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소아 암 환자에서의 급성 신손상의 발생 및 장기예후에 관한 연구

Acute kidney injury in pediatric cancer patients: Incidence and Outcome

2020 년 2 월

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지도교수 강 희 경

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박 평 강

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2020 년 1월

위 원 장 _____ (인)

부 위 원 장 _____ (인)

위 원 _____ (인)

ABSTRACT

Acute kidney injury in pediatric cancer patients: Incidence and Outcome

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To analyze the incidence of acute kidney injury (AKI) in the first year after cancer diagnosis in children and to evaluate the short-term and long-term effects on renal function and proteinuria, retrospective review of medical records was done on children who were diagnosed and treated for cancer at Seoul National University Hospital between 2004 and 2013. AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. The development of impaired renal function of estimated glomerular filtration rate less than 90ml/min/1.73m^2 and proteinuria of cancer survivors were assessed.

A total of 1868 patients who were diagnosed with cancer at the median age of 7.9 years were included in this study. During the course of treatment, 983 patients (52.6%) developed 1864 episodes of AKI, and the cumulative incidence at two weeks, three months, and one year after diagnosis was 28.9%, 39.6%, and 53.6%, respectively. The 1-year cumulative incidence was the highest in acute myeloid leukemia patients (88.4%). In all, 6.1% of

patients had more than four episodes of AKI, and 11.8% of patients had stage 3 AKI. Among the 1096 childhood cancer survivors, 22.6% were found to have impaired renal function. A greater number of AKI episodes (≥ 4 times) and nephrectomy were independent risk factors of impaired renal function. Also, 8.2% of the survivors developed proteinuria among 742 childhood cancer survivors.

In conclusion, this study showed that a large percentage of children with cancer experienced AKI during the course of treatment and that having AKI episode 4 or more times was associated with a higher risk of impaired long-term renal function.

Keywords: Acute kidney injury, pediatric cancer, chemotherapy, chronic kidney disease, proteinuria

Student number: 2018-28729

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LIST OF ABBREVIATIONS

AKI; acute kidney injury

TLS; tumor lysis syndrome

CKD; chronic kidney disease

Cr; creatinine

eGFR; estimated glomerular filtration rate

RRT; renal replacement therapy

CT; computed tomography

HSCT; hematopoietic stem cell transplantation

ALL; acute lymphoblastic leukemia

AML; acute myeloid leukemia

KDIGO; Kidney Disease: Improving Global Outcomes

NBL; neuroblastoma

WT; Wilms tumor

CTx; chemotherapy

IQ; interquartile

INTRODUCTION

Patients with cancer may experience various adverse events during the course of their disease, including acute kidney injury (AKI). In fact, cancer is a known risk factor of AKI[1-5]. AKI occurs in such patients because of tumor lysis syndrome (TLS), the use of nephrotoxic agents such as contrast media and chemotherapeutics, direct infiltration of the genitourinary system by cancer cells, or multi-organ failure following sepsis or other morbidities[1,5,6]. When AKI occurs during cancer treatment, certain treatment agents may require dose adjustments or complete elimination from the treatment strategy, which may adversely affect the outcome of cancer treatment. In critically ill patients, AKI itself may be associated with increased length of hospital stay and odds of mortality and may have a negative impact on the prognosis[7-9]. Moreover, AKI is a known risk factor of chronic kidney disease (CKD), further affecting the long-term quality of life of cancer survivors[10]. It is thus necessary for oncologists as well as nephrologists to be well aware of the characteristics of AKI that occur in patients with cancer and to be able to prevent and promptly manage it to improve their outcome and long-term quality of life.

AKI has been investigated in cancer patients in various studies. In a population-based cohort study that included patients of all ages, the incidence of AKI in the first year of cancer diagnosis was 25.8% among 37,267 cancer patients, and their 1-year cumulative risk was 17.5% and the

highest 1-year cumulative risk was observed in kidney cancer (44.0%)[11,12]. In another recent study, 12% of 3,558 adults admitted to a cancer center developed AKI and their highest AKI stage was 1, 2, and 3 in 68%, 21%, and 11% of them, respecitvely[9]. However, the incidence of AKI has not been well established in the pediatric population of cancer patients. In the few available studies, the incidence of AKI ranged between 11% and 84%, but these studies were limited to patients with hematological malignancies[13-16].

Cancer among children differs from that among adults in various aspects such as biology and epidemiology. Children rarely have epithelial tumors in solid organs, but usually have embryonal tumors in the hematopoietic system and the central nervous system[17]. Concomitant medical conditions, such as diabetes and hypertension, are rare in children. The epidemiology of diseases in children is thus expected to be different from that in adults. In addition, the impact of AKI on the development of CKD can be expected to be different in children due to the differences in underlying medical conditions. In general, AKI has been shown to be more common in children than in adults, as indicated in a systematic review of 312 studies with large number of overall patients (n=49,147,878), which reported higher incidence of AKI in children compared with adults (33.7%, 95% CI 26.9-41.3 vs. 21.6%, 95% CI 19.3-24.1) in hospital settings[18]. The incidence of AKI in

hospitalized children has recently been reported to be 34-40%, with two-thirds of them being stages 2 or 3[18-21].

Nonetheless, more focused and comprehensive data on AKI among children with cancer are limited. We thus aimed to evaluate the characteristics of AKI in children with cancer, including its incidence, change during the course of cancer treatment, and risk factors. We further analyzed the influence of AKI on long-term renal outcomes, including CKD and proteinuria, in this patient group. The methodology and results of this dissertation were published in the peer-reviewed scientific journal[22].

MATERIALS AND METHODS

We performed a retrospective review of the electronic medical record of Seoul National University Hospital with approval by the institutional review board (No. H-1509-051-702). This analysis included patients who were diagnosed with cancer between January 1, 2004 and December 31, 2013. Patients who were younger than 18 years at cancer diagnosis and who had serum creatinine levels (Cr) measured at least twice in the first year after diagnosis were eligible. Patients who had previously been diagnosed with CKD with an initial estimated glomerular filtration rate (eGFR) of lower than 15 ml/min/1.73m^2 or who had previously received renal replacement therapy (RRT) were not included.

The following clinical data were collected: initial blood test results, all available serum Cr levels and urinalysis data, development of TLS, performance of nephrectomy as a part of cancer treatment, use of contrast agents for computed tomography (CT) scans, use of RRT such as intermittent hemodialysis (IHD), and continuous RRT (CRRT). Data on cancer treatment were also collected, including chemotherapy, overall duration of chemotherapy treatment, administration of five chemotherapeutic agents that were widely used in children and were known to be nephrotoxic (carboplatin, cisplatin, cyclophosphamide, ifosfamide, and methotrexate), administration of high-dose chemotherapy and hematopoietic stem cell transplantation (HSCT), and treatment outcome of cancer.

Mortality data were obtained from both the institutional electronic medical record and the Vital Statistics reported on July 2016 by the Statistics Korea, a governmental organization for national statistics.

Cancer types of the patients were categorized into seven groups: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), lymphoma, neuroblastoma, Wilms tumor, brain tumor (including medulloblastoma, primitive neuroectodermal tumor, intracranial germ cell tumor, and other brain tumors), and other cancers (including retinoblastoma, hepatoblastoma, osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), extracranial germ cell tumor, and other unspecified cancers).

AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria with some modifications[20]. Stage 1 AKI was defined as a rise of Cr by 0.3 mg/dL in two days or by 1.5 times in seven days, stage 2 as a rise of Cr by two times, and stage 3 as a rise of Cr above 4 mg/dL or by three times. Cr had to be at least 0.5 mg/dL for the patients to be diagnosed with AKI when the fold-change criterion was used, in order to avoid over-diagnosis in young patients whose baseline Cr values were low[23,24]. When the Cr at presentation was high, a recovery of Cr by more than 50% or by 0.3 mg/dL was used for the diagnosis of AKI, as proposed in the KDIGO criteria. For the purpose of this study, the application of RRT was not used as a criterion of stage 3 AKI because it is often transiently used

for prompt management of TLS or toxic methotrexate levels in children with cancer, even without presumable actual renal dysfunction. In addition, the criterion concerning the urine output could not be used because of the retrospective nature of this study. Data on maximum AKI stage, number of AKI episodes, and time from cancer diagnosis to AKI were obtained. Deterioration of renal functions in the timeframe of four weeks from the onset of AKI was considered as a single episode.

Cr level measured either one year after the completion of cancer therapy or five years after the initial diagnosis was used as the final Cr to determine the long-term renal outcome. Final eGFRs of survivors were estimated with the Chronic Kidney Disease in Children (CKiD) "bedside Schwartz" equation, using their final serum Cr level and their height at the time of Cr measurement[25]. For patients aged 18 years or older at final Cr measurement, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to estimate the eGFR[26]. A final eGFR of less than 90 ml/min/1.73 m^2 was defined as impaired renal function. A urine albumin dipstick test result of greater than 1+ on at least two occasions at the time of final Cr measurement was defined as proteinuria.

The primary outcome measure was the development of AKI. Kaplan-Meier cumulative incidence curves of AKI were plotted at two weeks, three months, and one year after diagnosis by each cancer group. The Kaplan-Meier cumulative incidence curve was also plotted for stage 3 AKI. The

maximum stage and number of episodes of AKI were assessed for each cancer group. In the comparison analysis of patients who developed AKI and those who did not, the correlation between AKI and baseline patient characteristics, use of CT scans, and treatments were assessed. The application of RRT was described separately.

The secondary outcome measure was the development of renal impairment or proteinuria in childhood cancer survivors. For the risk factor analysis, patient characteristics, time interval from cancer diagnosis to first onset of AKI, number of AKI episodes, maximum stage of AKI, and use of RRT were assessed.

Continuous variables were presented as a median with interquartile (IQ) range regarding their normality, and categorical variables were presented as counts and percentages. All variables with a P value < 0.25 in the bivariate analysis were included in the multivariable analysis. A P value of < 0.05 was considered statistically significant. Statistical analysis was done by using R-project version 3.3.2.

RESULTS

A total of 2170 children were diagnosed with cancer during the study period, and 1877 of them had their serum Cr levels measured at least twice in the first year after cancer diagnosis. Of these patients, nine patients with CKD stage V were excluded. A total of 1868 patients (1059 male and 809 female) were eligible for analysis. These patients were diagnosed with cancer at a median age of 7.9 years old. Brain tumor, acute leukemia (ALL and AML), and lymphoma were the most common cancer types in our study population (Table 1). The median initial eGFR of the eligible patients was 90.0 ml/min/1.73m^2 (IQ range: 74.6 – 110.4). It was notable that 145 patients (7.8%) had an initial eGFR below 60 ml/min/1.73m^2. These patients were younger (median age of 1.7 years old), but the distribution of their cancer types was not significantly different from that of those without low initial eGFR.

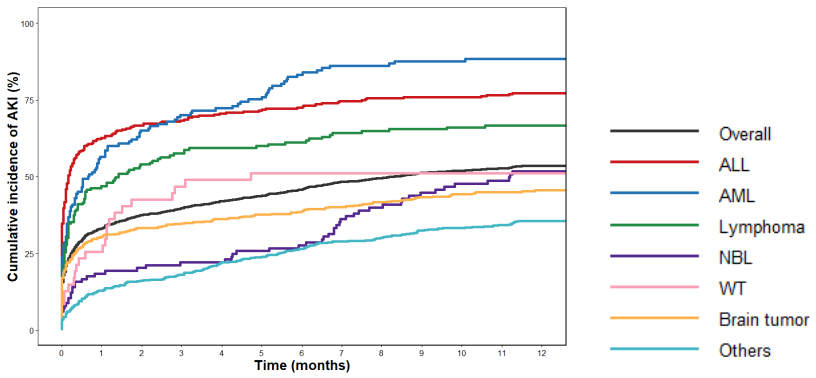
Patients were followed-up for a median duration of 5 years (IQ range: 2.26–6.16), and 1093 patients (58.5%) were followed-up for longer than 5 years. During the course of the treatment, 144 patients (7.7%) received RRT. Of these patients, 106 patients (73.6%) had RRT applied in the timeframe of one year, and 69 patients (47.9%) had it applied in the first month after cancer diagnosis. At five years from cancer diagnosis, a total of 1481 patients (79.3%) were alive.

Table 1. Baseline characteristics of the patients

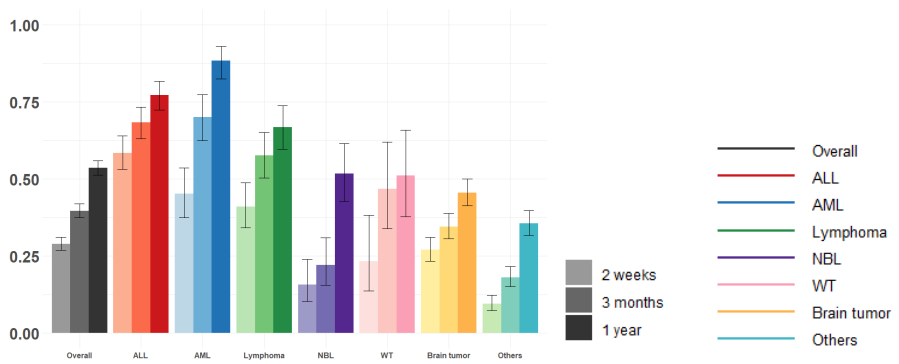
Variable	Value
Number of patients	1,868
No. (%) of male patients	1,059 (56.7)
Age at diagnosis, median (IQR), years	7.9 (2.5 – 12.7)
Age distribution – No. (%)	
Under 1 year	197 (10.5)
1 – 4 years	532 (28.5)
5 – 9 years	406 (21.7)
10 – 14 years	484 (25.9)
15 – 18 years	249 (13.3)
Initial eGFR at diagnosis, median (IQR), ml/min/1.73m^2	90.0 (74.6 – 110.4)
No. (%) of patients according to cancer group	
Acute leukemia	
Acute lymphoblastic leukemia	314 (16.8)
Acute myeloid leukemia	147 (7.9)
Lymphoma	173 (9.3)
Neuroblastoma	114 (6.1)
Wilms tumor	47 (2.5)
Brain tumor	
Intracranial germ cell tumor	123 (6.6)
Medulloblastoma	100 (5.4)
Primitive neuroectodermal tumor	55 (2.9)
Other brain tumor	229 (12.3)
Ewing sarcoma	38 (2.0)
Extracranial germ cell tumor	70 (3.7)
Hepatoblastoma	53 (2.8)
Non-rhabdomyosarcoma soft tissue sarcoma	59 (3.2)
Osteosarcoma	102 (5.5)
Retinoblastoma	109 (5.8)
Rhabdomyosarcoma	43 (2.3)
Other unspecified cancers	92 (4.9)

A total of 983 patients (52.6%) developed AKI, and they had a total of 1864 AKI episodes in the first year after cancer diagnosis (Figure 1a). A total of 293 patients (15.7%) had high Cr at presentation and actually presented with AKI at diagnosis, and the onset of the first episode of AKI was a median of 9 days (IQ range: 0–90.5) after cancer diagnosis. The cumulative incidence of AKI at two weeks, three months, and one year after diagnosis was 28.9% (95% confidence interval (CI): 26.9–31.1), 39.6% (95% CI: 37.5–41.9), and 53.6% (95% CI: 51.3–55.9), respectively. The 2-week cumulative incidence of AKI was the highest in ALL (58.5%, 95% CI: 53.1–64.0), followed by AML (45.2%, 95% CI: 37.5–53.6) and medulloblastoma (45.0%, 95% CI: 35.9–55.3). The 1-year cumulative incidence of AKI was the highest in AML (88.4%, 95% CI: 82.4–93.0), followed by ALL (77.2%, 95% CI: 72.4–81.7) and medulloblastoma (67.0%, 95% CI: 57.6–76.1). Overall, the 1-year cumulative incidence of AKI was the lowest in other cancers, more specifically in retinoblastoma (14.1%, 95% CI: 8.7–22.3) (Figure 1b, Table 2).

Figure 1. (a) Kaplan-Meier cumulative incidence curve of acute kidney injury (AKI) according to cancer group; (b) 2-week, 3-month, and 1-year cumulative incidence of AKI according to cancer group, with 95% confidence interval; (c) Kaplan-Meier cumulative incidence curve of stage 3 AKI, according to cancer group



(a)



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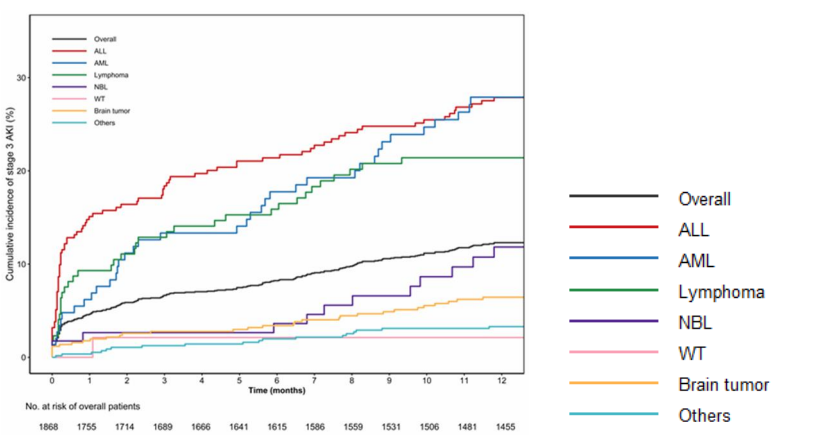

(c)

Table 2. Cumulative incidence of acute kidney injury, specified

Variable	2-week risk of AKI% (95% CI)	3-month risk of AKI% (95% CI)	1-year risk of AKI% (95% CI)
Overall	28.9 (26.9–31.1)	39.6 (37.5–41.9)	53.6 (51.3–55.9)
Acute leukemia			
Acute lymphoblastic leukemia	58.5 (53.1–64.0)	68.3 (63.1–73.4)	77.2 (72.4–81.7)
Acute myeloid leukemia	45.2 (37.5–53.6)	70.1 (62.4–77.4)	88.4 (82.4–93.0)
Lymphoma	41.1 (34.1–48.8)	57.6 (50.3–65.0)	66.7 (59.6–73.7)
Neuroblastoma	15.8 (10.3–23.9)	22.1 (15.5–30.9)	51.8 (42.7–61.6)
Wilms tumor	23.4 (13.7–38.3)	46.8 (33.8–61.9)	51.1 (37.8–65.9)
Brain tumor			
Intracranial germ cell tumor	19.5 (13.5–27.7)	28.5 (21.3–37.3)	36.7 (28.9–45.9)
Medulloblastoma	45.0 (35.9–55.3)	50.1 (40.8–60.2)	67.0 (57.6–76.1)
Primitive neuroectodermal tumor	23.6 (14.5–37.2)	31.0 (20.5–45.1)	48.7 (35.8–63.3)
Other brain tumor	24.0 (19.0–30.1)	31.9 (26.3–38.4)	40.4 (34.3–47.1)
Ewing sarcoma	7.9 (2.6–22.5)	13.2 (5.7–28.8)	59.8 (43.9–76.3)
Extracranial germ cell tumor	14.3 (8.0–24.9)	24.3 (15.9–36.1)	35.9 (25.9–48.4)
Hepatoblastoma	20.8 (12.1–34.3)	28.4 (18.2–42.6)	47.9 (35.4–62.2)
Non-rhabdomyosarcoma soft tissue sarcoma	6.8 (2.6–17.1)	10.2 (4.7–21.2)	23.1 (14.1–36.5)
Osteosarcoma	2.9 (1.0–8.8)	20.8 (14.1–30.1)	53.4 (43.8–63.6)
Retinoblastoma	6.5 (3.1–13.1)	7.4 (3.8–14.2)	14.1 (8.7–22.3)
Rhabdomyosarcoma	9.3 (3.6–22.9)	21.2 (11.7–36.9)	30.8 (19.2–47.1)
Other unspecified cancers	13.0 (7.6–21.8)	22.9 (15.6–33.0)	35.5 (26.6–46.4)

Cumulative incidence was calculated using Kaplan-Meier cumlative incidence curve.

Of the total of 1864 AKI episodes, 860 episodes (46.1%) were stage 1 AKI, 714 (38.3%) were stage 2, and 290 (15.6%) were stage 3. The cumulative incidence of stage 3 AKI in the first year after diagnosis was 12.3% (95% CI: 10.9–13.9, Figure 1c). The cumulative incidence of stage 3 AKI was the highest in ALL (27.9%, 95% CI: 23.2–33.3) and the lowest in Wilms tumor (2.1%, 95% CI: 0.3–14.2%).

In the first year after cancer diagnosis, AKI occurred once in 520 patients (27.8%), two or three times in 349 patients (18.7%), and more than four times in 114 patients (6.1%). Among the patients who experienced AKI more than four times, AML was the most frequent cancer type (23.1%), followed by ALL (13.4%) (Figure 2a, Table 3). The highest stage of AKI that a patient experienced in the first year of cancer diagnosis was stage 1 in 349 patients (18.7%), stage 2 in 413 patients (22.1%), and stage 3 in 221 patients (11.8%). Among the patients who experienced stage 3 AKI, ALL was the most frequent diagnosis (27.1%), followed by AML (25.9%) (Figure 2b, Table 4).

In the univariate analysis, a greater proportion of patients who experienced AKI had hematologic malignancies (ALL, AML, and lymphoma), lower eGFR at diagnosis, experienced TLS, had undergone a greater number of CT scans, had nephrotoxic chemotherapeutic agents administered (especially cyclophosphamide, ifosfamide, and methotrexate), had received HSCT, and had experienced cancer relapse.

Figure 2. (a) Number of acute kidney injury (AKI) episodes; (b) Maximum stage of AKI according to cancer group

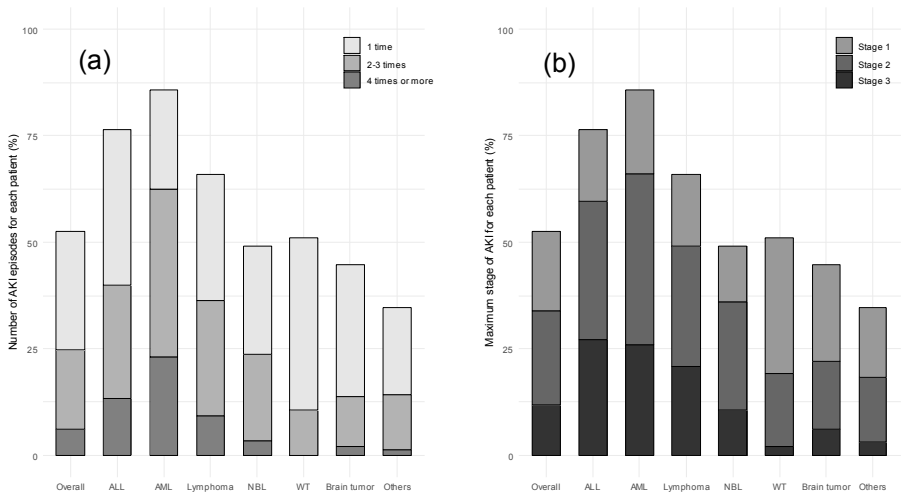

Table 3. Number of acute kidney injury episodes in first year after cancer diagnosis

Variable (No.)	1 time, No (%)	2-3 times, No. (%)	≥ 4 times, No. (%)
Overall (1868)	520 (27.8)	349 (18.7)	114 (6.1)
Acute leukemia			
Acute lymphoblastic leukemia (314)	115 (36.6)	83 (26.4)	42 (13.4)
Acute myeloid leukemia (147)	34 (23.1)	58 (39.5)	34 (23.1)
Lymphoma (173)	51 (29.5)	47 (27.2)	16 (9.2)
Neuroblastoma (114)	29 (25.4)	23 (20.2)	4 (3.5)
Wilms tumor (47)	19 (40.4)	5 (10.6)	0
Brain tumor			
Intracranial germ cell tumor (123)	34 (27.6)	9 (7.3)	2 (1.6)
Medulloblastoma (100)	33 (33.0)	27 (27.0)	6 (6.0)
Primitive neuroectodermal tumor (55)	15 (27.3)	8 (14.5)	2 (3.6)
Other brain tumor (229)	75 (32.8)	16 (7.0)	0
Ewing sarcoma (38)	10 (26.3)	10 (26.3)	1 (2.6)
Extracranial germ cell tumor (70)	15 (21.4)	10 (14.3)	0
Hepatoblastoma (53)	13 (24.5)	11 (20.8)	1 (1.9)
Non-rhabdomyosarcoma soft tissue sarcoma (59)	12 (20.3)	0	1 (1.7)
Osteosarcoma (102)	27 (26.5)	20 (19.6)	5 (4.9)
Retinoblastoma (109)	10 (9.2)	5 (4.6)	0
Rhabdomyosarcoma (43)	9 (20.9)	4 (9.3)	0
Other unspecified cancers (92)	19 (20.7)	13 (14.1)	0

Abbreviation: AKI, acute kidney injury
Percentages do not add up to 100% because the patients who did not experience AKI were not included.

Table 4. Maximum stage of acute kidney injury in first year after cancer diagnosis

Variable (No.)	Stage 1, No. (%)	Stage 2, No. (%)	Stage 3, No. (%)
Overall cancer (1868)	349 (18.7)	413 (22.1)	221 (11.8)
Acute leukemia			
Acute lymphoblastic leukemia (314)	53 (16.9)	102 (32.5)	85 (27.1)
Acute myeloid leukemia (147)	29 (19.7)	59 (40.1)	38 (25.9)
Lymphoma (173)	29 (16.8)	49 (28.3)	36 (20.8)
Neuroblastoma (114)	15 (13.2)	29 (25.4)	12 (10.5)
Wilms tumor (47)	15 (31.9)	8 (17.0)	1 (2.1)
Brain tumor			
Intracranial germ cell tumor (123)	33 (26.8)	9 (7.3)	3 (2.4)
Medulloblastoma (100)	27 (27.0)	32 (32.0)	7 (7.0)
Primitive neuroectodermal tumor (55)	9 (16.4)	8 (14.5)	8 (14.5)
Other brain tumor (229)	46 (20.1)	32 (14.0)	13 (5.7)
Ewing sarcoma (38)	10 (26.3)	8 (21.1)	3 (7.9)
Extracranial germ cell tumor (70)	12 (17.1)	10 (14.3)	3 (4.3)
Hepatoblastoma (53)	5 (9.4)	17 (32.1)	3 (5.7)
Non-rhabdomyosarcoma soft tissue sarcoma (59)	8 (13.6)	4 (6.8)	1 (1.7)
Osteosarcoma (102)	29 (28.4)	20 (19.6)	3 (2.9)
Retinoblastoma (109)	5 (4.6)	10 (9.2)	0
Rhabdomyosarcoma (43)	8 (18.6)	5 (11.6)	0
Other unspecified cancers (92)	16 (17.4)	11 (12.0)	5 (5.4)

Abbreviation: AKI, acute kidney injury
Percentages do not add up to 100% because the patients who did not experience AKI were not included.

In the current study, nephrectomy and the use of carboplatin and cisplatin did not increase the risk of AKI. In the multivariable analysis, statistically significant risk factors of AKI were cancer group (especially ALL and AML), lower eGFR at diagnosis, occurrence of TLS, use of methotrexate, administration of HSCT, and greater number of CT scans performed (Table 5).

Final eGFR values were available in a total of 1096 patients. At a median 5.2 years (IQ range: 5.0–5.5) after diagnosis, patients had a median eGFR of 107.6 ml/min/1.73m^2 (IQ range: 91.6–125.1). A total of 248 patients (22.6%) had impaired renal function of eGFR below 90 ml/min/1.73m^2. eGFR of the patients with impaired renal function was plotted and it revealed that eGFR of them decreased below 90ml/min/1.73m^2 about 50 months after cancer diagnosis (Figure 3). Impaired renal function was most frequent in survivors of Wilms tumor (36.8%), followed by NRSTS (34.6%). In the univariate analysis, patients who had renal impairment had the following characteristics: male gender, lower eGFR at diagnosis (below 60 ml/min/1.73m^2), chemotherapeutic agents not administered (especially cyclophosphamide), and nephrectomy performed. In the multivariable analysis, the statistically significant risk factors of renal impairment were male gender, lower eGFR at diagnosis, greater number of AKI episodes (more than four 4 times), and nephrectomy (Table 6). Receiving RRT also seemed to be correlated with impaired renal

function after cancer treatment completion. However, there was no significant risk of developing impaired renal function in patients with simple AKI occurrence itself. Cancer survivors with or without final eGFR measured did not differ in their percentages of patients who underwent nephrectomy or had AKI. However, the group with final eGFR was more likely to have undergone HSCT or have experienced relapse. Two of the survivors had final eGFR below 15 ml/min/1.73m^2. A boy who was treated surgically for colon cancer and who also had underlying Crohn's disease and complicated renal amyloidosis, is on close observation for his renal dysfunction, although he is not on RRT yet. Another girl with lymphoma who had experienced AKI more than 4 times, lost her kidney function about 2.5 years from cancer diagnosis and is currently on peritoneal dialysis. All other patients had final eGFRs between 60 ml/min/1.73m^2 and 90 ml/min/1.73m^2.

Urinalysis data were available for 742 survivors, and a total of 61 patients (8.2%) had proteinuria. Proteinuria was most frequent in survivors of AML (13.6%), followed by lymphoma (9.3%).

Figure 3. Mean estimated glomerular filtration rate after cancer diagnosis

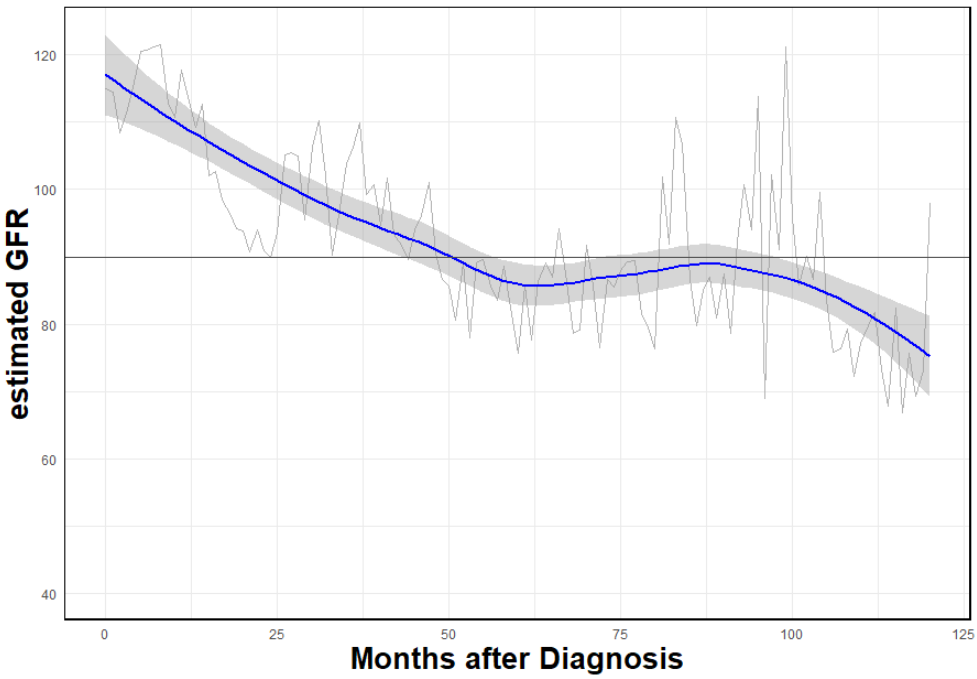

Table 5. Patient characteristics according to the occurrence of acute kidney injury

Variable	Patients without AKI (n = 885)	Patients with AKI (n = 983)	*P* value	Multivariable analysis (95% CI)[c]
No. (%) of female patients	399 (45.1)	410 (41.7)	0.16	1.02 (0.88–1.19)
Age at diagnosis, median (IQR), years	8.0 (2.3–13.3)	7.8 (2.9–12.3)	0.59	
Initial eGFR at diagnosis, median (IQR), ml/min/1.73^2	94.9 (79.6–114.9)	85.7 (70.3–105.3)	< 0.001	0.99 (0.98–0.99)
No. (%) of patients by cancer group[a]				
ALL	74 (8.4)	240 (24.4)	< 0.001	1.71 (1.10–2.68)
AML	21 (2.4)	126 (12.8)		3.35 (1.94–5.97)
Lymphoma	59 (6.7)	114 (11.6)		1.12 (0.70–1.78)
NBL	58 (6.6)	56 (5.7)		0.65 (0.40–1.05)
WT	23 (2.6)	24 (2.4)		0.95 (0.50–1.82)
Brain tumor	280 (31.6)	227 (23.1)		Ref.
Other cancer	370 (41.8)	196 (19.9)		0.41 (0.31–0.56)
No. (%) of patients who received CTx	659 (74.5)	880 (89.5)	< 0.001	1.29 (0.91–1.82)
No. (%) of patients who received specific CTx[b]				
Carboplatin	264 (29.8)	283 (28.8)	0.66	
Cisplatin	272 (30.7)	296 (30.1)	0.81	
Cyclophosphamide	434 (49.0)	628 (63.9)	< 0.001	0.91 (0.68–1.21)
Ifosfamide	171 (19.3)	239 (24.3)	0.011	1.20 (0.89–1.61)
Methotrexate	190 (21.5)	454 (46.2)	< 0.001	1.78 (1.29–2.46)
No. of CT scans performed, median (IQR), count	1 (0–4)	2 (0–6.5)	< 0.001	1.05 (1.03–1.07)
No. (%) of patients who experienced tumor lysis syndrome	1 (0.1)	53 (5.4)	< 0.001	14.79 (3.11–265.1)
No. (%) of patients who received HSCT	63 (7.1)	330 (33.6)	< 0.001	3.75 (2.67–5.34)
No. (%) of patients who had nephrectomy performed	28 (3.2)	28 (2.8)	0.79	
No. (%) of patients who experienced cancer relapse	92 (10.4)	205 (20.9)	< 0.001	1.22 (0.88–1.70)

[a]Reference to odds ratio in multivariable analysis is brain tumor in the cancer group and the absence of the corresponding risk factor.

[b]Patients could have received more than one of the specified chemotherapeutic agents. Reference to such patients is patients who did not receive any of the specified chemotherapeutic agents.

[c]The covariates assessed for the multivariable logistic-regression model were sex, initial eGFR at diagnosis, cancer group, chemotherapy, chemotherapy with cyclophosphamide, ifosfamide, or methotrexate; CT scans, tumor lysis syndrome, HSCT, or relapse.

Table 6. Patient characteristics according to the development of renal impairment[a]

Variable	Patients without renal impairment (n = 848)	Patients with renal impairment (n = 248)	*P* value	Multivariable analysis (95% CI)[d]
No. (%) of female patients	386 (45.5)	78 (31.5)	0.013	0.65 (0.52–0.81)
Age at diagnosis, median (IQR), years	7.2 (2.3–13.0)	8.7 (3.3–11.9)	0.57	
No. (%) of patients with Initial eGFR at diagnosis below 60 ml/min/1.73^2	56 (6.6%)	28 (11.3%)	0.021	1.80 (1.08–2.95)
No. (%) of patients by cancer group[b]			0.21	
ALL	166 (19.6)	40 (16.1)		0.70 (0.43–1.14)
AML	62 (7.3)	16 (6.5)		0.52 (0.25–1.03)
Lymphoma	100 (11.8)	25 (10.1)		0.63 (0.35–1.10)
NBL	49 (5.8)	12 (4.8)		0.61 (0.28–1.24)
WT	24 (2.8)	14 (5.6)		0.43 (0.10–1.80)
Brain tumor	183 (21.6)	65 (26.2)		Ref.
Other cancer	264 (31.1)	76 (30.6)		0.70 (0.46–1.06)
No. (%) of patients who received CTx	763 (90.0)	210 (84.7)	0.027	0.63 (0.37–1.06)
No. (%) of patients who received specific CTx[c]				
Carboplatin	253 (29.8)	82 (33.1)	0.37	
Cisplatin	246 (29.0)	64 (25.8)	0.36	
Cyclophosphamide	549 (64.7)	138 (55.6)	0.011	0.69 (0.47–1.02)
Ifosfamide	153 (18.0)	52 (21.0)	0.34	
Methotrexate	335 (39.5)	90 (36.3)	0.40	
No. of CT scans performed, median (IQR), count	1 (0–5)	2 (0–6.5)	0.17	1.02 (0.99–1.04)
No. (%) of patients according to timepoint at first onset of AKI				
Within 1 years	107 (12.6)	31 (12.5)	0.78	
Within 3 months	90 (10.6)	26 (10.5)		
Within 2 weeks	239 (28.2)	78 (31.5)		
No. (%) patients according to number of AKI episodes				
1 time	228 (26.9)	65 (26.2)	0.081	1.04 (0.72–1.50)
2-3 times	169 (19.9)	48 (19.4)		1.19 (0.77–1.82)
4 times or more	39 (4.6)	22 (8.9)		2.12 (1.09–4.03)
No. (%) patients according to maximum AKI stage experienced				
AKI stage 1	164 (19.3)	48 (19.4)	0.71	
AKI stage 2	195 (23.0)	59 (23.8)		
AKI stage 3	77 (9.1)	28 (11.3)		
No. (%) of patients who had RRT applied	37 (4.4)	18 (7.3)	0.095	1.56 (0.80–2.96)
No. (%) of patients who experienced tumor lysis syndrome	40 (4.7)	12 (4.8)	> 0.99	
No. (%) of patients who received HSCT	210 (24.8)	61 (24.6)	> 0.99	

No. (%) of patients who had nephrectomy performed	27 (3.2)	19 (7.7)	0.004	3.68 (1.05–13.72)
No. (%) of patients who experienced cancer relapse	79 (9.3)	30 (12.1)	0.24	1.29 (0.78–2.06)

[a]Impaired renal function was defined as final eGFR of less than 90 ml/min/1.73 m^2, which was calculated either at one year after the completion of cancer therapy or at five years after initial diagnosis of cancer.

[b]Reference to odds ratio in multivariable analysis is brain tumor in cancer group and the absence of the corresponding risk factor.

[c]Patients could have received more than one of the specified chemotherapeutic agents. Reference to such patients is patients who did not received any of the specified chemotherapeutic agents.

[d]The covariates assessed for the multivariable logistic-regression model were sex, initial eGFR at diagnosis, cancer group, chemotherapy, cyclophosphamide containing regimen, CT scans, AKI frequency, RRT, nephrectomy, or relapse.

DISCUSSION

Our study provides the first comprehensive evaluation of the characteristics of AKI, including the incidence, risk factors, and short-term and long-term outcome of AKI in children with cancer, including a large group of patients diagnosed with inclusive cancer types using established criteria for AKI—the KDIGO criteria. Reports on the incidence of AKI in children with cancer have offered variable results depending on the criteria used for the diagnosis of AKI. For example, while the incidence of AKI in recipients of HSCT was 78% within one year after cancer diagnosis in our study, the reported incidence of AKI in recipients of HSCT was much lower, about 11% and 21%, within a 2-year period in studies that defined AKI as the doubling of Cr[13,14]. However, when the pRIFLE (Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease) criteria were used, the reported incidence of AKI was 84% in recipients of HSCT within 100 days after transplantation, which was slightly higher than the result of our study, although the different timeframe should be considered for a more accurate comparison[16]. In a study that used the KDIGO criteria for AKI diagnosis, as in our study, 64% of AML patients treated with conventional chemotherapy developed AKI, while 74% of the AML patients treated with only conventional chemotherapy in our study developed AKI within one year after cancer diagnosis (data not shown)[27]. Since the KDIGO criteria are currently regarded as the standard criteria for evaluating AKI, the findings

of our study may be a useful clinical reference in the future.

The 1-year cumulative incidence of AKI in our study population of children with cancer was 52.6%, which was higher than the 12-18% in adults with cancer[11,27]. It is notable that half of the AKIs occurred within two weeks after diagnosis, with the first onset at a median 9 days after cancer diagnosis. This emphasizes the importance of closely monitoring renal functions and using the best possible nephroprotective measures, especially early after diagnosis.

The incidence of AKI differed between cancer types. Overall, the cumulative incidence of AKI was the highest in patients with hematologic malignancies both at two weeks and at one year after cancer diagnosis. The range of cumulative incidence among AKI in patients with acute leukemia was high, ranging between 45.2% and 58.5% at two weeks, and it was extremely high, ranging between 77.2% and 88.4%, at one year after diagnosis. Moreover, the severity of AKI was also higher in this patient group. This implies that cautious nephroprotective measures early after diagnosis and throughout the course of treatment is particularly crucial in this group of patients. This is in accordance with a study on adults with cancer, in which patients with hematological malignancy had a higher cumulative incidence of AKI than those with other cancer types[11]. In comparison, renal tumor was the most AKI-prone cancer in an adult study[11]. Interestingly, Wilms tumor, renal tumor in children, had a cumulative

incidence of AKI of 51.5% at one year after diagnosis, which was 8th in ranking among the cancer types in our study (Table 2). At our institute, most of the patients with Wilms tumor did not have nephrotoxic chemotherapeutics administered and they did not undergo intensive treatment periods, which may explain their low incidence of AKI.

In addition to the cancer group, the occurrence of TLS, greater number of CT scans performed, administration of chemotherapy, and administration of HSCT were found to be significant risk factors of AKI, as expected from the clinical experience[2,5,29,30]. Notably, methotrexate was found to be a significant risk factor of AKI, as found in a previous study[31]. The use of high-dose methotrexate from day 14 from the initial cycle of chemotherapy and throughout the treatment course for osteosarcoma in our institute may have contributed to the gradual increase in the cumulative incidence of AKI of this cancer type. Cisplatin and carboplatin were not shown to be risk factors of AKI in current study. One of our speculations is that they were used more often for solid tumors than for hematologic malignancies. Since AKI occurs more frequently in hematological malignancies, the effects of cancer types may have offset the risks of chemotherapeutics. On the other hand, cyclophosphamide was shown to be associated with unexpectedly high incidence of AKI in univariate analysis. In fact, cyclophosphamide is often used for hematological malignancies and for many of the aggressive and refractory cancers where patients can be vulnerable to AKI due to either

prolonged treatment or intense therapies. Administration of HSCT was another significant risk factor of AKI in our study, as previously reported[24]. In our institute, most patients with AML undergo HSCT after two cycles of induction chemotherapy and two cycles of consolidation chemotherapy over a four-week interval, and advanced neuroblastoma patients undergo HSCT after seven to eight cycles of chemotherapy, with a three- to four-week interval. Although it should be interpreted with caution, it is interesting to note that the timepoints when the stepwise increment of the cumulative incidence of AKI in AML and in neuroblastoma coincided with the usual timepoints of HSCT in these diseases, about 5.0 months and 6.5 months from diagnosis, respectively (Figure 2a). Patients who experienced relapse had high incidence of AKI in univariate analysis. This may have been due to their high initial cancer stage and their intensive treatment periods. However, it was not shown to be significant in multivariable analysis.

On long-term follow-up, more than one-fifth of the patients developed renal impairment and/or proteinuria. The occurrence of AKI was significantly associated with the development of long-term renal impairment, in accordance with a well-known finding that AKI is a risk factor of CKD[10]. In particular, the experience of multiple episodes of AKI, but not the onset time or the severity of AKI, was a risk factor of long-term renal impairment. Notably, among the risk factors of long-term renal impairment, the recurrence and thus the number of AKI episodes may be the only potentially

modifiable risk factor. It is also notable that patients with low initial eGFR was significantly associated with the development of long-term renal impairment. Close monitoring of renal function after the course of treatment in these patients may be helpful to mitigate poor outcomes. While Wilms tumor was ranked 8th regarding the development of AKI among the 17 different cancer types in our study, a high proportion (37%) of patients with Wilms tumor developed renal impairment in the long-term follow-up (Table 2). Moreover, nephrectomy was found to be an independent risk factor of long-term renal impairment. Decreased number of nephrons has direct effect on decreased renal function, although it is partly compensated by the increase in GFR per nephron[32,33]. In fact, one study reported that half of the nephrectomized patients with Wilms tumor or neuroblastoma had a final eGFR of less than 90 mL/min/1.73m^2 [33]. Thus, close monitoring of renal function and applications of nephroprotective measures are necessary in these patients. However, most of the patients had only mild kidney dysfunction, partly due to the lack of enough follow-up time. Our data should be interpreted with caution because the complete final eGFR data was missing in a large portion of survivors and the patients with this data tended to be those who have undergone prolonged or intensive treatment courses such as HSCT due to high cancer stage or relapse. The reported prevalence of proteinuria in cancer survivors is 3.2%[35]. In our study, a total of 8.2% of the patients developed proteinuria. However, our results may

have been biased and overestimated because patients who have not experienced clinically overt renal insults may not have had their urinalysis followed-up routinely. Also, as it is the result from random urinalysis, much of these findings may be due to the benign proteinuria which does not require specific management. Nonetheless, since proteinuria is a well-known risk factor of CKD progression, this subset of patients might need further evaluation to detect pathologic proteinuria in early stage to improve long-term renal outcome.

This study has the inherent limitation that it was a retrospective medical chart review and a single center study. The results should be interpreted with caution because the study population may have been a biased group of patients due to our institutional status as a referral center for pediatric patients in South Korea. In addition, the evaluation of AKI in this study was not fully comprehensive because the criterion involving urine output was not included. Also, defining impaired renal function as eGFR less than 90ml/min/1.73m^2 may be imprecise given the limited accuracy of Cr based eGFR in patients with mildly impaired kidney function, although it was partly due to the lack of patients with severely impaired kidney function for statistical analysis. Furthermore, not all of the factors that may have affected the development of AKI and the long-term renal outcome were sufficiently analyzed. For instance, the study did not evaluate the cancer stage, all the chemotherapeutic agents and regimens used (e.g., dosages and

schedules), or all the possibly nephrotoxic medications (e.g., antimicrobial agents). However, as we comprehensively analyzed incidence and risk factors of acute kidney injury in pediatric cancer patients for the first time, it will be used as informative baseline data for further studies.

In conclusion, the results of our study emphasize that AKI is very common in children with cancer, especially early after diagnosis, and that it is associated with adverse long-term renal outcomes. Further studies are needed to prospectively evaluate the trend of changes in renal functions throughout the treatment course in children with cancer and to further focus on long-term renal outcomes in childhood cancer survivors[36,37].

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국문 초록

본 연구는 소아 암 진단 후 첫 1 년 동안 급성 신손상의 발생율을 분석하며 급성 신손상이 신기능 및 단백뇨의 발생에 미치는 장단기적 영향을 알아보기 위하여 2004 년부터 2013 년까지 서울대학교병원에서 암으로 진단 및 치료받은 소아 환자들의 의무기록을 후향적으로 분석하였다. 급성 신손상은 국제지표인 Kidney Disease: Improving Global Outcomes 의 기준에 따라 정의하였으며, 신기능 저하는 추정사구체여과율 90ml/min/1.73m^2 으로 정의하였으며 단백뇨의 발생 여부에 대하여서도 확인하였다.

본 연구에서 1868 명의 소아 암 환자를 확인하였으며, 그들의 진단 당시 중위 연령은 7.9 세였다. 총 983 명(52.6%)에서 1868 회의 급성 신손상이 발생하였으며 진단 2 주 후, 3 개월 후, 1 년 후의 급성 신손상의 누적 발생율은 각각 28.9%, 39.6%, 53.6% 이었다. 급성 신손상의 1 년 누적 발생율은 급성 골수성 백혈병에서 가장 높았다(88.4%). 6.1%의 환자에서는 4 회 이상의 급성 신손상이 발생하였으며 11.8%의 환자에서는 3 기 급성 신손상이 발생하였다. 1096 명의 소아 암 생존자 중에서 22.6%의 환자에서 신기능 저하가 발생하였으며, 4 회 이상의 다수의 급성 신손상 발생과 신절제술의 과거력은 신기능 저하의 독립적인 위험 요인으로 밝혀졌다. 또한 742 명의 소아 암 생존자 중에서 8.2%의 환자에서 단백뇨가 확인되었다.

본 연구에서 우리는 큰 비율의 소아 암 환자들은 치료 과정에서 급성 신손상을 경험하며, 지속되는 급성 신손상은 후기 신기능 저하와 관련 있음을 밝혔다.

주요어 : 급성 신손상, 소아 암, 항암화학요법, 만성콩팥병, 단백뇨

학 번 : 2018-28729