Clinical Kidney Journal, 2020, vol. 13, no. 2, 133–141

doi: 10.1093/ckj/sfz158
Advance Access Publication Date: 18 November 2019
CKJ Review

CKJ REVIEW

Acute kidney injury and adverse outcomes of critical illness: correlation or causation?

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ABSTRACT

Critically ill patients who develop acute kidney injury (AKI) are more than twice as likely to die in hospital. However, it is not clear to what extent AKI is the cause of excess mortality, or merely a correlate of illness severity. The Bradford Hill criteria for causality (plausibility, temporality, magnitude, specificity, analogy, experiment & coherence, biological gradient and consistency) were applied to assess the extent to which AKI may be causative in adverse short-term outcomes of critical illness.

Plausible mechanisms exist to explain increased risk of death after AKI, both from direct pathophysiological effects of renal dysfunction and mechanisms of organ cross-talk in multiple-organ failure. The temporal relationship between increased mortality following AKI is consistent with its pathophysiology. AKI is associated with substantially increased mortality, an association that persists after accounting for known confounders. A biological gradient exists between increasing severity of AKI and increasing short-term mortality. This graded association shares similar features to the increased mortality observed in ARDS; an analogous condition with a multifactorial aetiology. Evidence for the outcomes of AKI from retrospective cohort studies and experimental animal models is coherent however both of these forms of evidence have intrinsic biases and shortcomings. The relationship between AKI and risk of death is maintained across a range of patient ages, comorbidities and underlying diagnoses.

In conclusion many features of the relationship between AKI and short-term mortality suggest causality. Prevention and mitigation of AKI and its complications are valid targets for studies seeking to improve short-term survival in critical care.

Keywords: AKI, critical care, epidemiology, outcomes, review

INTRODUCTION

In critically ill patients, AKI is common, affecting 26–67% of patients [1, 2], and is associated with poor patient outcomes including an approximate doubling of the risk of death in hospital [1, 3]. AKI survivors have poorer long-term outcomes including increased rates of death, development or progression of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) [3–5]. While long-term outcomes are of great importance, this review principally focuses on the well-studied association between the development of AKI and increased hospital mortality. Despite higher mortality rates, patients with AKI on average have more severe underlying illness, suggesting that the poor outcomes associated with AKI could simply be the consequence of selecting a sicker patient population [6, 7]. There is currently no clear

Received: 20.12.2018. Editorial decision: 7.10.2019

consensus to what extent the link between AKI and adverse outcomes is one of correlation or causation. This review uses the Bradford Hill criteria for causality as a framework to address this question.

MATERIALS AND METHODS

A background literature review was performed using PubMed (US National Library of Medicine) and the Web of Science (Clarivate Analytics) databases to examine the relevant evidence on the epidemiology of AKI in intensive care unit (ICU) populations. Publications prior to 2004 were excluded, as no standard diagnostic criteria for AKI existed before this date [8]. Publications included at each stage of the review are described in the relevant sections.

The Bradford Hill criteria describe a number of general features that characterize a causal relationship between an exposure and an outcome [9]. The literature was examined and applied to each criterion in turn to assess how far the association between AKI and adverse outcomes meets the grounds for causality. In order to assess the magnitude and specificity of the association, we used a random effects model to estimate weighted averages of the odds ratio (OR) or should read hazard ratio (HR) from each study.

The Bradford Hill criteria specified for the relationship between AKI and mortality include the following:

1. Plausibility: is there an accepted mechanism by which AKI could cause death?
2. Temporality: is the time frame between AKI and death consistent with the proposed mechanism?
3. Analogy: are there any similar exposure–outcome relationships that are comparable?
4. Magnitude: how large is the difference in mortality between AKI and non-AKI populations?
5. Specificity: does the association persist when other possible explanatory factors are excluded?
6. Coherence and experiment: is the proposed mechanism supported both by laboratory and experimental evidence?
7. Biological gradient: does mortality increase with increasing AKI severity?
8. Consistency: is the association reproducible across different patient populations?

RESULTS

Plausibility: are there accepted mechanisms by which AKI could cause death?

Before considering the complications of AKI, it is important to bear in mind the heterogeneity of the condition. In the critical care setting, most AKI arises from renal injuries linked to ischaemia, inflammation or toxaemia from by a broad range of aetiologies. Animal studies have observed drastically different genetic transcription patterns in renal cells affected by AKI caused by ischaemia–reperfusion compared with AKI caused by extracellular fluid depletion [10, 11]. This points to variation in the nature of AKI at a genetic, molecular and cellular level that may reasonably be expected to be paralleled by varying clinical phenotypes, limiting the scope of any general conclusions.

Fluid overload and direct physiological consequences of AKI. The three physiological hallmarks of severe AKI include hyperkalaemia, metabolic acidosis and fluid overload. Together they are suggested to account for between 33% and 70% of the excess mortality attributed to AKI during critical illness [19]. Hyperkalaemia and metabolic acidosis occur when glomerular and tubular mechanisms in the excretion of organic acids and metabolites are severely compromised. These metabolic abnormalities are synergistic both in their kinetic and dynamic properties, increasing the risk of arrhythmias and reducing cardiac contractility. While the use of such abnormalities can be readily corrected through renal replacement therapy (RRT), such supportive therapy only corrects the consequences of AKI, not the underlying pathology.

A significantly reduced glomerular filtration rate in severe AKI leads to oliguria or anuria and consequently to fluid overload. Pulmonary oedema is often reported as a cause of death in AKI patients, and the SOAP study, among others, observed that patients who died of AKI had significantly more positive fluid balance than survivors [15–17, 20]. Positive fluid balance remained an independent predictor of mortality even after correcting for comorbidity and disease severity [17, 21]. However, fluid accumulation is not only the result of AKI but also resuscitation or damage to other organ systems. In addition, fluid accumulation can itself lead to or worsen AKI via interstitial oedema, increased venous congestion and reduced renal blood flow [22]. Therefore the relationship between AKI and fluid overload is multidirectional.

RRT. Mortality in patients with the severest forms of AKI requiring RRT is high. Although lifesaving for some patients, RRT does not reverse the negative impact of AKI [23] and itself has been shown to be an independent risk factor for mortality [24]. However, these observations are likely to be confounded, as only the sickest patients receive RRT. A recent multicentre randomized controlled trial investigating the optimum timing of RRT in patients with severe AKI and sepsis showed that a 'watch and wait' approach resulted in less use of RRT and did not increase mortality [25]. Observational findings have shown that even in patients receiving RRT, there remains an independent negative impact of positive fluid balance on patient outcomes [26, 27]. Furthermore, although greater fluid overload is associated with increased mortality, higher net ultrafiltration rates to resolve fluid overload have also been correlated with adverse outcomes, indicating that once fluid overload has occurred in AKI, measures to rapidly resolve it with RRT may themselves be harmful [28]. Overall, distilling the impact of RRT on mortality is complex. The fact that RRT can manage electrolyte fluctuations, acid–base disturbance and fluid balance but does not eliminate excess mortality suggests that other mechanisms contribute to mortality in AKI.

Organ crosstalk and cardiovascular risk. AKI has been shown to have widespread deleterious effects on the cardiovascular, respiratory and neurological systems. This is an example of the 'organ crosstalk' concept, through which a kidney insult may trigger changes in distant systems [29]. AKI results in increased risk of acute lung injury, inflammation of the brain with disruption of the blood–brain barrier and cardiac impairment [30–32]. The mechanism by which signals are mediated between the afflicted kidney and distant organ sites is likely to be multifactorial, with cellular, molecular, immunological and epigenetic components [29].

While CKD is a well-established risk factor for cardiovascular disease [33, 34], less is known about the cardiovascular risk attributable to AKI. AKI has been found to worsen cardiovascular outcomes in those with existing cardiac disease, resulting in increased rates of heart failure and major adverse cardiac events (MACEs) [35, 36]. Where *de novo* cardiac events are concerned, AKI was observed to increase the risk of acute coronary events over the medium to long term by ~50%, but there is limited evidence about the risk of MACE in the context of acute AKI [37–39].

Multiple mechanisms have been suggested for this association. For patients who require RRT, the phenomenon of 'myocardial stunning' may play a role. In a study of AKI treated with intermittent haemodialysis, all patients developed new regional wall motion abnormalities and reduced left ventricular contractility during dialysis with evidence of myocardial ischaemia [40]. Mouse models have demonstrated apoptosis of cardiac myocytes during AKI with simultaneous reduced cardiac output [41]. The inflammatory state of AKI is also known to alter the circulating cytokine profile, which is in turn hypothesized to directly damage cardiac myocytes [42, 58].

The link between AKI and cardiovascular risk is confounded by high levels of comorbidity in AKI patients, known to have significantly higher rates of pre-existing heart failure, hypertension and diabetes [23]. While this could account for some of the outcomes observed, it cannot account for the real-time cardiac impairment described in the preceding literature.

Susceptibility to infection. Critically ill patients with AKI have been found to have approximately double the incidence of infection than those without AKI [43]. These infections are not trivial: in one large study, patients with AKI requiring RRT were more than twice as likely to develop severe sepsis [44]. This risk diminished with time but persisted even after resolution of the AKI [44].

The mechanism by which AKI increases the rate of infection is likely multifactorial. First, as a systemic inflammatory state, AKI may have a directly immunosuppressive effect through increased concentrations of circulating cytokines as well as impaired cell-mediated immunity, acting through key molecular mediators such as resistin [45–47]. Second, AKI is associated with increased length of stay (LOS), both in hospital and the ICU, which would be expected to increase the risk of infection [23, 48]. Even small increases in serum creatinine have been found to cause a statistically significant increase in LOS, and the magnitude of creatinine increase correlates with LOS [49]. RRT is a further complicating factor due to the presence of indwelling lines and devices resulting in an increased risk of nosocomial infection [50].

Despite the increased prevalence of infection, the clinical significance of the infection burden in AKI patients has been called into question by Bernier-Jean *et al.* [43] and Hoste *et al.* [50], both of whom observed no excess mortality attributable to the increased rate of infection.

Temporality: is the time course of short-term mortality consistent with hypothesized AKI pathophysiology?

The exact time frame used to define short-term mortality is generally taken as the duration of hospital or ICU admission. The mechanisms discussed above offer a plausible explanation for mortality on this timescale. Hyperkalaemia, acidosis and fluid overload are all acute complications with the capacity to cause death within hours or days. Other mechanisms, including systemic inflammation, infection, MACEs and organ crosstalk, appear to act over a more varied timescale and persist after recovery from critical illness. This makes their relationship with acute mortality more difficult to discern but does not necessarily detract from their clinical significance during an AKI episode.

Evidence is mounting that AKI is also a predisposing factor for the development of CKD and ESKD, contradicting the historical view of AKI as a wholly reversible condition [5, 51]. While tubules do have the capacity to regenerate following an initial insult, allowing measured renal function to apparently return to baseline, animal models reveal that the kidney often develops tubulointerstitial fibrosis after AKI, resulting in chronically impaired renal function [13, 52]. Overall, the pathophysiology of AKI is sufficiently heterogeneous to account for morbidity and mortality on a wide range of timescales.

Analogy: comparison between AKI and acute respiratory distress syndrome

Bradford Hill argued that the weight of evidence for a causal relationship between an exposure and outcome may be increased by an analogy to a similar exposure with a known causal association to a similar outcome [53]. Acute respiratory distress syndrome (ARDS) provides a model of clinical syndrome arising from an initial single-organ insult that results in distant organ damage and dysfunction, with an associated increase in mortality, much like AKI.

There are a number of similarities in the nature of the two diseases: the cause of AKI is often multifactorial and similarly ARDS has a range of causes, both pulmonary and extrapulmonary [54]. The subsequent impact on lung function often results in patients requiring mechanical ventilation as a supportive measure. The lack of any specific interventional treatments for ARDS reflects the complexity of the underlying pathophysiology, a problem also encountered in AKI. As more is discovered about both ARDS and AKI, researchers are uncovering distinct subtypes of each syndrome, each with unique characteristics and potentially distinct treatment targets [14, 55].

The diagnosis of ARDS, like AKI, is associated with worse short- and long-term outcomes. Short-term mortality has been found to vary widely between epidemiological studies, from 15% to 72%, and has decreased over time [56]. ICU-specific mortality has been estimated at 38% [57]. However, cause of death is most often ascribed either to the cause of or complications of ARDS rather than the lung injury itself [58]. Therefore, like AKI, there is no clear consensus on the degree to which ARDS directly causes mortality. This is likely to reflect the pathophysiology of multiorgan failure, where several organ injuries, including AKI and ARDS, combine to mediate the risk of death.

The impact on long-term morbidity has also been prospectively characterized for ARDS survivors, demonstrating significantly poorer overall health than predicted, up to 5 years after discharge from ICU [59]. The results of prospective studies are still pending for AKI in the ICU, but there is a large body of retrospective evidence linking AKI with worse longer-term outcomes [60]. The current lack of understanding of the pathophysiology of both ARDS and AKI limits further comparison, and a deeper understanding of the model of organ crosstalk is required to fully assess their similarities and differences.

Magnitude and specificity: how strong is the association between AKI and short-term mortality?

Table 1 compares studies examining short-term mortality for critically ill patients with and without AKI. Acute mortality was consistently higher in AKI patients (13.3–58.0%) than in those without

Table 1. Short-term mortality in ICU populations for those with and without AKI

Study	Patient group	Cohort size, *n*	AKI incidence (%)	Mortality (no AKI) (%)	Mortality (AKI) (%)	Adjusted OR/HR (95% CI)[a]	P-value*
Hoste *et al.* [64]	ICU	5383	67.2	5.5	13.3	–	–
Mandelbaum *et al.* [3]	ICU	14 524	57.0	6.7	16.0	–	–
Nisula *et al.* [65]	ICU	2907	39.3	10.2	25.6	–	–
Barrantes *et al.* [2]	ICU	471	25.5	16.4	45.8	3.7 (2.2–6.1)	–
Harris *et al.* [66]	Surgical ICU	624	47.0	4.0	19.0	1.08 (1.03–1.14)	0.003
Masewu *et al.* [67]	ICU	476	52.7	28.0	58.0	**1.82 (1.34–2.48)**	<0.001
Reddy *et al.* [68]	ICU	250	45.9	3.1	23.4	5.96 (1.9–18.6)	<0.002
Ralib and Nor [69]	ICU	143	65.0	10.0	30.1	**2.61 (1.06–6.42)**	0.001

CI, confidence interval. [a]Adjusted HR denoted by bold values.
*P-values refer to the adjusted OR/HR.

AKI (5.5–28.0%). It should be noted that the diagnostic criteria vary, but all studies used the closely related Risk, Injury, Failure, Loss, End-stage kidney disease (RIFLE), Acute Kidney Injury Network (AKIN) or Kidney Disease: Improving Global Outcomes (KDIGO) classifications [61, 62]. The incidence of AKI, defined as any AKI diagnosed during ICU admission, showed marked variability, ranging from 25.5% to 67.2%. This is consistent with other sources that reported rates between 5.7% and 67.2% [63].

However, these crude data alone are insufficient to quantify the magnitude of the association between AKI and the risk of death. As these are mostly retrospective cohort studies, the exposed (AKI) and unexposed (no AKI) populations were not matched at the time of candidate selection, introducing the possibility of confounding. In order to evaluate the specific impact of AKI on mortality and its statistical significance, this bias can be decreased by statistical correction for known confounders. Two main statistical methods have been used in the literature for this purpose: Cox proportional hazards regression analysis of time to event data and multivariate logistic regression analysis of survival at a specific time point. Variables adjusted for in observational AKI studies commonly include age, gender, comorbidity and critical illness severity scoring. These analyses provide adjusted ORs/HRs that can be compared between studies.

Using these metrics, the studies in Table 1 reported a relative increase in short-term risk of death (ORs or HRs) of between 1.08 and 5.96. The adjusted OR/HR is presented as a forest plot in Figure 1. These magnitudes were all statistically significant after adjusting for confounders ($P \leq 0.003$ for all studies), although reported confidence intervals were generally broad. These magnitudes are also highly clinically significant, although the variation in magnitude is striking.

Using a random effects model, we combined these results to calculate the weighted mean. This model estimated a 2.3-fold increase in the risk of death attributable to AKI, which was statistically significant. Even the lower bound on this estimate suggests a 30% increased risk of death, a highly important clinical finding for such a common condition.

It is relevant at this stage to consider the interaction between AKI and illness severity. As stated at the outset, many see the relationship between AKI and adverse outcomes as a corollary of the correlation between AKI and illness severity. Many of the included studies explored this relationship. Where the relevant analysis was included, authors consistently observed that AKI was associated with higher illness severity, as quantified by scores such as the Acute Physiology and Chronic Health Evaluation (APACHE) or the Simplified Acute Physiology Score (SAPS) II [2, 68, 69]. However, after multivariate analysis to correct for this, the relationship between AKI and mortality persisted and was consistently greater than the association between illness severity and mortality. Barrantes *et al.* [2] used a modified version of the APACHE to remove the contribution of renal function to the APACHE score. After multivariate logistic regression, AKI was again significantly associated with mortality, but the modified APACHE score was not. These findings confirm that the relationship between AKI and mortality is not explained by illness severity alone and support the case for an intrinsic link between AKI and adverse outcomes.

There are limitations to this evidence. Only a small number of studies have reported adjusted models for the association between AKI and risk of death in the ICU, with relatively modest sample sizes. In addition, there was significant heterogeneity between study designs, with differing analyses and survival time frames. Despite these limitations, the weight of evidence suggests that after correcting for confounding factors, AKI is strongly associated with a large, clinically important and statistically significant increase in mortality.

Experiment and coherence: is the relationship between AKI and adverse outcomes supported by experimental evidence?

Two main types of research provide the bulk of the evidence for assessing outcomes of AKI. First is epidemiological data arising primarily from retrospective cohort studies [65]. These may be weakened by selection bias, limited clinical detail and confounding due to the absence of a matched control group, making it more difficult to infer causality. Second, insights into the pathophysiology and complications of AKI are based almost exclusively on animal models, which provide limited comparisons to the human system.

Earlier in this review, mechanisms were discussed by which AKI may increase mortality, namely metabolic disturbance, fluid overload, organ crosstalk, cardiovascular risk and susceptibility to infection. If these truly mediate the link between AKI and death, then counteracting their effect should lead to a reduction in mortality.

To test the impact of reducing fluid overload in AKI, the Conservative vs. Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care trial randomized patients with septic shock to receive fluid according to either standard guidelines or a restrictive fluid management protocol [71]. In the latter group, AKI was significantly less likely to worsen, and mortality was lower, although the trial was not powered to identify significant mortality differences between the groups. Multicentre studies are under way to verify these preliminary findings. Conversely,

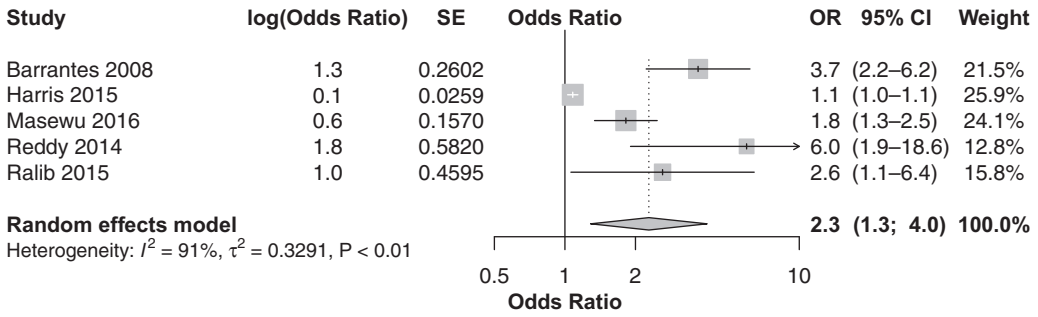

FIGURE 1: Short-term mortality in patients with AKI, relative to those without, adjusted for confounders. Factors adjusted for include the following. Barrantes *et al.* [2]: not specified—selected from univariate analysis; Harris *et al.* [66]: ethnicity, CKD, APACHE score, sepsis, mechanical ventilation, liver failure; Masewu *et al.* [67]: organ systems affected, oxygen saturations, tachypnoea; Reddy *et al.* [68]: age, APACHE score, admission creatinine, sepsis, RRT; Ralib and Nor [69]: age and Sequential Organ Failure Assessment score.

in the elective perioperative setting, conservative fluid management aimed at preventing fluid overload has been associated with increased risk of post-operative AKI, illustrating the complexity of the relationship between fluid status and AKI [72]. As discussed in the 'Plausibility: are there accepted mechanisms by which AKI could cause death?' section, in patients with the severest form of AKI requiring RRT, observational studies have suggested a harmful effect of fluid overload [16, 26–28, 73].

To probe the effect of cardiovascular risk reduction after AKI, investigators have explored the effect of statins on patient outcomes. Wu *et al.*'s [74] large cohort study of dialysis-requiring AKI patients observed that statin use was associated with significantly reduced mortality both during hospital admission and at the 1-year follow-up. In a population with AKI-on-CKD, statin use after AKI was associated with a significant reduction in mortality and readmission [75]. Surprisingly, the authors did not observe a significant reduction in the rate of cardiovascular events in the same time period, pointing to an alternative mechanism of mortality benefit [75].

Biological gradient: do adverse outcomes increase with increasing AKI severity?

A biological gradient is a relationship between the severity of an exposure and the magnitude of its outcome, akin to a pharmacological 'dose–response' phenomenon. This is convenient to study in AKI, as the diagnostic criteria include staged measures of severity.

Short-term mortality increases with increasing severity of AKI. Data from several studies describing short-term mortality stratified by AKI severity are demonstrated in Table 2 and Figure 2. As in Figure 1, studies have been included that corrected for confounding factors and therefore express mortality as adjusted ORs. Again, a random effects model has been used to calculate the weighted mean for mortality at each stage of AKI.

Unlike those studies examining adjusted risk of hospital mortality in AKI (Figure 1), studies examining AKI severity had larger sample sizes (1032–325 395) and a number were prospective. The pooled data clearly demonstrate an increase in mortality, with adjusted ORs of 1.5, 2.4 and 4.1 for Stages 1–3, respectively, although the confidence intervals do overlap between stages. The pooled data were weighted heavily by Thakar *et al.* [76], in a large study consisting of >300 000 patients. If this study is excluded, then mortality is still seen to increase with each stage of AKI, albeit with smaller ORs of 1.2, 1.7 and 2.9 for Stages 1–3, respectively.

Despite the biological gradient, there are exceptions. A possible explanation for the different trends seen between studies is that the definition of AKI Stage 2 is narrow, incorporating a relatively small range of serum creatinine values, making it more susceptible to outliers [3]. In addition, higher stages of AKI may have competing endpoints with mortality, such that a patient who dies with low-stage AKI is unable to progress to a higher stage. This may result in underestimation of the mortality associated with higher stages of AKI unless competing risks are considered in the analysis [77]. In one study, while the biological gradient is present, only severe (Stage 3) AKI was significantly associated with mortality [78]. This may suggest that while severe AKI is causative of mortality, less severe AKI is merely associated with the risk of death.

Overall, these data support the existence of the biological gradient between AKI severity and mortality with some variability that may be implicit in the AKI definition.

The presence of a biological gradient arising from the epidemiological data suggests that early diagnosis of AKI and prevention of progression should improve outcomes. Much research is under way to explore the role of urinary biomarkers in the early diagnosis of AKI, with promising results [79, 80]. Electronic alert systems are in use with the aim of expediting AKI detection and treatment, but such systems (including the Streams application; DeepMind Technology, London, UK [81]) have thus far failed to demonstrate significant improvements in clinical outcomes [82, 83]. A related software system was able to predict more than half of all AKI episodes and >90% of severe AKI requiring dialysis, although with a high false-positive rate [84]. AKI care bundles offer more promise. In two separate studies, Kolhe *et al.* [85, 86] observed that patients who had an AKI care bundle completed within 24 h of diagnosis had significantly reduced risk of death and progression of AKI. Further work is required to establish whether the improved outcomes result from preventing AKI progression or preventing physiological complications.

Consistency: is the association between AKI and mortality reproducible in different populations?

AKI has been found to be an independent risk factor for mortality among diverse patient groups, including general hospital inpatients, medical patients and surgical patients undergoing lung transplant, liver transplant and general or cardiothoracic surgery [49, 88–93]. Another measure of consistency is uniformity across a range of age groups, including the extremes of age. AKI independently increased mortality and LOS in paediatric ICU patients and children undergoing

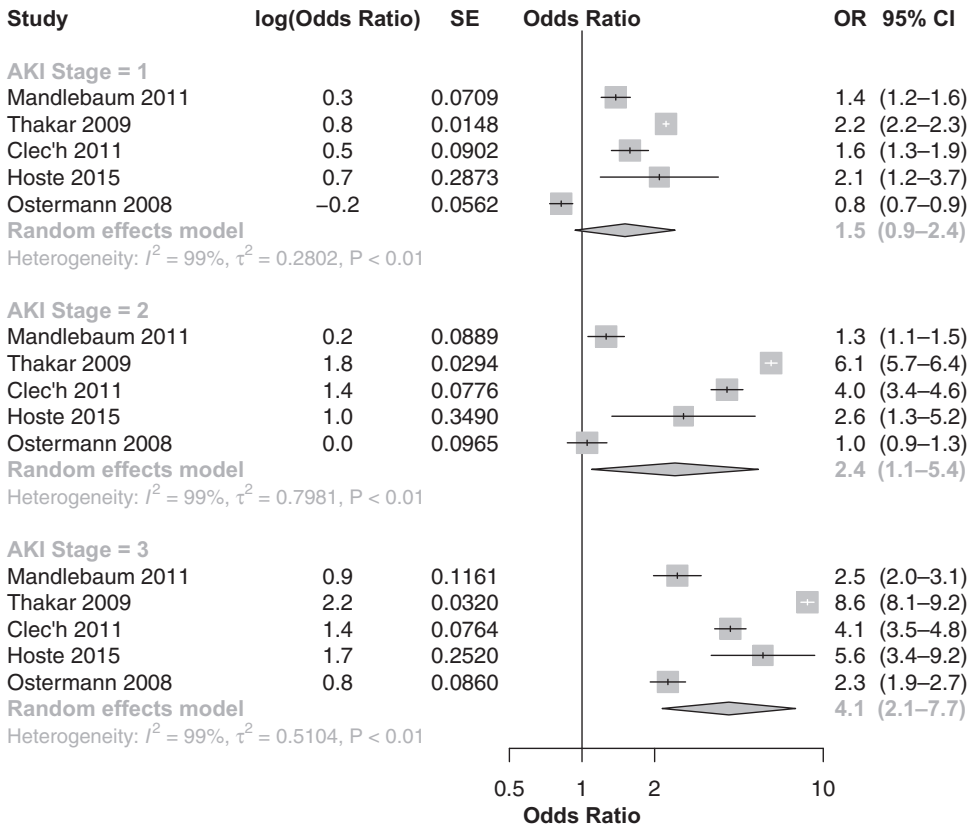

FIGURE 2: Forest plot demonstrating the relationship between AKI stage and short-term mortality. Stages 1–3 equate to AKIN/KDIGO 1, 2, 3 and RIFLE, respectively. ORs relate to comparison between the relevant stage of AKI and no-AKI after adjusting for confounders. Factors adjusted for include the following: Mandelbaum *et al.* [3]: age, non-renal SOFA score, comorbidity; Thakar *et al.* [76]: age, comorbidity, admission diagnosis, source of admission, 11 laboratory test results; Clec'h *et al.* [77]: non-renal SOFA score, McCabe class, admission source, organ failure; Hoste *et al.* [23]: admission source, serum creatinine on admission to ICU and non-specified 'fixed predictors'; Ostermann *et al.* [78]: age, SOFA score, number of organ failures, gender, chronic illness, mechanical ventilation, AKI categories, RRT and anaemia. SOFA, Sequential Organ Failure Assessment.

Table 2. Short-term mortality in patients with AKI stratified according to AKI severity

Study	Patient group	Severity score	Cohort size	Adjusted OR for mortality (95% CI)[a] Stage 1	Stage 2	Stage 3
Mandelbaum *et al.* [3]	ICU	AKIN	14 524	1.38 (1.2–1.59)	1.26 (1.05–1.50)	2.5 (1.98–3.12)
Thakar *et al.* [76]	ICU	Non-standard	325 359	2.23 (2.17–2.30)	6.08 (5.74–6.44)	8.60 (8.07–9.15)
Clec'h *et al.* [77]	ICU	RIFLE	8639	1.58 (1.32–1.88)	3.99 (3.43–4.65)	4.12 (3.55–4.79)
Hoste *et al.* [23]	ICU	KDIGO	1802	2.09 (1.19–3.67)	2.64 (1.33–5.22)	5.63 (3.43–9.22)
Ostermann *et al.* [78]	ICU	RIFLE	22 303	0.82 (0.73–0.91)	1.05 (0.87–1.27)	2.27 (1.92–2.69)
Weighted mean	–	–	–	**2.09**	**5.53**	**7.87**

[a]Stages 1–3 equate to AKIN/KDIGO 1, 2, 3 and RIFLE, respectively.

cardiac surgery [94–97]. Among the elderly population, only limited data are available, as most studies remove the effect of age as a potential confounder. From the few studies that do report data on the geriatric population, short-term mortality appears to be higher in those with AKI [99]. However, at least one study found no difference in outcome between the 'risk' and 'injury' groups when RIFLE criteria were used [98, 99]. This suggests that either the effect on mortality in this population is smaller or that the diagnostic criteria are less valid, possibly due to the physiological changes of ageing and increased burden of comorbidities. In our entire literature search, we did not identify any studies that reported no association between AKI and mortality.

DISCUSSION

Starting from the well-established finding that AKI is crudely associated with increased mortality, we applied the Bradford Hill criteria to test the strength of evidence and determine whether this association is causal.

AKI has a complex and heterogeneous pathophysiology with the potential to cause multiple systemic complications. The disease processes implicated in AKI provide plausible mechanisms by which it could directly increase short-term mortality, notably metabolic disturbance, fluid overload, infection risk and distant organ impairment. AKI was compared with the analogous system of ARDS, which provides a precedent for single-organ

dysfunction causing multisystem complications and adverse outcomes. Reviewing the epidemiological data in more detail, it was found that after correction for confounding factors, AKI specifically increases mortality with a magnitude that is both clinically and statistically significant. By grouping AKI patients according to severity (Stages 1–3), a biological gradient emerges from the data with mortality increasing with disease severity. The association has been consistently demonstrated across a broad spectrum of patient types, disease groups and age ranges.

There are a number of limitations to this review. Despite the quantitative treatment of certain aspects of the discussion, this is neither a systematic review nor a meta-analysis and our coverage of the literature is incomplete. Second, the Bradford Hill criteria, although well established, are just one of the many empirical approaches to establishing causality. The criteria were originally applied to the association between occupational or environmental exposures and disease, rather than disease and mortality as in this setting. Finally, the long-term complications of AKI, including mortality, CKD, ESKD and cardiovascular disease, which are of great clinical significance, have not been discussed in detail.

Based on our findings, it seems extremely likely that AKI is a direct contributing factor to mortality in the proportion of patients, but the heterogeneity of the condition and the variability of its causes and consequences mean that this conclusion cannot be drawn definitively for all.

Future work should focus on the prevention and mitigation of the complications of AKI that contribute to mortality. Areas of study should include practical interventions to reduce LOS, molecular treatments targeting the immunosuppressive and organ crosstalk pathways implicated in AKI, quantification and reduction of acute risk of MACEs during AKI, cardiovascular risk reduction after AKI and optimization of fluid balance through RRT, conservative and medical strategies.

CONFLICT OF INTEREST STATEMENT

None declared. This work has not previously been published in whole or in part.

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