Original Article

Cystatin C level is associated with the recovery of renal function in cancer patients after onset of acute kidney injury

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Background: The risk of injury to the kidney can be significantly exacerbated by the presence of tumors and the effects of related treatments. Kidney injury associated with cancer is common in multiple myeloma, tumor lysis syndrome, hematopoietic stem cell therapy, and chemotherapy. Cancer patients are at increased risk of infection, sepsis, tumor lysis syndrome, drug-related toxicity, and other comorbidities, leading to a significantly increased risk of acute kidney injury (AKI). This study retrospectively analyzed the clinical data of AKI in cancer patients and explored the predictive value of Cystatin C (CysC) in the prognosis of cancer patients with AKI.

Methods: Cancer patients attending the Fifth People's Hospital of Shenyang from April 2014 to March 2019 were enrolled according to inclusion and exclusion criteria. Cancer patients with AKI were divided into two groups according to the changes in renal function during the follow-up period: a renal function recovery group and a nonrecovery group. The differences in baseline data of the two groups were compared. Logistic univariate and multivariate regression analyses were conducted to determine the risk of renal function failure.

Results: A total of 3,127 cases were included. Among them, 659 cases (21.1%) had AKI, and 2,468 cases had no AKI. Among the 659 AKI patients, 473 (71.8%) patients' renal function recovered, while 186 (28.2%) did not. Logistic univariate and multivariate regression analyses indicated that age [odds ratio (OR) =1.133, 95% confidence interval (CI): 1.064–1.219], diabetes (OR =1.226, 95% CI: 1.093–1.385), chronic kidney disease (CKD) (OR =1.347, 95% CI: 1.108–1.624), hematological malignancies (OR =1.174, 95% CI: 1.063–1.311), chemotherapy (OR =1.119, 95% CI: 1.055–1.304), systolic blood pressure (OR =1.108, 95% CI: 1.062–1.267), serum creatinine (Scr) (OR =1.262, 95% CI: 1.105–1.446), and CysC (OR =1.416, 95% CI: 1.251–1.739) were related to the failure of renal function to recover after AKI.

Conclusions: Baseline CysC level is associated with the occurrence of AKI in cancer patients and a failure to recover renal function during follow-up.

Keywords: Cystatin C (CysC); cancer; acute kidney injury (AKI)

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Introduction

The tremendous progress in cancer treatment has significantly improved the quality of life and survival rate of patients. However, the tumor itself and related treatments can significantly increase the risk of kidney injury. Kidney injury associated with cancer is common in multiple myeloma, tumor lysis syndrome, hematopoietic stem cell therapy, and chemotherapy. Cancer patients are at increased risk of infection, sepsis, tumor lysis syndrome, drug-related

toxicity, and other comorbidities, leading to a significantly increased risk of acute kidney injury (AKI) (1,2), which, in turn, further increases the mortality rate and may limit the progress or efficacy of related treatments (1,2).

Two recent studies have shown that the total annual incidence of AKI in cancer patients is between 11% and 20%, with the risk to hematological cancer patients being even higher (3,4). A study in China surveyed 7 million patients, and the results showed that, depending on the type of hospital (community versus academic institution), the incidence of AKI (defined as a baseline increase in serum creatinine (Scr) by at least 50%) ranged from 14% to 20% (5). Some studies have pointed out that the actual incidence of AKI is much higher (60%) than that commonly reported (6,7). Regarding the prognosis of AKI in cancer patients, one Danish cohort study found that 5% of patients required renal replacement therapy (RRT) within 1 year after the onset of AKI (3). Another study of high-risk populations showed that, depending on the severity of AKI and potential comorbidities, 8% to 60% of patients require RRT (8). More recent research investigating the incidence of AKI in 163,071 patients receiving systemic therapy (9) reported a total cumulative incidence of 9.3%. The malignant tumors with the highest incidence of AKI in the past 5 years are myeloma (26.0%), bladder cancer (19.0%), and leukemia (15.4%). Interestingly, between 2007 and 2014, the annual incidence of AKI increased from 18 to 52 per 1,000 person-years (9). The risk factors associated with the occurrence of AKI in cancer patients are both cancer-specific and patient-specific, with hematological malignancies, elderly patients, and potential chronic kidney disease (CKD) being the largest baseline risk factors.

The occurrence of AKI in cancer patients can lead to increased mortality, longer hospital stays, and reduced cancer remission rates (7,10-15). However, studies have found that among cancer patients with AKI, renal function can be recovered in 82% of patients and be partially recovered in 12% of patients, with only 6% of patients requiring continuous RRT (11). Therefore, predicting the long-term risk of cancer patients after AKI has important clinical significance. At present, the treatment of AKI in cancer patients is mainly supportive treatment and alternative treatment. In terms of drugs, statins may be effective (16,17). The kidney is the only organ that removes Cystatin C (CysC) from the blood. The molecular weight of CysC is low, and it can thus be freely filtered by the glomerulus and distributed on the cell surface. It is almost completely absorbed in the proximal convoluted tubule (18), and its serum concentration mainly depends on kidney function. Consequently, this indicator can reflect the glomerular filtration rate (GFR) at an early stage. This study retrospectively analyzed the relevant data of AKI in cancer patients, and explored the predictive value of CysC in the prognosis of cancer patients with AKI. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-21-191).

Methods

Study population

Patients who were treated at the Fifth People's Hospital of Shenyang from April 2014 to March 2019 were included. The inclusion criteria for participants were the following: (I) age ≥18 years; (II) clear diagnosis of malignant tumor; (III) life expectancy ≥3 months; (IV) history of surgery, chemotherapy, or radiotherapy; (V) CysC test results available in the baseline data; (VI) regular renal function testing during the process of tumor treatment; (VII) fulfilling the definition of the AKI. Meanwhile, the exclusion criteria for participants were the following: (I) malignant tumors of the urinary system; (II) with severe heart failure, respiratory failure, liver failure; (III) with active connective tissue disease; (IV) incomplete follow-up data. This study was approved by the Ethics Committee of the Fifth People's Hospital of Shenyang. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

Data collection

The clinical data of patients, including demographic data (sex, age, etc.), general data (height, weight, smoking history, etc.), basic medical history data (underlying diseases, baseline blood pressure, heart rate, routine blood test indicators, such as white blood cell count, hemoglobin concentration, liver function, renal function, electrolytes, blood lipids, blood glucose, apolipoprotein, CysC, etc.), tumor-related data (tumor location, clinical stage, treatment methods, related drugs and their dosage), and follow-up data (outcome, changes in renal function, etc.), were collected. The definition of AKI is judged and staged according to an elevated level of Scr and/or urine output:

that is, (I) an increase in Scr within 48 hours exceeding 26.5 μmol/L, or an increase in Scr exceeding 1.5 times the baseline, either confirmed or speculated to occur within 7 days; or (II) urine output <0.5 mL/kg·h lasting for more than 6 hours (AKI can be diagnosed if one of the above conditions is met) (19).

Grouping

According to whether or not the renal function returned to the baseline level during the 1-year follow-up period after the occurrence of AKI, the patients were divided into two groups: a recovery group and a nonrecovery group. The baseline of the two groups was compared, and differences in clinical data and outcomes during follow-up were analyzed.

Statistical analysis

Statistical processing was performed using SPSS 23.0 statistical software (IBM Corp., Armonk, NY, USA). Quantitative data were tested for normal homogeneity. If the data conform to a normal distribution are represented by mean ± standard deviation, comparisons between groups were processed by the *t*-test. If the data did not conform to a normal distribution are represented by medians, the comparison between groups was processed by the rank-sum test. The qualitative data are expressed by numbers and percentages, and comparison between groups was performed by χ^2 test or Fisher's exact test if theoretical number was less than 1. Logistic single factor and multivariate analyses of factors related to whether or not AKI could be resolved were also performed. A P value <0.05 indicated that the difference was statistically significant.

Results

Patients baseline characteristics

A total of 4,741 adult cancer patients (those with urinary system tumors were excluded) were diagnosed and treated in our hospital from April 2014 to March 2019, including 1,628 cases of lung cancer, 994 cases of gastric cancer, 847 cases of colorectal cancer, 516 cases of liver cancer, 325 cases of hematological malignancies, and 431 cases with other malignant tumors. According to the inclusion and exclusion criteria, 3,127 cases were ultimately included. Among them, 659 cases (21.1%) had AKI, and 2,468 cases had no AKI. The patients' baseline information is shown in *Table 1*.

Follow-up outcome in cancer patients with AKI

We further analyzed the follow-up data of cancer patients with AKI, and the results showed that during the 1-year follow-up, 473 patients (accounting for 71.8% of patients with AKI) recovered to the baseline level, and 186 patients (accounting for 28.2% of patients with AKI) did not. Comparison of baseline data between the two groups is shown in *Table 2*. We found that there were statistical differences in some indicators between patients who recovered renal function and those who did not, including in age, body mass index (BMI), blood pressure level, blood sugar level, tumor stage, diuretic use, CysC and its change at the time of diagnosis of AKI, and others; however, the baseline level of creatinine, the increase in creatinine at the time of diagnosis of AKI, and the estimated glomerular filtration rate (eGFR) calculated from creatinine were not statistically different between the two groups.

Factors associated with prognosis after the diagnosis of AKI in cancer patients

Logistic univariate and multivariate regression analyses indicated that the baseline level of CysC was closely correlated with the recovery of renal function in cancer patients after the occurrence of AKI. A high baseline level of CysC indicated a significantly higher risk of renal function failure. Univariate analysis revealed that the factors related to the failure of renal function recovery included age, BMI, hypertension, diabetes, CKD, hematological malignancies, chemotherapy, systolic blood pressure, hemoglobin, Scr, CysC, and other factors. Further multivariate analysis suggested that age, diabetes, CKD, hematological malignancies, chemotherapy, systolic blood pressure, Scr, and CysC were related to the failure of renal function to recover after AKI (see *Table 3*).

Discussion

This study retrospectively analyzed the clinical data of cancer patients with AKI in our hospital in recent years, and found that AKI is common in cancer patients. After AKI, some patients required RRT and experienced improved renal function after treatment but did not return to the baseline level. This significantly hampered the subsequent treatment of the patient's cancer, resulting in a significantly

Table 1 Baseline data of patients

Characteristics	AKI (n=659)	Non-AKI (n=2,468)	t/χ^2 value	P value
Age (years)	57.9±6.8	57.2±5.4	2.789	0.005
Male (n, %)	436 (66.2)	1,547 (62.7)	2.713	0.100
Body mass index (kg/m^2)	22.7±2.1	22.8±1.6	1.328	0.184
Smoking (n, %)	87 (13.2)	319 (12.9)	0.035	0.851
Alcohol (n, %)	99 (15.0)	351 (14.2)	0.271	0.603
Hypertension (n, %)	62 (9.4)	171(6.9)	4.637	0.031
Diabetes (n, %)	43 (6.5)	91 (3.7)	10.212	0.001
Chronic kidney disease (n, %)	75 (11.4)	220 (8.9)	3.704	0.054
Tumor				
Lung (n, %)	216 (32.8)	858 (34.8)	0.912	0.340
Stomach (n, %)	127 (19.3)	529 (21.4)	1.468	0.226
Colorectal cancer (n, %)	114 (17.3)	443 (17.9)	0.151	0.698
Liver cancer (n, %)	68 (10.3)	273 (11.1)	0.230	0.587
Blood cancer (n, %)	69 (10.5)	152 (6.2)	14.721	0.0001
Other cancer (n, %)	65 (9.9)	213 (8.6)	0.976	0.323
Therapy				
Surgery (n, %)	482 (73.1)	1,827 (74.0)	0.212	0.646
Chemotherapy (n, %)	426 (64.6)	1,425 (57.7)	10.265	0.001
Radiotherapy (n, %)	218 (33.1)	833 (33.8)	0.105	0.746
≥2 therapies (n, %)	512 (77.7)	1,894 (76.7)	0.265	0.607
Statins (n, %)	21 (3.2)	137 (5.6)	6.061	0.014
Angiotensin-converting enzyme inhibitors (n, %)	33 (5.0)	97 (3.9)	1.515	0.218
Angiotensin receptor blockers (n, %)	20 (3.0)	78 (3.2)	0.027	0.870
Systolic blood pressure (mmHg)	113.8±10.4	114.8±9.5	2.352	0.019
Fast glucose (mmol/L)	5.62±0.31	5.64±0.29	1.550	0.121
White blood cell (×10^9/L)	5.48±0.73	5.53±0.62	1.736	0.083
Neutrophil (×10^9/L)	3.19±0.44	3.23±0.33	1.922	0.055
Red blood cell (×10^9/L)	4.37±0.51	4.39±0.45	0.985	0.325
Hemoglobin (g/L)	140.2±7.4	140.5±7.2	0.945	0.345
Platelet (×10^9/L)	209.7±24.5	211.2±23.8	1.428	0.153
Creatine (mmol/L)	79.3±8.5	78.7±7.7	1.728	0.082
Uric acid (mg/L)	326.9±28.1	324.5±26.3	1.794	0.073
Alanine aminotransferase (U/L)	23.8±3.1	23.7±2.5	0.865	0.387
Total cholesterol (mmol/L)	4.72±0.43	4.75±0.41	1.651	0.099
Triglyceride (mmol/L)	1.95±0.36	1.93±0.33	1.355	0.175
Cystatin C (mg/L)	1.45±0.22	1.32±0.18	15.676	<0.001

AKI, acute kidney injury.

Table 2 Comparison of baseline data between the recovery group and the nonrecovery group

Characteristics	RG (n=473)	NG (n=186)	t/χ^2 value	P value
Age (years)	57.5±7.2	58.9±7.6	2.333	0.026
Male (n, %)	319 (67.4)	117 (62.9)	1.228	0.268
BMI (kg/m^2)	23.1±2.7	21.7±3.2	5.676	<0.001
Smoking (n, %)	61 (12.9)	26(14.0)	0.136	0.712
Alcohol (n, %)	72 (15.2)	27 (14.5)	0.052	0.819
Hypertension (n, %)	37 (7.8)	25 (13.4)	4.945	0.026
Diabetes (n, %)	24 (5.1)	19 (10.2)	5.785	0.016
Chronic kidney disease	43 (9.1)	32 (17.2)	8.714	0.003
Tumor				
Lung (n, %)	161 (34.0)	55 (29.6)	1.210	0.271
Stomach (n, %)	89 (18.8)	38 (20.4)	0.224	0.636
Colorectal cancer (n, %)	80 (16.9)	34 (18.3)	0.174	0.676
Liver cancer (n, %)	48 (10.2)	20 (10.8)	0.053	0.818
Blood cancer (n, %)	40 (8.5)	29 (15.6)	7.250	0.007
Other cancer (n, %)	47 (9.9)	18 (9.7)	0.010	0.920
Therapy				
Surgery (n, %)	341 (72.1)	141 (75.8)	0.937	0.333
Chemotherapy (n, %)	291 (61.5)	135 (72.6)	7.143	0.008
Radiotherapy (n, %)	161 (34.0)	57 (30.7)	0.694	0.405
≥2 therapies (n, %)	355 (75.5)	154 (82.8)	4.044	0.044
Statins (n, %)	19 (4.0)	2 (1.1)	3.745	0.053
Angiotensin-converting enzyme inhibitors (n, %)	25 (5.3)	8 (4.3)	0.272	0.602
Angiotensin receptor blockers (n, %)	18 (3.8)	2 (1.1)	3.382	0.066
Systolic blood pressure (mmHg)	114.6±10.7	111.8±11.2	5.016	<0.001
Fast glucose (mmol/L)	5.61±0.33	5.65±0.37	2.190	0.029
White blood cell (×10^9/L)	5.50±0.75	5.43±0.81	1.054	0.292
Neutrophil (×10^9/L)	3.20±0.46	3.16±0.47	0.999	0.318
Red blood cell (×10^{12}/L)	4.39±0.53	4.32±0.56	1.502	0.134
Hemoglobin (g/L)	140.6±7.8	139.2±8.3	2.036	0.042
Platelet (×10^9/L)	210.6±25.7	207.4±26.9	1.420	0.156
Creatine (mmol/L)	78.1±8.9	82.4±9.7	3.163	0.002
Uric acid (mg/L)	325.4±29.3	330.7±30.3	2.070	0.039
Alanine aminotransferase (U/L)	23.7±3.3	24.1±4.1	1.304	0.193
Total cholesterol (mmol/L)	4.74±0.45	4.67±0.51	1.729	0.084
Triglyceride (mmol/L)	1.96±0.40	1.92±0.41	1.147	0.252
Cystatin C (mg/L)	1.36±0.25	1.68±0.30	13.951	<0.001

RG, recovery group; NG, nonrecovery group.

Table 3 Multivariate analysis and factors that cause renal failure in cancer patients after AKI

Factors	OR	95% CI	P value
Age	1.133	1.064–1.219	0.031
Diabetes	1.226	1.093–1.385	0.026
Chronic kidney disease	1.347	1.108–1.624	0.022
Blood cancer	1.174	1.063–1.311	0.037
Chemotherapy	1.119	1.055–1.304	0.041
Systolic blood pressure	1.108	1.062–1.267	0.044
Creatine	1.262	1.105–1.446	0.019
CysC	1.416	1.251–1.739	0.012

AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; CysC, Cystatin C.

worse prognosis. However, some of these patients were able to recover baseline levels after treatment. Further analysis found that the patient's baseline level of treatment CysC was significantly related to whether or not the patient's renal function could return to the baseline level. Other risk factors related to the recovery of kidney function after AKI in cancer patients included age, diabetes, CKD, hematological malignancies, chemotherapy, systolic blood pressure, and Scr. Some previous studies have suggested that these factors are closely related to the risk of AKI in cancer patients (1-4). In our study, we further found that these factors were related to the recovery of renal function after the occurrence of AKI. The results of these studies were consistent with each other, suggesting that patients with this type of cancer have an increased risk of AKI and have an increased risk of renal function failure after AKI.

Cystatin C is a biomarker that has been studied over recent years. It is mainly used in the prediction of renal function and has also been widely discussed in other diseases. The level of CysC is independent of sex and size, and reaches adult levels within the first year after birth (20). The results of a meta-analysis study showed that CysC has high diagnostic sensitivity for the detection of mild GFR decrease (21). Its role in the diagnosis and prediction of AKI has also been thoroughly examined (22,23). Some researchers believe that CysC is an accurate biomarker for the early detection of AKI and may be superior to creatinine for some populations; however, the relevant findings are sometimes inconsistent. For important outcomes, such as death and RRT, CysC has also demonstrated good predictive value. More research is needed, and the focus should be on the cost-effectiveness of early detection of AKI with CysC compared to that with creatinine, and whether or not the indicators have complementary value. As CysC is produced by nucleated cells, increased tumor burden may lead to increased serum levels of CysC (24). This elevated level has been observed in patients with metastatic cancer, but in the absence of related technology, it is impossible to assess whether the reduced kidney function is due to the tumor burden or the disease and its treatment. Cystatin C has been shown to be widely expressed in cells and tissues of various human solid tumors—albeit in uneven distribution—especially in head and neck cancer (25), lung cancer (26), gastrointestinal tumors (27), ovarian cancer (28), prostate cancer (29), kidney cancer (30), breast cancer (31), melanoma (32), central nervous system (CNS) tumors (33), hematological malignancies (such as leukemia) (34), lymphoma (35), and myeloma (36). Interestingly, clinical studies have emphasized the significant association between changes in the expression level of this molecule and clinical outcomes in cancer patients (37,38). Although these observations support the hypothesis that CysC is involved in cancer, its specific role in malignant diseases is still unclear. In fact, studies specifically aimed at revealing the role of CysC in tumor growth have shown that this molecule plays a series of complex roles that may inhibit or promote tumor cell growth and spread (39). Experimental studies conducted to clarify the potential opposite mechanism of action have shown that these phenomena may be partly related to the cathepsin inhibitory function of CysC, and therefore, to the context-sensitive role of these enzymes in different types of cancers and diseases, or to the different steps of malignant progression (39,40). However, emerging evidence suggests

that in addition to cathepsin inhibition, other mechanisms unrelated to this function may also explain the complex effects of CysC on tumor cell growth and spread (41,42).

Our study found that the baseline level of CysC can not only predict the occurrence of AKI in cancer patients, but is also related to the subsequent changes in renal function, independent of other risk factors. This result has important clinical significance. First, it implies that CysC can predict the risk of AKI in cancer patients. In high-risk patients, if CysC is high, it is unlikely that AKI will be resolved. These patients should be closely monitored and given intensive treatment. More specifically, clinicians can avoid drugs that damage kidney function, reduce the burden on the kidneys, administer drugs that protect kidney function, and perform other related measures. Though only about 18% patients cannot fully recover from cancer-related AKI, with the increasing absolute number and incidence of cancer cases, we believe CysC play an important role in predicting the prognosis of AKI in cancer patients.

Some limitations to this study should also be addressed. First, the study included a comparatively small number of patients and was single-center and retrospective in design; thus, the statistical power of the evidence is relatively weak. Second, the follow-up time of the study was short, and the relationship between subsequent changes in renal function and CysC remains uncertain. Therefore, further multicenter, large-sample studies with longer follow-up times are needed.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of the Fifth People's Hospital of Shenyang. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

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