Pharmaciana
Vol.15, No.1, March 2025, Page. 40-55
ISSN: 2088 4559; e-ISSN: 2477 0256
DOI: 10.12928/pharmaciana.v15i1.290

Assessment of medication-related liver and kidney impairment in admitted patients in Depok, Indonesia: an observational study employing the Naranjo algorithm

Nadia Farhanah Syafhan[1,2*], Ghea Shafa Aldora[1], Shinta Kamila[1]
[1]Faculty of Pharmacy, Universitas Indonesia, Depok, West Java, Indonesia
Jl. Prof. DR. Mahar Mardjono, Pondok Cina, Kecamatan Beji, West Java, Indonesia
[2]Unit of Pharmacy,Universitas Indonesia Hospital, West Java, Indonesia
Jl. Prof. DR. Bahder Djohan, Pondok Cina, Kecamatan Beji, West Java, Indonesia

Submitted: 11-06-2024 ***Reviewed: 02-01-2025*** ***Accepted: 06-03-2025***

ABSTRACT

Liver and kidney impairment caused by medications represents serious side effects that may extend hospital stays and increase the risk of patient death. Implementing strategies to recognize, document, and analyze cases of patient harm related to drug use is crucial for medicines optimization. This study aimed to evaluate the prevalence of medication-related liver and kidney impairment among hospitalized patients, while also identifying the specific medication categories implicated. A retrospective review of patient records was conducted at Universitas Indonesia Hospital (Depok, Indonesia), focusing on adult patients diagnosed with liver or kidney impairment during their 2021 hospital admission. The Naranjo algorithm was applied to assess the likelihood that these injuries were caused by medications. Among the 4,273 admitted patients, it was found that 1.01% experienced medication-related liver impairment (MRLI), while 0.77% experienced medication-related kidney impairment (MRKI). The most common medications associated with liver impairment were antibiotics (31.58%), cardiovascular medications (24.21%), pain relievers (14.74%), anti-ulcer medications (11.58%), antiviral medications (8.42%), antiemetics (8.42%), and antidiabetic medications (1.05%). In contrast, kidney disease was primarily linked to diuretics (29.76%), antibiotics (21.43%), ACE inhibitors/ARBs (21.43%), antiviral medications (9.52%), and NSAIDs (7.14%). Importantly, there was no statistically significant correlation between the occurrence of MRLI or MRKI and factors such as gender, age, body mass index (BMI), or the presence of other health conditions ($p > 0.05$). These findings underscore the need for heightened awareness regarding the potential for medication-related impairments in hospitalized patients and suggest that careful monitoring of medication use is essential to mitigate these risks.

Keywords: medication-related liver impairment, medication-related renal impairment, Naranjo algorithm

Corresponding author:
Nadia Farhanah Syafhan
Faculty of Pharmacy, Universitas Indonesia, West Java, Indonesia
Jl. Prof. DR. Mahar Mardjono, Pondok Cina, Kecamatan Beji, West Java, Indonesia
Unit of Pharmacy, Universitas Indonesia Hospital, Depok, West Java, Indonesia
Jl. Prof. DR. Bahder Djohan, Pondok Cina, Kecamatan Beji, West Java, Indonesia
Email: nadia.farhanah@farmasi.ui.ac.id

INTRODUCTION

Liver impairment (LI) is characterized by elevated levels of specific liver enzymes, namely AST (aspartate aminotransferase), ALT (alanine aminotransferase), ALP (alkaline phosphatase) or -glutamyl transpeptidase (Lescot et al., 2012). Research conducted in Jiangsu, China, indicated that 3.75% of the population experienced liver impairment (Wu et al., 2020). In Indonesia, the 2018 Basic Health Research Report documented a liver impairment prevalence of 0.39%, affecting 1,017,290 individuals (Riskesdas, 2018). Several factors can contribute to liver impairment, including hypoxic hepatitis, sepsis, parenteral nutrition, and certain medications (Lescot et al., 2012).

Acute kidney impairment (AKI) is characterized by a rapid reduction in kidney function occurring within a 7-day period (Welch et al., 2018). Research conducted in 2020 at the Gatot Soebroto Army Hospital in Indonesia indicated that 43% of patients in the intensive care unit (ICU) experienced acute kidney impairment (Jonny et al., 2020). AKI can be triggered by various pathological conditions, including sepsis, severe illness, circulatory shock, radiocontrast agents, and nephrotoxic medications (Rolland et al., 2021). It is a prevalent complication among hospitalized patients, associated with high rates of occurrence and mortality (Cheng et al., 2017). Furthermore, AKI contributes to increased healthcare expenditures (Cheng et al., 2017). A 2013 global study revealed AKI incidence rates of 21.6% in adults and 33.7% in children, with average mortality rates of 23.9% and 13.5%, respectively (Susantitaphong et al., 2013).

Damage to the liver resulting from standard medications, referred to as medication-related liver impairment (MRLI) signifies unforeseen harm to liver cells, including hepatocytes (Andrade et al., 2019). Although infrequent, MRLI represents a potentially life-threatening medication reaction, characterized by considerable variation in the time of onset and the specific type of liver damage (Hosack et al., 2023). Research in France indicated that MRLI affects 13.9 to 24 individuals per 100,000, translating to approximately 44,000 cases annually (Low et al., 2020). MRLI is categorized into intrinsic and idiosyncratic forms. Intrinsic MRLI is dose-dependent, manifesting predictably within hours to days of medication exposure. The underlying mechanisms of intrinsic MRLI involve the creation of reactive metabolites, immune-mediated liver toxicity, the "danger signal" theory, alterations in mitochondrial function, and disruptions in bile acid balance (Amacher, 2014; Andrade et al., 2019). Medications that cause intrinsic MRLI are typically fat-soluble, enabling them to easily penetrate the lipid membrane of liver cells, such as paracetamol, amiodarone, valproic acid, and statins. Conversely, idiosyncratic MRLI is often unrelated to dosage, unpredictable, infrequent, and challenging to diagnose. Its mechanisms encompass both immune-related (allergic) and non-immune-related responses. Minocycline and nitrofurantoin are known to trigger immune-mediated idiosyncratic MRLI, whereas azathioprine and anabolic steroids are associated with non-immune-mediated idiosyncratic MRLI. In a hospital-based study in Surabaya, antibiotics (45.45%), antisecretory medications (36.36%), antimetabolites (9.09%), and glucocorticoids (9.09%) were identified as medication categories responsible for MRLI (Arrang & Widyati, 2018). MRLI is a significant factor in liver transplantation and mortality. Research indicates that nearly 10% of patients either died or required a liver transplant within half a year of MRLI onset (Fontana et al., 2014).

AKI resulting from medications is also referred to as medication-related acute kidney impairment (MRKI). Medications harmful to the kidneys rank as the third most frequent cause of renal impairment, and their occurrence has risen in recent years, coinciding with heightened usage. Research indicates that 20% of kidney-damaging medications are administered to patients in critical care settings (Sales & Foresto, 2020). MRKI is more prevalent in hospitalized patients, with a 14-26% prevalence in the adult population and 16% in the pediatric population (Awdishu & Mehta, 2017). A study in Malaysia from 2000-2016 reported 616 cases of MRKI, with the most reported drugs from the renin-angiotensin system blocker group, then NSAIDs and aminoglycosides (Choong et al., 2017). Furthermore, data from the U.S. Food and Drug Administration's adverse event reporting system showed that MRKI accounted for 2.7% of cases between 2004 and 2015, with a fatality rate of 11.3% among all reported medication side effects (Welch et al., 2018). The ways in which medication-related AKI occurs involve direct harm to kidney tubules, blockages within the tubules, and localized

inflammation (Perazella & Rosner, 2022). Medications such as antibiotics, chemotherapy agents, calcineurin inhibitors, and contrast media are recognized contributors to direct tubular damage. Renal inflammation can be triggered by methotrexate, sulfa-based medications, and protease inhibitors. Blockages within the kidney tubules are linked to vancomycin, non-steroidal anti-inflammatory drugs, diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.

Ensuring medication safety is a crucial factor when optimizing patient medication therapy, aiming to achieve the most favorable results. To enhance medicines optimization, it is highly recommended to identify, report, and analyze instances or prevalence of medication-related patient safety issues (National Institut for Health and Care Excellence, 2015). Liver and acute kidney impairment associated with medications continue to pose challenges in clinical practice, necessitating thorough reporting and evaluation (Hosack et al., 2023; Perazella & Rosner, 2022). MRLI and MRKI are severe and clinically significant adverse drug reactions (ADRs) (Amacher, 2014). ADRs are unwanted and potentially dangerous responses to medications that occur at typical therapeutic dosages (Amacher, 2014) Assessing ADR causality can be accomplished through clinical evaluation, structured algorithms, or other methodologies, including probabilistic scales. The Naranjo algorithm, comprised of 10 questions with weighted scores, calculates a total score to determine the likelihood of ADR causality. This questionnaire is validated and frequently used in clinical environments (Murayama et al., 2018; Naranjo et al., 1981). This algorithmic approach is also employed for ADR causality assessment within Indonesia (BPOM, 2020).

Studies on the prevalence of MRLI and MRKI in Indonesia are still limited and restricted to specific medication types. This study is expected to provide data on the prevalence of MRLI and MRKI, the class of medications that have the potential to cause LI or AKI, and their predictors so that more stringent prevention or monitoring can be carried out to reduce the risk of MRLI and MRKI.

MATERIALS AND METHOD

A retrospective, cross-sectional analysis was performed at Universitas Indonesia Hospital (UIH) in Depok, Indonesia, utilizing patient medical record data from January 1st to December 31st, 2021. The study received approval from the UIH ethics review board (S-011/KETLIT/RSUI/III/2022 and S-16/KETLIT/RSUI/III/2022). The study population comprised all patients hospitalized during 2021, encompassing both intensive care unit (ICU) and general ward patients, who had been assigned one or more of the following ICD-10 diagnostic codes: K71 (toxic liver disease), K72 (hepatic failure, not elsewhere classified), K75 (other inflammatory liver diseases), K76.9 (liver disease, unspecified), R94.5 (abnormal results on liver function tests), N17 (acute renal failure), R94.4 (abnormal kidney function results), or Y40-Y59 (medications, medicaments, and biological substances causing adverse effects in therapeutic use). A comprehensive sampling method was employed to include all eligible patients, ensuring a thorough understanding of the population and eliminating potential bias inherent in random sampling. Due to the manageable size of the total population, this was feasible. Participants were included if they were at least 18 years old, diagnosed with liver or acute kidney impairment, and possessed liver or renal function test results. Patients with a pre-existing history of liver or kidney disease, those presenting with liver or kidney impairment upon hospital admission, pregnant or lactating individuals, and those with incomplete medical records (lacking demographic details, diagnoses, or medication therapy information) were excluded.

Medication hepatotoxicity and nephrotoxicity information were obtained from reliable and comprehensive medication monographs Lexicomp® Online™ (Wolters Kluwer Health), the electronic Medicines Compendium (eMC), and other literature sources. Medication causality analysis was carried out on hepatotoxic or nephrotoxic medication received by patients before liver impairment or AKI were diagnosed using the Naranjo algorithm. The Naranjo algorithm was used as a tool to evaluate the probability of MRLI and MRKI. This system incorporates ten variables: prior established reports, chronological progression, amelioration following cessation or intervention, recurrence upon re-challenge, alternative etiological factors, placebo response (when utilized), hematological evidence

of toxicity, dose-response relationship, antecedent similar reactions, and other objective findings. Each variable is assigned a numerical value, ranging from -1 to +2, based on the specific evidence observed. This questionnaire has been validated and widely used in clinical settings (Murayama et al., 2018; Naranjo et al., 1981). MRLI and MRKI were defined if the total score from the Naranjo algorithm-based evaluation was at least one or the causality degree was highly probable, probable or possible. The medication with the highest Naranjo score has the greatest potential to cause liver or kidney impairment.

The statistical processing of data was executed using SPSS version 25.0 (SPSS Inc., USA). Univariate analysis, presenting data as frequency distributions, percentages, and medians/means, was employed to delineate the characteristics of the research variables. Bivariate analysis, specifically utilizing the Chi-Square test, was conducted to assess the relationships between categorical data, particularly the association between MRLI or MRKI and relevant factors. In instances where the assumptions of the Chi-Square test were not satisfied, Fisher's Exact Test was implemented. A statistical significance threshold of 0.05 was established.

RESULT AND DISCUSSION

The total number of hospitalized patients at UIH in 2021 was 4,273 patients. A total of 120 adult patients diagnosed with LI and 397 adult patients were diagnosed with AKI. There were 38 patients with liver impairment and 47 patients with AKI included as study samples in causality assessment (Figure 1). Specific results for MRLI and MRKI were described separately below.

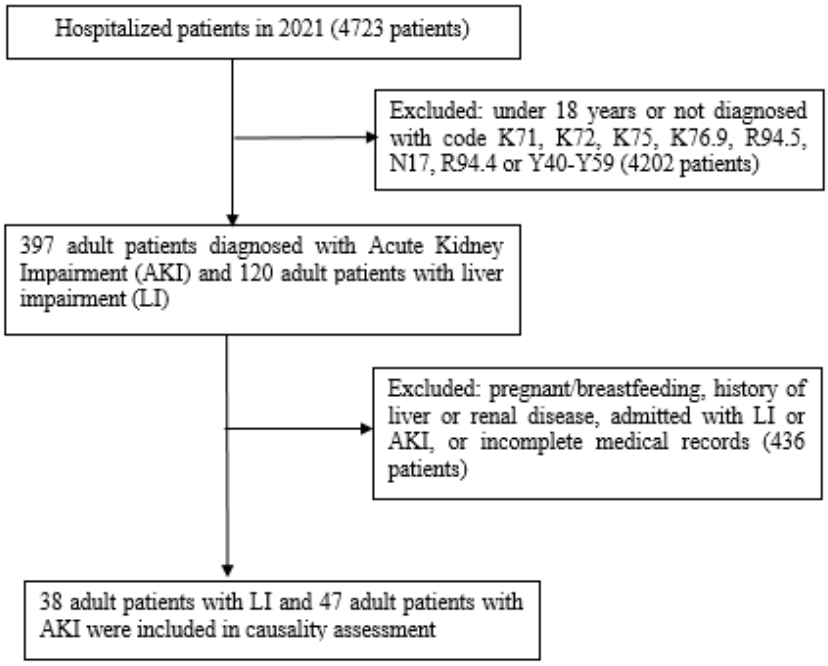

Figure 1. Flow chart of study population selection

MRLI

Characteristics of patients and MRLI prevalence

There were 47 patients who were 18-year-old, diagnosed with LI, and with LFT results (Figure 1). The majority of the patients were male (82.98%), aged 18-59 years (76.60%), had BMI ≥25.1 (51.06%), and had more than one medical problem (72.34%) listed in Table 1.

Table 1. Characteristics of patients with liver impairment

Patient Characteristics	Frequency (n=47)	Percentage (%)
Sex		
Male	39	82.9
Female	8	17.0
Age		
18-59 years	36	76.6
≥60 years	11	23.4
BMI		
<25.1	23	48.9
≥25.1	24	51.0
Number of medical problems		
<2	13	27.6
≥2	34	72.3
Median (min-max)	2.0(1.0-5.0)	

Note: n = number of patients; BMI = body mass index

Based on the results, an assessment of the degree of causality based on the Naranjo algorithm can be seen in Table 2. The prevalence of MRLI (proportions of patients with highly probable, probable and possible causality degree) was 35.83% (43 out of 120 patients with liver impairment during hospitalization and treatment). Meanwhile, the prevalence of MRLI in all hospitalized patients were 1.01% (43 out of 4273 inpatients).

Table 2. MRLI causality degree based on Naranjo algorithm

	Degree of Causality	Frequency (n=47). N (%)
MRLI	highly probable (≥9)	0 (0)
	probable (5-8)	1 (2.1)
	possible (1-4)	42 (89.4)
Non-MRLI	doubtful (≤0)	4 (8.5)

Note: n = number of patients; N (%) = number of patients with MRLI/total patient sample*100; MRLI = medication-related liver impairment

Class of medication potentially causing liver impairment

Seven pharmacological classes were found to have the capacity to elicit medication-related liver impairment (MRLI) within the studied cohort, with the degree of causality determined via the Naranjo algorithm, as delineated in Table 3. These classes included antibiotics (31.58%), cardiovascular agents (24.21%), analgesics (14.74%), anti-ulcer medications (11.58%), antiviral agents (8.42%), antiemetic agents (8.42%), and antidiabetic agents (1.05%).

Relationship of patient characteristics with MRLI

The majority of MRLI patients were male (81.4%), aged 18-59 years (76.7%), had BMI ≥25.1 (46.5%), and had several medical problems (69.8%), as listed in Table 4. This study also found no significant relationship between patient characteristics and MRLI ($p>0.05$). In this study, the most common medical problems in patients with MRLI were COVID-19 (34.43%), hypertension (13.11%), acute kidney impairment (AKI) (10.66%) as listed in Table 5.

Table 3. List of medications potentially causing liver impairment

Medication Class (n=95) N (%)	Medication	MRLI frequency (n=95) N (%)	Degree of Causality	
			Probable (score 5-8)	*Possible* (score 1-4)
Antibiotics 30 (31.58)	Levofloxacin	21 (22.1)	0	21
	Ceftriaxone	5 (5.3)	0	5
	Azithromycin	3 (3.1)	0	3
	Cefotaxime	1 (1.1)	0	1
Cardiovascular Agent 23 (24.21)	Heparin	17 (17.9)	0	17
	Enoxaparin Sodium	2 (2.1)	0	2
	Candesartan	2 (2.1)	0	2
	Amiodarone	1 (1.1)	0	1
	Ramipril	1 (1.1)	0	1
Analgesic 14 (14.74)	Acetaminophen	14 (14.7)	1	13
Antiulcer 11 (11. 58)	Omeprazole	10 (10.5)	0	10
	Ranitidine	1 (1.1)	0	1
Antivirus 8 (8.42)	Remdesivir	7 (7.4)	0	7
	Favipiravir	1 (1.1)	0	1
Antiemetic 8 (8.42)	Ondansetron	5 (5.3)	0	5
	Metoclopramide	2 (2.1)	0	2
	Dexamethasone	1 (1.1)	0	1
Antidiabetic 1 (1.05)	Metformin	1 (1.1)	0	1

Note: medication names are sorted based on the most use in each therapeutic class; n = number of MRLI cases; N (%) = number of treated cases/total MRLI cases*100; MRLI = medication-related liver impairment

Table 4. Bivariate analysis between patient characteristics and MRLI

Characteristics	MRLI N = 43 (%)	Non-MRLI N = 4 (%)	Total N = 47 (%)	*P value*	OR (95% CI)
Sex					
Male	35 (81.4)	4 (100)	39 (83)	1.000	1.133 (1.002-1.281)
Female	8 (18.6)	0 (0)	8 (17)		
Age					
18-59 years	33 (76.7)	3 (75)	36 (76.6)	1.000	1.100 (0.103-11.781)
≥60 years	10 (23.3)	1 (25)	11 (23.4)		
BMI (kg/m^2)					
<25.1	20 (46.5)	3 (75)	23 (48.9)	0.290	0.2901 (0.028-3.013)
≥25.1	23 (53.5)	1 (25)	24 (51.1)		
Number of medical problems				0.564	0.897 (0.807-0.998)
<2	13 (30.2)	0 (0)	13 (27.7)		
≥2	30 (69.8)	4 (100)	34 (72.3)		

Note: N = number of patients; OR = Odd Ratio; CI = Confidence Interval; * = significance value <0.05; BMI body mass index; MRLI = medication-related liver impairment

Table 5. Medical problems in patients with liver impairment

Medical problems	MRLI (n=110). N(%)	Non-MRLI (n=12). N(%)	Total (n=122). N(%)
Covid-19	42 (34.4)	2 (1.6)	44 (36.1)
Hypertension	16 (13.1)	2 (1.6)	18 (14.7)
AKI	13 (10.7)	0 (0.0)	13 (10.7)
Diabetes mellitus	12 (9.8)	2 (1.6)	14 (11.5)
Hyponatremia	5 (4.1)	2 (1.6)	7 (5.7)
Pneumonia	5 (4.1)	1 (0.8)	6 (4.9)
ARDS	5 (4.1)	0 (0.0)	5 (4.1)
Congestive Heart Failure	4 (3.3)	0 (0.0)	4 (3.3)
Sepsis	3 (2.5)	0 (0.0)	3 (2.5)
Anemia	1 (0.8)	1 (0.8)	2 (1.6)
Cardiovascular Disease	1 (0.8)	0 (0.0)	1 (0.8)
DHF	0 (0.0)	1 (0.8)	1 (0.8)
Typhoid fever	0 (0.0)	1 (0.8)	1 (0.8)
Pancreatitis	1 (0.8)	0 (0.0)	1 (0.8)
STEMI	1 (0.8)	0 (0.0)	1 (0.8)
Stroke	1 (0.8)	0 (0.0)	1 (0.8)

Notes: N = number of occurrences of medical problems; % = number of occurrences of medical problems /120*100; AKI = Acute Kidney Impairment; ARDS = Acute Respiratory Distress Syndrome; DHF = Dengue Hemorrhagic Fever; STEMI = ST elevation myocardial infarction; MRLI = medication-related liver impairment

MRKI

Characteristics of patients and MRKI prevalence

There were 38 patients (9.5% of the total population) who were 18-year-old, diagnosed with acute kidney impairment and with renal function test results (Figure 1). It was found that the majority of patients who experienced AKI during treatment were male, aged 18-59 years, used 15 concomitant medications, and had 4 medical problems (Table 6).

Table 6. Characteristics of patients with AKI

Characteristic	Total N=38	Percentage (%)
Sex		
Male	24	63.2
Female	14	36.8
Age		
18 – 59 years	22	57.9
≥ 60 years	16	42.1
Number of medicines		
<15	8	21.1
≥ 15	30	78.9
Number of medical problems		
< 4	13	34.2
≥ 4	25	65.8
Median (min-max)	4.0 (1.0 - 9.0)	

The majority of patients experiencing MRKI were in the possible category based on the Naranjo algorithm (Table 7). The prevalence of MRKI (Naranjo causality degree of highly probable, probable

and possible) in hospitalized patients in 2021 was 8.31% (33 out of 397 patients with an AKI diagnosis at admission and during treatment).

Table 7. MRKI causality degree based on Naranjo algorithm

	Degree of Causality	Frequency N (%)
MRKI	highly probable (≥9)	0 (0)
	probable (5-8)	3 (7.89)
	possible (1-4)	30 (78.9)
Non MRKI	doubtful (≤0)	5 (13.16)
	Total	38 (100)

Note: MRKI = medication-related kidney impairment

Class of medications potentially causing AKI

Medications that had the potential to induce AKI in this study were mostly diuretics (29.76%), followed by antibiotics (21.43%), ACEi/ARB (21.43%), antivirals (9.52%), NSAIDs (7.14%), anticonvulsants (4.76%), antifibrinolytics (2.38%), antiarrhythmics (2.38%), and antiretrovirals (1.19%) as listed in Table 8.

Table 8. List of medications potentially causing AKI

Medication Class n (%)	Medication N=21	MRKI Frequency n (%)	Naranjo Category	
			Probable	Possible
Diuretics	Furosemide	12 (14.3)	1	11
25 (29.76)	Spironolactone	9 (10.7)	0	9
	Hydrochlorothiazide	4 (4.8)	0	4
Antibiotics	Levofloxacin	5 (5.9)	0	5
18 (21.43)	Meropenem	4 (4.8)	0	4
	Amikacin	3 (3.6)	0	3
	piperacillin tazobactam	3 (3.6)	0	3
	Cefoperazone	1 (1.2)	0	1
	Azithromycin	1 (1.2)	0	1
	Co-trimoxazole	1 (1.2)	0	1
ACEi/ARB	Ramipril	13 (15.5)	1	12
18 (21.43)	Candesartan	5 (5.9)	0	5
Antiviral	Remdesivir			
8 (9.52)		8 (9.5)	0	8
NSAID	Ibuprofen	3 (3.6)	0	3
6 (7.14)	Ketorolac	1 (1.2)	0	1
	Meloxicam	1 (1.2)	1	0
	Aspirin	1 (1.2)	0	1
Anticonvulsant 4 **(**4.76**)**	Midazolam	4 (4.8)	0	4
Antifibrinolytic	Tranexamic acid			
2 (2.38)		2 (2.4)	0	2
Antiarrhythmic	Amiodarone			
2 (2.38)		2 (2.4)	0	2
Antiretroviral	Tenofovir			
1 (1.19)		1 (1.2)	0	1
Total		84 (100)	3	81

Note: n = frequency of occurrence of DI-ACI; NSAID = Nonsteroidal anti-inflammatory drug; ACEi = Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; MRKI = medication-related kidney impairment.

Relationship between patient characteristics and MRKI

Table 9 details the variations in patient characteristics between those with MRKI and those without. Statistical analysis, using the Chi-Square test, revealed no significant associations between MRKI and factors such as gender, age, the quantity of medications, or the number of health issues ($p > 0.05$). As shown in Table 10, the most frequently observed medical conditions in patients with MRKI were COVID-19 (16.9%), hypertension (9.0%), and diabetes mellitus (8.5%).

Table 9. Bivariate analysis between patient characteristics and MRKI

Characteristics	MRKI n (%)	Non MRKI n (%)	Total n (%) N=38	P value	OR (95% CI)
Sex					
Male	21 (63.6)	3 (60)	24 (63.2)	1.000	1.167 (0.170-7.995)
Female	12 (36.4)	2 (40)	14 (36.8)		
Age					
18-59 years old	19 (57.6)	3 (60)	22 (57.9)	1.000	0.905 (0.133-6.158)
≥ 60 years old	14 (42.4)	2 (40)	16 (42.1)		
Number of medicines					
< 15	6 (18.2)	2 (40)	8 (21.1)	0.279	0.333 (0.045-2.453)
≥ 15	27 (81.8)	3 (60)	30 (78.9)		
Number of medical problems					
< 4	12 (36.4)	1 (20)	13 (34.2)	0.643	2.286 (0.228-22.872)
≥ 4	21 (63.6)	4 (80)	25 (65.8)		

Note: MRKI = medication-related kidney impairment; OR= Odds Ratio; CI = Confidence Interval

Discussion

To improve medication safety and implement medicines optimisation, it is recommended to establish a system for detecting, documenting, and analyzing cases of patient harm related to medications use (National Institut for Health and Care Excellence, 2015). The present study utilized the Naranjo algorithm to determine the frequency of MRLI and MRKI. Additionally, the research identified medication classes associated with these diseases and explored factors that may predict their occurrence.

Within the group of patients who experienced liver impairment, MRLI was observed in 35.83% of cases. However, when considering the entire population of patients hospitalized at Universitas Indonesia Hospital in 2021, the overall prevalence of MRLI was 1.01%. This study's findings demonstrate a higher prevalence than both a prospective study from a Surabaya hospital, which reported 3.55% MRLI among liver patients, and a meta-analysis of COVID-19 patients, which found a 25.4% MRLI incidence.

Antibiotics were the most reported medications in the current study, with levofloxacin as the highest frequency. These findings are consistent with results of the previous study indicating that antibiotics (34.9%) are the most common class of medications causing MRLI in Western countries (Low et al., 2020). Antibiotics, particularly macrolides such as azithromycin and fluoroquinolones such as levofloxacin, are used to treat COVID-19 patients, which may explain the high incidence of

antibiotic-associated MRLI in this previous study (Xu et al., 2020). This current study concurs with a meta-analysis that found cardiovascular agents to be the second most common cause of MRLI, accounting for 17.3% of cases in Western countries (Low et al., 2020). However, the increase in heparin-induced aminotransferase levels is most likely due to a direct hepatotoxic effect on the liver (Livertox, 2017). A study in China reported that analgesics were the third most common medications class that caused MRLI (3.38%) (Liu et al., 2020). Acetaminophen has an intrinsic or direct type of MRLI mechanism that is dose-dependent and occurs rapidly (CIOMS, 2020). According to multiple studies, the risk of hepatotoxicity due to acetaminophen may increase with age (>40 years). In addition, patients who consume certain acetaminophen products may increase their risk of accidental liver impairment (Caparrotta et al., 2018; Lexicomp, 2022; Rotundo & Pyrsopoulos, 2020). This is in line with this present study, where the majority of patients who experienced liver impairment due to acetaminophen were >40 years old, and several patients consumed several acetaminophen products simultaneously. A study in Surabaya reported that from 11 cases of MRLI, 4 cases (36.36%) were found to be caused by anti-ulcers, namely, omeprazole and ranitidine (Arrang & Widyati, 2018). According to a meta-analysis of the incidence of MRLI in COVID-19 patients, 15.29% of MRLI incidents were attributable to remdesivir (Kulkarni et al., 2020). Several studies have reported liver damage due to ondansetron (Couse & Syed, 2020; Lewandowski & Chapman, 2008; Liss & Lewis, 2009). Metformin, one of the antidiabetic medications, was found to have the potential to cause MRLI in one case (1.05%) in this current study.

Previous studies reported a high incidence of hepatotoxicity in female patients. However, in some cases, the incidence of MRLI is comparable between male and female patients, and in some instances, it is higher in male patients. This incidence may be due to the unbalanced ratio of male to female samples, in which there were more male patients than female patients (Andrade et al., 2019; Arrang & Widyati, 2018; CIOMS, 2020; Lucena et al., 2020; Shen et al., 2019). Several studies, including a retrospective cohort study conducted in Australia (p=0.80), a case-control study conducted on hospitalized patients (p=0.879), and a study cohort conducted on MRLI patients due to antituberculosis medications (p=0.53), found no significant association between sex and MRLI (Jiang et al., 2021; Kong et al., 2021; Worland et al., 2020). It is reported that the incidence of MRLI increases with age, furthermore, it increases in people older than 35. In general, older patients take more medications, increasing the likelihood of developing MRLI (Andrade et al., 2019; Arrang & Widyati, 2018). A case-control study on hospitalized patients revealed a significant correlation between age and MRLI (p=0.002), with an OR of 0.99 (Kong et al., 2021). The differences that occur can be caused by differences in methods and the size of the sample used, thus the results are not able to represent the population and provide a statistically significant relationship. The results of this current study align with the results of a retrospective cohort study in Australia, Indiana, as well as a prospective study in Spain that reported a mean BMI ± SD in MRLI patients were 26.7 ± 5.9 kg/m^2; 28±7 kg/m^2; and 26±3.8 kg/m^2, respectively (Ghabril et al., 2019; Stephens et al., 2021; Worland et al., 2020). A cohort study of MRLI patients due to antituberculosis reported that there was no significant relationship between BMI and MRLI (p= 0.11) (Jiang et al., 2021). These results are also supported by a publication that states the lack of evidence to suggest that BMI can significantly influence the pattern, severity, and outcome of MRLI (Li et al., 2022).

The prevalence of MRKI among patients with an AKI was 8.31%. However, if we take into account the number of all hospitalized patients at Universitas Indonesia hospital in 2021 its prevalence was 1.01%. This number is lower than the results of a study in China which revealed that 38% of hospitalized patients had MRKI (Yu et al., 2020). During 2015-2017, a study of MRKI in Saudi Arabia discovered 38 cases (13%) of MRKI among 293 AKI patients (Alkhunaizi & Al Shammary, 2020).

Diuretics were the most reported medication class in this current study, with furosemide as the most reported medications, followed by spironolactone and hydrochlorothiazide. This finding is similar to that of Rolland et al, who discovered that diuretics cause AKI more frequently than other medication classes. In that study, furosemide was reported to be the diuretic that caused the most acute

kidney impairment (AKI), followed by hydrochlorothiazide and spironolactone. In this present study, it was discovered that antibiotics have the potential to cause AKI, with levofloxacin having the highest frequency. In a study by Pierson-Marchandise et al. (2017) and research by Liu et al. 2021, antibiotics were identified as the most prevalent class of medications associated with AKI. Antibiotics were the medications most frequently reported to cause AKI in both studies, indicating that antibiotics are frequently reported to cause AKI. This present study determined that ACEi and ARB medications also have the potential to cause AKI. The most reported medication was ramipril, followed by candesartan. This fact is comparable to the findings of Rolland et al.2021 who found that ramipril was the ACEi and ARB medication most frequently reported to cause AKI. By modulating intrarenal blood flow, this class of medications has the potential to induce or aggravate AKI. By inhibiting angiotensin-mediated efferent arteriolar vasoconstriction, ACEi and ARB will reduce intraglomerular pressure (Khan et al., 2017). In this current study, six cases of MRKI were linked to nonsteroidal anti-inflammatory drugs (NSAIDs), with ibuprofen having the highest frequency, followed by ketorolac, meloxicam, and aspirin. This fact is in line with the research conducted by Nurulmaya (Nurulmaya, 2016) and Sattar et al (Sattar et al., 2018). Due to their mechanism of action, which inhibits prostaglandin synthesis by inhibiting the cyclooxygenase enzyme, NSAIDs can cause AKI. Inhibition of prostaglandin synthesis by NSAIDs can cause vasoconstriction in afferent arterioles, thereby reducing renal perfusion and resulting in AKI (Sabatino et al., 2020). Remdesivir is one of the antiviral medications in this current study that has the potential to cause AKI. Remdesivir was also found to cause acute kidney impairment in the study (Chouchana et al., 2021). Unknown is the mechanism by which remdesivir causes AKI (Wu et al., 2022). This current study found that midazolam can potentially cause acute kidney impairmen (AKI). (Leite et al., 2015) conducted a cohort study from 2001 to 2008 comparing the incidence of acute kidney impairment (AKI) in ICU patients taking midazolam with patients taking propofol. This current study revealed that AKI was more prevalent in patients taking midazolam than in the group taking propofol. Tranexamic acid is a synthetic antifibrinolytic commonly used to prevent or treat bleeding disorders. According to our knowledge, AKI caused by tranexamic acid is rarely reported. One case report describes a patient who experienced AKI after taking tranexamic acid for 4 days at a dosage of 1 gram three times per day (Ko et al., 2017). AKI caused by amiodarone is still uncommon, and few studies have been conducted. One case report describes a 65-year-old male patient who developed AKI 24 hours after intravenous amiodarone administration (Paudel et al., 2016). In a case report, Mohamed et al.(2020)., also described a similar incident. In addition, tenovofir was identified as the medication with the potential to cause AKI in this current study. According to Wikman et al.2013., tenofovir also causes AKI in HIV patients. AKI due to tenofovir can manifest as a delayed effect between 16 months and 5 years after years of use (Kumar et al., 2020). In this current study, the patient had a five-year history of taking tenofovir.

This study observed a higher likelihood of MRKI in males, though not statistically significant ($p>0.05$, Table 9), which aligns with Pierson-Marchandise et al., 2017.'s findings. Conversely, (Yu et al., 2020) found no association between gender and MRKI incidence ($p=0.441$). Similarly, the 18-59 age group exhibited a higher MRKI incidence than those 60+, consistent with (Cui et al.(2021)'s results (mean age 51.1±16.4 years). However, (Pierson-Marchandise et al.(2017), Rolland et al., 2021 and Yu et al.(2020) reported higher MRKI prevalence in older patients. These discrepancies may stem from differing sample populations. Liu et al. also found no age-MRKI correlation ($p=0.94$). Despite the lack of statistical significance in this study, age remains a recognized MRKI risk factor, especially in the elderly (Shirali & Pazhayattil, 2014). This study showed MRKI patients consumed over 15 concomitant medications, similar to Yu et al.'s findings (76.5% vs. 23.5%). While (Yu et al.(2020) found a significant medication count-MRKI link ($p<0.001$), this study did not ($p=0.279$), possibly due to insufficient sample size. Polypharmacy can elevate AKI risk through drug interactions and renal overload, particularly with nephrotoxic agents (Kang & Hong, 2019). Comorbidities are confounders and risk factors for MRKI. In this study, most MRKI patients had four comorbidities. Increased comorbidities necessitate more procedures and medications, impacting kidney function, especially in

patients with diabetes or cardiovascular disease treated with nephrotoxic medications (Farooqi & Dickhout, 2016). However, this study found no significant relationship between comorbidity count and MRKI incidence (p=0.643).

More research is being conducted on the types of medical problems influencing the incidence of MRKI or AKI. In this current study, the sample size was insufficient to accurately represent the association between the number of medical problems and the incidence of MRKI. Therefore, research on the impact of a number of medical problems on the incidence of MRKI can be a subject for further study.

Table 10. Medical problems in patients with AKI

Medical Problems	MRKI n (%) N=146	Non MRKI n (%) N=31	Total n (%) N=177
COVID-19	30 (16.9)	5 (2.8)	35 (19.8)
Hypertension	16 (9.0)	0 (0)	16 (9.0)
Diabetes mellitus type 2	15 (8.5)	5 (2.8)	20 (11.3)
Liver function disorders	13 (7.3)	3 (1.7)	16 (9.0)
Hypercoagulation	12 (6.8)	2 (1.1)	14 (7.9)
Congestive heart failure	12 (6.8)	2 (1.1)	14 (7.9)
ARDS	11 (6.2)	2 (1.1)	13 (7.3)
Coronary heart disease	6 (3.4)	1 (0.5)	7 (3.9)
Sepsis	4 (2.3)	3 (1.7)	7 (3.9)
DIC	4 (2.3)	1 (0.5)	5 (2.8)
Atrial fibrillation	3 (1.7)	0 (0)	3 (1.7)
Hyponatremia	3 (1.7)	0 (0)	3 (1.7)
Hypernatremia	2 (1.1)	1 (0.5)	3 (1.7)
Hypoalbuminemia	2 (1.1)	1 (0.5)	3 (1.7)
Pneumonia	2 (1.1)	0 (0)	2 (1.1)
Pre-diabetes mellitus	2 (1.1)	0 (0)	2 (1.1)
Anemia	1 (0.5)	2 (1.1)	3 (1.7)
Urinary tract infection	1 (0.5)	1 (0.5)	2 (1.1)
Dyslipidaemia	1 (0.5)	0 (0)	1 (0.5)
Hydronephrosis	1(0.5)	0 (0)	1 (0.5)
Acute pulmonary embolism	1(0.5)	0 (0)	1 (0.5)
Ischemic stroke	1(0.5)	0 (0)	1 (0.5)
HIV	1(0.5)	0 (0)	1 (0.5)
Hyperuricemia	1(0.5)	0 (0)	1 (0.5)
Thrombocytopenia	1(0.5)	0 (0)	1 (0.5)
Diabetic ketoacidosis	0 (0)	1(0.5)	1(0.5)
Gastrointestinal bleeding	0 (0)	1(0.5	1(0.5)

Note: N = Total number of medical problems, % = (n/177)*100%; DIC: Disseminated Intravascular Coagulation; HIV: Human Immuno Deficiency Virus; MRKI = Medication-Related Kidney Impairment; ARDS= Acute Respiratory Distress Syndrome

CONCLUSION

In 2021, the incidence of medication-related liver impairment (MRLI) and medication-related kidney impairment (MRKI) at Universitas Indonesia Hospital was 1.01% and 0.77%, respectively. MRLI cases were associated with antibiotics, cardiovascular agents, pain relievers, anti-ulcer medications, antiviral medications, antiemetics, and antidiabetic medications. Conversely, MRKI cases were linked to diuretics, antibiotics, ACE inhibitors/ARBs, antiviral medications, and NSAIDs. No

significant correlation was observed between the occurrence of MRLI and factors such as age, gender, BMI, or the number of comorbidities. Similarly, there was no significant association between MRKI and age, gender, number of medications, or number of comorbidities. These findings emphasize the importance of recognizing potential medication-related diseases in hospitalized patients. Implementing careful medication monitoring is crucial for minimizing these risks.

ACKNOWLEDGEMENT

Researchers highly appreciate Universitas Indonesia Hospital for the assistance and support in facilitating the research.

REFERENCES

Alkhunaizi, A. M., & Al Shammary, M. (2020). In-hospital acute kidney injury. *Eastern Mediterranean Health Journal*, *28*(8), 967–970. https://doi.org/10.26719/emhj.19.100

Amacher, D. E. (2014). Female gender as a susceptibility factor for drug-induced liver injury. *Human & Experimental Toxicology*, *33*(9), 928–939. https://doi.org/10.1177/0960327113512860

Andrade, R. J., Chalasani, N., Björnsson, E. S., Suzuki, A., Kullak-Ublick, G. A., Watkins, P. B., Devarbhavi, H., Merz, M., Lucena, M. I., Kaplowitz, N., & Aithal, G. P. (2019). Drug-induced liver injury. *Nature Reviews Disease Primers*, *5*(1), 58. https://doi.org/10.1038/s41572-019-0105-0

Arrang, S. T., & Widyati, W. (2018). The Incidence and risk factor analysis of drug induced liver injury (Dili) in a Surabaya Hospital. *Jurnal Farmasi Galenika (Galenika Journal of Pharmacy) (e-Journal)*, *4*(2), 79–86. https://doi.org/10.22487/j24428744.2018.v4.i2.10459

Awdishu, L., & Mehta, R. L. (2017). The 6R's of drug induced nephrotoxicity. *BMC Nephrology*, *18*(1), 124. https://doi.org/10.1186/s12882-017-0536-3

BPOM. (2020). *Modul Farmakovigilans Dasar*. Badan Pengawasan Obat dan Makanan. https://e-meso.pom.go.id/web/useruploads/files/reference/5eaa2698c3abc_Modul Farmakovigilans Dasar.pdf

Caparrotta, T. M., Antoine, D. J., & Dear, J. W. (2018). Are some people at increased risk of paracetamol-induced liver injury? A critical review of the literature. *European Journal of Clinical Pharmacology*, *74*(2), 147–160. https://doi.org/10.1007/s00228-017-2356-6

Cheng, X., Wu, B., Liu, Y., Mao, H., & Xing, C. (2017). Incidence and diagnosis of Acute kidney injury in hospitalized adult patients: a retrospective observational study in a tertiary teaching Hospital in Southeast China. *BMC Nephrology*, *18*(1), 203. https://doi.org/10.1186/s12882-017-0622-6

Choong, C. L., Lee, F. Y., Wong, H. S., Mohamed Ali, N., & Tay, J. F. (2017). 154 Drug-induced acute kidney injury in Malaysia. *Kidney International Reports*, *2*(4), S23–S24. https://doi.org/10.1016/j.ekir.2017.06.081

Chouchana, L., Preta, L.-H., Tisseyre, M., Terrier, B., Treluyer, J.-M., & Montastruc, F. (2021). Kidney disorders as serious adverse drug reactions of remdesivir in coronavirus disease 2019: a retrospective case–noncase study. *Kidney International*, *99*(5), 1235–1236. https://doi.org/10.1016/j.kint.2021.02.015

CIOMS. (2020). *Drug-Induced Liver Injury (DILI): Current status and future directions for drug development and the post-market setting*. https://doi.org/10.56759/ojsg8296

Couse, M., & Syed, S. (2020). A rise in aspartate transaminase and alanine transaminase associated with ondansetron administration in a pregnant female. *Cureus*. 12(11), e11540 https://doi.org/10.7759/cureus.11540

Cui, Y., Yang, Y., Lei, W., Lang, X., & Chen, J. (2021). The clinicopathological features of drug-induced acute kidney injury—a single-center retrospective analysis. *Annals of Translational Medicine*, *9*(5), 400–400. https://doi.org/10.21037/atm-20-3826

Farooqi, S., & Dickhout, J. G. (2016). Major comorbid disease processes associated with increased incidence of acute kidney injury. *World Journal of Nephrology*, *5*(2), 139.

https://doi.org/10.5527/wjn.v5.i2.139

Fontana, R. J., Hayashi, P. H., Gu, J., Reddy, K. R., Barnhart, H., Watkins, P. B., Serrano, J., Lee, W. M., Chalasani, N., Stolz, A., Davern, T., & Talwakar, J. A. (2014). Idiosyncratic drug-induced liver injury is associated with substantial morbidity and mortality within 6 months from onset. *Gastroenterology*, *147*(1), 96-108.e4. https://doi.org/10.1053/j.gastro.2014.03.045

Ghabril, M., Gu, J., Yoder, L., Corbito, L., Ringel, A., Beyer, C. D., Vuppalanchi, R., Barnhart, H., Hayashi, P. H., & Chalasani, N. (2019). Development and validation of a model consisting of comorbidity burden to calculate risk of death within 6 months for patients with suspected drug-induced liver injury. *Gastroenterology*, *157*(5), 1245-1252.e3. https://doi.org/10.1053/j.gastro.2019.07.006

Hosack, T., Damry, D., & Biswas, S. (2023). Drug-induced liver injury: a comprehensive review. *Therapeutic Advances in Gastroenterology*, *16*. https://doi.org/10.1177/17562848231163410

Jiang, F., Yan, H., Liang, L., Du, J., Jin, S., Yang, S., Wang, H., Hu, T., Zhu, Y., Wang, G., Hu, Y., Cai, T., & Aithal, G. P. (2021). Incidence and risk factors of anti-tuberculosis drug induced liver injury (DILI): Large cohort study involving 4652 Chinese adult tuberculosis patients. *Liver International*, *41*(7), 1565–1575. https://doi.org/10.1111/liv.14896

Jonny, J., Hasyim, M., Angelia, V., Jahya, A. N., Hilman, L. P., Kusumaningrum, V. F., & Srisawat, N. (2020). Incidence of acute kidney injury and use of renal replacement therapy in intensive care unit patients in Indonesia. *BMC Nephrology*, *21*(1), 191. https://doi.org/10.1186/s12882-020-01849-y

Kang, H., & Hong, S. H. (2019). Risk of kidney dysfunction from polypharmacy among older patients: a nested case-control study of the south Korean senior cohort. *Scientific Reports*, *9*(1), 10440. https://doi.org/10.1038/s41598-019-46849-7

Khan, S., Loi, V., & Rosner, M. H. (2017). Drug-induced kidney injury in the elderly. *Drugs & Aging*, *34*(10), 729–741. https://doi.org/10.1007/s40266-017-0484-4

Ko, D. H., Kim, T. H., Kim, J. W., Gu, J. J., Yoon, B. H., Oh, J. H., & Hong, S. G. (2017). Tranexamic acid-induced acute renal cortical necrosis in post-endoscopic Papillectomy Bleeding. *Clinical Endoscopy*, *50*(6), 609–613. https://doi.org/10.5946/ce.2017.021

Kong, X., Guo, D., Liu, S., Zhu, Y., & Yu, C. (2021). Incidence, characteristics and risk factors for drug-induced liver injury in hospitalized patients: A matched case-control study. *British Journal of Clinical Pharmacology*, *87*(11), 4304–4312. https://doi.org/10.1111/bcp.14847

Kulkarni, A. V., Kumar, P., Tevethia, H. V., Premkumar, M., Arab, J. P., Candia, R., Talukdar, R., Sharma, M., Qi, X., Rao, P. N., & Reddy, D. N. (2020). Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. *Alimentary Pharmacology & Therapeutics*, *52*(4), 584–599. https://doi.org/10.1111/apt.15916

Kumar, B., Prabhakar, R., & Thangavelu, S. (2020). Tenofovir-induced delayed nephro-osteo toxicity. *Journal of the Royal College of Physicians of Edinburgh*, *50*(3), 291–294. https://doi.org/10.4997/jrcpe.2020.316

Leite, T. T., Macedo, E., Martins, I. da S., Neves, F. M. de O., & Libório, A. B. (2015). Renal outcomes in critically ill patients receiving propofol or midazolam. *Clinical Journal of the American Society of Nephrology*, *10*(11), 1937–1945. https://doi.org/10.2215/CJN.02330315

Lescot, T., Karvellas, C., Beaussier, M., Magder, S., & Riou, B. (2012). Acquired liver injury in the intensive care unit. *Anesthesiology*, *117*(4), 898–904. https://doi.org/10.1097/ALN.0b013e318266c6df

Lewandowski, M. J., & Chapman, S. A. (2008). Ondansetron-induced aminotransferase level elevation: case report and review of the literature. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *28*(12), 1542–1546. https://doi.org/10.1592/phco.28.12.1542

Lexicomp. (2022). *Lexicomp (version 7.4.1) [mobile application software]*.

Li, X., Tang, J., & Mao, Y. (2022). Incidence and risk factors of drug-induced liver injury. *Liver International*, *42*(9), 1999–2014. https://doi.org/10.1111/liv.15262

Liss, G., & Lewis, J. H. (2009). Drug-induced liver injury: what was new in 2008? *Expert Opinion on*

Drug Metabolism & Toxicology, *5*(8), 843–860. https://doi.org/10.1517/17425250903018904

Liu, C., Yan, S., Wang, Y., Wang, J., Fu, X., Song, H., Tong, R., Dong, M., Ge, W., Wang, J., Yang, H., Wang, C., Xia, P., Zhao, L., Shen, S., Xie, J., Xu, Y., Ma, P., Li, H., … Yang, L. (2021). Drug-induced hospital-acquired acute kidney injury in China: a multicenter cross-sectional survey. *Kidney Diseases*, *7*(2), 143–155. https://doi.org/10.1159/000510455

Liu, Y., Zhan, S., Song, L., Chen, Y., Jia, Y., Liu, F., Sun, F., Wang, Q., & Xia, P. (2020). Drug-induced liver injury: Clinical and etiologic features at a large tertiary teaching hospital in China. *Medical Science Monitor*, *26*, *e919435*. https://doi.org/10.12659/MSM.919435

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Heparin. [Updated 2017 Nov 13]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548126/

Low, E. X. S., Zheng, Q., Chan, E., & Lim, S. G. (2020). Drug induced liver injury: East versus West – a systematic review and meta-analysis. *Clinical and Molecular Hepatology*, *26*(2), 142–154. https://doi.org/10.3350/cmh.2019.1003

Lucena, M. I., Sanabria, J., García-Cortes, M., Stephens, C., & Andrade, R. J. (2020). Drug-induced liver injury in older people. *The Lancet Gastroenterology & Hepatology*, *5*(9), 862–874. https://doi.org/10.1016/S2468-1253(20)30006-6

Mohamed, M., Al-Hillan, A., Flores, M., Kaunzinger, C., Mushtaq, A., Asif, A., & Hossain, M. (2020). Concomitant acute hepatic failure and renal failure induced by intravenous amiodarone: a case report and literature review. *Gastroenterology Research*, *13*(1), 40–43. https://doi.org/10.14740/gr1254

Murayama, H., Sakuma, M., Takahashi, Y., & Morimoto, T. (2018). Improving the assessment of adverse drug reactions using the Naranjo Algorithm in daily practice: The Japan Adverse Drug Events Study. *Pharmacology Research & Perspectives*, *6*(1), e00373.. https://doi.org/10.1002/prp2.373

Naranjo, C. A., Busto, U., Sellers, E. M., Sandor, P., Ruiz, I., Roberts, E. A., Janecek, E., Domecq, C., & Greenblatt, D. J. (1981). A method for estimating the probability of adverse drug reactions. *Clinical Pharmacology and Therapeutics*, *30*(2), 239–245. https://doi.org/10.1038/clpt.1981.154

National Institut for Health and Care Excellence. (2015). *Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes NICE guideline*. www.nice.org.uk/guidance/ng5

Nurulmaya. (2016). *Analysis of adverse drug reactions related to drug-induced renal injury based on spontaneous adverse drug reactions reporting in Malaysia 2016*. Universiti Teknologi Mara.

Paudel, R., Dogra, P., Suman, S., Acharya, S., & Matta, J. (2016). Acute liver and renal failure: a rare adverse effect exclusive to intravenous form of amiodarone. *Case Reports in Critical Care*, *2016*, 1–4. https://doi.org/10.1155/2016/5232804

Perazella, M. A., & Rosner, M. H. (2022). Drug-induced acute kidney injury. *Clinical Journal of the American Society of Nephrology*, *17*(8), 1220–1233. https://doi.org/10.2215/CJN.11290821

Pierson-Marchandise, M., Gras, V., Moragny, J., Micallef, J., Gaboriau, L., Picard, S., Choukroun, G., Masmoudi, K., & Liabeuf, S. (2017). The drugs that mostly frequently induce acute kidney injury: a case − noncase study of a pharmacovigilance database. *British Journal of Clinical Pharmacology*, *83*(6), 1341–1349. https://doi.org/10.1111/bcp.13216

Riskesdas. (2018). *Laporan Nasional Riskesda 2018*. https://repository.badankebijakan.kemkes.go.id/id/eprint/3514/1/Laporan Riskesdas 2018 Nasional.pdf

Rolland, A.-L., Garnier, A.-S., Meunier, K., Drablier, G., & Briet, M. (2021). Drug-induced acute kidney injury: a study from the french medical administrative and the french national pharmacovigilance databases using capture-recapture method. *Journal of Clinical Medicine*, *10*(2), 168. https://doi.org/10.3390/jcm10020168

Rotundo, L., & Pyrsopoulos, N. (2020). Liver injury induced by paracetamol and challenges

associated with intentional and unintentional use. *World Journal of Hepatology*, *12*(4), 125–136. https://doi.org/10.4254/wjh.v12.i4.125

Sabatino, D., Tillman, M., Pawasauskas, J., & Brothers, T. (2020). Nonsteroidal anti-inflammatory drug induced acute kidney injury; A review and case study. *Journal of Renal Injury Prevention*, *9*(4), e30–e30. https://doi.org/10.34172/jrip.2020.30

Sales, G. T. M., & Foresto, R. D. (2020). Drug-induced nephrotoxicity. *Revista Da Associação Médica Brasileira*, *66*(suppl 1), s82–s90. https://doi.org/10.1590/1806-9282.66.s1.82

Sattar, S., Hasan, M. J., Ray, N. C., & Quddus, A. R. (2018). Non-steroidal anti-inflammatory drugs induced acute kidney injury: incidence, clinical presentation, management and outcomes of patients at Tertiary Hospital based longitudinal study in Mymensingh, Bangladesh. *Community Based Medical Journal*, *7*(2), 9–16. https://doi.org/10.3329/cbmj.v7i2.55450

Shen, T., Liu, Y., Shang, J., Xie, Q., Li, J., Yan, M., Xu, J., Niu, J., Liu, J., Watkins, P. B., Aithal, G. P., Andrade, R. J., Dou, X., Yao, L., Lv, F., Wang, Q., Li, Y., Zhou, X., Zhang, Y., … Chen, C. (2019). Incidence and etiology of drug-induced liver injury in Mainland China. *Gastroenterology*, *156*(8), 2230-2241.e11. https://doi.org/10.1053/j.gastro.2019.02.002

Shirali, A., & Pazhayattil, G. S. (2014). Drug-induced impairment of renal function. *International Journal of Nephrology and Renovascular Disease*, 457. https://doi.org/10.2147/IJNRD.S39747

Stephens, C., Robles-Diaz, M., Medina-Caliz, I., Garcia-Cortes, M., Ortega-Alonso, A., Sanabria-Cabrera, J., Gonzalez-Jimenez, A., Alvarez-Alvarez, I., Slim, M., Jimenez-Perez, M., Gonzalez-Grande, R., Fernández, M. C., Casado, M., Soriano, G., Román, E., Hallal, H., Romero-Gomez, M., Castiella, A., Conde, I., … Lara, C. (2021). Comprehensive analysis and insights gained from long-term experience of the Spanish DILI Registry. *Journal of Hepatology*, *75*(1), 86–97. https://doi.org/10.1016/j.jhep.2021.01.029

Susantitaphong, P., Cruz, D. N., Cerda, J., Abulfaraj, M., Alqahtani, F., Koulouridis, I., & Jaber, B. L. (2013). World incidence of AKI. *Clinical Journal of the American Society of Nephrology*, *8*(9), 1482–1493. https://doi.org/10.2215/CJN.00710113

Welch, H. K., Kellum, J. A., & Kane-Gill, S. L. (2018). Drug-associated acute kidney injury identified in the united states food and drug administration adverse event reporting system satabase. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *38*(8), 785–793. https://doi.org/10.1002/phar.2152

Wikman, P., Safont, P., Palacio, M. Del, Moreno, A., Moreno, S., & Casado, J. L. (2013). The significance of antiretroviral-associated acute kidney injury in a cohort of ambulatory human immunodeficiency virus-infected patients. *Nephrology Dialysis Transplantation*, *28*(8), 2073–2081. https://doi.org/10.1093/ndt/gft210

Worland, T., Chin, K. L., Rodrigues, B., & Nicoll, A. (2020). A retrospective case-controlled cohort study of inpatient drug induced liver injury: the RIDDLE study. *Translational Gastroenterology and Hepatology*, *5*, 33–33. https://doi.org/10.21037/tgh.2019.10.15

Wu, B., Luo, M., Wu, F., He, Z., Li, Y., & Xu, T. (2022). Acute kidney injury associated with remdesivir: a comprehensive pharmacovigilance analysis of COVID-19 reports in FAERS. *Frontiers in Pharmacology*, *13692828*. https://doi.org/10.3389/fphar.2022.692828

Wu, J., Liu, J., Zhao, X., Liu, C., Wang, W., Wang, D., Xu, W., Zhang, C., Yu, J., Jiang, B., Cao, H., & Li, L. (2020). Clinical characteristics of imported cases of Coronavirus Disease 2019 (COVID-19) in Jiangsu Province: a multicenter descriptive study. *Clinical Infectious Diseases*, *71*(15), 706–712. https://doi.org/10.1093/cid/ciaa199

Xu, L., Liu, J., Lu, M., Yang, D., & Zheng, X. (2020). Liver injury during highly pathogenic human coronavirus infections. In *Liver International*, 40(5),998–1004. Blackwell Publishing Ltd. https://doi.org/10.1111/liv.14435

Yu, C., Guo, D., Yao, C., Yang, H., Liu, S., Zhu, Y., & Kong, X. (2020). Clinical characteristics of hospitalized patients with drug-induced acute kidney injury and associated risk factors: a case-control study. *BioMed Research International*, *2020(9742754)*, *1-8*. https://doi.org/10.1155/2020/9742754