**RESEARCH PAPER**

# Acute Kidney Injury to Acute Kidney Disease Transition During Platinum-Based and Non-Platinum Alkylating Chemotherapy: A Prospective Cohort Study

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**ABSTRACT**

Platinum-based and non-platinum alkylating agents have nephrotoxic potential, yet acute kidney injury (AKI)–to–acute kidney disease (AKD) transition across chemotherapy cycles remains insufficiently characterised. This prospective cohort study evaluated AKI incidence, AKI-to-AKD transition, inter-cycle recovery, and subsequent kidney outcomes among adults with hematologic and non-hematologic malignancies receiving cisplatin, carboplatin, oxaliplatin, cyclophosphamide, or ifosfamide at a tertiary referral hospital in Makassar, Indonesia. Serum creatinine was measured before and after the first three chemotherapy cycles. AKI was defined using KDIGO serum creatinine criteria. Recovery was classified as complete, partial, or neither complete nor partial resolution. Serum creatinine–based AKD was defined as persistent serum creatinine ≥1.2 times baseline more than 7 days and within 90 days after AKI. Among 94 patients, AKI occurred in 11 (11.7%) after cycle 1. Before cycle 2, complete resolution occurred in 3 (27.3%), partial resolution in 2 (18.2%), and neither complete nor partial resolution in 6 (54.5%); consequently, 8 (72.7%) met the AKD criterion. AKI also occurred in 11 patients (11.7%) after cycle 2, of whom 8 (72.7%) met the AKD criterion before cycle 3. New AKI after cycle 2 occurred in 7 of 83 patients without cycle-1 AKI (8.4%). Recurrent AKI occurred in 1 of 5 patients with preceding complete or partial resolution, while further AKI or kidney function worsening occurred in 3 of 6 patients without such resolution. A substantial proportion of patients with AKI met the serum creatinine–based AKD criterion before the subsequent chemotherapy cycle, supporting serial serum creatinine monitoring throughout chemotherapy.

**Keywords:** Acute Kidney Disease; Acute Kidney Injury; Antineoplastic Agents; Creatinine; Nephrotoxicity; Prospective Studies.

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## INTRODUCTION

Chemotherapy remains one of the principal treatment modalities for malignancy and has contributed substantially to improvements in cancer survival. However, its clinical benefits are accompanied by adverse effects, including nephrotoxicity. The kidneys are particularly vulnerable to chemotherapy-induced injury because of their high blood flow, active tubular transport, central role in drug and metabolite excretion, and involvement in fluid, electrolyte, and acid–base homeostasis. Chemotherapy-related kidney dysfunction may manifest as an asymptomatic increase in serum creatinine, acute kidney injury (AKI), acute kidney disease (AKD), electrolyte disturbances, or progressive chronic kidney disease.[1–3]

Among conventional chemotherapeutic agents, platinum-based agents and other alkylating agents are clinically important causes of kidney injury. Platinum compounds, particularly cisplatin, are well recognized for their nephrotoxic potential, whereas non-platinum alkylating agents, including cyclophosphamide and ifosfamide, may also induce kidney injury through distinct mechanisms.[1,4] Chemotherapy-associated nephrotoxicity may involve acute tubular injury, oxidative stress, mitochondrial dysfunction, DNA damage, vascular and hemodynamic disturbances, thrombotic microangiopathy, inflammatory or immune-mediated injury, and intratubular obstruction. The severity and reversibility of kidney injury may vary according to the chemotherapeutic agent, cumulative exposure, treatment cycle, baseline kidney function, comorbidities, supportive care, and individual susceptibility.[1,2,4]

Kidney injury during chemotherapy should not be regarded as a single static event, but rather as a dynamic process that may develop, resolve, persist, worsen, or recur across consecutive treatment cycles. According to KDIGO criteria, AKI is defined by an increase in serum creatinine of ≥0.3 mg/dL within 48 hours, an increase to

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≥1.5 times baseline within the preceding 7 days, or reduced urine output.[5] AKD encompasses functional or structural kidney abnormalities with health implications occurring for up to 3 months, including kidney dysfunction that persists beyond the initial 7-day AKI period.[6] The recent KDIGO framework further distinguishes complete resolution, partial resolution, and absence of resolution after AKI, while recurrent AKI refers to a new episode occurring after complete or partial resolution of the preceding episode.[7] Accordingly, patients with persistent serum creatinine elevation beyond 7 days may meet criteria for AKD, including those who have achieved only partial resolution.[7] In oncology practice, serial assessment of serum creatinine before and after chemotherapy remains a practical method for detecting clinically relevant changes in kidney function, particularly where tubular injury biomarkers are not routinely available.[3,5,6]

Previous studies have shown that chemotherapy-associated nephrotoxicity varies according to drug class, cancer population, chemotherapy regimen, cumulative exposure, supportive care, baseline kidney function, and the definition of nephrotoxicity applied. Cisplatin-induced AKI has been reported in approximately 30% of patients receiving cisplatin-containing chemotherapy.[4] In a cohort of adult patients with cancer in Uganda, Isiiko et al. reported nephrotoxicity in approximately one-third of patients and identified platinum-agent exposure, hypertension, and age older than 50 years as relevant risk factors.[8] In Indonesia, Prasaja et al. reported cisplatin-induced nephrotoxicity in 34.1% of adult patients with cancer treated at Dharmais National Cancer Hospital.[9] However, most available studies have focused on cisplatin-based chemotherapy or solid malignancies, whereas prospective evidence characterizing AKI-to-AKD transition, inter-cycle recovery, and subsequent kidney outcomes across sequential chemotherapy cycles among patients receiving both platinum-based and non-platinum alkylating agents remains limited.

Therefore, this study aimed to evaluate AKI incidence and AKI-to-AKD transition across sequential chemotherapy cycles and to characterize inter-cycle kidney recovery, new AKI, recurrent AKI after documented resolution, and further kidney function worsening among adults with hematologic and non-hematologic malignancies receiving platinum-based and non-platinum alkylating agents.

## METHODS

### *Study Design and Setting*

This was a single-centre prospective cohort study conducted at Dr. Wahidin Sudirohusodo General Hospital, a tertiary referral centre in Makassar, Indonesia. Recruitment began in April 2026 and continued until the target sample size was achieved in June 2026. The study followed adult patients with hematologic and non-hematologic malignancies who were scheduled to receive chemotherapy containing platinum-based or non-platinum alkylating agents. Kidney function was assessed serially before and after chemotherapy cycles to evaluate acute changes in serum creatinine, AKI-to-AKD transition, inter-cycle kidney recovery, new AKI, recurrent AKI after documented resolution, and further kidney function worsening among patients whose preceding AKI had not resolved.

### *Participants*

Consecutive adult patients with malignancy who met the eligibility criteria were screened and enrolled. Non-hematologic malignancies were confirmed by histopathological examination verified by an anatomical pathologist, whereas hematologic malignancies were confirmed by bone marrow examination, cytology, or immunophenotyping verified by a clinical pathologist.

Patients were included if they were aged >18 years, had a confirmed hematologic or non-hematologic malignancy, were considered eligible for chemotherapy by the treating oncologist, had a baseline estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m², and were scheduled to receive chemotherapy containing one of the target agents. Patients were excluded if they had pre-existing kidney disease or a malignancy directly involving, compressing, or obstructing the kidney. Eligible patients were followed for a minimum of two chemotherapy cycles.

The minimum sample size was calculated using a paired mean-difference formula because the study aimed to evaluate within-patient changes in kidney function before and after chemotherapy. The calculation used a two-sided significance level of 5%, corresponding to a $Z\alpha/2$ value of 1.96, and 80% power, corresponding to a $Z\beta$ value of 0.84. The expected mean difference in serum creatinine was 0.19 mg/dL, with a standard deviation of 0.51 mg/dL, based on a previous study of adult patients with cancer receiving cisplatin chemotherapy.[10] The calculated minimum sample size was 57 participants. After adjustment for an anticipated 20% loss to follow-up, the minimum required sample size was 72 participants. Consecutive sampling was performed until the target sample size was achieved.

### *Chemotherapy Exposure and Kidney Function Assessment*

The exposure of interest was chemotherapy containing platinum-based or non-platinum alkylating agents available at the study hospital. Platinum-based agents included cisplatin, carboplatin, and oxaliplatin, whereas non-platinum alkylating agents included cyclophosphamide and ifosfamide. Fitness for chemotherapy was assessed by the treating oncologist using the Eastern Cooperative Oncology Group performance status.

Kidney function was assessed using serial serum creatinine measurements obtained before and after chemotherapy. Serum creatinine was recorded before and after the first, second, and third chemotherapy cycles. For each cycle, acute kidney function changes were evaluated by comparing the post-chemotherapy serum creatinine value with the corresponding pre-chemotherapy value.

Inter-cycle kidney recovery was assessed by comparing serum creatinine before the subsequent cycle with the baseline value preceding the initial AKI episode. The interval between AKI detection and the subsequent pre-cycle assessment was determined for each patient to establish whether the AKD duration criterion of more than 7 days and within 90 days was fulfilled.

Baseline and clinical variables included age, age category (<50 and ≥50 years), sex, employment status, malignancy type, comorbidity status, chemotherapy agent, chemotherapy category, and serial serum creatinine values. Malignancy type was classified as hematologic or non-hematologic. The comorbidities evaluated were diabetes mellitus and hypertension. Diabetes mellitus was defined according to the American Diabetes Association Standards of Care in Diabetes as fasting plasma glucose ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL during a 75-g oral glucose tolerance test, random plasma glucose ≥200 mg/dL in individuals with classic symptoms of hyperglycemia or hyperglycemic crisis, HbA1c ≥6.5%, or current use of antidiabetic medication.[11] Hypertension was defined as blood pressure ≥140/90 mmHg or current use of antihypertensive medication, in accordance with the 2024 European Society of Cardiology guideline.[12]

***Outcome Definitions***

The primary kidney outcomes were AKI incidence, severity, and serial changes in serum creatinine across chemotherapy cycles. AKI-to-AKD transition and inter-cycle kidney recovery following an AKI episode were additional kidney outcomes. Secondary outcomes included new AKI, recurrent AKI after documented resolution of a preceding episode, and further kidney function worsening among patients whose preceding AKI had not achieved complete or partial resolution.

AKI was defined and staged using the Kidney Disease: Improving Global Outcomes criteria based on serum creatinine changes. Urine-output criteria were not applied because complete and standardised urine-output data were unavailable. Stage 1 AKI was defined as an increase in serum creatinine of ≥0.3 mg/dL or an increase to 1.5–1.9 times baseline. Stage 2 AKI was defined as an increase to 2.0–2.9 times baseline. Stage 3 AKI was defined as an increase to ≥3.0 times baseline, an increase in serum creatinine to ≥4.0 mg/dL, or initiation of kidney replacement therapy.[5] An absolute increase of exactly 0.30 mg/dL was considered to meet the AKI criterion.

For each chemotherapy cycle, AKI was determined by comparing the post-chemotherapy serum creatinine value with the corresponding pre-chemotherapy value. Thus, AKI after cycle 1 was assessed using the pre-cycle-1 value as the reference, whereas AKI after cycles 2 and 3 was assessed using the corresponding pre-cycle value as the reference.

Inter-cycle kidney recovery after AKI was classified according to the KDIGO 2026 public-review framework. Complete resolution was defined as serum creatinine <1.2 times the baseline value preceding the AKI episode. Partial resolution was defined as serum creatinine ≥1.2 but <1.5 times baseline. Absence of complete or partial resolution was defined as serum creatinine remaining ≥1.5 times baseline at the assessment before the subsequent chemotherapy cycle.[7]

For AKI occurring after cycle 1, recovery status was determined using the ratio of pre-cycle-2 serum creatinine to pre-cycle-1 serum creatinine. For AKI occurring after cycle 2, recovery status was determined using the ratio of pre-cycle-3 serum creatinine to pre-cycle-2 serum creatinine. New AKI after cycle 2 was defined as AKI occurring after the second chemotherapy cycle among patients who had not experienced AKI after cycle 1.

Recurrent AKI was defined as a new AKI episode occurring after complete or partial resolution of a preceding AKI episode.[7] Accordingly, recurrent AKI after cycle 2 was assessed only among patients who had experienced AKI after cycle 1 and subsequently achieved complete or partial resolution before cycle 2. Recurrent AKI after cycle 3 was assessed only among patients who had experienced AKI after cycle 2 and achieved complete or partial resolution before cycle 3.

An increase meeting the AKI criteria after a subsequent chemotherapy cycle among patients whose preceding AKI had not achieved complete or partial resolution was classified separately as further AKI or kidney function worsening and was not considered recurrent AKI.

AKD was defined as persistent kidney dysfunction beyond the initial 7-day AKI period and within 90 days after AKI onset.[6,7] In this study, serum creatinine–based AKD was assigned to patients with preceding AKI whose serum creatinine remained ≥1.2 times the baseline value at the subsequent pre-cycle assessment, provided that the assessment occurred more than 7 days and within 90 days after the preceding AKI episode.[7] Accordingly, patients with partial resolution or neither complete nor partial resolution who fulfilled the duration criterion were classified as having AKD, whereas patients with complete resolution were classified as not having AKD.

***Statistical Analysis***

Data were analysed using IBM SPSS Statistics version 30. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as mean and standard deviation when normally distributed or as median and range when non-normally distributed. For each chemotherapy cycle, the absolute change in serum creatinine was calculated as the post-chemotherapy value minus the corresponding pre-chemotherapy value. The serum creatinine ratio was calculated by dividing the post-chemotherapy value by the corresponding pre-chemotherapy value. The relative percentage change was calculated as the difference between post- and pre-chemotherapy serum creatinine divided by the pre-chemotherapy value and multiplied by 100. Threshold values were applied inclusively; therefore, an absolute serum creatinine increase of exactly 0.30 mg/dL was classified as AKI.

The incidence and severity of AKI were summarised after each chemotherapy cycle. New AKI after cycle 2 was analysed among patients without AKI after cycle 1. Among patients with AKI after cycle 1 or cycle 2, inter-cycle kidney recovery was classified as complete resolution, partial resolution, or absence of complete or partial resolution. AKD was summarised among patients with preceding AKI who fulfilled the duration criterion, with partial resolution and absence of complete or partial resolution classified as AKD. Recurrent AKI was analysed only among patients who had achieved complete or partial resolution of the preceding episode. Further AKI or kidney function worsening among patients without complete or partial resolution was analysed separately.

Associations between baseline characteristics and AKI outcomes were evaluated using the Pearson chi-square test or Fisher's exact test, as appropriate. Fisher's exact test was used when expected cell counts were less than five. Analyses of recurrent AKI and further kidney function worsening were considered exploratory because of the small subgroup sizes and limited number of events. A two-sided p-value of <0.05 was considered statistically significant.

### *Ethical Considerations*

The study protocol was approved by the Research Ethics Committee of Hasanuddin University, Makassar, Indonesia, under ethical approval number 491/UN4.6.4.5.31/PP36/2026 and protocol number UH26030382 on 10 April 2026. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before enrolment. Patient confidentiality was protected by anonymising all data before analysis.

## RESULTS

### Study Flow and Baseline Characteristics

A total of 100 patients were initially enrolled in the study. During follow-up, 6 patients died before completing the minimum observation period; therefore, 94 patients were included in the final analysis. The study flow is presented in Figure 1.

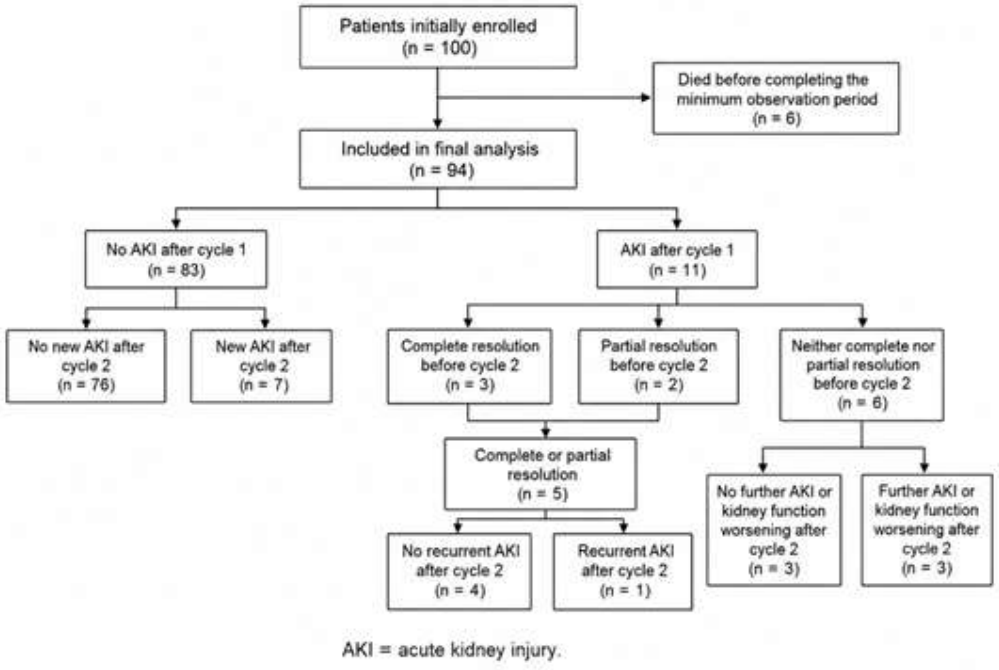


**Figure 1.** Study Flowchart

The mean age of the analysed patients was 45.57 ± 13.65 years. Most patients were aged <50 years (62.8%), were male (52.1%), had non-hematologic malignancies (83.0%), and had no documented comorbidity (71.3%). Platinum-based agents were used in 53 patients (56.4%), while non-platinum alkylating agents were used in 41 patients (43.6%). The most frequently administered chemotherapy agent was cyclophosphamide (37.2%), followed by oxaliplatin (26.6%), cisplatin (21.3%), carboplatin (8.5%), and ifosfamide (6.4%) (Table 1).

**Table 1.** Baseline characteristics and chemotherapy exposure of the study population (n = 94)

| Variable | Value |
|---|---|
| **Age, years, mean ± SD** | 45.57 ± 13.65 |
| **Age category** | |
| <50 years | 59 (62.8) |
| ≥50 years | 35 (37.2) |

| | |
|---|---|
| **Sex** | |
| Male | 49 (52.1) |
| Female | 45 (47.9) |
| **Malignancy type** | |
| Hematologic malignancy | 16 (17.0) |
| Non-hematologic malignancy | 78 (83.0) |
| **Comorbidity** | |
| No comorbidity | 67 (71.3) |
| With comorbidity | 27 (28.7) |
| **Chemotherapy category** | |
| Platinum-based agents | 53 (56.4) |
| Non-platinum alkylating agents | 41 (43.6) |
| **Chemotherapy agent** | |
| Cyclophosphamide | 35 (37.2) |
| Oxaliplatin | 25 (26.6) |
| Cisplatin | 20 (21.3) |
| Carboplatin | 8 (8.5) |
| Ifosfamide | 6 (6.4) |

Note: Categorical variables are presented as n (%), and continuous variables are presented as mean ± standard deviation.

**Changes in Serum Creatinine Across Chemotherapy Cycles**

Mean serum creatinine increased after chemotherapy across all three assessed cycles. During cycle 1, mean serum creatinine increased from 0.7480 ± 0.24286 mg/dL before chemotherapy to 0.8706 ± 0.48277 mg/dL after chemotherapy, corresponding to an absolute increase of 0.1226 mg/dL or 16.39%. During cycle 2, mean serum creatinine increased from 0.7657 ± 0.35833 mg/dL before chemotherapy to 0.8564 ± 0.48587 mg/dL after chemotherapy, corresponding to an absolute increase of 0.0907 mg/dL or 11.85%. During cycle 3, mean serum creatinine increased from 0.8298 ± 0.49793 mg/dL before chemotherapy to 0.8906 ± 0.66748 mg/dL after chemotherapy, corresponding to an absolute increase of 0.0609 mg/dL or 7.33% (Table 2). Although the group-level changes did not meet the AKI threshold, AKI classification was conducted at the individual patient level using the corresponding pre-chemotherapy serum creatinine value for each cycle.

**Table 2.** Changes in serum creatinine before and after chemotherapy across cycles

| Cycle | Pre-chemotherapy sCr, mean ± SD (mg/dL) | Post-chemotherapy sCr, mean ± SD (mg/dL) | Mean difference (mg/dL) | Increase (%) |
|---|---|---|---|---|
| Cycle 1 | 0.7480 ± 0.24286 | 0.8706 ± 0.48277 | 0.1226 | 16.39 |
| Cycle 2 | 0.7657 ± 0.35833 | 0.8564 ± 0.48587 | 0.0907 | 11.85 |
| Cycle 3 | 0.8298 ± 0.49793 | 0.8906 ± 0.66748 | 0.0609 | 7.33 |

Note: sCr = serum creatinine. Mean difference was calculated as post-chemotherapy sCr minus pre-chemotherapy sCr. Percentage increase was calculated as [(post-chemotherapy sCr − pre-chemotherapy sCr) / pre-chemotherapy sCr] × 100%.

**Incidence and Severity of Acute Kidney Injury**

After the first chemotherapy cycle, AKI occurred in 11 of 94 patients (11.7%). Most events were stage 1 AKI, observed in 8 patients (8.5%), whereas stage 2 and stage 3 AKI occurred in 2 patients (2.1%) and 1 patient (1.1%), respectively. Overall, AKI after cycle 2 occurred in 11 patients (11.7%), comprising 9 stage 1 events (9.6%) and 2 stage 3 events (2.1%). No stage 2 AKI was identified after cycle 2. Among the 83 patients who had not developed AKI after cycle 1, 7 patients (8.4%) developed new AKI after cycle 2. All new AKI events in this subgroup were stage 1. After cycle 3, AKI occurred in 5 patients (5.3%), including 2 stage 1 events (2.1%), 2 stage 2 events (2.1%), and 1 stage 3 event (1.1%) (Table 3).

**Table 3.** Incidence and severity of AKI across chemotherapy cycles

| AKI outcome | Cycle 1, n (%) | Cycle 2 overall, n (%) | New AKI after cycle 2 among patients without cycle-1 AKI, n (%) | Cycle 3 overall, n (%) |
|---|---|---|---|---|
| No AKI | 83 (88.3) | 83 (88.3) | 76 (91.6) | 89 (94.7) |
| AKI | 11 (11.7) | 11 (11.7) | 7 (8.4) | 5 (5.3) |
| Stage 1 AKI | 8 (8.5) | 9 (9.6) | 7 (8.4) | 2 (2.1) |
| Stage 2 AKI | 2 (2.1) | 0 (0.0) | 0 (0.0) | 2 (2.1) |

| | | | | |
|---|---|---|---|---|
| Stage 3 AKI | 1 (1.1) | 2 (2.1) | 0 (0.0) | 1 (1.1) |
| Total analysed | 94 (100.0) | 94 (100.0) | 83 (100.0) | 94 (100.0) |

**Note:** AKI = acute kidney injury. The new-AKI analysis after cycle 2 included only patients who did not develop AKI after cycle 1.

Transition from Acute Kidney Injury to Acute Kidney Disease Across Chemotherapy Cycles

Among the 11 patients who developed AKI after cycle 1, complete resolution before cycle 2 was observed in 3 patients (27.3%), partial resolution in 2 patients (18.2%), and neither complete nor partial resolution in 6 patients (54.5%). The interval between the preceding AKI episode and the pre-cycle-2 assessment was more than 7 days and within 90 days. Therefore, the 2 patients with partial resolution and the 6 patients with neither complete nor partial resolution were classified as having serum creatinine–based acute kidney disease (AKD). Overall, AKD before cycle 2 occurred in 8 of 11 patients (72.7%), whereas 3 patients (27.3%) did not meet the serum creatinine–based AKD criterion.

Among the 11 patients who developed AKI after cycle 2, complete resolution before cycle 3 was observed in 3 patients (27.3%), partial resolution in 6 patients (54.5%), and neither complete nor partial resolution in 2 patients (18.2%). Because the pre-cycle-3 assessment was performed more than 7 days and within 90 days after the preceding AKI episode, the 6 patients with partial resolution and the 2 patients with neither complete nor partial resolution were classified as having serum creatinine–based AKD. Accordingly, AKD before cycle 3 occurred in 8 of 11 patients (72.7%), whereas 3 patients (27.3%) did not meet the serum creatinine–based AKD criterion (Table 4).

**Table 4.** Transition from acute kidney injury to acute kidney disease across chemotherapy cycles

| Assessment and outcome pattern | n (%) |
|---|---|
| **After cycle-1 AKI** | |
| **Patients with AKI after cycle 1** | **11 (100.0)** |
| Complete resolution before cycle 2 | 3 (27.3) |
| Partial resolution before cycle 2 | 2 (18.2) |
| Neither complete nor partial resolution before cycle 2 | 6 (54.5) |
| **Patients assessed for AKD before cycle 2** | **11 (100.0)** |
| **AKD before cycle 2** | **8 (72.7)** |
| **Did not meet the serum creatinine–based AKD criterion before cycle 2** | **3 (27.3)** |
| **After cycle-2 AKI** | |
| **Patients with AKI after cycle 2** | **11 (100.0)** |
| Complete resolution before cycle 3 | 3 (27.3) |
| Partial resolution before cycle 3 | 6 (54.5) |
| Neither complete nor partial resolution before cycle 3 | 2 (18.2) |
| **Patients assessed for AKD before cycle 3** | **11 (100.0)** |
| **AKD before cycle 3** | **8 (72.7)** |
| **Did not meet the serum creatinine–based AKD criterion before cycle 3** | **3 (27.3)** |

**Note: AKI = acute kidney injury; AKD = acute kidney disease; sCr = serum creatinine. AKI, inter-cycle recovery, and AKD were classified according to the KDIGO 2026 framework. Percentages were calculated using patients with AKI after the corresponding cycle as the denominator.**

Subsequent Kidney Outcomes After Inter-Cycle Assessment

Among the 5 patients who achieved complete or partial resolution after cycle-1 AKI, 1 patient (20.0%) developed recurrent AKI after cycle 2, whereas 4 patients (80.0%) did not. Among the 6 patients who had not achieved complete or partial resolution before cycle 2, 3 patients (50.0%) experienced further AKI or kidney function worsening after cycle 2, whereas the remaining 3 patients (50.0%) did not. Further AKI or worsening in patients whose preceding episode had not resolved was classified separately and was not considered recurrent AKI.

Among the 9 patients who achieved complete or partial resolution after cycle-2 AKI, 3 patients (33.3%) developed recurrent AKI after cycle 3, whereas 6 patients (66.7%) did not. Among the 2 patients who had not achieved complete or partial resolution before cycle 3, neither experienced further AKI or kidney function worsening after cycle 3 (Table 5).

**Table 5.** Subsequent kidney outcomes after inter-cycle assessment

| Assessment and outcome pattern | n (%) |
|---|---|

| | |
|---|---|
| **After cycle-1 AKI** | |
| **Patients with complete or partial resolution before cycle 2** | **5 (100.0)** |
| No recurrent AKI after cycle 2 | 4 (80.0) |
| Recurrent AKI after cycle 2 | 1 (20.0) |
| **Patients with neither complete nor partial resolution before cycle 2** | **6 (100.0)** |
| No further AKI or kidney function worsening after cycle 2 | 3 (50.0) |
| Further AKI or kidney function worsening after cycle 2 | 3 (50.0) |
| **After cycle-2 AKI** | |
| **Patients with complete or partial resolution before cycle 3** | **9 (100.0)** |
| No recurrent AKI after cycle 3 | 6 (66.7) |
| Recurrent AKI after cycle 3 | 3 (33.3) |
| **Patients with neither complete nor partial resolution before cycle 3** | **2 (100.0)** |
| No further AKI or kidney function worsening after cycle 3 | 2 (100.0) |
| Further AKI or kidney function worsening after cycle 3 | 0 (0.0) |

**Note: AKI = acute kidney injury. Recurrent AKI was defined as a new AKI episode after complete or partial resolution of the preceding episode. Further AKI or kidney function worsening in patients without prior resolution was classified separately. Percentages were calculated using the relevant subgroup denominator.**

Factors Associated with Acute Kidney Injury Outcomes

Bivariate analysis showed that no baseline characteristic was significantly associated with AKI after the first chemotherapy cycle. Among the 94 patients included in the analysis, 11 patients (11.7%) developed AKI after cycle 1, whereas 83 patients (88.3%) did not. AKI occurred in 9 of 59 patients aged <50 years (15.3%) and 2 of 35 patients aged ≥50 years (5.7%; p = 0.202). No significant differences were observed according to sex, malignancy type, comorbidity status, or chemotherapy category (Table 6).

**Table 6.** Factors associated with AKI after cycle 1 in the total study population

| Variable | No AKI, n (%) | AKI, n (%) | p-value |
|---|---|---|---|
| **Overall** | 83 (88.3) | 11 (11.7) | - |
| **Age category** | | | **0.202** |
| <50 years | 50 (84.7) | 9 (15.3) | |
| ≥50 years | 33 (94.3) | 2 (5.7) | |
| **Sex** | | | **0.265** |
| Male | 45 (91.8) | 4 (8.2) | |
| Female | 38 (84.4) | 7 (15.6) | |
| **Malignancy type** | | | **1.000** |
| Hematologic malignancy | 14 (87.5) | 2 (12.5) | |
| Non-hematologic malignancy | 69 (88.5) | 9 (11.5) | |
| **Comorbidity** | | | **0.724** |
| No comorbidity | 60 (89.6) | 7 (10.4) | |
| With comorbidity | 23 (85.2) | 4 (14.8) | |
| **Chemotherapy category** | | | **0.525** |
| Platinum-based agents | 48 (90.6) | 5 (9.4) | |
| Non-platinum alkylating agents | 35 (85.4) | 6 (14.6) | |

**Note:** AKI = acute kidney injury. The analysis included all 94 patients. Percentages were calculated within each row category. P-values were obtained using Pearson's chi-square test or Fisher's exact test, as appropriate.

Among the 83 patients without AKI after cycle 1, 7 patients (8.4%) developed new AKI after cycle 2, whereas 76 patients (91.6%) remained free of AKI. No baseline characteristic was significantly associated with new AKI after cycle 2. New AKI occurred in 6 of 48 patients receiving platinum-based agents (12.5%) and 1 of 35 patients receiving non-platinum alkylating agents (2.9%), but the difference was not statistically significant (p = 0.230) (Table 7).

**Table 7.** Factors associated with new AKI after cycle 2 among patients without cycle-1 AKI

| Variable | No new AKI, n (%) | New AKI, n (%) | p-value |
|---|---|---|---|
| **Overall** | 76 (91.6) | 7 (8.4) | - |
| **Age category** | | | **0.697** |

| | | | |
|---|---|---|---|
| <50 years | 45 (90.0) | 5 (10.0) | |
| ≥50 years | 31 (93.9) | 2 (6.1) | |
| **Sex** | | | **0.697** |
| Male | 42 (93.3) | 3 (6.7) | |
| Female | 34 (89.5) | 4 (10.5) | |
| **Malignancy type** | | | **0.596** |
| Hematologic malignancy | 14 (100.0) | 0 (0.0) | |
| Non-hematologic malignancy | 62 (89.9) | 7 (10.1) | |
| **Comorbidity** | | | **0.390** |
| No comorbidity | 56 (93.3) | 4 (6.7) | |
| With comorbidity | 20 (87.0) | 3 (13.0) | |
| **Chemotherapy category** | | | **0.230** |
| Platinum-based agents | 42 (87.5) | 6 (12.5) | |
| Non-platinum alkylating agents | 34 (97.1) | 1 (2.9) | |

**Note:** AKI = acute kidney injury. The analysis was restricted to the 83 patients who did not develop AKI after cycle 1. Percentages were calculated within each row category. P-values were obtained using Pearson's chi-square test or Fisher's exact test, as appropriate.

Exploratory Factors Associated with Recurrent Acute Kidney Injury

The exploratory analysis of recurrent AKI after cycle 2 was restricted to the 5 patients who achieved complete or partial resolution after cycle-1 AKI. Recurrent AKI occurred in 1 patient (20.0%). No statistically significant differences in recurrent AKI were detected according to age category, sex, malignancy type, comorbidity status, or chemotherapy category. The two-sided Fisher's exact p-values were 0.400 for age category, 0.400 for sex, 1.000 for malignancy type, 0.200 for comorbidity status, and 0.400 for chemotherapy category (Table 8). These findings should be interpreted cautiously because the analysis included only 5 eligible patients and one recurrent AKI event.

**Table 8.** Exploratory factors associated with recurrent AKI after cycle 2 among patients with complete or partial resolution

| Variable | No recurrent AKI, n (%) | Recurrent AKI, n (%) | P-value |
|---|---|---|---|
| **Age category** | | | **0.400** |
| <50 years | 3 (100.0) | 0 (0.0) | |
| ≥50 years | 1 (50.0) | 1 (50.0) | |
| **Sex** | | | **0.400** |
| Male | 1 (50.0) | 1 (50.0) | |
| Female | 3 (100.0) | 0 (0.0) | |
| **Malignancy type** | | | **1.000** |
| Hematologic malignancy | 2 (100.0) | 0 (0.0) | |
| Non-hematologic malignancy | 2 (66.7) | 1 (33.3) | |
| **Comorbidity** | | | **0.200** |
| No comorbidity | 4 (100.0) | 0 (0.0) | |
| With comorbidity | 0 (0.0) | 1 (100.0) | |
| **Chemotherapy category** | | | **0.400** |
| Platinum-based agents | 1 (50.0) | 1 (50.0) | |
| Non-platinum alkylating agents | 3 (100.0) | 0 (0.0) | |

**Note:** AKI = acute kidney injury. This exploratory analysis included only patients who achieved complete or partial resolution after cycle-1 AKI (n = 5). Percentages were calculated within each row category. P-values were obtained using the two-sided Fisher's exact test.

## DISCUSSION

This prospective cohort study demonstrates that chemotherapy-associated kidney dysfunction may evolve dynamically from AKI to AKD across consecutive treatment cycles. AKI occurred in 11.7% of patients after cycle 1, with most events classified as stage 1. Among patients with cycle-1 AKI, complete resolution was observed in 27.3%, partial resolution in 18.2%, and neither complete nor partial resolution in 54.5% before cycle 2. Overall, 72.7% transitioned to serum creatinine–based AKD before cycle 2. Similarly, 72.7% of patients with cycle-2 AKI met the AKD criterion before cycle 3. New AKI developed after cycle 2 in 8.4% of patients without cycle-1 AKI. Recurrent AKI and further kidney function worsening were also observed, highlighting the coexistence of persistent dysfunction, recovery, recurrence, and new injury across treatment cycles.

Mean serum creatinine increased by 16.39% after cycle 1, 11.85% after cycle 2, and 7.33% after cycle 3. Although these group-level changes did not meet the AKI threshold,

this does not indicate an absence of clinically relevant nephrotoxicity because AKI is determined by individual changes from baseline rather than the mean change of the overall cohort.[5] Group averages may therefore conceal substantial kidney function changes in susceptible patients. Conventional cytotoxic chemotherapy remains an important cause of kidney toxicity and may produce acute tubular injury, tubulointerstitial injury, thrombotic microangiopathy, electrolyte abnormalities, AKI, AKD, and progressive CKD.[1,3,13] These findings reinforce the importance of patient-level serial assessment rather than reliance on aggregate creatinine changes.

The observed incidence of AKI after cycle 1 was lower than the approximately one-third nephrotoxicity rates reported in some previous cohorts.[8,9] Differences across studies may reflect variation in malignancy type, chemotherapy regimen, cumulative exposure, hydration protocols, concomitant nephrotoxic medications, baseline kidney function, and outcome definitions.[1–3] The relatively lower incidence in the present cohort may partly be explained by the inclusion of patients with baseline eGFR >60 mL/min/1.73 m² and no pre-existing kidney disease. Nevertheless, stage 3 AKI occurred after each observed cycle, indicating that clinically severe injury may still develop despite initially preserved kidney function.

Most cycle-1 AKI events were stage 1. Although stage 1 AKI is sometimes perceived as mild, even small increases in serum creatinine may represent clinically meaningful kidney injury and are associated with adverse outcomes in broader AKI populations.[5,14,15] In oncology practice, relatively modest kidney function changes may affect chemotherapy eligibility, dose adjustment, hydration requirements, and decisions regarding concurrent nephrotoxic medications.[16,17] The predominance of stage 1 AKI should therefore support early detection and intervention rather than clinical reassurance, particularly because more than half of patients with cycle-1 AKI had not achieved complete or partial resolution before the subsequent cycle.

A key contribution of this study is the characterisation of AKI-to-AKD transition and inter-cycle kidney recovery. Among 11 patients with cycle-1 AKI, 3 achieved complete resolution, 2 achieved partial resolution, and 6 remained at least 1.5 times above their preceding baseline at the pre-cycle-2 assessment. Because these abnormalities persisted beyond 7 days and within 90 days after the preceding AKI episode, the 2 patients with partial resolution and the 6 patients with neither complete nor partial resolution were classified as having serum creatinine–based AKD. Thus, 8 of 11 patients (72.7%) transitioned from AKI to AKD before cycle 2. The same proportion was observed after cycle-2 AKI, although the distribution differed, with partial resolution accounting for most AKD cases before cycle 3. The distinction between complete, partial, and absent resolution provides a more informative description than a binary classification based solely on return to baseline.7 Partial resolution reflects meaningful improvement but does not indicate complete recovery and may still fulfil the AKD criterion when the duration requirement is met.[6,7]

Recurrent AKI and further worsening before resolution represent clinically distinct trajectories. Among the 5 patients who achieved complete or partial resolution after cycle-1 AKI, 1 developed recurrent AKI after cycle 2. In contrast, 3 of the 6 patients who had not achieved resolution experienced further AKI or worsening after the subsequent cycle. Combining these groups would overestimate recurrent AKI because recurrence requires a new AKI episode after complete or partial resolution of the preceding episode.[7] Clinically, both trajectories remain important. Patients who recover may remain vulnerable to recurrent injury after re-exposure, whereas patients entering the next cycle with unresolved dysfunction may have reduced renal reserve and a greater risk of further deterioration. Accurate kidney function assessment is therefore essential because renal impairment may affect treatment eligibility, drug dosing, and toxicity risk.[16,18]

The development of new AKI after cycle 2 among patients without cycle-1 AKI further supports continued monitoring beyond the initial chemotherapy exposure. Of the 83 patients who remained free of AKI after cycle 1, 7 developed new AKI after cycle 2. AKI was also identified in 5.3% of patients after cycle 3. The absence of AKI after an earlier cycle therefore does not eliminate subsequent risk. Repeated tubular stress, cumulative chemotherapy exposure, intercurrent illness, hydration status, and changes in renal reserve may contribute to kidney injury during later treatment cycles.[1,2] Recent consensus recommendations similarly emphasise longitudinal surveillance because nephrotoxicity may emerge during ongoing treatment and influence subsequent cancer-management decisions.[3,13]

No baseline characteristic was significantly associated with AKI after cycle 1 or new AKI after cycle 2. These negative findings should be interpreted as inconclusive rather than as evidence that age, sex, malignancy type, comorbidity, or chemotherapy category are clinically irrelevant. The limited number of AKI events, preserved baseline kidney function, and heterogeneity of malignancies and chemotherapy exposure reduced the ability to detect associations. Previous studies have identified older age, hypertension, impaired baseline kidney function, platinum exposure, cumulative dose, hydration status, and concomitant nephrotoxic medications as relevant determinants of chemotherapy-associated kidney injury.[1–3]

The exploratory recurrent-AKI analysis was restricted to only 5 patients who had achieved complete or partial resolution, and only one recurrent event occurred. No statistically significant differences were detected according to age, sex, malignancy type, comorbidity status, or chemotherapy category. Although the recurrent event occurred in a patient receiving platinum-based chemotherapy, the comparison between platinum-based and non-platinum agents was not statistically significant.

This result cannot establish either the presence or absence of an association because of the very small denominator and limited number of events. Platinum compounds, particularly cisplatin, nevertheless remain established nephrotoxic agents through proximal tubular accumulation, DNA damage, mitochondrial dysfunction, oxidative stress, inflammatory responses, and tubular cell death.[4] Similarly, the absence of recurrent AKI among the three eligible patients receiving non-platinum agents should not be interpreted as renal safety, as ifosfamide has been associated with tubular dysfunction and kidney impairment in adults.[19]

Serial serum creatinine assessment remains feasible and clinically relevant in oncology practice. Although serum creatinine may not detect early tubular injury before functional decline becomes measurable, it remains central to KDIGO-based AKI classification and is widely available in routine care.[3,5] Kidney function assessment is particularly important in patients with cancer because renal function influences anticancer drug dosing, chemotherapy eligibility, supportive care, and clinical-trial participation.[16,17,20] In the present cohort, serial measurements enabled the identification of post-cycle AKI, inter-cycle recovery status, new AKI, recurrent AKI after resolution, and further worsening among patients whose preceding kidney dysfunction had not resolved.

These findings have several clinical implications. Kidney function should be assessed before and after each chemotherapy cycle rather than only at treatment initiation. Patients who develop AKI should undergo reassessment before subsequent treatment to identify AKI-to-AKD transition and distinguish complete resolution, partial resolution, and absence of complete or partial resolution. Patients with AKD may require closer review of hydration, concurrent nephrotoxic medications, chemotherapy dose, and the potential need for nephrology involvement. Monitoring should also continue in patients who remain free of AKI after the first cycle because new injury may occur during later exposure. These implications are consistent with consensus recommendations emphasising prevention, early recognition, longitudinal monitoring, and individualised management of anticancer therapy-associated nephrotoxicity.[3,13]

This study has several limitations. It was conducted at a single tertiary referral centre, which may limit generalisability. The study was not specifically powered to estimate AKI-to-AKD transition because the sample-size calculation was based on within-patient changes in serum creatinine. The number of AKI events was relatively small, reducing statistical power for risk-factor analyses. The recurrent-AKI analysis was particularly limited because only 5 patients had achieved complete or partial resolution after cycle-1 AKI and only one recurrent event occurred. Accordingly, the absence of statistically significant associations should not be interpreted as evidence of no association. Kidney injury and AKD were assessed using serum creatinine without urine-output data, structural kidney markers, or tubular injury biomarkers, which may have underestimated early or subclinical injury and incompletely characterised AKD. Chemotherapy dose intensity, cumulative dose, hydration protocols, concomitant nephrotoxic medications, and cancer-specific regimens were not analysed in detail. Nevertheless, the prospective design and serial assessment across three chemotherapy cycles provide clinically relevant information regarding AKI incidence, AKI-to-AKD transition, inter-cycle recovery, new AKI, recurrent AKI after resolution, and further kidney function worsening.

## CONCLUSIONS

Chemotherapy-associated kidney dysfunction evolved dynamically across consecutive treatment cycles. AKI occurred in 11.7% of patients after both cycles 1 and 2. Among the relatively small subgroups with AKI, 72.7% met the serum creatinine–based AKD criterion before the subsequent chemotherapy cycle. New AKI developed among patients without previous AKI, whereas recurrent AKI occurred after documented complete or partial resolution, and further kidney function worsening occurred separately among patients without such resolution. No baseline characteristic was significantly associated with AKI or recurrent AKI, although these analyses were limited by the small number of events. Serial serum creatinine monitoring before and after each chemotherapy cycle may facilitate detection of AKI-to-AKD transition, characterisation of inter-cycle recovery, and individualised kidney-protective management.

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**Author Contributions**

AAKS contributed to conceptualization, methodology, investigation, data curation, formal analysis, visualization, and writing—original draft. HR contributed to conceptualization, methodology, supervision, validation, writing—review and editing, and project administration. DB contributed to methodology, formal analysis, validation, visualization, and writing—review and editing. SB, HDS, and DSD contributed to supervision, clinical interpretation, validation, and writing—review and editing. AAZ contributed to formal analysis, statistical validation, methodology, and writing—review and editing. All authors reviewed and approved the final version of the manuscript.

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**Conflict of Interest**

The authors declare no conflicts of interest.

**Data Availability**

The datasets generated and analysed during the current study are not publicly available due to patient confidentiality and ethical restrictions, but may be

available from the corresponding author upon reasonable request and with permission from the relevant institutional ethics committee.

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