Impact of Cancer on Survival of Patients with AKI on CRRT

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Authors' contributions

This work was carried out in collaboration between both authors. Author 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. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Few studies have examined cancer patients with acute kidney injury (AKI) who require continuous renal replacement therapy (CRRT). The aim of this study was to compare the characteristics and outcomes of patients with and without cancer requiring CRRT for AKI in general intensive care units (ICUs).
Methods: We studied a retrospective cohort study in an ICU. A total of 200 patients (without cancer 79%; with cancer 21%) were included over a 24 month period. Predictors of all-cause death were examined using Kaplan-Meier and Cox proportional hazards analyses in both treatment groups for statistical analysis.
Results: The 1st contributing factors of AKI was cardiac dysfunction (40%) and 2nd factors was sepsis (38%). The cause of AKI was multifactorial in 78% of cancer patients and in 71% of patients without cancer. Hospital mortality rates were higher in patients with cancer (69%) than in patients without cancer (49.4 %) (P = 0.023). In multivariate analyses, older age, medical admission, poor chronic health status, comorbidities, ICU days until RRT start, number of associated organ dysfunctions, and diagnosis of cancer were associated with hospital mortality. The diagnosis of

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cancer was independently associated with mortality [odds ratio = 1.68 (95% confidence interval, 1.10–2.59), P = 0.017].

Conclusions: The presence of cancer may be independently associated with mortality in our study.

1. INTRODUCTION

The development of medicine has led to improve the prognosis of cancer patients substantially over the past two decades [1]. The advancements of novel or established chemotherapeutic regimens and best supportive cares can allow this improvement. However, the use of these modalities is also associated with an increased risk of life-threatening complications [2].

Almost half of cancer patients are treated for acute kidney injury (AKI), most of them experience severe renal dysfunction that requires renal replacement therapy while in the ICU [3-7]. AKI in these patients occurs either as a result of the cancer itself (urinary tract obstruction, systemic anticancer chemotherapy, major surgical procedure), or associated severe clinical conditions such as sepsis and hypovolemic shock [6,8].

Although survival of cancer patients seems to have improved recently, the development of AKI in critically severe cancer patients remains associated with high mortality rates [3,5,6,9-11]. Those seriously ill patients who require renal replacement therapy commonly show hemodynamic instability, then hard to proceed renal conventional intermittent hemodialysis. Therefore, continuous renal replacement therapy (CRRT) has emerged as the predominant form of renal replacement therapy because it reduces hemodynamic instability.

Some data suggest that renal replacement therapy before the onset of severe AKI may reduce kidney-specific and non-kidney organ injury from acidemia, uremia, fluid overload and systemic inflammation and potentially translate into improved survival and earlier recovery of kidney function.

However, few studies have examined the characteristics and outcomes of AKI patients with and without cancer who require specific CRRT while some data has examined from general renal replacement therapy including daily conventional dialysis, daily extended dialysis, and CRRT [12].

The purposes of this study were to evaluate and compare the characteristics and outcomes of cancer and non-cancer patients with AKI requiring CRRT, to determine the impact of cancer diagnosis on hospital mortality and lastly compare outcome predictors between the two groups of patients.

2. MATERIALS AND METHODS

We conducted a retrospective cohort study in our tertiary care hospital. We evaluated patients with acute kidney injury who were treated in the intensive care unit at Kosin University Gospel Hospital, from January 1st, 2010 to December 31th, 2011. A total of 200 (158 non-cancer AKI patients 79%; 42 cancer AKI patients 21%) patients were included into two groups.

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 ($> 1.5 \times$ baseline value), decreased calculated creatinine clearance ($< 0.75 \times$ baseline creatinine clearance estimated using the MDRD equation, and oliguria (< 0.5 ml/kg/h for 6 h) [12]. AKI was classified using the RIFLE criteria at the time of initiation of RRT. 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. Hepatorenal 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.

We excluded from the analysis patients receiving below 24 hours of continuous renal replacement therapy at enrollment, those who weighed less than 50 or more than 120 kg, patients with non-renal indications for renal replacement therapy, end-stage renal disease requiring chronic dialysis, those with a hospital stay less than 24 hours, readmissions were not considered. Institutional Review Board approval was obtained prior to the start of the study.

All CRRT sessions were conducted using Prisma or Prismaflex dialysis machines (Gambro). CRRT was initiated and managed by the attending nephrologist, and nafamostat mesilate was used for anticoagulation when heparin was contraindicated. The replacement fluid rate was typically 1–2 L/hour, which is an average of 35 mL/kg/hour (range: 30–42 mL/kg/hour), when CVVHDF was used as the modality. The blood flow rate was 80–180 mL/minute and the dialysate flow rate was 1–2 L/hour.

There were described in results about characteristics of patients treated with continuous renal replacements therapy (example: sex, age, chronic kidney disease, death, cause of death, clinical setting, etc), about etiology of acute kidney injury (example: cardiac dysfunction, infection etc), about reason to start CRRT (example: oliguria/auria, high BUN/Cr, fluid overload etc), about characteristics of CRRT (example: days to start to CRRT treatment, IUC length of stay etc), about underlying malignancy, about cancer site and about cox regression analysis of factors associated with mortality.

Data are expressed as means ± standard deviations. Discrete variables were compared with categorical and continuous variables by chi-square and *t*-tests, respectively. Predictors of all-cause death were examined using Kaplan-Meier and Cox proportional hazards analyses in both treatment groups for statistical analysis. All data were analyzed using SPSS version 18 (SPSS Inc, Chicago, Il, USA).

3. RESULTS

Two hundred patients with acute kidney injury were enrolled in this study. The baseline characteristics of patients were presented in Table 1. As this table shows, 158 (79%) patients did not have cancer, and 42 (21%) patients had cancer. Compared to the non-cancer group,

hospital mortality rates were higher in patients in cancer group (49.4% versus 69.0%). Also incidence of multiple organ failure was higher in cancer group, but incidence of cardiac death or cerebral infarction was higher in non-cancer group. There was no statistical difference in clinical setting between groups. In non-cancer group, there were more patients admitted due to unscheduled operation. On the other hand, more patients admitted for scheduled operation in cancer group. Diabetes mellitus (DM) was the most common underlying disease, followed by hypertension in both groups. The presence of sepsis was higher in patients with cancer than in patients without cancer.

The underlying causes of AKI are shown in Table 2. Infection was the most common cause, followed by hepatorenal syndrome in cancer patients. Cardiac dysfunction was the most common cause in non-cancer patients, followed by infection.

The indications for CRRT in our patient cohort are given in Table 3. Oliguria was the most common indication, followed by high blood urea nitrogen (BUN)/ creatinine (Cr) in both groups. Elevated BUN or serum Cr is more common cause of CRRT in non-cancer group, and decreased urinary volume, uncontrolled metabolic acidosis, or hyperkalemia is more common in cancer group.

Table 4 shows the characteristics of CRRT. The mean duration to the start of CRRT was longer in cancer patients than in non-cancer patients. There was no statistical difference in filter life span, or the CRRT setting such as blood flow rate, ultrafiltration dose, replacement flow rate, or dialysate flow rate. Also the mean prescribed dose of CRRT, anticoagulant, and vascular access for CRRT were similar between the two treatment groups. Patient status at the conclusion of CRRT was similar between the two treatment groups in terms of renal function recovery, chronic kidney disease and maintenance of hemodialysis. Because our patients' volume status was hypervolemic and they had pulmonary edema, we removed high volume of net UF in critically ill patients while administration of many vasoactive drugs.

Table 1. Characteristics of patients treated with continuous renal replacements therapy

No. of patients	Non-cancer (n=158)	Cancer (n=42)	P value
Male:female	84:74	31:11	0.016
Age, year (range)	65.8±13.0	65.2±10.3	0.771
CKD (%)	58 (36.7)	11 (26.2)	0.202
Death (%)	78 (49.4)	29 (69.0)	0.023
Cause of death (%)			
MOF	37 (51.4)	20 (74.1)	0.002
Cardiac	25 (34.7)	2 (7.4)	
Cerebral	5 (6.9)	0 (0)	
Respiratory	5 (6.9)	2 (7.4)	
Tumor recurrence	NA	3 (11.1)	
Clinical setting			0.861
Medical (%)	123 (78.2)	32 (76.9)	
Surgical (%)	35 (21.8)	10 (23.1)	
Form of admission			0.026
Unscheduled operation	23 (15.0)	1 (2.6)	
Medical	123 (78.2)	32 (76.9)	
Scheduled operation	32 (6.8)	9 (20.5)	
Oliguria (%)	96 (60.8)	26 (63.2)	0.794
Mechanical ventilation (%)	111 (70.1)	24 (57.9)	0.151
Vasoactive drug (%)	101 (64.1)	27 (64.1)	1
Bleeding tendency (%)	71 (44.9)	19 (45.9)	0.912
Sepsis (%)	82 (52.1)	31 (74.4)	0.013
Underlying disease (%)			0.043
No	44 (27.8)	21 (50.0)	
DM	72 (45.6)	13 (31.0)	
HBP	30 (19.0)	8 (19.0)	
LC	11 (7.0)	0 (0)	
Heart disease	1 (0.6)	0 (0)	
No. of organ failure (range)	1.3±0.8	1.5±0.5	0.338
Renal function at initial dialysis			
Urine output, mL/24 hrs	656±845	579±626	0.604
BUN, mg/dL	53.8±30.1	71.5±39.5	0.002
Serum creatinine, mg/dL	4.2±3.0	4.3±2.4	0.805

CKD: Chronic Kidney Disease, MOF: Multiple Organ Failure, DM: Diabetes Mellitus, HBP: Hypertension, LC: Liver Cirrhosis, BUN: Blood Urea Nitrogen

Table 2. Etiology of acute kidney injury

Etiology	Non-cancer (n=158)	Cancer (n=42)	P value
Cardiac dysfunction	84 (53.1)	2 (5.1)	0.001
Infection	58 (36.1)	25 (59.0)	0.001
Hepatorenal	2 (1.4)	6 (12.8)	0.001
Rhabdomyolysis	0 (0)	1 (2.6)	0.001
Lactic acidosis	4 (2.7)	0 (0)	0.001
Malignancy	0 (0)	4 (10.3)	0.001
Trauma	1 (0.7)	0 (0)	0.001
Hypovolemic shock	3 (2.0)	4 (10.3)	0.001
DIC	2 (1.4)	0 (0)	0.001
Metabolic	4 (2.7)	0 (0)	0.001

Table 3. Reasons to start CRRT

Reason	Non-cancer (n=158)	Cancer (n=42)	P value
Oliguria/anuria	76 (48.3)	23 (55.3)	0.001
High BUN/Cr	35 (34.4)	7 (15.8)	0.001
Fluid overload	33 (21.1)	3 (5.3)	0.001
Metabolic acidosis	4 (2.7)	4 (10.5)	0.001
Hyperkalemia	7 (4.1)	4 (10.5)	0.001
Others	3 (2.0)	1 (2.6)	0.001

Table 4. Characteristics of CRRT

Variables	Non-cancer (n=158)	Cancer (n=42)	P value
Days to start CRRT treatment (days)	5.7±10.0	15.6±30.3	0.054
ICU length of stay (days)	15.6±19.9	11.9±11.1	0.280
Duration of treatment (hours)	173±386	122±130	0.428
Mode of CRRT			1.000
CVVHDF (%)	100 (100)	100 (100)	
CVVH (%)	0 (0)	0 (0)	
Filter life span, hr	23.4±17.5	21.5±15.8	0.560
Filter pressure, mmHg	112.2±51.5	107.6±48.7	0.687
Effluent pressure, mmHg	4.6±65.6	3.0±47.3	0.908
TMP, mmHg	71.3±41.1	85.8±115.1	0.325
Blood flow rate, mL/min	116±24	140±147	0.342
Net ultrafiltration, mL/hr	165.8±56.2	194.3±75.2	0.594
Replacement flow rate, mL/min	1097±293	1143±270	0.390
Dialysate flow rate, mL/min	1080±217	1100±198	0.614
Effluent flow rate(CRRT dose), mL/kg/hr	39.0±8.2	40.6±8.4	0.305
Anticoagulation			0.151
Heparin (%)	93 (58.9)	23 (55.3)	
Nafamostat mesilate (%)	65 (41.1)	19 (43.7)	
Insertion site of two-lumen catheter			0.510
Rt int jugular vein (%)	150 (95.4)	42 (100)	
Lt int jugular vein (%)	6 (3.7)	0 (0)	
Femoral vein (%)	2 (0.9)	0 (0)	
Patient's status at ending of CRRT			0.352
recovery of renal function	40 (25.0)	7 (15.6)	
chronic kidney disease	21 (13.4)	3 (7.7)	
maintenance of hemodialysis	19 (12.2)	3 (7.7)	
death	78 (49.9)	29 (69.0)	

Tables 5 and 6 present the underlying malignancies and cancer sites. A solid tumor was the most common underlying malignancy, followed by multiple myeloma. The pulmonary organs as lung, bronchus or trachea were the most common cancer origin, followed by the liver.

Table 7 shows the results of the univariate Cox regression analysis of factors associated with mortality. The results showed that APACHE II score, presence of cancer, presence of sepsis, the use of vasoactive drugs, the number of failed organs, initial arterial pH and arterial pH on the second CRRT day were significant predictors of mortality. On the other hand, age, gender, and the mean prescribed dose of CRRT showed no statistical significance.

Table 5. Underlying malignancy

Cancer	N (percents)
Acute leukemia	1 (2.4%)
lymphoma	2 (4.7%)
Myeloma	5 (11.9%)
Solid tumors	33 (78.6%)
miscellaneous malignancies	1 (2.4%)
Total	42 (100%)

Table 6. Cancer site

Site	N
Prostate	1 (2.4%)
Urinary bladder	1 (2.4%)
Kidney	2 (4.8%)
Cervix uteri	2 (4.8%)
Lymphoma	2 (4.8%)
Leukemia	1 (2.4%)
Multiple myeloma	5 (11.9%)
Rectum	2 (4.8%)
Stomach	5 (11.9%)
Esophagus	1 (2.4%)
Liver	6 (14.3)
Gall bladder/biliary tract	2 (4.8%)
Pancreas	3 (7.1%)
Lung/bronchus/trachea	8 (19.0%)
Other sites	1 (2.4%)
Total	42 (100%)

Table 8 shows the results of the multivariate Cox regression analysis of factors associated with mortality, which revealed that male gender, the presence of cancer and the number of failed organs were significant predictors of mortality. Age, APACHE II score, presence of sepsis, initial arterial pH and arterial pH on the second CRRT day showed no statistical significance.

Half-lives calculated from Kaplan-Meier curves for overall survival Fig. 1 shows that the duration of median survival was 16 days in the cancer group and 80 days in the non-cancer group.

4. DISCUSSION

In this study, one in five AKI patients requiring CRRT in general ICUs has cancer and the presence of cancer may be independently associated with mortality in the our retrospective cohort. The few studies comparing characteristics and outcomes between critically ill in those studies, most of the patients had hematological malignancies[3]. The present study was carried out in general ICUs and, as expected, patients more frequently had solid tumors.

Table 7. Univariate cox regression analysis of factors associated with mortality

Variable	Unit increase	Hazard ratio (95% CI)	P value
Age	Year	1.007 (0.992–1.023)	0.351
Gender	vs. male	1.243 (0.849–1.822)	0.263
APACHE score	1	1.011 (1.004–1.018)	0.001
Cancer	vs. absence	1.689 (1.100–2.592)	0.017
Sepsis	vs. absence	1.846 (1.210–2.816)	0.004
Vasoactive drugs	vs. absence	2.419 (1.513–3.868)	0.001
Number of organ failures	1	1.471 (1.180–1.836)	0.001
Effluent flow rate	1	0.979 (0.949–1.010)	0.178
Initial arterial pH	0.1	0.189 (0.057–0.622)	0.006
Arterial pH at 2nd CRRT day	0.1	0.047 (0.006–0.343)	0.003

Table 8. Multivariate cox regression analysis of factors associated with mortality

| Variable	Unit increase	Hazard ratio (95% CI)	P value
Age	Year	1.008 (0.984–1.033)	0.500
Gender	vs. male	1.925 (1.050–3.529)	0.034
APACHE score	1	1.005 (0.996–1.014)	0.294
Cancer	vs. absence	1.971 (1.051–3.697)	0.035
Sepsis	vs. absence	1.280 (0.703–2.330)	0.419
Vasoactive drugs	vs. absence	1.943 (0.939–4.020)	0.073
Number of organ failures	1	1.651 (1.172–2.325)	0.004
Effluent flow rate	1	0.969 (0.933–1.007)	0.111
Initial arterial pH	0.1	0.956 (0.127–7.191)	0.965
Arterial pH at 2nd CRRT day	0.1	0.099 (0.003–2.890)	0.179
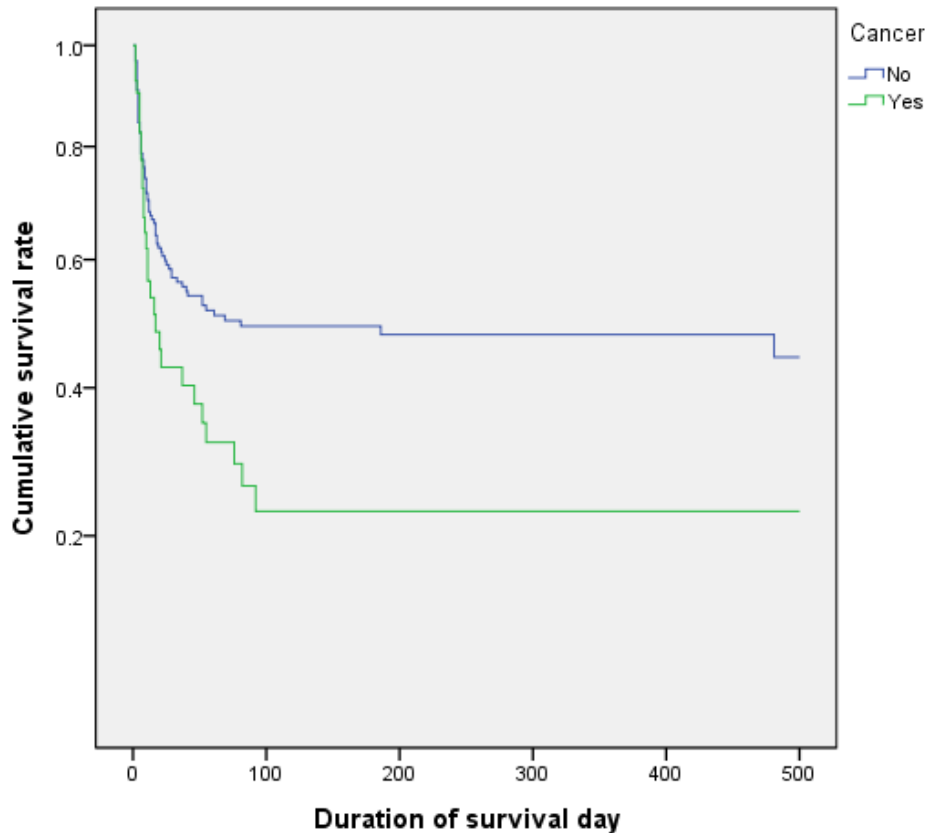
Fig. 1. Patient survival rate in cancer group and non-cancer group (p = 0.014)

As we know, cancer patients have a higher incidence of acute kidney injury required renal replacement therapy than patients without cancer [2]. Moreover, cancer patients are very vulnerable and sensitive in critical condition, and AKI in patients with cancer was more frequently multifactorial and developed usually in the context of multiple organ failure than non-cancer patients. Cancer patients presented higher severity of organ dysfunctions and required more often using vasopressors than non-cancer patients. CRRT was originally developed as an alternative option to conventional intermittent hemodialysis (IHD) for patients who have acute kidney injury and cannot tolerate IHD because that CRRT their vital signs are unstable. Despite the mortality of cancer patients who received CRRT was higher than that of non-cancer patients in our result, the role of CRRT in cancer patients with AKI will expand. In addition, several studies in different settings worldwide have now shown that the presence of an underlying cancer alone can no longer be considered a contraindication to start RRT [3,5,6,9].

Our study also shows some predictors of mortality in AKI patients receiving CRRT with or without cancer. We performed multivariate analyses to identify independent predictors of mortality. Adjusting for other covariates, including gender, presence of cancer, and the number of failed organs were significantly dependent on well-known predictors of mortality such as older age, poor chronic health status, presence of comorbidities, number of failed organs, time to start of RRT in the ICU and oliguria [13-15]. Our result reinforce that the main prognostic factor in critically severe patients with cancer is the severity of organ dysfunctions, [4,16-18] and the presence of cancer was independently associated with mortality in the our retrospective cohort.

Our study has several potential limitations. First, data were retrieved from a retrospective database of three tertiary care hospitals. We were not able to analyze subgroups of patients with cancer, and hence our study lacked statistical power to evaluate patients with

hematological malignances. Second, we cannot rule out possible selection biases with regard to regional differences in the standard of care, including criteria used to determine the need for dialysis, implement end of life decisions and admission/discharge policies. Third, complications were not assessed based on predefined criteria, but were judged by the attending nephrologist.

5. CONCLUSION

In conclusion, our result showed that the main prognostic factor in cancer patients with AKI is the severity of organ dysfunctions, and the presence of cancer may be independently associated with mortality. Thus the role of CRRT in cancer patient with AKI will expand and additional studies are needed to compare the outcomes of cancer patients admitted to specialized and general ICUs.

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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