



Comparison of acute kidney injury incidence after doxorubicin and cyclophosphamide chemotherapy in breast cancer patients with and without adequate oral hydration prevention

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ABSTRACT

Background: Breast cancer is the leading cause of cancer death among Indonesian women, and the Doxorubicin and Cyclophosphamide (AC) regimen remains one of the primary systemic therapy options. This regimen carries significant nephrotoxic effects that can trigger acute kidney injury (AKI) in 10%–32.8% of patients, potentially causing permanent kidney damage and disrupting treatment continuity. Adequate oral hydration (30 mL/kg body weight/day) is an economical, practical preventive approach that accelerates drug metabolite excretion, but its effectiveness in reducing AKI incidence in clinical practice remains unclear. Aim: To compare AKI incidence in breast cancer patients undergoing AC chemotherapy between those who received adequate oral hydration prevention and those who did not. Methods: A prospective cohort study was conducted at the Surgical Oncology Clinic of Dr. Hasan Sadikin General Hospital, Bandung, from October 2025 to February 2026. Fifty-six subjects selected by consecutive sampling were divided into a prevention group and a no-prevention group (28 each). AKI was assessed using KDIGO criteria via serum creatinine at 48 hours and 7 days post-chemotherapy, and data were analyzed with the Chi-Square test. Results: Overall AKI incidence was 25% (14 of 56 subjects): 8 cases (28.5%) in the no-prevention group versus 6 cases (21.4%) in the prevention group. The Pearson Chi-Square test yielded $p = 0.469$ ($p > 0.05$). Conclusion: Although AKI cases were numerically lower in the prevention group, adequate oral hydration did not significantly reduce AKI incidence compared with no prevention in breast cancer patients undergoing AC chemotherapy.

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1. INTRODUCTION

Breast cancer is one of the most commonly diagnosed cancers among women in Indonesia, with an estimated 66,271 new cases in 2022. This makes breast cancer the leading cause of cancer-related deaths among Indonesian women, with more than 22,000 deaths in the same year. Treatment options for breast cancer include not only surgery but also chemotherapy, hormonal therapy, targeted therapy, and radiation therapy. The choice of treatment must also be tailored to the stage

and condition of the patient's breast cancer (Achmad et al., 2023; *Global Cancer Observatory: Cancer Today*, 2022; Moo et al., 2018).

Chemotherapy is a cancer treatment involving the administration of cytostatic drugs aimed at killing cancer cells, this therapy has systemic effects resulting from both the drug's response and side effects (Ajmeera & Ajumeera, 2024; Anand et al., 2023; Kopacz-Bednarska & Król, 2022; Koper et al., 2023; Yousefi Rizi et al., 2022). The choice of chemotherapy regimens varies widely. Considerations for selecting a chemotherapy regimen are generally based on the cancer subtype, history of prior chemotherapy, or the specific condition of the cancer affecting the patient (Achmad et al., 2023; Moo et al., 2018).

According to the 2023 Breast Cancer Management Guidelines, chemotherapy with a doxorubicin and cyclophosphamide regimen is the first-line treatment for certain groups of breast cancer patients. This is certainly a cause for concern because this regimen can cause acute kidney injury (AKI) (Horie et al., 2018; Sukesu et al., 2023).

This condition can occur in approximately 10%–25% of patients after receiving doxorubicin and in about 15%–32.8% after receiving cyclophosphamide. Although these numbers are small, the occurrence of AKI has the potential to cause irreversible kidney damage. This can also affect patients' quality of life and increase the morbidity of their disease. Furthermore, treatment goals may not be achieved because chemotherapy must be discontinued due to AKI. Post-chemotherapy AKI can disrupt the course of cancer treatment, worsen patients' prognosis, prolong hospital stays, and increase treatment costs (Braet et al., 2022; Horie et al., 2018; Sukesu et al., 2023).

Chemotherapy with a combination regimen of doxorubicin and cyclophosphamide is the most commonly used regimen for patients with breast cancer at Dr. Hasan Sadikin General Hospital in Bandung. Therefore, the incidence of AKI resulting from this chemotherapy regimen is important to monitor (Tacar et al., 2013).

According to KDIGO criteria, AKI is defined as an increase in serum creatinine of 0.3 mg/dL or more within 48 hours, or an increase in serum creatinine to 1.5 times the baseline value or more within the past 7 days, or urine output of less than 0.5 mL/kg/hour for 6 hours (Sukesu et al., 2023).

Adequate hydration, or sufficient body fluid intake, is a key factor in preventing and managing AKI, particularly that caused by nephrotoxic drugs. Increasing fluid intake can help improve renal blood flow and glomerular filtration rate, thereby accelerating the excretion of drugs and their metabolites and reducing the risk of kidney injury (Horie et al., 2018).

Adequate oral intake of water plays a crucial role in preventing AKI induced by doxorubicin and cyclophosphamide. Doxorubicin and Cyclophosphamide can cause kidney damage through various mechanisms, including oxidative stress and direct injury to the renal tubules. Adequate hydration can help reduce the risk of nephrotoxicity by increasing renal blood flow and accelerating the excretion of potentially damaging metabolites of Doxorubicin and Cyclophosphamide (Horie et al., 2018).

Although intravenous (IV) hydration protocols are well-established for highly nephrotoxic agents like cisplatin, current supportive care guidelines offer limited and inconsistent guidance regarding non-invasive, cost-effective prevention strategies for moderately nephrotoxic regimens such as doxorubicin and cyclophosphamide (AC) (Cosmai et al., 2021; Horie et al., 2018).

Existing literature on chemotherapy-induced nephrotoxicity has predominantly focused on targeted pharmacological agents or intensive IV hydration in inpatient settings (Cosmai et al., 2021; Santos et al., 2020). Consequently, a critical research gap exists regarding whether a structured, patient-managed oral hydration protocol can provide measurable protection against cumulative renal injury in outpatients receiving AC chemotherapy (Cosmai et al., 2021; Horie et al., 2018).

To address this gap, this study evaluated the clinical contribution of an adequate oral hydration protocol (30 mL/kg/day) as an accessible adjunct measure to standard IV pre-hydration (Horie et al., 2018; Sukesu et al., 2023). By prospectively comparing the incidence of AKI across four AC cycles between patients receiving structured oral hydration and those without, this study aims to

provide empirical evidence to inform practical, scalable, and low-cost supportive care protocols in routine oncology practice, particularly in resource-limited settings where minimizing hospitalization burden and treatment disruptions is essential.

2. RESEARCH METHOD

This prospective cohort analytic study was conducted at the Surgical Oncology Clinic of Dr. Hasan Sadikin General Hospital, Bandung, from October 2025 to February 2026. The study population comprised all breast cancer patients undergoing the AC chemotherapy regimen at this institution who met the inclusion criteria.

Inclusion criteria were: (1) confirmed diagnosis of breast cancer; (2) receiving the Doxorubicin and Cyclophosphamide chemotherapy regimen; and (3) willing to participate and signing the informed consent form. Exclusion criteria included: (1) pre-chemotherapy serum creatinine >1.11 mg/dL; (2) discontinuation of chemotherapy; and (3) prior history of radiotherapy.

The sampling method used in this study was consecutive sampling, in which subjects who arrived in sequence and met the selection criteria were included in the study until the required number of subjects was reached (Gannika et al., 2025; Nilmart et al., 2025; Ogino & Tadi, 2024). Sample size was calculated using the Lemeshow formula with P_1 (AKI proportion in the control group) = 32.8%, P_2 (AKI proportion in the intervention group) = 5%, 95% confidence level, and 70% power, yielding a minimum of 24 subjects per group. Adding 15% for potential dropouts, the final sample was 28 subjects per group, for a total of 56 subjects.

The prevention group received an adequate oral hydration protocol, defined as a minimum fluid intake of 30 mL/kg body weight/day of mineral water starting one day before chemotherapy and continuing until two days after each cycle. This 30 mL/kg/day target was established based on standard physiological fluid maintenance guidelines to maintain optimal renal perfusion, sustain glomerular filtration rate, and accelerate the urinary excretion of nephrotoxic Doxorubicin and Cyclophosphamide metabolites (Horie et al., 2018; Sukesu et al., 2023). Subjects in this group logged daily fluid intake using a graduated water bottle provided by the researcher. The no-prevention group received no structured oral hydration intervention but recorded their routine fluid intake over the same period.

To comply with ethical standards and institutional protocols, both groups received intravenous (IV) 0.9% NaCl 500 mL as a pre-chemotherapy loading dose. While this standardized IV pre-hydration minimized pre-renal AKI as a confounding factor, it established a baseline nephroprotective threshold across both study arms. Consequently, this study design specifically evaluated the incremental protective benefit of structured oral hydration over standard IV pre-hydration; this baseline hydration likely attenuated the observable difference in AKI incidence between groups, contributing to a non-statistically significant result (Cosmai et al., 2021).

Data were analyzed using SPSS version 29.0. Univariate analysis was performed to describe frequency distributions (Fulk, 2023). Bivariate analysis using the Pearson Chi-Square test compared AKI incidence between groups, with statistical significance set at $p \leq 0.05$ (Carr & Smith, 2026; Ho, 2022; Kwak, 2023).

3. RESULTS AND DISCUSSION

Results

A total of 56 subjects were enrolled, 28 in each group. Two subjects who died during the study period were replaced with new participants. The youngest subject was 32 years old and the oldest was 73 years old. The prevention group had a mean age of 51.71 years (range 33–73 years), while the no-prevention group had a mean age of 49.17 years (range 32–72 years).

Table 1 presents the characteristics of the study subjects. No significant differences were found between the two groups in terms of age ($p = 0.453$), cancer staging ($p = 0.892$), or molecular subtype ($p = 0.364$), indicating good baseline comparability. The majority of subjects were at stage IIIA, with Luminal B being the most common subtype.

Table 1. Characteristics and AKI incidence of study subjects

Variable	Prevention (n=28)	No Prevention (n=28)	p-Value
Age (years)			
Mean	51.71	49.17	0.453
Median	50	47	
Range	33–73	32–72	
Stage			
IIB	3	4	0.892
IIIA	17	15	
IIIB	8	9	
Molecular Subtype			
Luminal A	4	3	0.364
Luminal B	16	20	
HER2-type	6	2	
Triple Negative	2	3	
AKI Incidence			
Cycle I	1 (3.57%)	1 (3.57%)	0.469
Cycle II	1 (3.57%)	1 (3.57%)	
Cycle III	2 (7.14%)	3 (10.71%)	
Cycle IV	4 (14.28%)	6 (21.42%)	

Note. AKI = acute kidney injury. p-values calculated using the Pearson Chi-Square test.

The overall AKI incidence across 56 subjects was 25% (14 cases). In the prevention group, 6 subjects (21.4%) experienced AKI, while in the no-prevention group, 8 subjects (28.5%) experienced AKI. Both groups showed identical AKI rates in Cycles I and II (3.57% each).

From Cycle III onward, the no-prevention group showed a more pronounced increase: 10.71% in Cycle III and 21.42% in Cycle IV, compared to 7.14% and 14.28% in the prevention group, respectively. A positive correlation was observed between the number of chemotherapy cycles and AKI incidence in both groups, suggesting a cumulative nephrotoxic effect.

Bivariate analysis using the Pearson Chi-Square test yielded a p-value of 0.469 ($p > 0.05$), indicating no statistically significant difference in AKI incidence between the prevention and no-prevention groups. In the prevention group, 6 subjects experienced AKI events, 2 of whom experienced AKI in two separate cycles. In the no-prevention group, 8 subjects experienced AKI events, 2 of whom experienced AKI twice and 1 subject experienced AKI in three cycles.

Discussion

This study demonstrates a progressive, cumulative increase in AKI incidence across consecutive cycles of AC chemotherapy in both study arms. The overall AKI incidence of 25% (14 of 56 subjects) and the control group incidence of 28.5% are concordant with the reported literature range of 10%–32.8% for doxorubicin- and cyclophosphamide-containing regimens (Galizia et al., 2018; Santos et al., 2020). This finding validates the external consistency of our study cohort and confirms that the AC regimen poses a substantial nephrotoxic risk in routine oncology practice.

Although the prevention group consistently exhibited lower AKI rates than the no-prevention group—most notably in Cycle III (7.14% vs. 10.71%) and Cycle IV (14.28% vs. 21.42%)—the difference was not statistically significant ($p = 0.469$). From a clinical perspective, however, this numerical reduction corresponds to an absolute risk reduction of 7.1%.

In clinical oncology, preventing AKI in approximately 1 out of every 14 patients carries substantial pragmatic value, as even mild Stage 1 AKI can prompt chemotherapy dose modifications, treatment delays, or enhanced drug toxicity due to impaired renal clearance (Braet et al., 2022; Cosmai et al., 2021). Given that structured oral hydration is cost-free, non-invasive, and devoid of side effects, this absolute risk reduction underscores its clinical utility despite the lack of statistical power in our sample.

When compared with broader literature on chemotherapy-induced nephrotoxicity prevention, these results mirror findings by (Cosmai et al., 2021; Horie et al., 2018). While aggressive IV hydration protocols are established standard-of-care for highly nephrotoxic regimens like

cisplatin, the role of patient-managed oral hydration in moderately nephrotoxic outpatient regimens remains less definitive.

The biological plausibility of oral hydration—accelerating tubular fluid velocity and shortening nephrotoxin dwell time—is well accepted (Horie et al., 2018). However, because both study arms in our trial received a standard 500 mL IV NaCl 0.9% pre-loading dose per institutional protocol, the incremental protective effect of oral hydration was attenuated, leading to a smaller observable effect size between groups.

A key clinical implication of our findings pertains to the timing of renal function monitoring during AC chemotherapy. In both groups, AKI incidence was low during Cycle I (3.57%) and Cycle II (3.57%), but escalated markedly in Cycle III (7.14% vs. 10.71%) and peaked in Cycle IV (14.28% vs. 21.42%). This trajectory illustrates the cumulative nature of anthracycline and alkylating agent nephrotoxicity, where repeated tubular oxidative stress and subclinical parenchymal injury gradually exhaust the kidney's functional reserve (Galizia et al., 2018; Horie et al., 2018).

Consequently, oncology clinicians should not rely solely on baseline renal function; renal monitoring (serum creatinine at 48 hours and Day 7 post-chemotherapy) must be intensified starting from Cycle III onward. Furthermore, clinical counseling regarding strict fluid adherence should be actively reinforced prior to later chemotherapy cycles.

Several study limitations must be acknowledged. First, hydration compliance relied on self-reported fluid logs, introducing potential reporting bias. Second, the sample size ($n = 56$) was powered at 70%, which restricted the statistical capacity to detect subtle differences between intervention arms. Third, observation was limited to four AC cycles, precluding long-term assessment of renal recovery. Despite these limitations, this study provides valuable prospective evidence supporting structured oral hydration (30 mL/kg/day) as a practical, low-cost supportive measure, while highlighting the necessity of stage-specific renal vigilance during cumulative AC chemotherapy.

4. CONCLUSION

Although structured oral hydration (30mL/kg body weight/day) did not yield a statistically significant reduction in overall AKI incidence (21.4% in the prevention group vs. 28.5% in the no-prevention group; $p = 0.469$), it demonstrated a consistent numerical trend toward lower AKI rates across all cycles, corresponding to a clinically meaningful absolute risk reduction of 7.1%. Furthermore, AKI risk accumulated progressively across consecutive chemotherapy cycles, escalating markedly from Cycle III onward and peaking in Cycle IV.

Structured oral hydration should be implemented as a routine, non-invasive, and cost-effective supportive care adjunct to standard IV pre-hydration in outpatient AC chemotherapy protocols. Given its high safety profile and feasibility, integrating structured oral fluid counseling provides a practical safeguard against chemotherapy-induced renal compromise, particularly in resource-limited settings.

To optimize AKI prevention in clinical practice, renal function monitoring (serum creatinine at 48 hours and Day 7 post-chemotherapy) should be intensified starting from Cycle III onward, when cumulative tubular injury exceeds functional baseline thresholds. Additionally, patient education and compliance verification regarding daily fluid intake should be actively reinforced prior to later treatment cycles.

Future research should focus on adequately powered, multicenter randomized trials with larger sample sizes to confirm these clinical trends. Studies should incorporate objective biomarkers of hydration status (such as urine specific gravity or osmolality) to overcome self-reporting bias, extend renal follow-up beyond four treatment cycles, and perform subgroup analyses stratified by patient risk factors, including age, baseline eGFR, and comorbid conditions.

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