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## Reappraisal of nonsteroidal anti-inflammatory drugs' effects on kidney outcomes

### Abstract

**Introduction:** Nonsteroidal anti-inflammatory drugs are the most common drugs as a prescription or over-the-counter drugs, and acute kidney injury (AKI) is one of the dangerous complications of these drugs. This research aims to assess the risk and effect of nonsteroidal anti-inflammatory drugs on kidney outcomes. **Methods:** In the prospective analytic (experimental) study type with randomized clinical trial design and article type of systematic review and meta-analysis, 32 patients with nonsteroidal anti-inflammatory drug-induced nephropathy were enrolled. The prevalence of complications, relative risk, and odds ratio as effective measures of endpoints were assessed in the present research. **Results:** Of 32 patients in non-steroidal anti-inflammatory induced nephropathy, 16 patients (16/32, 50%) were male, and sixteen patients (16/32, 50%) were women. AKI was the most common complication of these drugs (14/32, 43.7%), and the prevalence of diclofenac sodium was 34.3% (11/32) as the most common drug in the induction of nonsteroidal anti-inflammatory drugs nephropathy. Relative risk and odds ratio of AKI in patients with nonsteroidal anti-inflammatory induced nephropathy were evaluated at 0.94 with 95% confidence level of 0.09803 to 6.247 and 0.75 with 95% CI of 0.06368 to 8.8339, respectively. **Conclusion:** Nonsteroidal anti-inflammatory drugs were accompanied by low risk and Odds ratio of AKI in the present investigation. In the present research, diclofenac sodium was reported as the most common drug in nonsteroidal anti-inflammatory-induced nephropathy.

### Keywords

Risk, Kidney, Sodium, drugs, Diclofenac, factors, Acute, injury, anti-inflammatory, Nonsteroidal

## Reappraisal of nonsteroidal anti-inflammatory drugs' effects on kidney outcomes

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### Abstract

**Introduction:** Nonsteroidal anti-inflammatory drugs are the most common drugs as a prescription or over-the-counter drugs, and acute kidney injury (AKI) is one of the dangerous complications of these drugs. This research aims to assess the risk and effect of nonsteroidal anti-inflammatory drugs on kidney outcomes. **Methods:** In the prospective analytic (experimental) study type with randomized clinical trial design and article type of systematic review and meta-analysis, 32 patients with nonsteroidal anti-inflammatory drug-induced nephropathy were enrolled. The prevalence of complications, relative risk, and odds ratio as effective measures of endpoints were assessed in the present research. **Results:** Of 32 patients in nonsteroidal anti-inflammatory induced nephropathy, 16 patients (16/32, 50%) were male, and sixteen patients (16/32, 50%) were women. AKI was the most common complication of these drugs (14/32, 43.7%), and the prevalence of diclofenac sodium was 34.3% (11/32) as the most common drug in the induction of nonsteroidal anti-inflammatory drugs nephropathy. Relative risk and odds ratio of AKI in patients with nonsteroidal anti-inflammatory induced nephropathy were evaluated at 0.94 with 95% confidence level of 0.09803 to 6.247 and 0.75 with 95% CI of 0.06368 to 8.8339, respectively. **Conclusion:** Nonsteroidal anti-inflammatory drugs were accompanied by low risk and Odds ratio of AKI in the present investigation. In the present research, diclofenac sodium was reported as the most common drug in nonsteroidal anti-inflammatory-induced nephropathy.

**Keywords:** Acute kidney injury; Diclofenac Sodium; Nonsteroidal anti-inflammatory drugs; Risk factors.

### INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are analgesic drugs that reduce pain, fever, and inflammation. NSAIDs are categorized on chemical structure or selective inhibition of cyclooxygenase (COX) enzymes. Herein they are classified into two major groups and include COX-2 selective inhibitors (COXIBs) and nonselective NSAIDs. Many have a chiral structure, and others have an S enantiomer. Other NSAIDs contain an R enantiomer and the R enantiomer of some chiral NSAIDs that can be metabolized to S enantiomer in humans. Naproxen is a single pharmacologically active enantiomer, and ibuprofen exists as its racemate form. Currently, S-Ibuprofen is found in some countries. (S)-Ibuprofen is active as a pain and fever allayer, while its R enantiomer is inactive. The S enantiomer of naproxen is an active pain reliever, but its R enantiomer is a liver toxin. Enantiomeric inversion can be bidirectional in some spe-

cies [1]. The mechanism of action of NSAIDs is the inhibition of prostaglandins and prostanoids (prostanoids and thromboxanes) through COX enzymes from arachidonic acids in the arachidonic acid cascade [2, 3]. There are two isoforms of COX enzymes; COX-1 (constitutive enzyme) and COX-2 (inducible enzyme). COX-3, a variant of COX-1, is also identified recognized. COX-1 exists in all body tissues, but COX-2 is involved in the development of the kidneys. One hypothesis for supposing NSAIDs' side effects is the ion channel theory that Ca<sup>2+</sup>-induced K<sup>+</sup> channels are used as a target for these adverse effects. Another theory proposes the role of drug transporters in the efficacy and safety of NSAIDs [4, 5]. This research aims to assess the risk and effect of NSAIDs on kidney outcomes.

### METHODS

Among a total of 453 (google scholar=102; PubMed Central (PMC)=351) identified articles (Google Scholar = 102; PMC =

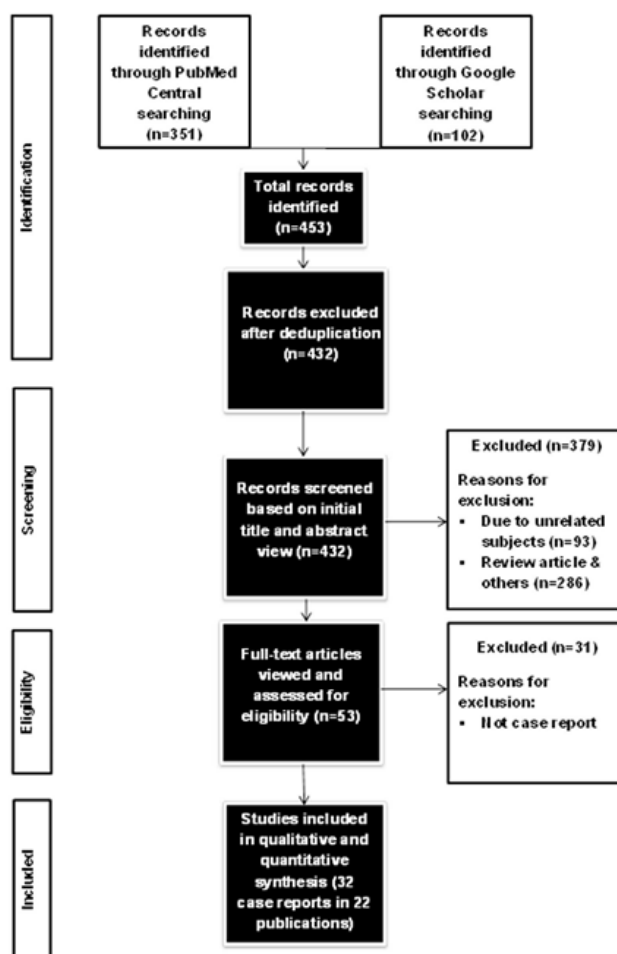
351), twenty-one articles were duplicated and 432 articles were selected. Three-hundred seventy-nine articles were excluded due to unrelated topics ( $n = 93$ ), review articles ( $n = 286$ ), and 53 full-text articles were eligible for this investigation. Of 53 eligible articles, 31 articles were excluded as they were not casing reports. The 32 case reports in twenty-two published articles included in this research were considered for quantitative and qualitative synthesis. All articles were obtained via electronic search in PubMed Central and Google Scholar databases. All papers that included participants with NSAIDs usage and kidney adverse effects were enrolled in this investigation. Primary endpoints consist of acute kidney injury (AKI), death, persistent dialysis, and elevated aminotransferases, and outcomes such as urinary tract infection (UTI), proteinuria, and decreased eGFR were considered secondary endpoints. Data from this research were extracted by searching PubMed Central and Google Scholar databases from their inception until July 2021.

This research was a systematic review and meta-analysis and assessed the association between intervention or exposure and outcome. The mentioned terms in this research were nonsteroidal anti-inflammatory drugs, kidney disease, And case reports in the PMC database. This search was done in google scholar with nonsteroidal anti-inflammatory drugs And kidney disease. The author reviewed references of included articles and performed a hand search of related articles to identify the additional relevant articles. Data were extracted from articles: title, first author, journal name, year of publication, location, type of clinical study, study design, period of intervention, and intervention characteristics. Data extracted in this

research contained NSAID classification, AKI, hypertension, hyponatremia, hyperkalemia, tubulointerstitial nephritis, type IV of allergy, analgesic nephropathy, and urologic cancer. In supplementary table 1 (Table S1), definitions and staging of acute kidney injury have been described thoroughly. Each study design has different assessment tools, and case reports were analyzed using criteria developed by the Joanna Briggs Institute Critical Appraisal tool. The evaluation tool has eight questionable items for case reports. Data were entered into Microsoft Excel 2010 software. Categorical variables were assessed as frequency (N) and percentage (%). Continuous variables were determined whether they were normally distributed using the Kolmogorov-Smirnov or Shapiro-Wilk test. Continuous variables with normal distribution were reported as mean  $\pm$  standard deviation (SD), and variables with not-normally distribution were expressed as the median and interquartile range (IQR). The comparison between two continuous variables was assessed with the two-tailed student t-test. Relative risk and odds ratio were used to assess NSAIDs' effect on kidney outcomes. The significance level was assessed with a p-value of  $< 0.05$ .

## RESULTS

The author identified 453 after searching through PubMed Central and Google Scholar databases through electronic search, and thirty-two patients in twenty-two published articles were included in the present investigation (Figure 1). Assessment of risk of bias and quality of included articles led to eight scores in 37.5% of patients, seven in 46.8% of patients, six in five in 6.25%, and three-score in 3.1% of patients (Table S2).



**Figure (1):** Workflow of included studies.

This research included thirty-two patients in twenty-two published articles for qualitative and quantitative synthesis. These 32 patients had impaired kidney function and a history of NSAIDs usage (Table S3). The complications and risk factors for NSAID-induced nephropathy are multifactorial and are described in Table S4. In the present research, acute renal failure (ARF) was observed in thirteen of 32 patients (13/32, 40.6%) as the most common complication of NSAIDs consumption. The most common drugs in NSAID-induced nephropathy are diclofenac sodium in 34.3% (11/32) patients and ibuprofen in 18.7% (6/32) in the current investigation. In the present research, the mean average age of the patients at the time of diagnosis was assessed at  $50.71 \pm 21.13$

years old (ranging from 5 to 83 years old). Sixteen patients were male, and 16 were female (16/32, 50%) in the present investigation. The mean average age of male patients

was  $48.68 \pm 19.58$  years and  $52.75 \pm 22.40$  years old in females. The age range in the males was evaluated from 7 to 77 years, and this range in females was from 5 to 83 years old. This research showed no statistically significant difference in age between the two sex levels in NSAID-induced nephropathy (p-value: 0.60) (Table S5). In the present investigation, the most common symptoms of NSAID-induced nephropathy were vomiting in 12.5% (4/32), flank pain, and edema in 9.37% (3/32) patients. There was hypertension in 15.6% (5/32), type 2 diabetes mellitus (T2DM), and a history of drinking in 12.5% (4/32) patients in the present investigation (Table S6). Four out of 32 patients (4/32, 12.5%) appeared dehydrated in general appearance examination. In vital signs, a high temperature was observed in 9.3% (3/32) and bradycardia in 3.1% (1/32) of patients in this investigation. Moist, coarse lung rales of 6.25% (2/32), and ascites in 3.1% (1/32) of patients were seen. A lack of urinary output

(anuria) in 3.1% (1/32) and lower extremity edema in 12.5% (4/32) of patients were observed in the present research (Table S7). Serum creatinine was measured in 90.6% (29/32) of patients, that elevated serum creatinine levels were seen in 72.4% (21/29) with an average of  $3.02 \pm 1.86$  mg/dl. Serum potassium concentration was measured in 46.8% (15/32) of patients, and hyperkalemia was seen in 40% (6/15) with an average of  $7.4 \pm 3.21$  mEq/l in the present investigation. Serum sodium levels were measured in 31.2% (10/32) of patients, that hyponatremia was seen in 30% (3/10) in the present investigation. Serum chloride was measured in 9.37% (3/32) of patients, and hypochloremia was seen in 66.6% (2/3) in NSAID-induced nephropathy. Serum transaminases of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured in 18.75% (6/32) of patients, and that elevated AST level was seen in 33.3% (2/6) with an average of  $34.5 \pm 3.5$  IU/l (Table S8). Kidney biopsies have been performed in 28.1% (9/32) of patients, with abnormal findings in 77.7% (7/9) of cases. There was acute interstitial nephritis in 22.2% (2/9), acute tubular necrosis (ATN), tubulonephritis, and acute changes of acute on chronic pyelonephritis in 11.1% (1/9) of patients in the current research. Furthermore, there was interstitial nephritis in 11.1% (1/9) of a patient in autopsy. Abdominal sonography was performed in 15.6% (5/32) of patients, and 80% (4/5) had abnormal abdominal sonography. Kidney ultrasound was performed in 6.25% (2/32) of these patients, and small bilateral kidneys

were seen in 50% (1/2) of patients (Table S9). Intravenous (IV) rehydration was used in 31.25% (10/32), and furosemide was given to 18.75% (6/32) of patients in NSAID-induced nephropathy. Hemodialysis was used in 15.6% (5/32) of patients in the present investigation (Table S10). During follow-up, serum creatinine was measured in 53.1% (17/32) of patients. SCR measurement time was assessed with a median of 11 and IQR of 47.5 days. Three out of 17 patients (3/17, 35.2%) developed a two-fold increase in serum creatinine with baseline level or initial SCr level, and 5.8% (1/17) of patients continued KRT (dialysis) during follow-up. The outcome was defined as an SCr increase of 2-fold of baseline level or KRT initiation. The mean average of elevated SCr patients with NSAID-induced nephropathy during follow-up was assessed at  $4.69 \pm 2.47$  mg/dl. The relative risk and odds ratio of AKI (as a risk factor) after NSAIDs consumption in creating NSAIDs nephrotoxicity were assessed 0.94 with 95% confidence level 0.09804 to 6.247 and 0.75 with 95% CI 0.06368 to 8.8339, respectively (Table 1). Elevated liver transaminases were observed in 3.1% (1/32) of patients. Dialysis continued in 12.5% (4/32) of patients during follow-up and then discontinued in 75% (3/4) of them. The death occurred in 9.3% (3/32) of patients, and the cause of death in one of them was diagnosed as cerebral hemorrhage. The events mentioned above were described as primary endpoints.

**Table (1):** Methods for calculating statistical analyses in patients with NSAIDs nephrotoxicity. **Risk ratio and Odds ratio of AKI due to NSAIDs usage**

<b>Disease +/- Exposure +/-</b>	<b>NSAIDs- nephrotoxicity</b>	<b>Non-NSAIDs nephrotoxicity</b>	<b>Total</b>	<b>Relative Risk</b>	<b>Odds ratio</b>
<b>AKI (Group I)</b>	3 (a)	1 (b)	4 (n1)	$a/a+b \div c/c+d$ $3/3+1=$ $0.75$ $20/20+5=0.80$ $0.75 \div 0.80=0.94$	$a*d/b*c$ $3*5=15$ $20*1=20$ $15 \div 20=0.75$
<b>Non-AKI (Group II)</b>	20 (c)	5 (d)	25 (n0)		
	23 (m1)	6 (m0)	29 (N)	0.94	0.75

<b>Disease +/- Exposure +/-</b>	<b>NSAIDs- nephrotoxicity</b>	<b>Non-NSAIDs nephrotoxicity</b>	<b>Total</b>	<b>Relative Risk</b>	<b>Odds ratio</b>
<b>Effect of NSAIDs usage on AKI as an outcome in RCT</b>					
Frequency and percentage of baseline SCr level measurement	Frequency and percentage of nephrotoxicity patients based on elevated SCr level > normal value	Frequency and percentage of non-nephrotoxicity patients based on normal baseline SCr level	Frequency and percentage of elevated SCr level > 2 fold of baseline level or KRT initiation, at last, follow up	Frequency and percentage of elevated SCr level > 2 fold of baseline level or KRT initiation, at last, follow up	Proportion difference with p-value
29/32 (90.6%)	23/29 (79.3%)	23/29 (79.3%)	3/23 (13.04%)	1/6 (16.6%)	3.6% (95% CI of -19.84% to 44.19%); p-value: 0.82

AKI, acute kidney injury; KRT, kidney replacement therapy; NSAIDs, nonsteroidal anti-inflammatory drugs; RCT, randomized clinical trial; SCr, serum creatinine.

In the current research, secondary endpoints consisted of UTI, proteinuria, and declined eGFR. UTIs, nephrotic-range proteinuria (7.5 g/day) with nephrotic syndrome, and declined eGFR were observed in 3.1% (1/32) of patients in NSAID-induced nephropathy (Table S11). All results of this research with statistical assessment were summarized in Table 2.

**Table (2):** Summary of the study results in the present research.

<b>Study results</b>	<b>NSAID-induced nephropathy</b>
<b>Prevalence of complications</b>	14/32 (43.7%)
Acute kidney injury	5/32 (15.6%)
Acute interstitial nephritis	4/32 (12.5%)
Acute pyelonephritis	3/32 (9.3%)
Chronic Kidney Disease	2/32 (6.25%)
Nephrotic syndrome	2/32 (6.25%)
Nephro-hepatotoxicity	2/32 (6.25%)
Cholestatic hepatitis	1/32 (3.1%)

<b>Study results</b>	<b>NSAID-induced nephropathy</b>
<b>Other</b>	
<b>Prevalence of NSAIDs</b>	
Diclofenac sodium	11/32 (34.3%)
Ibuprofen	6/32 (18.7%)
Naproxen	5/32 (15.6%)
Acetaminophen	3/32 (9.3%)
Piroxicam	3/32 (9.3%)
Mefenamic acid	2/32 (6.25%)
Indomethacin	2/32 (6.25%)
Ketorolac	2/32 (6.25%)
<b>Age (years)</b>	
Overall Mean age ± SD	50.71±21.13 (y/o)
Mean age ± SD	
Male	
Female	48.68±19.58 (y/o)
p-value	52.75±22.40 (y/o) 0.6
<b>Sex</b>	
Male	16/32 (50%)
Female	16/32 (50%)
<b>Symptoms</b>	
Vomiting	4/32 (12.5%)
Flank Pain	3/32 (9.37%)
Edema	3/32 (9.37%)

Study results	NSAID-induced nephropathy
History of fever	2/32 (6.25%)
History of anuria	2/32 (6.25%)
Other	2/32 (6.25%)
<b>Signs</b>	
High temperature	3/32 (9.3%)
Bradycardia	1/32 (3.1%)
Dehydration	4/32 (12.5%)
Lower extremity edema	4/32 (12.5%)
<b>Co-morbidities</b>	
Hypertension	5/32 (15.6%)
Type 2 DM	4/32 (12.5%)
History of drinking	4/32 (12.5%)
History of smoking	2/32 (6.25%)
HIV	2/32 (6.25%)
<b>Laboratory data</b>	
<b>↑ Scr</b>	
Prevalence	21/29 (72.4%)
Mean±SD of Scr	3.02±1.86 mg/dl
<b>↑ Serum Urea</b>	
Prevalence	8/10 (80%)
Mean±SD of SU	83.2±22.85 mg/dl
<b>Hyperkalemia</b>	
Prevalence	6/15 (40%)
Mean±SD	7.4±3.21 mEq/l
<b>Hypokalemia</b>	
Prevalence	2/15 (13.3%)
Mean±SD	3.05±0.15 mEq/l
<b>Hyponatremia</b>	
Prevalence	3/10 (30%)
<b>Hypochloremia</b>	
Prevalence	2/3 (66.6%)
<b>Hypophosphatemia</b>	
Prevalence	2/6 (33.3%)
Mean±SD	0.68±0.18 mg/dl
<b>Leukocytosis</b>	
Prevalence	4/6 (66.6%)
Mean±SD	23000±12622.99 cells/ml
<b>Neutrophilia</b>	
Prevalence	4/5 (80%)
Mean±SD	83.3±6.11%
<b>Eosinophilia</b>	
Prevalence	1/32 (3.12%)
<b>Eosinophiluria</b>	
Prevalence	

Study results	NSAID-induced nephropathy
<b>Anemia</b>	
Prevalence	1/32 (3.12%)
Mean±SD	
<b>Thrombocytosis</b>	4/9 (44.4%)
Prevalence	10±0.75 g/dl
<b>↑ESR</b>	
Prevalence	1/8 (12.5%)
Mean±SD	
<b>↑ CRP</b>	3/3 (100%)
Prevalence	95.3±19.34 mm/hr
Mean±SD	
<b>Significant Proteinuria</b>	
Prevalence	5/6 (83.3%)
Mean±SD	28.82±20.18 mg/dl
<b>Nephritic syndrome</b>	
prevalence	
<b>Waxy cast/hyaline cast</b>	3/7 (42.8%)
Prevalence	5.25±1.55 g/gCr
<b>Hypoalbuminemia</b>	
Prevalence	5/32 (15.6%)
<b>↑AST</b>	
Prevalence	1/32 (3.12%)
Mean±SD	
<b>Hyperbilirubinemia</b>	4/8 (50%)
Prevalence	
Mean±SD	2/6 (33.3%)
<b>↓eGFR</b>	34.5±3.5 IU/l
Prevalence	2/2 (100%)
Mean±SD	16.78±15.61 mg/dl
<b>↓HCO<sub>3</sub><sup>-</sup></b>	
Prevalence	
Mean±SD	4/5 (80%)
<b>Hyperglobulinemia A</b>	76.27±34.47 ml/min/1.73m <sup>2</sup>
Prevalence	
Mean±SD	2/6 (33.3%)
<b>Hyper IgE</b>	13±5.9 mEq/l
Prevalence	
<b>Hyper IgG</b>	2/32 (6.25%)
Prevalence	342.5 ± 2.5 mg/dl
<b>↑ UNAG</b>	
Prevalence	

Study results	NSAID-induced nephropathy
<b>↑ B2MG</b>	1/32 (3.12%)
Prevalence	1/32 (3.12%)
	1/32 (3.12%)
	1/32 (3.12%)
<b>Imaging</b>	
<b>CXR</b>	
Abnormal	1/5 (20%)
Abnormal abdominal sonography	4/5 (80%)
<b>Kidney sonography</b>	1/2 (50%)
Bilateral small-sized kidneys	1/2 (50%)
<b>Abdominal CT Scan</b>	
Abnormal	2/32 (6.25%)
<b>Bone Scintigraphy</b>	
Prevalence	1/32 (3.1%)
<b>Gallium-67 Scan</b>	
Prevalence	1/32 (3.1%)
<b>Lung CT Scan</b>	
Prevalence	1/32 (3.1%)
<b>IVP</b>	
Prevalence	
<b>Pathology</b>	
Kidney biopsy	9/32 (28.1%)
Acute interstitial nephritis	2/9 (22.2%)
Acute tubular necrosis	1/9 (11.1%)
Tubulonephritis	1/9 (11.1%)
Changes in acute to chronic pyelonephritis	1/9 (11.1%)
<b>Autopsy</b>	1/32 (3.1%)
Interstitial nephritis	
<b>Treatment</b>	
IV rehydration	10/32 (31.25%)
Furosemide	6/32 (18.75%)
Hemodialysis	5/32 (15.6%)
<b>Outcome</b>	
Time of SCr assessing	IQR of 47.5 days
<b>Primary endpoints</b>	
<b>↑ SCR × 2 fold</b>	
Prevalence (single proportion)	3/17 (17.6%)
Mean±SD	4.69 ± 2.47

Study results	NSAID-induced nephropathy
<b>The relative risk of AKI</b>	mg/dl
%95 CI	0.94
<b>The odds ratio of AKI</b>	0.09804 to 6.247
95% CI	0.75
<b>Permanent kidney impairment</b>	0.06368 to 8.8339
Prevalence	
<b>↑ liver transaminases</b>	1/17 (5.8%)
Prevalence	1/32 (3.1%)
<b>Persistent Hemodialysis</b>	2/32 (6.25%)
<b>Death</b>	1/4 (25%)
<b>Secondary endpoints</b>	3/32 (9.3%)
UTI	
Nephrotic-range proteinuria	1/32 (3.1%)
↓ Urinary output	1/32 (3.1%)

AKI, acute kidney injury; AST, alanine transaminase; B<sub>2</sub>MG, beta-2 microglobulin; CRP, C-reactive protein; CT scan, computed tomography scan; CI, confidence interval; Cr, creatinine; CXR, chest x-ray; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; g, gram; HCO<sub>3</sub><sup>-</sup>, bicarbonate; HIV, human immunodeficiency virus; hr, hour; IgE, immunoglobulin E; IQR, interquartile range; IU/l, international unit per liter; IV, intravenous; IVP, intravenous pyelography; KRT, kidney replacement therapy; mm, millimeter; mg/dl, milligram per deciliter; min, minute; mEq/l, milliequivalent per liter; m<sup>2</sup>, square meter; NSAIDs, nonsteroidal anti-inflammatory agents; Scr, serum creatinine; SD, standard deviation; SU, serum urea; UNAG, urinary N-acetyl-β-D-glucosaminidase; UTI, urinary tract infection; y/o, years old. The signs show an increase and decrease in parameters.

## DISCUSSION

NSAID agents are prescribed to treat pain, fever, and inflammation. NSAIDs are rarely associated with nephrotoxicity and cause chronic kidney disease (CKD) in the presence of long-term usage. NSAIDs are drugs with a relatively high cost, and their benefits must be weighed against their risks and cause twenty to thirty percent complica-

tions in hospital admissions. In other words, these drugs are harmless and are converted into dangerous enemies as needed. So, the most caution should be used for these over-the-counter drugs (OTC), especially in the kidney, as such consumption may cause AKI in elderly patients only with an elevation of 0.1 mg/dl in SCr.

Furthermore, these adverse effects may appear in clinical practice even with one tablet or rectal or topical drug consumption. In addition to aminoglycosides, NSAIDs are the second most common cause of drug nephrotoxicity in treating acute kidney injury and failure [6], and this complication is reported at 13%, with the mean average of  $4.69 \pm 2.47$  mg/dl in the present research. Another side effect of NSAIDs is nephrotic syndrome, a complex immune disease. On the other hand, minimally modified glomerular diseases and membranous nephropathy are the most common types of nephrotic syndrome in biopsy-proven specimens [7]. This adverse effect was observed in our study's 6.25% (2/32) and required special attention. In this way, physicians should always prescribe the lowest effective dose of NSAIDs for the shortest possible time of  $\leq 5$  days. One of the side effects of NSAIDs is hypophosphatemia observed in 33.3% (2/6) cases of our study with the mean average of  $0.68 \pm 0.18$  mg/dl, and increased phosphate secretion seems to be the most probable cause mechanism of this complication, and it is an infrequent side effect of NSAIDs. The most critical point in the current investigation is to mention risk factors for AKI. These risk factors for acute renal insufficiency include age 60, vascular disease, renal or functional volume depletion, pre-existing renal insufficiency, high renin-angiotensin states, and systemic erythematous lupus [8]. The relative risk and odds ratio of AKI by NSAIDs in our study was low in disagreement with the study by Chou et al. [9, 10], and this risk in current and recent consumers was high for hospitalization for AKI (adjusted odds ratio of 2.73 and 1.17). The risk of heart attack from NSAIDs is dangerous and hazardous, and these adverse effects need special attention [1].

Additionally, NSAIDs can enhance the risk of thrombosis and acute renal failure in

patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). They cause bronchoconstriction and acute respiratory distress syndrome (ARDS) due to the release of leukotrienes during COVID-19 infection [11]. Another adverse effect of NSAIDs is attributed to the unfavorable effects of oxidative stress in the kidney. The study by Hur et al. demonstrated that the therapeutic dose of NSAIDs led to histopathologically proven renal cell damage and an increase in oxidative stress into erythrocytes and subsequently increased lipid peroxidation and inhibition of endothelial superoxide dismutase (eSOD) activity [12]. Another great lesson about the consumption of NSAIDs is related to kidney transplant recipients such a study by Mulka-Gierek described that 63% of kidney transplant recipients regularly took OTC painkillers, and 30% were unaware of the harmful effects. This research requires calls for continuous education for kidney transplant recipients about the risk of OTC consumption of NSAIDs or analgesic use [13]. Recently, NSAID prodrugs have been developed. These drugs are reversible derivatives of pharmacologically active agents that undergo a chemical transformation and /or enzymatic cleavage in vivo, releasing the parent drug that depicts the desired pharmacological impact. A new class of drugs, cyclooxygenase inhibitor nitric oxide donor (CINOD), was developed by adding the nitric oxide group to the parent NSAIDs with an ester link [6, 14]. These novel agents promise to decrease the side effects of NSAIDs and optimize drug usage for their utilization. Moreover, the production of these novel agents craves future research.

## CONCLUSION

Prevalence of NSAID-induced nephropathy was equal in both sex levels, while the mean average age in the female group occurred at higher ages than in the male group. The relative risk and odds ratio of AKI in patients with NSAID-induced nephropathy were assessed low in the present investigation.

## Declarations

Ethics approval and consent to participate

This research has been written based on electronic data through scientific databases.

### Consent for publication

Authors of published case reports performed this consent.

### Availability of data and materials

The author located the data sets (supplementary tables) in the figshare repository with doi:  
<http://doi.org/10.6084/m9.figshare.14287085>.  
 The DOI becomes active when the article is published.

### Author's contribution

**Fateme Shamekhi Amiri:** conceptualization, writing-original draft, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing review & editing.

### Competing interest

There are no conflicts of interest.

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