ANALYSIS

24(106), November - December, 2020

ISSN 2321–7359 EISSN 2321–7367

Medical Science

# Incidence of Acute Kidney Injury among Adult Cancer Patients Receiving Nephrotoxic Chemotherapy at King Abdulaziz University Hospital

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**Citation**
Shadi S Alkhayyat, Mohammed K Basourrah, Hanadi M Alhozali, Rolina Al-Wassiah, Faris R Albardi, Hashim H Khairallah, Saeed A Alghamdi, Abdullah H Sultan, Naeem Qusty. Incidence of Acute Kidney Injury among Adult Cancer Patients Receiving Nephrotoxic Chemotherapy at King Abdulaziz University Hospital. *Medical Science*, 2020, 24(106), 4341-4351

## ABSTRACT

*Background:* Acute kidney injury (AKI) is an acute decrease in renal function that leads to an elevation in the serum blood urea nitrogen, creatinine, and other nitrogenous waste products. Acute kidney injury is a known complication of cancer patients receiving chemotherapy. *Aim:* To evaluate the occurrence of AKI at King Abdulaziz University Hospital (KAUH) among adult cancer patients undergoing nephrotoxic chemotherapy drugs (Cisplatin, Carboplatin, Cyclophosphamide, and Gemcitabine). *Methods:* In this retrospective study, medical records of 1229 adult cancer patients were obtained. Of those, 682 were selected based on the use of the drugs chosen for this study, and a total of 767 admissions were included. Acute kidney injury was diagnosed by evidence of an increase in the creatinine level by 0.3 mg/dL or more between two successive cycles. *Results:* Out of the 767 admissions that were obtained, 58 were found to have AKI. The study included 4 drugs: cisplatin (n=151, 19.7%); carboplatin (n=142, 18.5%); gemcitabine

(n=114, 14.9%); cyclophosphamide (n=320, 41.7%); as well as combinations consisting of cisplatin plus gemcitabine (n=22, 2.9%) and carboplatin plus gemcitabine (n=18, 2.3%). The incidences of AKI with each were: cisplatin (n=14, 24.1%, P=0.475); carboplatin (n=7, 12.1%, P=0.255); gemcitabine (n=12, 20.7%, P=0.269); cyclophosphamide (n=19, 32.8%, P=0.193); cisplatin plus gemcitabine (n=5, 8.6%, P=0.020); and carboplatin plus gemcitabine (n=1, 1.7%, P=1.00). *Conclusion:* Acute kidney injury is more likely to develop if these factors are found; male sex, mean age of 59 or older, using a protocol which includes a combination of cisplatin and gemcitabine, and having a creatinine level above 115 µmol/L before the first cycle.

**Keywords:** Acute Kidney Injury; Nephrotoxic Chemotherapy, Cyclophosphamide, Gemcitabine

## 1. INTRODUCTION

Acute kidney injury (AKI) is an acute decrease in renal function that leads to elevation of blood urea nitrogen (BUN), creatinine, and other nitrogenous waste products, which will disturb the balance of the extracellular volume and electrolytes (Palevsky, 2018). The kidney disease Improving Global Outcomes (KIDGO) known as one of the recent staging system and preferred definition, it defines AKI as follow (Khwaja, 2012):

1) Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 micromol/L) within 48 hours, or
2) Increase in serum creatinine to ≥ 1.5 times baseline which known to have occurred within the previous 7 days, or
3) Urine volume > 0.5 mL/kg/hour for six hours.

Unfortunately, it is found that, commonly, cancer patients develop AKI as a complication from the disease, and up to 30% of these patients have impaired kidney function from cancer (Miller et al., 2010). This may be due to the risk factors related to cancer including old age, prerenal conditions, chronic kidney disease (CKD), exposure to nephrotoxins, and obstruction (Campbell et al., 2014).

According to a study in the European Journal of Internal Medicine, among 37,267 cancer patients, 9613 (25.8%) developed acute kidney injury (Christiansen et al., 2011). Also, a study carried out at the Anderson Cancer Centre, Texas, USA, in 2006, stated that out of 3558 cancer patients admitted to the center, 12% were affected by acute kidney injury (Salahudeen et al., 2013).

However, studies have shown that some of the drugs commonly used in the management of cancer patients have certain effects on the kidney - a major elimination pathway for many antineoplastic drugs and their metabolites( Humphreys et al., 2005; Perazella, 2012; Jhaveri et al., 2013; Jhaveri et al., 2014; Perazella and Izzedine, 2015 ; Izzedine & Pera, 2017).

Anticancer-drug toxicity is an important cause of AKI because of the effects of the cancer drugs on the nephrons, vessels of the kidney, glomerular and interstitial function, and renal tubules (Filipski et al., 2008). Our focusing anticancer medications (cisplatin, carboplatin, cyclophosphamide, and gemcitabine) beginning with cisplatin which is known as one of the most common anticancer drugs with a major side effect of nephrotoxicity through multiple mechanisms concerning to chloride ions in the cis position of the drug, nonetheless it may cause toxicity in tubular epithelial cells, reduce blood flow to renal vessels and provoke proinflammatory cytokines to be released( Dobyan et al., 1980; Gaver et al 1987; Luke et al., 1992; Kintzel, 2001; Ramesh & Reeves, 2002 ; Ramesh & Reeves, 2005).

carboplatin one of the platinum derivatives that discovered a long time ago and can bind actively to plasma proteins and used to treat many types of cancer (Stewart et al., 1985 and Goren et al., 1987), according to Gorgen et al carboplatin may induce enzymuria and proteinuria, this study advocate that some patient may develop subclinical tubular damage and with ongoing treatment, it can progress to nephrotoxicity (Stankiewicz & Skrzydlewska, 2003; Lawson et al., 2008). A study of the mechanism of action of multiple anticancer treatments showed that Gemcitabine can cause acute tubular necrosis, diabetes insipidus and acute tubular acidosis by decreasing GFR via constriction of the arteriolar and mesangial cell due to nephrotoxicity (Humphreys et al., 2005). Cyclophosphamide has been known since the 1950s in treating both neoplastic and non-neoplastic diseases (Abraham & Rabi, 2009). It may induce nephrotoxicity via the rising amount of proteins in the kidneys as a result of a reduction in lysosomal protein enzymes activity. According to some studies, cyclophosphamide plays a conclusive aspect of provoking kidney damage by increasing both reactive oxygen and nitrogen species (Ayhanci et al., 2010; Mizunoet al., 2013; Shirali & Perazella, 2014).

While understanding the relation between nephrotoxic chemotherapy drugs and the incidence of AKI is important in the management of cancer patients, not many studies in the literature estimate the incidence of AKI among cancer patients receiving these drugs. Thus, we aim to focus on four common nephrotoxic drugs (cisplatin, carboplatin, cyclophosphamide, and gemcitabine) and to relate their use with the incidence of AKI among adult patients at King Abdulaziz University Hospital (KAUH) to increase awareness on this topic.

## 2. METHODS

This retrospective study was conducted during June 2019 at KAUH, a tertiary center in Jeddah, Saudi Arabia. It was conducted in the Department of Medicine (Oncology) and was approved by the Research Ethics Committee at KAUH. Medical records of patients from July 2010 to December 2016 were reviewed. There were 1229 adult cancer patients; of whom 682 were selected based on being treated by the drugs chosen for this study.

A confidence interval of 95% was used to obtain the sample size, and the margin of error was 6%.

Information obtained from the medical records included age, sex, height, weight, state (living/deceased), type of cancer, type of drug, the dose of drug, creatinine and BUN levels, diabetes mellitus (DM), hypertension (HTN), and chronic artery disease. The values were inserted into Google Forms manually from the medical records.

Based on KIDGO criteria the incidence of AKI was calculated by observing an increase in the creatinine level of 0.3 mg/dL or more between two successive cycles. Patients who met this criterion were considered AKI patients, while those who did not were non-AKI patients. These finding will increase medical-staff awareness of the effects of nephrotoxic chemotherapy on the incidence of AKI and to help improve the management of patients and decrease morbidity and mortality rates.

This research involved adult cancer patients (18 years and above) of both sexes who received between one to six cycles of cisplatin, cyclophosphamide, carboplatin, or gemcitabine. Any new admission to adult patients has been included more than once if it meets the following criteria: taking the same prescription for more than 6 months or receiving multiple protocols. Pediatric patients and patients given a single cycle or other nephrotoxic drugs were excluded.

Statistical analysis was done using IBM SPSS Statistics version 21. Mean and the standard deviation were calculated to describe continuous variables while frequencies and percentages were used for categorical variables. Independent t-test and chi-square test were used to evaluate the differences between continuous and categorical variables, respectively. A *P* value <0.05 was considered significant.

## 3. RESULTS

There were 767 admissions for adult patients with a mean age of 59.35 ± 11.06 years; males (n = 199, 25.9%), females (n = 568, 74.1%); and mean patient weight (69.83 ± 17.18 Kg). The sample included Saudi patients (n = 244, 31.8%) and non-Saudi patients (n = 523, 68.2%), and included patients who were living at the time of the study (n = 583, 76.5%) as well as patients who were deceased (n = 179, 23.5%), Table 1.

The study included 4 drugs: cisplatin (n = 151, 19.7%), carboplatin (n = 142, 18.5%), gemcitabine (n = 114, 14.9%), and cyclophosphamide (n = 320, 41.7%); as well as the combinations cisplatin plus gemcitabine (n = 22, 2.9%) and carboplatin plus gemcitabine (n = 18, 2.3%). The numbers of patients who developed AKI with each drug or combination were as follows: cisplatin (n = 14, 24.1%, *P* = 0.475), carboplatin (n = 7, 12.1%, *P* = 0.255), gemcitabine (n = 12, 20.7%, *P* = 0.269), cyclophosphamide (n = 19, 32.8%, *P* = 0.193), cisplatin plus gemcitabine (n = 5, 8.6%, *P* = 0.020), and carboplatin plus gemcitabine (n = 1, 1.7%, *P* = 1.00). Incidence of AKI according to the difference between the first and second cycles was 48.3%; second and third cycles 22.4%; third and fourth cycles 17.2%; fourth and fifth cycles 8.6%; and between the fifth and sixth cycles 3.4%.

The incidence of AKI according to median age was 59.35 ± 11.06 years (*P* = 0.046); male sex (n = 23, 39.7%); and female sex (n = 35, 60.3%); and *P* value for patient sex = 0.020 (Table3). Table 2 lists incidences of AKI according to type of cancer, including breast (n = 20, 34.5%), ovarian (n = 6, 10.3%), bladder (n = 6, 10.3%), non-Hodgkin lymphoma (n = 5, 8.6%), and others, *P* value according to the type of cancer = 0.054. Incidence of AKI according to comorbidities such as DM (n = 13, 22.4%, *P* = 0.347), HTN (n = 12, 20.7%, *P* = 0.228), and chronic artery disease (n = 1, 1.7%, *P* = 0.416).

**Table 1.** Incidence of Acute Kidney Injury

| Acute Kidney Injury Incidence | **Frequency (N = 767)** | **%** |
|---|---|---|
| After the 2nd Cycle | 28 | 3.7 |
| After the 3rd Cycle | 13 | 1.7 |
| After the 4th Cycle | 10 | 1.3 |
| After the 5th Cycle | 5 | 0.7 |
| After the 6th Cycle | 2 | 0.3 |
| Total | 58 | 7.6 |

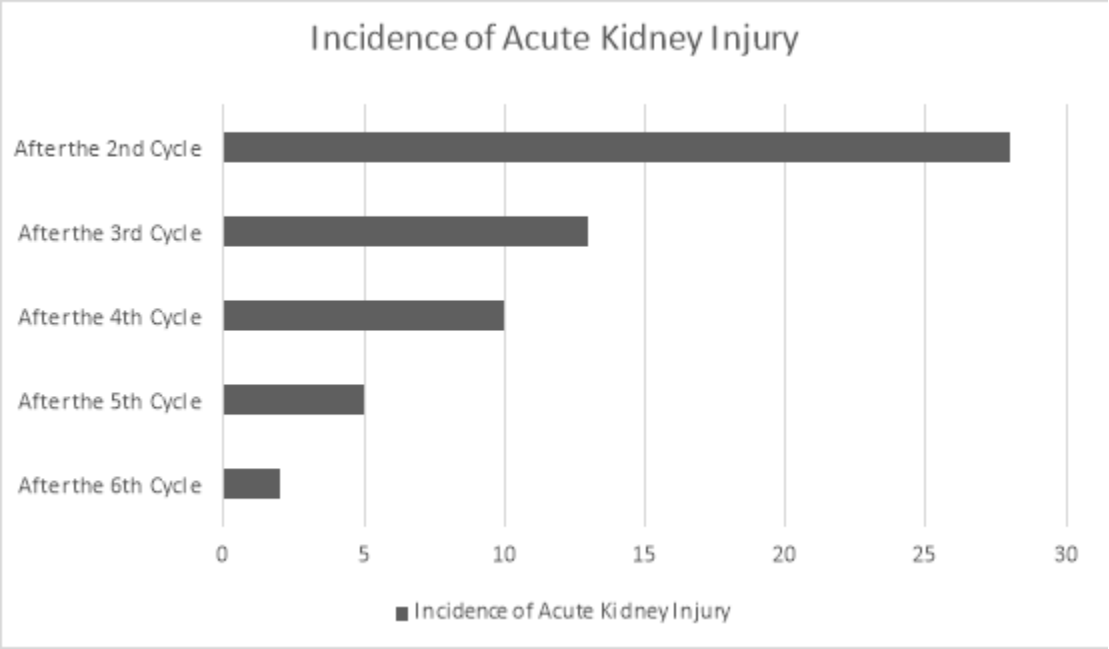


**Chart 1.** Incidence of Acute Kidney Injury

**Table 2.** Acute Kidney Injury Incidence in Relation to Descriptive Variables

| | | **Total** | | **Acute Kidney Injury** | | **No Acute Kidney Injury** | | |
|---|---|---|---|---|---|---|---|---|
| **Variable** | | **Frequency (N = 767)** | **%** | **Frequency (N = 58)** | **%** | **Frequency (N = 709)** | **%** | **Significance** |
| Demographics | | | | | | | | |
| Sex | Male | 199 | 25.9 | 23 | 39.7 | 176 | 24.8 | 0.020 |
| | Female | 568 | 74.1 | 35 | 60.3 | 533 | 75.2 | |
| Nationality | Saudi | 244 | 31.8 | 19 | 32.8 | 225 | 31.7 | 0.989 |
| | Non-Saudi | 523 | 68.2 | 39 | 67.2 | 484 | 68.3 | |
| State[a] | Alive | 583 **(n = 762)** | 76.5 | 41 (n = 57) | 71.9 | 542 **(n = 705)** | 76.9 | 0.493 |
| | Deceased | 179 **(n = 762)** | 23.5 | 16 (n = 57) | 28.1 | 163 **(n = 705)** | 23.1 | |
| Comorbidities | | | | | | | | |
| Hypertension | | 111 | 14.5 | 12 | 20.7 | 99 | 14.0 | 0.228 |
| Diabetes mellitus | | 131 | 17.1 | 13 | 22.4 | 118 | 16.6 | 0.347 |
| Chronic artery disease | | 12 | 1.6 | 1 | 1.7 | 11 | 1.6 | 0.614 |
| Type of Cancer[b] | | **(n = 762)** | | | | **(n = 704)** | | |
| Breast | | 318 | 41.7 | 20 | 34.5 | 298 | 42.3 | 0.054 |
| Nasopharyngeal | | 36 | 4.7 | 2 | 3.5 | 34 | 4.8 | |
| Ovarian | | 102 | 13.4 | 6 | 10.3 | 96 | 13.6 | |
| Non-Hodgkin lymphoma | | 67 | 8.8 | 5 | 8.6 | 62 | 8.8 | |
| Esophageal | | 18 | 2.3 | 0 | 0 | 18 | 2.6 | |
| Gastric | | 14 | 1.8 | 2 | 3.5 | 12 | 1.7 | |
| Pancreatic | | 27 | 3.5 | 4 | 6.9 | 23 | 3.3 | |
| Lung | | 28 | 3.7 | 3 | 5.2 | 25 | 3.6 | |
| Endometrial | | 11 | 1.4 | 1 | 1.7 | 10 | 1.4 | |
| Laryngeal | | 11 | 1.4 | 0 | 0 | 11 | 1.6 | |
| Uterine | | 12 | 1.6 | 0 | 0 | 12 | 1.7 | |
| Cervical | | 29 | 3.8 | 1 | 1.7 | 28 | 4.0 | |
| Multiple myeloma | | 9 | 1.2 | 1 | 1.7 | 8 | 1.1 | |
| Bladder | | 20 | 2.6 | 6 | 10.3 | 14 | 2.0 | |
| Others | | 60 | 7.9 | 7 | 12.1 | 53 | 7.5 | |
| Type of Protocol | | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cisplatin | 151 | 19.7 | 14 | 24.1 | 137 | 19.3 | 0.475 |
| Carboplatin | 142 | 18.5 | 7 | 12.1 | 135 | 19.0 | 0.255 |
| Gemcitabine | 114 | 14.9 | 12 | 20.7 | 102 | 14.4 | 0.269 |
| Cyclophosphamide | 320 | 41.7 | 19 | 32.8 | 301 | 42.5 | 0.193 |
| Cisplatin & Gemcitabine | 22 | 2.9 | 5 | 8.6 | 17 | 2.4 | 0.020 |
| Carboplatin & Gemcitabine | 18 | 2.3 | 1 | 1.7 | 17 | 2.4 | 1.000 |

[a]Missing data: n = 5.
[b]Missing data: n = 5.

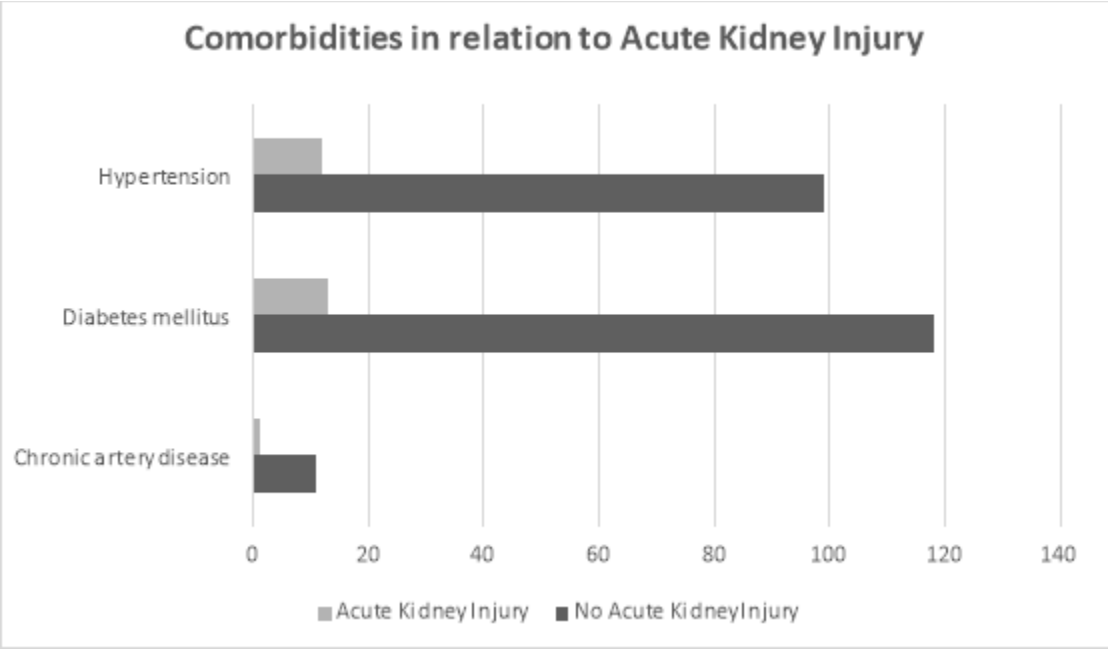


**Chart 2.** Comorbidities in relation to Acute Kidney Injury

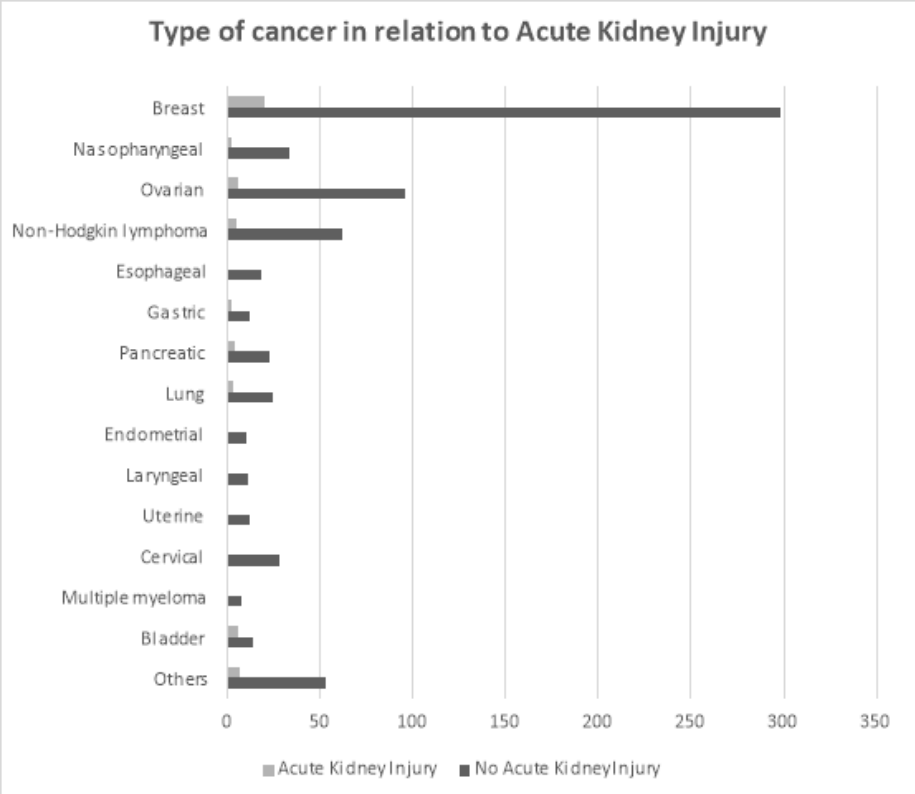


**Chart 3.** Type of cancer in relation to Acute Kidney Injury

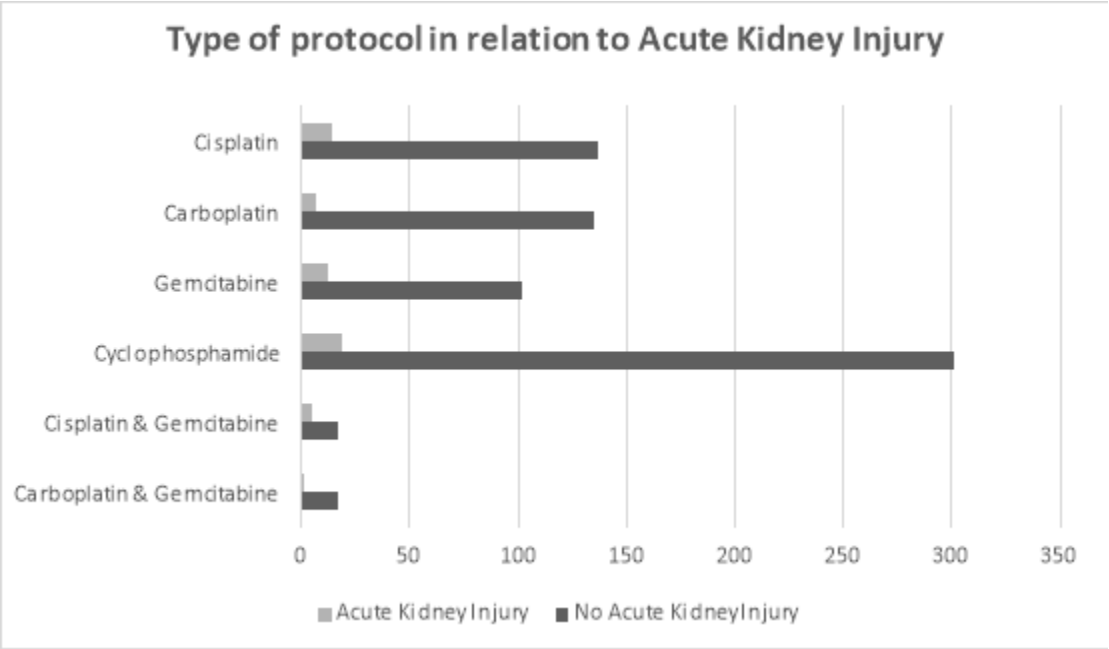


**Chart 4.** Type of protocol in relation to Acute Kidney Injury

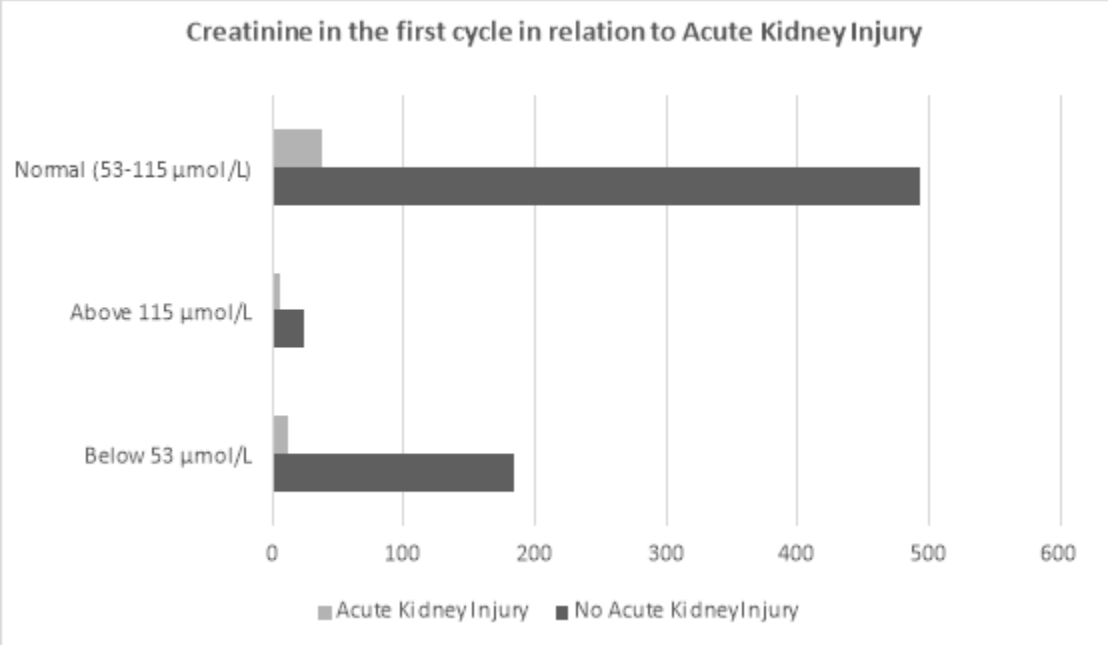


**Chart 5.** Creatinine in the first cycle in relation to Acute Kidney Injury

**Table 3.** Frequency of Acute Kidney Injury Incidents in Relation to Other Variables

| | **Total** | | **Acute Kidney Injury (AKI)** | | **No Acute Kidney Injury (NO AKI)** | | |
|---|---|---|---|---|---|---|---|
| Variable | **Frequency (N = 767)** | **Mean ± Std. Deviation** | **Frequency (n = 58)** | **Mean ± Std. Deviation** | **Frequency (n = 709)** | **Mean ± Std. Deviation** | **Significance** |
| Demographics[a] | | | | | | | |
| Age (years) | 765 | 54.41 ± 13.01 | 58 | 59.35 ± 11.06 | 707 | 54.00 ± 13.08 | 0.046 |
| Height (cm) | 764 | 156.76 ± 9.02 | 58 | 157.99 ± 8.36 | 706 | 156.66 ± 9.07 | 0.660 |
| Weight (kg) | 763 | 69.91 ± 17.33 | 58 | 71.05 ± 19.26 | 705 | 69.83 ± 17.18 | 0.285 |
| Dose of Medication[b] | | | | | | | |
| Cisplatin ($mg/m^2$) | 171 (n = 173) | 64.83 ± 47.97 | 18 (n = 19) | 61.67 ± 19.78 | 153 (n = 154) | 65.20 ± 50.3 | 0.520 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gemcitabine ($mg/m^2$) | 153 (n = 154) | 957.19 ± 88.19 | 18 (n = 18) | 975.00 ± 103.26 | 135 (n = 136) | 954.82 ± 86.14 | 0.806 |
| Cyclophosphamide ($mg/m^2$) | 317 (n = 320) | 616.88 ± 104.22 | 19 (n = 19) | 578.95 ± 129.44 | 298 (n = 301) | 619.30 ± 102.20 | 0.156 |
| 1st Cycle Creatinine[c] | (n = 755) | | (n = 54) | | (n = 701) | | |
| Normal (53-115 µmol/L) | 530 | 72.06 ± 13.08 | 37 | 77.37 ± 14.2 | 493 | 71.66 ± 12.92 | 0.395 |
| Above 115 µmol/L | 29 | 265.10 ± 300.47 | 5 | 462.40 ± 529.32 | 24 | 224.00 ± 225.73 | 0.021 |
| Below 53 µmol/L | 196 | 34.65 ± 19.72 | 12 | 36.01 ± 19.04 | 184 | 34.56 ± 19.82 | 0.636 |

[a]Missing Age data, n = 2; missing Height data, n = 3; missing Weight data, n = 4.
[b]Total frequency for each drug is calculated from the total number of doses recorded for that medication and written next to the medication's frequency under AKI or No AKI; missing Cisplatin dose data, n = 2; missing Gemcitabine dose data, n = 1; missing Cyclophosphamide dose data, n = 3.
[c]Missing data, n = 12.

## 4. DISCUSSION

Our aim in this study is to increase medical-staff awareness of the effects of nephrotoxic chemotherapy on the incidence of AKI and to help improve the management of patients and decrease morbidity and mortality rates.

We found that the mean age of the patients in the admissions we included was 59.35 ± 11.06 years ($P$ = 0.046). The significance of the relation between age and incidence of AKI might be confounded by the fact that we looked in our study at adult patients only. Another reason can be that adults are more prone to chronic diseases.

Our findings show that 39.7% of the AKI admissions were men, despite the majority of the patients in the admissions being women. A study by Shirali & Perazella (2014) mentioned that being a female is a risk factor and that females are more exposed to chemotherapy-associated nephrotoxicity (Patschan & Müller, 2017). Data analysis showed this relation to have statistical significance ($P$ = 0.020). Reasons behind this relationship are unclear and few studies have compared the incidence of AKI between males and females in humans.

Although some studies have shown a relationship between DM and AKI induced by nephrotoxic chemotherapy (Angeles et al., 2019; Dylewska et al., 2019), our data analysis showed the relation between the two variables to be insignificant statistically, as in only 22.4% of admissions for AKI were the patient diabetic. As for HTN, our results suggest the relation between HTN and AKI to be insignificant: in only 20.7% of AKI admissions were the patient known to be hypertensive, however, a significant relationship between them has been suggested (Stewart et al., 1997 & Kemlin et al., 2005). Many studies have reached similar results and found the relation between the two variables DM and HTN and AKI incidence to be insignificant (Gatzemeier et al., 2000; Noda et al., 2002 & Faig et al., 2018).

Our results also showed that the percentage of admissions in which the patient had chronic artery disease and developed AKI was 1.7%, even though many studies have demonstrated a strong relationship between chronic artery disease and the incidence of AKI.

Our findings show that 24.1% of AKI patients had received cisplatin, despite that, the relation between the two was found to be statistically insignificant. Cisplatin is widely used in the treatment of different types of cancers, such as small-cell (Planting et al., 1999) and non-small lung cancer (Loehrer et al., 1998), head and neck (Hoskins et al., 2000), testicular (Bolis et al., 1997), ovarian cancers (Coppin et al., 1996 & Rose et al., 1999), and others (Braakhuis et al., 1995 and Ciarimboli et al., 2005), due to its cytotoxic actions on cancer cells. These actions, however, play a major role in cisplatin's effects on the proximal tubular cells of the kidneys (von der Maase et al., 2000).

Nowadays, cisplatin combined with gemcitabine has been proven to treat many types of cancers. Because they are highly potent drugs, they are commonly used together, to give a synergistic effect, in the treatment of late and metastatic stages of cancer (Fung et al., 1999 & Daviet et al., 2019). This explains the reason for them having statistical significance (P = 0.020), where 22.7% of the patients receiving this protocol were found to have AKI, despite that only 2.9% of the total admissions were receiving it.

We found that in 12.1% of AKI admissions the patients were receiving carboplatin. This percentage is relatively small because the majority of the patients at KAUH are treated with cyclophosphamide or cisplatin, which have both been shown to have insignificant relations with AKI. In patients receiving a protocol containing carboplatin and gemcitabine, 1.7% developed AKI, which was also statistically insignificant.

In a study by Daviet et al. gemcitabine was found to be associated with thrombotic microangiopathy, which leads to acute renal failure and death in severe cases. Also, from 1998 gemcitabine was known in treating pancreatic cancer (48). In our study, the

relation between gemcitabine and AKI was statistically insignificant (P = 0.269), Table 2, as the results showed that AKI developed in 10.5% of the admissions in which the patients were receiving gemcitabine. A study by Fung et al. supports our results, as it also showed that gemcitabine is rare to cause the hemolytic uremic syndrome, which is a major cause of AKI (Daviet et al., 2019).

We also looked at cyclophosphamide, which was insignificantly associated with AKI (32.8% of AKI admissions). The high percentage of patients receiving cyclophosphamide in our study can be explained by the fact that the majority of patients in our admissions were females, and a great number of them were being treated for breast cancer. Cyclophosphamide was one of the most common drugs used to treat breast cancer in our data.

We observed the incidence of AKI during the first six cycles in patients who received at least one of our chosen drugs. We determined AKI by measuring the difference between every two consecutive cycles. Our data show that 58 cancer patients developed AKI, and in the majority of these patients, AKI occurred after the first two cycles (48.3%). This might be related to the sudden exposure of the kidneys to these nephrotoxic drugs after the first dose. Moreover, we also found a gradual decline in the incidence of AKI from the third to the sixth cycles, which could be due to adaptation of the kidneys to the given protocol. A study conducted by Faig et al. showed similar percentages of AKI incidence, supporting our results (Gatzemeier et al., 2000).

The relation between high levels of creatinine (Above 115 µmol/L) at the time of the first cycle and the incidence of AKI was statistically significant (P = 0.021), where the mean value of creatinine in AKI admissions where creatinine levels were above 115 µmol/L was 462.4 ± 529.32 µmol/L. Reasons behind this that those are patient with chronic kidney disease. Generally, will be affected greatly from any nephrotoxic drugs, so it shows that people with higher creatinine levels at the time of the first cycle of chemotherapy are more likely to develop AKI than people with normal or low creatinine levels.

**Limitations**

The limitations of our study include that it was retrospective, the sample size was not large enough, some of the patients in the admissions had not received six cycles of the medication but were included in the study according to the methodology, and some patients had more than one hospital admission for nephrotoxicity by chemotherapy drugs. The study did not include diseases that might have affected the kidneys even in the absence of nephrotoxic chemotherapeutic drugs. The study also did not include other nephrotoxic drugs the patients may have received. Some patients received the same protocol but with a gap of fewer than six months between doses and hence were included in the same admission, which are common challenges in retrospective data.

**Recommendations**

It is important before administering chemotherapy to test patients' renal function and to maintain serum creatinine levels within the normal range. Having a nephrologist on the team is important to be involved in evaluating patients with impaired kidney function. Alternative protocol should be considered in such patients.

## 5. CONCLUSION

AKI is a known complication in cancer patient receiving antineoplastic agents. We are reporting AKI in patient received cisplatin, carboplatin, gemcitabine, cyclophosphamide alone or in combination. We had 767 admissions; 58 patients developed AKI. We found that AKI is more likely to develop in males than females, older age was found to be associated with AKI. The use combined protocol (Cisplatin & Gemcitabine) was associated with higher AKI rates, and 1st Cycle Creatinine level above 115 umol/L increase the risk of getting an AKI while using nephrotoxic antineoplastic agents. Creatinine levels are often advised to be checked to ensure they are within acceptable range before beginning chemotherapy.

**Acknowledgement**

We like to thank research summer school 2019 for helping us in this paper, Abdulqader S Babhair, Ibrahim S Alghamdi, Adel A Alzahrani, Khalid A Alghamdi, Mohammed A Safhi, Maha A Safhi, Suzan A Alkhodair for their contribution in our research.

**Author continuations**

Mr./Mrs. Shadi S Alkhayyat: idea, writing, reviewing, patient selection
Mr./Mrs. Mohammed K Basourrah: writing, analysis, data collection, reviewing, team coordination.
Mr./Mrs. Hanadi M Alhozali: idea, analysis
Mr./Mrs. Rolina K Al-wassia: patient selection
Mr./Mrs. Faris R Albardi:data collection, writing
Mr./Mrs. Hashim H Khairallah: data collection, writing

Mr./Mrs. Saeed A Alghamdi: data collection, writing, analysis
Mr./Mrs. Abdullah H Sultan: data collection, writing
Mr./Mrs. Naeem Qusty: manuscript review

**Funding**
This study has not received any external funding.

**Conflict of interest**
The authors declare that there are no conflict of interests.

**Ethical approval**
The study was approved by the Medical Ethics Committee of King Abdulaziz University (ethical approval code: 406-19).

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**Data and materials Availability**

All data associated with this study are present in the paper.

**Peer-review**

External peer-review was done through double-blind method.

**Article History**

Received: 10 October 2020
Reviewed & Revised: 12/October/2020 *to* 16/November/2020
Accepted: 16 November 2020
E-publication: 23 November 2020
P-Publication: November - December 2020



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