Research Article

ลักษณะทางคลินิกของอาการไม่พึงประสงค์ชนิดภูมิไวเกินจากยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์: การเปรียบเทียบระหว่างยาที่ยับยั้งไซโคลออกซีจีเนส-1 และไซโคลออกซีจีเนส-2

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บทคัดย่อ

ลักษณะทางคลินิกของอาการไม่พึงประสงค์ชนิดภูมิไวเกินจากยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์: การเปรียบเทียบระหว่างยาที่ยับยั้งไซโคลออกซีจีเนส-1 และไซโคลออกซีจีเนส-2

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ยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์เป็นสาเหตุที่พบบ่อยของภาวะภูมิไวเกินจากยา ซึ่งมีลักษณะอาการทางคลินิกที่หลากหลาย ตั้งแต่ปฏิกิริยาแบบการตอบสนองที่เกิดขึ้นในลักษณะไขว้กันระหว่างกลุ่มยา ที่เกี่ยวข้องกับการยับยั้งไซโคลออกซีจีเนส-1 ไปจนถึงปฏิกิริยาทางภูมิคุ้มกันแบบจำเพาะ อย่างไรก็ตาม ข้อมูลเชิงเปรียบเทียบจากสภาวะการใช้งานจริงระหว่างยากลุ่มยับยั้งไซโคลออกซีจีเนส-1 และไซโคลออกซีจีเนส-2 ยังมีจำกัด การศึกษานี้มีวัตถุประสงค์เพื่อเปรียบเทียบลักษณะทางคลินิก ระดับความรุนแรงและความร้ายแรงของภาวะภูมิไวเกินจากยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ระหว่างกลุ่มยาที่ยับยั้งไซโคลออกซีจีเนส-1 และ ไซโคลออกซีจีเนส-2 **วิธีการศึกษา:** การศึกษานี้เป็นการศึกษาแบบย้อนหลังโดยใช้เฉพาะกลุ่มกรณีศึกษา ที่โรงพยาบาลศรีนครินทร์ ระหว่างปี พ.ศ. 2564 ถึง 2566 คัดเลือกผู้ป่วยที่เกิดภาวะภูมิไวเกินจา กยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ จากรหัสวินิจฉัยในเวชระเบียนอิเล็กทรอนิกส์ และยืนยันด้วยการทบทวนข้อมู ลทางคลินิกร่วมกับการประเมินความสัมพันธ์เชิงสาเหตุโดยใช้ นารันโจ อัลกอริทึม ผู้ป่วยถูกจำแนกเป็นผู้ได้รับยา ไซโคลออกซีจีเนส-1 และ ไซโคลออกซีจีเนส-2 อินฮิบิเตอร์ ทำการเปรียบเทียบลักษณะอาการทางคลินิก ระดับความรุนแรงและความร้ายแรงของภาวะภูมิไวเกินระหว่างกลุ่ม และใช้การวิเคราะห์ถดถอยแบบลอค-ไบนอเมียล เพื่อระบุปัจจัยที่มีความสัมพันธ์อย่างอิสระกับลักษณะของอาการ โดยใช้ข้อมูลเฉพาะผู้ป่วยที่มีข้อมูลครบถ้วน **ผลการศึกษา:** จากผู้ป่วยทั้งหมด 1,167 ราย (ไซโคลออกซีจีเนส-1: 939 ราย; ไซโคลออกซีจีเนส-2: 228 ราย) ลักษณะพื้นฐานใกล้เคียงกัน ยกเว้นกลุ่ม ไซโคลออกซีจีเนส-2 มีอายุสูงกว่าอย่างมีนัยสำคัญ ($p<0.001$) โรคทางระบบกระดูกและกล้ามเนื้อพบมากในกลุ่ม ไซโคลออกซีจีเนส-2 ขณะที่โรคระบบทางเดินหายใจและโรคระบบอวัยวะสืบพันธุ์และทางเดินปัสสาวะพบมากในกลุ่ม ไซโคลออกซีจีเนส-1 ($p<0.05$) อาการทางผิวหนังเป็นลักษณะเด่นในทั้งสองกลุ่ม ภาวะแอนาฟิแล็กซิส พบมากกว่าในกลุ่ม ไซโคลออกซีจีเนส-1 อินฮิบิเตอร์ (6.84% เทียบกับ 3.12%, $p=0.037$) ขณะที่ fixed drug eruption, Stevens–Johnson syndrome และ mucositis พบมากกว่าในกลุ่ม ไซโคลออกซีจีเนส-2 ($p<0.05$) ระดับความรุนแรงและความร้ายแรงไม่แตกต่างกันอย่างมีนัยสำคัญ อายุมีความสัมพันธ์กับความแตกต่างของลักษณะอาการภายในกลุ่มผู้ป่วยที่เกิด ภาวะภูมิไวเกินอย่า งมีนัยสำคัญทางสถิติ (aRR 1.01 ต่อปี; 95% CI 1.01–1.02; $p<0.001$) **สรุปผล:** ยากลุ่ม ไซโคลออกซีจีเนส-1 อินฮิบิเตอร์และ ไซโคลออกซีจีเนส-2 อินฮิบิเตอร์มีรูปแบบอาการทางคลินิกแตกต่างกัน แต่มีระดับความรุนแรงใกล้เคียงกัน และอายุมีความสัมพันธ์กับความแตกต่างของลักษณะอาการภายในกลุ่มผู้ป่วยที่เกิดภาวะภูมิไวเกิน

คำสำคัญ: ไซโคลออกซีจีเนส-1 อินฮิบิเตอร์, ไซโคลออกซีจีเนส-2 อินฮิบิเตอร์, ภาวะภูมิไวเกินจากยา, นารันโจ อัลกอริทึม

Clinical Characteristics of Hypersensitivity Reactons to NSAIDs: A Comparison between COX-1 and COX-2 Inhibitors

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Abstract

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are a common cause of drug-induced hypersensitivity reactions (HSRs). These reactions present with diverse clinical manifestations, ranging from cross-reactive responses related to cyclooxygenase-1 (COX-1) inhibition to selective immunologically mediated reactions. However, real-world comparative data on HSRs between COX-1 and COX-2 inhibitors remain limited. This study aimed to compare the clinical characteristics, severity, and seriousness of NSAID-induced HSRs between COX-1 inhibitors and COX-2 inhibitors. **Methods:** We conducted a retrospective case-only study at Srinagarind Hospital between 1 January 2021 and 31 December 2023. Adult patients with NSAID-related HSRs were identified using diagnostic codes and subsequently validated through detailed review of clinical documentation. Causality was assessed using the Naranjo algorithm. Patients were classified according to the type of NSAID exposure into COX-1 inhibitor and COX-2 inhibitor groups. Clinical manifestations, severity, and seriousness of HSRs were compared between groups. Multivariable log-binomial regression analysis was performed to identify factors independently associated with differences in HSR characteristics, using a complete-case approach. **Results:** Among 1,167 patients (COX-1: n=939; COX-2: n=228), baseline characteristics were similar, although the COX-2 inhibitor group was older ($p<0.001$). Musculoskeletal disorders were more frequent in COX-2 users, while respiratory and genitourinary diseases were more common in COX-1 users ($p<0.05$). Cutaneous reactions predominated in both groups. Anaphylaxis was more common with the COX-1 inhibitor (6.84% vs 3.12%, $p=0.037$), whereas fixed drug eruption, Stevens–Johnson syndrome, and mucositis were more frequent with the COX-2 inhibitor ($p<0.05$). Severity and seriousness profiles did not differ significantly. Age was significantly associated with differences in the clinical characteristics of HSRs among patients. (adjusted risk reduction (aRR) 1.01 per year; 95% CI 1.01–1.02; $p<0.001$). **Conclusion:** Cyclooxygenase-1 inhibitors and cyclooxygenase-2 inhibitors have different patterns of clinical manifestations but similar levels of severity, and age is associated with differences in the characteristics of clinical manifestations within the group of patients who develop hypersensitivity reactions.

Keywords: COX-1 inhibitor, COX-2 inhibitor, hypersensitivity reaction, Naranjo algorithm

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed and self-administered medications worldwide for the management of pain, inflammation, and fever. Despite their widespread use and established efficacy, NSAIDs are consistently reported as one of the most common causes of drug HSRs worldwide, accounting for approximately 20–30% of all drug-induced HSRs in adults (Johansson *et al.*, 2004). The estimated prevalence of NSAID hypersensitivity in the general population ranges from 0.6% to 2.5%, (Nurmesa *et al.*, 2025) but this prevalence increases substantially in cross-reactive phenotypes, particularly those with chronic spontaneous urticaria, asthma, and aspirin-exacerbated respiratory disease (AERD), (Kennedy *et al.*, 2016) in whom reported rates range from approximately 20% to over 40%, depending on the population studied. Moreover, cross-reactive COX-1–mediated reactions constitute the majority of NSAID hypersensitivity cases, whereas selective reactions are less frequent but often clinically unpredictable and potentially severe (Koh *et al.*, 2025; Wöhrl, 2018; Romano *et al.*, 2023). Their pharmacological effects are mediated primarily through inhibition of cyclooxygenase (COX) enzymes, which exist as two major isoforms: COX-1 and COX-2. COX-1 is constitutively expressed and plays a critical role in maintaining gastrointestinal mucosal integrity, renal homeostasis, and platelet function, whereas COX-2 is inducible and predominantly responsible for the synthesis of pro-inflammatory prostaglandins during inflammatory processes (Nurmesa *et al.*, 2025; Blumenthal *et al.*, 2017).

Clinical characteristics of NSAID-induced HSRs (Kowalski *et al.*, 2013) are highly heterogeneous and depend on the underlying mechanisms, COX selectivity, and patient-specific risk factors. Cross-reactive reactions, predominantly mediated by COX-1 inhibition, account for the majority of cases and are characterized by reproducibility across structurally unrelated NSAIDs. These reactions typically occur within minutes to hours after drug exposure and may present as urticaria, angioedema, rhino-conjunctivitis, bronchospasm, or exacerbation of underlying respiratory disease. In contrast, selective HSRs are generally immunologically mediated, occurring in response to a single NSAID or chemically related agents, and may manifest as immediate IgE-mediated reactions or delayed T-cell–mediated responses, including severe cutaneous adverse reactions (SCARs) (Romano *et al.*, 2023; Blumenthal *et al.*, 2017).

Several factors are associated with NSAID-induced HSRs. Epidemiologic studies consistently show that these reactions are associated with factors such as female sex, middle age, and a history of atopic disease (Sánchez-Borges and Capriles-Hulett, 2000). In addition, respiratory comorbidities, particularly asthma and aspirin-exacerbated respiratory disease (AERD) (Abu Esba *et al.*, 2025; Asero, 2007), are strongly associated with cross-reactive reactions mediated by COX-1 inhibition. These findings indicate that underlying disease states and patient characteristics are associated with the clinical presentation of HSRs. Despite advances in understanding the pathophysiology of NSAID hypersensitivity, important challenges persist in clinical practice. Accurate phenotyping of hypersensitivity reactions (HSRs), differentiation between cross-reactive and selective responses, and identification of safe therapeutic alternatives remain complex and require systematic evaluation. Accordingly, structured causality assessment is essential. The Naranjo algorithm is a validated and widely used tool for evaluating adverse drug reactions, employing a weighted questionnaire to classify the likelihood that a specific NSAID caused an HSR as definite (≥9), probable (5–8), possible (1–4), or doubtful (≤0). Although selective COX-2 inhibitors are frequently considered safer alternatives in patients with suspected cross-reactive reactions, reports of severe hypersensitivity associated with these agents underscore the need for careful clinical assessment rather than reliance solely on pharmacologic selectivity. Furthermore, although previous studies have described

the epidemiology and clinical phenotypes of NSAID-induced HSRs, direct comparative analyses evaluating differences in clinical characteristics, severity, and associated factors between COX-1- and COX-2-inhibiting NSAIDs remain limited. In particular, real-world hospital-based data examining demographic characteristics, comorbidities, laboratory findings, and severity profiles according to COX selectivity are insufficient. This gap in evidence may hinder optimal clinical decision-making in routine practice.

Therefore, this study aimed to compare the clinical manifestations, severity, and seriousness of HSR to NSAIDs between COX-1 inhibitors and COX-2 inhibitors. Additionally, multivariable regression analysis was performed to identify factors independently associated with the clinical characteristics of HSRs among patients.

Methods

Study design and setting

This retrospective case only-design was conducted at the Department of Pharmacy, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand, using data from the hospital's electronic medical record system collected between 1 January 2021 and 31 December 2023.

Study population

Patients who received NSAIDs during the study period and developed a HSR were identified from electronic medical records. HSRs were defined using ICD-10 diagnostic codes (patients could have more than one diagnosis; therefore, the total percentage exceeds 100%) and were confirmed through detailed clinical documentation. Causality between NSAID exposure and HSR was further assessed using the Naranjo algorithm, as presented in Figure 1.

Inclusion criteria

1. Adults aged ≥18 years at the time of first NSAID exposure.

2. Patients receiving care at the Department of Pharmacy, Srinagarind Hospital.

3. Patients exposed to at least one NSAID, either as single-agent or combination therapy, during their first recorded exposure at the hospital.

4. Availability of baseline renal function data, including estimated glomerular filtration rate (eGFR).

5. Classification of baseline kidney function according to KDIGO GFR stages (G1–G5).

Patients with complete clinical and laboratory data required for hypersensitivity assessment.

Exclusion criteria

1. Evidence of acute kidney injury at baseline or significant laboratory abnormalities, including creatinine clearance, aspartate aminotransferase (AST), alanine aminotransferase (ALT), or eGFR.

2. Incomplete clinical data or missing information required for hypersensitivity evaluation.

3. Unclear temporal relationship between NSAID exposure and onset of hypersensitivity reaction.

4. Terminal illness or poor prognosis with an expected survival of less than three months.

Patients receiving renal replacement therapy or maintenance hemodialysis at baseline.

5. Conditions deemed by investigators to make study participation inappropriate.

Assessment of NSAID-Induced HSRs: Causality and Clinical manifestation.

Assessment of NSAID-induced HSRs involves evaluation of both causality and clinical manifestation. Causality assessment was performed using the Naranjo algorithm to determine the likelihood that a specific NSAID was responsible for the reaction, while clinical characteristics described the phenotypic presentation of hypersensitivity in practice. The Naranjo algorithm is a structured 10-item questionnaire that assesses key elements, including the temporal relationship between NSAID exposure and symptom onset, response to drug discontinuation (dechallenge), recurrence upon re-exposure (rechallenge, when available), the presence of alternative etiologies, prior history of similar reactions, and supporting objective clinical evidence. Each item is assigned a weighted score, and the total score categorizes causality as definite (≥9), probable (5–8),

possible (1–4), or doubtful (≤0). This standardized approach facilitates consistent identification of the suspected culprit NSAID and supports reproducible documentation of drug HSRs.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics. Continuous variables were reported as mean ± standard deviation (SD) or as median with interquartile range, as appropriate for normally distributed or skewed data, while categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using the Pearson's chi-square test or Fisher's exact test for categorical variables (e.g., gender, eGFR stage) and the independent t-test or Mann–Whitney U test for continuous variables (e.g., age, BMI, eGFR, creatinine, liver enzyme, INR, EO, and HbA1c), depending on data distribution.

Multivariable analyses were performed using log-binomial regression models with robust variance estimation to estimate relative risks (RRs) and adjusted relative risks (aRRs) with 95% confidence interval (CI) was reported. Each outcome variable was dichotomized prior to analysis, and separate models were constructed for each clinical endpoint. Variables with $p < 0.10$ in univariate analysis were included in the multivariable model. Causality between NSAID exposure and HSR was assessed using the Naranjo algorithm, as described in the methods section. Statistical significance was defined as a two-sided p-value < 0.05. All analyses were performed using Stata version 18.0 (StataCorp, College Station, TX, USA). This study was approved by the Ethics Committee of the Faculty of Medicine, Khon Kaen University, under approval number HE681190.

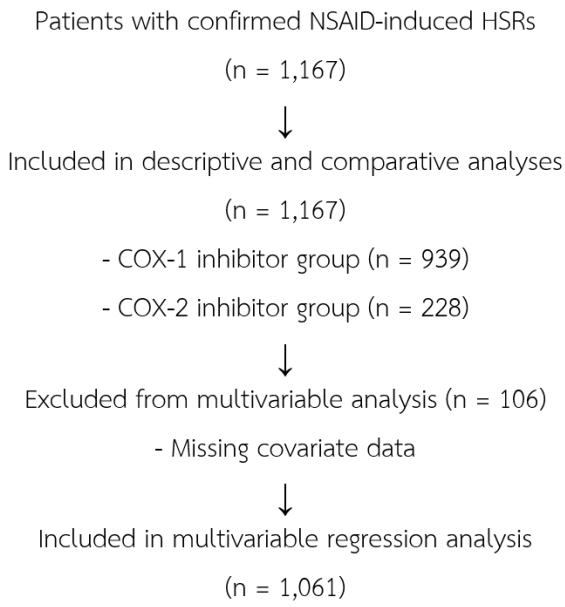

Figure 1. Flow diagram of patient selection and inclusion indescriptive and multivariable analyses (n=1,167 vs 1,061)

Results

Baseline characteristics were largely comparable between the COX-1 inhibitor (n=939) and COX-2 inhibitor (n=228) groups. The majority of patients were female (approximately 70%), with no significant difference in gender distribution between groups (p=0.652). Patients in the COX-2 group were significantly older than those in the COX-1 group (median 57 (46–65.5) vs 54 (37–64) years, p<0.001). No statistically significant differences were observed in anthropometric measures (weight, height, BMI),

renal function parameters (eGFR, eGFR stage, creatinine), liver enzymes (AST, ALT), hematologic and coagulation parameters (HCT, INR), inflammatory markers (eosinophil and neutrophil counts), or metabolic status (HbA1c) between the two groups (all p>0.05). The distribution of eGFR stages (available data) was also similar between groups (p=0.662) as presented in Table 1.

The distribution of primary diagnoses, as defined by ICD-10 codes, differed between the COX-1 and COX-2 inhibitor groups across several clinical characteristics. Patients receiving COX-2 inhibitors were significantly more likely to have musculoskeletal and connective tissue disorders compared with those receiving COX-1 inhibitors (33.92% vs 16.93%, p < 0.001). In contrast, respiratory system diseases (3.52% vs 8.36%, p = 0.013) and genitourinary system diseases (3.96% vs 8.57%, p = 0.019) were more frequently observed in the COX-1 inhibitor group. Skin and subcutaneous tissue disorders were significantly more common in the COX-2 inhibitor group (11.89% vs 7.50%, p = 0.032). Metabolic diseases showed a borderline difference between groups (1.76% vs 4.61%, p = 0.051). No statistically significant differences were observed for cancer, cardiovascular disease, essential (primary) hypertension, digestive and nervous system disorders, mental and behavioral disorders, infectious and parasitic diseases, or other diagnoses (all p > 0.05). Overall, musculoskeletal disorders were the most prevalent diagnosis in the COX-2 inhibitor group, whereas the distribution of other comorbid conditions was largely comparable between groups.

Table 1. Baseline characteristics of patients receiving COX-1 and COX-2 inhibitors (n, %) (n = 1,167)

	Total (n=1167)	COX-1 (n=939)	COX-2 (n=228)	p-value
Gender				0.652[p]
Female	820 (70.27)	657 (69.97)	163 (71.49)	
Male	347 (29.73)	282 (30.03)	65 (28.51)	
Age (years); Median (IQR)	55 (40, 64)	54 (37, 64)	57 (46, 65.5)	<0.001[u]
Weight (kg); Median (IQR) (n = 1,110)	60.45 (53, 70) (n=1110)	60 (52, 71) (n=888)	61 (54, 69) (n=222)	0.915[u]
Height (cm); Median (IQR) (n = 1,113)	160 (155, 165) (n=1113)	160 (155, 165) (n=891)	159.5 (153, 165) (n=222)	0.291[u]
BMI; Median (IQR) (n = 1,108)	23.77 (20.83, 26.91) (n=1108)	23.73 (20.81, 27.06) (n=887)	23.89 (21.09, 26.44) (n=221)	0.768[u]
eGFR (ml/min/1.73m2); Median (IQR)	88.76 (71.39, 102.39) (n=327)	89.24 (71.67, 103.45) (n=271)	85.17 (70.45, 98.94) (n=56)	0.403[u]
eGFR stage (ml/min/1.73m^2) (n = 327) (available data)				0.662[f]
Stage 1 (normal): ≥ 90	156 (47.71)	134 (49.45)	22 (39.29)	

	Total (n=1167)	COX-1 (n=939)	COX-2 (n=228)	p-value
Stage 2 (mildly decreased): 60-89	122 (37.31)	96 (35.42)	26 (46.43)	
Stage 3a (mildly to moderately decreased): 45-59	27 (8.26)	22 (8.12)	5 (8.93)	
Stage 3b (moderately to severely decreased): 30-44	10 (3.06)	9 (3.32)	1 (1.79)	
Stage 4 (severely decreased): 15-29	5 (1.53)	4 (1.48)	1 (1.79)	
Stage 5 (kidney failure): < 15	7 (2.14)	6 (2.21)	1 (1.79)	
Creatinine (mg/dL); Median (IQR)	0.82 (0.68, 1.02) (n=331)	0.81 (0.68, 1.02) (n=275)	0.84 (0.71, 0.99) (n=56)	0.591[u]
AST (U/L); Median (IQR)	25 (20, 34) (n=223)	25 (20, 34) (n=185)	24 (18, 41) (n=38)	0.783[u]
ALT(U/L); Median (IQR)	25 (20, 34) (n=223)	25 (20, 34) (n=185)	24 (18, 41) (n=38)	0.783[u]
HCT; Mean ± SD	37 ± 5.94 (n=321)	36.98 ± 6.11 (n=266)	37.11 ± 5.08 (n=55)	0.884[t]
INR; Median (IQR)	1.05 (0.99, 1.17) (n=146)	1.05 (1, 1.17) (n=123)	1.04 (0.97, 1.2) (n=23)	0.469[u]
EO (%); Median (IQR)	1.8 (0.7, 4.2) (n=321)	1.8 (0.7, 4.1) (n=266)	1.6 (0.6, 4.6) (n=55)	0.589[u]
NE (%); Mean ± SD	65.54 ± 13.08 (n=321)	65.7 ± 13.12 (n=266)	64.79 ± 12.95 (n=55)	0.640[t]
HbA1c; Median (IQR) (n = 95)	5.9 (5.5, 6.4) (n=95)	5.9 (5.4, 6.5) (n=81)	5.75 (5.5, 6.1) (n=14)	0.718[u]

Note: Data are presented as n (%), mean ± standard deviation (SD), or median (interquartile range, IQR), as appropriate.

p-values were calculated using Pearson's chi-squared test (p), Fisher's exact test (f), Independent t-test (t), or Mann–Whitney U test (u), as appropriate. eGFR stages were classified according to kidney function categories (Stage 1–5) with KDIGO recommendation.

Abbreviations: BMI (body mass index); eGFR (estimated glomerular filtration rate); AST (aspartate aminotransferase); ALT, alanine aminotransferase; HCT (hematocrit); INR (international normalized ratio); EO (eosinophil); NE (neutrophil); HbA1c (glycated hemoglobin).

Table 2. Primary diagnoses categorized by ICD-10 classification in patients treated with COX-1 and COX-2 inhibitors (n, %) (n = 1,167)

Diagnosis (ICD-10)	Total (n=1167)	COX-1 (n=939)	COX-2 (n=228)	p-value
Cancer	97 (8.36)	81 (8.68)	16 (7.05)	0.430[p]
Cardiovascular disease	48 (4.14)	39 (4.18)	9 (3.96)	0.884[p]
Essential (primary) hypertension	15 (1.29)	10 (1.07)	5 (2.2)	0.189[f]
Metabolic disease	47 (4.05)	43 (4.61)	4 (1.76)	0.051[p]
Musculoskeletal system and connective tissue	235 (20.26)	158 (16.93)	77 (33.92)	<0.001[p]
Respiratory system	86 (7.41)	78 (8.36)	8 (3.52)	0.013[p]
Digestive system	57 (4.91)	50 (5.36)	7 (3.08)	0.155[p]
Genitourinary system	89 (7.67)	80 (8.57)	9 (3.96)	0.019[p]
Skin and subcutaneous tissue	97 (8.36)	70 (7.5)	27 (11.89)	0.032[p]
Nervous system	48 (4.14)	40 (4.29)	8 (3.52)	0.605[p]
Mental and behavioral disorders	22 (1.9)	18 (1.93)	4 (1.76)	>0.999[f]
Infectious and parasitic disease	28 (2.41)	24 (2.57)	4 (1.76)	0.476[p]
Other diagnosis	291 (25.09)	242 (25.94)	49 (21.59)	0.175[p]

Note: Data are presented as n (%). p-values were calculated using Pearson's chi-squared test (p) or Fisher's exact test (f), as appropriate.

Abbreviations: ICD-10 (International Classification of Diseases, 10th Revision); COX (cyclooxygenase).

Statistical significance was defined as a two-tailed p-value < 0.05. Patients may have been classified into more than one diagnostic category or multiple diagnoses per patient.

Clinical characteristics differed between patients receiving COX-1 and COX-2 inhibitors. The most common manifestation overall was rash and itching (26.38%), followed by angioedema (23.93%), generalized skin eruption (11.09%), and allergic urticaria (9.87%). Angioedema and rash were similarly distributed between the two groups (p=0.184 and p=0.725, respectively). Severe HSRs demonstrated significant differences between groups. Anaphylaxis occurred more frequently in patients receiving a COX-1 inhibitor than in those receiving a COX-2 inhibitor (6.84% vs 3.12%, p = 0.037). In contrast, fixed drug eruption was markedly more common among COX-2 inhibitor users (7.14% vs 0.65%, p<0.001). Stevens–Johnson syndrome (SJS) was also significantly more frequent in the COX-2 inhibitor group (1.79% vs 0.22%, p=0.015). Additionally, mucositis occurred more often in the COX-2 inhibitor group (2.23% vs 0.65%, p=0.045). Borderline differences were observed for burn (p=0.052), erythema multiforme (p=0.054), and generalized drug-induced skin eruption (p=0.053). Other manifestation, including allergic urticaria, bronchospasm, palpitations, and systemic symptoms, did not differ significantly between groups (all p > 0.05). Overall, while cutaneous manifestations predominated in both groups, COX-1 inhibitors were more frequently associated with anaphylaxis, whereas COX-2 inhibitors were more strongly associated with fixed drug eruptions and severe mucocutaneous reactions such as SJS, as presented in Table 3.

Table 3 Clinical characteristics of NSAIDs hypersensitivity (n, %) (n = 1,167)

Clinical characteristics	Total (n=1167)	COX-1 (n=939)	COX-2 (n=228)	p-value
Acute generalized exanthematous pustulosis (AGEP)	2 (0.17)	2 (0.22)	0 (0)	>0.999[f]
Allergic urticaria	113 (9.87)	98 (10.64)	15 (6.7)	0.076[p]
Anaphylaxis	70 (6.11)	63 (6.84)	7 (3.12)	0.037[p]
Angioedema	274 (23.93)	228 (24.76)	46 (20.54)	0.184[p]
Blister	4 (0.35)	3 (0.33)	1 (0.45)	0.582[f]
Bronchospasm	16 (1.4)	15 (1.63)	1 (0.45)	0.336[f]
Burn	8 (0.7)	4 (0.43)	4 (1.79)	0.052[f]
Chest pain, Dyspnea	7 (0.61)	7 (0.76)	0 (0)	0.357[f]
Dizziness / Vertigo, Nausea / Vomiting	8 (0.7)	6 (0.65)	2 (0.89)	0.658[f]
DRESS	3 (0.26)	3 (0.33)	0 (0)	>0.999[f]
Drug induced pharmacology effects	1 (0.09)	1 (0.11)	0 (0)	>0.999[f]
Palpitation	67 (5.85)	59 (6.41)	8 (3.57)	0.105[p]
Edema/ Eczema	78 (6.81)	59 (6.41)	19 (8.48)	0.269[p]
Erythema multiforme, unspecified	5 (0.44)	2 (0.22)	3 (1.34)	0.054[f]
Fixed drugs eruption	22 (1.92)	6 (0.65)	16 (7.14)	<0.001[f]
Generalized skin eruption due to drugs and medicaments	127 (11.09)	94 (10.21)	33 (14.73)	0.053[p]
Hepatitis	2 (0.17)	2 (0.22)	0 (0)	>0.999[f]
Hypotension	1 (0.09)	1 (0.11)	0 (0)	>0.999[f]
Localized skin eruption due to drugs and medicaments, unspecified	9 (0.79)	9 (0.98)	0 (0)	0.219[f]
Mouth irritation	3 (0.26)	2 (0.22)	1 (0.45)	0.480[f]
Mucositis	11 (0.96)	6 (0.65)	5 (2.23)	0.045[f]
Petichiae	3 (0.26)	1 (0.11)	2 (0.89)	0.100[f]
Rash and Itching	302 (26.38)	245 (26.6)	57 (25.45)	0.725[p]
Severe Headaches/ Hypertension	1 (0.09)	1 (0.11)	0 (0)	>0.999[f]
Stevens-Johnson Syndrome (SJS)	6 (0.52)	2 (0.22)	4 (1.79)	0.015[f]
Wheezing	2 (0.17)	2 (0.22)	0 (0)	>0.999[f]

Note: Data are presented as n (%), p-values were calculated using Pearson's chi-squared test or Fisher's exact test, as appropriate. Abbreviations: AGEP (acute generalized exanthematous pustulosis); DRESS (drug reaction with eosinophilia and systemic symptoms); SJS (Stevens–Johnson syndrome); COX (cyclooxygenase).

Statistical significance was defined as a two-tailed p-value <0.05.

Multiple clinical phenotypes may occur in a single patient, the total percentages exceed 100%

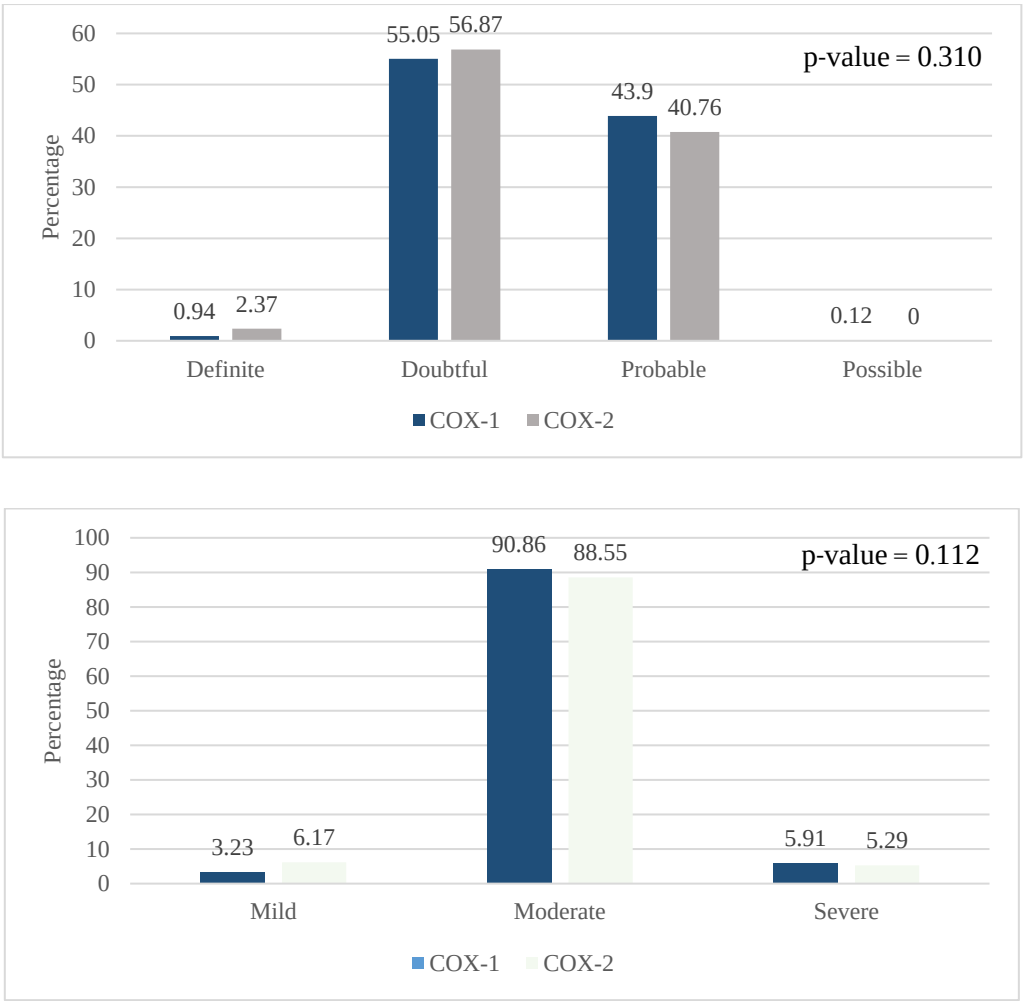

Figure 2. Assessment of NSAID-induced HSRs involves determining both causality with the Naranjo algorithm and severity (%) (n=1,167)

Note: Data are presented as n (%). Causality was classified as definite, probable, possible, or doubtful according to Naranjo's Algorithm. Severity was graded as mild, moderate, or severe based on clinical criteria. p-values for causality were calculated using Fisher's exact test. p-values for severity were calculated using Pearson's chi-squared test.

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; HSR, hypersensitivity reaction; COX, cyclooxygenase. Statistical significance was defined as a two-tailed p-value < 0.05

Causality categories did not significantly differ between patients receiving COX-1 and COX-2 inhibitors (p = 0.310). Overall, most reactions were classified as doubtful (55.41%) or probable (43.27%), whereas definite reactions were uncommon (1.22%) and possible reactions were rare (0.09%). The proportions of each causality category were comparable between groups. Similarly, ADR severity did not significantly differ between groups (p = 0.112). The majority of HSRs were moderate in severity (90.41%), followed by severe (5.79%) and mild (3.80%) reactions. The distribution of mild, moderate, and severe reactions was similar in the COX-1 and COX-2 groups. Overall, both the causality assessment and severity grading demonstrated comparable patterns for COX-1 and COX-2 inhibitor–associated HSRs, as presented in Figure 2.

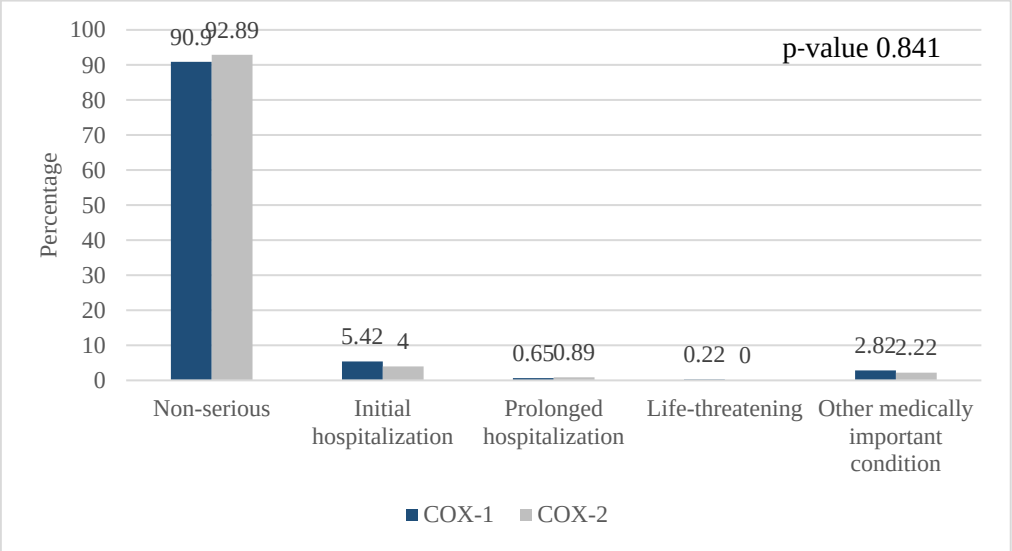

Figure 3 Distribution of seriousness categories of HSRs according to COX inhibitor (%) (n=1,167)

Note: Data are presented as percentages within each COX inhibitor group. Group comparisons were performed using Fisher's exact test. Abbreviations: NS (non-serious); IH (initial hospitalization); PH (prolonged hospitalization); LT (life-threatening); OMIC (other medically important condition) defined according to ICH E2A criteria.

The distribution of HSR seriousness categories by COX inhibitor. Most reactions were non-serious in both groups (COX-1: 90.9%; COX-2: 92.89%). Initial hospitalization occurred in 5.42% and 4.0% of cases, respectively, while prolonged hospitalization was rare (0.65% vs 0.89%). Life-threatening events were uncommon, occurring only in the COX-1 inhibitor group (0.22%). Other medically important conditions were infrequent in both groups (2.82% vs 2.22%). Fisher's exact test demonstrated no significant difference in seriousness distribution between the COX-1 and COX-2 inhibitor groups (p = 0.841), indicating that the COX inhibitor was not associated with the seriousness profile of HSRs, as presented in Figure 3.

In univariate analysis, increasing age was significantly associated with HSRs (RR 1.01; 95% CI 1.01–1.02; p<0.001). This association remained statistically significant in the multivariable model (aRR 1.01; 95% CI 1.01–1.02; p<0.001). Gender was not significantly associated with HSRs (male vs female: RR 0.94; 95% CI 0.73–1.22; p=0.653). Similarly, BMI, eGFR, eGFR stage, creatinine, liver enzymes (AST, ALT), hematologic parameters (HCT, eosinophils, neutrophils), INR, and HbA1c showed no statistically significant associations. Regarding causality assessment, compared with the definite category, probable causality was significantly associated with a lower risk of HSRs in both univariate (RR 0.49; 95% CI 0.24–0.99; p=0.048) and multivariable analyses (aRR 0.49; 95% CI 0.24–0.99; p=0.045). Doubtful causality showed a borderline association in the multivariable model (aRR 0.52; 95% CI 0.26–1.05; p=0.068). Severity classification was also significantly associated with outcomes. Compared with mild reactions, moderate reactions were associated with significantly lower likelihood in both univariate (RR 0.60; 95% CI 0.39–0.95; p = 0.028) and multivariable analyses (aRR 0.57; 95% CI 0.37–0.88; p = 0.012). Severe reactions were not significant in univariate analysis (p=0.093) but became statistically significant after adjustment (aRR 0.48; 95% CI 0.24–0.95; p=0.034). Seriousness categories were not significantly associated with HSRs. Multivariable analysis was performed using generalized linear models with a binomial distribution and log link function. Variables with p<0.1 in univariate analysis were included in the adjusted model as presented in Table 4.

Table 4. Factors associated with HSRs among patients exposed to NSAIDs: Univariate and multivariable generalized linear model analysis

	n	Univariate			Multivariate (n=1061)		
		Relative risk (RR)	95%CI	p-value	Adjusted RR	95%CI	p-value
Gender	1,167						
Female		Ref.					
Male		0.94	0.73, 1.22	0.653			
Age (years)	1167	1.01	1.01, 1.02	<0.001	1.01	1.01, 1.02	<0.001
BMI	1,108	1.00	0.97, 1.02	0.756			
eGFR(ml/min/1.73m2)	327	1.00	0.99, 1.01	0.662			
eGFR stages (ml/min/1.73m2)	327						
Stage 1		Ref.					
Stage 2		1.51	0.9, 2.53	0.117			
Stage 3a		1.31	0.54, 3.17	0.544			
Stage 3b		0.71	0.11, 4.74	0.723			
Stage 4		1.42	0.24, 8.54	0.703			
Stage 5		1.01	0.16, 6.48	0.989			
Creatinine (mg/dL)	331	0.86	0.6, 1.25	0.437			
AST (U/L)	223	1.00	1, 1.01	0.729			
ALT(U/L)	223	1.00	1, 1.01	0.729			
HCT	321	1.00	0.96, 1.04	0.886			
INR	146	1.29	0.2, 8.38	0.790			
EO (%)	321	1.00	0.94, 1.07	0.942			
NE (%)	321	1.00	0.98, 1.01	0.640			
HbA1c	95	0.82	0.49, 1.37	0.453			
Causality assessment	1,062						
Definite		Ref.			Ref.		
Doubtful		0.53	0.26, 1.07	0.078	0.52	0.26, 1.05	0.068
Probable		0.49	0.24, 0.99	0.048	0.49	0.24, 0.99	0.045
Possible		NA			NA		
Serious category	1,146						
Non-serious		Ref.					
Hospitalization-initial		0.76	0.41, 1.41	0.392			
Hospitalization-prolonged		1.25	0.38, 4.19	0.713			
Life-threatening		NA	NA	NA			
Serious-Other		0.81	0.36, 1.82	0.608			

	n	Univariate			Multivariate (n=1061)		
		Relative risk (RR)	95%CI	p-value	Adjusted RR	95%CI	p-value
Severity	1,157						
Mild		Ref.			Ref.		
Moderate		0.60	0.39, 0.95	0.028	0.57	0.37, 0.88	0.012
Severe		0.56	0.29, 1.1	0.093	0.48	0.24, 0.95	0.034

Note: RR (relative risk); aRR (adjusted relative risk); CI (confidence interval); Ref. (reference category); NA (not applicable). Multivariable analysis was performed using generalized linear models with a binomial distribution and log link function. Variables with $p<0.1$ in univariate analysis were included in the multivariable model. Causality was classified as definite, probable, possible, or doubtful according to the WHO-UMC criteria. Seriousness was defined in accordance with ICH E2A guidelines. Severity was graded as mild, moderate, or severe based on clinical presentation.

Discussion

In this retrospective case-only study of patients exposed to NSAIDs, age was significantly associated with differences in the clinical characteristics of HSRs among patients. The association remained robust after multivariable adjustment, suggesting a clinically meaningful cumulative impact in older populations. Age-related immunosenescence, altered drug metabolism, polypharmacy, and increased comorbidity burden may partially explain this observation (Sánchez-Borges and Capriles-Hulett, 2000; Abu Esba *et al.*, 2025; Asero, 2007). Prior studies on drug hypersensitivity have reported heterogeneous associations with age, with some demonstrating increased susceptibility in older adults, while others report no clear relationship. Our findings contribute to this ongoing debate by demonstrating a consistent age-dependent effect in NSAID-exposed patients. In contrast, gender was not independently associated with HSRs. Although female predominance has been reported in certain drug allergy manifestation, (Ghiordanescu *et al.*, 2025; Lee *et al.*, 2019) our data suggest that in NSAID-associated reactions, gender differences may be less pronounced. Variability in reaction manifestation, genetic predisposition, and reporting behavior may explain discrepancies across studies (Sánchez-Borges *et al.*, 2017; Yuenyongviwat *et al.*, 2021; Amo *et al.*, 2025).

Importantly, renal function indices—including eGFR and eGFR stage—were not associated with HSRs. This finding supports the concept that NSAID-induced hypersensitivity is primarily immunologically mediated and mechanistically distinct from dose-dependent nephrotoxicity. Baseline laboratory parameters, including liver enzymes, hematologic indices, and eosinophil percentage, were similarly not predictive. Notably, baseline eosinophilia showed no association with eosinophil levels during acute immunologic reactions, highlighting the limited utility of routine laboratory markers in characterizing patients with acute immunologic reactions (Asero, 2007; Sánchez-Borges *et al.*, 2017; Amo *et al.*, 2025).

Causality classification demonstrated differences in distribution across categories, with the “probable” group showing lower estimates compared with the “definite” group. This likely reflects inherent characteristics of pharmacovigilance assessment tools rather than true biological differences in susceptibility. Accordingly, these findings should be interpreted as differences in causality classification patterns rather than causal or protective effects. Similarly, severity classification showed variation in the distribution of clinical manifestations across categories. Moderate and severe reactions demonstrated lower adjusted estimates compared with mild reactions, reflecting differences in clinical presentation of HSRs across severity strata rather than differences in underlying susceptibility. Overall, these results should be interpreted

as associations with HSR manifestation patterns and differences in clinical and classification characteristics, rather than as predictors of risk or causation.

Several limitations should be acknowledged. This study has several limitations that should be acknowledged. First, the study design is a case-only (case–case) analysis, which does not include a non-HSR control group; therefore, it cannot be used to estimate incidence or risk. Second, the observed associations may be affected by selection bias inherent to hospital-based retrospective data. In addition, the possibility of residual confounding cannot be excluded due to unmeasured or incompletely captured clinical variables. Clinical phenotypes were not formally classified according to the full EAACI/ENDA guideline framework because detailed allergy workup data—such as provocation testing, respiratory challenge testing, or immunologic investigations—were not routinely available in this retrospective dataset. Consequently, the phenotype classification relied primarily on documented clinical manifestations and temporal associations with NSAID exposure. This limitation may reduce comparability with studies using standardized EAACI/ENDA phenotyping and may introduce heterogeneity in clinical classification.

Despite these limitations, the findings provide clinically relevant insights into differences in HSR phenotypic characteristics, particularly between COX-1 and COX-2 inhibitors. These differences may support clinical decision-making by assisting clinicians in selecting alternative NSAIDs in patients with a history of hypersensitivity reactions, especially in guiding safer prescribing strategies and individualized drug selection.

This study has several notable strengths. First, it is based on a relatively large case-only cohort of NSAID-exposed patients with hypersensitivity reactions, which enhances analytical robustness and allows for multivariable modeling of factors associated with clinical outcomes. Second, the use of generalized linear models with a binomial distribution and log link function enabled estimation of relative risks, which are more interpretable than odds ratios in the context of common outcomes. Third, a wide range of clinically relevant variables, including demographic characteristics, laboratory parameters, causality assessment, and severity classification, were systematically incorporated, providing a comprehensive evaluation of factors associated with hypersensitivity phenotypes. Fourth, the study reflects real-world clinical practice in a tertiary care setting, supporting the applicability of the findings to similar healthcare environments. In addition, differentiation between severity and seriousness classifications allowed a more detailed characterization of hypersensitivity manifestations. Together, these strengths enhance the methodological rigor and clinical relevance of the study, particularly in describing patterns of NSAID-associated HSRs. From a clinical standpoint, our findings suggest that traditional demographic and routine laboratory parameters have limited utility in stratifying patients with NSAID-induced HSRs. Although age showed a statistically significant association, the effect size was small and should be interpreted as a gradual difference in clinical characteristics rather than a strong determinant of hypersensitivity presentation. Clinicians should therefore maintain clinical awareness in older patients while recognizing the inherently unpredictable nature of immunologic drug reactions. Overall, routine pre-prescription laboratory testing alone is unlikely to substantially improve the identification of patients who may develop HSRs. Future research should focus on mechanistic and biomarker-based approaches, including genetic susceptibility (e.g., HLA associations), immune phenotyping, and pharmacogenomic profiling (Amo *et al.*, 2025) including, classification in the context of EAACI/ENDA concepts. Prospective multicenter studies with standardized phenotyping of hypersensitivity reactions are also needed to improve consistency in classification and reduce variability in causality assessment and reporting. Integrative models combining clinical, immunologic, and genetic data may ultimately improve characterization of hypersensitivity phenotypes beyond conventional clinical variables.

Conclusion

In this retrospective case-only study of patients exposed to NSAID with HSRs, increasing age showed a modest association with differences in clinical presentation. Conventional demographic characteristics and routine laboratory parameters, including renal and hepatic indices, were not meaningfully associated with hypersensitivity phenotypes. Observed differences related to causality and severity classifications likely reflect methodological features of pharmacovigilance assessment rather than underlying biological determinants. Overall, NSAID-induced HSRs remain largely unpredictable based on standard clinical variables alone. These findings highlight the limitations of conventional clinical and laboratory parameters in characterizing hypersensitivity phenotypes and support the need for improved stratification approaches incorporating immunologic and genetic factors to enhance individualized NSAID safety.

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Conflict of interest

The authors declare that they have no conflict of interest related to this study.

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