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Original Article

Risk Factors for Cisplatin-Induced Nephrotoxicity among Cancer Patients in Bangladesh: A Multicenter Cross-Sectional Study

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Abstract

Background: Nephrotoxicity is a common complication of Cisplatin based chemotherapeutics. Several factors are anticipated to be associated with this outcome.

Objectives: This study aimed to determine the potential risk factors associated with Cisplatin-induced nephrotoxicity among Cancer patients in Bangladesh.

Materials and Methods: A multicenter cross-sectional study was conducted in tertiary-level hospitals. A total of 87 Cancer patients receiving cisplatin-based chemotherapy were enrolled. Serum creatinine and estimated glomerular filtration rate (eGFR) as indicative of nephrotoxicity were measured before and after each chemotherapy cycle. Statistical analyses were performed to evaluate the risk factors associated with Cisplatin-induced nephrotoxicity.

Results: Mean age of the patients was 47.0±12.6 years with 54% female and 46% male. Among 87 participants, nephrotoxicity was observed in 17.2% of patients. The Mann-Whitney U test showed a significant difference in age, baseline creatinine, and eGFR between normal and nephrotoxic groups (p=0.002, 0.001, 0.003 respectively). Binary logistic regression revealed increased odds of nephrotoxicity with increasing age (Odds Ratio (OR) =1.090, 95% CI: 1.026–1.157, p=0.005), diabetes (OR=8.500, 95% CI: 1.949–37.074, p=0.004), dose of cisplatin (OR=1.043, 95% CI: 1.003–1.085, p=0.037), and baseline eGFR (OR=0.953, 95% CI: 0.922–0.986, p=0.005). Diabetes increased the odds of nephrotoxicity by 8.5 times than non-diabetic.

Conclusion: Increased age, being diabetic, high baseline creatinine and low baseline eGFR were key risk factors for nephrotoxicity. Adopting early preventive measures for risk groups may reduce the impact of Cisplatin-induced nephrotoxicity.

Keywords: Cisplatin, Nephrotoxicity, Cancer, Chemotherapy, Risk factors.

Introduction

Cisplatin is a potent chemotherapeutic agent used for various solid neoplasia.[1, 2, 3] It is frequently used as an adjunct with other chemotherapeutic drugs.[1] It exerts its cytotoxic anticancer properties by interfering with cellular replication through direct Deoxy-ribonucleic acid (DNA) damage which leads to defective gene expression and the production of Reactive oxygen species (ROS), and eventually cellular damage and death.[1, 3, 4, 5] Despite its potency in Cancer treatment, it demonstrates multisystem cytotoxic effects like gastrointestinal toxicity, neurotoxicity, ototoxicity, marrow suppression, immunological reaction and notably nephrotoxicity with varying degrees of renal impairment which limits it use now-a-days. Among all these side effects of Cisplatin, nephrotoxicity is considered the most important and complicated

because of the complexity of dose modification and ambiguous risk benefit ratio. Studies revealed that cisplatin can induce nephrotoxicity in 8-40% of cases.[1, 2, 5, 7, 8]

Several risk factors including increasing age, sex, diabetes, hypertension, cardiovascular diseases, cisplatin dose, genetic predisposition, other nephrotoxic drugs are associated with cisplatin induced renal toxicity. [4, 5, 7-13] It is evident from studies that the risk of developing nephrotoxicity multiplies with increasing age.[6, 12-15] Usually, ageing is a renal impairing factor and renal function declines gradually after 40 years.[15] Neoplasia in older age shows increased susceptibility to drug induced nephrotoxicity due to predisposing muscle wasting, increasing sensitivity to reactive oxygen species, and reduced tubulo-glomerular function.[6, 12, 13] Diabetes, as a general comorbid factor for renal impairment in normal patients, may also be associated with nephrotoxicity caused by Cisplatin. A study showed that cisplatin invoked nephrotoxicity among Diabetic patients in 22.1% of cases.[5]. Cisplatin induced nephrotoxicity can be intensified by diabetes and atherosclerotic cardiovascular diseases.[12] Hypertension is another risk factor found in several other studies for renal impairment.[1, 14] Moreover, Cisplatin is a dose-modifying nephrotoxic drug which has substantial cumulative effect for nephrotoxicity with repeated, higher dose, and reduced renal clearance rate. Since nearly 90% of cisplatin excretes through kidney, higher dose and reduced clearance rate increase the deposition of cisplatin metabolites in renal tubule which eventually causes inflammation, cellular damage by production of ROS and ultimately cellular death.[4] In this study, we tried to figure out some of these potential risk factors and their roles on cisplatin-invoked nephrotoxicity in context to neoplastic patients in Bangladesh. This multicenter study aimed at capturing an upfront picture of pharmacological management of cancer patients with cisplatin-based chemotherapy.

Materials and Methods

Study Design and Population

This cross-sectional study was conducted in the Pharmacology Department of Sir Salimullah Medical College. It included 87 Cancer patients aged >18 years and received at least ≥55mg/m2 of 3 cycles cisplatin-based chemotherapy. Nephrotoxicity was defined as a decline in renal function, measured by an eGFR <60 ml/min, occurring from the first cycle of cisplatin therapy until one month after the third cycle. Patients with pre-existing chronic kidney disease were excluded.

Data collection and processing

Data was collected conveniently from the oncology department of Sir Salimullah Medical College Hospital, Dhaka Medical College Hospital, and National Institute Cancer and Research Hospital of Bangladesh from 2021 to 2022. These three centers were selected purposively as these centers usually handle high burden of all types of cancer patients in Dhaka. We categorized some related factors for declining renal function such as age (<40 years and ≥ 40years), cisplatin dose (<70 mg/m2 and ≥70 mg/m2), body built of the patients (Body Mass Index (BMI)-Underweight (<18.5 Kg/m2), Normal weight (18.5-24.9 Kg/m2), Overweight (25.0-29.9 Kg/m2) and Obese (≥30.0 Kg/m2) etc. Prechemotherapy clinical data like DM, HTN and relevant laboratory data were taken from record review. We had obtained serum creatinine and eGFR values before and after each cycle of chemotherapy. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula.

Statistical Analysis

Data analysis was carried out using SPSS version 25.0. Quantitative variables were stated as mean±SD. Qualitative data were expressed as frequency and percentage. We employed Mann-Whitney U test to compare Age, BMI, Cisplatin dose, Baseline

Creatinine, and Baseline eGFR between normal and nephrotoxic patients. Binary logistic regression analysis was used to find the Odds Ratio of Age, Sex, Diabetes, Hypertension, Cisplatin dose, Baseline creatinine, Baseline eGFR as predictors of nephrotoxicity. P-value less than 0.05 at the 95% Confidence Interval was considered as statistically significant.

Ethical Considerations

Ethical approval was obtained from the institutional review boards of Sir Salimullah Medical College and informed written consent was taken from all participants.

Results

In this study, mean age of the patients was 47.0±12.6 years. Among these patients 54% were female and 46% were male. Nephrotoxicity was observed in 17.2% cases after completing three cycles of cisplatin therapy. Patient's other demographic and clinical characteristics are shown in table- I.

Table I: Demographic and clinical characteristics of the patients (n=87)

Characteristics	Frequency	Percentage (%)
Age (Years)		
Age<40 years	20	23.0
Age≥40 years	67	77.0
(Mean±SD)	47.0±12.6	
Gender		
Female	47	54.0
Male	40	46.0
Body built of the patients (BMI)		
Underweight (<18.5 Kg/m^2)	18	20.7
Normal weight (18.5-24.9 Kg/m^2)	52	59.8
Overweight (25.0-29.9 Kg/m^2)	15	17.2
Obese (≥30.0 Kg/m^2)	2	2.3
Characteristics	**Frequency**	**Percentage (%)**
Age (Years)		
Comorbidity		
Diabetes Mellitus	9	10.3
Hypertension	7	8.0
Cisplatin dose		
<70 mg/m^2	41	47.1
≥70 mg/m^2	46	52.9
Baseline Creatinine (mg/dl) (mean±SD)	0.78±0.16	
Baseline eGFR (mean±SD)	103.12±26.40	
Outcome		
Normal	72	82.8
Nephrotoxicity	15	17.2

Table II: Comparison of risk variables between normal and nephrotoxic groups

Variables	Normal (Mean Rank)	Nephrotoxic (Mean Rank)	U value	Z value	P value*
Age	40.09	62.77	258.5	-3.170	p=0.002
BMI	43.57	46.07	509.0	-0.349	p=0.727
Cisplatin dose	42.13	53.00	405.0	-1.599	p=0.110
Baseline Creatinine	39.95	63.43	248.5	-3.280	P=0.001
Baseline eGFR	47.64	26.53	278.0	-2.945	P=0.003

two groups in Mann-Whitney U test (p=0.002, 0.001, 0.003 respectively). The Nephrotoxic group had a higher mean rank for age and baseline creatinine compared to the Normal group. For baseline eGFR, it showed inverse direction as the Nephrotoxic group had a lower mean rank than normal group. BMI (p=0.727) and Cisplatin Dose (p=0.110) showed no significant differences between the groups.

Table III: Unadjusted Binary Logistic Regression Analysis of Factors Associated with Nephrotoxicity

Variable	B	df	p-value	Odds Ratio (Unadjusted)	95% Confidence Interval
Age (Years)	0.086	1	0.005	1.090	(1.026 - 1.157)
Gender (Male)	0.034	1	0.953	1.034	(0.339 – 3.154)
Diabetes (Yes)	2.140	1	0.004	8.500	(1.949 – 37.074)
Hypertension (Yes)	0.723	1	0.416	2.062	(0.360-11.793)
Cisplatin dose (mg/m^2)	0.042	1	0.037	1.043	(1.003-1.085)
Baseline creatinine (mg/dL)	5.600	1	0.003	270.318	(6.355-11498.445)
Baseline eGFR	-0.048	1	0.005	0.953	(0.922-0.986)

Binary logistic regression showed the association of risk factors with nephrotoxicity (Table III). We found that the odds of nephrotoxicity among the participants increase significantly by 9% with each unit increase in age (OR =1.090, 95% CI: 1.026–1.157). It indicated that older individuals had a higher likelihood of developing nephrotoxicity. The OR for gender was 1.034 (p=0.953), indicating no significant difference in nephrotoxicity between male and female Cancer patients receiving Cisplatin. Diabetes was significantly associated with nephrotoxicity (OR=8.500, 95% CI: 1.949–37.074). Individuals with diabetes were 8.5 times more likely to develop nephrotoxicity compared to those without diabetes (p=0.004). Though Hypertension is a common risk factor for renal impairment, it didn't show any significant association with nephrotoxicity in this scenario (p=0.416). The dose of cisplatin, baseline creatinine, and baseline eGFR were significantly associated with nephrotoxicity (OR=1.043, 95% CI: 1.003–1.085, p=0.037; OR=270.318, 95% CI: 6.355–11,498.445, p=0.003; and OR=0.953, 95% CI: 0.922–0.986, p=0.005 respectively). These results indicated that for each unit increase in cisplatin dose, the odds of nephrotoxicity increased by 4.3%. In case of eGFR, a lower baseline value was associated with an increased likelihood of nephrotoxicity.

Discussion

The data was collected at three tertiary level multi-disciplined hospitals in Bangladesh where patients usually come from all over the country. All eligible patients receiving cisplatin-based chemotherapy during the study period were included. Cisplatin is a potent chemotherapeutic agent often used in conjunction with other chemotherapeutic drugs.[1] Several risk factors like age, sex, comorbidities, BMI, cisplatin dose, gene expression are associated with cisplatin induced renal toxicity.[3] Most of the patients were older adults (Mean age 47.0±12.6 years) and odds of nephrotoxicity increased by 9% with the increasing age. It indicated that older individuals had a higher likelihood of developing nephrotoxicity. Usually, increasing age is a renal impairing factor and renal function declines gradually after 40 years.[15] Neoplasia in older age shows increased susceptibility to drug induced nephrotoxicity due to predisposing muscle wasting, increasing threat to reactive oxygen species, and reduced tubulo-glomerular function.[6, 12, 13] Our sample had 54% female and 46% male patients. Similar male-female distribution was also found in several other studies.[1, 14] Nephrotoxicity was observed in 17.2% cases after completing three cycles of cisplatin therapy in this study. Some studies showed that prevalence of nephrotoxicity due to cisplatin-based chemotherapeutics ranges from 8% to 40% of cases.[1, 14]

The Mann-Whitney U test showed direct relation of age as well as baseline creatinine and an inverse relation of baseline eGFR with Nephrotoxicity. Patients who had higher creatinine or lower eGFR or both at baseline were more likely to develop nephrotoxicity after cisplatin therapy. Diabetes, as a general comorbid risk factors for renal impairment in normal patients, was also significantly associated with nephrotoxicity caused by Cisplatin. Individuals with diabetes were 8.5 times more likely to develop nephrotoxicity compared to non-diabetic. A study on cisplatin induced nephrotoxicity among Diabetes Mellitus showed that nephrotoxicity occurs in 22.1% of Diabetic Cancer patients receiving this drug, possibly because of the reduction in renal autophagy.[5] Cisplatin induced nephrotoxicity can be intensified by diabetes and atherosclerotic cardiovascular diseases.[12]. Though

Hypertension is another risk factor found in several other studies for renal impairment.[1, 14] this study didn't find any significant association of hypertension with nephrotoxicity in this scenario. The dose of cisplatin, baseline creatinine, and baseline eGFR were significantly associated with nephrotoxicity.

These results indicated that for each unit increase in cisplatin dose, the odds of nephrotoxicity increased by 4.3%. One unit decrease in baseline eGFR increased the odds of nephrotoxicity by 4.7%. Cisplatin being a dose-modifying nephrotoxic drug has significant cumulative effect for nephrotoxicity with higher dose and reduced renal clearance rate. Since nearly 90% of cisplatin excretes through kidney, higher dose and reduced clearance rate increase the deposition of cisplatin metabolites in renal tubule which eventually causes inflammation, cellular damage by production of ROS and ultimately cellular death.[4] For each unit increase in baseline creatinine value, the odds of nephrotoxicity increased greatly with a wide variability in confidence interval, indicating that higher baseline creatinine were strongly associated with nephrotoxicity but at the same time with considerable uncertainty. This could be due to small samples and disproportionate effect of the scale of measurement between creatinine and outcome variable.

As a retrospective cross-sectional study, this study had limited scope for generalizing comparability between nephrotoxic and normal patients. In addition, the effect of adjunct therapy and other risk factors could not be controlled in this setting which may yield to sub-estimate or overestimate. Further research, potentially with adjusted models, would be needed to refine these associations and explore causal relationships. Despite these facts, this study will contribute substantially to prevention and clinical management of nephrotoxicity among Cancer patients receiving cisplatin in Bangladesh.

Conclusion

This study sheds light on the pressing risk of cisplatin-induced nephrotoxicity among cancer patients, especially those who are older, diabetics, receive higher doses, or start with poor kidney function. These findings underscore the importance of close monitoring and early screening to protect vulnerable patients during treatment. The study also highlights the need for future, more detailed research to better guide treatment decisions and protect patients from avoidable harm.

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Conflicts of interest

All authors declare no conflict of interest related to the matters discussed in this paper.

References

1. Hammami MB, Gudino P, Rodriguez Salazar JD, Vegivinti C, Qasim A, Acharya A. Assessing the prevalence and severity of cisplatin-induced nephrotoxicity in a minority- low socioeconomic population in the Bronx, New York. Journal of Chemotherapy [Internet]. 2025 Apr 3; 37(3): 278–83. Available from: https:// www. tandfonline. com/doi/ full/ 10.1080/1120009X. 2024.2363105
2. Higuchi K, Yanagawa T. Evaluating dose of cisplatin responsible for causing nephrotoxicity. Abe H, editor. PLoS One [Internet]. 2019 Apr 25; 14 (4):e0215757. Available from: https:// dx. plos. org/ 10.1371/journal.pone.0215757
3. McSweeney KR, Gadanec LK, Qaradakhi T, Ali BA, Zulli A, Apostolopoulos V. Mechanisms of Cisplatin-Induced Acute Kidney Injury: Pathological Mechanisms, Pharmacological Interventions, and Genetic Mitigations. Cancers (Basel) [Internet]. 2021 Mar 29;13(7):1572. Available from: https://www. mdpi.com/2072-6694/13/7/1572
4. Duffy E, Fitzgerald W, Boyle K, Rohatgi R. Nephrotoxicity: Evidence in Patients Receiving Cisplatin Therapy. Clin J Oncol Nurs [Internet]. 2018 Apr 1;22(2):175–83. Available

from: http://cjon.ons.org/cjon/22/2/ nephrotoxicity-evidence- patients- receiving- cisplatin- therapy

5. Saito Y, Kobayashi M, Tamaki S, Nakamura K, Hirate D, Takahashi K, et al. Risk factor analysis for cisplatin-induced nephrotoxicity with the short hydration method in diabetic patients. Sci Rep [Internet]. 2023 Oct 10;13(1):17126. Available from: https://www. nature.com/ articles/s41598-023-44477-w
6. Perazella MA. Renal Vulnerability to Drug Toxicity. Clinical Journal of the American Society of Nephrology [Internet]. 2009 Jul;4(7):1275–83. Available from: https://journals. lww.com/ 01277230-200907000-00022
7. Miyoshi T, Uoi M, Omura F, Tsumagari K, Maesaki S, Yokota C. Risk Factors for Cisplatin-Induced Nephrotoxicity: A Multicenter Retrospective Study. Oncology [Internet]. 2021 Feb 1;99(2):105–13. Available from: https:// karger. com/article/doi/10.1159/000510384
8. Kidera Y, Kawakami H, Sakiyama T, Okamoto K, Tanaka K, Takeda M, et al. Risk Factors for Cisplatin-Induced Nephrotoxicity and Potential of Magnesium Supplementation for Renal Protection. Lee JH, editor. PLoS One [Internet]. 2014 Jul 14;9(7):e101902. Available from: https://dx.plos.org/10.1371/journal.pone.0101902
9. Galfetti E, Cerutti A, Ghielmini M, Zucca E, Wannesson L. Risk factors for renal toxicity after inpatient cisplatin administration. BMC Pharmacol Toxicol [Internet]. 2020 Dec 2;21(1):19. Available from: https:// bmcpharmacoltoxicol.biomedcentral. com/articles/10.1186/s40360-020-0398-3
10. Bennis Y, Savry A, Rocca M, Gauthier-Villano L, Pisano P, Pourroy B. Cisplatin dose adjustment in patients with renal impairment, which recommendations should we follow? Int J Clin Pharm [Internet]. 2014 Apr 17;36(2):420–9. Available from: http://link. springer. com/10. 1007/s11096-013-9912-7
11. Saito Y, Sakamoto T, Takekuma Y, Kobayashi M, Okamoto K, Shinagawa N, et al. Diabetes mellitus degenerates cisplatin-induced nephrotoxicity in short hydration method: a propensity score-matching analysis. Sci Rep [Internet]. 2022 Dec 17;12(1):21819. Available from: https:// www. nature.com/articles/s41598-022-26454-x
12. Máthé C, Bohács A, Duffek L, Lukácsovits J, Komlosi ZI, Szondy K, et al. Cisplatin nephrotoxicity aggravated by cardiovascular disease and diabetes in lung cancer patients. European Respiratory Journal [Internet]. 2011 Apr 1;37(4):888–94. Available from: https:// publications. ersnet.org/lookup/doi/10.1183/09031936.00055110
13. Caglar K. Cumulative prior dose of cisplatin as a cause of the nephrotoxicity of high-dose chemotherapy followed by autologous stem-cell transplantation. Nephrology Dialysis Transplantation [Internet]. 2002 Nov 1;17(11):1931–5. Available from: https://academic.oup. com/ndt/article- lookup/ doi/10. 1093/ndt/17.11.1931
14. Prasaja Y, Sutandyo N, Andrajati R. Incidence of Cisplatin-Induced Nephrotoxicity and Associated Factors among Cancer Patients in Indonesia. Asian Pacific Journal of Cancer Prevention [Internet]. 2015 Mar 4;16(3):1117–22. Available from: http:// koreascience. or.kr/journal/ view. jsp?kj= POCPA9 &py=2015&vnc=v16n3&sp=1117
15. Bell JS, Blacker N, Leblanc VT, Alderman CP, Phillips A, Rowett D, et al. Prescribing for older people with chronic renal impairment. Aust Fam Physician [Internet]. 2013;42(1–2):24–8. Available from: http:// www.ncbi. nlm.nih.gov/ pubmed/ 23529455
16. Naughton CA. Drug-Induced Nephrotoxicity [Internet]. 2008. Available from: www.aafp. org/afp.
17. CDC US. US CDC. 2024 [cited 2025 Jun 22]. Adult BMI Categories. Available from: https:// www. cdc. gov/bmi/adult-calculator/bmi-categories.html

TMSS Medical College Journal 2025; 24(15-20):