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INCIDENCE AND RISK FACTORS OF CISPLATIN-INDUCED ACUTE KIDNEY INJURY IN PATIENTS UNDERGOING CONCURRENT CHEMORADIOTHERAPY: A RETROSPECTIVE STUDY

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ABSTRACT

Background

Cisplatin is a fundamental chemotherapeutic agent for solid tumors; however, its use is constrained by dose-dependent nephrotoxicity, frequently presenting as acute kidney injury (AKI). Data regarding the incidence and risk factors of acute kidney injury (AKI) in resource-limited settings such as Nepal are limited, highlighting the need for region-specific insights to enhance therapeutic strategies. This retrospective study sought to assess the incidence of cisplatin-induced acute kidney injury (AKI) and to identify associated risk factors among patients receiving weekly cisplatin in conjunction with radiotherapy at a tertiary care center in Nepal.

Methods

We analyzed 92 patients treated between 2022 and 2024, aged ≥18 years, with solid tumors. Patients received weekly cisplatin (approximately 40 mg/m²) alongside radiotherapy. AKI was defined using KDIGO criteria. Data on demographics, cancer characteristics, treatment parameters, and comorbidities were extracted from electronic medical records. Univariate and multivariate logistic regression analyses identified AKI predictors.

Results

AKI occurred in 30 patients (32.6 percent), with 25.0 percent stage 1, 6.5 percent stage 2, and 1.1 percent stage 3; none required renal replacement therapy. Mean age was 54.8 years (SD 13.3), with 60.9 percent male. Head and neck cancers predominated (58.7 percent). Multivariate analysis identified older age (OR 1.05 per year, 95% CI 1.01–1.09, p=0.009) as a significant risk factor and higher cumulative cisplatin dose (OR 1.09 per 10 mg/m², 95% CI 1.00–1.19, p=0.06) as borderline significant. Hypertension showed no significant association (p=0.29).

Conclusion

Approximately one-third of patients developed AKI, primarily mild, with older age and higher cisplatin doses as key risk factors. These findings underscore the need for vigilant renal monitoring in elderly patients and those receiving prolonged cisplatin therapy, informing strategies to enhance treatment safety in Nepal.

Keywords: Cisplatin, Acute Kidney Injury, Nephrotoxicity, Chemoradiotherapy, Risk Factors, Nepal

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INTRODUCTION

Cisplatin, a platinum-based chemotherapeutic agent, has been a cornerstone in the treatment of various solid tumors since its introduction in the 1970s. Initially discovered for its antitumor properties by Rosenberg et al., cisplatin has demonstrated remarkable efficacy against a range of malignancies, including head and neck, cervical, lung, and ovarian cancers[1]. Its mechanism of action involves the formation of DNA crosslinks that inhibit cancer cell replication, making it a potent cytotoxic agent[2]. Frequently, cisplatin is administered in combination with radiotherapy to enhance therapeutic outcomes, a strategy that has proven particularly effective in locally advanced cancers such as head and neck squamous cell carcinoma[3]. Despite its widespread use and effectiveness, the clinical utility of cisplatin is significantly limited by its dose-dependent nephrotoxicity, which often manifests as acute kidney injury (AKI) in a substantial proportion of treated patients[4].

The nephrotoxic effects of cisplatin predominantly target the proximal tubular epithelial cells of the kidneys, where the drug accumulates in high concentrations. This accumulation triggers a cascade of pathological processes, including tubular injury, oxidative stress, inflammation, and vascular damage[5]. The underlying mechanisms involve the formation of DNA adducts, disruption of mitochondrial function, and activation of apoptotic pathways, all of which contribute to renal cell death[6]. Clinically, cisplatin-induced AKI is characterized by a rise in serum creatinine levels, reduced glomerular filtration rate, oliguria, and, in severe cases, the need for renal replacement therapy[7]. The incidence of AKI among cisplatin-treated patients varies widely, with studies reporting rates between 20 percent and 40 percent, depending on factors such as cumulative dose, administration frequency, hydration protocols, and individual patient risk factors like age, pre-existing renal function, and comorbidities[8,9]. Preventive strategies, including aggressive hydration and the use of renoprotective agents, have been employed to mitigate this toxicity, yet AKI remains a significant barrier to optimizing cisplatin-based therapy[10].

While cisplatin is used globally, its nephrotoxic profile and associated clinical burden may differ across populations, particularly in resource-limited settings where access to supportive care and monitoring may be constrained. In Nepal, for instance, the rising incidence of cancer—driven by an aging population and increasing prevalence of risk factors—has led to greater reliance on cisplatin-based chemoradiotherapy[11]. However, data on the local incidence of cisplatin-induced AKI and its risk factors remain scarce, potentially compromising patient management and outcomes in this context. The lack of region-specific evidence highlights a critical knowledge gap, as variations in genetics, healthcare infrastructure, and treatment practices could influence the prevalence and severity of AKI. Addressing this gap is essential for developing tailored nephroprotective strategies and improving the safety of cisplatin therapy in Nepal.

This retrospective study seeks to investigate the incidence and risk factors of cisplatin-induced AKI in patients receiving weekly cisplatin with concurrent radiotherapy at a tertiary care center in Nepal. By analyzing a cohort of 92 patients treated between 2022 and 2024, we aim to determine the prevalence of AKI, identify key predictors related to patient demographics and treatment parameters, and provide actionable insights to guide clinical practice. Ultimately, this research intends to contribute to the optimization of cisplatin-based therapy in Nepal by informing strategies to minimize nephrotoxicity while preserving therapeutic efficacy.

METHODS

This retrospective cohort study was performed at Purbanchal Cancer Hospital, a tertiary cancer care facility in Birtamode, Jhapa, Nepal. The objective was to assess the incidence of acute kidney injury (AKI) and its associated risk factors in patients undergoing weekly cisplatin chemotherapy in conjunction with radiotherapy from January 1, 2022, to December 31, 2024. Ethical approval was secured from the hospital's Institutional Review Committee, which granted a waiver of informed consent owing to the retrospective nature of the study and the utilization of de-identified data. Eligible patients were aged 18 years or older, diagnosed with a solid tumor (e.g., head and neck, cervical, lung, esophageal, or bladder cancer), treated with weekly cisplatin (typically 40 mg/m² per week) alongside radiotherapy, and had at least three serum creatinine measurements, including one baseline (pre-treatment) and two or more during or post-treatment. Patients with pre-existing end-stage renal disease (eGFR <15 mL/min/1.73m², equivalent to chronic kidney disease stage 5), incomplete medical records (e.g., missing cisplatin dosing details or fewer than three creatinine measurements), or those treated with cisplatin without concurrent radiotherapy were excluded. The cohort was identified using diagnostic and treatment codes within the hospital's electronic medical record (EMR) system to ensure a systematic and unbiased selection process. Data were extracted from the EMR using a standardized abstraction form created in Microsoft Excel, capturing demographic data (age in years, sex), cancer characteristics (tumor type, TNM stage), treatment parameters (cumulative cisplatin dose in mg/m², total radiotherapy dose in Gy, number of radiotherapy fractions), and clinical factors (comorbidities such as hypertension, diabetes, or

cardiovascular disease; smoking status; alcohol consumption; baseline serum creatinine in mg/dL; and serial creatinine levels after each weekly cisplatin cycle, up to five measurements).

Acute Kidney Injury (AKI) was defined and staged according to the KidneyDisease: Improving Global Outcomes (KDIGO) criteria, diagnosing AKI if serum creatinine increased by ≥0.3 mg/dL within 48 hours or reached ≥1.5 times the baseline value within 7 days. Acute kidney injury (AKI) severity is categorized into three stages: stage 1, defined by serum creatinine levels 1.5–1.9 times the baseline or an increase of ≥0.3 mg/dL; stage 2, characterized by serum creatinine levels 2.0–2.9 times the baseline; and stage 3, indicated by serum creatinine levels ≥3.0 times the baseline, an increase to ≥4.0 mg/dL, or the initiation of renal replacement therapy. Baseline creatinine was the most recent pre-treatment measurement (Cr1), with the highest creatinine value during treatment used to determine AKI status and stage, selecting the value reflecting the most severe stage if multiple measurements existed within a 7-day period.

SPSS version 26.0 (IBM Corp., Armonk, NY) was used for all statistical analyses; descriptive statistics—mean ± standard deviations for normally distributed continuous variables, medians and interquartile ranges for non-normal data, and frequencies and percentages for categorical variables—summarized patient characteristics. Univariate analyses compared AKI and non-AKI groups, using chi-square tests for categorical variables and independent t-tests for continuous variables with normal distribution.

Using a backward stepwise elimination technique and reporting results as odds ratios with 95% confidence intervals, a multivariate logistic regression model found independent AKI predictors including variables with $p<0.10$ in univariate analysis or those clinically significant (e.g., age, cumulative cisplatin dosage). Statistical significance defined as $p<0.05$.

RESULTS

Patient Characteristics

The study included 92 patients receiving weekly concurrent cisplatin with radiotherapy. The mean age was 54.8 ± 13.3 years, with 56 patients (60.9 percent) being male. Cancer diagnoses included head and neck cancers (e.g., alveolus, buccal mucosa, tongue; 54 patients, 58.7 percent), cervical cancer (33 patients, 35.9 percent), and other types (e.g., esophagus, endometrium; 5 patients, 5.4 percent). The mean radiotherapy dose was 60.8 ± 8.6 Gy and the mean number of fractions was 30.5 ± 4.6, corresponding to an estimated mean cumulative cisplatin dose of 244 ± 36.8 mg/m², assuming 40 mg/m² weekly over the number of weeks (calculated as ceiling of fractions / 5). Hypertension was present in 14 patients, and diabetes in 7 patients. Baseline characteristics are summarized in **Table 1**.

Table 1: Patient Characteristics

Variable	Total (n=92)	AKI (n=30)	No AKI (n=62)
Age (years, mean ± SD)	54.8 ± 13.3	59.7 ± 11.8	52.4 ± 13.5
Male, n (%)	56 (60.9%)	19 (63.3%)	37 (59.7%)
Hypertension, n (%)	14 (15.2%)	6 (20.0%)	8 (12.9%)
Diabetes, n (%)	7 (7.6%)	3 (10.0%)	4 (6.5%)
Cumulative cisplatin dose (mg/m², mean ± SD)	244 ± 36.8	252 ± 38.2	240 ± 35.6
Radiotherapy dose (Gy, mean ± SD)	60.8 ± 8.6	61.7 ± 8.2	60.3 ± 8.8
Cancer type, n (%)			
- Head and neck	54 (58.7%)	19 (63.3%)	35 (56.5%)
- Cervical	33 (35.9%)	10 (33.3%)	23 (37.1%)
- Other	5 (5.4%)	1 (3.3%)	4 (6.5%)

Incidence of AKI

AKI was determined using the KDIGO criteria: an increase in serum creatinine by ≥0.3 mg/dL from Cr1 (baseline) to any of Cr2–Cr5, or any Cr2–Cr5 value ≥1.5 times Cr1. All 92 patients had Cr1 recorded, and at least one subsequent measurement (Cr2–Cr5) was available for each. After applying the criteria to the dataset:

- 30 patients (32.6 percent) developed AKI.
  - 20 patients (21.7 percent) had an increase of ≥0.3 mg/dL from Cr1.
  - 10 patients (10.9 percent) had a creatinine level ≥1.5 times Cr1 (some overlapped with the first criterion).
- AKI staging (based on maximum creatinine increase):
  - Stage 1 (1.5–1.9 times baseline or ≥0.3 mg/dL increase): 23 patients (25.0 percent).
  - Stage 2 (2.0–2.9 times baseline): 6 patients (6.5 percent).
  - Stage 3 (≥3.0 times baseline): 1 patient (1.1 percent).
- No patients required renal replacement therapy.

Risk Factor Analysis

Univariate Analysis

Risk factors analyzed included age, sex, hypertension, diabetes, cumulative cisplatin dose, radiotherapy dose, and cancer type. Key findings:

- Age: AKI patients were older (59.7 ± 11.8 vs. 52.4 ± 13.5 years, $p = 0.01$, t-test).
- Cumulative cisplatin dose: Higher in AKI group (252 ± 38.2 vs. 240 ± 35.6 mg/m², $p = 0.17$, t-test).
- Hypertension: More prevalent in AKI group (20.0% vs. 12.9%, $p = 0.36$, chi-square).

- No significant differences were found for sex (p = 0.74), diabetes (p = 0.56), radiotherapy dose (p = 0.47), or cancer type (p = 0.72).

Multivariate Logistic Regression

A logistic regression model adjusted for age, cumulative cisplatin dose, and hypertension (selected based on univariate trends and clinical relevance) identified:

- Age: OR 1.05 per year (95% CI 1.01–1.09, p = 0.009), indicating a 5 percent increased odds of AKI per year of age.
- Cumulative cisplatin dose: OR 1.09 per 10 mg/m² (95% CI 1.00–1.19, p = 0.06), suggesting a borderline significant 9 percent increased odds per 10 mg/m².
- Hypertension: OR 1.9 (95% CI 0.6–6.2, p = 0.29), not statistically significant.

Table 2: Multivariate Logistic Regression for AKI Risk Factors

Variable	Odds Ratio	95% CI	p-value
Age (per year)	1.05	1.01–1.09	0.009
Cumulative cisplatin dose (per 10 mg/m²)	1.09	1.00–1.19	0.06
Hypertension (yes vs. no)	1.9	0.6–6.2	0.29

About 32.6 percent of patients experienced acute kidney injury (AKI), primarily stage 1, which aligns with the nephrotoxic effects of cisplatin in this context. Advanced age emerged as a notable independent predictor of acute kidney injury, whereas an increased cumulative dose of cisplatin demonstrated a pronounced trend towards significance. The impact of hypertension was not statistically significant, likely attributable to the limited number of affected patients. The findings indicate that elderly patients and individuals receiving higher cumulative doses may necessitate more rigorous monitoring of renal function throughout treatment.

DISCUSSION

Our retrospective analysis of 92 patients receiving weekly cisplatin with concurrent radiotherapy revealed an acute kidney injury (AKI) incidence of 32.6%, with 30 patients affected. This rate aligns with the 20–40% range reported in a systematic review of cisplatin-induced nephrotoxicity, which synthesized data from diverse patient populations and treatment regimens across multiple studies[10]. This analysis emphasized that AKI incidence varies with cisplatin dose intensity, administration frequency (weekly vs. tri-weekly), and hydration protocols, suggesting that our 32.6% incidence reflects a typical outcome for a weekly regimen. Similarly, a comparable incidence of renal dysfunction was reported in a cohort of 400 patients with advanced ovarian cancer treated with weekly high-dose cisplatin (70–85 mg/m²), noting that mild renal impairment was frequent, while severe cases were rare[11]. In our study, most AKI cases were stage 1 (25.0%, n=23), with fewer stage 2 (6.5%, n=6) and only one stage 3 (1.1%) instance, consistent with de Jongh et al.'s findings of predominantly mild renal effects[11]. This distribution aligns with the kidney disease: Improving Global Outcomes (KDIGO) criteria, which standardize AKI diagnosis based on serum creatinine changes, reinforcing the reliability of our assessment[12]. The low rate of severe AKI, with no patients requiring renal replacement therapy, may reflect the exclusion of those with pre-existing end-stage renal disease or basic supportive measures like hydration, though specific hydration data were unavailable, a limitation also noted a study of long-term renal outcomes post-cisplatin[13].

The identification of older age as a significant risk factor for AKI, with each additional year increasing the odds by 5% (OR 1.05, 95% CI 1.01–1.09, p=0.009), is well-supported by the literature. It was found that patients over 60 years had a higher nephrotoxicity risk, attributing this to age-related declines in glomerular filtration rate (GFR) and renal reserve[11]. The mechanistic basis, explaining that cisplatin's accumulation in proximal tubular cells triggers oxidative stress and apoptosis, processes exacerbated in aging kidneys with reduced regenerative capacity[14]. Their review cites animal studies showing greater tubular damage in older rats, mirroring our human data. Elderly patients often have subclinical renal impairment, increasing susceptibility to cisplatin's toxic effects even at standard doses[15]. This vulnerability is particularly relevant in Nepal, whererising cancer incidence among aging population, with over 10,000 new cases annually[16]. Our finding that the AKI group had a mean age of 59.7 years compared to 52.4 years in the no-AKI group underscores the need for tailored monitoring in older patients, a point also emphasized in a studythat advocate for pre-treatment renal function assessments in elderly cancer patients[17].

Cumulative cisplatin dose showed a near-significant association with AKI (OR 1.09 per 10 mg/m², 95% CI 1.00–1.19, p=0.06), corroborating the dose-dependent nephrotoxicity[14]. Higher cumulative exposure increases cisplatin uptake by renal tubular cells, leading to DNA damage, mitochondrial dysfunction, and cell death. Patients receiving cumulative doses above 300 mg/m² face a markedly higher AKI risk, often after multiple cycles[18]. Our study's mean cumulative dose of 252 mg/m² in the AKI group versus 240 mg/m² in the no-AKI group aligns with this dose-response relationship, though the lack of full significance may stem from our modest sample size (n=92) or the lower weekly dose (approximately 40 mg/m²) compared to high-dose regimens (e.g., 100 mg/m² every 3 weeks). In preclinical models, repeated

cisplatin administration progressively impairs tubular function, supporting our findings that even moderate doses pose a risk when accumulated[19]. Additionally, it was highlight that cumulative dosing exacerbates oxidative stress, further explaining our observed trend[20].

Hypertension, present in 20.0% of AKI patients versus 12.9% of no-AKI patients, was not a significant risk factor (OR 1.9, 95% CI 0.6–6.2, p=0.29). This contrasts with who identified hypertension as a predictor of acute renal failure in over 1,000 patients with chronic kidney disease, citing its role in compromising renal vascular integrity (OR 1.5–2.0)[21]. Our non-significant result may reflect limited statistical power due to only 14 hypertensive patients or the dominance of cisplatin's direct tubular toxicity[22]. The argument that cisplatin induced nephrotoxicity primarily results from proximal tubular uptake via organic cation transporters, a mechanism less influenced by hypertensive vascular changes. This divergence suggests cisplatin-related AKI may differ from other AKI etiologies, a point also noted in several studies that found cisplatin's tubular damage overshadows systemic factors like hypertension in experimental models[23].

Clinically, our findings suggest actionable steps. The role of age and cumulative dose implies that older patients and those on prolonged cisplatin regimens require frequent renal function monitoring, such as weekly creatinine assessments. Recommend aggressive hydration and magnesium supplementation, citing trials where these reduced AKI incidence by up to 30%[24]. Our results contrast with other studies, who reported severe nephrotoxicity in pediatric populations at higher cisplatin doses, indicating age-specific risk profiles[25]. Future research could explore novel renoprotective agents, such as antioxidants to mitigate cisplatin-induced oxidative stress[26]. Additionally, an advocate for early AKI biomarkers like urinary neutrophil gelatinase-associated lipocalin (NGAL), which could enhance detection in our setting[27].

This study has several limitations. Its retrospective design risks selection bias and incomplete data, such as hydration protocols or concurrent medications. The single-center setting limits generalizability, as patient demographics and practices may vary. The absence of urine output data, a KDIGO criterion, may underestimate AKI incidence. Future prospective, multi-center studies could address these gaps and validate our findings in diverse populations.

CONCLUSION

Our study found a 32.6 percent incidence of AKI in patients receiving cisplatin with radiotherapy, with age and cumulative cisplatin dose as key risk factors. These findings reinforce the need for tailored renal monitoring and potential treatment modifications in high-risk patients. While consistent with existing literature, the results highlight the ongoing challenge of nephrotoxicity in cisplatin-based therapy and call for further research to optimize prevention strategies and improve patient outcomes.

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