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Review Article

Causes of Death in Patients with Acute Kidney Injury Treated with Renal Replacement Therapy - A Systematic Review

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Abstract

Background: The mortality of patients with acute kidney injury (AKI) has not decreased over the last 60 years and is even higher in patients treated with renal replacement therapy (RRT). Recent studies suggest that fluid overload, immunological impairment and the cardiorenal syndrome may contribute to mortality among AKI-patients. In order to determine the most important cause of death among AKI-patients, we performed the current literature study.

Methods: Cochrane, PubMed, Embase and Web of Science were searched for original articles describing the cause of death in AKI patients treated with RRT. Studies were analyzed according to their type of primary endpoint, either in-hospital mortality or mortality after hospital discharge.

Results: Eleven studies with a total of 8804 patients were included. Both in-hospital mortality and mortality after discharge occurred significantly more frequently among patients with Acute Kidney Injury Network (AKIN) stage 3 than among patients with AKIN stage 1 (40 vs 16% and 34 vs 16% respectively, $p < 0.00001$). Infection was the most frequently recorded cause of in-hospital death, ranging from 35 to 81%, followed by cardiac causes, ranging from 8 to 32%. After hospital discharge, cardiovascular causes of death were most frequently reported, with an incidence similar to the incidence in the general population.

Conclusion: This study demonstrates that for AKI-patients treated with RRT, the most important cause of in-hospital death was infection. After hospital discharge however, the main cause of death among AKI-patients was cardiovascular, with an incidence similar to the incidence in the general population.

Keywords: *Acute Kidney Injury; Renal Replacement Therapy; Cause of Death; Infection*

Introduction

Despite improvement in intensive care, the mortality of patients developing acute kidney injury (AKI) has not declined over the last 60 years. In their review of the literature, Ympa and colleagues demonstrated that mortality in patients with AKI ranged from 42 to 63% between 1956 and 2003 [1]. A recent large study confirmed an in hospital mortality of more than 50% among AKI-patients treated between 2000 and 2008 [2]. Mortality has been shown to depend on AKI severity, with patients treated with renal replacement therapy (RRT) having a more than 1.5-fold risk of dying compared to patients not treated with RRT [3,4]. Moreover, even years after hospital discharge, AKI-patients have an increased mortality risk, ranging from 26% to 61%, depending on AKI-severity [5,6]. The cause of this increased mortality among AKI-patients has been extensively studied in recent years and appears to be multifactorial [7]. First of all, AKI may entail electrolyte disturbances and fluid overload, which has been demonstrated to be related to a negative outcome in several stud-

ies [8-13]. In addition, acute worsening of kidney function may cause cardiac dysfunction, defined as the cardiorenal syndrome type 3, leading to a worse outcome than AKI alone [14]. Finally, renal failure induces immunological impairment, leading to an increased rate of infections [7]. Renal failure can cause cellular immunologic incompetence, comprising a diminished phagocytic capacity of macrophages and a reduction in invariant natural killer T-cells [15,16]. In addition, in response to the recognition of pathogen associated molecular patterns (PAMPs), the kidney produces interleukin (IL)-1β and IL-18, contributing to both apoptosis and necrosis of renal cells and to sepsis-induced mortality [17,18]. This phenomenon might further be enhanced by impaired renal cytokine clearance. Finally, the production of anti-inflammatory cytokines such as IL-10 is impaired [18]. All these phenomena render patients with AKI more susceptible to sepsis-induced mortality and emphasize the role of the kidney in critical illness. We hypothesized that infection due to immunological impairment is the main cause of death among AKI-patients treated with RRT. In order to test this hypothesis, we performed the current literature study.

Methods

Literature search

We conducted a systematic review according to the PRISMA statement [19]. PubMed, EMBASE, Cochrane and Web of science were searched using the key words and Medical Sub Headings (MeSH) cause of death, acute kidney (or renal) injury, acute kidney (or renal) failure, acute kidney (or renal) insufficiency, AKI, renal replacement therapy, RRT, hemofiltration and dialysis. Original articles describing causes of death as an outcome in patients with AKI admitted to a hospital and treated with RRT were included. Articles concerning pediatric patients and patients with chronic kidney disease (CKD) were excluded. Languages were limited to English and Dutch.

Quality assessment

The quality of the articles was assessed using the STROBE checklist for cohort studies and the CONSORT checklist for controlled trials, with 22 and 25 items respectively [20,21]. Studies were considered to be of sufficient quality if at least 12 of the items were adequately described.

Endpoints

The primary endpoint was cause of death in patients with AKI. Studies were analyzed according to their type of primary endpoint, either in hospital mortality or mortality after hospital discharge.

Statistical analysis

Two by two table analysis was used to compare incidences between groups.

Results

Study population

Eleven studies were included. Figure 1 shows the flow diagram of the literature search and table 1 shows the characteristics of the included studies. The studies were all published in the last 25 years and comprised one randomised controlled trial (RCT) and ten observational studies. All studies adequately described at least 14 criteria of the STROBE and CONSORT quality checklists and were therefore judged to be of sufficient quality. The RCT compared the in-hospital mortality rates of two groups of critically ill AKI patients requiring hemodialysis, either treated with a cuprophane or a polyacrylonitrile hemodialyser membrane [22]. The ten observational studies evaluated mortality rates of critically ill patients treated with renal replacement therapy. Three studies were limited to a specific patient group: patients after cardiothoracic surgery, patients with diabetes and burn patients [23-25]. The ten observational studies differed both in AKI definition and time period studied. Four studies defined AKI by means of the Risk Injury Failure Loss End stage kidney disease (RIFLE) or Acute Kidney Injury Network (AKIN) criteria [23,26-28]. One study included only patients with a serum creatinine level > 600 μmol/l

or requiring dialysis, which comes down to AKIN stage 3 [29]. In the remaining five studies, AKI was defined by an increased serum creatinine, using different cutoff values [24,25,30-32]. Five studies mentioned comorbidities, with hypertension occurring in 29 to 71% of the patients and diabetes occurring in 15 to 100% [23,25-27,31]. Four observational studies investigated the outcome of patients treated within a time period of a year or less, whereas the other six studies reviewed the outcome of treatment over several years.

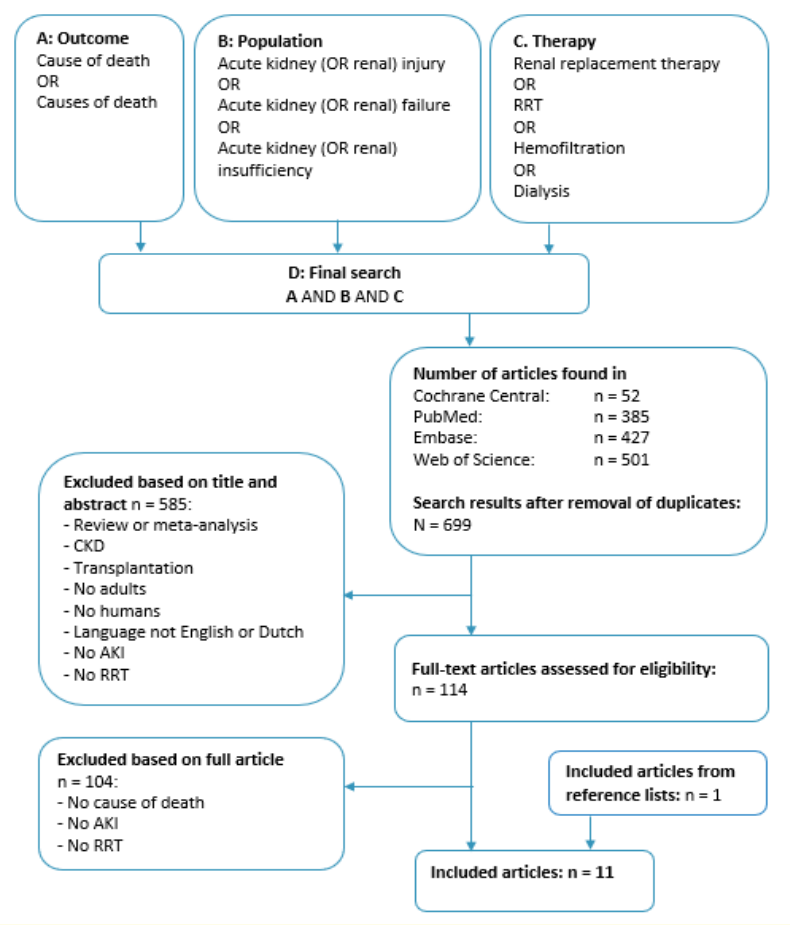

Figure 1: *Flow diagram of the literature search.*

AKI: Acute Kidney Injury; CKD: Chronic Kidney Disease; RRT: Renal Replacement Therapy.

Causes of AKI

Seven of the eleven included studies described the cause of AKI in terms of admission type: surgical or medical. Two studies analyzed only surgical patients [23,24] and one study analyzed only patients with diabetes [25]. Among three of the remaining eight studies, medical patients were most prevalent. Three studies listed ischemia as the main cause of AKI, ranging from 48 to 73% [27,30,31], whereas in three other studies sepsis was the main cause, ranging from 69 to 75% [23-25]. Overall, among the 1327 patients for whom a cause of AKI was listed, ischemia was most prevalent, followed by sepsis and nephrotoxic drugs.

Mortality

The definition of mortality differed among the included studies. In five studies, mortality was defined either as ICU mortality, mortality during acute illness or in-hospital mortality [24,26,28,29,32]. In three studies, the observed mortality was probably in-hospital mortality, although not explicitly defined as such [22,30,31]. Three studies used a fixed date to define mortality: Pereira, *et al.* measured mortality on May 31 2008 for patients included between January 2005 and January 2007, Khan, *et al*. measured mortality at the end of the study and Hobson, *et al*. determined survival by a one day search in 2006 [23,25,27].

Mortality related to kidney injury severity

Three of the eleven included studies used a disease severity score (APACHE II, Charlson index and Khan index) and five studies used a classification system to quantify AKI severity (either AKIN or RIFLE) (Table 2). The percentage patients treated with RRT ranged from 2.5 to 100% (Table 1). Among the studies with in-hospital mortality as an endpoint, the distribution of AKI severity was significantly different, with the percentage patients with AKIN 1 ranging from 19 to 62% and the percentage patients with AKIN 3 ranging from 17 to 100% (Table 2). Among the studies with mortality after hospital discharge as an endpoint, a similar difference in distribution was noticed, with the percentage patients with AKIN 1 ranging from 27 to 50% and the percentage patients with AKIN 3 ranging from 19 to 49% (Table 2). Both in-hospital mortality and mortality after hospital discharge were significantly higher among patients with AKIN stage 3 than among patients with AKIN stage 1 (40% vs 16% and 34 vs 16% respectively, $p < 0.00001$) (Table 2).

In hospital mortality

Authors	n	AKIN 1 n (%)	AKIN 2 n (%)	AKIN 3 n (%)	✚AKIN 1 n (%)	✚AKIN 2 n (%)	✚AKIN 3 n (%)	✚AKIN 1 vs 3
Selby	3930	2437 (62)	811 (21)	682 (17)	397 (16)	243 (30)	218 (32)	p < 0.0001
Cruz	234	45 (19)	82 (35)	107 (46)	9 (20)	24 (29)	52 (49)	p < 0.001
Woodrow	1458			1458 (100)			638 (44)	
Total	5622	2482 (44)	893 (16)	2247 (40)	406 (16)	267 (30)	906 (40)	p < 0.00001

Mortality after hospital discharge

Authors	n	AKNI I n (%)	AKIN 2 n (%)	AKIN 3 n (%)	✚AKIN 1 n (%)	✚AKIN 2 n (%)	✚AKIN 3 n (%)	✚AKIN I vs 3
Hobson	1265	637 (50)	386 (31)	242 (19)	73 (11)	71 (18)	83 (34)	p < 0.00001
Pereira	507	135 (27)	122 (24)	250 (49)	54 (40)	53 (43)	86 (34)	NS
Total	1772	772 (44)	508 (29)	492 (28)	127 (16)	124 (24)	169 (34)	p < 0.00001

Table 2: *Mortality according to AKI severity.*
AKI: Acute Kidney Injury; CoD: Cause of Death, ✚: *Mortality.*

Trends in mortality over time

Three single center studies analyzed trends in mortality among AKI patients with study periods ranging from 10 to 33 years [23,29,31]. A change in pattern of causes of death was demonstrated in the study by Woodrow and Turney, with an increase in cardiovascular abnormalities and withdrawal of therapy as causes of death [29]. The study by Hobson, *et al.* analyzed a cohort of patients discharged after cardiothoracic surgery between 1992 and 2002. Patients with AKI had a significantly worse long-term survival, with a 1 year survival of 89% and a 10 year survival of 44% compared to 1 and 10 year survivals of 95% and 63% respectively for patients without AKI [23].

Causes of death

Among the studies analyzing in-hospital mortality, the cause of death was documented in more than 90% of the cases, whereas the studies analyzing mortality after hospital discharge reported a cause of death in only 17% of the cases. In-hospital mortality ranged from 17 to 85% and mortality after hospital discharge from 38 to 81%. Among the studies analyzing in-hospital mortality, infection was the most frequently recorded cause of death, ranging from 35 to 81%, followed by cardiovascular causes, ranging from 8 to 32% (Table 3). Among the studies analyzing mortality after hospital discharge, cardiovascular causes of death were most frequently reported, ranging from 2 to 20%, whereas infection was reported as the cause of death in only 0.8%.

In-hospital mortality

Authors	Year	AKI, n	Deaths, n(%)	CoD documented, n(%)	Infection, n(%)	Cardiovascular, n(%)	Bleeding, n(%)
Schiffl, *et al.*	1995	76	39 (51)	39 (100)	27 (69)	7 (18)	5 (13)
Selby, *et al.*	2012	3930	859 (22)	802 (93)	353 (41)	165 (19)	9 (1)
Woodrow, *et al.*	1992	1458	753 (52)	636 (84)	270 (43)	168 (26)	27 (4)
Liano, *et al.*	1996	748	337 (45)	333 (99)	160 (47)	50 (15)	15 (4)
Druml, *et al.*	2014	243	148 (61)	148 (100)	55 (37)	47 (32)	13 (9)
Cruz, *et al.*	2007	234	85 (36)	45 (53)	30 (67)	11 (13)	4 (4)
Barretti, *et al.*	1997	200	93 (47)	93 (100)	35 (38)	17 (18)	7 (8)
Holm, *et al.*	1999	48	41 (85)	41 (100)	30 (73)	4 (10)	
Khan, *et al.*	2015	95	16 (17)	16 (100)	13 (81)		
Total		7032	2371 (34)	2153 (91)	973 (41)	469 (20)	80 (3)

Mortality after hospital discharge

Authors	Year	AKI, n	Deaths, n(%)	CoD documented, n(%)	Infection, n(%)	Cardiovascular, (%)	Neoplasm, n (%)
Hobson, *et al.*	2009	1265	1024 (81)	41 (4)	10 (1)	22 (2)	
Pereira, *et al.*	2012	507	193 (38)	164 (85)		47 (29)	33 (20)
Total		1772	1217 (69)	205 (17)	10 (0.8)	69 (6)	33 (3)

Table 3: *Causes of death among patients with AKI.*

AKI: Acute Kidney Injury; CoD: Cause of Death.

Factors influencing mortality

Seven studies analyzed factors influencing mortality, four of these using a regression model to calculate hazard ratios or odds ratios [23,26-28]. In all four studies the presence of AKI was associated with an increased hazard ratio for mortality, ranging from 1.38 for any type of AKI to 4.8 for AKI stage 3 [23,26]. Two studies found a relationship between age and mortality with hazard ratios ranging from 1.2 to 3.5 [23,28]. However, the other nine studies did not find such a relationship.

Discussion

In this systematic review, we analyzed the causes of death of patients with AKI treated with RRT. Among the 8804 patients included in the eleven analyzed studies, 3588 patients died (41%). Among the studies analyzing in hospital mortality, infection was the most fre-

quently occurring cause of death (40%), followed by cardiovascular causes (19%). Among the studies analyzing mortality after hospital discharge, cardiovascular causes were most frequently reported as the cause of death (5%), whereas infections were reported as the cause of death in only 0.8%. One of the two studies analyzing mortality after hospital discharge reported no infections as cause of death and the other study reported the cause of death in only 4% of the cases, which might have induced a bias. Nevertheless, our study suggests that infection is the main cause of in-hospital death of AKI-patients, whereas cardiovascular causes of death are more important after hospital discharge. However, the incidence of cardiovascular deaths among AKI-patients after hospital discharge was similar to the incidence in the general population.

AKI patients are prone to infections due to impaired cellular and humoral immunity [15-18]. In a large multicenter observational study among critically ill patients consulted for AKI, Mehta, *et al.* demonstrated that 40% of the patients developed sepsis a median of five days after AKI had occurred, whereas 28% had sepsis before AKI developed [33]. Mortality rates among these patient groups were 44 and 48% respectively. These data are compatible with our result that infection was the cause of in-hospital death in 40% of AKI patients.

In our study, the most important causes of death among AKI patients after hospital discharge were cardiovascular. However, the incidence of these cardiovascular deaths was similar to the incidence in the general population. Several authors have demonstrated that the risk of dying among ICU-patients remains increased after hospital discharge [34,35]. It has also been demonstrated that the cause of death of ICU-patients after hospital discharge is most frequently related to their cause of ICU-admission [36,37].

Our study confirmed that mortality among AKI-patients is related to AKI severity, with hazard ratios for mortality ranging from 1.38 for any type of AKI to 4.8 for AKI stage 3. This has previously been found by several other authors [3,38,39]. However, odds ratios for mortality varied greatly among the different studies according to the classification used and the adjustments made. Using patients without AKI as a reference, Hoste, *et al.* found a hazard ratio for mortality of 2.7 (95%CI 2.03 - 3.55) among patients with RIFLE failure as compared to patients without AKI [3]. After correction for age and APACHE II score, Levi, *et al*. found an odds ratio for mortality of 4.74 (95%CI 1.60 - 14.03) for patients with Kidney Disease Improving Global Outcomes (KDIGO) stage 3 as compared to patients without AKI [38]. Zeng, *et al.* found an odds ratio for mortality of 10.1 (95%CI 7.1 - 14.4) for patients with KDIGO stage 3 as compared to patients without AKI [39].

In recent years, much attention has been paid to fluid overload as a risk factor for mortality in patients with AKI. In several cohort studies, a correlation between oliguria, positive fluid balance and mortality among AKI patients was found [4,8-13]. In a recent meta-analysis, the odds ratio for mortality among AKI patients with fluid overload was 2.23 (95% CI 1.66 - 3.01) [40]. Fluid overload causes a higher central venous pressure, which may cause renal interstitial edema, leading to lower perfusion pressure in the kidneys, thus perpetuating AKI [41]. Moreover, fluid overload may lead to gut edema, facilitating the translocation of gut flora, which may lead to the development of sepsis and multiple organ failure [33]. The deleterious influence of fluid overload might explain why mortality is higher among patients needing renal replacement therapy [4,42,43]. A recent prospective study confirmed that patients with fluid overload at the start of renal replacement therapy had a significantly higher 60-day mortality [44]. However, the presence of fluid overload was not investigated in the studies included in this review.

Limitations of the Study

Our study has several limitations. First of all, the heterogeneity in terms of case mix was considerable among the included studies. In 84% of the included patients, AKI severity was classified, with percentages AKIN stage 3 patients ranging from 17 to 100% (Table 2). This heterogeneity is also reflected by the percentage of patients treated with RRT, ranging from 2.5 to 100% (Table 1). Moreover, in only 66% of the patients the cause of death was determined. Thereby, a systematic analysis was not possible. However, when only the studies that determined the cause of death in 100% of the included patients are taken into account, infection still accounted for 37% of the deaths, followed by cardiac causes, accounting for 20%.

Conclusion

This systematic review demonstrates that for AKI-patients treated with RRT, the most important cause of in-hospital death was infection. After hospital discharge however, the main cause of death among AKI-patients was cardiovascular, with an incidence similar to the incidence in the general population.

Disclosure Statement

The authors report no conflicts of interest.

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