

PARACETAMOL AND NSAIDS ADVERSE DRUG REACTIONS IN THE EMERGENCY DEPARTMENT: POTENTIAL ROLE OF THE GUT MICROBIOTA

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Abstract – Introduction: Adverse drug reactions (ADRs) are defined as undesirable effects occurring following the administration of a drug and represent a major cause of morbidity, mortality, and healthcare costs. The primary aim of this study was to retrospectively assess the incidence, characteristics, and clinical outcomes of adverse drug reactions associated with paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) over an extended study period. A secondary objective was to identify and analyze the most frequent adverse events associated with each drug.

Patients and Methods: All patients diagnosed with ADRs who presented to our Emergency Department between 2015 and 2021 were retrospectively enrolled. Patients whose ADRs were specifically attributed to paracetamol or NSAIDs were extracted. The study population included all non-pregnant patients who met the pre-defined inclusion criteria.

Results: Among 897 patients with ADRs, 107 cases (62 females; mean age 37 ± 23 years) were identified as related to paracetamol and/or NSAID use. Of these, 29 patients (22 females; mean age 33 ± 22 years) presented ADRs related to paracetamol, 73 (34 females; mean age 47 ± 21 years) to NSAIDs, and 7 (6 females; mean age 31 ± 26 years) to both drug classes. Voluntary and unintentional poisoning were found to be significantly more frequent in the paracetamol group ($p < 0.0001$ and $p < 0.002$, respectively), while allergic reactions were significantly more common among patients exposed to NSAIDs ($p < 0.0001$). Moreover, gastritis, gastrointestinal bleeding, and renal failure were observed exclusively in the NSAID group, whereas the increase in hepatic enzyme levels showed a comparable distribution between the two groups. Finally, no significant difference was observed in hospitalization rates between patients with paracetamol-related and NSAID-related ADRs (38% vs. 27%, respectively; $p = ns$).

Conclusions: This study confirms that ADRs are more frequent in female patients and that paracetamol and NSAIDs exhibit distinct toxicity profiles. Paracetamol is generally safer with respect to unintentional ADRs, whereas NSAIDs are more commonly associated with gastrointestinal, allergic, and renal complications. Since gut microbiota alterations may play a pivotal role in the occurrence of ADRs, further studies are needed in order to test how they may increase the risk.

Keywords: Microbiota, Microbiome, Adverse drug reaction, NSAIDS, Paracetamol.



INTRODUCTION

Adverse drug reactions (ADRs) are defined as undesirable effects occurring following the administration of a drug and represent a major cause of morbidity, mortality, and healthcare costs^{1,2}. For this reason, ADRs remain a significant challenge both in healthcare and in Emergency Departments (EDs), particularly in light of the growing complexity of pharmacological therapies, the increasing age of the general population, and the rising prevalence of multimorbidity³.

Pharmacovigilance systems have therefore been established to identify and prevent potential ADRs. Drugs most frequently implicated in ADRs-related hospital admissions include antiplatelet agents, anticoagulants, cytotoxic drugs, immunosuppressants, diuretics, antidiabetics, and antibiotics. The severity of ADRs can range from mild and transient manifestations to severe and life-threatening events. When fatal ADRs occur, they are often due to drug overdose or hemorrhagic complications, typically resulting from the concomitant use of multiple drugs that increase bleeding risk — for instance, the co-administration of an antithrombotic or anticoagulant with a NSAID⁴.

In recent years, increasing attention has been directed towards gut microbiota as a key factor influencing both drug efficacy and toxicity. The gut microbial ecosystem plays an essential role in modulating drug metabolism, immune responses, and intestinal barrier integrity^{5,6}. Dysbiosis — an imbalance in microbial composition and function — can lead to altered biotransformation of xenobiotics, accumulation of toxic metabolites, and enhanced systemic inflammation. Scholars have demonstrated that the microbiota can either detoxify or activate specific drugs through enzymatic pathways, particularly involving bacterial β -glucuronidases, sulfatases, and reductases⁷. Therefore, interindividual variability in microbial composition may explain, at least in part, the heterogeneity of ADRs observed in clinical practice.

Paracetamol, the active metabolite of phenacetin, is an analgesic and antipyretic agent widely used for the treatment of mild to moderate pain and fever. Overall, paracetamol is considered a safe and well-tolerated drug, characterized by an excellent efficacy-safety profile. Its mechanism of action is predominantly central, as demonstrated by higher concentrations found in cerebrospinal fluid (CSF) compared with plasma levels. Several hypotheses have been proposed to explain its pharmacodynamic mechanism, including the involvement of the prostaglandin system, endogenous cannabinoids, the NMDA receptor system, nitric oxide, and serotonin pathways⁸.

From a pharmacokinetic perspective, paracetamol exhibits excellent bioavailability, with a plasma peak at approximately 30 minutes under fasting conditions and 60 minutes when taken with food. Its half-life ranges from 2 to 3 hours, with an analgesic effect lasting 4-6 hours. This duration may be prolonged in cases of hepatic impairment or overdose, where the half-life can double. Renal function has minimal influence on the drug's elimination, since only about 5% of the dose is excreted unchanged in urine, while the remainder undergoes hepatic metabolism through conjugation reactions, leading to the formation of inactive metabolites^{9,10}.

However, recent evidence suggests that the gut-liver axis may play a pivotal role in modulating paracetamol hepatotoxicity. Bacterial β -glucuronidases can deconjugate paracetamol-glucuronide within the intestinal lumen, regenerating the parent compound and facilitating its reabsorption. This enterohepatic recycling can increase the hepatic burden of paracetamol and enhance the formation of the toxic metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI)¹¹. Moreover, dysbiosis-associated alterations in microbial production of sulphur-containing amino acids may reduce hepatic glutathione synthesis, by compromising detoxification pathways and thereby predisposing to hepatocellular injury.

Pharmacovigilance data and clinical studies indicate that paracetamol, when administered within the recommended dosage range, is generally safe and well tolerated¹². Apart from occasional and mild elevations in transaminases, adverse effects are uncommon. Allergic reactions are rare; however, excessive dosing may lead to hepatotoxicity. In adults, doses of 10-15 g are considered hepatotoxic, while 20-25 g (corresponding to 200-250 mg/kg) may be fatal. Predisposing conditions such as malnutrition, chronic alcohol abuse, or liver cirrhosis can deplete hepatic glutathione stores, rendering paracetamol hepatotoxic even at lower doses. The most frequently reported adverse effects include nausea, vomiting, urticaria, and hepatic failure. Although liver failure is a rare adverse reaction, it may be severe and potentially life-threatening^{13,14}.

NSAIDs constitute a large family of compounds with anti-inflammatory, antipyretic, and analgesic properties mediated through their interaction with cyclooxygenase (COX) enzymes. Non-selective NSAIDs inhibit both COX-1 and COX-2 isoforms, and their interference with COX-1 — which is physiologically expressed in the gastrointestinal mucosa — accounts for their gastrotoxic poten-

tial¹⁵. This mechanism explains the common gastrointestinal adverse effects associated with this drug class. Conversely, selective COX-2 inhibitors (COXibs) demonstrate improved gastrointestinal safety profiles but are associated with an increased cardiovascular risk in predisposed individuals.

The pharmacodynamic action of NSAIDs derives from their inhibition of COX enzymes, which catalyze the conversion of arachidonic acid into prostaglandins — key mediators in nociception and inflammation. Pharmacokinetically, NSAIDs are generally well absorbed following oral administration, reaching plasma peak concentrations within 1-4 hours. They undergo hepatic metabolism and are excreted primarily *via* the kidneys through both glomerular filtration and tubular secretion. The elimination half-life varies depending on the specific molecule.

Gut microbiota also contributes to the gastrointestinal and systemic toxicity of NSAIDs. Many NSAIDs undergo enterohepatic circulation, returning to the intestinal lumen as glucuronide conjugates. Bacterial β -glucuronidases can hydrolyze these conjugates, reactivating the parent drug and promoting local mucosal injury¹⁶. Moreover, chronic NSAID exposure alters the gut microbial ecosystem by reducing commensal taxa (e.g., *Lactobacillus*, *Bifidobacterium*) and increasing pro-inflammatory Gram-negative species, thereby compromising barrier integrity and amplifying mucosal inflammation¹⁷. This dysbiotic state not only favors gastrointestinal damage but may also enhance renal and systemic inflammatory responses through the translocation of bacterial endotoxins and immune activation.

The most frequent adverse effects of NSAIDs remain gastrointestinal^{18,19}, secondary to COX-1 inhibition and reduced prostaglandin synthesis¹⁹. Meta-analyses have shown that approximately 0.2% of patients develop endoscopically detectable peptic ulcers, which become symptomatic in 0.014% of cases, while gastrointestinal bleeding occurs in about 0.007% of cases²⁰. The risk is further increased in patients with chronic *Helicobacter pylori* infection, alcohol abuse, or concomitant glucocorticoid therapy. Although gastrointestinal toxicity is well recognized, there is no consensus regarding the temporal pattern of risk; some studies suggest that it may emerge as early as the first month of NSAID therapy²¹. Similarly, the necessity and timing of gastroprotective strategies remain debated²²⁻²⁴.

Certain NSAIDs also affect platelet function by exerting an antiplatelet effect; acetylsalicylic acid (ASA) is the prototypical example, irreversibly acetylating platelet COX enzymes and thereby inhibiting thromboxane A₂ synthesis for the entire platelet lifespan^{25,26}. Moreover, NSAIDs can impact renal perfusion since prostaglandins normally reduce afferent arteriolar resistance²⁷. The concomitant use of multiple NSAIDs is generally discouraged due to synergistic toxicity. A common association involves ASA use in patients with elevated cardiovascular risk²⁸. Some studies have also reported a potential pharmacodynamic antagonism between certain NSAIDs and ASA, whereby NSAIDs may hinder ASA binding to platelet COX enzymes, attenuating its antiplatelet efficacy and compromising cardiovascular protection²⁹.

Altogether, these findings suggest that host-microbiota interactions may significantly contribute to interindividual variability in ADRs, influencing both hepatic and gastrointestinal tolerance to paracetamol and NSAIDs. Understanding this interface may open new avenues for microbiota-informed pharmacovigilance and personalized therapy. Although this review does not analyze direct microbiome data, it discusses possible implications of the gut microbiota in ADR based on the existing literature.

PATIENTS AND METHODS

Primary Endpoint

The primary aim of this study was to retrospectively assess the incidence, characteristics, and clinical outcomes of adverse drug reactions associated with paracetamol and NSAIDs observed in the ED of the Fondazione Policlinico Universitario A. Gemelli IRCCS over an extended study period.

Secondary Endpoints

A secondary objective was to identify and analyze the most frequent adverse events associated with each drug. Particular attention was given to the severity of symptoms related to paracetamol

and NSAID use, as well as to the number of ED visits due to ADRs, hospital admissions resulting from these events, and the level of care required during hospitalization.

Study Design

This was a retrospective observational study. The study was approved in 03-08-2022 by the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli - IRCCS of Rome, Italy (protocol ID: 5121, Protocol number: 0025817/22).

Population and Study Duration

All patients diagnosed with ADRs who presented to our ED between 2015 and 2021 were retrospectively enrolled. From this cohort, data were extracted for patients whose ADRs were specifically attributed to paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs). The study population included all non-pregnant patients who met the predefined inclusion criteria. The overall duration of the study was five months, encompassing data extraction, statistical analysis, and scientific reporting.

Inclusion Criteria

- Patients ≥ 18 years old;
- Patients under 18 years of age with parental or legal guardian consent to participate in the study and to process personal data;
- Patients with a diagnosis of ADR during the ED evaluation;
- Signed written informed consent for study participation and personal data processing.

Exclusion Criteria

- Pregnant women;
- Refusal to sign written informed consent for study participation and personal data processing.

Variables and Procedures

Retrospective data were retrieved from the institutional electronic health records for all patients presenting to the ED who met the inclusion criteria. Patients were subsequently contacted by telephone to provide informed consent for the use of their anonymized clinical data. The variables collected included the following:

- Age and sex;
- Clinical presentation of enrolled patients at the time of ED evaluation;
- Description of the adverse reaction and the type of drug involved;
- Any overdose and/or inappropriate drug intake;
- Patient outcome (hospital admission or discharge).

Statistical Analysis

The study sample was described in terms of clinical and demographic characteristics using descriptive statistics. Categorical variables were reported as absolute and relative frequencies (%), whereas continuous variables were expressed as mean \pm standard deviation (SD) or median with interquartile range (IQR), as appropriate based on data distribution. Comparisons between groups were performed using the Student's *t*-test for continuous variables.

All statistical analyses were performed using IBM SPSS Statistics (Version 23.0; IBM Corp., Armonk, NY, USA). A *p*-value < 0.05 was considered statistically significant.

RESULTS

A total of 897 patients presenting to our ED between 2015 and 2021 with a diagnosis of ADR were retrospectively included. Of these, 548 were adult females (61%), while the pediatric population (<18 years) accounted for 6% of total admissions. The main drug classes involved included dicoumarols, direct oral anticoagulants, benzodiazepines, opioids, antiarrhythmics, beta-blockers, paracetamol, and NSAIDs. Overall, 226 of the 897 patients required hospitalization, whereas 671 experienced only mild symptoms that necessitated brief observation before discharge. Table 1 summarizes the general characteristics of the study population.

TABLE 1. AGE AND GENDER DIFFERENCES BETWEEN PARACETAMOL AND NSAIDS-INDUCED ADRS.

ADR	Number of patients	Age years (Mean ± SD)	Sex female (%)
Paracetamol	29	33±22	22 (75.8)
NSAIDs	73	47±21	34 (46.5)
Both	7	31±26	6 (85.7)

Among all patients with ADRs, 107 cases (62 females; mean age 37 ± 23 years) were identified as related to paracetamol and/or NSAID use. The NSAIDs most frequently associated with adverse events were ketoprofen, diclofenac, aspirin, ibuprofen, coxibs, and nimesulide. Of these, 29 patients (22 females; mean age 33 ± 22 years) presented ADRs related to paracetamol, 73 (34 females; mean age 47 ± 21 years) to NSAIDs, and 7 (6 females; mean age 31 ± 26 years) to both drug classes.

With regard to paracetamol-related reactions, the most common events were intentional overdose (16/29), unintentional overdose (6/29), allergic reactions (5/29), and elevated hepatic enzyme levels (3/29). In the NSAID group, the most frequent ADRs included gastritis (39/73), allergic reactions (24/73), intentional overdose (5/73), unintentional overdose (4/73), elevated hepatic enzymes (4/73), gastrointestinal bleeding (6/73), and acute renal failure (1/73). Among patients who experienced ADRs related to both paracetamol and NSAIDs, intentional overdose occurred in 5 out of 7 cases, allergic reaction in 1 case, and elevated hepatic enzymes in 1 case (Table 2).

TABLE 2. MAIN ADVERSE EVENTS OBSERVED STRATIFIED FOR TYPE OF DRUG.

	Paracetamol (%)	NSAIDs (%)	Both (%)
Intentional overdose	16/29 (55.1)	5/73 (6.8)	5/7 (71.4)
Unintentional overdose	6/29 (20.6)	4/73 (5.4)	0 (0)
Allergy	5/29 (17.2)	24/73 (32.8)	1/7 (14.2)
Elevated hepatic enzymes	3/29 (10.3)	4/73 (5.4)	1/7 (14.2)
Gastritis	0 (0)	39/73 (53.4)	0 (0)
GI Bleeding	0 (0)	6/73 (8.2)	0 (0)
Renal Failure	0 (0)	1/73 (1.3)	0 (0)

Overall, female patients represented most ADR cases, and the gastrointestinal system was the most frequently affected. Intentional intoxication accounted for a substantial proportion of cases, particularly among younger patients.

When comparing the main ADRs associated with paracetamol and NSAIDs, voluntary and unintentional poisoning were found to be significantly more frequent in the paracetamol group ($p < 0.0001$ and $p < 0.002$, respectively). Conversely, allergic reactions were significantly more common

among patients exposed to NSAIDs ($p < 0.0001$). Moreover, gastritis, gastrointestinal bleeding, and renal failure were observed only in the NSAID group, whereas the increase in hepatic enzyme levels showed a comparable distribution between the two groups (Figure 1). Finally, no significant difference was observed in hospitalization rates between patients with paracetamol-related and NSAID-related ADRs (38% vs. 27%, respectively; $p = ns$).

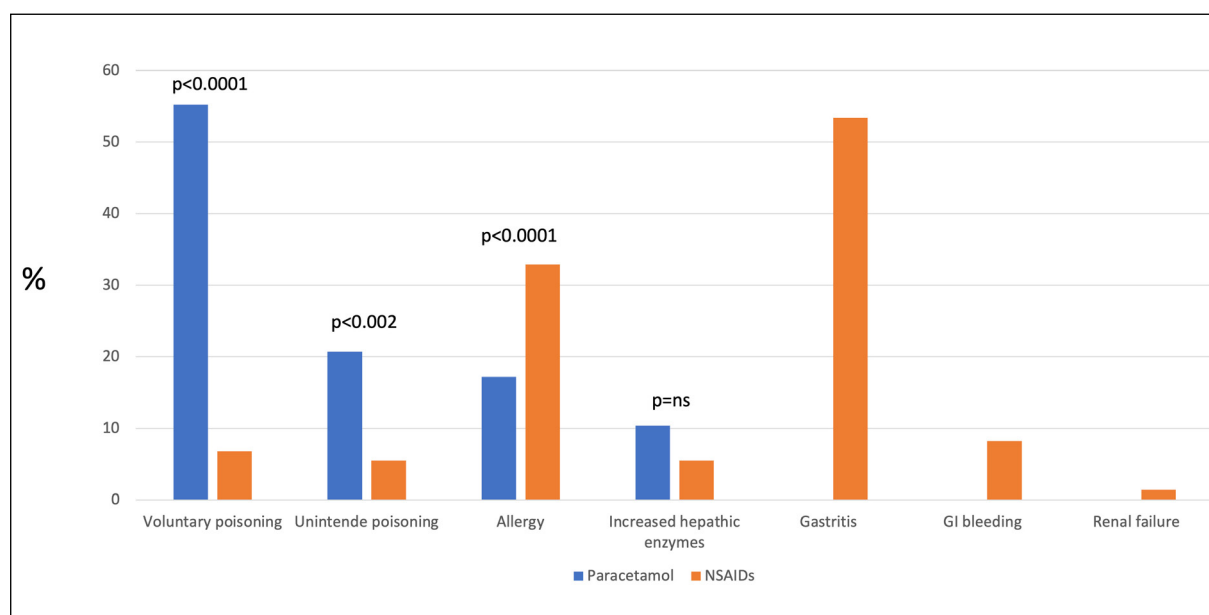


Figure 1. Comparison between the adverse reaction of NSAIDs and paracetamol.

These findings highlight the distinct toxicity profiles between paracetamol and NSAIDs, with hepatotoxicity predominantly associated with paracetamol exposure and gastrointestinal and allergic adverse events more frequently linked to NSAID use.

DISCUSSION

This retrospective study provides an overview of ADRs associated with paracetamol and NSAIDs in the ED setting of a large tertiary-care hospital. Consistent with previous pharmacovigilance data, these two classes of drugs account for a relevant proportion of drug-related ED visits, confirming their epidemiological importance despite their widespread and often unsupervised use.

Our findings highlight two major observations. First, ADRs were significantly more frequent among female patients, a trend observed across most drug classes, including paracetamol and NSAIDs. Second, the types and severity of ADRs differed substantially between the two drugs: paracetamol-related events were dominated by intentional or unintentional overdoses, whereas NSAIDs were primarily associated with gastrointestinal, allergic, and renal adverse events.

Sex-Related Differences and the Potential Role of the Gut Microbiota

Sex-based differences in drug responses are well documented and are often attributed to variations in pharmacokinetics, hormonal status, and immune reactivity. Women tend to have slower gastric emptying, higher body fat percentage, and differences in hepatic enzyme expression, all of which can modify drug bioavailability and metabolism. However, these physiological aspects alone may not fully explain the higher frequency of ADRs observed in female patients.

Emerging evidence suggests that the gut microbiota may represent a key biological interface mediating sex-related differences in drug response and toxicity. The human gut microbiome ex-

hibits sexual dimorphism in both composition and metabolic capacity, which is influenced by sex hormones, dietary habits, and genetic factors. Studies have demonstrated that premenopausal women often have a greater abundance of *Bacteroides* and *Firmicutes* species involved in bile acid and xenobiotic metabolism, whereas male microbiota tend to be enriched in species with pro-inflammatory and proteolytic profiles. These microbial variations may contribute to different susceptibility to drug-induced toxicity between sexes.

In women, certain microbial taxa may enhance the bioactivation of paracetamol *via* deconjugation processes mediated by bacterial β -glucuronidases, increasing the pool of toxic metabolites, such as *N*-acetyl-*p*-benzoquinone imine (NAPQI). Conversely, estrogens have been shown to regulate both hepatic CYP450 activity and microbial composition, potentially amplifying or mitigating hepatotoxic risk in a context-dependent manner. In the case of NSAIDs, sex-related differences in microbiota composition may alter local mucosal integrity and intestinal barrier function. Dysbiosis characterized by reduced *Lactobacillus* and *Bifidobacterium* species — which normally produce short-chain fatty acids (SCFAs) with anti-inflammatory and barrier-preserving properties — has been associated with higher gastrointestinal permeability and susceptibility to NSAID-induced enteropathy.

Microbiota-Drug Interactions and ADR Pathophysiology

The gut microbiota is increasingly recognized as an active metabolic “organ” that participates in drug transformation. More than 30% of commonly prescribed drugs are known to undergo biotransformation mediated, at least in part, by intestinal bacteria. These microbial reactions can result in drug activation, detoxification, or the formation of reactive metabolites capable of damaging host tissues.

For paracetamol, bacterial enzymes such as β -glucuronidase and sulfatase can regenerate the parent compound from its conjugated, excretory forms, thereby increasing systemic exposure and hepatic burden. Experimental studies have demonstrated that inhibition of bacterial β -glucuronidases can mitigate paracetamol-induced hepatotoxicity in murine models, supporting the concept of a gut-liver axis in ADR development. Additionally, dysbiosis may reduce hepatic glutathione synthesis through altered microbial production of cysteine and methionine, thereby decreasing detoxification capacity and increasing vulnerability to oxidative stress.

For NSAIDs, the role of microbiota is even more complex. Many NSAIDs undergo enterohepatic circulation, re-entering the gut lumen as glucuronide conjugates that are hydrolyzed by bacterial β -glucuronidases. This deconjugation liberates the active drug locally, leading to repeated mucosal exposure and inflammation. Furthermore, NSAIDs alter the intestinal microbial ecology by reducing protective species and promoting Gram-negative bacterial overgrowth, which increases lipopolysaccharide (LPS) translocation and systemic inflammation. This process establishes a vicious cycle: NSAIDs damage the mucosal barrier, dysbiosis exacerbates inflammation, and inflammation amplifies drug toxicity.

Renal effects may also be influenced by gut microbiota. Dysbiosis and increased circulating LPS levels can impair renal microcirculation and augment oxidative stress, potentially predisposing certain patients to NSAID-induced nephrotoxicity.

Integrating Microbiota into Pharmacovigilance and Personalized Medicine

The growing understanding of gut microbiota’s involvement in drug metabolism and host response offers new opportunities for personalized pharmacotherapy. Identifying microbiome profiles associated with increased susceptibility to specific ADRs could allow clinicians to stratify patients according to risk and develop microbiota-targeted interventions — such as probiotics, prebiotics, or dietary modulation — aimed at mitigating toxicity.

In the context of paracetamol and NSAID use, future research should integrate pharmacovigilance data with microbiome sequencing and metabolomic analyses. These combined approaches could elucidate the mechanisms by which microbial diversity, microbial gene expression, and host-microbiota crosstalk influence ADR risk. Moreover, considering the observed female predominance in ADR occurrence, studies should specifically investigate the interaction between sex hor-

mones, microbiota composition, and drug metabolism, which may represent a major determinant of interindividual variability. Integrating microbiota screening could identify high-risk patients allowing for personalized risk stratification and preventive strategies such as probiotic supplementation with *Lactobacillus* or *Bifidobacterium* species to bolster mucosal defense and reduce enterohepatic drug recycling. However, current microbiota profiling techniques remain costly and complex for routine clinical use; more affordable alternatives, such as targeted biomarker panels or predictive algorithms based on dietary and clinical history, may represent a practical initial step toward microbiota-informed pharmacovigilance in the management of analgesics-induced ADRs.

Study limitations

The present study has some limitations. Its retrospective single-center design limits causal inference, and microbiota composition was not directly assessed in the enrolled population. Nonetheless, the large sample size and long observation period strengthen the epidemiological relevance of our findings. A major limitation is that the role of the gut microbiota is inferred only from indirect evidence, as no microbiome data were collected; therefore, these considerations remain speculative. Importantly, the hypothesis of a microbiota-mediated mechanism in ADRs, although not tested here, is biologically plausible and supported by both preclinical and translational evidence.

CONCLUSIONS

In summary, this study confirms that ADRs are more frequent in female patients and that paracetamol and NSAIDs present distinct toxicity profiles. Paracetamol is generally safer in terms of unintentional ADRs, whereas NSAIDs are more commonly associated with gastrointestinal, allergic and renal complications.

The gut microbiota may play a central role in modulating these outcomes by influencing drug metabolism, mucosal defense, and systemic inflammation, although this remains hypothetical due to the absence of direct microbiome data. Differences in microbiota composition between sexes may further explain the higher ADR prevalence among women. Future multicenter prospective studies integrating clinical pharmacology, microbiome profiling, and metabolomic analysis are needed to validate these findings and to pave the way for microbiota-informed approaches to drug safety and personalized therapy.

Data Availability

The study data are available from the corresponding author upon reasonable request.

Informed Consent

Informed consent was obtained from all participants included in the study.

Ethics Approval

The study was approved in 03-08-2022 by the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli - IRCCS of Rome, Italy (protocol ID: 5121, Protocol number: 0025817/22).

Conflict of Interest

The authors declare no conflicts of interest.

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Authors' Contributions

F. Franceschi and M. Covino: Conceptualization, validation and supervision; A. Piccioni: Methodology and formal analysis; A. Saviano, M. C. Bungaro, and F. Valletta: Investigation and data curation; F. Manca: Writing—original draft preparation; M. Candelli: Conceptualization and writing—review and editing

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REFERENCES

- Patton K, Borshoff DC. Adverse Drug Reactions. *Anesthesia* 2018; 73 Suppl 1: 76-84.
- Durand M, Castelli C, Roux-Marson C, Kinowski JM, Leguelinel-Blache G. Evaluating the Costs of Adverse Drug Events in Hospitalized Patients: A Systematic Review. *Health Econ Rev* 2024; 14: 11.
- Skains RM, Hayes JM, Selman K, Zhang Y, Thatphet P, Toda K, Hayes BD, Tayes C, Casey MF, Moreton E, Kennedy RE, Lee S, Liu SW. Emergency Department Programs to Support Medication Safety in Older Adults: A Systematic Review and Meta-Analysis. *JAMA Netw Open* 2025; 8: e250814.
- Zheng Y, Zhang N, Tse G, Li G, Lip GH, Liu T. Co-administered Oral Anticoagulants with Nonsteroidal Anti-Inflammatory Drugs and the Risk of Bleeding: A Systematic Review and Meta-Analysis. *Thromb Res* 2023; 232: 15-26.
- Verdegaal AA, Goodman AL. Integrating the gut microbiome and pharmacology. *Sci Transl Med* 2024; 16: eadg8357.
- Pant A, Maiti TK, Mahajan D, Das B. Human Gut Microbiota and Drug Metabolism. *Microb Ecol* 2023; 86: 97-111.
- He J, Liu X, Zhang J, Wang R, Cao X, Liu G. Gut microbiome-derived hydrolases—an underrated target of natural product metabolism. *Front Cell Infect Microbiol* 2024; 14: 1392249.
- Mallet C, Desmeules J, Pegahi R, Eschalièr A. An Updated Review on the Metabolite (AM404)-Mediated Central Mechanism of Action of Paracetamol (Acetaminophen): Experimental Evidence and Potential Clinical Impact. *J Pain Res* 2023; 16: 1081-1094.
- Mazaleuskaya LL, Sangkuhl K, Thorn CF, FitzGerald GA, Altman RB, Klein TE. PharmGKB summary: pathways of acetaminophen metabolism at the therapeutic versus toxic doses. *Pharmacogenet Genomics* 2015; 25: 416-426.
- Freo U, Ruocco C, Valerio A, Scagnol I, Nisoli E. Paracetamol: A Review of Guideline Recommendations. *J Clin Med* 2021; 10: 3420.
- Malfatti MA, Kuhn EA, Muruges DK, Mendez ME, Hum N, Thissen JB, Jaing CJ, Loots GG. Manipulation of the Gut Microbiome Alters Acetaminophen Biodisposition in Mice. *Sci Rep* 2020; 10: 4571.
- Alchin J. Why Paracetamol (Acetaminophen) Is a Suitable First-Line Analgesic for Acute Mild-to-Moderate Pain *Curr Med Res Opin* 2022; 38: 597–607.
- Ramachandran A, Jaeschke H. Clinically Relevant Therapeutic Approaches against Acetaminophen-Induced Liver Injury. *Biochim Biophys Acta Rev Cancer* 2024; 1879: 188988.
- Martínez-Martínez LM, Rosales-Sotomayor G, Jasso-Baltazar EA, Torres-Díaz JA, Aguirre-Villarreal D, Hurtado-Díaz de León I, Páez-Zayas VM, Sánchez-Cedillo A, Martínez-Vázquez SE, Tadeo-Espinoza HN, Guerrero-Cabrera JP, García-Alanis M, García-Juárez I. Acute liver failure: Management update and prognosis. *Rev Gastroenterol Mex* 2024; 89: 404-417.
- Tai FWD, McAlindon ME. Non-steroidal anti-inflammatory drugs and the gastrointestinal tract. *Clin Med* 2021; 21: 131-134.
- Brossier C, Jardou M, Janaszkiwicz A, Firoud D, Petit I, Arnion H, Pinault E, Sauvage FL, Druilhe A, Picard N, Di Meo F, Marquet P, Lawson R. Gut microbiota biotransformation of drug glucuronides leading to gastrointestinal toxicity: Therapeutic potential of bacterial β -glucuronidase inhibition in mycophenolate-induced enteropathy. *Life Sci* 2024; 351: 122792.
- Zádori ZS, Király K, Al-Khrasani M, Gyires K. Interactions between NSAIDs, opioids and the gut microbiota - Future perspectives in the management of inflammation and pain. *Pharmacol Ther* 2023; 241: 108327.
- Sohail R, Mathew M, Patel KK, Reddy SA, Haider Z, Naria M, Habib A, Abdin ZU, Razzaq Chaudhry W, Akbar A. Effects of Non-steroidal Anti-inflammatory Drugs (NSAIDs) and Gastroprotective NSAIDs on the Gastrointestinal Tract: A Narrative Review. *Cureus* 2023; 15: e37080
- Khalil NA, Ahmed EM, Tharwat T, Mahmoud Z. NSAIDs between past and present; a long journey towards an ideal COX-2 inhibitor lead. *RSC Adv* 2024; 14: 30647-30661.
- Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. *J Pharm Pharm Sci* 2013; 16: 821-847.
- Sostres C, Gargallo CJ, Lanás A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. *Arthritis Res Ther* 2013; 15 Suppl 3: S3.

22. Freedberg DE, Kim LS, Yang YX. The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association. *Gastroenterology* 2017; 152: 706-715.
23. Abrignani MG, Gatta L, Gabrielli D, Milazzo G, De Francesco V, De Luca L, Francese M, Imazio M, Riccio E, Rossini R, Scotto di Uccio F, Soncini M, Zullo A, Colivicchi F, Di Lenarda A, Gulizia MM, Monica F. Gastroprotection in patients on antiplatelet and/or anticoagulant therapy: a position paper of National Association of Hospital Cardiologists (ANMCO) and the Italian Association of Hospital Gastroenterologists and Endoscopists (AIGO). *Eur J Intern Med* 2021; 85: 1-13.
24. aldovinos-García LR, Villar-Chávez AS, Huerta-Iga FM, Amieva-Balmori M, Arenas-Martínez JS, Bernal-Reyes R, Coss-Adame E, Gómez-Escudero O, Gómez-Castaños PC, González-Martínez M, Morel-Cerda EC, Remes-Troche JM, Rodríguez-Leal MC, Ruiz-Romero D, Valdovinos-Díaz MA, Vázquez-Elizondo G, Velarde-Ruiz Velasco JA, Zavala-Solares MR. Good clinical practice recommendations for proton pump inhibitor prescription and deprescription. A review by experts from the AMG. *Rev Gastroenterol Mex* 2025; 90: 111-130.
25. Bruno A, Tacconelli S, Contursi A, Ballerini P, Patrignani P. Cyclooxygenases and platelet functions. *Adv Pharmacol.* 2023; 97: 133-165.
26. Corazzi T, Leone M, Maucci R, Corazzi L, Gresele P. Direct and irreversible inhibition of cyclooxygenase-1 by nitroaspirin (NCX 4016). *J Pharmacol Exp Ther* 2005; 315: 1331-1337.
27. Perazella MA, Rosner MH. Drug-Induced Acute Kidney Injury. *Clin J Am Soc Nephrol* 2022; 17: 1220-1233.
28. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Böck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wannier C, Williams B; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021; 42: 3227-3337.
29. Krauss E, Cronin M, Dengler N, Segal A. Interaction Between Low-Dose Aspirin and Nonsteroidal Anti-Inflammatory Drugs Can Compromise Aspirin's Efficacy in Preventing Venous Thrombosis Following Total Joint Arthroplasty. *Clin Appl Thromb Hemost* 2020; 26: 1076029620920373.