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Outcomes of Acute Kidney Injury Patients with and Without Cancer: A Single Center Study

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Authors' contributions

This work was carried out in collaboration between all authors. Authors JL and YNK participated in the design of the study performed the statistical analysis. Author HSS conceived of the study, and participated in its design and coordination. All authors read and approved the final manuscript.

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ABSTRACT

Background: Acute kidney injury (AKI) is a frequent complication in hospitalized patients. Incidence of AKI in hospitalized patients with cancer is increasing, but there have been few studies on AKI in patients with cancer. The purposes of this study were: 1. To evaluate and compare the characteristics and outcomes of cancer and non-cancer AKI patients; 2. To determine the impact of cancer diagnosis on hospital mortality of AKI patients; and 3. To compare outcome predictors between the two groups of AKI patients.
Methods: We conducted a retrospective cohort study in a South Korean tertiary care hospital. A total of 2211 consecutive patients (without cancer 61.5%; with cancer 38.5%) were included over a 140-month period. Predictors of all-cause death were examined using the Kaplan-Meier method and the Cox proportional hazards model.
Results: The main contributing factors of AKI were sepsis (31.1%) and ischemia (52.7%). AKI was multifactorial in 78% of patients with cancer and in 71% of patients without cancer. Hospital mortality rates were higher in patients with cancer (42.8%) than in patients without cancer (22.5%)

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(P = 0.014). In multivariate analyses, diabetes mellitus (DM) and cancer diagnosis were associated with hospital mortality. Cancer diagnosis was independently associated with mortality [odds ratio = 3.010 (95% confidence interval, 2.340-3.873), P = 0.001]. Kaplan-Meier analysis revealed that subjects with DM and cancer (n = 146) had lower survival rates than subjects with DM and without cancer (n = 687) (log rank test, P = 0.001).

Conclusion: The presence of DM and cancer were independently associated with mortality in AKI patients both with and without cancer. Studies are warranted to determine whether proactive measures may limit AKI and improve outcomes.

Keywords: Acute kidney injury; cancer; DM; mortality.

1. INTRODUCTION

Acute kidney injury (AKI) is a frequent complication in hospitalized patients [1,2]. The main cause of in hospital AKI is acute tubular necrosis resulting from multiple nephrotoxic insults such as sepsis, hypotension, and the use of nephrotoxic drugs or radiocontrast media [3]. AKI in cancer patients may also be secondary to special conditions, including poor oral intake, vomiting, diarrhea, malignant infiltration, tumor lysis syndrome, light chain diseas, extrarenal obstruction, and secondary effects of treatment [4].

Many cancer cases are cured, and others are rendered chronic and manageable. The benefits of such therapies are, however, not fully realized, in part because of the high frequency of therapy-associated organ injury, including of the kidneys [5]. AKI seems to be on the rise in hospitalized patients with cancer. The risk of AKI was 18%, during the 1st year after cancer diagnosis. Up to 50% of cancer patients experience AKI while in the ICU. AKI occurs either as a consequence of the cancer itself, anticancer treatment or a diversity of associated severe clinical conditions. Although survival seems to have improved over the last decade, the development of AKI in cancer patients remains associated with high mortality rates [6]. To our knowledge, the outcome of AKI in hospitalized patients with and without cancer (especially solid caner) or the extent of its effect on clinical outcomes has not been reported.

The purposes of this study were: 1. To evaluate and compare the characteristics and outcomes of cancer and non-cancer AKI patients; 2. To determine the impact of cancer diagnosis on hospital mortality of AKI patients; and 3. To compare outcome predictors between the two groups of AKI patients.

2. MATERIALS AND METHODS

We conducted a retrospective cohort study of patients with AKI who were treated at Kosin University Gospel Hospital during a 14-year period. The patients were divided into two major groups: 1,360 AKI patients without cancer and 851 AKI patients with cancer.

To be included in the study, patients with cancer must have had a pathologically proven diagnosis of malignancy, and both cancer and non-cancer patients had to have at least one of the following: elevated serum creatinine (> 1.5 × baseline value), decreased calculated creatinine clearance (< 0.75 × baseline creatinine clearance estimated using the MDRD equation, and oliguria (< 0.5 ml/kg/h for 6 h) [7]. AKI was classified using the RIFLE (Risk Injury Failure Loss Endstage) criteria at the time of initiation of renal replacement therapy (RRT) [8-10]. Serum creatinine was measured using a Jaffe alkaline picrate assay (Abbott Aeroset analyzer). The Jaffe assay was calibrated to isotope dilution mass spectrometry-traceable creatinine values using the Roche enzymatic creatinine assay. The time for an increase in serum creatinine from admission included any time during hospitalization. The baseline serum creatinine was the first serum creatinine that was measured after admission. In addition to the original electronic data, electronic case records of individual patients who developed AKI were accessed (chart check) to obtain additional information. Additionally, included patients also had at least one of the following: significant organ (example, lung etc) edema, oliguria despite fluid resuscitation and diuretic use, anuria, severe azotemia, and medically intractable hyperkalemia.

The following subjects were excluded from the analysis: 1. Patients with non-renal indications for RRT; RRT was initiated and managed by the attending nephrologist, We typically use the renal

criteria described by Ronco and Bellomo to determine the indications for RRT. 2. Those with end-stage renal disease requiring chronic dialysis. 3. Those with hospital stay less than 24 hours and re-admission. 4. hepatorenal syndrome. This syndrome was diagnosed when the following criteria were satisfied all

1st, Cirrhosis with ascites
2nd, Serum creatinine > 1.5 mg/dL
3rd, No improvement in serum creatinine after at least 2 days with diuretic withdrawal and volume expansion with albumin.
4th, Absence of shock
5th, No current or recent treatment with nephrotoxic drugs
6th, Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/day, microhematuria (> 50 red blood cells per high power field) and/or abnormal renal ultrasound

Institutional Review Board approval was obtained prior to the start of the study.

2.1 Statistical Analysis

We compared of noncontinuous variables by chi-square T-tests for categorical and continuous variables. Predictors of all-cause death were examined using Kaplan-Meier and Cox proportional hazards analyses in both treatment groups. P value was < 0.05 was considered to represent a statistically significant difference. Statistical analyses were carried out by using the Social Sciences (SPSS) version 18.0.

3. RESULTS

3.1 Patient Characteristics and Outcomes

The mean age ± SD was 61±14.1; 58% of patients were male. Among patients admitted, 38.5% were cancer patients, 61.5% were non-cancer. Hospital mortality rates were higher in patients with cancer (42.8%) than in patients without cancer (22.5%) (P = 0.014). ICU mortality was higher in cancer patients (79.9%) than in non-cancer patients (59.6%). Infection was the most common cause of death (52.3% of non-cancer patients), followed by cardiovascular disease (CVD) (16.7% of non-cancer patients) in non cancer groups. And cancer (64.2%) or other unidentified reasons (infection 31.0%, etc) were the most common cause of death in cancer group (Table 1). Among type of caner, number of metastatic solid tumor was most, followed by number of locoregional solid tumor (Tabel 1). For cancer status, uncontrolled / recurrence, progression state was most common.

Solid tumors were the most common underlying malignancy (92.6%), followed by lymphoma (2.7%). The liver was the most common cancer site (19.7%), followed by the stomach (18.0%) (Tables 3, 4).

3.2 Clinical and Laboratory Data Related to Kidney Function

AKI was multifactorial in 78% of patients with cancer and in 71% of patients without cancer. The baseline value of serum creatinine was 0.8 mg/dL in cancer patient and 0.6 mg/dL in non cancer patient (data was not shown). The most common etiologies of AKI were ischemia (41.1%) followed by sepsis (32.8%) in cancer patients. And the most common etiologies of AKI were ischemia (60%) followed by sepsis (30%) in non-cancer patients (Table 2).

3.3 Compare Outcome Predictors between the Two Groups of Patients

Tables 5 and 6 show the results of the multivariate Cox regression analysis in all patients. Diabetes mellitus (DM) and cancer diagnosis were associated with hospital mortality. Cancer diagnosis was independently associated with mortality [odds ratio = 3.010 (95% confidence interval, 2.340-3.873), P = 0.001]. Kaplan-Meier analysis revealed that subjects with DM and cancer (n = 146) had lower survival rates than subjects with DM and without cancer (n = 687) (log rank test, P = 0.001).

Table 7 shows the results of the multivariate Cox regression analysis in non-cancer patients. DM was significantly (P-value = 0.032) and CKD was marginally (P-value = 0.075) associated with hospital mortality in non-cancer patients.

Among cancer patients with DM, the median survival duration was 4.6 months (Fig. 1). Among cancer patients without DM, the median survival duration was 9.7 months (Fig. 2).

4. DISSCUSION

In this study the presence of DM and cancer were independently associated with mortality in AKI patients both with and without cancer in the our retrospective cohort. The outcome of AKI in

Table 1. Main patient characteristics and outcomes

Variables	All patients	Non-cancer patients	Cancer patients	P-value
	(n = 2211)	(n = 1360, 61.5%)	(n = 851, 38.5%)	
Age (years)	61.1±14.1	61.4±15.3	60.7±12.1	0.221
Male gender	1356(61.3%)	789(58%)	567(66.6%)	0.001
DM	833(37.7%)	687(50.5%)	146(17.1%)	0.001
Sepsis	687(31.1%)	442(32.5%)	245(28.7%)	0.001
Hospital mortality	671(30.3%)	306(22.5%)	365(42.8%)	0.001
ICU admission	523(23.7%)	385(28.3%)	138(16.2%)	0.001
ICU mortality	340(65.0%)	230(59.7%)	110(79.9%)	0.001
Inotropics	607(27.4%)	441(30.2%)	166(19.5%)	0.001
Mechanical ventilator	480(21.7%)	385(28.3%)	95(11.2%)	0.001
Chronic hepatitis B	211(9.5%)	93(6.8%)	118(13.8%)	0.001
Chronic hepatitis C	185(8.4%)	114(8.4%)	71(8.3%)	0.512
Cause of death				
Cancer/unidentified	234(34.9%)	NA	234(64.2%)	
Cerebrovascular disease	58(8.6%)	51(16.7%)	7(1.9%)	0.001
Heart disease	49(7.3%)	45(14.7%)	4(1.0%)	0.001
DM	1(0.2%)	1(0.3%)	0	0.001
Infection	273(40.8%)	160(52.3%)	113(31.0%)	0.001
Liver diease	53(7.7%)	46(15.0%)	7(1.9%)	0.001
Hypertensive disease	3(0.5%)	3(1.0%)	0	0.001
Type of cancer				
Locoregional solid tumor	189(8.5%)		189(22.2%)	NA
Metastatic solid tumor	604(27.4%)		604(71.0%)	
Hematological malignancy	58(2.6%)		58(6.8%)	
Cancer status				
Controlled	143(6.4%)	NA	143(16.8%)	
Uncontrolled / newly diagnosed	81(3.6%)	NA	81(9.5%)	
Uncontrolled / recurrence, progression	627(28.3%)	NA	627(73.8%)	

hospitalized patients with and without cancer or the extent of its effect on clinical outcomes has not been reported Hospital mortality rates were higher in patients with cancer (42.8%) than in patients without cancer (22.5%) (P = 0.014). ICU mortality was higher in cancer patients (42.8% and 79.9%) than in non-cancer patients (22.5% and 59.6%).

According to outcome analyses, AKI in patients with cancer was associated with higher for deaths and longer ICU stays. The etiology of AKIs in hospitalized patients with cancer is often multifactorial. Infection was the most common cause of death, followed by CVD in non cancer groups. And cancer was the most common cause of death, followed by infection in cancer groups [1].

The portion of CKD was 10.4% of patients with cancer and in 25% of patients without cancer. Patients with chronic kidney disease may be at risk for the development of transient decreases in renal function consistent with acute kidney injury. The mechanisms by which these decreases occur include failure of autoregulation, abnormal vasodilatation, susceptibility to antihypertensive agents, and side effects of medication (with drugs such as diuretic agents, antihypertensive agents etc) [11].

The presence of diabetes is a well known factor for AKI-particularly for radiocontrast nephrotoxicity-but not in hospitalized patients with cancer [12]. AKI is a common complication in patients with cancer and may occur as a consequence of cancer itself, its treatment, and associated severe complications such as sepsis and hypercalcemia. Factors associated with AKI in cancer patients have been extensively studied and some factors, i.e. hemodynamic instability, sepsis, and nephrotoxins [13,14], have also been found in other critical patients. In our cancer patients the most common etiologies of AKI were ischemia followed by sepsis and vasoactive drugs were needed by 19.5% of cancer patients.

Table 2. Clinical and laboratory data related to kidney function

Variables	All patients	Non-cancer patients	Cancer patients	P-value
	(n = 2211)	(n = 1360, 61.5%)	(n = 851, 38.5%)	
Chronic kidney disease	428(20.1%)	340(25%)	88(10.4%)	0.001
DM as cause of CKD	232(52.2%)	197(58.1%)	35(39.7%)	0.001
Etiology of AKI				
Sepsis	687(31.1%)	408(30.0%)	279(32.8%)	0.001
Ischemia or shock	1165(52.7%)	816(60.0%)	349(41.1%)	0.001
Radiocontrast or nephrotoxin	179(8.1%)	73(5.4%)	106(12.5%)	0.001
Hemolysis or rhabdomyolysis	51(2.3%)	41(3%)	10(1.1%)	0.001
Urinary tract obstruction	113(5.1%)	19(1.4%)	94(11.0%)	0.001
Tumor lysis syndrome	9(0.4%)	NA	9(1.0%)	NA
Continuous renal replacement therapy	306(13.8%)	256(18.8%)	50(5.8%)	0.001
Conventional hemodialysis	174(7.8%)	107(7.8%)	67(7.8%)	0.001
Laboratory data at diagnosis of AKI				
Creatinine (mg/dL)	1.4±1.3	1.6±1.0	1.3±0.9	0.001
Estimate glomerular filtration rate (mL/min/1.73m^2)	30±16	25±12	35±8	0.001
Urea (mg/dL)	42±16	53±18	40±13	0.001
Sodium (mEq/L)	138.0±4.8	139.0±4.7	136.9±4.8	0.001
Potassium (mEq/L)	4.3±0.6	4.3±0.7	4.3±0.6	0.700
Phosphorus (mg/dL)	3.7±2.3	3.8±3.2	3.6±0.9	0.184
pH	7.42±0.05	7.42±0.06	7.43±0.05	0.080
Bicarbonate (mEq/L)	22.4±4.5	22.4±4.9	22.3±4.1	0.689

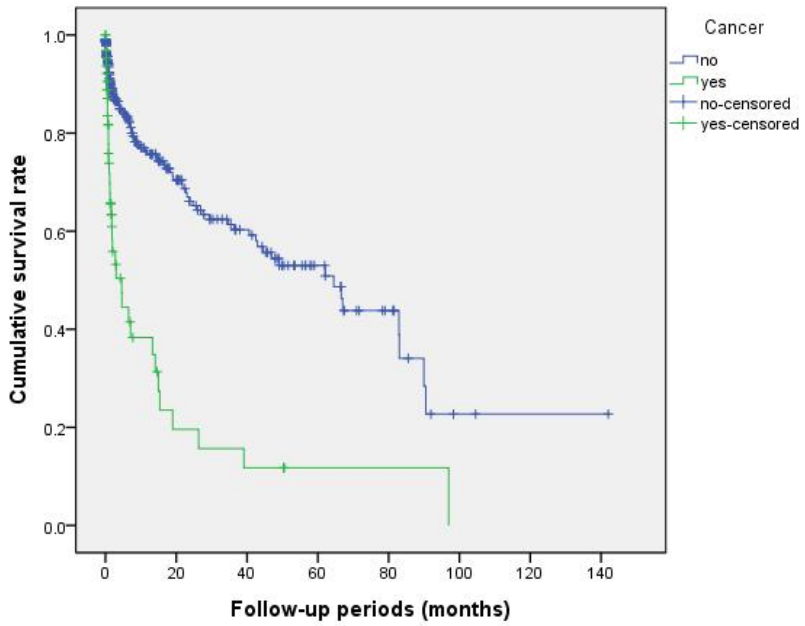

Fig. 1. Survival curve in cancer and non-cancer patients with DM

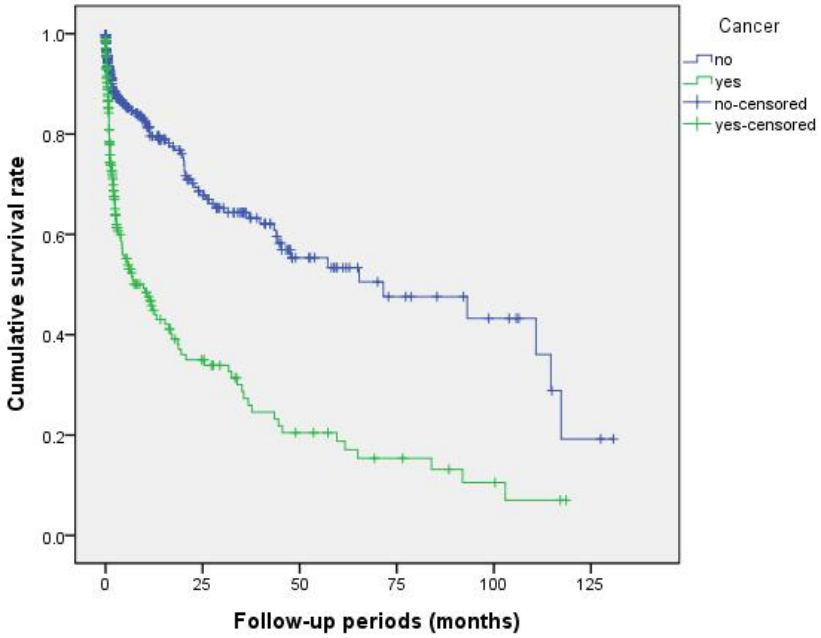

Fig. 2. Survival curve in cancer and non-cancer patients without DM

Table 3. Underlying malignancy

Cancer	N
Acute leukemia	12(1.4%)
lymphoma	23(2.7%)
Myeloma	23(2.7%)
Solid tumors	788(92.6%)
Miscellaneous malignancies	5(0.6%)
Total	**851(100%)**

The mean age of our patients was 61 years, and age in the multivariate analysis did not differ between the cancer and non-cancer group. This finding suggests that factors other than age were important for AKI in our patients with cancer. An important issue, not addressed in this study, is whether development of AKI influenced the choice and dosing of chemotherapy or whether such necessitated change in chemotherapy due to AKI influenced the cancer outcomes. Delay in diagnosing AKI or overestimating the GFR on the basis of serum creatinine can lead to the administration of higher than required doses of chemotherapeutic agents, thus creating a vicious cycle of systemic toxicity and worsening kidney function, leading to neutropenic sepsis and multiorgan failure.

The effect of AKI on the clinical and fiscal outcomes in hospitalized patients in the noncancer setting is known, according to Chertow et al. [15] AKI in hospital was associated with a 6.5-fold increase in the odds of death, a 3.5-day increase in length of hospital stay, and a $7500 increase in hospital costs; in our patients with cancer, the odds of death value was 4.7-fold.

Table 4. Cancer site

Site	N
Prostate	9(1.1%)
Urinary bladder	20(2.4%)
Kidney	18(2.1%)
Ovary	27(3.2%)
Corpus uteri	8(1.0%)
Cervix uteri	53(6.3%)
Lymphoma	23(2.7%)
Leukemia	12(1.4%)
Multiple myeloma	23(2.7%)
Colon	30(3.5%)
Rectum	34(4.0%)
Stomach	153(18.0%)
Esophagus	3(0.4%)
Liver	167(19.7%)
Gall bladder/biliary tract	99(11.5%)
Pancreas	30(3.6%)
Breast	6(0.7%)
Lung/bronchus/trachea	97(11.2%)
Brain/CNS	3(0.3%)
Malignant melanoma	2(0.2%)
Other sites	34(4.0%)
Total	**851(100%)**

Table 5. Multivariate Cox proportional hazards analysis of mortality in all patients (n = 2211)

Variables	Unit increase	Hazard ratio (95% CI)	P-value
CKD	vs. Absence	0.749 (0.547-1.024)	0.070
DM	vs. Absence	1.463 (1.194-1.604)	0.047
Mechanical ventilation	vs. Absence	0.952 (0.725-1.250)	0.724
Cancer	vs. Absence	3.010 (2.340-3.873)	0.001
Sex	vs. Female	1.129 (0.895-1.423)	0.303
Sepsis	vs. Absence	1.000 (0.787-1.270)	0.998
Age	vs. ≤ 64 yrears	1.038 (0.829-1.298)	0.998

Table 6. Multivariate Cox proportional hazards analysis of mortality in cancer (n =851)

Variables	Unit increase	Hazard ratio (95% CI)	P-value
CKD	vs. Absence	0.934 (0.503-1.736)	0.830
DM	vs. Absence	1.497 (1.008-2.221)	0.045
Mechanical ventilation	vs. Absence	1.179 (0.740-1.878)	0.486
Sex	vs. Female	1.088 (0.754-1.570)	0.652
Sepsis	vs. Absence	0.890 (0.630-1.256)	0.507
Age	vs. ≤ 64 yrears	0.951 (0.675-1.339)	0.773

Table 7. Multivariate Cox proportional hazards analysis of mortality in non-cancer (n =1360)

Variables	Unit increase	Hazard ratio (95% CI)	P-value
CKD	vs. Absence	0.676 (0.470-1.272)	0.075
DM	vs. Absence	1.149 (1.154-1.546)	0.032
Mechanical ventilation	vs. Absence	0.839 (0.599-1.176)	0.309
Sex	vs. Female	1.201 (0.882-1.635)	0.244
Sepsis	vs. Absence	1.123 (0.804-1.569)	0.495
Age	vs. ≤ 64 yrears	1.109 (0.816-1.508)	0.507

In critically ill patients with cancer, AKI usually occurs in the context of multiple organ dysfunction and is associated with mortality rates ranging from 53 to 93% [2,16]. In a large retrospective study, Samuels et al. [16] also described a mortality rate of roughly 50% among ICU cancer patients with a rise in serum creatinine of only 1 mg/dl. Our mortality rate was 42.8% in patients with any degree of AKI, which is comparable with other studies. Among cancer patients with DM, the median survival duration was 4.6 months. Among cancer patients without DM, the median survival duration was 9.7 months.

Our study had a number of limitations. First**,** it is a retrospective study. We were not able to analyze subgroups of patients with cancer, cancer stage and organ involvement. Second, we cannot rule out possible selection biases with regard to regional differences related to the standard of care. Third, we cannot definitively explain the reason sepsis was not significantly associated with hospital mortality in the two treatment groups. Fourth, we did not show data about the chemical therapy in cancer patients.

5. CONCLUSION

In conclusion, hospital mortality rates were higher in cancer patients than in non-cancer patients. DM and cancer were associated with hospital mortality, and cancer diagnosis was independently associated with mortality.

CONSENT

Informed consent was waived by Institutional Review Board approval.

ETHICAL APPROVAL

Institutional Review Board approval was obtained prior to the start of the study.

COMPETING INTERESTS

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