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Original article

Epidemiology of Acute Kidney Injury and Associated Factors Among Patients with Malignancy

Analysis of Hospital Inpatients Database in Benha University Hospital Internal Medicine Departement, Hematology and Oncology Unit

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Abstract:

Background: One of the most serious complications among cancer patients is Acute Kidney Injury (AKI). This study aimed to detect the AKI incidence in cancer patients, to discover which clinical factors could increase the risks of AKI, and to assess the effect of AKI on in-hospital mortality, length of stay. **Methods:** This prospective cohort study was conducted on 276 malignant patients (AKI: 40 cases and no AKI: 236 cases). Serum creatinine, blood urea, complete blood count, uric acid, Electrolyte" potassium, sodium, calcium", urine analysis with comment on RBCs cast, liver function test" ALT, AST, Albumin and bilirubin" were measured every three weeks, and urine albumin creatinine ratio was done before chemotherapy and after finishing treatment. **Results:** pre-existing comorbidities including hypertension (HTN), diabetes (DM), and coronary heart disease are significant predictors for increased risk of AKI in cancer patients. Patients with hyponatremia, hypokalemia and hyperuricemia shared a significantly higher risk of AKI (a OR = 2.95, 2.49, and 3.01). Cox regression analysis revealed that HTN and DM also increased the mortality risk when adjusting demographic and clinical features. The mean survival rate was significantly lower in group with AKI compared to group without AKI (16.331 versus 19.589). AKI stage II and III had longer median length of hospital stay compared to stage I. (In our studied patient, there is high admission rate of patient with cancer to intensive care units, and most of critically ill patients with cancer are susceptible to AKI and the incidence of requiring kidney Replacement Therapy. The most common risk factors that developed with cancer patient was septic shock, exposure to nephrotoxins as "chemotherapy", severe dehydration due to associated vomiting and GIT upset, and others All of this risk factor are precipitating factor for AKI. Incidence of AKI itself will cause high mortality rate among cancer patient in compared with ill patient without cancer, and also the need for Renal Replacement Therapy entails high mortality rate. So, according to our results, we find mean survival rate in cancer patient with AKI is lower than that in patient without AKI.) **Conclusion:** The in-hospital mortality was 5% in cancer patients with AKI. The severe AKI was associated with poor clinical outcome, long hospital stays and high daily costs. Pre-existing comorbidities and electrolyte disturbances are the predicting factors for AKI incidence.

Keywords: Acute Kidney Injury; Malignancy; Epidemiology.

Introduction

A major public health problem is" Malignant Tumor" [1]. In 2016, the newly estimated number of cancer cases Worldwide reached 18.1 million, which raised by 28% over the last decade [2].

According to the Global Cancer Observatory (GCO) of the World Health Organization (WHO), the most commonly diagnosed cancers in Egypt are breast cancer, lung cancer, liver cancer, and bladder cancer (1). In 2020, it was estimated that there were 115,500 new cases of cancer in Egypt, with 63,500 cases occurring in males and 52,000 cases occurring in females. The age-standardized incidence rate (ASIR) of all cancers in Egypt is 101.6 per 100,000 population. The ASIR for males is 125.6 per 100,000 population, and for females, it is 75.8 per 100,000 population. Breast cancer is the most common cancer in females in Egypt, with an estimated 29,000 new cases in 2020. Lung cancer is the most common cancer in males, with an estimated 11,000 new cases in 2020. Liver cancer and bladder cancer are also relatively common in Egypt, with an estimated 9,100 and 6,600 new cases in 2020, respectively [1].

One of the most serious complications among cancer patients is Acute Kidney Injury [3]. There has been a long-time association between cancer and kidney disease [4].

It is one of the new clinical challenges that facing malignant patients during the journey of their treatment because any degree of Renal impairment will interfere with the choice and continuation of anti-cancer therapy, and also lead to the development of a very bad prognosis in cancer patients [5].

Some sorts of Malignancy are directly associated with AKI such as Multiple Myeloma, Renal tumor, Malignant obstructive uropathy, On other hands, the nephrotoxic effect of antineoplastic therapy, and oncologic emergency such as Tumor Lysis Syndrome (TLS) [3, 6].

According to previous studies, the definition of acute kidney injury by KDIGO criteria was defined as an absolute increase in SCr by >0.3mg/dL within 48 hr, or >1.5-time from the baseline within the previous 7 days [7].

Screening should involve assessment of kidney functions "SCr, electrolytes Na and potassium, albumin, hemoglobin, white blood cell, and uric acid [8].

The purpose of this study was to detect the AKI incidence in cancer patients, to discover which clinical factors could increase the risks of AKI, and to assess the effect of AKI on in-hospital mortality, length of stay (LOS).

Patients and methods

This study was designed as a prospective cohort study that was conducted on 276 malignant patients (40 cases with AKI and 236 cases without AKI) depending on the hospital inpatient database in Benha University Hospital, Benha city, Egypt.

The calculated sample size was 276 malignant patients, that admitted to Benha University Hospital between 1 January to 30 June 2022

An informed consent was obtained from every Patients before enrollment of the study. The study was done after being approved by the Research Ethics Committee in Benha, Faculty of Medicine. Every patient received an explanation of the purpose of the study and had a secret code number.

Inclusion criteria were age between (20 – 65) years, malignancy under chemotherapy, and patients with a stay of admission > 24 hr.

Exclusion criteria were a stay of admission < 24 hr, CKD stage 3B-5(glomerular filtration rate GFR < 44ml/min per 1.73m), patients on renal replacement therapy (RRT), patients with renal transplantation, patients with < one serum creatinine (SCr) test, and other nephrotoxic drugs as NSAIDs, or contrast dye.

If any patient was hospitalized several times during the study period, each hospitalization was considered as an independent case.

All studied cases were subjected to a complete interview and clinical examination with special stress on demographic characteristics (age, gender, body mass index score), LOS, information on admission and discharge diagnosis, therapeutic regimen, pre-existing comorbidities, clinical assessment including (history of hemorrhage, GI loss of fluid, burn, heart disease, liver disease, history of drug intake "NSAIDs, Radiocontrast, Antibiotic, calcineurin inhibitors, and chemotherapy, history of major surgery, or obstetric complication, history of fever, arthralgias, rash following exposure to a new drug for allergic interstitial nephritis, history of colicky flank pain radiating to the groin, suprapubic pain for Ureteric Obstruction and bladder distention, history of auto-immune disease as SLE, Vasculitis, history of nocturia, frequency, hesitancy and enlargement of the Prostate, general Examination" heart rate, blood pressure, temperature, respiratory rate", cardiac Examination for Heart failure, and chest Examination for bibasilar lung rales with raised jugular venous pressure, weight gain, dependent edema may precipitate sever pulmonary edema.

The following investigation was performed every three weeks to every patient: SCr, blood urea, CBC, S. uric acid, Electrolyte" s.K, s.Na, s.Ca", urine analysis with comment on RBCs cast, liver function test" ALT, AST, S. Albumin and s. bilirubin", urine albumin creatinine ratio was done before chemotherapy and after finishing treatment.

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Statistical analysis

Key results were tabulated and analyzed by suitable statistical methods using the computer program Statistical Package for the Social Sciences (SPSS) (SPSS Inc., Chicago, Illinois, USA) version 28 software (IBM Inc., Chicago, IL, USA). Categorical data were presented as number and percentages while quantitative data were expressed as mean ± standard deviation (SD), and range. Comparison of numerical variables between the study groups was done using Student t test (t-test) which compares between 2 means of 2 independent groups when normally distributed; t-value is the ratio of the difference between the two means/calculated SD of this difference. Logistic, Cox regression and multiple analysis was done to evaluate independent prognostic variables affecting OS times. Kaplan-Meier method was used to estimate survival (DFS and OS). Predictor and prognostic variables were related to survival using log rank test. A two tailed $P \leq 0.05$ was deemed statistically significant.

Results

Regarding demographic data of the studied patients, age had mean of 51.28± 9.05 years. There were 180 (65.22%) males and 96 (34.78%) females. Regarding residency, 145 (52.73%) lived in urban areas and 131 (47.64%) lived in rural areas. Weight had a mean of 67.5± 7.58 Kg. Height had a mean of 1.6± 0.06 m. BMI had a mean of 26.46± 3.46 Kg/m^2. Regarding comorbidities, 42 (15.2%) patients were free from any other comorbidities, 143 (51.81%) were hypertensive, 117 (42.39%) were diabetic and 33 (11.96%) had CHD. Regarding CBC findings, Hb had a mean of 9.43± 1.1mg/dl. WBCs had a mean of 10.31± 3.83 10^9/L. Platelets had a mean of 200.72± 29.710^9/L. Regarding Liver function test, AST had a mean of 34.17± 9.74 U/L. ALT had a mean of 31.4± 11.8 U/L. Serum albumin had a mean of 2.87± 0.67 g/L. Total bilirubin had a mean of 0.92± 1.37 (mg/dL). Direct bilirubin had a mean of 0.31± 0.63(mg/dL). Total protein had a mean of 4.87± 1.38 (mg/dL). Serum potassium had a mean of 4.57± 1.04 mEq/L. Serum sodium had a mean of

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75.33 ± 8.57 mEq/L. Serum ca had a mean of 11.06 ± 1.46 mg/dL. Blood urea had a mean of 65.53± 52 mg/dL. Serum creatinine had a mean of 1.8± 0.7 mg/dL. Table 1

Urinary albumin creatinine ratio was significantly higher after chemotherapy compared to before chemotherapy. Table 2

Regarding the regimen of chemotherapy, 72 (26.1%) patients were receiving Paclitaxel & Carboplatin, 59 (8.7%) patients were receiving Gemcitabine & Carboplatin, 41 (14.9%) patients were receiving Rituximab& Doxorubicin, 26 (3.8%) patients were receiving Gemcitabine, 23 (3.4%) patients were receiving Bendamustine, 8 (2.9%) patients were receiving Docetaxel & Doxorubicin & Cyclophosphamide, 7 (1.0%) patients were receiving Bortezomib & Cyclophosphamide, 5 (1.8%) patients were receiving Paclitaxel & Carboplatin& Gemcitabine, 4 (1.4%) patients were receiving Paclitaxel & Doxorubicin & Cyclophosphamide and 3 (1.1%) patients were receiving Paclitaxel & Carboplatin & Doxorubicin & Cyclophosphamide. Table 3

Table 1: Demographic data, comorbidities, CBC findings, liver function test, kidney function test and electrolytes of the studied patients.

			N=276
Demographics	Age (years)		51.28± 9.05
	Sex	Male	180 (65.22%)
		Female	96 (34.78%)
	Residency	Urban	145 (52.73%)
		Rural	131 (47.64%)
	Weight (Kg)		67.5± 7.58
	Height (m)		1.6± 0.06
	BMI (Kg/m^2)		26.46± 3.46
Comorbidities	HTN		143 (51.81%)
	DM		117 (42.39%)
	CHD		33 (11.96%)
CBC findings	Hb (mg/dl)		9.43± 1.1
	WBCs (10^9/L)		10.31± 3.83
	Platelets (10^9/L)		200.72± 29.7
	Blood glucose level (mg/dl)		121.91± 16.82
Liver function	AST (U/L)		34.17± 9.74
	ALT (U/L)		31.4± 11.8
	Serum albumin (g/L)		2.87± 0.67
	Total bilirubin (mg/dL)		0.92± 1.37
	Direct bilirubin (mg/dL)		0.31± 0.63
	Total protein (mg/dL)		4.87± 1.38
Kidney function test and electrolytes	Serum potassium (mEq/L)		4.57 ± 1.04
	Serum sodium (mEq/L)		75.33 ± 8.57
	Serum calcium (mg/dL)		11.06 ± 1.46
	Blood urea (mg/dL)		65.53 ± 52
	Serum creatinine (mg/dL)		1.8 ± 0.7

Data is presented as mean ± SD, or number (%). BMI: body mass index, HTN: Hypertension, DM: Diabetes mellitus, CHD: Coronary heart disease, Hb: Hemoglobin, WBCs: white blood cell, AST: aspartate aminotransferase, ALT: Alanine aminotransferase.

Table 2: Urinary albumin creatinine ratio of the studied patients before and after chemotherapy.

		Before	After	P value
Albumin creatinine ratio	Mean ± SD	0.50 ± 0.23	0.56 ± 0.26	0.004*
	Range	0.11-0.9	0.15-1	
	Median (IQR)	0.51 (0.31- 0.72)	0.56 (0.34 -0.78)	

Data is presented as mean ± SD, range, and median (IQR), * significant as P value ≤ 0.05. IQR: Interquartile range.

Table 3: Regimen of Chemotherapy of the studied patients.

	N=276
Paclitaxel & Carboplatin	72 (26.1%)
Gemcitabine & Carboplatin	59 (8.7%)
Rituximab& Doxorubicin	41 (14.9%)
Gemcitabine	26 (3.8%)
Bendamustine (alkylating agent)	23 (3.4%)
Docetaxel & Doxorubicin & Cyclophosphamide	8 (2.9%)
Bortezomib & Cyclophosphamide	7 (1.0%)
Paclitaxel & Carboplatin& Gemcitabine	5 (1.8%)
Paclitaxel & Doxorubicin & Cyclophosphamide	4 (1.4%)
Paclitaxel & Carboplatin& Doxorubicin & Cyclophosphamide	3 (1.1%)

Data is presented as number (Percentage).

Regarding incidence of AKI, 22.8% of patients had breast cancer, 14.9% of patients had colon cancer, 11.2% of patients had lung cancer, 9.4% of patients had ovarian cancer, 8.3% of patients had lymphoma, 5.8% of patients had pancreatic cancer, 5.1% of patients had prostate cancer, 4.7% of patients had bone tumor, 4.7% of patients had endometrial cancer, 4.3% of patients had gastric cancer, 4.3% of patients had liver cancer, 2.5% of patients had multiple myeloma, 1.1% of patients had skin cancer and 0.7% of patients had esophageal cancer. The causes of cancer-induced AKI in the studied patients were sepsis in 4 (1.4%) patients, extraluminal obstruction in 15 (5.4%) patients, intraluminal obstruction in 11 (4.0%) patients, hypovolemia in 75 (27.2%) patients, tumor lysis syndrome (due to solid tumors as hepatic tumors) in 25 (9.1%) patients, hypercalcemia in 65 (23.6%) patients, drug-induced in 115 (41.7%) patients, contrast-induced in 25 (9.1%) patients, and ischemia in 15 (5.4%) patients. The risk factors of cancer-induced AKI in the studied patients were diabetes in 117 (42.4%) patients, hypertension in 143 (51.8%) patients, advanced-stage cancer in 25 (9.1%) patients, Hypoalbuminemia in 191 (69.2%) patients, hypovolemia in 125 (45.3%) patients, chemotherapy in 200 (72.5%) patients, antibiotics in 95 (34.4%) patients and NSAID in 125 (45.3%) patients. Table 4

Regarding risk factors for AKI incidence, pre-existing comorbidities including hypertension, diabetes, and CHD are significant predictors increased the risk of AKI in cancer patients. Compared with untreated/palliative care, patients receiving surgery, chemotherapy, and interventional therapy were more predisposed to AKI. Other positive associations factors that predisposed AKI incidence were also observed in electrolyte abnormities. Patients with hyponatremia, hypokalemia and hyperuricemia shared a significantly higher risk of AKI (aOR = 2.95, 2.49, and 3.01. regarding in-hospital mortality among AKI patients, cox regression analysis revealed that HTN and DM also increased the mortality risk when adjusting

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demographic and clinical features. Other factors predicting in-hospital mortality in AKI patients included chemotherapy (aHR = 20.97), interventional therapy (aHR = 8.54), hypokalemia (aHR = 1.19). Table 5

The mean survival rate was significantly lower in group with AKI compared to group without AKI (16.331 versus 19.589). The mean survival rate was significantly higher in Stage I AKI compared Stage II and Stage III (16.331 versus 19.589). Stage II and Stage III was associated with higher mortality incidence compared to Stage I with Hazard ratio (0.1076 (95 % CI: 0.01559 to 0.7427), (0.1122 (95% CI: 0.01675 to 0.7514). Figure 1

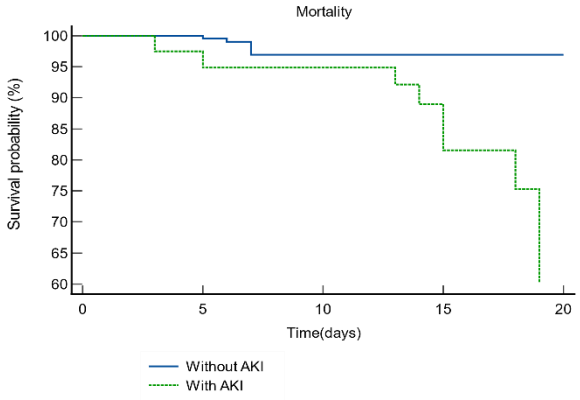
On multiple regression analysis, only CHD, Chemotherapy and creatinine were significant predictors for of AKI incidence (P value <0.05). Table 6

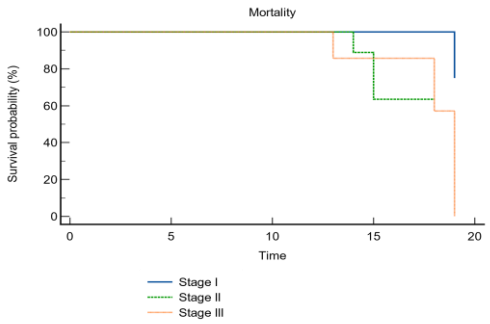
AKI cases usually shared a longer LOS and higher hospital cost during hospitalization. According to AKI, length of hospital stay of AKI patients were longer that non-AKI patients (7 days versus 15 days). According to AKI stages, AKI stage II and III had longer median length of hospital stay compared to stage I (19 ,16,9.5 days respectively). Regarding the fate of AKI in cancer patients, 215 (78.47%) patients improved, 48 (17.52%) patients improved after one or two sessions of dialysis and 11 (4.01%) patients developed CKD. Figure 2

Table 4: Incidence of AKI in different Cancer types of the studied patients.

		N (%)
Incidence of AKI	Breast cancer	63 (22.8%)
	Colon cancer	41 (14.9%)
	Lung cancer	31 (11.2%)
	Ovarian cancer	26 (9.4%)
	Lymphoma	23 (8.3%)
	Pancreatic cancer	16 (5.8%)
	Prostate cancer	14 (5.1%)
	Bone tumor	13 (4.7%)
	Endometrial cancer	13 (4.7%)
	Gastric cancer	12 (4.3%)
	Liver cancer	12 (4.3%)
	Multiple myeloma	7 (2.5%)
	Skin cancer	3 (1.1%)
	Esophageal cancer	2 (0.7%)
Causes of cancer-induced AKI	Sepsis	4 (1.4%)
	Extraluminal obstruction	15 (5.4%)
	Intraluminal obstruction	11 (4.0%)
	Hypovolemia	75 (27.2%)
	Tumor lysis syndrome	25 (9.1%)
	Hypercalcemia	65 (23.6%)
	Drug-induced	115 (41.7%)
	Contrast	25 (9.1%)
	Ischemia	15 (5.4%)
Risk factors of cancer-induced AKI	Diabetes	117 (42.4%)
	Hypertension	143 (51.8%)
	Advanced-stage cancer	25 (9.1%)
	Hypoalbuminemia	191 (69.2%)
	Hypovolemia	125 (45.3%)
	Chemotherapy	200 (72.5%)
	Antibiotics	95 (34.4%)
	NSAID	125 (45.3%)

(A)





(B)

Figure 1: Kaplan Meier curve of in hospital mortality (A) stratified with AKI incidence, and (B) stratified with AKI types.

Table 5: Risk factors for AKI incidence, and in-hospital mortality among AKI patients (N=40).

	N%	aOR (95% CI)	P value
Risk factors for AKI incidence		**Comorbidities**	
	HTN	1.69 (1.0180 - 1.95)	<0.001
	DM	1.40 (1.01- 1.89)	<0.001
	CHD	1.20 (1.78 -9.26)	<0.001
		Treatment	
	Chemotherapy	2.7199 (1.30 to 2.67)	<0.001
	Surgery	3.3675(1.6394 to 6.9172)	0.0009
	Intervention	2.0715 (1.4422 to 2.5962)	<0.001
	Palliative treatment	0.4096 (0.1202 to 1.3952)	0.153
		Electrolyte disturbance	
	Hyponatremia	2.95(2.96-4.07)	0.002
	Hypokalemia	2.49 (2.27–3.73)	<0.001
	Hyperuricemia	3.01(2.38–3.88)	<0.001
	N%	**aHR (95% CI)**	
in-hospital mortality among AKI patients		**Comorbidities**	
	HTN	4.1 (2.2-7.6)	
	DM	3.5 (1.9-3.4)	
	CHD	1.81 (0.59-2.14)	
		Treatment	
	Chemotherapy	20.97 (8.12-42.87)	
	Surgery	0.99 (0.23-1.79)	
	Intervention	8.97(2.80-29.68)	
	Palliative treatment	5.15(0.95-60.98)	
		Electrolyte disturbance	
	Hyponatremia	1.57 (1.23-2.54)	
	Hypokalemia	1.19 (1.5-2.9)	
	Hyperuricemia	1.78 (1.38-2.76)	

AKI: acute kidney injury; DM: Diabetes mellitus; CHD: coronary heart disease; CKD: chronic kidney disease; aOR: adjusted odds ratio; aHR: adjusted hazard ratio; CI: confidence interval; BMI: body mass index. aOR/aHR was adjusted for the demographic and clinical factors as age, gender, residence, BMI, cancer type, and stage in logistic and Cox proportional hazard model, respectively.

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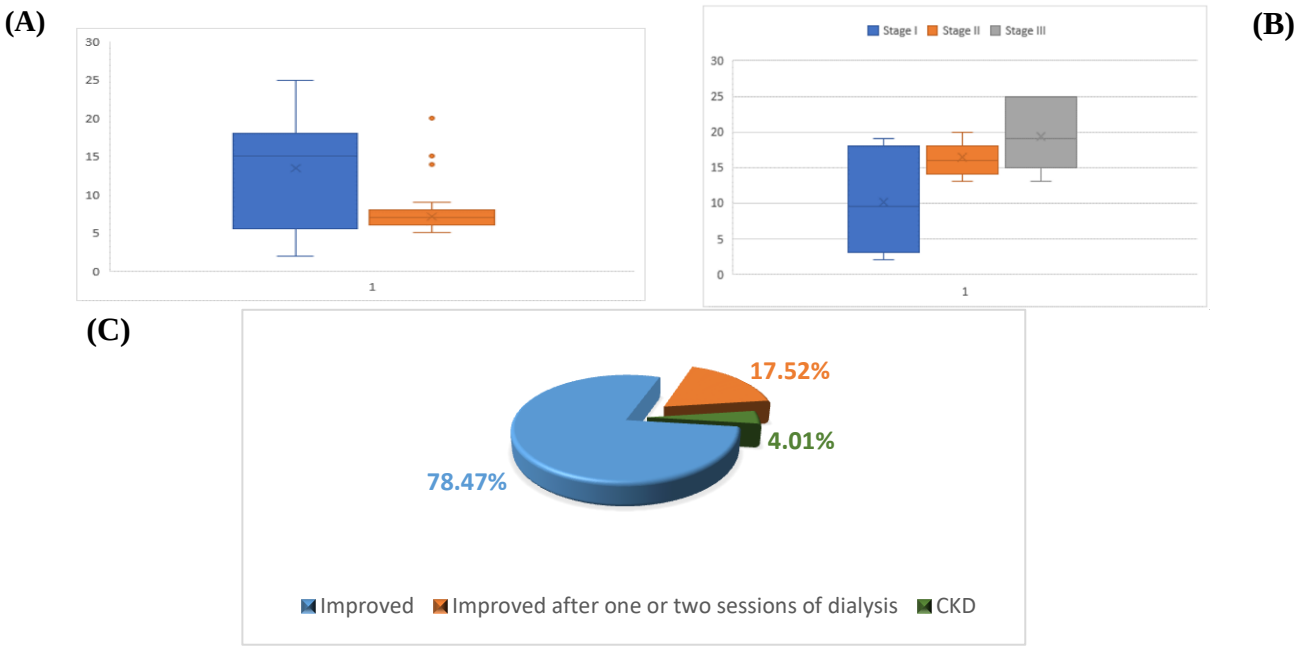

Figure 2: (A) Median of hospital stay in different AKI stages, (B) Median of hospital stay in different AKI stage patients, and (C) Fate of AKI in cancer patients.

Table 6: Multiple regression analysis for prediction of AKI incidence.

Independent variables	Coefficient	Std. Error	t	P	$r_{partial}$	$r_{semipartial}$
Age	0.001652	0.001	1.567	0.118	0.09747	0.040
Sex	0.0004	0.019	0.0209	0.983	0.001306	0.0005
Weight	0.0002	0.001	0.172	0.863	0.01078	0.004
DM	-0.018	0.023	-0.796	0.427	-0.04968	0.020
HTN	0.0020	0.029	0.0688	0.945	0.004302	0.001
CHD	0.093	0.032	2.872	**0.004***	0.1767	0.073
Chemotherapy	0.0706	0.031	2.262	**0.025***	0.1400	0.057
Hypokalemia	0.119	0.080	1.480	0.140	0.09209	0.037
Hyponatremia	-0.021	0.050	-0.427	0.670	-0.02665	0.010
Hb	-0.0022	0.008	-0.261	0.794	-0.01630	0.006
WBC	-0.0016	0.002	-0.667	0.505	-0.04162	0.017
PLT	0.0003	0.0003	1.123	0.26	0.07003	0.028
K	-0.01148	0.013	-0.880	0.379	-0.05494	0.022
Na	0.002174	0.0019	1.128	0.260	0.07034	0.028
Serum albumin	-0.01070	0.0136	-0.782	0.434	-0.04883	0.019
Total protein	0.001447	0.006	0.217	0.828	0.01355	0.0055
Ca	0.002103	0.0032	0.638	0.524	0.03983	0.016
Creatine	0.08691	0.002	30.08	**<0.001***	0.8829	0.768
ACR	0.02630	0.0413	0.636	0.525	0.03973	0.016

AKI: acute kidney injury, DM: diabetes mellitus, HTN: hypertension, CHD: chronic heart disease, Hb: hemoglobin, WBC: white blood cell, PLT: platelets, ACR: albumin creatinine ratio, *: statistically significant as P value <0.05.

Discussion

Acute kidney injury (AKI) is one of the dreaded complications among cancer patients. Due to the inefficient renal function, patients suffered with AKI had less access to optimal anti-cancer therapy, which usually resulted in an ominous prognosis. It was estimated that the global AKI incidence and associated mortality in cancer patients were 21.3% and 25.7%, respectively [(9)].

In this study, regarding the regimen of chemotherapy, 72 (26.1%) patients were receiving Paclitaxel & Carboplatin, 59 (8.7%) patients were receiving Gemcitabine & Carboplatin, 41 (14.9%) patients were receiving Rituximab& Doxorubicin, 26 (3.8%) patients were receiving Gemcitabine, 23 (3.4%) patients were receiving Bendamustine (alkylating agent), 8 (2.9%) patients were receiving Docetaxel & Doxorubicin & Cyclophosphamide, 7 (1.0%) patients were receiving Bortezomib & Cyclophosphamide, 5 (1.8%) patients were receiving Paclitaxel & Carboplatin& Gemcitabine, 4 (1.4%) patients were receiving Paclitaxel & Doxorubicin & Cyclophosphamide and 3 (1.1%) patients were receiving Paclitaxel & Carboplatin & Doxorubicin & Cyclophosphamide.

According to Launay-Vacher et al., they found that over 80% of cancer patients have a medication history of nephrotoxic drugs including non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2-inhibitors (COX-2-I), bisphosphonates, and methotrexate [(10)].

In our study, 40 (14.5%) cancer patients were recognized as AKI.

While in hospitalization. Of them, 22 (55%) patients located in AKI stage 1, and another 11 (27.5%) and 7 (17.5%) cases developed to stage 2 and stage 3, respectively. This was slightly lower than other studies in France (16.9%) [(11)], Japan (17.9%) [(12)], the mainland of China (18.6%) [(13)], Taiwan (23.3%) [(14)], but higher the United States (12.0%) [(15)].

Also, our rate is higher than Li et al. study which reported that the risk among cancer patients was significantly higher (12.4% vs 10.3%, RR = 1.20) as compared with patients without malignancy. Although multiple imputation of SCr value was applied in the process of data sorting, SCr values were still missing in some patients in hospitalization. Consequently, the AKI incidence in their study might be underestimated [(16)].

Moreover, Nazzal et al. revealed that 6.9% of cancer patients' admissions had AKI based on the adjusted RIFLE criteria. The distribution of patients with any degree of AKI was risk (3.3%), injury (1.7%), and failure (1.9%) [(17)].

However, most of these studies were restricted to the select group at high risk of AKI, such as hematological malignancies, patients treated with surgery and in ICU unit [(18, 19)]. Moreover, the incidence of AKI is dependent on the definition of baseline creatinine level [(20)]. Many retrospective studies use lowest or admission serum creatinine as the baseline value [(19)].

In the current study, we found that the AKI incidence increased significantly from 30% in the youngest group to 70% in patients aged above 50 years (95% CI: 1.543 to 4.325, Relative risk = 2.5).

Similarly, Máthé et al. and Kidera et al. have demonstrated that old age (≥70 years) increase the risk of AKI in lung cancer patients [(21, 22)].

Our results disagree with a previous study who reported that there was no significant difference in AKI incidences between the elderly and younger patients in palliative chemotherapy in lung cancer patients [(23)].

The present study showed that, male cancer patients accounted for a slightly higher incidence than the female (22 (55%) vs 18 (45%)).

In agreement with us, a Kim et al. aimed to determine the incidence and predictive factors of AKI after gastric surgery for gastric cancer and its effects on the clinical outcomes reported that male gender was identified as independent predictor for postoperative AKI [(24)].

In contrast, Máthé et al. and Kidera et al. have demonstrated that female sex increase the risk of AKI in lung cancer patients [(21, 22)].

In our study, Serum creatinine ranged from 1.2-5 mg/dL with a mean of 1.8± 0.7 mg/dL.

This agreed with Li et al. who reported that about half of AKI patients were found

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with an initially increasing SCr value on admission [16].

In this study, the AKI incidence was 65% in patients with hematologic cancer, whereas it was 35% in patients with solid tumor Relative risk = 1.857, 95% CI: 1.149 to 3.001).

Park et al. reported similar results that children with hematologic malignancies had the highest incidence of AKI [25].

By contrast, Xiong et al. showed that AKI was more frequent in children with urinary system cancer, hepatic cancer, and retroperitoneal malignancies than in patients with other types of malignancies, including hematologic malignancies [26].

In our study, 22.8% of patients had breast cancer, 14.9% of patients had colon cancer, 11.2% of patients had lung cancer, 9.4% of patients had ovarian cancer, 8.3% of patients had lymphoma, 5.8% of patients had pancreatic cancer, 5.1% of patients had prostate cancer, 4.7% of patients had bone tumor, 4.7% of patients had endometrial cancer, 4.3% of patients had gastric cancer, 4.3% of patients had liver cancer, 2.5% of patients had multiple myeloma, 1.1% of patients had skin cancer and 0.7% of patients had esophageal cancer.

In this study, the causes of cancer-induced AKI in the studied patients were sepsis in 4 (1.4%) patients, extraluminal obstruction in 15 (5.4%) patients, intraluminal obstruction in 11 (4.0%) patients, hypovolemia in 75 (27.2%) patients, tumor lysis syndrome (due to solid tumors as hepatic tumors) in 25 (9.1%) patients, hypercalcemia in 65 (23.6%) patients, drug-induced in 115 (41.7%) patients, contrast-induced in 25 (9.1%) patients, and ischemia in 15 (5.4%) patients.

While Cheng et al. showed that AKI more likely occurred in patients with bladder cancer, lymphoma or leukemia [27]. The possible cause includes renal interstitial infiltration by lymphoma cells and tumor lysis syndrome after treatment [28]. Urinary tract obstruction is frequently seen due to the tumor infiltration in bladder cancer. Cheng et al also found that urinary tract obstruction was a major risk factor of AKI in their study.

Cancer and its treatment can be associated with multiple AKI-inducing events [29].

Nazzal et al. reported that, hypercalcemia and sepsis were a strong and independent clinical association with AKI [17]. In addition, there is an important correlation between hypercalcemia and poor health outcomes in cancer patients, suggesting hypercalcemia as a potential marker for sicker patients. Hypercalcemia occurs in approximately 20% to 30% of all malignancies and is a common cause of AKI [30].

AKI is 4.4 times more likely to develop among sepsis cancer hospitalizations compared to sepsis-free hospitalizations. The kidney is one of the most frequently affected organs after sepsis, causing AKI-related sepsis and contributing to sepsis morbidity and mortality [31]. This can be due to renal hypoperfusion, DIC, multisystem failure, and increased ICU admission probability [32].

The current study showed that pre-existing comorbidities including hypertension, diabetes, and CHD are significant predictors that increased the risk of AKI in cancer patients.

This is in agreement with a study which reported that some comorbidities have been shown to be strongly associated with AKI, congestive heart failure. Uncontrolled congestive heart failure is associated with a rapid loss of renal function [17].

This disagrees with Park et al. who investigated the incidence, risk factors, and clinical outcomes of AKI caused by palliative chemotherapy in lung cancer patients. The study reported that, comorbidities did not affect the occurrence of AKI during chemotherapy [23].

In this study, compared with untreated/palliative care, patients receiving surgery, chemotherapy, and interventional therapy were more predisposed to AKI

This agreed with Li et al. who reported that, patients receiving chemical (aOR = 2.28) and interventional therapy (aOR = 2.08) were also more likely to suffer with AKI [16]. Furthermore, a sustained growth of AKI incidence along with the repeated admissions also suggested that the long-term chemotherapy might contribute to the occurrence of AKI.

Kwon et al. included 886 patients who underwent radical cystectomy for bladder cancer, found that 33.1% developed AKI in the first week after surgery [33].

According to Park et al. the occurrence of AKI was only associated with the number of chemotherapy cycles administered. Nephrotoxicity was found in 18.9% of patients who received cisplatin-based combination chemotherapy; moreover, the odds ratio of developing AKI increased by 1.61 times with an increase in a single cycle of chemotherapy [23].

Leblanc et al. reported that a cumulative exposure to cisplatin can cause acute tubular necrosis and may lead to glomerular damage [34]. In another study, nephrotoxicity developed in 28-36% patients who received a single dose (50 mg/m^2) of cisplatin [35].

Kim et al. found that 14.4% of these patients developed postoperative AKI and that 2.1% of these patients required renal replacement therapy. Use of diuretics, vasopressors, packed RBC transfusion and contrast agents were identified as independent predictors for postoperative AKI [24].

Radiocontrast agents in interventional therapy also posed patients at risk of AKI. It could lower the GFR level and renal medullary blood flow as they exhibit vasoconstrictor effects on kidney vasculature [36].

In this study, other positive associations factors that predisposed AKI incidence were also observed in electrolyte abnormalities. Patients with hyponatremia, hypokalemia and hyperuricemia shared a significantly higher risk of AKI (aOR = 2.95, 2.49, and 3.01).

Electrolyte disturbance was also commonly encountered in cancer patients, which was accompanied by the occurrence of AKI [9].

This is in harmony with another study, they found that both hyponatremia and hypokalemia were the independent risk factors for AKI (aOR = 2.84 and 2.42). It suggested that monitoring electrolyte abnormities on admission could facilitate predicting the incidence of AKI, especially for community-acquired (CA)-AKI. Moreover, it was observed that abnormal biochemical tests also related to the higher AKI risk. To this end, correcting these modifiable factors on the initiation of anti-cancer treatment could prevent the occurrence of AKI.

According to a national report of the United Kingdom, AKI could have been avoided in one-fifth of patients who developed it after admission to hospital if they had received better monitoring of electrolytes, recognition of risk factors, and prompt management [37].

This study showed that the overall in-hospital mortality for cancer patients was 3%. In AKI cases, this rate was 5% (Relative risk = 2.956 ,95% CI: 1.305 to 6.696), which was higher than those without AKI (0.8%). Compared with patients in AKI stage 1 (4.5%), patients in AKI stage 2 and stage 3 had a greater probability of in-hospital mortality (18.18% and 14.2%) ($P<0.001$).

In our study, AKI cases usually shared a longer LOS and higher hospital cost during hospitalization. According to AKI stages, AKI stage II and III had longer median length of hospital stay compared to stage I (19 ,16,9.5 days respectively).

A previous study reported that AKI was associated with a 1.94-fold increase in the Hazard Ratios (HR) of in-hospital mortality, a prolonged LOS, and high hospital cost. The LOS in hospital was correspondingly prolonged. By contrast, patients with mild hospital-acquired (HA)-AKI (stage 1) can discharge from hospital earlier and receive regular outpatient

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follow-up. However, they found that CA-AKI patients accounted for a higher proportion of surgery treatment compared with HA-AKI. It could contribute to improving the in-hospital survival for CA-AKI patients while spending more hospital cost as well [16].

Zeng et al. and Xu et al. demonstrated that the in-hospital mortality were associated with severity of AKI in hospitalized patients [38, 39].

Nazzal et al. found that the in-hospital mortality rate was 5.2% for all cancer hospitalizations. Of these, 39.3% (13 patients) were complicated with AKI. Also, AKI in cancer patients was associated with higher odds for more extended hospital stays [17].

Similar findings were observed by Xiong et al. on pediatric patients with malignancy, as they found that more advanced AKI stage being associated with a higher in-hospital mortality rate. Moreover, AKI in pediatric cancer patients was associated with increased LOS and higher daily costs [26].

Hafez et al. reported that, patients with AKI had a longer stay in ICU and a significantly higher all-cause ICU and hospital mortality than patients without AKI [40].

Abosaif et al. applied the RIFLE classification to 183 ICU patients and found that ICU mortality increased from 38.3% among patients with RIFLE risk to 50% in the injury group and to 74.5% among patients [41].

Cheng et al. described a much higher in-hospital mortality of 8.3% and 13.0% in cancer patients with CA-AKI and HA-AKI. In their analyses, they illustrated that the association between AKI and in-hospital mortality was strongly confounded by a number of other variables, except baseline creatinine level. AKI severity also had a positive association with LOS and daily costs after adjusting for other potential confounders, and the effect size displayed an increasing trend with the LOS and daily costs [27].

Although elevated baseline creatinine level have been proved to be a significant risk factors of AKI, the rising degree of creatinine, instead of baseline level, determines the severe outcome when AKI have developed [42].

In the present study, the mean survival rate was significantly lower in group with AKI compared to group without AKI (16.331 versus 19.589).

This is in contrast to a study which reported that progression-free survival (PFS) and overall survival (OS) was not different between the two groups. The reason for the discrepancy between time to treatment failure (TTF) and PFS is likely that AKI that developed in the early cycles of the first-line chemotherapy was mild and reversible, and the chemotherapy could be continued in most cases; conversely, AKI developed in the late cycles of the first-line chemotherapy was caused by long-term chemotherapy [23].

In our study, other factors predicting in-hospital mortality in AKI patients included chemotherapy (aHR = 20.97), interventional therapy (aHR = 8.54), hypokalemia (aHR = 1.19).

Park et al. reported that, AKI that developed during chemotherapy did not affect survival, and it was not determined on the basis of the AKI grade. In our study, prognosis of AKI during chemotherapy was favorable as none of the patients with AKI developed ESRD [23].

On multiple regression analysis, only CHD, Chemotherapy and creatinine were significant predictors for of AKI incidence (P value <0.05).

Similar to our study, many studies reported that chemotherapy is a significant factor in developing AKI [15, 23].

Moreover, a study reported that their patients' mean age was 55 years, and age in the multivariate analysis did not differ between the AKI and non-AKI groups. This finding suggests that factors other than age were important for AKI in their patients with cancer. While chemotherapy

was not found in their research, and the negative correlation may be secondary to preventive measures taken when chemotherapy was administered [17].

Regarding the fate of AKI in cancer patients, 215 (78.47%) patients improved, 48 (17.52%) patients needed dialysis and 11 (4.01%) patients developed CKD.

One study revealed that an incidence of 8.5% for AKI, defined as either a 50% increase in SCr level or requirement of dialysis, developing after gastric bypass surgery for morbid obesity [43].

Conclusion

The incidence of AKI was 14.5% and top two cancer types were breast cancer and colon cancer. The in-hospital mortality was 5% in cancer patients with AKI. The severe AKI was associated with poor clinical outcome, long hospital stay and high daily costs. Pre-existing comorbidities and electrolyte disturbances are the predicting factors for AKI incidence.

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Author contribution

Authors contributed equally in the study**.**

Conflicts of interest

No conflicts of interest

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