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Original Article

Nephrotoxic Spectrum and Temporal Trends of Cisplatin: A Real-World Pharmacovigilance Study Based on FAERS and EudraVigilance Databases (2004–2025)

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Abstract:

Background: Cisplatin-induced nephrotoxicity remains a critical dose-limiting adverse event (AE). This study aimed to comprehensively evaluate the real-world nephrotoxic landscape and temporal trends of cisplatin using large-scale pharmacovigilance databases.

Methods: Adverse event reports were retrieved from the FDA Adverse Event Reporting System (FAERS) and EudraVigilance (EV) databases (2004–2025). Disproportionality analyses were performed using four algorithms: ROR, PRR, IC, and EBGM. Time-to-onset (TTO) and demographic-stratified analyses were conducted to characterize clinical profiles.

Results: A total of 2,437 reports from FAERS and 3,561 from EV were identified. In FAERS, cisplatin-associated nephrotoxicity peaked in 2019, with a male predominance (56.79%) and high clinical severity (98.24% serious cases). The median TTO was 10.00 days (IQR: 5.00–29.00), with females exhibiting a significantly shorter latency period than males (9.5 vs. 11.0 days, P = 0.0289). Disproportionality analysis revealed robust signals for Acute Kidney Injury (AKI, ROR=5.05) and exceptionally high signal intensities for Renal Salt-Wasting Syndrome (RSWS, ROR=481.57) and urinary tract structural damage (e.g., bladder necrosis). Subgroup analysis identified age-specific vulnerabilities: the geriatric cohort showed a markedly elevated risk of RSWS (ROR = 737.90) and obstructive complications, such as hydronephrosis. These findings were consistently validated in the EV database, where the RSWS signal remained robust (ROR = 208.08) even after the sensitivity analysis excluding concomitant medications.

Conclusions: This study provides multi-database evidence of the multifaceted nephrotoxic footprint of cisplatin. Beyond classic AKI, clinicians should prioritize monitoring for rapid-onset electrolyte disturbances (RSWS) and obstructive uropathy in elderly populations.

Keywords: Cisplatin; Nephrotoxicity; Pharmacovigilance; FAERS; EudraVigilance

Introduction

Cisplatin has long been established as a cornerstone of systemic oncological therapy12. Since its FDA approval in 1978, this platinum-based powerhouse has remained indispensable for treating a vast array of malignancies, from testicular and ovarian cancers to head and neck squamous cell carcinomas345. However, its therapeutic brilliance is perennially shadowed by its most notorious Achilles' heel: nephrotoxicity. Despite decades of research into hydration protocols and chemoprotectants, renal impairment remains the primary dose-limiting factor, forcing

clinicians into a precarious balancing act between oncological efficacy and irreversible organ damage678.

While the classic manifestation of cisplatin-induced nephrotoxicity (CINT) is Acute Kidney Injury (AKI), the clinical reality is far more complex91011. Modern oncology is increasingly recognizing that CINT is not a monolithic event but a broad spectrum of pathologies, ranging from subtle electrolyte disturbances (such as refractory hypomagnesemia) and proximal tubular dysfunction to chronic kidney disease (CKD) and thrombotic microangiopathy12. Most of our current understanding, however, stems from controlled clinical trials or small-scale cohort studies. These environments, while rigorous, often lack the diversity of the "real-world" patient population—those with multiple comorbidities, polypharmacy, and varying genetic predispositions who are typically excluded from Phase III trials.

The landscape of pharmacovigilance offers a powerful lens to bridge this gap. Large-scale spontaneous reporting systems (SRSs) provide a high-volume, longitudinal perspective on drug safety that traditional trials cannot match. To date, most studies focusing on cisplatin-related renal adverse events (AEs) have relied on single databases, often limited by geographic bias or specific timeframes. Furthermore, the temporal trends of these reports, how the reporting patterns have shifted over the last two decades in the context of evolving supportive care and the rise of combination therapies (like ICIs), remain largely underexplored.

In this study, we conducted a comprehensive, cross-continental pharmacovigilance analysis by integrating data from the US Food and Drug Administration Adverse Event Reporting System (FAERS) and the European Medicines Agency's EudraVigilance (EV) database13. Spanning over 20 years (2004–2025), this dual-database approach aims to:(1)Map the full nephrotoxic spectrum of cisplatin beyond simple AKI;(2)Identify specific high-risk signals through disproportionality analysis;(3)Analyze temporal trends to determine if modern clinical practices have effectively mitigated the renal burden of cisplatin.

2. Methods

2.1 Data Source and Study Design

A retrospective pharmacovigilance study was conducted using data from the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database, covering the period from 2004 to 2025. This study aimed to characterize the nephrotoxicity profile associated with cisplatin. To ensure the robustness of the findings, external validation was performed using the EudraVigilance (EV) database for the same period.

2.2 Data Extraction and Processing

Adverse event (AE) reports were retrieved where cisplatin was identified as the "primary suspect" (PS). We utilized the Medical Dictionary for Regulatory Activities (MedDRA, version 27.0) to identify nephrotoxic events. Cases were filtered using the System Organ Class (SOC) "Renal and urinary disorders." Duplicate reports were removed according to the FDA's recommendations by prioritizing the most recent primaryid. Demographic variables, including age, gender, reporter type, and clinical outcomes (e.g., hospitalization, death), were extracted.

2.3 Definition of Outcomes and Clinical Characteristics

The severity of AEs was classified as "serious" if they resulted in death, life-threatening conditions, hospitalization, or significant disability. Time-to-onset (TTO) was defined as the interval between the date of cisplatin administration and the date of AE occurrence. Reports with missing or erroneous date entries were excluded from the TTO analysis.

2.4 Disproportionality Analysis and Signal Detection

To identify potential signals of cisplatin-induced nephrotoxicity, disproportionality analysis was performed using four validated algorithms:Reporting Odds Ratio (ROR);Proportional Reporting Ratio (PRR);Information Component (IC);Empirical Bayes Geometric Mean (EBGM).

A signal was considered statistically significant when the lower limit of the 95% confidence interval (CI) for ROR was > 1, the PRR ≥ 2 (with a $\chi^2 \geq 4$), the IC > 0, or the EBGM > 2, with at least 3 cases reported.

2.5 Subgroup and Sensitivity Analysis

Stratified analyses were performed by gender (male vs. female) and age (pediatric: <18 years; adult: 18–64 years; geriatric: ≥65 years) to explore demographic-specific vulnerability. A sensitivity analysis was conducted in both FAERS and EV databases by excluding reports with concomitant nephrotoxic medications to assess the independent association between cisplatin and specific phenotypes like Renal Salt-Wasting Syndrome (RSWS).

2.6 Statistical Analysis

Categorical variables were presented as frequencies and percentages. Continuous variables (e.g., TTO) were expressed as medians with interquartile ranges (IQR). The Wilcoxon rank-sum test was employed to compare TTO between gender groups. Statistical significance was defined as $P < 0.05$. All data processing and statistical analyses were performed using R (version 4.3.0) and SAS (version 9.4).

3. Results

Descriptive Epidemiology and Temporal Trends in FAERS

A retrospective analysis of the FAERS database from 2004 to 2025 identified a significant cohort of cisplatin-induced nephrotoxicity reports. The reporting frequency exhibited a temporal evolution, reaching a peak in 2019 with 217 cases (Figure 1).

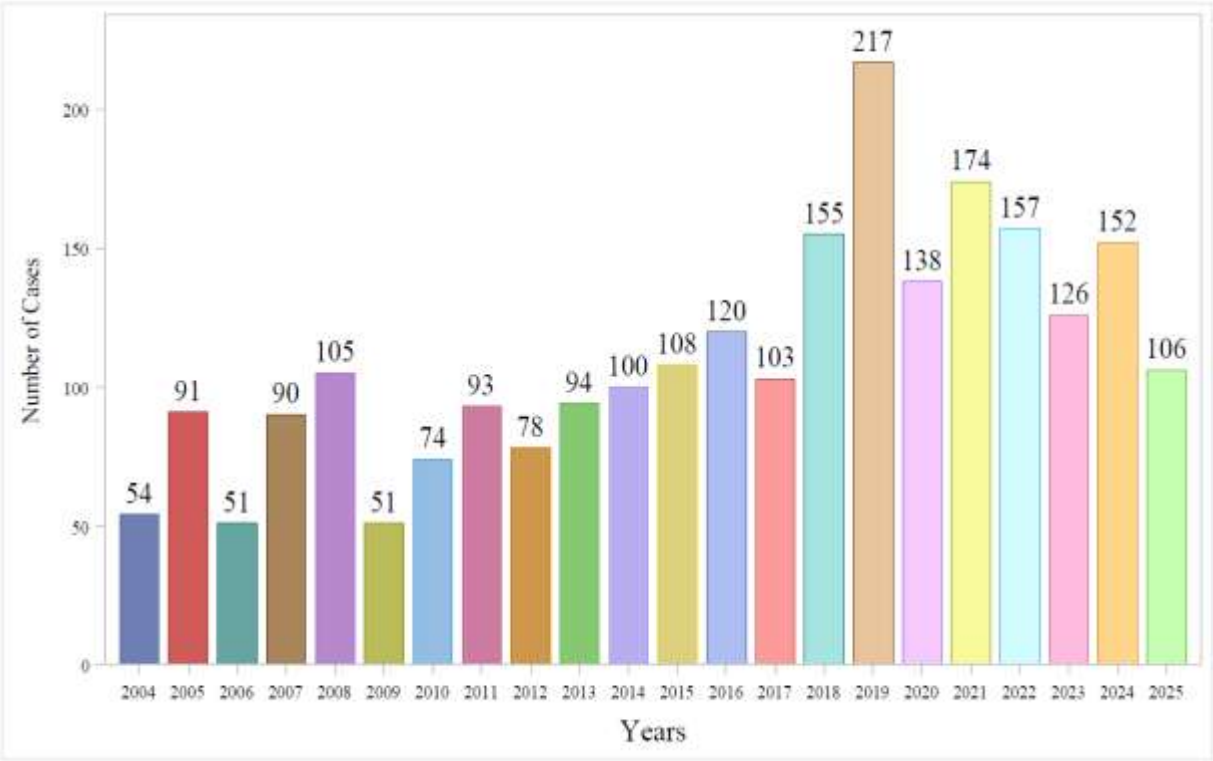


Figure 1: Annual Distribution of AE Reports

Demographic evaluation revealed a male predominance (56.79%, n=1,384)(Figure 2A), with the highest distribution of adverse events (AEs) concentrated in the 45–64 age group (32.7%, n=797)(Figure 2B). The source of reporting was predominantly healthcare professionals, specifically pharmacists (31.39%, n=765) and physicians (22.94%, n=559) (Figure 2C), ensuring high clinical validity of the data.

In terms of clinical outcomes, the toxicity profile was characterized by high severity; 98.24% of events were classified as serious(Figure 2D).

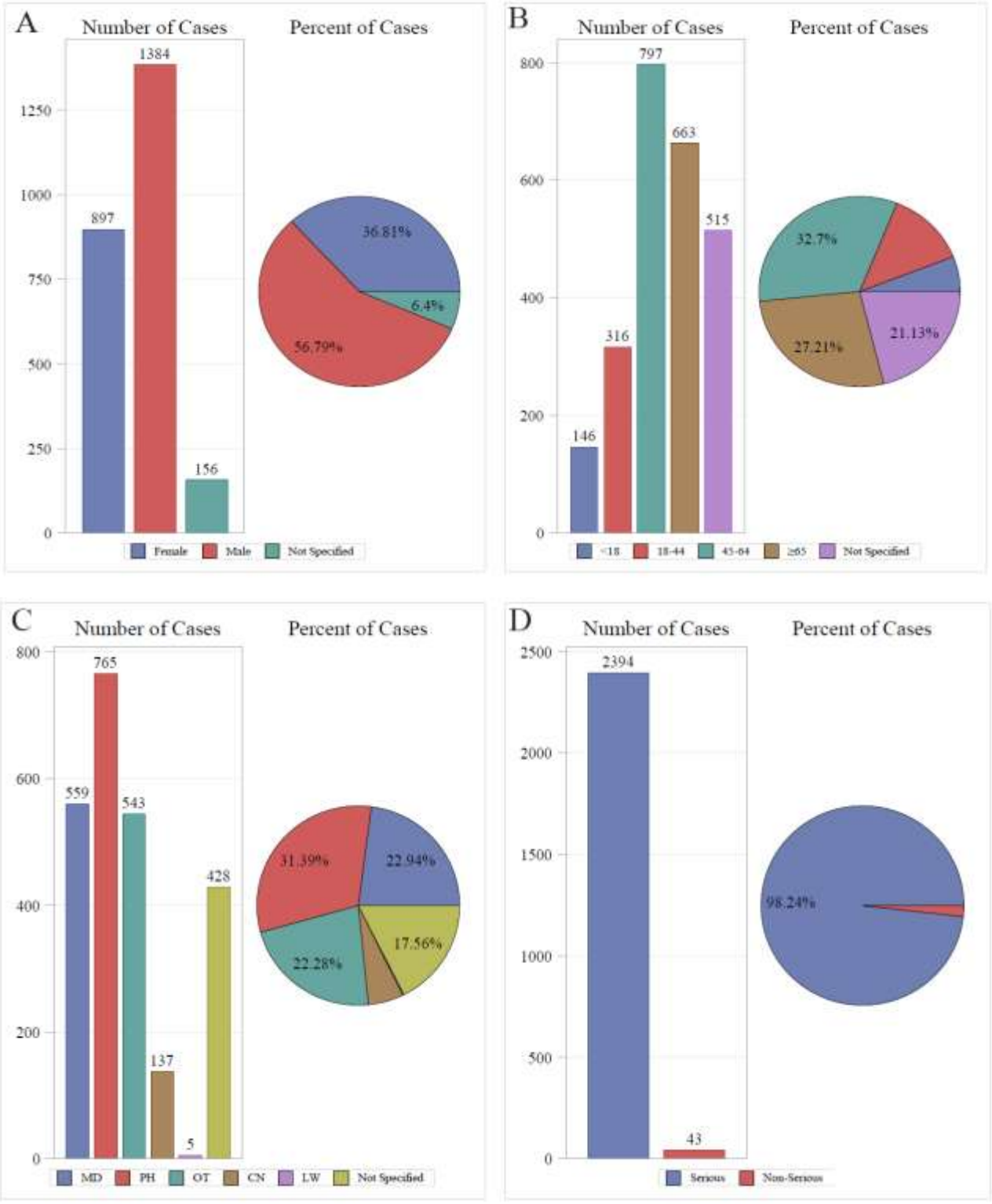


Figure 2: Distribution of AE Reports by (A) Sex, (B) Age, (C) Reporter Type, and (D) Seriousness

Hospitalization (64.3%) and death (14.73%) were the most frequent sequelae(Figure 3).

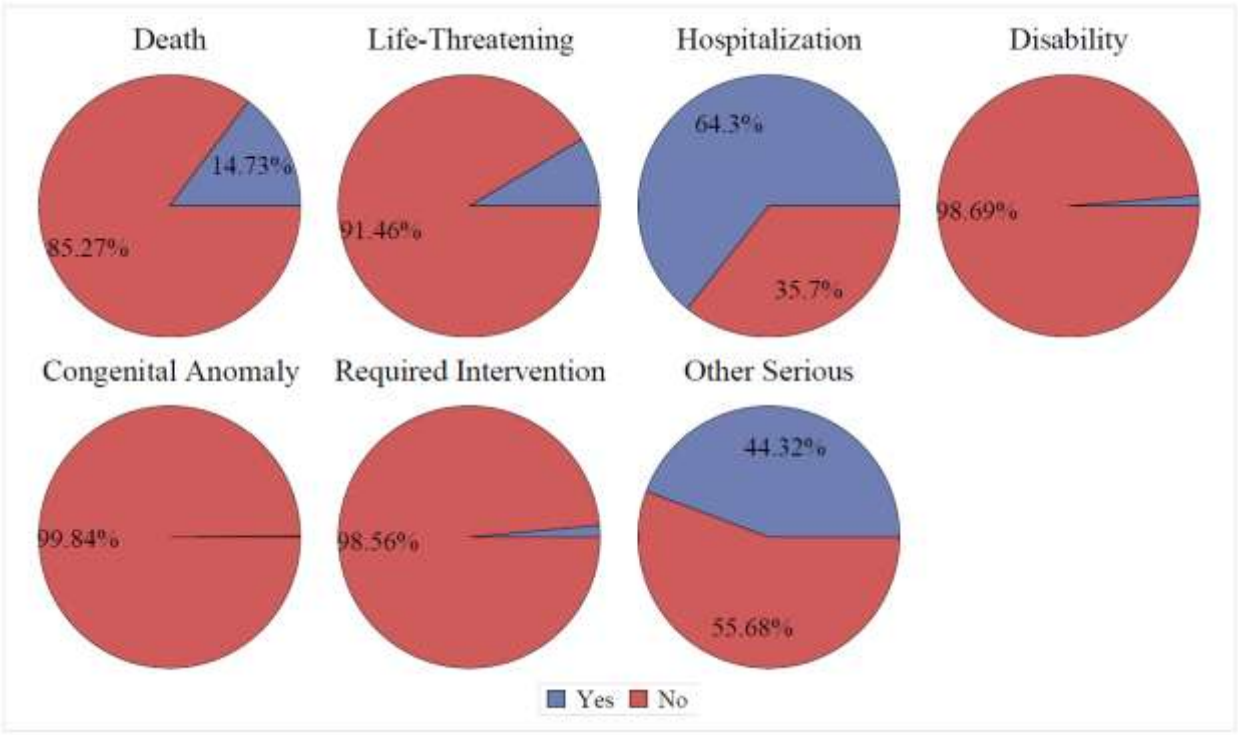
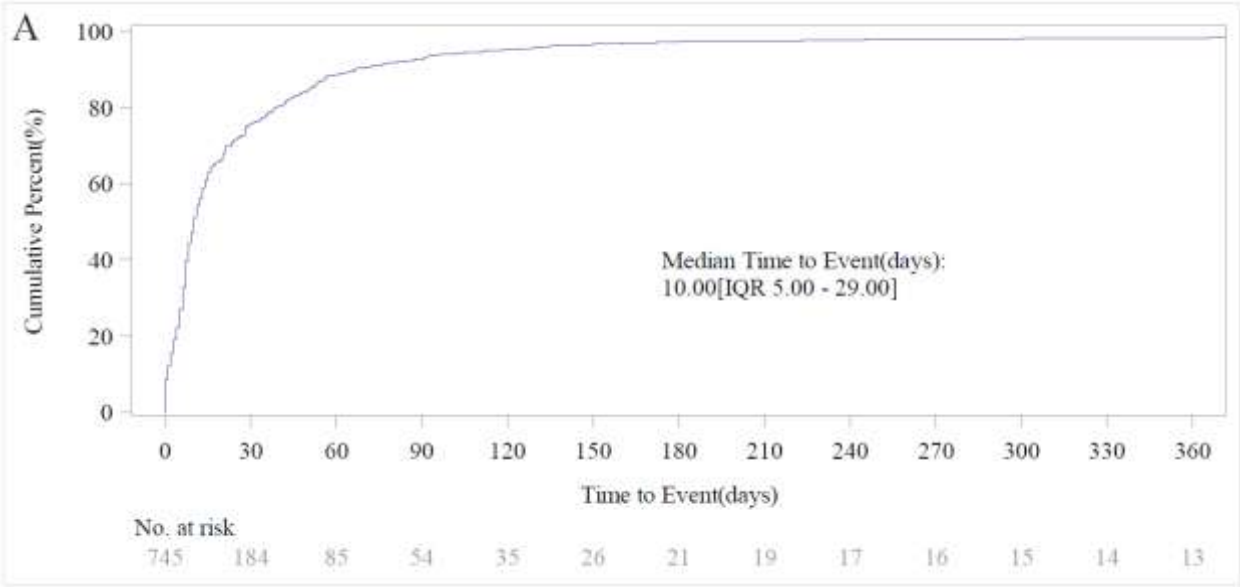


Figure 3: Distribution of Adverse Outcome Reports

Time-to-onset analysis demonstrated a rapid development of nephrotoxicity, with an overall median onset of 10.00 days (IQR: 5.00–29.00)(Figure 4A) and 75.84% of cases occurring within the first 30 days of treatment(Figure 5). Notably, a gender-stratified analysis indicated a statistically significant shorter latency period in females (median 9.50 days; IQR: 4.00–20.00) compared to males (median 11.00 days; IQR: 5.00–33.00) (Wilcoxon test, P = 0.0289)(Figure 4B).



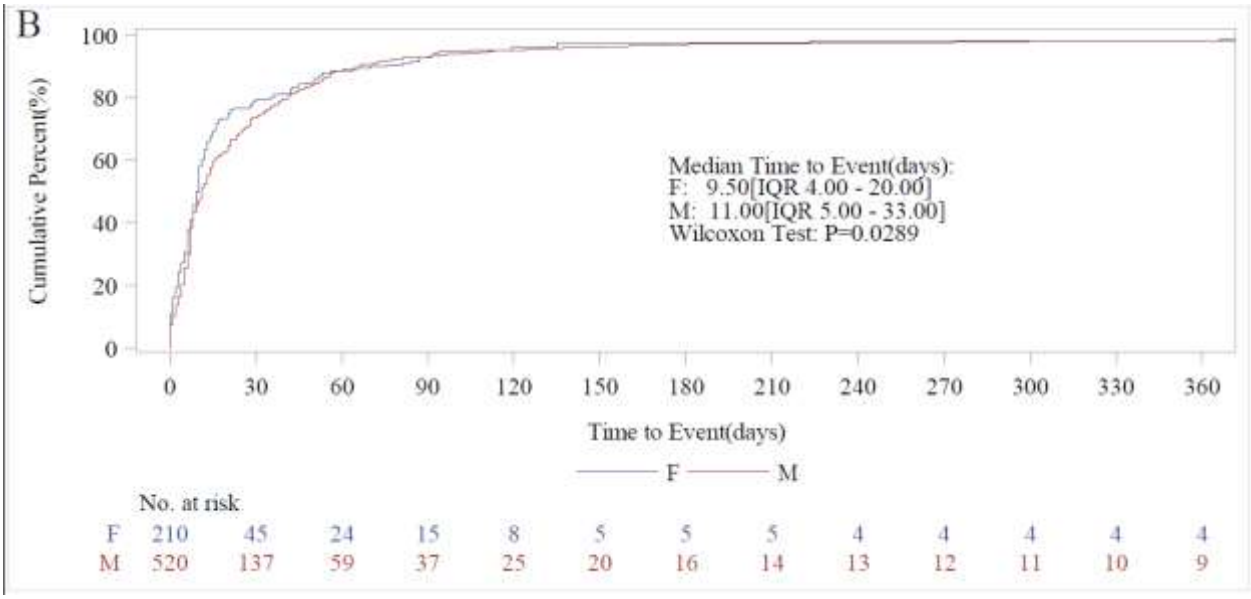


Figure 4: (A) Overall Cumulative Incidence; (B) Cumulative Incidence by Sex

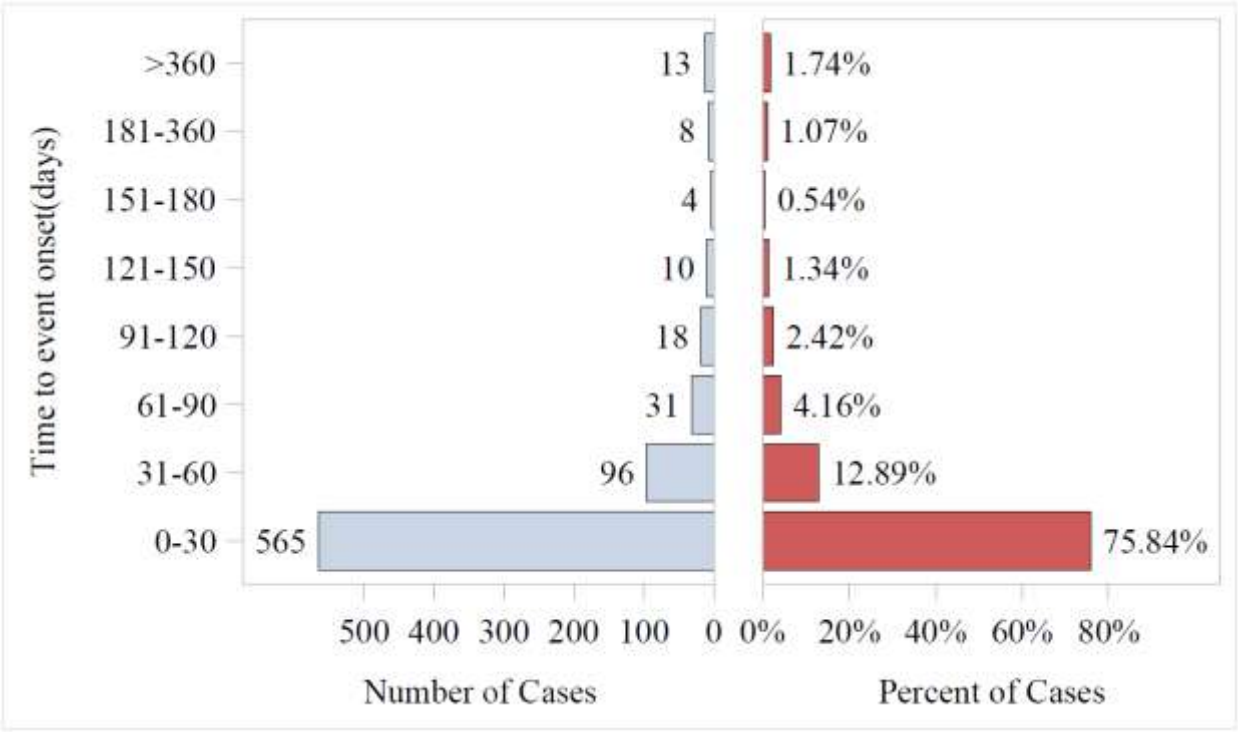


Figure 5: Distribution of Time-to-Onset for AE Reports

Disproportionality Analysis and Signal Detection

Systematic disproportionality analysis identified a robust spectrum of nephrotoxic signals within the "Renal and urinary disorders" System Organ Class (SOC), showing consistency across all four algorithmic metrics (ROR, PRR, IC, and EBGM). While Acute Kidney Injury (AKI) represented the most prevalent phenotype (n=1,070; ROR= 5.05, 95% CI: 4.75–5.37)(Figure 6), the highest signal intensities were associated with specific tubular dysfunctions and electrolyte disturbances.

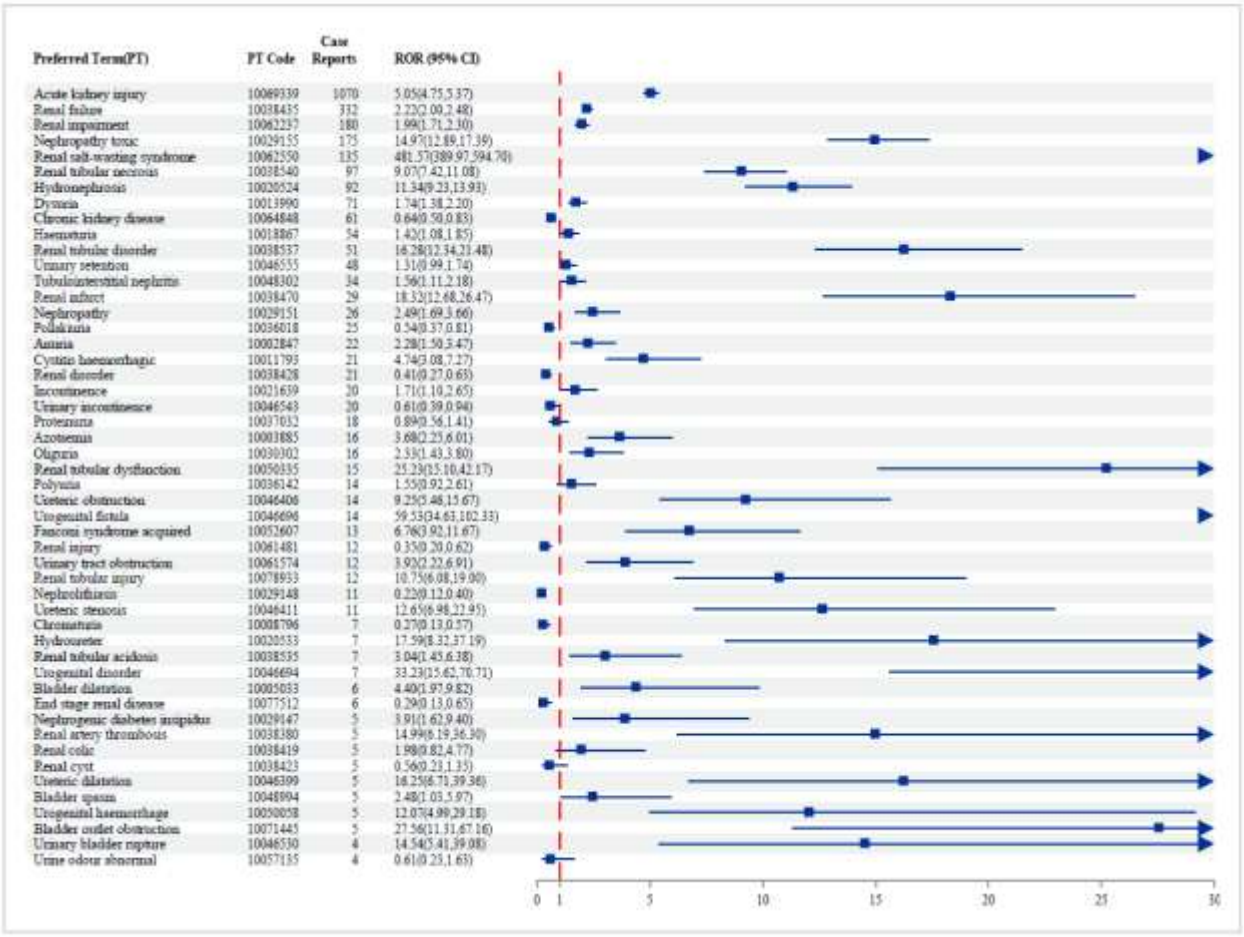


Figure 6: The top 50 frequent of PTs

Renal Salt-Wasting Syndrome (RSWS) exhibited an exceptionally strong signal intensity (ROR= 481.57, 95% CI: 396.67–584.65), accompanied by significant signals for Hypermagnesemia (ROR= 122.06, 95% CI: 104.57–142.48). Furthermore, the analysis unveiled rare but clinically critical structural pathologies extending beyond traditional parenchymal damage. Significant disproportionality was observed for urinary tract toxicity (ROR= 1790.72), urogenital fistulae, bladder necrosis, and chyluria (ROR= 269.32), suggesting a multifaceted toxicological footprint affecting the entire urinary tract architecture(Table 1).

Table 1 Signal Detection Across MedDRA Hierarchical Levels

PT	ROR(95% CI)	PRR(95% CI)	IC(IC025)	EBGM(EBGM05)	ROR Signal	PRR Signal	IC Signal	EBGM Signal
Acute kidney injury	5.05(4.75,5.37)	4.99(4.70,5.29)	2.31(2.22)	4.96(4.67)	Y	Y	Y	Y
Renal failure	2.22(2.00,2.48)	2.22(1.99,2.47)	1.15(0.98)	2.21(1.99)	Y	Y	Y	N
Renal impairment	1.99(1.71,2.30)	1.98(1.71,2.29)	0.99(0.76)	1.98(1.71)	Y	Y	Y	N
Nephropathy toxic	14.97(12.89,17.39)	14.93(12.86,17.34)	3.88(3.55)	14.69(12.65)	Y	Y	Y	Y
Renal salt-wasting	481.57(389.	480.62(389.	8.27(6	307.96(2	Y	Y	Y	Y

syndrome	97,594.70)	30,593.36)	.27)	49.38)				
Renal tubular necrosis	9.07(7.42,11.08)	9.05(7.41,11.06)	3.17(2.76)	8.97(7.34)	Y	Y	Y	Y
Hydronephrosis	11.34(9.23,13.93)	11.33(9.22,13.91)	3.48(3.03)	11.19(9.11)	Y	Y	Y	Y
Dysuria	1.74(1.38,2.20)	1.74(1.38,2.20)	0.80(0.44)	1.74(1.38)	Y	Y	Y	N
Chronic kidney disease	0.64(0.50,0.83)	0.64(0.50,0.83)	-0.63(-0.99)	0.65(0.50)	N	N	N	N
Haematuria	1.42(1.08,1.85)	1.42(1.08,1.85)	0.50(0.10)	1.41(1.08)	Y	Y	Y	N
Renal tubular disorder	16.28(12.34,21.48)	16.27(12.33,21.46)	4.00(3.23)	15.98(12.11)	Y	Y	Y	Y
Urinary retention	1.31(0.99,1.74)	1.31(0.99,1.74)	0.39(-0.03)	1.31(0.99)	N	N	N	N
Tubulointerstitial nephritis	1.56(1.11,2.18)	1.55(1.11,2.18)	0.64(0.12)	1.55(1.11)	Y	Y	Y	N
Renal infarct	18.32(12.68,26.47)	18.31(12.68,26.45)	4.17(2.99)	17.95(12.42)	Y	Y	Y	Y
Nephropathy	2.49(1.69,3.66)	2.49(1.69,3.66)	1.31(0.68)	2.48(1.69)	Y	Y	Y	N
Pollakiuria	0.54(0.37,0.81)	0.55(0.37,0.81)	-0.87(-1.42)	0.55(0.37)	N	N	N	N
Anuria	2.28(1.50,3.47)	2.28(1.50,3.47)	1.19(0.51)	2.28(1.50)	Y	Y	Y	N
Cystitis haemorrhagic	4.74(3.08,7.27)	4.73(3.08,7.27)	2.24(1.39)	4.71(3.07)	Y	Y	Y	Y
Renal disorder	0.41(0.27,0.63)	0.41(0.27,0.63)	-1.29(-1.87)	0.41(0.27)	N	N	N	N
Incontinence	1.71(1.10,2.65)	1.71(1.10,2.65)	0.77(0.09)	1.71(1.10)	Y	Y	Y	N
Urinary incontinence	0.61(0.39,0.94)	0.61(0.39,0.94)	-0.72(-1.32)	0.61(0.39)	N	N	N	N
Proteinuria	0.89(0.56,1.41)	0.89(0.56,1.41)	-0.17(-0.82)	0.89(0.56)	N	N	N	N
Azotaemia	3.68(2.25,6.01)	3.68(2.25,6.01)	1.87(0.96)	3.67(2.24)	Y	Y	Y	Y
Oliguria	2.33(1.43,3.80)	2.33(1.43,3.80)	1.22(0.41)	2.32(1.42)	Y	Y	Y	N
Renal tubular dysfunction	25.23(15.10,42.17)	25.23(15.10,42.16)	4.62(2.58)	24.53(14.68)	Y	Y	Y	Y
Polyuria	1.55(0.92,2.61)	1.55(0.92,2.61)	0.63(-0.17)	1.54(0.91)	N	N	N	N
Ureteric obstruction	9.25(5.46,15.67)	9.25(5.46,15.66)	3.20(1.82)	9.16(5.41)	Y	Y	Y	Y
Urogenital fistula	59.53(34.63	59.51(34.62	5.80(2	55.70(32.	Y	Y	Y	Y

	,102.33)	,102.30)	.81)	40)				
Fanconi syndrome acquired	6.76(3.92,11.67)	6.76(3.92,11.67)	2.75(1.48)	6.72(3.89)	Y	Y	Y	Y
Renal injury	0.35(0.20,0.62)	0.35(0.20,0.62)	-1.50(-2.22)	0.35(0.20)	N	N	N	N
Urinary tract obstruction	3.92(2.22,6.91)	3.92(2.22,6.91)	1.97(0.87)	3.91(2.22)	Y	Y	Y	Y
Renal tubular injury	10.75(6.08,19.00)	10.75(6.08,18.99)	3.41(1.80)	10.63(6.01)	Y	Y	Y	Y
Nephrolithiasis	0.22(0.12,0.40)	0.22(0.12,0.40)	-2.17(-2.91)	0.22(0.12)	N	N	N	N
Ureteric stenosis	12.65(6.98,22.95)	12.65(6.98,22.94)	3.64(1.83)	12.48(6.88)	Y	Y	Y	Y
Chromaturia	0.27(0.13,0.57)	0.27(0.13,0.57)	-1.87(-2.75)	0.27(0.13)	N	N	N	N
Hydroureter	17.59(8.32,37.19)	17.59(8.32,37.18)	4.11(1.48)	17.26(8.16)	Y	Y	Y	Y
Renal tubular acidosis	3.04(1.45,6.38)	3.04(1.45,6.38)	1.60(0.25)	3.03(1.44)	Y	Y	Y	N
Urogenital disorder	33.23(15.62,70.71)	33.23(15.62,70.70)	5.00(1.67)	32.02(15.05)	Y	Y	Y	Y
Bladder dilatation	4.40(1.97,9.82)	4.40(1.97,9.82)	2.13(0.47)	4.39(1.97)	Y	Y	Y	N
End stage renal disease	0.29(0.13,0.65)	0.29(0.13,0.65)	-1.78(-2.71)	0.29(0.13)	N	N	N	N
Nephrogenic diabetes insipidus	3.91(1.62,9.40)	3.91(1.62,9.40)	1.96(0.21)	3.89(1.62)	Y	Y	Y	N
Renal artery thrombosis	14.99(6.19,36.30)	14.99(6.19,36.29)	3.88(0.97)	14.75(6.09)	Y	Y	Y	Y
Renal colic	1.98(0.82,4.77)	1.98(0.82,4.77)	0.99(-0.41)	1.98(0.82)	N	N	N	N
Renal cyst	0.56(0.23,1.35)	0.56(0.23,1.35)	-0.83(-1.90)	0.56(0.23)	N	N	N	N
Ureteric dilatation	16.25(6.71,39.36)	16.24(6.71,39.35)	4.00(1.00)	15.96(6.59)	Y	Y	Y	Y
Bladder spasm	2.48(1.03,5.97)	2.48(1.03,5.97)	1.31(-0.19)	2.48(1.03)	Y	Y	N	N
Urogenital haemorrhage	12.07(4.99,29.18)	12.07(4.99,29.17)	3.57(0.89)	11.91(4.93)	Y	Y	Y	Y
Bladder outlet obstruction	27.56(11.31,67.16)	27.56(11.31,67.15)	4.74(1.14)	26.73(10.97)	Y	Y	Y	Y
Urinary bladder rupture	14.54(5.41,39.08)	14.54(5.41,39.07)	3.84(0.66)	14.32(5.33)	Y	Y	Y	Y
Urine odour abnormal	0.61(0.23,1.63)	0.61(0.23,1.63)	-0.71(-1.88)	0.61(0.23)	N	N	N	N

Pyelocaliectasis	3.84(1.44,10.26)	3.84(1.44,10.25)	1.94(-0.01)	3.83(1.43)	Y	Y	N	N
Bladder perforation	9.19(3.43,24.61)	9.19(3.43,24.61)	3.19(0.50)	9.10(3.40)	Y	Y	Y	Y
Bladder sphincter atony	17.80(5.67,55.85)	17.80(5.67,55.84)	4.13(0.31)	17.46(5.56)	Y	Y	Y	Y
Glomerulonephritis rapidly progressive	2.53(0.81,7.85)	2.53(0.81,7.85)	1.34(-0.58)	2.52(0.81)	N	N	N	N
Hypercalciuria	5.42(1.74,16.86)	5.42(1.74,16.86)	2.43(-0.09)	5.39(1.73)	Y	Y	N	N
Nephrosclerosis	2.31(0.74,7.17)	2.31(0.74,7.16)	1.20(-0.65)	2.30(0.74)	N	N	N	N
Nocturia	0.23(0.07,0.70)	0.23(0.07,0.70)	-2.15(-3.28)	0.23(0.07)	N	N	N	N
Urate nephropathy	24.41(7.75,76.92)	24.41(7.75,76.92)	4.57(0.36)	23.76(7.54)	Y	Y	Y	Y
Urinary bladder haemorrhage	1.28(0.41,3.97)	1.28(0.41,3.97)	0.35(-1.19)	1.28(0.41)	N	N	N	N
Urine abnormality	0.63(0.20,1.96)	0.63(0.20,1.96)	-0.66(-1.96)	0.63(0.20)	N	N	N	N
Urine flow decreased	1.12(0.36,3.48)	1.12(0.36,3.48)	0.17(-1.32)	1.12(0.36)	N	N	N	N
Urethral stenosis	3.99(1.28,12.41)	3.99(1.28,12.41)	1.99(-0.26)	3.98(1.28)	Y	Y	N	N
Urinary tract toxicity	82.69(25.28,270.49)	82.69(25.28,270.46)	6.24(0.42)	75.48(23.07)	Y	Y	Y	Y
Albuminuria	3.53(0.88,14.16)	3.53(0.88,14.16)	1.82(-0.74)	3.52(0.88)	N	N	N	N
Bladder obstruction	3.61(0.90,14.49)	3.61(0.90,14.49)	1.85(-0.72)	3.60(0.90)	N	N	N	N
Bladder pain	0.59(0.15,2.35)	0.59(0.15,2.35)	-0.77(-2.22)	0.59(0.15)	N	N	N	N
Glomerulonephritis	0.72(0.18,2.90)	0.72(0.18,2.90)	-0.47(-1.99)	0.72(0.18)	N	N	N	N
Glycosuria	1.35(0.34,5.41)	1.35(0.34,5.41)	0.43(-1.39)	1.35(0.34)	N	N	N	N
Haemoglobinuria	1.57(0.39,6.28)	1.57(0.39,6.28)	0.65(-1.27)	1.57(0.39)	N	N	N	N
Micturition urgency	0.16(0.04,0.65)	0.16(0.04,0.65)	-2.63(-3.82)	0.16(0.04)	N	N	N	N
Nephrotic syndrome	0.27(0.07,1.07)	0.27(0.07,1.07)	-1.90(-3.17)	0.27(0.07)	N	N	N	N
Renal atrophy	1.41(0.35,5.64)	1.41(0.35,5.64)	0.49(-1.36)	1.41(0.35)	N	N	N	N
Renal hypertension	5.62(1.40,2	5.62(1.40,2	2.48(-	5.59(1.39	N	N	N	N

	2.58)	2.58)	0.53)	)				
Renal pain	0.17(0.04,0.68)	0.17(0.04,0.68)	-2.54(-3.74)	0.17(0.04)	N	N	N	N
Strangury	11.70(2.90,47.25)	11.70(2.90,47.25)	3.53(-0.33)	11.56(2.86)	N	N	N	Y
Urinary hesitation	0.74(0.19,2.98)	0.74(0.19,2.98)	-0.43(-1.97)	0.74(0.19)	N	N	N	N
Vesical fistula	7.15(1.78,28.76)	7.15(1.78,28.76)	2.83(-0.45)	7.10(1.77)	N	N	N	N
Hypocalciuria	32.24(7.86,132.31)	32.24(7.86,132.31)	4.96(-0.22)	31.11(7.58)	N	N	N	Y
Bladder necrosis	27.56(6.74,112.69)	27.56(6.74,112.68)	4.74(-0.22)	26.73(6.54)	N	N	N	Y
Renal pelvis fistula	170.89(37.44,779.98)	170.89(37.44,779.92)	7.16(-0.28)	142.57(31.24)	N	N	N	Y
Hypocitraturia	28.02(6.85,114.58)	28.01(6.85,114.57)	4.76(-0.22)	27.16(6.64)	N	N	N	Y
Prerenal failure	1.33(0.33,5.31)	1.33(0.33,5.31)	0.41(-1.41)	1.33(0.33)	N	N	N	N
Urinary bladder toxicity	77.68(18.27,330.35)	77.68(18.27,330.33)	6.16(-0.22)	71.29(16.76)	N	N	N	Y
Genitourinary symptom	10.88(2.70,43.91)	10.88(2.70,43.91)	3.43(-0.34)	10.76(2.67)	N	N	N	Y
Subcapsular renal haematoma	4.47(1.11,17.95)	4.47(1.11,17.95)	2.16(-0.62)	4.46(1.11)	N	N	N	N
Renal-limited thrombotic microangiopathy	10.88(2.70,43.91)	10.88(2.70,43.91)	3.43(-0.34)	10.76(2.67)	N	N	N	Y
Calculus bladder	0.66(0.09,4.69)	0.66(0.09,4.69)	-0.60(-2.37)	0.66(0.09)	N	N	N	N
Chyluria	170.89(19.96,1462.80)	170.89(19.96,1462.74)	7.16(-1.33)	142.57(16.66)	N	N	N	Y
Cystitis ulcerative	14.73(2.04,106.36)	14.73(2.04,106.36)	3.86(-1.17)	14.50(2.01)	N	N	N	Y
Glomerulonephritis acute	4.34(0.61,30.95)	4.34(0.61,30.94)	2.11(-1.35)	4.32(0.61)	N	N	N	N
Glomerulonephritis minimal lesion	1.29(0.18,9.19)	1.29(0.18,9.19)	0.37(-1.87)	1.29(0.18)	N	N	N	N
Glomerulonephritis proliferative	2.42(0.34,17.23)	2.42(0.34,17.23)	1.27(-1.55)	2.42(0.34)	N	N	N	N
Hypertonic bladder	0.32(0.05,2.28)	0.32(0.05,2.28)	-1.64(-3.08)	0.32(0.05)	N	N	N	N
IgA nephropathy	0.60(0.08,4.27)	0.60(0.08,4.27)	-0.74(-2.46)	0.60(0.08)	N	N	N	N
Kidney fibrosis	0.50(0.07,3.55)	0.50(0.07,3.55)	-1.00(-	0.50(0.07)	N	N	N	N

			2.63)					
Micturition disorder	0.26(0.04,1.84)	0.26(0.04,1.84)	-1.95(-3.32)	0.26(0.04)	N	N	N	N
Nephritis	0.28(0.04,1.99)	0.28(0.04,1.99)	-1.84(-3.23)	0.28(0.04)	N	N	N	N
Neurogenic bladder	0.42(0.06,2.95)	0.42(0.06,2.95)	-1.27(-2.81)	0.42(0.06)	N	N	N	N
Renal artery stenosis	0.63(0.09,4.50)	0.63(0.09,4.50)	-0.66(-2.41)	0.63(0.09)	N	N	N	N
Renal failure neonatal	4.13(0.58,29.44)	4.13(0.58,29.44)	2.04(-1.37)	4.11(0.58)	N	N	N	N
Renal hypertrophy	4.88(0.68,34.86)	4.88(0.68,34.86)	2.28(-1.32)	4.86(0.68)	N	N	N	N
Renal vein thrombosis	1.42(0.20,10.13)	1.42(0.20,10.13)	0.51(-1.81)	1.42(0.20)	N	N	N	N
Ureteric fistula	18.99(2.62,137.75)	18.99(2.62,137.75)	4.22(-1.16)	18.60(2.56)	N	N	N	Y
Urethral discharge	7.24(1.01,51.84)	7.24(1.01,51.83)	2.85(-1.25)	7.19(1.00)	N	N	N	N
Urethral disorder	1.89(0.27,13.48)	1.89(0.27,13.48)	0.92(-1.66)	1.89(0.27)	N	N	N	N
Urethral pain	1.59(0.22,11.27)	1.59(0.22,11.27)	0.66(-1.75)	1.58(0.22)	N	N	N	N
Kidney enlargement	0.82(0.12,5.83)	0.82(0.12,5.83)	-0.28(-2.19)	0.82(0.12)	N	N	N	N
Ureteric rupture	25.13(3.44,183.59)	25.13(3.44,183.59)	4.61(-1.16)	24.44(3.35)	N	N	N	Y
Leukocyturia	1.11(0.16,7.87)	1.11(0.16,7.87)	0.15(-1.97)	1.11(0.16)	N	N	N	N
Costovertebral angle tenderness	5.37(0.75,38.39)	5.37(0.75,38.39)	2.42(-1.30)	5.35(0.75)	N	N	N	N
Glomerulonephropathy	3.35(0.47,23.88)	3.35(0.47,23.88)	1.74(-1.43)	3.34(0.47)	N	N	N	N
Hypertensive nephropathy	0.81(0.11,5.78)	0.81(0.11,5.78)	-0.30(-2.20)	0.81(0.11)	N	N	N	N
Haemorrhage urinary tract	0.35(0.05,2.51)	0.35(0.05,2.51)	-1.50(-2.98)	0.35(0.05)	N	N	N	N
Postrenal failure	1.98(0.28,14.11)	1.98(0.28,14.11)	0.99(-1.64)	1.98(0.28)	N	N	N	N
Diabetic nephropathy	0.40(0.06,2.84)	0.40(0.06,2.84)	-1.32(-2.85)	0.40(0.06)	N	N	N	N
Ureteral disorder	2.17(0.30,15.43)	2.17(0.30,15.43)	1.11(-1.59)	2.17(0.30)	N	N	N	N

Renal embolism	4.67(0.65,33.33)	4.67(0.65,33.32)	2.22(-1.33)	4.65(0.65)	N	N	N	N
Urinary fistula	7.43(1.04,53.20)	7.43(1.04,53.20)	2.88(-1.24)	7.37(1.03)	N	N	N	N
Bladder dysfunction	0.90(0.13,6.38)	0.90(0.13,6.38)	-0.16(-2.12)	0.90(0.13)	N	N	N	N
Hypermagnesuria	122.06(15.02,992.16)	122.06(15.02,992.12)	6.74(-1.27)	106.93(13.16)	N	N	N	Y
Crystal nephropathy	1.63(0.23,11.62)	1.63(0.23,11.62)	0.71(-1.73)	1.63(0.23)	N	N	N	N
Acquired aminoaciduria	21.36(2.94,155.39)	21.36(2.94,155.38)	4.38(-1.16)	20.86(2.87)	N	N	N	Y
Myeloma cast nephropathy	6.24(0.87,44.60)	6.24(0.87,44.59)	2.63(-1.27)	6.20(0.87)	N	N	N	N
Ureterolithiasis	0.51(0.07,3.59)	0.51(0.07,3.59)	-0.98(-2.62)	0.51(0.07)	N	N	N	N
Subacute kidney injury	44.97(6.02,335.95)	44.97(6.02,335.93)	5.42(-1.17)	42.77(5.73)	N	N	N	Y

Subgroup Analysis by Age and Gender

Stratified analyses elucidated distinct toxicity profiles across demographic subgroups. Gender-based segmentation indicated that while nephrotoxic signals were robust in both sexes, males exhibited a higher reporting frequency for AKI and related tubular disorders (Table 2).

Table 2 Sex-Stratified Signal Detection Across MedDRA Hierarchical Levels

	PT	ROR(95% CI)	PRR(95% CI)	IC(IC025)	EBGM(EBGM05)	ROR Signal	PRR Signal	IC Signal	EBGM Signal
Male	Acute kidney injury	4.48(4.16,4.84)	4.42(4.10,4.76)	2.13(2.02)	4.39(4.07)	Y	Y	Y	Y
Female	Acute kidney injury	5.43(4.87,6.06)	5.38(4.83,5.99)	2.42(2.24)	5.36(4.81)	Y	Y	Y	Y
Male	Renal failure	1.68(1.46,1.94)	1.68(1.46,1.94)	0.75(0.53)	1.68(1.45)	Y	Y	Y	N
Female	Renal failure	2.78(2.33,3.32)	2.77(2.32,3.31)	1.47(1.19)	2.77(2.32)	Y	Y	Y	Y
Male	Nephropathy toxic	13.64(11.25,16.54)	13.60(11.22,16.49)	3.73(3.29)	13.29(10.96)	Y	Y	Y	Y
Male	Renal impairment	1.39(1.13,1.71)	1.39(1.13,1.71)	0.47(0.17)	1.39(1.13)	Y	Y	Y	N
Female	Hydronephrosis	29.19(23.24,36.66)	29.11(23.20,36.54)	4.83(4.06)	28.44(22.65)	Y	Y	Y	Y
Male	Renal salt-wasting syndrome	340.32(252.29,459.08)	339.67(251.89,458.04)	7.71(5.33)	208.69(154.71)	Y	Y	Y	Y
Female	Renal impairment	2.30(1.79,2.95)	2.29(1.79,2.94)	1.20(0.80)	2.29(1.78)	Y	Y	Y	N

Female	Renal salt-wasting syndrome	572.95(417.74,785.83)	571.76(417.06,783.85)	8.60(5.22)	386.91(282.10)	Y	Y	Y	Y
Female	Dysuria	3.82(2.92,4.99)	3.81(2.92,4.98)	1.93(1.47)	3.80(2.91)	Y	Y	Y	Y
Male	Renal tubular necrosis	6.24(4.76,8.18)	6.23(4.75,8.16)	2.63(2.10)	6.17(4.70)	Y	Y	Y	Y
Female	Nephropathy toxic	18.75(14.18,24.80)	18.72(14.16,24.74)	4.20(3.37)	18.44(13.94)	Y	Y	Y	Y
Not Specified	Acute kidney injury	2.47(1.84,3.31)	2.45(1.83,3.28)	1.29(0.82)	2.45(1.82)	Y	Y	Y	N
Female	Renal tubular necrosis	13.23(9.76,17.93)	13.21(9.75,17.90)	3.71(2.91)	13.07(9.64)	Y	Y	Y	Y
Male	Urinary retention	1.00(0.70,1.43)	1.00(0.70,1.43)	0.00(-0.52)	1.00(0.70)	N	N	N	N
Male	Renal tubular disorder	11.18(7.74,16.15)	11.17(7.74,16.14)	3.46(2.51)	10.97(7.59)	Y	Y	Y	Y
Male	Chronic kidney disease	0.51(0.35,0.73)	0.51(0.35,0.73)	-0.98(-1.48)	0.51(0.35)	N	N	N	N
Male	Haematuria	0.81(0.56,1.17)	0.81(0.56,1.17)	-0.31(-0.83)	0.81(0.56)	N	N	N	N
Not Specified	Renal impairment	3.77(2.56,5.54)	3.75(2.55,5.50)	1.90(1.21)	3.74(2.54)	Y	Y	Y	Y
Female	Chronic kidney disease	1.04(0.70,1.53)	1.04(0.70,1.53)	0.05(-0.52)	1.04(0.70)	N	N	N	N
Female	Haematuria	2.51(1.67,3.78)	2.51(1.67,3.77)	1.32(0.65)	2.50(1.66)	Y	Y	Y	N
Not Specified	Renal failure	2.05(1.35,3.12)	2.04(1.35,3.10)	1.03(0.36)	2.04(1.34)	Y	Y	Y	N
Male	Renal infarct	18.11(11.72,27.97)	18.10(11.72,27.95)	4.13(2.70)	17.54(11.35)	Y	Y	Y	Y
Not Specified	Nephropathy toxic	10.10(6.43,15.88)	10.06(6.41,15.78)	3.32(2.14)	9.99(6.36)	Y	Y	Y	Y
Male	Tubulointerstitial nephritis	1.30(0.83,2.03)	1.30(0.83,2.03)	0.37(-0.30)	1.29(0.83)	N	N	N	N
Male	Cystitis haemorrhagic	6.23(3.91,9.91)	6.22(3.91,9.90)	2.62(1.61)	6.16(3.87)	Y	Y	Y	Y
Male	Nephropathy	2.31(1.46,3.68)	2.31(1.46,3.68)	1.21(0.45)	2.31(1.45)	Y	Y	Y	N
Male	Renal disorder	0.54(0.34,0.86)	0.54(0.34,0.86)	-0.89(-1.51)	0.54(0.34)	N	N	N	N
Female	Renal tubular disorder	21.67(13.60,34.55)	21.66(13.59,34.52)	4.41(2.69)	21.29(13.36)	Y	Y	Y	Y
Male	Dysuria	0.56(0.34,0.91)	0.56(0.34,0.91)	-0.85(-1.51)	0.56(0.34)	N	N	N	N
Female	Urinary retention	1.55(0.95,2.53)	1.55(0.95,2.53)	0.63(-0.12)	1.55(0.95)	N	N	N	N
Female	Tubulointerstitial nephritis	2.48(1.49,4.11)	2.48(1.49,4.11)	1.31(0.46)	2.47(1.49)	Y	Y	Y	N
Female	Pollakiuria	0.82(0.48,1.38)	0.82(0.48,1.38)	-0.29(-1.02)	0.82(0.48)	N	N	N	N

Male	Polyuria	2.00(1.16,3.44)	2.00(1.16,3.44)	1.00(0.12)	1.99(1.16)	Y	Y	Y	N
Female	Urogenital fistula	92.96(52.86,163.48)	92.92(52.85,163.37)	6.43(2.80)	86.28(49.06)	Y	Y	Y	Y
Male	Anuria	1.74(0.99,3.07)	1.74(0.99,3.06)	0.80(-0.09)	1.74(0.99)	N	N	N	N
Male	Hydronephrosis	2.04(1.16,3.60)	2.04(1.16,3.59)	1.03(0.11)	2.04(1.15)	Y	Y	Y	N
Female	Ureteric obstruction	23.45(13.24,41.53)	23.44(13.24,41.51)	4.52(2.29)	23.01(12.99)	Y	Y	Y	Y
Female	Incontinence	2.22(1.23,4.00)	2.22(1.23,4.00)	1.15(0.17)	2.21(1.23)	Y	Y	Y	N
Male	Pollakiuria	0.38(0.21,0.68)	0.38(0.21,0.68)	-1.41(-2.16)	0.38(0.21)	N	N	N	N
Male	Proteinuria	0.78(0.43,1.41)	0.78(0.43,1.41)	-0.35(-1.16)	0.78(0.43)	N	N	N	N
Male	Urinary incontinence	0.63(0.35,1.14)	0.63(0.35,1.14)	-0.67(-1.46)	0.63(0.35)	N	N	N	N
Female	Oliguria	4.22(2.27,7.85)	4.22(2.27,7.85)	2.07(0.83)	4.21(2.26)	Y	Y	Y	Y
Female	Anuria	2.82(1.46,5.42)	2.82(1.46,5.42)	1.49(0.34)	2.81(1.46)	Y	Y	Y	N
Male	Azotaemia	2.54(1.32,4.89)	2.54(1.32,4.88)	1.34(0.22)	2.53(1.31)	Y	Y	Y	N
Male	Nephrolithiasis	0.29(0.15,0.56)	0.29(0.15,0.56)	-1.78(-2.58)	0.29(0.15)	N	N	N	N
Female	Urinary incontinence	0.63(0.33,1.22)	0.63(0.33,1.22)	-0.66(-1.52)	0.63(0.33)	N	N	N	N
Female	Renal tubular dysfunction	62.48(31.96,122.14)	62.46(31.96,122.07)	5.89(2.18)	59.40(30.39)	Y	Y	Y	Y
Male	Incontinence	1.26(0.63,2.52)	1.26(0.63,2.52)	0.33(-0.67)	1.26(0.63)	N	N	N	N
Male	Renal injury	0.31(0.16,0.62)	0.31(0.16,0.63)	-1.68(-2.52)	0.31(0.16)	N	N	N	N
Not Specified	Renal salt-wasting syndrome	1114.77(439.75,2825.99)	1112.62(439.34,2817.72)	9.27(1.98)	618.57(244.01)	Y	Y	Y	Y
Female	Hydroureter	56.86(26.63,121.37)	56.84(26.63,121.32)	5.76(1.78)	54.30(25.44)	Y	Y	Y	Y
Female	Nephropathy	2.15(1.02,4.51)	2.15(1.02,4.51)	1.10(-0.11)	2.15(1.02)	Y	Y	N	N
Female	Renal infarct	13.52(6.42,28.49)	13.52(6.42,28.48)	3.74(1.37)	13.38(6.35)	Y	Y	Y	Y
Female	Ureteric stenosis	28.05(13.25,59.35)	28.04(13.25,59.32)	4.78(1.64)	27.42(12.96)	Y	Y	Y	Y
Male	Fanconi syndrome acquired	3.81(1.81,8.01)	3.81(1.81,8.01)	1.92(0.46)	3.79(1.80)	Y	Y	Y	N
Not Specified	Chronic kidney disease	0.46(0.22,0.96)	0.46(0.22,0.96)	-1.12(-2.04)	0.46(0.22)	N	N	N	N
Female	Proteinuria	0.99(0.44,2	0.99(0.44,2	-0.02(-	0.99(0	N	N	N	N

		.20)	.20)	1.11)	.44)				
Female	Renal tubular acidosis	7.74(3.47,17.27)	7.73(3.47,17.26)	2.94(0.88)	7.69(3.45)	Y	Y	Y	Y
Male	Renal tubular dysfunction	15.84(7.03,35.68)	15.84(7.03,35.67)	3.95(1.22)	15.42(6.85)	Y	Y	Y	Y
Female	Fanconi syndrome acquired	13.49(6.03,30.17)	13.49(6.03,30.16)	3.74(1.17)	13.35(5.97)	Y	Y	Y	Y
Male	Urinary tract obstruction	2.04(0.92,4.55)	2.04(0.92,4.55)	1.03(-0.27)	2.04(0.91)	N	N	N	N
Female	Urinary tract obstruction	8.62(3.86,19.25)	8.62(3.86,19.24)	3.10(0.95)	8.56(3.84)	Y	Y	Y	Y
Female	Azotaemia	3.97(1.65,9.56)	3.97(1.65,9.56)	1.99(0.23)	3.96(1.65)	Y	Y	Y	N
Male	Chromaturia	0.29(0.12,0.71)	0.29(0.12,0.71)	-1.76(-2.76)	0.29(0.12)	N	N	N	N
Male	Oliguria	1.07(0.45,2.58)	1.07(0.45,2.58)	0.10(-1.10)	1.07(0.45)	N	N	N	N
Female	Urogenital disorder	99.49(39.95,247.76)	99.47(39.95,247.68)	6.52(1.28)	91.90(36.90)	Y	Y	Y	Y
Male	Urogenital haemorrhage	14.18(5.83,34.45)	14.17(5.83,34.45)	3.79(0.94)	13.84(5.69)	Y	Y	Y	Y
Female	Renal tubular injury	15.39(6.37,37.18)	15.38(6.37,37.16)	3.93(0.99)	15.20(6.29)	Y	Y	Y	Y
Male	Renal tubular injury	5.47(2.27,13.21)	5.47(2.27,13.21)	2.44(0.46)	5.43(2.25)	Y	Y	Y	Y
Male	Bladder dilatation	3.61(1.35,9.65)	3.61(1.35,9.65)	1.84(-0.05)	3.59(1.34)	Y	Y	N	N
Not Specified	Hydronephrosis	8.49(3.17,22.69)	8.48(3.17,22.65)	3.08(0.47)	8.43(3.15)	Y	Y	Y	Y
Male	Nephrogenic diabetes insipidus	4.04(1.51,10.81)	4.04(1.51,10.81)	2.01(0.03)	4.02(1.50)	Y	Y	Y	N
Male	Renal cyst	0.67(0.25,1.78)	0.67(0.25,1.78)	-0.58(-1.77)	0.67(0.25)	N	N	N	N
Not Specified	Renal tubular disorder	19.27(7.18,51.71)	19.25(7.18,51.61)	4.25(0.74)	19.00(7.08)	Y	Y	Y	Y
Female	Urinary bladder rupture	37.02(13.68,100.14)	37.01(13.68,100.11)	5.17(0.85)	35.93(13.28)	Y	Y	Y	Y
Male	End stage renal disease	0.33(0.12,0.87)	0.33(0.12,0.87)	-1.62(-2.70)	0.33(0.12)	N	N	N	N
Female	Cystitis haemorrhagic	2.48(0.80,7.69)	2.48(0.80,7.69)	1.31(-0.59)	2.47(0.80)	N	N	N	N
Male	Glomerulonephritis rapidly progressive	3.76(1.21,11.70)	3.76(1.21,11.70)	1.90(-0.30)	3.74(1.20)	Y	Y	N	N
Not Specified	Haematuria	1.40(0.45,4.36)	1.40(0.45,4.35)	0.49(-1.09)	1.40(0.45)	N	N	N	N
Male	Hypercalciuria	8.98(2.87,28.10)	8.98(2.87,28.10)	3.15(0.12)	8.85(2.83)	Y	Y	Y	Y
Male	Nephrosclerosis	3.22(1.03,1	3.22(1.03,1	1.68(-	3.21(1	Y	Y	N	N

		0.02)	0.01)	0.40)	.03)				
Male	Nocturia	0.29(0.09,0.89)	0.29(0.09,0.89)	-1.80(-2.96)	0.29(0.09)	N	N	N	N
Female	Renal colic	3.69(1.19,11.46)	3.69(1.19,11.45)	1.88(-0.31)	3.68(1.18)	Y	Y	N	N
Male	Ureteric dilatation	12.72(4.05,39.98)	12.72(4.05,39.98)	3.64(0.22)	12.45(3.96)	Y	Y	Y	Y
Male	Ureteric stenosis	4.53(1.45,14.10)	4.53(1.45,14.10)	2.17(-0.19)	4.50(1.44)	Y	Y	N	N
Female	Urinary bladder haemorrhage	5.07(1.63,15.75)	5.07(1.63,15.74)	2.34(-0.12)	5.05(1.62)	Y	Y	N	N
Female	Urine abnormality	1.45(0.47,4.51)	1.45(0.47,4.51)	0.54(-1.06)	1.45(0.47)	N	N	N	N
Male	Urine flow decreased	1.01(0.32,3.13)	1.01(0.32,3.13)	0.01(-1.44)	1.01(0.32)	N	N	N	N
Female	Bladder spasm	3.24(1.04,10.07)	3.24(1.04,10.07)	1.69(-0.39)	3.24(1.04)	Y	Y	N	N
Female	Bladder perforation	19.90(6.36,62.28)	19.89(6.36,62.26)	4.29(0.33)	19.58(6.26)	Y	Y	Y	Y
Female	Bladder outlet obstruction	170.54(50.87,571.80)	170.53(50.87,571.67)	7.22(0.42)	149.34(44.54)	Y	Y	Y	Y
Female	Urinary tract toxicity	1790.72(299.20,10717.5)	1790.52(299.19,10715.5)	9.49(0.13)	716.81(119.77)	Y	Y	Y	Y
Female	Albuminuria	13.12(3.26,52.86)	13.12(3.26,52.85)	3.70(-0.30)	12.99(3.22)	N	N	N	Y
Not Specified	Azotaemia	9.09(2.26,36.54)	9.09(2.26,36.50)	3.18(-0.38)	9.04(2.25)	N	N	N	Y
Female	Bladder dilatation	4.96(1.24,19.91)	4.96(1.24,19.90)	2.31(-0.58)	4.95(1.23)	N	N	N	N
Male	Bladder sphincter atony	21.99(5.35,90.41)	21.98(5.35,90.40)	4.40(-0.26)	21.16(5.15)	N	N	N	Y
Female	Chromaturia	0.21(0.05,0.86)	0.21(0.05,0.86)	-2.22(-3.45)	0.21(0.05)	N	N	N	N
Female	Haemoglobinuria	6.47(1.61,25.97)	6.47(1.61,25.97)	2.69(-0.48)	6.44(1.60)	N	N	N	N
Female	Micturition urgency	0.40(0.10,1.59)	0.40(0.10,1.60)	-1.33(-2.67)	0.40(0.10)	N	N	N	N
Female	Nephrolithiasis	0.11(0.03,0.42)	0.11(0.03,0.42)	-3.24(-4.40)	0.11(0.03)	N	N	N	N
Not Specified	Renal artery thrombosis	92.76(22.16,388.29)	92.72(22.16,387.85)	6.44(-0.19)	86.99(20.78)	N	N	N	Y
Male	Renal artery thrombosis	7.69(1.91,31.07)	7.69(1.91,31.07)	2.93(-0.44)	7.60(1.88)	N	N	N	N
Male	Renal colic	1.06(0.27,4.26)	1.06(0.27,4.26)	0.09(-1.61)	1.06(0.27)	N	N	N	N
Female	Renal disorder	0.11(0.03,0.44)	0.11(0.03,0.44)	-3.20(-4.35)	0.11(0.03)	N	N	N	N
Male	Renal hypertension	7.33(1.82,29.58)	7.33(1.82,29.58)	2.86(-0.45)	7.24(1.79)	N	N	N	N

Female	Renal pain	0.43(0.11,1.72)	0.43(0.11,1.72)	-1.22(-2.58)	0.43(0.11)	N	N	N	N
Not Specified	Renal tubular necrosis	3.59(0.90,14.41)	3.59(0.90,14.39)	1.84(-0.72)	3.59(0.90)	N	N	N	N
Male	Strangury	12.38(3.05,50.31)	12.38(3.05,50.30)	3.60(-0.33)	12.13(2.98)	N	N	N	Y
Female	Urate nephropathy	56.85(13.76,234.85)	56.84(13.76,234.81)	5.76(-0.19)	54.30(13.14)	N	N	N	Y
Female	Ureteric dilatation	20.76(5.13,84.02)	20.76(5.13,84.01)	4.35(-0.24)	20.42(5.05)	N	N	N	Y
Male	Ureteric obstruction	1.90(0.47,7.63)	1.90(0.47,7.63)	0.93(-1.12)	1.90(0.47)	N	N	N	N
Male	Urinary hesitation	0.84(0.21,3.35)	0.84(0.21,3.35)	-0.26(-1.84)	0.84(0.21)	N	N	N	N
Not Specified	Urinary retention	1.00(0.25,4.00)	1.00(0.25,4.00)	0.00(-1.67)	1.00(0.25)	N	N	N	N
Female	Vesical fistula	21.90(5.41,88.70)	21.90(5.41,88.69)	4.43(-0.23)	21.53(5.32)	N	N	N	Y
Male	Bladder spasm	2.24(0.56,9.00)	2.24(0.56,9.00)	1.16(-1.01)	2.24(0.56)	N	N	N	N
Female	Bladder necrosis	82.33(19.64,345.05)	82.32(19.64,344.99)	6.27(-0.20)	77.08(18.39)	N	N	N	Y
Male	Renal pelvis fistula	269.33(49.33,1470.50)	269.31(49.33,1470.33)	7.49(-0.42)	179.87(32.94)	N	N	N	Y
Female	Urine odour abnormal	0.63(0.16,2.51)	0.63(0.16,2.51)	-0.67(-2.15)	0.63(0.16)	N	N	N	N
Male	Urine odour abnormal	0.79(0.20,3.15)	0.79(0.20,3.15)	-0.35(-1.91)	0.79(0.20)	N	N	N	N
Female	Renal injury	0.22(0.06,0.88)	0.22(0.06,0.88)	-2.18(-3.41)	0.22(0.06)	N	N	N	N
Not Specified	Renal injury	0.64(0.16,2.56)	0.64(0.16,2.56)	-0.64(-2.12)	0.64(0.16)	N	N	N	N
Female	Pyelocaliectasis	7.17(1.79,28.79)	7.17(1.79,28.78)	2.83(-0.45)	7.13(1.78)	N	N	N	N
Male	Pyelocaliectasis	2.51(0.63,10.07)	2.51(0.63,10.07)	1.32(-0.94)	2.50(0.62)	N	N	N	N
Male	Urethral stenosis	2.44(0.61,9.78)	2.44(0.61,9.78)	1.28(-0.95)	2.43(0.61)	N	N	N	N
Male	Hypocitraturia	63.37(14.64,274.30)	63.37(14.64,274.27)	5.83(-0.25)	56.80(13.12)	N	N	N	Y
Male	Prerenal failure	1.69(0.42,6.76)	1.69(0.42,6.76)	0.75(-1.22)	1.68(0.42)	N	N	N	N
Female	Genitourinary symptom	45.05(10.98,184.86)	45.04(10.98,184.83)	5.44(-0.19)	43.44(10.59)	N	N	N	Y
Not Specified	End stage renal disease	0.53(0.13,2.14)	0.53(0.13,2.14)	-0.90(-2.33)	0.53(0.13)	N	N	N	N
Not Specified	Renal tubular injury	37.61(9.23,153.24)	37.59(9.23,153.07)	5.19(-0.19)	36.63(8.99)	N	N	N	Y
Female	Subcapsular renal haematoma	17.30(4.28,69.88)	17.30(4.28,69.87)	4.09(-0.26)	17.07(4.23)	N	N	N	Y

Not Specified	Anuria	1.98(0.28,14.05)	1.98(0.28,14.04)	0.98(-1.64)	1.97(0.28)	N	N	N	N
Female	Bladder obstruction	10.95(1.53,78.45)	10.95(1.53,78.44)	3.44(-1.19)	10.86(1.52)	N	N	N	N
Male	Bladder obstruction	1.62(0.23,11.52)	1.62(0.23,11.52)	0.69(-1.74)	1.62(0.23)	N	N	N	N
Male	Bladder pain	0.77(0.11,5.51)	0.77(0.11,5.51)	-0.37(-2.24)	0.78(0.11)	N	N	N	N
Female	Bladder pain	0.60(0.08,4.23)	0.60(0.08,4.23)	-0.75(-2.46)	0.60(0.08)	N	N	N	N
Female	Bladder sphincter atony	13.88(1.93,99.67)	13.88(1.93,99.66)	3.78(-1.17)	13.73(1.91)	N	N	N	N
Female	Calculus bladder	2.90(0.41,20.67)	2.90(0.41,20.67)	1.54(-1.47)	2.90(0.41)	N	N	N	N
Male	Chyluria	269.32(24.42,2970.29)	269.31(24.42,2970.08)	7.49(-1.51)	179.87(16.31)	N	N	N	Y
Female	Cystitis ulcerative	51.90(7.01,384.34)	51.90(7.01,384.30)	5.64(-1.15)	49.78(6.72)	N	N	N	Y
Not Specified	Dysuria	0.56(0.08,4.00)	0.56(0.08,4.00)	-0.83(-2.51)	0.56(0.08)	N	N	N	N
Male	Glomerulonephritis	0.52(0.07,3.66)	0.52(0.07,3.66)	-0.95(-2.60)	0.52(0.07)	N	N	N	N
Female	Glomerulonephritis	1.19(0.17,8.42)	1.19(0.17,8.42)	0.25(-1.93)	1.19(0.17)	N	N	N	N
Male	Glomerulonephritis acute	5.28(0.74,37.85)	5.28(0.74,37.85)	2.39(-1.31)	5.24(0.73)	N	N	N	N
Female	Glomerulonephritis minimal lesion	6.00(0.84,42.80)	6.00(0.84,42.79)	2.58(-1.27)	5.97(0.84)	N	N	N	N
Male	Glomerulonephritis proliferative	2.81(0.39,20.02)	2.81(0.39,20.02)	1.48(-1.49)	2.80(0.39)	N	N	N	N
Male	Glycosuria	0.88(0.12,6.25)	0.88(0.12,6.25)	-0.19(-2.14)	0.88(0.12)	N	N	N	N
Female	Glycosuria	2.16(0.30,15.38)	2.16(0.30,15.38)	1.11(-1.59)	2.16(0.30)	N	N	N	N
Male	Hypertonic bladder	0.77(0.11,5.46)	0.77(0.11,5.46)	-0.38(-2.25)	0.77(0.11)	N	N	N	N
Male	IgA nephropathy	0.64(0.09,4.54)	0.64(0.09,4.54)	-0.65(-2.40)	0.64(0.09)	N	N	N	N
Not Specified	Incontinence	2.10(0.30,14.96)	2.10(0.30,14.96)	1.07(-1.61)	2.10(0.30)	N	N	N	N
Female	Kidney fibrosis	1.73(0.24,12.28)	1.73(0.24,12.28)	0.79(-1.70)	1.73(0.24)	N	N	N	N
Male	Micturition disorder	0.35(0.05,2.52)	0.35(0.05,2.52)	-1.50(-2.98)	0.35(0.05)	N	N	N	N
Female	Nephritis	0.89(0.12,6.29)	0.89(0.12,6.29)	-0.18(-2.13)	0.89(0.12)	N	N	N	N
Not Specified	Nephrogenic diabetes insipidus	12.53(1.75,89.78)	12.53(1.75,89.72)	3.64(-1.17)	12.43(1.73)	N	N	N	N

Not Specified	Nephropathy	1.64(0.23,11.63)	1.64(0.23,11.63)	0.71(-1.73)	1.64(0.23)	N	N	N	N
Not Specified	Nephrotic syndrome	1.75(0.25,12.41)	1.75(0.25,12.40)	0.80(-1.70)	1.74(0.25)	N	N	N	N
Male	Nephrotic syndrome	0.17(0.02,1.22)	0.17(0.02,1.22)	-2.54(-3.81)	0.17(0.02)	N	N	N	N
Male	Neurogenic bladder	0.77(0.11,5.49)	0.77(0.11,5.49)	-0.37(-2.24)	0.77(0.11)	N	N	N	N
Not Specified	Oliguria	2.62(0.37,18.64)	2.62(0.37,18.62)	1.39(-1.51)	2.62(0.37)	N	N	N	N
Female	Polyuria	0.33(0.05,2.34)	0.33(0.05,2.34)	-1.60(-3.05)	0.33(0.05)	N	N	N	N
Not Specified	Proteinuria	0.57(0.08,4.05)	0.57(0.08,4.05)	-0.81(-2.50)	0.57(0.08)	N	N	N	N
Male	Renal artery stenosis	0.91(0.13,6.47)	0.91(0.13,6.47)	-0.14(-2.11)	0.91(0.13)	N	N	N	N
Female	Renal artery thrombosis	10.38(1.45,74.32)	10.38(1.45,74.32)	3.36(-1.19)	10.30(1.44)	N	N	N	N
Female	Renal atrophy	1.80(0.25,12.80)	1.80(0.25,12.80)	0.85(-1.68)	1.80(0.25)	N	N	N	N
Male	Renal atrophy	1.14(0.16,8.14)	1.14(0.16,8.14)	0.19(-1.95)	1.14(0.16)	N	N	N	N
Female	Renal cyst	0.31(0.04,2.22)	0.31(0.04,2.22)	-1.68(-3.11)	0.31(0.04)	N	N	N	N
Not Specified	Renal disorder	0.34(0.05,2.41)	0.34(0.05,2.41)	-1.56(-3.02)	0.34(0.05)	N	N	N	N
Female	Renal failure neonatal	15.11(2.10,108.61)	15.11(2.10,108.60)	3.90(-1.16)	14.93(2.08)	N	N	N	Y
Male	Renal hypertrophy	7.92(1.10,57.05)	7.92(1.10,57.04)	2.97(-1.25)	7.82(1.09)	N	N	N	N
Not Specified	Renal infarct	12.65(1.77,90.60)	12.64(1.77,90.54)	3.65(-1.17)	12.54(1.75)	N	N	N	N
Male	Renal tubular acidosis	0.64(0.09,4.55)	0.64(0.09,4.55)	-0.64(-2.40)	0.64(0.09)	N	N	N	N
Female	Renal vein thrombosis	3.98(0.56,28.34)	3.98(0.56,28.34)	1.99(-1.37)	3.97(0.56)	N	N	N	N
Male	Urate nephropathy	11.97(1.65,86.84)	11.97(1.65,86.83)	3.55(-1.20)	11.73(1.62)	N	N	N	N
Female	Ureteric fistula	59.69(8.01,444.76)	59.68(8.01,444.71)	5.83(-1.16)	56.89(7.63)	N	N	N	Y
Not Specified	Ureteric stenosis	15.81(2.20,113.50)	15.80(2.20,113.43)	3.97(-1.15)	15.64(2.18)	N	N	N	Y
Female	Urethral discharge	36.17(4.95,264.50)	36.17(4.95,264.47)	5.13(-1.14)	35.14(4.81)	N	N	N	Y
Female	Urethral disorder	5.31(0.74,37.83)	5.31(0.74,37.83)	2.40(-1.30)	5.29(0.74)	N	N	N	N
Female	Urethral pain	4.34(0.61,30.93)	4.34(0.61,30.92)	2.11(-1.35)	4.33(0.61)	N	N	N	N
Male	Urogenital disorder	7.59(1.05,54.61)	7.59(1.05,54.60)	2.91(-1.25)	7.49(1.04)	N	N	N	N
Not	Urogenital	28.39(3.92,	28.38(3.92,	4.80(-	27.84(	N	N	N	Y

Specified	disorder	205.65)	205.50)	1.13)	3.84)				
Not Specified	Urogenital fistula	51.52(7.00, 379.26)	51.51(7.00, 378.99)	5.64(-1.14)	49.71(6.75)	N	N	N	Y
Male	Kidney enlargement	1.24(0.17,8.81)	1.24(0.17,8.81)	0.31(-1.90)	1.24(0.17)	N	N	N	N
Female	Ureteric rupture	108.52(14.01,840.61)	108.52(14.01,840.52)	6.64(-1.21)	99.56(12.85)	N	N	N	Y
Female	Leukocyturia	2.68(0.38,19.09)	2.68(0.38,19.08)	1.42(-1.50)	2.68(0.38)	N	N	N	N
Male	Hypocalciuria	29.92(3.99, 224.17)	29.92(3.99, 224.15)	4.83(-1.19)	28.40(3.79)	N	N	N	Y
Female	Hypocalciuria	45.91(6.23, 338.36)	45.91(6.23, 338.32)	5.47(-1.15)	44.25(6.00)	N	N	N	Y
Female	Costovertebral angle tenderness	11.82(1.65, 84.73)	11.82(1.65, 84.72)	3.55(-1.18)	11.71(1.63)	N	N	N	N
Male	Glomerulonephropathy	4.21(0.59,30.10)	4.21(0.59,30.10)	2.06(-1.37)	4.18(0.58)	N	N	N	N
Male	Hypertensive nephropathy	1.20(0.17,8.57)	1.20(0.17,8.57)	0.27(-1.92)	1.20(0.17)	N	N	N	N
Male	Haemorrhage urinary tract	0.38(0.05,2.67)	0.38(0.05,2.67)	-1.41(-2.91)	0.38(0.05)	N	N	N	N
Female	Postrenal failure	9.55(1.33,68.33)	9.55(1.33,68.32)	3.25(-1.20)	9.48(1.33)	N	N	N	N
Male	Diabetic nephropathy	0.52(0.07,3.69)	0.52(0.07,3.69)	-0.94(-2.59)	0.52(0.07)	N	N	N	N
Female	Ureteral disorder	5.88(0.82,41.95)	5.88(0.82,41.95)	2.55(-1.28)	5.86(0.82)	N	N	N	N
Male	Renal embolism	6.19(0.86,44.45)	6.19(0.86,44.45)	2.62(-1.28)	6.13(0.85)	N	N	N	N
Not Specified	Bladder perforation	57.96(7.84, 428.57)	57.95(7.84, 428.27)	5.80(-1.14)	55.67(7.53)	N	N	N	Y
Not Specified	Urinary fistula	86.94(11.53,655.78)	86.92(11.53,655.32)	6.36(-1.17)	81.87(10.85)	N	N	N	Y
Not Specified	Urethral stenosis	28.98(4.00, 210.02)	28.97(4.00, 209.87)	4.83(-1.13)	28.40(3.92)	N	N	N	Y
Male	Bladder dysfunction	1.63(0.23,11.59)	1.63(0.23,11.59)	0.70(-1.74)	1.63(0.23)	N	N	N	N
Female	Hypermagnesuria	397.91(41.39,3825.58)	397.89(41.39,3825.20)	8.22(-1.42)	298.67(31.07)	N	N	N	Y
Male	Bladder outlet obstruction	4.60(0.64,32.96)	4.60(0.64,32.96)	2.19(-1.34)	4.57(0.64)	N	N	N	N
Not Specified	Bladder outlet obstruction	81.83(10.89,615.04)	81.81(10.89,614.61)	6.27(-1.17)	77.32(10.29)	N	N	N	Y
Male	Crystal nephropathy	2.58(0.36,18.38)	2.58(0.36,18.38)	1.36(-1.53)	2.57(0.36)	N	N	N	N
Male	Urinary bladder toxicity	67.33(8.42, 538.35)	67.33(8.42, 538.31)	5.91(-1.26)	59.96(7.50)	N	N	N	Y
Not Specified	Urinary bladder toxicity	154.57(19.58,1220.33)	154.53(19.58,1219.49)	7.12(-1.23)	139.18(17.63)	N	N	N	Y

Male	Acquired aminoaciduria	29.92(3.99,224.17)	29.92(3.99,224.15)	4.83(-1.19)	28.40(3.79)	N	N	N	Y
Male	Myeloma cast nephropathy	7.09(0.99,50.97)	7.09(0.99,50.96)	2.81(-1.26)	7.01(0.97)	N	N	N	N
Female	Ureterolithiasis	1.59(0.22,11.28)	1.59(0.22,11.28)	0.67(-1.75)	1.59(0.22)	N	N	N	N
Female	Subacute kidney injury	198.95(23.95,1652.67)	198.95(23.95,1652.50)	7.42(-1.29)	170.67(20.55)	N	N	N	Y
Male	Renal-limited thrombotic microangiopathy	6.82(0.95,49.01)	6.82(0.95,49.00)	2.75(-1.27)	6.75(0.94)	N	N	N	N
Female	Renal-limited thrombotic microangiopathy	18.09(2.51,130.32)	18.09(2.51,130.31)	4.16(-1.15)	17.83(2.47)	N	N	N	Y

Conversely, age-stratified analysis revealed a heterogeneous landscape of vulnerability. The geriatric cohort (≥65 years) demonstrated a markedly elevated risk for Renal Salt-Wasting Syndrome (ROR= 737.90, 95% CI: 345.54–1575.64) and showed unique susceptibility to obstructive complications, including Hydronephrosis (ROR= 6.90, 95% CI: 5.17–9.21), alongside chronic kidney disease and renal failure (Table 3).

Table 3: Age-Stratified Signal Detection Across MedDRA Hierarchical Levels

	PT	ROR(95% CI)	PRR(95% CI)	IC(IC025)	EBGM(EBGM05)	ROR Signal	PRR Signal	IC Signal	EBGM Signal
45-64	Acute kidney injury	4.71(4.25,5.22)	4.65(4.20,5.15)	2.21(2.04)	4.62(4.17)	Y	Y	Y	Y
≥65	Acute kidney injury	3.57(3.19,3.99)	3.52(3.15,3.93)	1.81(1.63)	3.51(3.14)	Y	Y	Y	Y
NS	Acute kidney injury	6.89(6.03,7.87)	6.81(5.97,7.76)	2.76(2.53)	6.78(5.93)	Y	Y	Y	Y
18-44	Acute kidney injury	6.83(5.72,8.16)	6.75(5.66,8.04)	2.75(2.42)	6.71(5.61)	Y	Y	Y	Y
45-64	Renal failure	2.11(1.76,2.54)	2.11(1.76,2.53)	1.07(0.79)	2.11(1.75)	Y	Y	Y	N
≥65	Renal failure	1.95(1.58,2.39)	1.94(1.58,2.38)	0.96(0.64)	1.94(1.58)	Y	Y	Y	N
NS	Renal failure	2.10(1.67,2.64)	2.09(1.66,2.63)	1.06(0.71)	2.09(1.66)	Y	Y	Y	N
NS	Nephropathy toxic	22.79(17.79,29.19)	22.70(17.74,29.06)	4.48(3.71)	22.32(17.42)	Y	Y	Y	Y
≥65	Renal impairment	1.55(1.18,2.02)	1.54(1.18,2.02)	0.63(0.22)	1.54(1.18)	Y	Y	Y	N
45-64	Renal salt-wasting syndrome	613.46(415.22,906.33)	612.09(414.48,903.92)	8.25(4.98)	303.52(205.44)	Y	Y	Y	Y
45-64	Renal impairment	1.68(1.26,2.22)	1.67(1.26,2.22)	0.74(0.31)	1.67(1.26)	Y	Y	Y	N
45-64	Nephropathy	10.78(8.0	10.76(7.99,1	3.40(2.	10.59(7	Y	Y	Y	Y

	toxic	0,14.53)	4.50)	69)	.86)				
NS	Renal impairment	2.18(1.62, 2.94)	2.18(1.61,2. 93)	1.12(0. 65)	2.17(1. 61)	Y	Y	Y	N
≥65	Renal salt-wasting syndrome	737.90(48 5.52,1121 .48)	735.97(484. 53,1117.91)	8.59(4. 74)	385.19(253.45)	Y	Y	Y	Y
45-64	Renal tubular necrosis	8.08(5.94, 11.00)	8.07(5.93,10 .98)	3.00(2. 32)	7.97(5. 86)	Y	Y	Y	Y
<18	Acute kidney injury	4.59(3.34, 6.30)	4.55(3.33,6. 22)	2.18(1. 60)	4.53(3. 30)	Y	Y	Y	Y
18-44	Renal failure	3.09(2.23, 4.27)	3.08(2.23,4. 25)	1.62(1. 07)	3.07(2. 22)	Y	Y	Y	Y
≥65	Renal tubular necrosis	9.34(6.59, 13.24)	9.32(6.58,13 .20)	3.21(2. 38)	9.23(6. 51)	Y	Y	Y	Y
NS	Hydronephrosis	19.55(13. 54,28.22)	19.52(13.53, 28.16)	4.27(3. 05)	19.23(1 3.32)	Y	Y	Y	Y
<18	Nephropathy toxic	23.30(16. 06,33.80)	23.11(15.98, 33.43)	4.48(3. 17)	22.33(1 5.39)	Y	Y	Y	Y
18-44	Hydronephrosis	27.18(18. 53,39.86)	27.10(18.50, 39.70)	4.72(3. 24)	26.38(1 7.98)	Y	Y	Y	Y
18-44	Renal impairment	3.96(2.70, 5.83)	3.96(2.69,5. 81)	1.98(1. 27)	3.94(2. 68)	Y	Y	Y	Y
≥65	Dysuria	1.98(1.34, 2.93)	1.98(1.34,2. 93)	0.98(0. 36)	1.97(1. 33)	Y	Y	Y	N
18-44	Renal salt-wasting syndrome	612.25(37 0.39,1012 .04)	610.56(369. 68,1008.39)	8.54(3. 94)	372.45(225.32)	Y	Y	Y	Y
≥65	Nephropathy toxic	9.83(6.57, 14.71)	9.82(6.57,14 .68)	3.28(2. 27)	9.71(6. 49)	Y	Y	Y	Y
NS	Urinary retention	3.03(2.01, 4.56)	3.03(2.01,4. 56)	1.60(0. 89)	3.02(2. 01)	Y	Y	Y	Y
45-64	Hydronephrosis	6.61(4.25, 10.27)	6.60(4.25,10 .26)	2.71(1. 74)	6.54(4. 21)	Y	Y	Y	Y
45-64	Renal infarct	27.61(17. 64,43.24)	27.59(17.63, 43.19)	4.72(2. 93)	26.42(1 6.87)	Y	Y	Y	Y
45-64	Chronic kidney disease	0.56(0.36, 0.87)	0.56(0.36,0. 87)	-0.83(- 1.43)	0.56(0. 36)	N	N	N	N
45-64	Dysuria	1.35(0.86, 2.11)	1.35(0.86,2. 11)	0.43(- 0.24)	1.35(0. 86)	N	N	N	N
<18	Renal tubular disorder	32.54(20. 24,52.32)	32.38(20.19, 51.94)	4.95(2. 90)	30.85(1 9.19)	Y	Y	Y	Y
≥65	Haematuria	0.98(0.61, 1.58)	0.98(0.61,1. 58)	-0.03(- 0.71)	0.98(0. 61)	N	N	N	N
45-64	Haematuria	1.40(0.85, 2.28)	1.40(0.85,2. 28)	0.48(- 0.25)	1.39(0. 85)	N	N	N	N
≥65	Hydronephrosis	6.90(4.21, 11.28)	6.89(4.21,11 .27)	2.77(1. 64)	6.84(4. 18)	Y	Y	Y	Y
<18	Renal failure	3.89(2.38, 6.36)	3.87(2.37,6. 33)	1.95(1. 02)	3.86(2. 36)	Y	Y	Y	Y
NS	Dysuria	1.61(0.95, 2.72)	1.61(0.95,2. 71)	0.68(- 0.12)	1.61(0. 95)	N	N	N	N

18-44	Nephropathy toxic	10.35(6.11,17.53)	10.34(6.11,17.50)	3.36(1.91)	10.24(6.04)	Y	Y	Y	Y
<18	Chronic kidney disease	20.20(11.85,34.43)	20.13(11.83,34.23)	4.29(2.37)	19.53(11.46)	Y	Y	Y	Y
18-44	Dysuria	2.70(1.57,4.66)	2.70(1.57,4.66)	1.43(0.49)	2.70(1.56)	Y	Y	Y	N
45-64	Renal tubular disorder	10.26(5.93,17.75)	10.25(5.93,17.73)	3.34(1.83)	10.10(5.83)	Y	Y	Y	Y
NS	Chronic kidney disease	0.42(0.24,0.73)	0.42(0.25,0.73)	-1.24(-1.95)	0.42(0.25)	N	N	N	N
NS	Haematuria	1.97(1.12,3.47)	1.97(1.12,3.47)	0.98(0.07)	1.97(1.12)	Y	Y	Y	N
45-64	Tubulointerstitial nephritis	1.45(0.82,2.56)	1.45(0.83,2.56)	0.54(-0.31)	1.45(0.82)	N	N	N	N
NS	Renal tubular necrosis	9.57(5.29,17.32)	9.56(5.29,17.31)	3.25(1.64)	9.50(5.25)	Y	Y	Y	Y
≥65	Urinary retention	0.81(0.45,1.46)	0.81(0.45,1.46)	-0.31(-1.12)	0.81(0.45)	N	N	N	N
≥65	Chronic kidney disease	0.61(0.34,1.10)	0.61(0.34,1.10)	-0.71(-1.50)	0.61(0.34)	N	N	N	N
45-64	Incontinence	2.72(1.46,5.06)	2.72(1.46,5.06)	1.44(0.36)	2.71(1.46)	Y	Y	Y	N
≥65	Nephropathy	4.14(2.22,7.71)	4.14(2.22,7.70)	2.04(0.81)	4.12(2.21)	Y	Y	Y	Y
<18	Renal impairment	3.45(1.85,6.42)	3.44(1.85,6.40)	1.78(0.61)	3.43(1.84)	Y	Y	Y	N
18-44	Cystitis haemorrhagic	11.06(5.73,21.34)	11.05(5.73,21.30)	3.45(1.54)	10.93(5.66)	Y	Y	Y	Y
18-44	Renal tubular necrosis	5.91(3.07,11.38)	5.90(3.07,11.37)	2.55(1.06)	5.87(3.05)	Y	Y	Y	Y
45-64	Urinary retention	0.88(0.46,1.69)	0.88(0.46,1.69)	-0.19(-1.08)	0.88(0.46)	N	N	N	N
18-44	Tubulointerstitial nephritis	3.54(1.84,6.81)	3.54(1.84,6.81)	1.82(0.58)	3.53(1.83)	Y	Y	Y	N
NS	Renal salt-wasting syndrome	431.25(202.05,920.45)	431.02(202.00,919.67)	8.32(2.25)	320.44(150.13)	Y	Y	Y	Y
NS	Anuria	6.36(3.18,12.75)	6.36(3.18,12.74)	2.66(1.03)	6.33(3.16)	Y	Y	Y	Y
18-44	Haematuria	2.60(1.30,5.20)	2.59(1.30,5.19)	1.37(0.17)	2.59(1.29)	Y	Y	Y	N
18-44	Pollakiuria	1.84(0.92,3.68)	1.84(0.92,3.67)	0.88(-0.22)	1.84(0.92)	N	N	N	N
NS	Pollakiuria	0.68(0.34,1.36)	0.68(0.34,1.36)	-0.56(-1.47)	0.68(0.34)	N	N	N	N
≥65	Renal tubular disorder	9.89(4.93,19.87)	9.89(4.93,19.86)	3.29(1.34)	9.78(4.87)	Y	Y	Y	Y
45-64	Urinary incontinence	0.70(0.35,1.40)	0.70(0.35,1.40)	-0.52(-1.43)	0.70(0.35)	N	N	N	N
≥65	Urinary tract obstruction	6.86(3.42,13.75)	6.85(3.42,13.74)	2.77(1.08)	6.80(3.39)	Y	Y	Y	Y

<18	Renal salt-wasting syndrome	63.91(30.86,132.34)	63.76(30.84,131.84)	5.86(1.97)	57.99(28.00)	Y	Y	Y	Y
<18	Cystitis haemorrhagic	6.74(3.20,14.21)	6.73(3.20,14.16)	2.74(0.94)	6.67(3.16)	Y	Y	Y	Y
18-44	Nephropathy	7.24(3.44,15.23)	7.23(3.44,15.21)	2.84(0.99)	7.18(3.41)	Y	Y	Y	Y
≥65	Pollakiuria	0.51(0.24,1.08)	0.51(0.25,1.08)	-0.96(-1.89)	0.51(0.25)	N	N	N	N
≥65	Renal disorder	0.45(0.22,0.95)	0.45(0.22,0.95)	-1.15(-2.06)	0.45(0.22)	N	N	N	N
≥65	Urinary incontinence	0.69(0.33,1.44)	0.69(0.33,1.44)	-0.54(-1.51)	0.69(0.33)	N	N	N	N
18-44	Renal tubular dysfunction	111.21(50.82,243.35)	111.12(50.81,243.03)	6.64(1.82)	99.62(45.52)	Y	Y	Y	Y
≥65	Anuria	1.62(0.73,3.60)	1.62(0.73,3.60)	0.69(-0.52)	1.62(0.72)	N	N	N	N
45-64	Anuria	1.75(0.79,3.91)	1.75(0.79,3.91)	0.81(-0.43)	1.75(0.79)	N	N	N	N
45-64	Azotaemia	3.71(1.66,8.28)	3.71(1.66,8.27)	1.88(0.32)	3.69(1.65)	Y	Y	Y	N
45-64	Renal disorder	0.41(0.18,0.91)	0.41(0.18,0.91)	-1.29(-2.26)	0.41(0.18)	N	N	N	N
NS	Renal tubular disorder	14.80(6.62,33.10)	14.79(6.62,33.08)	3.87(1.21)	14.63(6.54)	Y	Y	Y	Y
18-44	Renal tubular disorder	13.91(6.21,31.16)	13.90(6.21,31.12)	3.78(1.18)	13.72(6.13)	Y	Y	Y	Y
45-64	Ureteric obstruction	9.81(4.38,21.99)	9.81(4.38,21.98)	3.27(1.01)	9.67(4.32)	Y	Y	Y	Y
NS	Urogenital disorder	79.51(34.83,181.51)	79.48(34.82,181.39)	6.22(1.57)	74.77(32.75)	Y	Y	Y	Y
NS	Urogenital fistula	122.52(52.96,283.44)	122.47(52.96,283.26)	6.80(1.59)	111.60(48.24)	Y	Y	Y	Y
≥65	Tubulointerstitial nephritis	0.91(0.41,2.03)	0.91(0.41,2.02)	-0.14(-1.21)	0.91(0.41)	N	N	N	N
45-64	Fanconi syndrome acquired	5.37(2.40,11.99)	5.37(2.40,11.99)	2.41(0.62)	5.33(2.38)	Y	Y	Y	Y
45-64	Renal tubular injury	12.04(5.37,27.03)	12.04(5.37,27.02)	3.56(1.11)	11.82(5.27)	Y	Y	Y	Y
NS	Azotaemia	7.59(3.15,18.30)	7.59(3.15,18.29)	2.92(0.67)	7.55(3.13)	Y	Y	Y	Y
45-64	Oliguria	2.11(0.88,5.07)	2.11(0.88,5.07)	1.07(-0.35)	2.10(0.87)	N	N	N	N
18-44	Proteinuria	1.78(0.74,4.28)	1.78(0.74,4.27)	0.83(-0.53)	1.78(0.74)	N	N	N	N
≥65	Renal infarct	13.76(5.68,33.31)	13.76(5.68,33.29)	3.76(0.94)	13.54(5.59)	Y	Y	Y	Y

18-44	Ureteric obstruction	31.77(13.03,77.45)	31.75(13.03,77.37)	4.94(1.17)	30.76(12.61)	Y	Y	Y	Y
NS	Ureteric stenosis	27.19(11.21,65.97)	27.19(11.21,65.93)	4.73(1.14)	26.63(10.98)	Y	Y	Y	Y
<18	Tubulointerstitial nephritis	3.14(1.30,7.57)	3.14(1.30,7.55)	1.65(0.02)	3.13(1.30)	Y	Y	Y	N
≥65	Urogenital haemorrhage	22.52(9.26,54.78)	22.52(9.26,54.75)	4.45(1.09)	21.93(9.02)	Y	Y	Y	Y
≥65	Renal injury	1.02(0.43,2.46)	1.02(0.43,2.46)	0.03(-1.15)	1.02(0.43)	N	N	N	N
18-44	Hydroureter	108.90(38.70,306.47)	108.85(38.70,306.21)	6.61(0.89)	97.79(34.75)	Y	Y	Y	Y
≥65	Incontinence	1.09(0.41,2.90)	1.09(0.41,2.90)	0.12(-1.20)	1.09(0.41)	N	N	N	N
NS	Incontinence	1.45(0.54,3.87)	1.45(0.54,3.87)	0.54(-0.88)	1.45(0.54)	N	N	N	N
45-64	Nephrogenic diabetes insipidus	5.62(2.10,15.05)	5.62(2.10,15.05)	2.48(0.24)	5.58(2.08)	Y	Y	Y	Y
NS	Nephrolithiasis	0.31(0.12,0.83)	0.31(0.12,0.83)	-1.68(-2.76)	0.31(0.12)	N	N	N	N
<18	Nephropathy	17.15(6.35,46.34)	17.13(6.35,46.23)	4.06(0.70)	16.71(6.18)	Y	Y	Y	Y
≥65	Oliguria	1.68(0.63,4.49)	1.68(0.63,4.49)	0.75(-0.73)	1.68(0.63)	N	N	N	N
18-44	Oliguria	4.17(1.56,11.12)	4.16(1.56,11.12)	2.05(0.05)	4.15(1.55)	Y	Y	Y	N
45-64	Polyuria	1.18(0.44,3.14)	1.18(0.44,3.14)	0.23(-1.11)	1.18(0.44)	N	N	N	N
≥65	Proteinuria	0.80(0.30,2.13)	0.80(0.30,2.13)	-0.32(-1.55)	0.80(0.30)	N	N	N	N
45-64	Proteinuria	0.57(0.21,1.51)	0.57(0.21,1.51)	-0.82(-1.98)	0.57(0.21)	N	N	N	N
≥65	Renal colic	8.96(3.34,24.00)	8.96(3.34,23.99)	3.15(0.48)	8.87(3.31)	Y	Y	Y	Y
<18	Renal disorder	4.35(1.62,11.63)	4.34(1.63,11.60)	2.11(0.08)	4.32(1.61)	Y	Y	Y	N
18-44	Renal tubular acidosis	9.16(3.42,24.53)	9.16(3.42,24.51)	3.18(0.50)	9.08(3.39)	Y	Y	Y	Y
<18	Renal tubular necrosis	5.58(2.08,14.93)	5.57(2.08,14.90)	2.47(0.24)	5.53(2.07)	Y	Y	Y	Y
18-44	Urinary bladder rupture	105.88(37.68,297.52)	105.83(37.68,297.27)	6.58(0.89)	95.35(33.93)	Y	Y	Y	Y
45-64	Renal tubular dysfunction	15.79(5.85,42.63)	15.79(5.85,42.62)	3.95(0.68)	15.41(5.71)	Y	Y	Y	Y
18-44	Fanconi syndrome acquired	15.75(5.86,42.31)	15.74(5.86,42.28)	3.95(0.69)	15.50(5.77)	Y	Y	Y	Y
45-64	Pyelocaliectasis	19.36(7.1	19.36(7.15,5	4.23(0.	18.78(6	Y	Y	Y	Y

		5,52.41)	2.39)	73)	.94)				
18-44	Renal tubular injury	14.38(5.36,38.61)	14.38(5.36,38.58)	3.83(0.66)	14.18(5.28)	Y	Y	Y	Y
≥65	Azotaemia	1.67(0.54,5.19)	1.67(0.54,5.18)	0.74(-0.93)	1.67(0.54)	N	N	N	N
18-44	Chromaturia	0.94(0.30,2.92)	0.94(0.30,2.92)	-0.09(-1.51)	0.94(0.30)	N	N	N	N
≥65	Cystitis haemorrhagic	4.23(1.36,13.15)	4.23(1.36,13.15)	2.07(-0.23)	4.21(1.35)	Y	Y	N	N
<18	Hypercalciuria	14.65(4.66,46.06)	14.64(4.66,45.98)	3.84(0.26)	14.33(4.56)	Y	Y	Y	Y
<18	Nephrolithiasis	2.70(0.87,8.38)	2.69(0.87,8.37)	1.43(-0.53)	2.69(0.86)	N	N	N	N
45-64	Nephrolithiasis	0.15(0.05,0.45)	0.15(0.05,0.45)	-2.77(-3.87)	0.15(0.05)	N	N	N	N
NS	Nephropathy	1.07(0.34,3.32)	1.07(0.34,3.32)	0.10(-1.37)	1.07(0.34)	N	N	N	N
18-44	Nephrosclerosis	21.82(6.95,68.54)	21.81(6.95,68.50)	4.42(0.34)	21.35(6.80)	Y	Y	Y	Y
NS	Oliguria	3.62(1.17,11.26)	3.62(1.17,11.25)	1.85(-0.32)	3.62(1.16)	Y	Y	N	N
≥65	Polyuria	1.20(0.39,3.73)	1.20(0.39,3.73)	0.27(-1.25)	1.20(0.39)	N	N	N	N
NS	Polyuria	1.83(0.59,5.66)	1.82(0.59,5.66)	0.87(-0.85)	1.82(0.59)	N	N	N	N
<18	Proteinuria	1.89(0.61,5.87)	1.89(0.61,5.86)	0.92(-0.82)	1.89(0.61)	N	N	N	N
NS	Renal cyst	1.44(0.46,4.47)	1.44(0.46,4.47)	0.53(-1.07)	1.44(0.46)	N	N	N	N
18-44	Renal infarct	8.90(2.86,27.76)	8.90(2.86,27.74)	3.14(0.12)	8.83(2.83)	Y	Y	Y	Y
≥65	Ureteric dilatation	62.02(19.16,200.70)	62.01(19.16,200.63)	5.85(0.42)	57.65(17.81)	Y	Y	Y	Y
≥65	Ureteric stenosis	16.02(5.11,50.23)	16.01(5.11,50.21)	3.97(0.29)	15.72(5.01)	Y	Y	Y	Y
45-64	Ureteric stenosis	10.41(3.32,32.59)	10.41(3.32,32.58)	3.36(0.17)	10.25(3.27)	Y	Y	Y	Y
18-44	Urinary retention	0.77(0.25,2.38)	0.77(0.25,2.38)	-0.38(-1.74)	0.77(0.25)	N	N	N	N
45-64	Urogenital fistula	24.01(7.57,76.13)	24.00(7.57,76.11)	4.53(0.34)	23.12(7.29)	Y	Y	Y	Y
≥65	Urogenital fistula	83.40(25.40,273.82)	83.39(25.40,273.71)	6.24(0.41)	75.66(23.05)	Y	Y	Y	Y
<18	Renal tubular dysfunction	35.67(11.14,114.20)	35.64(11.14,114.00)	5.08(0.38)	33.78(10.55)	Y	Y	Y	Y
<18	Fanconi syndrome acquired	17.83(5.66,56.21)	17.82(5.66,56.11)	4.12(0.30)	17.36(5.51)	Y	Y	Y	Y

NS	Renal injury	0.28(0.09,0.86)	0.28(0.09,0.86)	-1.84(-3.00)	0.28(0.09)	N	N	N	N
18-44	Renal injury	0.88(0.28,2.72)	0.88(0.28,2.72)	-0.19(-1.59)	0.88(0.28)	N	N	N	N
NS	Bladder perforation	31.13(9.90,97.91)	31.13(9.90,97.88)	4.93(0.40)	30.39(9.66)	Y	Y	Y	Y
18-44	Chronic kidney disease	0.46(0.15,1.42)	0.46(0.15,1.42)	-1.12(-2.36)	0.46(0.15)	N	N	N	N
≥65	Bladder outlet obstruction	40.99(12.85,130.78)	40.99(12.85,130.73)	5.29(0.40)	39.05(12.24)	Y	Y	Y	Y
NS	Urinary tract toxicity	169.83(50.82,567.46)	169.79(50.83,567.24)	7.22(0.42)	149.54(44.75)	Y	Y	Y	Y
<18	Anuria	2.18(0.54,8.75)	2.18(0.54,8.74)	1.12(-1.03)	2.18(0.54)	N	N	N	N
18-44	Azotaemia	4.89(1.22,19.61)	4.88(1.22,19.60)	2.28(-0.59)	4.86(1.21)	N	N	N	N
45-64	Bladder dilatation	5.02(1.25,20.20)	5.02(1.25,20.19)	2.32(-0.58)	4.99(1.24)	N	N	N	N
≥65	Bladder dilatation	4.83(1.20,19.38)	4.83(1.20,19.38)	2.26(-0.59)	4.80(1.20)	N	N	N	N
≥65	Bladder sphincter atony	29.86(7.28,122.47)	29.85(7.28,122.44)	4.85(-0.22)	28.82(7.03)	N	N	N	Y
≥65	Chromaturia	0.28(0.07,1.14)	0.28(0.07,1.14)	-1.81(-3.09)	0.28(0.07)	N	N	N	N
NS	Chromaturia	0.37(0.09,1.49)	0.37(0.09,1.49)	-1.42(-2.75)	0.37(0.09)	N	N	N	N
45-64	Cystitis haemorrhagic	1.61(0.40,6.46)	1.61(0.40,6.46)	0.69(-1.25)	1.61(0.40)	N	N	N	N
≥65	Glomerulonephritis rapidly progressive	3.68(0.92,14.77)	3.68(0.92,14.76)	1.88(-0.72)	3.67(0.91)	N	N	N	N
≥65	Haemoglobinuria	14.02(3.46,56.74)	14.02(3.46,56.73)	3.79(-0.30)	13.80(3.41)	N	N	N	Y
18-44	Incontinence	1.65(0.41,6.60)	1.65(0.41,6.60)	0.72(-1.23)	1.65(0.41)	N	N	N	N
45-64	Nephropathy	0.50(0.12,1.98)	0.50(0.12,1.98)	-1.01(-2.41)	0.50(0.12)	N	N	N	N
NS	Nocturia	0.53(0.13,2.14)	0.53(0.13,2.14)	-0.90(-2.33)	0.53(0.13)	N	N	N	N
45-64	Pollakiuria	0.14(0.03,0.54)	0.14(0.03,0.54)	-2.88(-4.06)	0.14(0.03)	N	N	N	N
18-44	Polyuria	1.56(0.39,6.25)	1.56(0.39,6.24)	0.64(-1.27)	1.56(0.39)	N	N	N	N
<18	Polyuria	3.01(0.75,12.07)	3.01(0.75,12.05)	1.58(-0.83)	3.00(0.75)	N	N	N	N
NS	Proteinuria	0.47(0.12,1.86)	0.47(0.12,1.86)	-1.10(-2.49)	0.47(0.12)	N	N	N	N
NS	Renal artery thrombosis	46.99(11.45,192.85	46.99(11.45,192.80)	5.50(-0.19)	45.31(11.04)	N	N	N	Y

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45-64	Renal artery thrombosis	15.59(3.83,63.46)	15.59(3.83,63.44)	3.93(-0.29)	15.22(3.74)	N	N	N	Y
NS	Renal disorder	0.13(0.03,0.52)	0.13(0.03,0.52)	-2.95(-4.12)	0.13(0.03)	N	N	N	N
18-44	Renal disorder	0.68(0.17,2.72)	0.68(0.17,2.72)	-0.55(-2.06)	0.68(0.17)	N	N	N	N
45-64	Renal hypertension	15.79(3.88,64.31)	15.79(3.88,64.29)	3.95(-0.29)	15.41(3.79)	N	N	N	Y
45-64	Renal pain	0.38(0.09,1.52)	0.38(0.09,1.52)	-1.40(-2.73)	0.38(0.09)	N	N	N	N
<18	Renal tubular acidosis	6.43(1.60,25.90)	6.43(1.60,25.86)	2.67(-0.49)	6.37(1.58)	N	N	N	N
45-64	Strangury	57.16(13.40,243.78)	57.15(13.40,243.73)	5.71(-0.24)	52.27(12.25)	N	N	N	Y
18-44	Ureteric dilatation	48.86(11.80,202.36)	48.84(11.80,202.25)	5.54(-0.20)	46.51(11.23)	N	N	N	Y
NS	Ureteric obstruction	7.16(1.78,28.73)	7.16(1.78,28.73)	2.83(-0.45)	7.12(1.77)	N	N	N	N
18-44	Urinary bladder haemorrhage	20.27(4.99,82.26)	20.27(5.00,82.22)	4.31(-0.25)	19.86(4.89)	N	N	N	Y
18-44	Urinary incontinence	0.53(0.13,2.11)	0.53(0.13,2.11)	-0.92(-2.34)	0.53(0.13)	N	N	N	N
NS	Urinary incontinence	0.29(0.07,1.16)	0.29(0.07,1.16)	-1.78(-3.06)	0.29(0.07)	N	N	N	N
<18	Urinary retention	1.29(0.32,5.15)	1.29(0.32,5.15)	0.36(-1.44)	1.29(0.32)	N	N	N	N
45-64	Urine abnormality	1.13(0.28,4.53)	1.13(0.28,4.52)	0.18(-1.55)	1.13(0.28)	N	N	N	N
NS	Urine flow decreased	3.00(0.75,12.02)	3.00(0.75,12.02)	1.58(-0.82)	3.00(0.75)	N	N	N	N
18-44	Urogenital fistula	54.44(13.09,226.38)	54.43(13.09,226.26)	5.69(-0.20)	51.54(12.39)	N	N	N	Y
NS	Vesical fistula	28.63(7.05,116.31)	28.62(7.05,116.27)	4.81(-0.21)	28.00(6.89)	N	N	N	Y
NS	Tubulointerstitial nephritis	0.50(0.12,2.00)	0.50(0.12,2.00)	-1.00(-2.40)	0.50(0.12)	N	N	N	N
18-44	Bladder spasm	8.82(2.19,35.50)	8.82(2.19,35.48)	3.13(-0.39)	8.75(2.17)	N	N	N	Y
NS	Bladder spasm	4.03(1.01,16.15)	4.03(1.01,16.15)	2.01(-0.67)	4.02(1.00)	N	N	N	N
≥65	Renal pelvis fistula	1612.34(146.19,17782.8)	1612.14(146.18,17778.9)	9.07(-0.63)	538.05(48.78)	N	N	N	Y
NS	Urinary tract obstruction	3.22(0.80,12.91)	3.22(0.80,12.90)	1.69(-0.78)	3.22(0.80)	N	N	N	N
45-64	Urinary tract obstruction	1.97(0.49,7.91)	1.97(0.49,7.91)	0.98(-1.10)	1.97(0.49)	N	N	N	N

18-44	Urethral stenosis	21.41(5.27,86.95)	21.40(5.27,86.91)	4.39(-0.24)	20.96(5.16)	N	N	N	Y
<18	Hypocitraturia	140.00(30.24,648.21)	139.92(30.24,647.38)	6.84(-0.31)	114.66(24.77)	N	N	N	Y
NS	Genitourinary symptom	40.17(9.83,164.24)	40.17(9.83,164.20)	5.28(-0.19)	38.94(9.52)	N	N	N	Y
18-44	End stage renal disease	1.14(0.29,4.58)	1.14(0.29,4.58)	0.19(-1.54)	1.14(0.29)	N	N	N	N
NS	End stage renal disease	0.28(0.07,1.14)	0.28(0.07,1.14)	-1.81(-3.09)	0.28(0.07)	N	N	N	N
NS	Subcapsular renal haematoma	42.21(10.31,172.79)	42.21(10.31,172.74)	5.35(-0.19)	40.86(9.98)	N	N	N	Y
18-44	Renal-limited thrombotic microangiopathy	68.05(16.21,285.70)	68.03(16.21,285.55)	5.99(-0.21)	63.56(15.14)	N	N	N	Y
45-64	Albuminuria	4.41(0.62,31.55)	4.41(0.62,31.55)	2.13(-1.35)	4.39(0.61)	N	N	N	N
NS	Albuminuria	10.46(1.46,74.91)	10.46(1.46,74.89)	3.38(-1.19)	10.38(1.45)	N	N	N	N
NS	Bladder dilatation	4.10(0.58,29.18)	4.10(0.58,29.17)	2.03(-1.36)	4.09(0.57)	N	N	N	N
18-44	Bladder dilatation	4.56(0.64,32.51)	4.56(0.64,32.50)	2.18(-1.34)	4.54(0.64)	N	N	N	N
≥65	Bladder obstruction	4.18(0.59,29.80)	4.18(0.59,29.80)	2.06(-1.36)	4.16(0.58)	N	N	N	N
NS	Bladder obstruction	8.14(1.14,58.15)	8.14(1.14,58.14)	3.02(-1.22)	8.09(1.13)	N	N	N	N
≥65	Bladder pain	1.08(0.15,7.69)	1.08(0.15,7.69)	0.11(-1.99)	1.08(0.15)	N	N	N	N
18-44	Bladder pain	2.22(0.31,15.80)	2.22(0.31,15.80)	1.15(-1.58)	2.22(0.31)	N	N	N	N
45-64	Bladder sphincter atony	15.00(2.06,109.14)	15.00(2.06,109.13)	3.87(-1.19)	14.66(2.02)	N	N	N	Y
45-64	Calculus bladder	1.96(0.28,13.97)	1.96(0.28,13.97)	0.97(-1.64)	1.96(0.27)	N	N	N	N
≥65	Chyluria	-	-	9.66(-1.89)	807.07(.)	N	N	N	N
NS	Cystitis ulcerative	124.52(15.94,972.84)	124.52(15.94,972.67)	6.82(-1.22)	113.29(14.50)	N	N	N	Y
≥65	Glomerulonephritis	1.42(0.20,10.08)	1.42(0.20,10.07)	0.50(-1.82)	1.42(0.20)	N	N	N	N
<18	Glomerulonephritis	5.04(0.70,36.06)	5.04(0.70,36.03)	2.32(-1.32)	5.01(0.70)	N	N	N	N
NS	Glomerulonephritis acute	31.93(4.39,232.42)	31.93(4.39,232.38)	4.96(-1.14)	31.15(4.28)	N	N	N	Y
≥65	Glomerulonephritis minimal	4.45(0.62,31.79)	4.45(0.62,31.79)	2.15(-1.35)	4.43(0.62)	N	N	N	N

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18-44	Glomerulonephritis proliferative	11.21(1.56,80.49)	11.21(1.56,80.46)	3.47(-1.19)	11.09(1.54)	N	N	N	N
45-64	Glomerulonephritis rapidly progressive	2.34(0.33,16.71)	2.34(0.33,16.70)	1.23(-1.56)	2.34(0.33)	N	N	N	N
45-64	Glycosuria	1.45(0.20,10.29)	1.45(0.20,10.29)	0.53(-1.81)	1.44(0.20)	N	N	N	N
18-44	Glycosuria	3.54(0.50,25.23)	3.54(0.50,25.23)	1.82(-1.41)	3.53(0.50)	N	N	N	N
<18	Haematuria	0.52(0.07,3.66)	0.52(0.07,3.66)	-0.96(-2.60)	0.52(0.07)	N	N	N	N
≥65	Hydroureter	8.86(1.23,63.57)	8.86(1.23,63.56)	3.13(-1.22)	8.77(1.22)	N	N	N	N
45-64	Hydroureter	6.59(0.92,47.32)	6.59(0.92,47.32)	2.71(-1.27)	6.53(0.91)	N	N	N	N
NS	Hydroureter	13.11(1.83,94.02)	13.11(1.83,94.01)	3.70(-1.17)	12.98(1.81)	N	N	N	N
45-64	Hypertonic bladder	0.99(0.14,7.01)	0.99(0.14,7.01)	-0.02(-2.06)	0.99(0.14)	N	N	N	N
18-44	IgA nephropathy	2.52(0.35,17.94)	2.52(0.35,17.93)	1.33(-1.53)	2.52(0.35)	N	N	N	N
45-64	Kidney fibrosis	1.26(0.18,8.99)	1.26(0.18,8.99)	0.34(-1.89)	1.26(0.18)	N	N	N	N
≥65	Micturition disorder	0.93(0.13,6.63)	0.93(0.13,6.63)	-0.10(-2.09)	0.93(0.13)	N	N	N	N
18-44	Micturition urgency	0.62(0.09,4.41)	0.62(0.09,4.40)	-0.69(-2.43)	0.62(0.09)	N	N	N	N
≥65	Micturition urgency	0.30(0.04,2.13)	0.30(0.04,2.13)	-1.73(-3.16)	0.30(0.04)	N	N	N	N
45-64	Nephritis	0.77(0.11,5.48)	0.77(0.11,5.48)	-0.38(-2.24)	0.77(0.11)	N	N	N	N
NS	Nephrogenic diabetes insipidus	6.45(0.90,46.04)	6.45(0.90,46.03)	2.68(-1.26)	6.42(0.90)	N	N	N	N
≥65	Nephrolithiasis	0.10(0.01,0.74)	0.10(0.01,0.74)	-3.26(-4.44)	0.10(0.01)	N	N	N	N
NS	Nephrotic syndrome	0.74(0.10,5.25)	0.74(0.10,5.25)	-0.44(-2.28)	0.74(0.10)	N	N	N	N
45-64	Nephrotic syndrome	0.40(0.06,2.84)	0.40(0.06,2.84)	-1.32(-2.85)	0.40(0.06)	N	N	N	N
NS	Neurogenic bladder	2.12(0.30,15.06)	2.12(0.30,15.06)	1.08(-1.60)	2.12(0.30)	N	N	N	N
45-64	Nocturia	0.28(0.04,2.01)	0.28(0.04,2.01)	-1.82(-3.22)	0.28(0.04)	N	N	N	N
NS	Renal artery stenosis	3.26(0.46,23.20)	3.26(0.46,23.20)	1.70(-1.43)	3.25(0.46)	N	N	N	N
18-44	Renal artery thrombosis	12.37(1.72,88.96)	12.37(1.72,88.93)	3.61(-1.18)	12.22(1.70)	N	N	N	N
NS	Renal atrophy	2.80(0.39,19.96)	2.80(0.39,19.95)	1.49(-1.49)	2.80(0.39)	N	N	N	N

≥65	Renal atrophy	2.35(0.33,16.73)	2.35(0.33,16.73)	1.23(-1.56)	2.35(0.33)	N	N	N	N
45-64	Renal colic	0.85(0.12,6.08)	0.85(0.12,6.08)	-0.23(-2.16)	0.86(0.12)	N	N	N	N
<18	Renal cyst	8.07(1.12,58.06)	8.07(1.12,58.02)	3.00(-1.24)	7.98(1.11)	N	N	N	N
≥65	Renal cyst	0.34(0.05,2.41)	0.34(0.05,2.41)	-1.56(-3.02)	0.34(0.05)	N	N	N	N
NS	Renal failure neonatal	12.45(1.74,89.28)	12.45(1.74,89.26)	3.63(-1.17)	12.34(1.72)	N	N	N	N
45-64	Renal hypertrophy	28.58(3.84,212.46)	28.58(3.84,212.44)	4.77(-1.18)	27.32(3.67)	N	N	N	Y
NS	Renal infarct	4.92(0.69,35.08)	4.92(0.69,35.07)	2.29(-1.32)	4.91(0.69)	N	N	N	N
45-64	Renal tubular acidosis	1.01(0.14,7.16)	1.01(0.14,7.16)	0.01(-2.04)	1.01(0.14)	N	N	N	N
45-64	Renal vein thrombosis	4.00(0.56,28.59)	4.00(0.56,28.59)	1.99(-1.38)	3.98(0.56)	N	N	N	N
NS	Urate nephropathy	42.94(5.85,315.24)	42.94(5.85,315.19)	5.38(-1.14)	41.54(5.66)	N	N	N	Y
45-64	Urate nephropathy	16.22(2.23,118.22)	16.22(2.23,118.21)	3.98(-1.18)	15.82(2.17)	N	N	N	Y
≥65	Urate nephropathy	44.78(5.98,335.50)	44.78(5.98,335.44)	5.41(-1.18)	42.48(5.67)	N	N	N	Y
45-64	Ureteric fistula	46.16(6.04,352.91)	46.16(6.04,352.86)	5.42(-1.21)	42.93(5.62)	N	N	N	Y
≥65	Ureteric obstruction	2.36(0.33,16.78)	2.36(0.33,16.78)	1.23(-1.56)	2.35(0.33)	N	N	N	N
≥65	Urethral discharge	38.39(5.16,285.40)	38.38(5.16,285.35)	5.20(-1.17)	36.68(4.93)	N	N	N	Y
<18	Urethral disorder	28.63(3.86,212.45)	28.62(3.86,212.28)	4.78(-1.18)	27.42(3.69)	N	N	N	Y
45-64	Urethral pain	4.26(0.60,30.43)	4.26(0.60,30.42)	2.08(-1.36)	4.23(0.59)	N	N	N	N
NS	Urinary bladder haemorrhage	2.04(0.29,14.52)	2.04(0.29,14.51)	1.03(-1.62)	2.04(0.29)	N	N	N	N
≥65	Urinary hesitation	1.37(0.19,9.75)	1.37(0.19,9.75)	0.45(-1.84)	1.37(0.19)	N	N	N	N
18-44	Urinary hesitation	2.84(0.40,20.25)	2.84(0.40,20.24)	1.50(-1.48)	2.84(0.40)	N	N	N	N
<18	Urinary incontinence	0.76(0.11,5.43)	0.76(0.11,5.42)	-0.39(-2.25)	0.76(0.11)	N	N	N	N
≥65	Urine abnormality	0.88(0.12,6.23)	0.88(0.12,6.23)	-0.19(-2.14)	0.88(0.12)	N	N	N	N
45-64	Urine flow decreased	1.20(0.17,8.50)	1.20(0.17,8.50)	0.26(-1.92)	1.20(0.17)	N	N	N	N
45-64	Urogenital disorder	18.75(2.56,137.25)	18.75(2.56,137.23)	4.19(-1.18)	18.21(2.49)	N	N	N	Y
<18	Kidney enlargement	3.96(0.55,28.30)	3.96(0.55,28.28)	1.98(-1.38)	3.94(0.55)	N	N	N	N
≥65	Bladder spasm	2.08(0.29,	2.08(0.29,14	1.06(-	2.08(0.	N	N	N	N

		14.83)	.82)	1.61)	29)				
≥65	Ureteric rupture	57.58(7.57,437.91)	57.58(7.57,437.84)	5.75(-1.19)	53.80(7.07)	N	N	N	Y
NS	Renal tubular dysfunction	6.88(0.96,49.11)	6.88(0.96,49.10)	2.78(-1.25)	6.85(0.96)	N	N	N	N
≥65	Leukocyturia	3.29(0.46,23.45)	3.29(0.46,23.45)	1.71(-1.43)	3.28(0.46)	N	N	N	N
NS	Hypocalciuria	113.20(14.61,876.90)	113.20(14.61,876.75)	6.70(-1.21)	103.85(13.41)	N	N	N	Y
<18	Hypocalciuria	629.83(39.39,10071.9)	629.65(39.39,10065.1)	8.30(-1.64)	315.33(19.72)	N	N	N	Y
≥65	Bladder necrosis	26.00(3.55,190.50)	26.00(3.55,190.47)	4.66(-1.16)	25.22(3.44)	N	N	N	Y
45-64	Bladder necrosis	46.16(6.04,352.91)	46.16(6.04,352.86)	5.42(-1.21)	42.93(5.62)	N	N	N	Y
NS	Costovertebral angle tenderness	32.77(4.50,238.69)	32.77(4.50,238.65)	5.00(-1.14)	31.95(4.39)	N	N	N	Y
45-64	Glomerulonephropathy	9.53(1.32,68.68)	9.53(1.32,68.68)	3.23(-1.22)	9.39(1.30)	N	N	N	N
18-44	Hypertensive nephropathy	12.53(1.74,90.14)	12.53(1.74,90.11)	3.63(-1.18)	12.38(1.72)	N	N	N	N
≥65	Haemorrhage urinary tract	0.74(0.10,5.25)	0.74(0.10,5.25)	-0.43(-2.28)	0.74(0.10)	N	N	N	N
NS	Urine odour abnormal	0.63(0.09,4.44)	0.63(0.09,4.44)	-0.68(-2.42)	0.63(0.09)	N	N	N	N
18-44	Urine odour abnormal	1.52(0.21,10.80)	1.52(0.21,10.80)	0.60(-1.77)	1.52(0.21)	N	N	N	N
45-64	Urine odour abnormal	0.42(0.06,2.98)	0.42(0.06,2.98)	-1.25(-2.80)	0.42(0.06)	N	N	N	N
≥65	Urine odour abnormal	0.56(0.08,3.95)	0.56(0.08,3.95)	-0.85(-2.53)	0.56(0.08)	N	N	N	N
18-44	Postrenal failure	52.92(7.06,396.47)	52.91(7.06,396.35)	5.65(-1.17)	50.18(6.70)	N	N	N	Y
45-64	Renal injury	0.07(0.01,0.53)	0.07(0.01,0.53)	-3.75(-4.89)	0.07(0.01)	N	N	N	N
18-44	Diabetic nephropathy	5.29(0.74,37.78)	5.29(0.74,37.77)	2.40(-1.30)	5.27(0.74)	N	N	N	N
45-64	Ureteral disorder	6.90(0.96,49.53)	6.90(0.96,49.52)	2.77(-1.26)	6.83(0.95)	N	N	N	N
18-44	Renal embolism	24.42(3.36,177.80)	24.42(3.36,177.75)	4.58(-1.15)	23.84(3.27)	N	N	N	Y
18-44	Bladder perforation	15.88(2.20,114.57)	15.87(2.20,114.53)	3.97(-1.16)	15.63(2.17)	N	N	N	Y
NS	Urinary fistula	31.93(4.39,232.42)	31.93(4.39,232.38)	4.96(-1.14)	31.15(4.28)	N	N	N	Y
NS	Urethral stenosis	5.66(0.79,40.36)	5.66(0.79,40.36)	2.50(-1.29)	5.64(0.79)	N	N	N	N
45-64	Bladder dysfunction	2.17(0.30,15.44)	2.17(0.30,15.43)	1.11(-1.60)	2.16(0.30)	N	N	N	N

NS	Hypermagnesuria	415.08(43.17,3990.74)	415.05(43.17,3990.09)	8.28(-1.42)	311.54(32.40)	N	N	N	Y
NS	Bladder outlet obstruction	18.05(2.51,129.95)	18.05(2.51,129.93)	4.15(-1.15)	17.80(2.47)	N	N	N	Y
45-64	Bladder outlet obstruction	26.09(3.52,193.22)	26.09(3.52,193.19)	4.65(-1.18)	25.05(3.38)	N	N	N	Y
≥65	Crystal nephropathy	3.17(0.45,22.62)	3.17(0.45,22.62)	1.66(-1.45)	3.16(0.44)	N	N	N	N
18-44	Prerenal failure	14.43(2.00,104.00)	14.43(2.00,103.97)	3.83(-1.17)	14.23(1.97)	N	N	N	N
≥65	Prerenal failure	1.25(0.18,8.86)	1.25(0.18,8.86)	0.32(-1.89)	1.25(0.18)	N	N	N	N
NS	Urinary bladder toxicity	95.79(12.53,732.29)	95.78(12.53,732.16)	6.48(-1.19)	89.01(11.64)	N	N	N	Y
18-44	Urinary bladder toxicity	476.29(43.18,5253.29)	476.23(43.19,5251.78)	8.31(-1.51)	317.82(28.82)	N	N	N	Y
18-44	Acquired aminoaciduria	-	-	9.90(-1.89)	953.47(.)	N	N	N	N
45-64	Myeloma cast nephropathy	12.00(1.66,86.89)	12.00(1.66,86.88)	3.56(-1.20)	11.79(1.63)	N	N	N	N
<18	End stage renal disease	4.77(0.67,34.13)	4.77(0.67,34.11)	2.25(-1.33)	4.74(0.66)	N	N	N	N
≥65	End stage renal disease	0.31(0.04,2.24)	0.31(0.04,2.24)	-1.67(-3.10)	0.32(0.04)	N	N	N	N
45-64	Ureterolithiasis	1.08(0.15,7.66)	1.08(0.15,7.66)	0.11(-1.99)	1.08(0.15)	N	N	N	N
NS	Renal tubular injury	10.73(1.50,76.86)	10.73(1.50,76.85)	3.41(-1.19)	10.65(1.49)	N	N	N	N
<18	Renal tubular injury	13.40(1.85,97.15)	13.40(1.85,97.07)	3.72(-1.19)	13.14(1.81)	N	N	N	N
≥65	Subacute kidney injury	115.16(14.17,936.08)	115.15(14.17,935.92)	6.66(-1.27)	100.88(12.41)	N	N	N	Y

External Validation via EudraVigilance Database

To corroborate the findings from FAERS, a validation analysis was performed using the EudraVigilance (EV) database (2004–2025), comprising 3,561 reports. The EV data mirrored the FAERS trends, showing a progressive increase in reporting (peaking in 2017)(Figure S1) and a distinct male predominance (61.33% vs. 33.16%)(Figure S2). Consistent with the primary analysis, AKI was the most frequent adverse event (n=1,142; ROR= 4.22). Crucially, the EV analysis validated the high-intensity signals for specific toxicities, including Urinary Bladder Toxicity (ROR= 251.74) and Renal Salt-Wasting Syndrome (ROR= 205.36)(Figure S3). Sensitivity analysis excluding concomitant medications confirmed the stability of the RSWS signal (ROR= 208.08)(Figure S4), reinforcing the conclusion that these nephrotoxic manifestations are primarily attributable to cisplatin monotherapy.

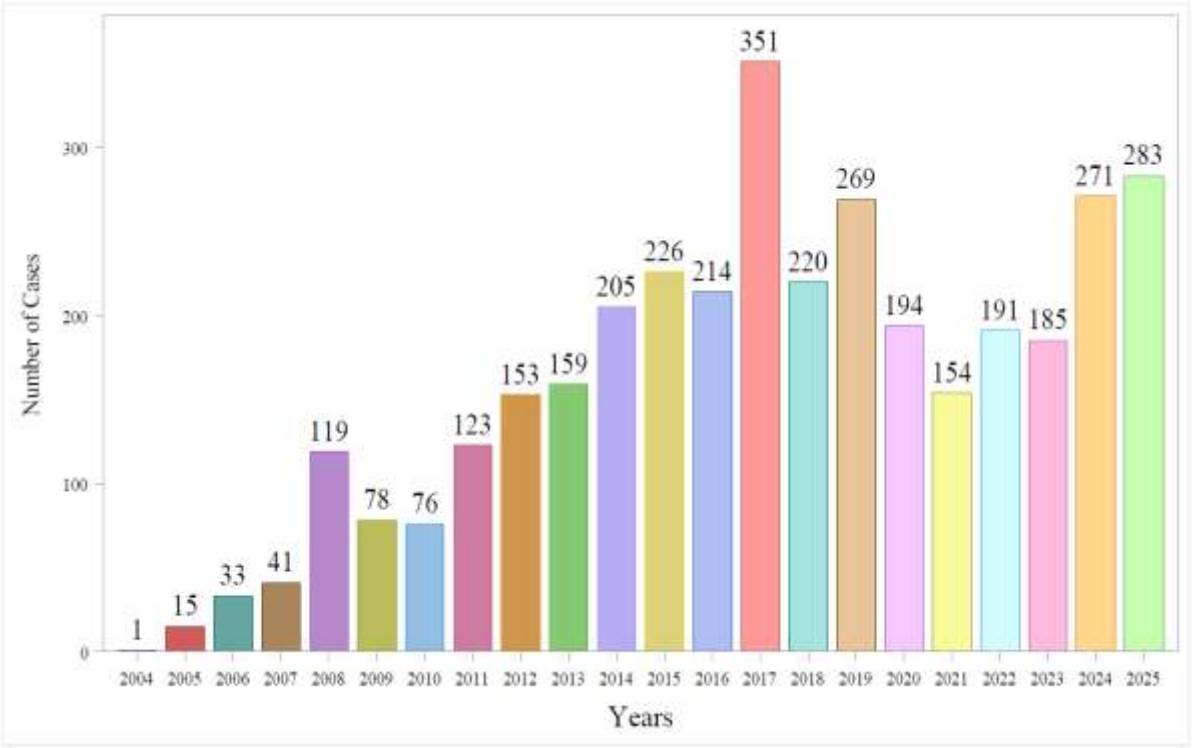

Figure S1: Annual Distribution of AE Reports(EV)

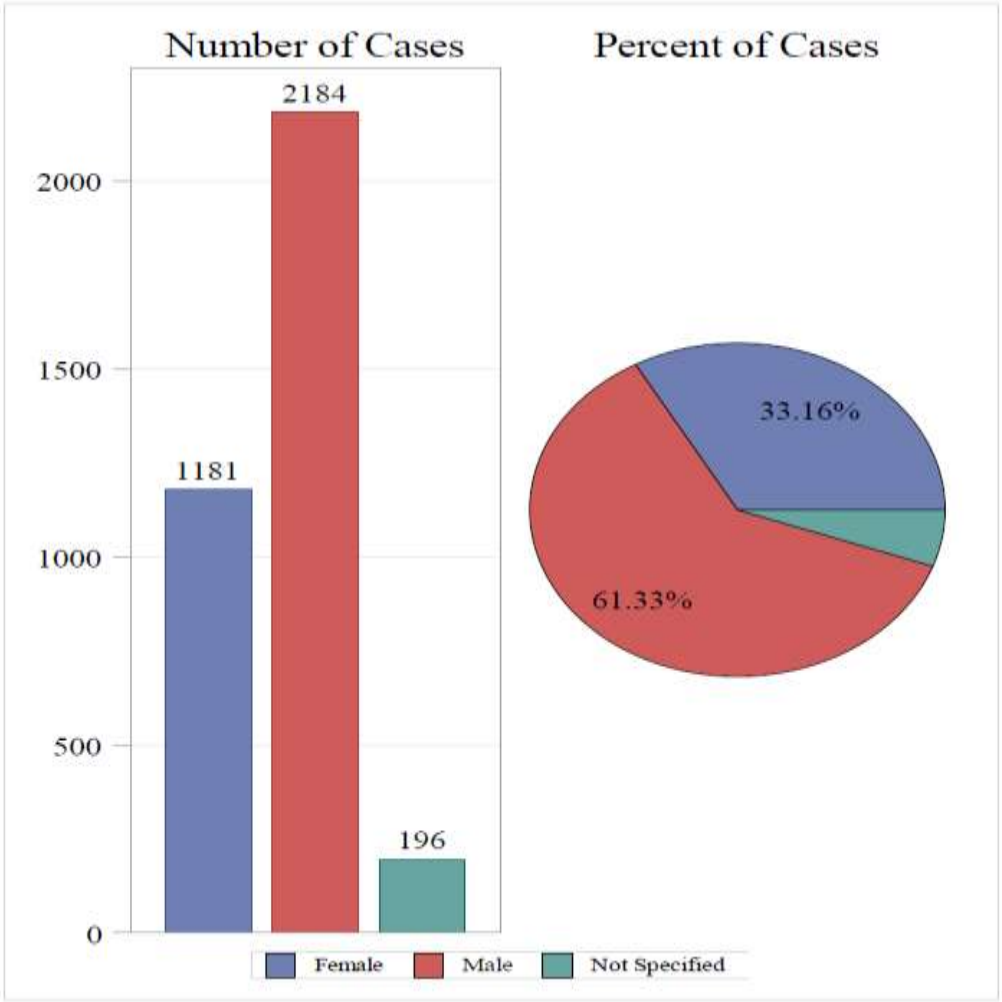

Figure S2: Sex Distribution of AE Reports(EV)

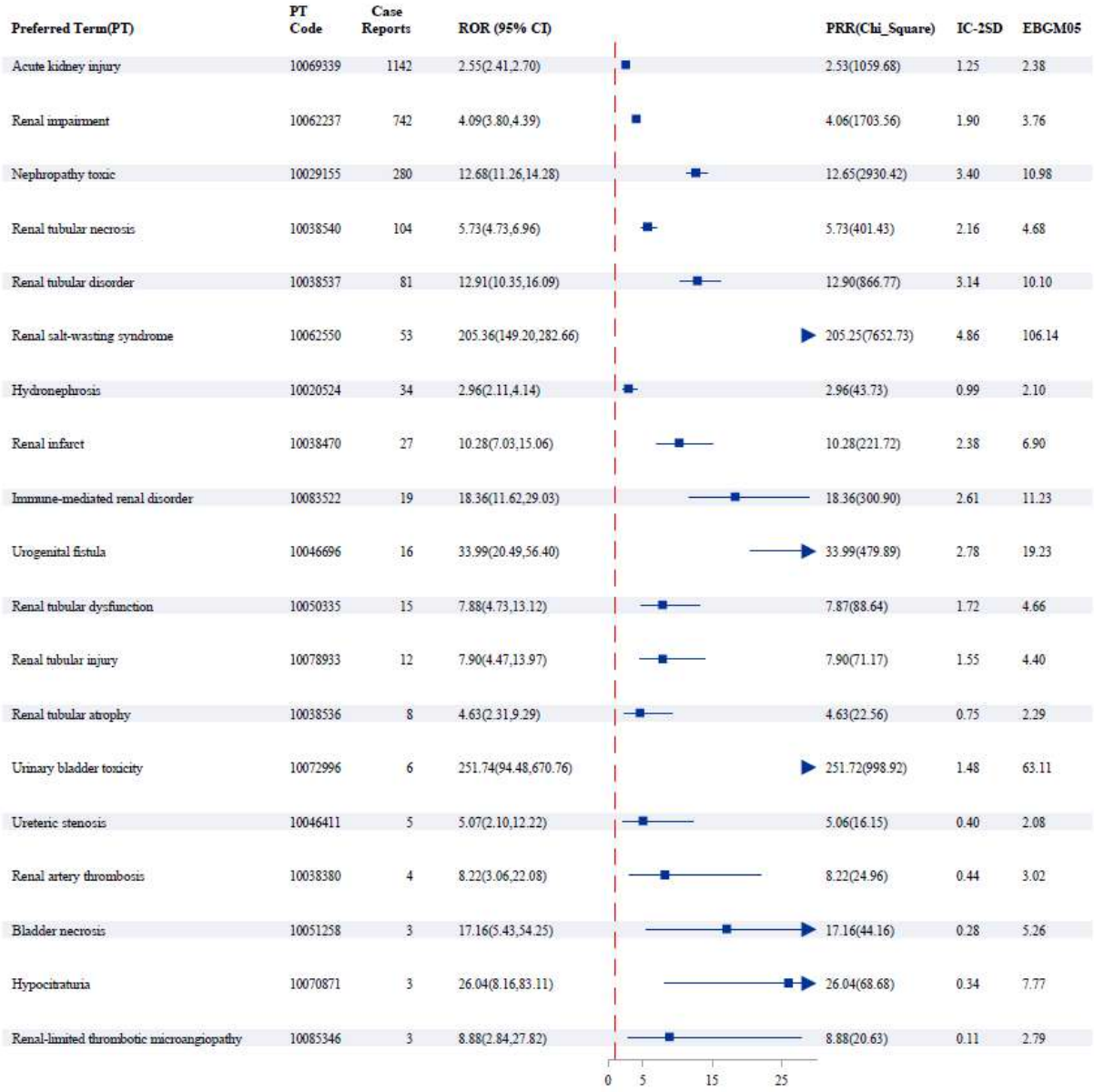

Figure S3: Signal strength of adverse events at the Preferred Term level ranked by Reports

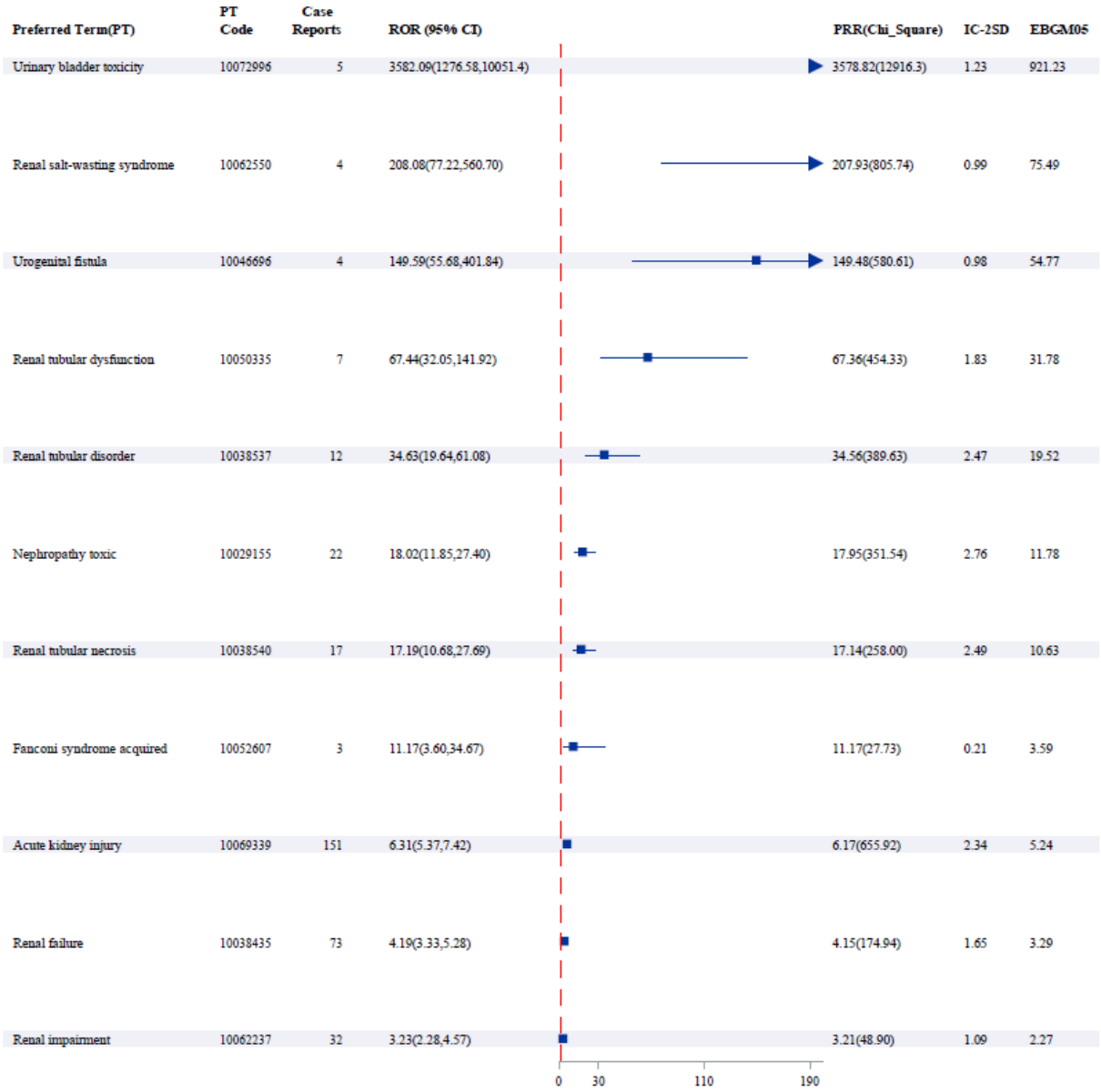

Figure S4: Sensitivity Analysis for PT-Level Signals (Ranked by ROR; Excluding Concomitant Medications)

4. Discussion

The present retrospective surveillance analysis of the FAERS database from 2004 to 2025 underscores the persistent and severe clinical burden of cisplatin-induced nephrotoxicity (CIN), a complication that remains a dose-limiting factor in oncological practice despite the advent of renoprotective strategies. Our findings reveal a high frequency of serious adverse events, with over 98% of reported cases classified as serious and a mortality rate of 14.73%, significantly exceeding the background mortality rates typically associated with general drug-induced nephrotoxicity14. The peak in reporting frequency observed in 2019 likely reflects both the increasing global cancer burden and improved pharmacovigilance awareness among healthcare professionals. The predominance of reports originating from pharmacists and physicians (over 54%) lends high clinical validity to these data, suggesting that the captured signals represent medically verified diagnoses rather than patient-reported approximations.

Central to our disproportionality analysis was the robust signal for Acute Kidney Injury (AKI), which represented the most prevalent phenotype with an ROR of 5.05. This aligns with established pathophysiological mechanisms where cisplatin accumulates in proximal tubular epithelial cells via the organic cation transporter 2 (OCT2), triggering a cascade of oxidative stress, DNA damage, and subsequent apoptotic and necrotic cell death15. While AKI is a known consequence, the sheer magnitude of the signal in this large-scale dataset reaffirms that current hydration protocols, though standard, do not fully mitigate the risk of acute filtration failure16. The high rate of hospitalization (64.3%) associated with these events emphasizes the significant healthcare resource utilization driven by cisplatin toxicity.

The most striking finding of this study is the specific and potent disruptive effect of cisplatin on the sodium-handling machinery of the distal nephron, manifested by a signal for Renal Salt-Wasting Syndrome (RSWS) that far exceeds typical acute kidney injury (ROR > 481)17. This suggests that RSWS is a severely under-recognized feature of cisplatin's toxicological profile. Furthermore, the analysis reveals a broad "multifaceted toxicological footprint." Beyond the paradoxical signal for hypermagnesemia, potentially secondary to profound GFR decline or aggressive over-correction, the study unexpectedly identified structural urothelial injuries, such as bladder necrosis and urogenital fistulae18. These may result from direct chemical injury to the urothelium by high concentrations of active urinary platinum metabolites. Validated by the EudraVigilance database and sensitivity analyses excluding concomitant medications, these RSWS and bladder toxicity signals demonstrate high robustness and consistency.

Temporal and subgroup analyses highlight distinct kinetic profiles and demographic variations in cisplatin toxicity. The onset is rapid (median: 10 days), with females exhibiting a significantly shorter latency than males, likely due to biological differences such as OCT2 expression, suggesting a need for earlier monitoring in women1219. Although males dominate the total number of reports (approximately 57%–61%), consistent with cancer epidemiology and a potential biological susceptibility to severe necrotic injury, the geriatric population shows heightened vulnerability, particularly to RSWS and obstructive nephropathies (e.g., hydronephrosis) driven by drug-induced inflammation or scarring20.

Cisplatin nephrotoxicity is not a monolithic "kidney failure" but a broad-spectrum syndrome ranging from electrolyte wasting to structural obstruction. Given that 98.24% of cases are classified as serious with a mortality rate of 14.73%, current hydration and protective protocols remain insufficient. A paradigm shift in clinical monitoring is urgently required: moving from generic serum creatinine testing toward tailored precision management. This includes prioritizing electrolyte surveillance in pediatric and RSWS-high-risk populations, screening for urinary tract structural integrity in the elderly, and implementing intensive monitoring during the early onset window for female patients.

5. Conclusion

This study characterizes the broad spectrum of cisplatin-induced nephrotoxicity using data from two large-scale pharmacovigilance databases. Beyond conventional acute kidney injury, we identified specific toxicity profiles, including a rapid onset of adverse events in females and distinct age-related risks. Notably, the robust signals for Renal Salt-Wasting Syndrome (RSWS) and obstructive uropathy in the geriatric population highlight the necessity for age-stratified monitoring. Validated across both FAERS and EudraVigilance, these findings emphasize the importance of early electrolyte management and targeted vigilance to mitigate

severe outcomes, such as hospitalization and mortality, in patients undergoing cisplatin chemotherapy.

6. Limitation

Several limitations inherent to spontaneous reporting systems apply to this study. First, the existence of reporting bias and underreporting in FAERS and EudraVigilance prevents the calculation of true incidence rates. Second, while disproportionality analysis detects statistical associations, it does not establish definitive causality. Although sensitivity analyses were conducted, confounding factors such as underlying malignancies and prior chemotherapy cycles cannot be fully excluded. Additionally, incomplete clinical data regarding cisplatin dosage and baseline renal function in some reports may limit the precision of time-to-onset and severity assessments. Consequently, prospective clinical studies are required to further validate these specific toxicological phenotypes.

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Availability of Data and Materials: All the data for the present article can be found on the US FDA Adverse Event Reporting System (FAERS) database and the EudraVigilance (EV) database

Authors' Contributions: Nouth Nita and Hong Seng An collected, analyzed, and interpreted the data, wrote the manuscript. Qionglin Huang, Ruiying Chen and Pengkhun Nov designed, revised, and supervised the study. All authors had reviewed and approved the final manuscript

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Clinical Trial Number: Not applicable

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