Association of Acute Kidney Injury Receiving Kidney Replacement Therapy With Prognosis of Critically Ill Patients With and Without Cancer: A Retrospective Study

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OBJECTIVES: To assess outcomes of cancer patients receiving kidney replacement therapy due to acute kidney injury in ICUs and compare these with other patient groups receiving kidney replacement therapy in ICUs.

DESIGN: Retrospective registry analysis.

SETTING: Prospectively collected database of 296,424 ICU patients.

PATIENTS: Patients with and without solid cancer with acute kidney injury necessitating kidney replacement therapy were identified and compared with those without acute kidney injury necessitating kidney replacement therapy.

INTERVENTIONS: Descriptive statistics were used to ascertain prevalence of acute kidney injury necessitating kidney replacement therapy and solid cancer in ICU patients. Association of acute kidney injury necessitating kidney replacement therapy and cancer with prognosis was assessed using logistic regression analysis. To compare the attributable mortality of acute kidney injury necessitating kidney replacement therapy, 20,154 noncancer patients and 2,411 cancer patients without acute kidney injury necessitating kidney replacement therapy were matched with 12,827 noncancer patients and 1,079 cancer patients with acute kidney injury necessitating kidney replacement therapy.

MEASUREMENTS AND MAIN RESULTS: Thirty-five thousand three hundred fifty-six ICU patients (11.9%) had solid cancer. Acute kidney injury necessitating kidney replacement therapy was present in 1,408 (4.0%) cancer patients and 13,637 (5.2%) noncancer patients. Crude ICU and hospital mortality was higher in the cancer group (646 [45.9%] vs 4,674 [34.3%], $p < 0.001$, and 787 [55.9%] vs 5,935 [43.5%], $p < 0.001$). In multivariable logistic regression analyses, odds ratio (95% CI) for hospital mortality was 1.73 (1.62–1.85) for cancer compared with no cancer 3.57 (3.32–3.83) for acute kidney injury necessitating kidney replacement therapy and 1.07 (0.86–1.33) for their interaction. In the matched subcohort, attributable hospital mortality of acute kidney injury necessitating kidney replacement therapy was 56.7% in noncancer patients and 48.0% in cancer patients.

CONCLUSIONS: Occurrence rate of acute kidney injury necessitating kidney replacement therapy and prognosis in ICU patients with solid cancer are comparable with other ICU patient groups. In cancer, acute kidney injury necessitating kidney replacement therapy is associated with higher crude hospital mortality. However, the specific attributable mortality conveyed by acute kidney injury necessitating kidney replacement therapy is actually lower in cancer patients than in noncancer patients. Diagnosis of cancer per se does not justify withholding kidney replacement therapy.

KEY WORDS: acute kidney injury; intensive care units; mortality; neoplasms; prognosis; renal replacement therapy

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In earlier days, patients with solid cancer have rarely been cared for at ICUs. Metastatic cancer has been regarded as a contraindication to ICU admission in general. This situation has changed dramatically during the last decade (1). Due to tremendous achievements and advances in anticancer therapy, many tumors have become chronic disease processes; cancer patients now present an increasing portion of ICU patients (2).

Several studies have clearly demonstrated that prognosis in cancer patients admitted to ICU because of acute, intermittent, and potentially reversible conditions is not necessarily worse than that in other patient groups (3–5). Several other "classical" ICU patient groups, such as those with congestive heart failure, cirrhosis of the liver, or decompensated chronic obstructive pulmonary disease, have a much worse ICU life expectancy than many cancer patients (6–8).

In contrast to hemato-oncologic patients admitted to ICU, where increasing information has accumulated during recent years, less is known on whether and how specific intermittent complications occurring during ICU stay affect outcome in patients with solid cancer (9). Acute kidney injury (AKI) represents a complication that exerts a pronounced effect on the course of disease and the occurrence of additional complications; it is associated with a specific, "attributable" impact on mortality (10–13).

AKI is a frequent complication in ICU patients with cancer with a more complex pathophysiology than in other ICU patients (14–16). Several studies have investigated the epidemiology of AKI in critically ill cancer patients, but none have addressed the specific effect of AKI on outcome compared with noncancer ICU patients (15, 17–21). In some patient groups, such as those with cirrhosis of the liver, accompanying AKI is an ominous sign and kidney replacement therapy (KRT) is employed extremely restrictively (22). Whether such practice is justified in cancer patients in the ICU as well is subject to much controversy (23, 24).

In the present investigation, we analyze the occurrence rate of AKI requiring KRT (AKI-3D) and its association with outcomes in a large group of ICU patients with cancer compared with patients without solid malignancies. In an analysis of a matched subgroup adjusted for a broad range of acute and chronic confounding factors, we defined the specific effect on mortality induced by solid cancer ("attributable mortality" [AM]) in patients with AKI-3D in the ICU.

MATERIALS AND METHODS

This study was a retrospective analysis of prospectively collected registry data. The Austrian Center for Documentation and Quality Assurance in Intensive Care Medicine (ASDI) database was used to generate the necessary dataset for this study. The ASDI database and its data contents were described previously (25).

In short, sociodemographic data (age, sex, and chronic conditions), the reason for ICU admission, severity of illness (measured by Simplified Acute Physiology Score 3 [SAPS 3] [26]), intensity of provided care (measured by Simplified Therapeutic Intervention Scoring System 28 [27]), length of ICU and hospital stay, and outcome data (survival status at ICU and hospital discharge) were recorded.

Within this dataset, preexisting malignancies are documented based on SAPS 3 definitions (26): nonmetastasizing solid malignancies are documented, if cancer without proven distant metastases (but possibly regional lymph node infiltration) is known, and metastasizing solid cancer is documented, if cancer with distant metastases proven by surgery, CT scan, or any other method is present. Hematologic diseases (lymphoma, leukemia, or multiple myeloma) are documented separately from the aforementioned data fields.

Study Patient Cohorts

Out of this large database, adult patients (greater than or equal to 18 yr old at ICU admission) admitted to ICU from January 1, 2012, to December 31, 2018, were selected (total cohort). Patients with documented solid malignancies were categorized in a "cancer" group, and those without any documented malignancies were categorized in a "no cancer" group.

Patients who received any modality of KRT (hemodialysis, hemofiltration, or hemodiafiltration; AKI stage 3D according to KDIGO) at least once during their ICU stay were classified as suffering from AKI-3D (28) and formed the KRT cohort (KRT cohort).

A matching score using SAPS 3 variables unrelated to either solid malignancy or AKI was calculated, that is, SAPS 3 score was calculated omitting points for serum creatinine levels, cancer, and cancer therapy. All patients were grouped into groups according to ICU,

deciles of the calculated matching score, age groups of 10 years each (where patients over 90 were grouped in one group), sex, and admission type. Whenever more than four controls could be matched, four matching controls were chosen at random.

All cases with AKI-3D that could be matched to at least one control in their respective patient group were included. For cases that could be matched to more than four controls, four controls were chosen at random. The resulting patient group made up the matched cohort.

Ethical Considerations

The ethics committee of the Medical University of Graz (IRB00002556) approved the study. The need for informed consent was waived by the institutional review board, since no additional interventions were performed, and all data used were anonymized and could not be traced back to individual patients.

Statistical Analysis

Unless otherwise specified, descriptive results are expressed as median and interquartile range or number (*n*) and percentage (%).

For main analysis, a logistic regression analysis model for hospital mortality as the dependent variable was fitted for the total cohort. Solid cancer, AKI receiving KRT (AKI-3D), and other preexisting conditions according to the SAPS 3 score were included as binary covariables, and other SAPS 3 predictors were included using their respective point values (**Table S1**, http://links.lww.com/CCM/G518). An interaction term between solid cancer and AKI-3D was included to investigate a potential specific influence on mortality conveyed by concurrence of AKI-3D and solid malignancies. For sensitivity analysis, the same model was fitted for ICU mortality as the dependent variable.

To compare between-group differences in the matched cohort, Kruskal-Wallis, chi-square, and Fisher exact tests were used as appropriate. Bonferroni correction was used to adjust for multiple testing. For these comparisons, an overall two-sided significance level of less than 0.05 was applied. To compare ICU mortality and hospital mortality between the groups in the matched cohort, Mantel-Haenszel tests stratified by matching groups were performed at a two-sided significance level of 0.005.

AM (attributable fraction of the exposed) was calculated as AM = $(I_e - I_u)/I_e$, where I_e is mortality (occurrence rate) in the (exposed) group of patients with AKI-3D and I_u is mortality (occurrence rate) in (unexposed) patients without AKI-3D.

All statistical analyses were performed using R Version 4.0.0 (R Foundation for Statistical Computing; http://www.r-project.org).

RESULTS

Overall Cohort

During the timeframe of investigation, 296,424 first patient admissions to ICUs participating in the registry were documented. These patients were predominantly male (57.4%), and had a median age of 69 years (56–77 yr) and a median SAPS 3 score of 46 (36–57) (**Table 1**).

Of these, 35,356 (11.9%) critically ill patients had any kind of cancer documented at admission; these percentages were relatively constant over the whole observation period. Of these, 22,408 (63.4%) had nonmetastasizing solid cancer and 12,948 (36.6%) had metastatic solid malignancies. Although 13,637 noncancer patients (5.2%) received any form of KRT at least once during their ICU stay, only 1,408 patients (4.0%) did so in the cancer group (Table 1).

Baseline characteristics were similar between the patients with cancer and those without. 149,257 patients (57.2%) without a malignancy were male and their median age was 69 years (55–78 yr); in comparison, 20,982 patients (59.3%) suffering from a malignancy were male and their median age was 69 years (60–77 yr). Median SAPS 3 scores were 46 (36–57) and 47 (37–59), respectively (Table 1).

Minor differences in outcomes were observed between these groups: median length of ICU stay was identical between patients without cancer and those suffering from cancer (3 d [2–5 d] vs 3 d [2–5 d], $p = 0.99$), median length of hospital stay was higher in patients with cancer (11 d [5–20 d] vs 14 d [8–24 d], $p < 0.001$). Mortality rates within the ICU were similar (23,225 [8.9%] vs 3,336 [9.4%], $p = 0.09$), and mortality rates within the hospital were somewhat higher in patients with malignancies (34,567 [13.2%] vs 5,533 [15.6%], $p < 0.001$) (Table 1).

Kidney Replacement Therapy Cohort

Fifteen thousand forty-five patients (5.1%) required KRT due to AKI at least once during their ICU stay. These had

TABLE 1.

Baseline Patient Characteristics and Outcomes in the Total Patient Cohort, in Patients With and Without Acute Kidney Injury Requiring Kidney Replacement Therapy in the ICU, and in Patients With and Without Solid Cancer

Variable	Total Registry Cohort	Acute Kidney Injury With KRT in ICU		Solid Cancer	
		No	Yes	No	Yes
No. of patients	296,424	281,379	15,045	261,068	35,356
Age, median (IQR)	69 (56–77)	69 (56–78)	69 (60–77)	69 (55–78)	69 (60–77)
Male sex, *n* (%)	170,239 (57.4)	160,675 (57.1)	9,564 (63.6)	149,257 (57.2)	20,982 (59.3)
Simplified Acute Physiology Score 3, median (IQR)	46 (36-57)	45 (36–56)	62 (51–73)	46 (36–57)	47 (37–59)
Type of ICU admission, *n* (%)					
Medical	140,127 (47)	130,183 (46)	9,944 (66)	131,524 (50)	8,603 (24)
Postoperative, scheduled	93,943 (32)	91,782 (33)	2,161 (14)	73,356 (28)	20,587 (58)
Postoperative, unscheduled	62,354 (21)	59,414 (21)	2,940 (20)	56,188 (22)	6,166 (18)
Preexisting conditions, *n* (%)					
Chronic heart failure NYHA 2	30,925 (10.4)	29,291 (10.4)	1,634 (10.9)	27,203 (10.4)	3,722 (10.5)
Chronic heart failure NYHA 3	26,424 (8.9)	24,307 (8.6)	2,117 (14.1)	24,132 (9.2)	2,292 (6.5)
Chronic heart failure NYHA 4	9,948 (3.4)	8,820 (3.1)	1,128 (7.5)	9,295 (3.6)	653 (1.8)
Arterial hypertension	151,327 (51.1)	142,574 (50.7)	8,753 (58.2)	132,119 (50.6)	19,208 (54.3)
Chronic obstructive pulmonary disease	40,892 (13.8)	38,149 (13.6)	2,743 (18.2)	35,188 (13.5)	5,704 (16.1)
Chronic respiratory failure	22,597 (7.6)	20,968 (7.5)	1,629 (10.8)	19,761 (7.6)	2,836 (8.0)
Chronic renal failure	40,524 (13.7)	34,478 (12.3)	6,046 (40.2)	35,950 (13.8)	4,574 (12.9)
Liver cirrhosis	6,775 (2.3)	5,883 (2.1)	892 (5.9)	5,909 (2.3)	866 (2.4)
Diabetes, insulin-therapy	16,401 (5.5)	14,550 (5.2)	1,851 (12.3)	14,735 (5.6)	1,666 (4.7)
Diabetes, noninsulin-dependent	33,188 (11.2)	30,731 (10.9)	2,457 (16.3)	29,038 (11.1)	4,150 (11.7)
Steroid treatment	6,748 (2.3)	6,074 (2.2)	674 (4.5)	5,519 (2.1)	1,229 (16.1)
Radiotherapy	2,987 (1.0)	2,855 (1.0)	132 (0.9)	443 (0.2)	2,544 (7.2)
Chemotherapy	6,402 (2.2)	6,030 (2.1)	372 (2.5)	1,566 (0.6)	4,836 (13.7)
Hematological disease	5,606 (1.9)	4,985 (1.8)	621 (4.1)	4,703 (1.8)	903 (2.6)
Solid malignancy	35,648 (12.0)	34,231 (12.1)	1,408 (9.4)	0 (0.0)	35,356 (100)
Nonmetastasizing	22,408 (7.6)	21,445 (7.6)	963 (6.4)	0 (0)	22,408 (63.4)
Metastasizing	12,948 (4.4)	12,503 (4.4)	445 (3.0)	0 (0)	12,948 (36.6)
Kidney replacement therapy (KRT), *n* (%)	14,617 (4.9)	0 (0)	15,045 (100)	13,238 (5.1)	1,379 (3.9)
Length of stay, d, median (IQR)					
ICU	3 (2–5)	3 (2–5)	9 (4–19)	3 (2–5)	3 (2–5)
Hospital	11 (6–21)	11 (6–20)	20 (9–38)	11 (5–20)	14 (8–24)
Mortality, *n* (%)					
ICU	26,561 (9.0)	21,241 (7.5)	5,320 (35.4)	23,225 (8.9)	3,336 (9.4)
Hospital	40,100 (13.5)	33,378 (11.9)	6,722 (44.7)	34,567 (13.2)	5,533 (15.6)

IQR = interquartile range, KRT = kidney replacement therapy, NYHA = New York Heart Association.

TABLE 2.

Baseline Patient Characteristics and Outcomes in Patients With and Without Solid Cancer Who Develop Acute Kidney Injury Receiving Kidney Replacement Therapy in the ICU

	Acute Kidney Injury With KRT in ICU	Solid Cancer	
		No	Yes
No. of patients	15,045	13,637	1,408
Age, median (IQR)	69 (60–77)	69 (59–77)	71 (64–77)
Male sex, *n* (%)	9,564 (63.6)	8,638 (63.3)	926 (65.8)
Simplified Acute Physiology Score 3, median (IQR)	62 (51–73)	61 (51–73)	66 (55–79)
Type of ICU admission, *n* (%)			
Medical	9,944 (66)	9,268 (68)	676 (48)
Postoperative, scheduled	2,161 (14)	1,787 (13)	374 (27)
Postoperative, unscheduled	2,940 (20)	2,582 (19)	358 (25)
Preexisting conditions, *n* (%)			
Chronic heart failure NYHA 2	1,634 (10.9)	1,444 (10.6)	190 (13.5)
Chronic heart failure NYHA 3	2,117 (14.1)	1,962 (14.4)	155 (11.0)
Chronic heart failure NYHA 4	1,128 (7.5)	1,052 (7.7)	76 (5.4)
Arterial hypertension	8,753 (58.2)	7,831 (57.4)	922 (65.5)
Chronic obstructive pulmonary disease	2,743 (18.2)	2,474 (18.1)	269 (19.1)
Chronic respiratory failure	1,629 (10.8)	1,464 (10.7)	165 (11.7)
Chronic renal failure	6,046 (40.2)	5,491 (40.3)	555 (39.4)
Liver cirrhosis	892 (5.9)	815 (6.0)	77 (5.5)
Diabetes, insulin therapy	1,851 (12.3)	1,714 (12.6)	137 (9.7)
Diabetes, noninsulin-dependent	2,457 (16.3)	2,215 (16.2)	242 (17.2)
Steroid treatment	674 (4.5)	606 (4.4)	68 (4.8)
Radiotherapy	132 (0.9)	25 (0.2)	107 (7.6)
Chemotherapy	372 (2.5)	148 (1.1)	224 (15.9)
Hematological disease	621 (4.1)	540 (4.0)	81 (5.8)
Solid malignancy	1,408 (9.4)	0 (0)	1,408 (100.0)
Nonmetastasizing solid cancer	963 (6.4)	0 (0)	963 (68.4)
Metastasizing solid cancer	445 (3.0)	0 (0)	445 (31.6)
Time to first KRT, d, median (IQR)	1 (0–2)	1 (0–2)	1 (0–3)
Total duration of KRT, d, median (IQR)	4 (2–9)	4 (2–9)	4 (3–9)
Length of stay, d, median (IQR)			
ICU	9 (4–19)	9 (4–19)	10 (5–22)
Hospital	20 (9–38)	20 (9–38)	23 (10–42)
Mortality, *n* (%)			
ICU	5,320 (35.4)	4,674 (34.3)	646 (45.9)
Hospital	6,722 (44.7)	5,935 (43.5)	787 (55.9)

IQR = interquartile range, KRT = kidney replacement therapy, NYHA = New York Heart Association.

a median age of 69 years (60–77 yr) and a high severity of illness upon ICU admission as assessed by a median SAPS 3 score of 62 (51–73). Consequently, median length of stay was high both in the ICU (9 d [4–19 d]) and in the hospital (20 d [9–38 d]). Crude mortality was also high; 5,320 patients (35.4%) died in the ICU; 6,722 patients (44.7%) died during hospital stay (**Table 2**).

There were notable differences in unadjusted outcomes between patients with cancer and those without in this cohort. Although 4,674 patients (34.3%) without cancer

TABLE 3.
Multivariable Logistic Regression Analysis for ICU Mortality and Hospital Mortality

	ICU Mortality			Hospital Mortality		
	OR (95% CI)			OR (95% CI)		
Solid cancer	1.48	1.37	1.61	1.73	1.62	1.85
AKI receiving kidney replacement therapy	3.89	3.60	4.20	3.57	3.32	3.83
Interaction: solid cancer–AKI-3D	1.27	1.01	1.59	1.07	0.86	1.33
Male sex	1.00	0.95	1.05	1.03	0.99	1.07
Simplified Acute Physiology Score 3 points (per point) for						
Age	1.11	1.10	1.11	1.14	1.13	1.14
Intrahospital origin before ICU admission	1.05	1.04	1.06	1.05	1.05	1.06
Hospital stay before ICU admission, d	1.05	1.04	1.07	1.10	1.08	1.11
Planned/unplanned ICU admission	1.29	1.25	1.32	1.25	1.22	1.28
Surgical status at ICU admission	1.04	1.03	1.06	1.05	1.04	1.06
Anatomic site of surgery	1.04	1.03	1.06	1.03	1.01	1.04
Reason for ICU admission	1.08	1.07	1.09	1.08	1.07	1.09
Infection at ICU admission	1.07	1.06	1.09	1.09	1.07	1.10
Vasoactive therapy	1.12	1.10	1.14	1.09	1.07	1.11
Glasgow Coma Scale	1.12	1.12	1.13	1.12	1.11	1.12
Serum bilirubin	1.11	1.09	1.13	1.12	1.10	1.14
Body temperature	1.06	1.04	1.07	1.05	1.04	1.07
Heart rate	1.07	1.06	1.08	1.07	1.06	1.08
Leucocyte count	1.13	1.10	1.16	1.15	1.13	1.18
pH	1.25	1.23	1.28	1.22	1.19	1.24
Platelet count	1.10	1.09	1.12	1.10	1.09	1.11
Systolic arterial pressure	1.14	1.13	1.15	1.11	1.10	1.12
Oxygenation index	1.06	1.05	1.07	1.05	1.04	1.05
Chronic heart failure New York Heart Association 4	1.85	1.67	2.04	1.92	1.76	2.09
Hematological disease	1.60	1.40	1.84	1.75	1.56	1.97
Liver cirrhosis	1.89	1.68	2.13	2.20	1.98	2.44
AIDS	2.43	1.19	4.94	1.95	1.01	3.76

AKI = acute kidney injury, OR = odds ratio.
ICU ID included as fixed effects not shown.

died in the ICU, 646 patients (45.9%) with cancer deceased ($p < 0.001$). During the whole hospital stay, 5,935 patients (43.5%) without cancer died, whereas 787 patients (55.9%) with cancer deceased ($p < 0.001$) (Table 2).

Logistic Regression Analysis

Logistic regression analysis in 296,402 complete patient datasets essentially confirmed the above-described findings. Odds ratios (ORs) and 95% CIs for hospital mortality were 3.57 (3.32–3.83) for AKI-3D and 1.73 (1.62–1.85) for solid cancer. A significant contribution of the concurrence of AKI-3D and solid cancer could not be identified; OR (95% CI) for the interaction term was 1.07 (0.86–1.33) (**Table 3**).

ORs and 95% CIs for ICU mortality were 3.89 (3.60–4.20) for AKI-3D and 1.48 (1.37–1.61) for solid cancer. Here, a limited, yet significant contribution

of the concurrence of AKI-3D and solid cancer was found; OR (95% CI) for the interaction term was 1.27 (1.01–1.59) (Table 3).

For sensitivity analysis, nonmetastasizing solid cancer and metastasizing solid cancer were analyzed as separate factor levels. OR (95% CI) for hospital mortality and ICU mortality were 1.20 (1.10–1.31) and 1.11 (0.99–1.23) for the former as well as 2.82 (2.58–3.09) and 2.18 (1.95–2.44) for the latter, respectively. OR (95% CI) for hospital mortality for the interaction terms between AKI-3D and nonmetastasizing solid cancer or metastasizing solid cancer was 1.07 (0.74–1.56) and 1.22 (0.94–1.59), respectively; OR (95% CI) for ICU mortality for the interaction terms between AKI-3D and nonmetastasizing solid cancer or metastasizing solid cancer was 1.35 (0.93–1.97) and 1.38 (1.05–1.81), respectively (**Table S2**, http://links.lww.com/CCM/G518).

Prediction by these models was adequate; areas under the curve were 0.87 for hospital mortality and 0.89 for ICU mortality, respectively.

Matched Cohort

Out of the no-cancer group, 12,827 patients with AKI-3D were matched with 20,154 patients without AKI-3D; out of the cancer group, 1,079 patients with AKI-3D were matched with 2,411 patients without AKI-3D. Groups for analysis were well matched with regard to age, gender, severity of acute illness, and preexisting conditions (**Table 4**).

In the no-cancer group, ICU mortality was 2,707 (13.4%) compared with 4,425 (34.5%) in patients without and with AKI-3D, respectively; hospital mortality was 3,825 (19.0%) compared with 5,623 (43.8%) in patients without and with AKI-3D, respectively. Common ORs (95% CI) for ICU mortality and hospital mortality were 3.21 (3.01–3.43), $p < 0.001$, and 3.21 (3.02–3.41), $p < 0.001$, respectively (**Fig. 1**).

In the cancer group, ICU mortality was 475 (19.7%) compared with 492 (45.6%) in patients without and with AKI-3D, respectively; hospital mortality was 698 (29.0%) compared with 601 (55.7%) in patients without and with AKI-3D, respectively. Common ORs (95% CI) for ICU mortality and hospital mortality were 3.58 (2.98–4.31), $p < 0.001$, and 3.20 (2.77–3.97), $p < 0.001$, respectively.

Attributable ICU mortality of AKI-3D was calculated as 56.7% in the noncancer group compared with 48.0% in the cancer group. Attributable hospital mortality of AKI-3D was calculated as 61.1% in the noncancer group compared with 56.8% in the cancer group.

DISCUSSION

In this investigation in the largest data set on the subject to date, we analyzed the epidemiology of AKI-3D in the ICU and identified its association with outcomes and its AM of concomitant solid cancer on prognosis of patients with AKI-3D. Patients with cancer represented a sizeable proportion of almost 12% of patients admitted to ICU.

Occurrence rate of AKI-3D was comparable in cancer and noncancer ICU-patients. Cancer patients had a similar age and severity of disease upon ICU admission as noncancer patients. Unadjusted relative risk of mortality in cancer patients with AKI-3D was about 30% higher than that in noncancer patients. In an analysis of a matched subgroup of patients, specific mortality attributable to AKI-3D both in the ICU and inhospital was actually found to be lower in patients with solid cancer than those without.

Several investigations on AKI in patients with malignant disease have included both hemato-oncologic and solid cancer patients; most reviews mix these groups of patients (2, 3, 29). However, pathology in hemato-oncologic diseases fundamentally differs from patients with solid cancer since not only nephrotoxicity due to anticancer treatment but also graft-versus-host disease, veno-occlusive disease, engraftment syndrome, stem cell transplantation–associated thrombotic microangiopathy, hypercalcemia, and tumor-lysis syndrome may play an important role (30, 31). This investigation was thus focused on patients with solid cancer only.

AKI may certainly have a complex pattern of specific causes in patients with solid cancer as well, predominantly mediated not only by toxic effects of systemic chemotherapy (15, 16, 32). These include direct tubular injury (such as by Platinum-containing regimens), tubulointerstitial disease, and crystalline nephropathy, but also induction of glomerular injury and glomerular disease (focal segmental sclerosis) and thrombotic microangiopathy (16). Renal side effects can also be seen during recently introduced targeted therapies and immunotherapy-based anticancer treatment modalities such as immune checkpoint inhibitors (33, 34). Indirect effects may also be mediated by cytokine release, capillary leak syndrome, and hypovolemia.

TABLE 4.

Baseline Patient Characteristics and Outcomes for the Matched Cohort of Patients With and Without Solid Malignancies Grouped by the Need for Kidney Replacement Therapy Due To Acute Kidney Injury

	No Solid Cancer		Solid Cancer	
	No AKI-3D	AKI-3D	No AKI-3D	AKI-3D
No. of patients	20,154	12,827	2,411	1,079
Age, median (IQR)	68 (57–77)	70 (60–77)	73 (66–78)	72 (66–78)
Male sex, *n* (%)	12,125 (60.2)	8,190 (63.8)	1,636 (67.9)	737 (68.3)
Simplified Acute Physiology Score 3, median (IQR)	54 (45–64)	61 (51–73)	62 (50–75)	66 (54–80)
Type of ICU admission, *n* (%)				
Medical	12,140 (60)	8,900 (69)	1,027 (43)	516 (48)
Postoperative, scheduled	3,249 (16)	1,623 (13)	549 (23)	312 (29)
Postoperative, unscheduled	4,765 (24)	2,304 (18)	835 (34)	251 (23)
Preexisting conditions, *n* (%)				
Chronic heart failure NYHA 2	1,971 (9.8)	1,377 (10.7)	307 (12.7)	158 (14.6)
Chronic heart failure NYHA 3	1,930 (9.6)	1,870 (14.6)	210 (8.7)	124 (11.5)
Chronic heart failure NYHA 4	1,012 (5.0)	1,010 (7.9)	71 (2.9)	57 (5.3)
Chronic obstructive pulmonary disease	3,392 (16.8)	2,371 (18.5)	555 (23.0)	214 (19.8)
Chronic respiratory failure	1,844 (9.1)	1,383 (10.8)	316 (13.1)	128 (11.9)
Chronic renal failure	2,815 (14.0)	5,253 (41.0)	423 (17.5)	427 (39.6)
Liver cirrhosis	858 (4.3)	765 (6.0)	104 (4.3)	50 (4.6)
Diabetes, insulin-therapy	2,457 (12.2)	2,135 (16.6)	340 (14.1)	203 (18.8)
Diabetes, noninsulin-dependent	1,245 (6.2)	1,639 (12.8)	123 (5.1)	104 (9.6)
Steroid treatment	594 (2.9)	555 (4.3)	97 (4.0)	43 (4.0)
Radiotherapy	52 (0.3)	25 (0.2)	213 (8.8)	77 (7.1)
Chemotherapy	216 (1.1)	145 (1.1)	381 (15.8)	158 (14.6)
Hematological disease	620 (3.1)	513 (4.0)	120 (5.0)	67 (6.2)
Solid malignancy				
Nonmetastasizing	0 (0)	0 (0)	1,447 (60)	738 (68)
Metastasizing	0 (0)	0 (0)	964 (40)	341 (32)
Time to first KRT, d, median (IQR)	N/A	1 (0–2)	N/A	1 (0–3)
Total duration of KRT, d, median (IQR)	N/A	4 (2–9)	N/A	4 (3–10)
Length of stay, d, median (IQR)				
ICU	3 (2–7)	9 (4–19)	4 (2–7)	10 (5–23)
Hospital	13 (6–24)	20 (9–37)	16 (8–27)	23 (10–42)
Mortality, *n* (%)				
ICU	2,707 (13.4)	4,425 (34.5)	475 (19.7)	492 (45.6)
Hospital	3,825 (19.0)	5,623 (43.8)	698 (29.0)	601 (55.7)

AKI = acute kidney injury, IQR = interquartile range, KRT = kidney replacement therapy, N/A = not applicable, NYHA = New York Heart Association.

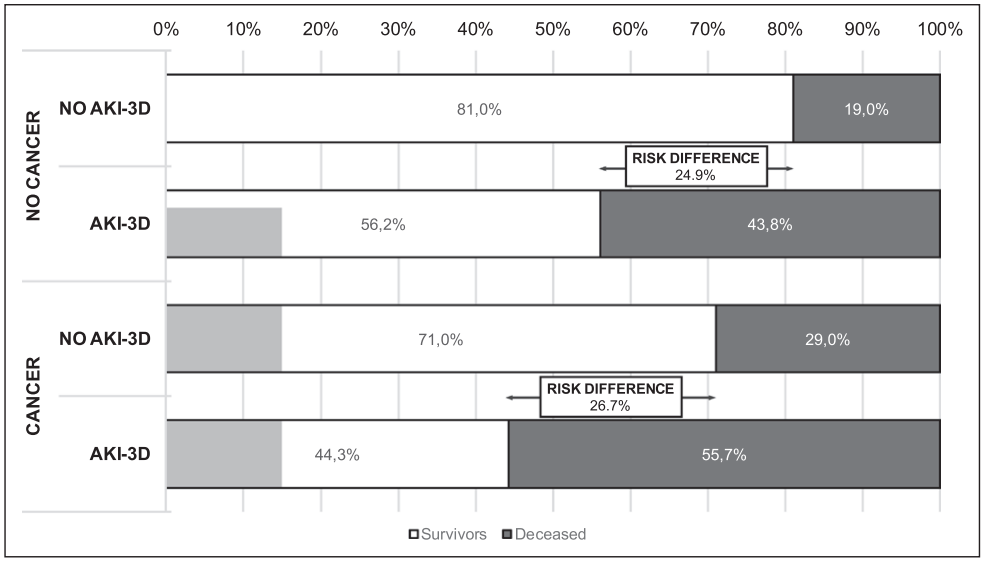

Figure 1. Hospital mortality rates in the matched cohort stratified by noncancer and cancer group as well as acute kidney injury requiring kidney replacement therapy (AKI-3D).

Generally accepted risk factors for AKI, such as age, diabetes mellitus, preexisting renal disease, or sepsis, are similar in cancer patients and other patient populations (35, 36). Sepsis certainly is more frequent in neutropenic patients with cancer. The question whether neoplastic disease per se confers additional risk remains unanswered, however. Especially in patients with metastatic disease, associated inflammatory reactions might lead to increased rates of AKI, which is suggested by the finding that risk of AKI after contrast media exposure is increased in cancer patients (37). However, in contrast to previous investigations, we could not find a higher occurrence rate of AKI in cancer patients than that in noncancer patients (38).

AKI is nowadays recognized as a systemic disease process associated with a broad pattern of short-term and long-term consequences that exert profound effects on outcome (10, 11). Even patients with milder stages of AKI have impaired prognosis (39, 40). AKI is a main predictor for short- and long-term outcomes in patients with cancer as well (41).

AKI confers a specific, "attributable" mortality that has been estimated to be 24.3% in a general ICU population in our original investigation and 19.4% in the more recent FINNAKI study (12, 13). This specific increase in mortality conferred by AKI may differ between various patient groups (13). In patients with liver disease or heart failure, kidney dysfunction is the main denominator of prognosis (22). Using matched analysis in a subpopulation of our total cohort, we were able to demonstrate that the AM of AKI-3D is actually 8.7% lower in patients with cancer than those without.

The presence of AKI may increase toxic effects of systemic chemotherapy but may also jeopardize continuation of effective cancer therapies, as it may necessitate dose reductions (42). This potential additional impact of AKI has never been assessed appropriately.

Premorbid state is obviously a significant influencing factor on patients' chances of survival and recovery and will therefore always be taken into account by healthcare professionals in their decision-making. Historically, the presence of solid malignancies was oftentimes considered an exclusion criterion for the initiation of invasive organ replacement therapies. However, solid cancer has become a chronic disease process in many instances. Prognosis of patients with solid cancer actually is not necessarily worse than that in other ICU patient groups.

Critical care providers are thus continuously tasked with the burden to decide in which patients to start KRT and in whom to refrain from this intervention. Although there was a significant difference, overall mortality is high in both patient groups and therefore comparable. KRT may therefore be considered a viable option in select critically ill patients with AKI, who suffer from cancer (24, 43, 44).

The present analysis is a retrospective evaluation of prospectively collected registry data and therefore subject to all limitations of retrospective analyses. Post hoc analyses are prone to selection bias introduced by decision-making processes of treating healthcare professionals. Although we have adjusted and matched for underlying severity of illness, we cannot rule out the possibility that KRT has been employed differently in patients with cancer and in those without. These decision-making processes are most likely based on the perceived prognosis of both the acute and underlying condition; findings can therefore not necessarily be extrapolated to all critically ill patients with cancer.

Another limitation is the fact that causes of AKI are not part of this database and could therefore not be analyzed in detail. The condition has therefore been derived from the need for any modality of KRT in the ICU. Similarly, detailed oncologic information, such as cancer type or staging, is not part of the underlying database and can therefore not be incorporated into this study. Although this certainly represents a limitation of this study, it again highlights the need for multidisciplinary input and prognostication when treating critically ill patients with cancer.

This study's strengths are the large group of patients recorded in the database, which makes analysis of a clinically relevant cohorts of patients possible, and the quality of this database, which contains detailed information on a broad array of variables including acute and chronic factors, severity of disease, and need for therapeutic interventions. This has enabled us to analyze a broad spectrum of factors that might affect the relationship of AKI and outcomes. Quality of documented data is regularly assessed at units cooperating is this ICU quality initiative.

Data are supplied from a large number of ICUs in Austria. This has allowed us to analyze a large and diverse patient cohort. However, healthcare systems may vary substantially between countries and regions, especially with regard to availability and usage of intensive care. Austria has been shown to have a comparably high number if ICU resources available (45); this usually allows for clinician-led intensive care treatment of patients based on their verbalized, presumed, or documented wishes.

CONCLUSIONS

In conclusion, we demonstrate that patients with cancer in the ICU represent a highly relevant patient group nowadays. Characteristics and outcomes in these patients are not necessarily different from those in patients without cancer. Occurrence rate of AKI is not different between patients without or with solid cancer. Crude mortality of cancer patients who develop AKI-3D is 30% higher than that of noncancer patients. However, inhospital mortality specifically "attributable" to AKI-3D actually was 8.7% lower in patients with cancer compared with a general ICU population without cancer. Presence of cancer per se thus is not a reason to forego institution of KRT in critically ill patients. Decisions must be based on thorough assessment of the situation of each individual patient.

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