretic use [23]. The presence of CKD is also commonly associated with AKI in patients exposed to TW [24], which has been proposed to be named as “quadruple whammy” [25].

AKI associated with TW seems to be generally associated in the short term after exposure, ranging from 6 to 9 days, depending on the different drugs combined [26], which is the most frequent kind of prescription for gout flares: short-term, high-dose of potent NSAIDs [4]. Patients with gout and CKD should be especially considered when designing treatment [27]. Proper clinical control of gout, therefore avoiding flares, and thus NSAIDs prescription has been associated with improvement in renal function, especially in those patients with previously reduced renal function while on NSAIDs prescription [28].

Alternatives to NSAIDs in patients at risk of developing serious adverse events include corticosteroids, corticotropin and derivatives, and interleukin-1 inhibitors [29]. Reviews comparing NSAIDs with corticosteroids for gout are mostly centered on short-term trials for the treatment of flares, where safety is mainly focused on gastrointestinal tolerability, as patients with kidney disease are systematically excluded [30]. Therefore, there is a lack of longitudinal data on the renal effects of repeated exposure to NSAIDs in patients with gout.

There are limitations to the study. Data on the specific NSAID, dose, and time of exposure to NSAIDs were not collected or available, as the electronic prescription started in 2011. Also, AKI event was considered as any AKI ever previous to inclusion, but data on repeated events were not collected, and a previous history of suffering a previous AKI associated with NSAIDs could be a relevant risk factor for suffering a subsequent AKI event.

Conclusions and clinical implications

We have observed an increase in the cumulative rate of AKI in patients with gout. Severity of the disease, as a surrogate for more frequent use of NSAIDs, renal function impairment, and exposure to the TW, has been observed to be significantly and independently associated with a higher risk of AKI. Avoiding the TW combination should be firmly encouraged, especially in patients with CKD, as today we do not have "nephro-protective" medications to prevent AKI as we have PPIs for UGB.

Patients at risk of AKI should be considered for alternative therapies to NSAIDs. Alternatives, such as corticosteroids or interleukin-1 inhibitors, should be considered. Proper ULT is associated with a reduction of flares and should be considered the milestone of the treatment of gout.

Abbreviations

ACEi: angiotensin converting enzyme inhibitors

AKI: acute kidney injury

ARA2: angiotensin II receptor antagonists

CKD: chronic kidney disease

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

D1: decade 1 from 2005 to 2014

D2: decade 2 from 2015 to 2024

eGFR: estimated glomerular filtration rate

KDIGO: Kidney Disease: Improving Global Outcomes

MDRD: Modification of Diet in Renal Disease

NSAIDs: non-steroidal anti-inflammatory drugs

PPIs: proton pump inhibitors

RIFLE: risk, injury, failure, loss, end stage

TW: triple whammy

UGB: upper gastrointestinal bleeding

ULT: urate-lowering therapy

Declarations

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Author contributions

NPH: Conceptualization, Formal analysis, Validation, Writing—original draft, Writing—review & editing. JMUG: Validation, Writing—original draft, Writing—review & editing. FPR: Funding acquisition, Conceptualization, Investigation, Formal analysis, Validation, Writing—original draft, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

Fernando Perez-Ruiz, who is the Editor-in-Chief and Guest Editor of *Exploration of Musculoskeletal Diseases*, had no involvement in the decision-making or the review process of this manuscript. Other conflicts of interest related to the topic of the paper: Fernando Perez-Ruiz: advisor for Amgen, Arthrosi, Crystalyx, Protalix, Shanton, SNIPR, and SOBI; speaker for Menarini, EULAR, and Spanish Foundation for Rheumatology; grants from Cruces Rheumatology Association. Educational work for Spanish Foundation for Rheumatology; editorial work for Wolters-Kluwer. The other authors declare no conflicts of interest.

Ethical approval

The present cohort recruitment was approved by the OSI EEC Clinical Investigation Ethics Committee with approval reference code E03/45.

Consent to participate

Informed consent to participation in the study was obtained from all participants.

Consent to publication

Not applicable.

Availability of data and materials

The datasets generated for this study can be shared on request to the corresponding author, provided CEIC OSI EEC approval.

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Publisher's note

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