# The RIFLE criteria and mortality in acute kidney injury: A systematic review

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**In 2004, the Acute Dialysis Quality Initiative workgroup proposed a multilevel classification system for acute kidney injury (AKI) identified by the acronym RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease). Several studies have been published aiming to validate and apply it in clinical practice, verifying whether outcome progressively worsened with the severity of AKI. A literature search from August 2004 to June 2007 was conducted: 24 studies in which the RIFLE classification was used to define AKI were identified. In 13 studies, patient-level data on mortality were available for Risk, Injury, and Failure patients, as well as those without AKI (non-AKI). Death was reported at ICU discharge, hospital discharge, 28, 30, 60, and 90 days. The pooled estimate of relative risk (RR) for mortality for patients with R, I, or F levels compared with non-AKI patients were analyzed. Over 71 000 patients were included in the analysis of published reports. With respect to non-AKI, there appeared to be a stepwise increase in RR for death going from Risk (RR = 2.40) to Injury (RR = 4.15) to Failure (6.37, $P < 0.0001$ for all). There was significant intertrial heterogeneity as expected with the varying patient populations studied. The RIFLE classification is a simple, readily available clinical tool to classify AKI in different populations. It seems to be a good outcome predictor, with a progressive increase in mortality with worsening RIFLE class. It also suggests that even mild degrees of kidney dysfunction may have a negative impact on outcome. Further refinement of RIFLE nomenclature and classification is ongoing.**

*Kidney International* (2008) **73,** 538–546; doi:10.1038/sj.ki.5002743; published online 26 December 2007

KEYWORDS: acute renal failure definition; epidemiology; outcome; RIFLE criteria

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**Received 12 December 2006; revised 22 September 2007; accepted 9 October 2007; published online 26 December 2007**

Despite several advances in our treatment and understanding of the pathogenesis of acute kidney injury (AKI), many aspects in this field remain subject to controversy, confusion, and lack of consensus. One of these important aspects is the definition of AKI; in fact, it can neither be proven nor denied that someone has AKI unless one agrees ahead of time on what the term means, as this syndrome is mostly an artificial concept. The scientific community needs a clear consensus definition to describe and to understand epidemiology, to randomize patients in controlled trials, to test therapies in similar groups of patients, to develop animal models, and to validate diagnostic tests. To make consensus-based recommendations and delineate key questions for future studies, the Acute Dialysis Quality Initiative (ADQI) workgroup identified a definition/classification system for AKI.[1] The workgroup considered that the definition of AKI necessarily required the following features: ease of use and clinical applicability across different centers; sensitivity and specificity for different populations and research questions; consideration of creatinine change from baseline; and implementation of classifications for acute on chronic renal disease. A classification system should therefore include and distinguish between mild or severe, and early or late cases. This would allow such a classification to detect patients in whom renal function is mildly affected (high sensitivity for the detection of kidney malfunction but limited specificity for its presence) and patients in whom renal function is markedly affected (high specificity for true renal dysfunction but limited sensitivity in picking up early and more subtle loss of function). Accordingly, a multilevel classification system was proposed, in which the complete spectrum of acute renal dysfunction could be included, such as Risk of renal dysfunction, Injury to the kidney, Failure or Loss of kidney function, and End-stage kidney disease; these criteria (Figure 1) are identified by the acronym RIFLE. Of course, if patients are admitted with AKI without any baseline measure of renal function, a theoretical baseline serum creatinine value for a given patient assuming a normal glomerular filtration rate (GFR) should be estimated. By normalizing the GFR to the body surface area, and assuming a GFR of approximately 75–100 $ml\,min^{-1}$ per 1.73 $m^2$, the simplified 'modification of diet in renal disease' formula was selected by the workgroup to provide an estimate of GFR relative to

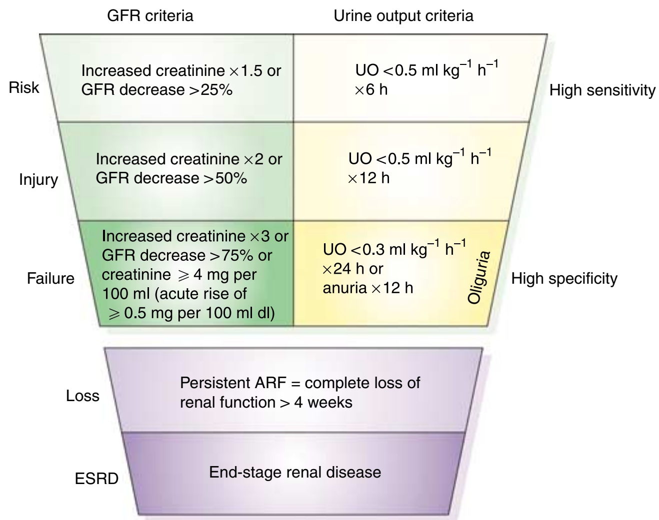


**Figure 1 | The RIFLE classification separates criteria for serum creatinine and urine output (UO).** The criteria that lead to the worst possible classification should be used. RIFLE-F is present even if the increase in serum creatinine is below threefold, as long as the new serum creatinine is 4.0 mg per 100 ml or above in the setting of an acute increase of at least 0.5 mg per 100 ml. The shape of the figure denotes the fact that more patients (high sensitivity) will be included in the mild category, including some without actually having renal failure (less specificity). In contrast, at the bottom, the criteria are strict and therefore specific, but some patients will be missed. GFR, glomerular filtration rate; ARF, acute renal failure. From Bellomo *et al.*[1]

serum creatinine based on age, race, and sex: estimated $\text{GFR} = 75\ (\text{ml min}^{-1}\ \text{per}\ 1.73\,\text{m}^2) = 186 \times (\text{serum creatinine (SCr)}) - 1.154 \times (\text{age}) - 0.0203 \times (0.742\ \text{if female}) \times (1.210\ \text{if black})$.[2]

After the proposal by the ADQI workgroup in 2004, 24 studies were published[3–26] (Table 1) with the aim to validate this classification or apply it in clinical practice. Most of these studies evaluated mortality of critically ill patients with AKI in patients in the first three levels (Risk (R), Injury (I), and Failure (F)) of disease severity. Some authors also wished to verify the degree of sensitivity and specificity of this classification and compared RIFLE criteria to more commonly used severity of illness scores. The aim of this literature search was to summarize the clinical literature on AKI as defined by the RIFLE criteria. A general discussion about the more important studies is also presented.

## RESULTS

More than 71 000 patients were included in the analysis of published reports. Among the 13 studies in which patient level data on mortality were available for patients without AKI (non-AKI),[3–15] mortality was 6.9% in non-AKI patients and 31.2% in AKI patients. Mortality was 18.9, 36.1, and 46.5% in class Risk, Injury, and Failure, respectively. With respect to non-AKI patients, there appeared to be a stepwise increase in relative risk (RR) for death going from Risk to Failure: Risk (RR = 2.40), Injury (RR = 4.15), and Failure (RR = 6.15) (Table 2; Figure 2). The comparison between RR for mortality of patients in different RIFLE classes in different studies is shown in Table 2. Although there was significant heterogeneity among the studies as estimated by $\chi^2$-test, as expected with the diverse populations studied, the results were qualitatively similar for most of them. In general, the stepwise relationship was seen in different types of patients, with the notable exception of the two studies in which only AKI patients requiring renal replacement therapy (RRT) were evaluated.[16,17] The negative effect of AKI on mortality appeared to be most pronounced among cardiac surgery patients; however, the confidence intervals were quite wide (Table 2). Among the included studies, the urine output criteria for RIFLE were either not used,[8,14,15,19] or its use was not specified.[7,13] Among the studies conducted in general medical intensive care units (ICUs), the RR for death appeared to be higher when only the creatinine criteria were used (Table 2).

## DISCUSSION

Acute kidney injury is a complex disorder that occurs in a variety of settings with clinical manifestations ranging from a minimal elevation in serum creatinine to anuric renal failure.[27,28] It is often under recognized and it is associated with severe consequences. Recent epidemiological studies demonstrate the wide variation in etiologies and risk factors, describe the increased mortality associated with this disease (particularly, when dialysis is required),[29–31] and suggest a relationship to the subsequent development of chronic kidney disease and progression to dialysis dependency.[32] Emerging evidence suggests that even minor changes in serum creatinine are associated with increased inpatient mortality.[33] AKI has been the focus of extensive clinical and basic research efforts over the last decades. The lack of a universally recognized definition of AKI has posed a significant limitation. Despite the significant progress made in understanding the biology and mechanism of AKI in animal models, translation of this knowledge into improved management and outcomes for patients has been limited. Recently, ADQI group and representatives from three nephrology societies (ASN, ISN, and NKF) and the European Society of Intensive Care Medicine, proposed the term AKI to reflect the entire spectrum of acute renal dysfunction, recognizing that an acute decline in kidney function is often secondary to an injury that causes functional or structural changes in the kidneys.[28] In this light, RIFLE criteria seem to provide a uniform definition of AKI, with the primary aim of reliably identifying different stages of disease progression. A broader utilization of RIFLE criteria might, in the coming years, provide original, reliable, and generalizable information on the impact of AKI on clinical practice.

Since its original publication in 2004, many investigators have already implemented the RIFLE classification for research purposes. In fact, if we exclude several abstracts presented at international meetings, 24 original investigations, several reviews, and at least 2 'workgroup relations'

**Table 1 | Summary of original investigations using the RIFLE classification**

| Author | Year | N, total | Population studied | Retrospective/ prospective | Single/ multicenter | Mortality end point | Criteria used for RIFLE | AKI incidence | Main results |
|---|---|---|---|---|---|---|---|---|---|
| Abosaif[a] | 2005 | 183 | ICU | Retrospective | Single | ICU, 6 months | Cr, UO | NA | Mortality rate in the ICU was significantly greater in the F group compared with all other groups |
| Åhlström[a] | 2006 | 668 | ICU | Prospective | Two | Hospital | Cr, UO | 52.0% | RIFLE maximum for the first 3 days in the ICU was found to be an independent predictor of hospital mortality |
| Cruz[a] | 2006 | 2164 | ICU | Prospective | Multi | ICU | Cr, UO | 10.8% | RIFLE class is an independent predictor of mortality. Mortality was highest in class F |
| Hoste[a] | 2006 | 5383 | ICU | Retrospective | Single | Hospital | Cr, UO | 67.2% | Patients with RIFLE class R are at high risk of progression to class I or class F. RIFLE class I or class F have a significantly increased length of stay and an increased risk of in-hospital mortality |
| Lopes[a] | 2007 | 182 | ICU (sepsis) | Retrospective | Single | 60 days | NS | 37.4% | RIFLE is predictive of mortality in sepsis |
| Lopes[a] | 2007 | 97 | HIV | Retrospective | Single | 60 days | NS | 47.4% | RIFLE is predictive of mortality in HIV patients |
| Ostermann[a] | 2007 | 41 972 | ICU | Retrospective | Multi | ICU, hospital | Cr, GFR | 35.8% | There is a good association between AKI and hospital outcome, but associated organ failure, nonsurgical admission, and admission after emergency surgery had a greater impact on prognosis |
| Bell[b] | 2005 | 8136 | ICU treated with RRT | Retrospective | Single | 30 days, 6 months | Cr, UO | NA (2.5% RRT) | 60-day follow-up is sufficient to catch the majority of deaths in AKI patients treated with CRRT. The patients in the RIFLE-F category had a significantly higher mortality |
| Maccariello[b] | 2006 | 214 | ICU treated with RRT | Prospective | Multi | ICU, hospital | Cr, UO | NA | The RIFLE classification did not discriminate the prognosis in patients with AKI in need for RRT |
| Lopes[a] | 2007 | 126 | Burn unit | Retrospective | Single | NS | Cr, UO | 35.7% | RIFLE is predictive of mortality in burned patients |
| Coca[a] | 2007 | 304 | Burn unit | Retrospective | Single | Hospital | Cr | 26.6% | The RIFLE classification added prognostic information regarding mortality in patients with milder forms of AKI |
| Lopes[a] | 2006 | 140 | Hematopoietic cell transplantation | Retrospective | Single | NS | Cr, UO | 37.8% | RIFLE is predictive of mortality in hematopoietic cell transplantation patients |
| Kuitunen[a] | 2006 | 808 | Cardiac surgery | Retrospective | Single | 90 days postoperative | Cr, UO | 19.3% | RIFLE classification was an independent risk factor for 90-day mortality, unlike change in GFR and change in plasma creatinine |
| Lin[a] | 2006 | 46 | Cardiac surgery (ECMO) | Retrospective | Single | Hospital | Cr, UO | 78% | RIFLE criteria can be reliably applied to ECMO patients with AKI |
| Heringlake | 2006 | NA | Cardiac surgery (practice survey ) | NA | Multi | NA | Cr | 15.4% | AKI is a frequent complication following cardiac surgery. Varying incidence in centers may be related to different strategies regarding fluid therapy and vasopressors |
| Uchino[a] | 2006 | 20 126 | Hospital admissions | Retrospective | Single | Hospital | Cr, GFR | 18.0% | All RIFLE criteria were significantly predictive factors for hospital mortality, with an almost linear increase in odds ratios from Risk to Failure |
| Ali[b] | 2007 | 5321 | Population based | Retrospective | Multi | Hospital, 90 days, 6 months | Cr, GFR | 1811 p.m.p. | The RIFLE classification is useful for identifying patients at greatest risk of adverse short-term outcomes |
| Akcan-Arikan | 2007 | 150 | Pediatric ICU | Prospective | NS | 28 days, hospital | Cr, UO | 82% | Modified pediatric RIFLE criteria serves to characterize the pattern of AKI in critically ill children |
| Guitard | 2006 | 97 | Liver transplant | Retrospective | Single | 1 year post transplant | Cr, GFR | 63.8% | RIFLE was helpful in identifying and describing the impact of AKI on mortality after liver transplantation |
| O'Riordan | 2007 | 300 | Liver transplant | Retrospective | Multi | 30 days, 1 year post transplant | Cr, GFR | 36.8 % | RIFLE was helpful in identifying AKI patients after liver transplantation |
| Lerolle | 2006 | 35 | ICU | Prospective | Single | Not an end point | Cr, UO | 65.8% | Doppler-based determination of renal artery resistive index on day 1 of septic shock predicts AKI |
| Herget-Rosenthal | 2004 | 85 | ICU | Prospective | Single | Not an end point | Cr, GFR | NA | Cystatin C is a useful detecting marker of AKI as defined by RIFLE classification |
| Hoste | 2004 | 704 | ICU treated with RRT | Prospective | Single | Not an end point | NA | NA | RRT patients who develop nosocomial bloodstream infection were more likely to have Loss of kidney function or ESRD |
| Tallgren | 2007 | 69 | Elective abdominal aortic surgery | Prospective | Single | Hospital | Cr, UO, cystatin C | 22% | 22% of patients undergoing elective abdominal surgery develop acute renal dysfunction |

AKI, acute kidney injury; Cr, creatinine; CRRT, continuous renal replacement therapy; ESRD, end-stage renal disease; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; ICU, intensive care unit; NA, not applicable; NS, not stated in the article; p.m.p., per million population; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; RRT, renal replacement therapy; UO, urine output.

[a]Mortality data for non-AKI patients stated in article. These studies were used for all the analyses (see Table 2).

[b]Mortality data for non-AKI patients not available in article. These three studies were used only in the analyses among different RIFLE categories.

**Table 2 | Analysis performed on different settings**

| Compared AKI levels | No of studies | RR | 95% CI | *P* (overall effect) | *P* (heterogeneity) |
|---|---|---|---|---|---|
| *All studies* | | | | | |
| Risk vs non-AKI | 13[a] | 2.40 | 1.94, 2.97 | <0.00001 | 0.0001 |
| Injury vs non-AKI | 13[a] | 4.15 | 3.14, 5.48 | <0.0001 | <0.00001 |
| Failure vs non-AKI | 13[a] | 6.37 | 5.14, 7.90 | <0.0001 | <0.00001 |
| Injury vs Risk | 16[b] | 1.51 | 1.23, 1.86 | <0.0001 | <0.00001 |
| Failure vs Risk | 16[b] | 2.24 | 1.79, 2.81 | <0.0001 | <0.00001 |
| Failure vs Injury | 16[b] | 1.45 | 1.25, 1.69 | <0.0001 | <0.00001 |
| *General ICU (use of both Cr and urine output criteria)* | | | | | |
| Risk vs non-AKI | 4 | 1.77 | 1.39, 2.26 | <0.0001 | 0.75 |
| Injury vs non-AKI | 4 | 2.35 | 1.95, 2.83 | <0.0001 | 0.42 |
| Failure vs non-AKI | 4 | 4.63 | 3.99, 5.38 | <0.0001 | 0.91 |
| Injury vs Risk | 4 | 1.32 | 1.07, 1.62 | 0.008 | 0.99 |
| Failure vs Risk | 4 | 2.33 | 1.75, 3.11 | <0.0001 | 0.13 |
| Failure vs Injury | 4 | 1.74 | 1.28, 2.35 | 0.0003 | 0.02 |
| *General ICU (without use of urine output criteria)* | | | | | |
| Risk vs non-AKI | 3 | 2.48 | 2.33, 2.63 | <0.0001 | 0.90 |
| Injury vs non-AKI | 3 | 4.02 | 2.44, 6.64 | <0.0001 | 0.07 |
| Failure vs non-AKI | 3 | 5.15 | 3.16, 8.41 | <0.0001 | 0.02 |
| Injury vs Risk | 3 | 1.82 | 1.22, 2.74 | 0.004 | 0.2 |
| Failure vs Risk | 3 | 2.19 | 1.41, 3.40 | <0.0001 | 0.11 |
| Failure vs Injury | 3 | 1.25 | 1.19, 1.30 | <0.0001 | 0.43 |
| *Cardiosurgery* | | | | | |
| Risk vs non-AKI | 2 | 5.46 | 1.87, 15.95 | 0.002 | 0.22 |
| Injury vs non-AKI | 2 | 9.42 | 1.22, 72.89 | 0.03 | 0.01 |
| Failure vs non-AKI | 2 | 13.85 | 1.80, 106.76 | 0.01 | 0.008 |
| Injury vs Risk | 2 | 1.70 | 0.80, 3.61 | 0.17 | 0.21 |
| Failure vs Risk | 2 | 2.57 | 1.05, 6.34 | 0.04 | 0.09 |
| Failure vs Injury | 2 | 1.4 | 1.07, 1.83 | 0.02 | 0.77 |
| *Other ICU* | | | | | |
| Risk vs non-AKI | 3 | 1.28 | 0.54, 3.03 | 0.57 | 0.88 |
| Injury vs non-AKI | 3 | 6.02 | 2.13, 16.99 | 0.0007 | 0.08 |
| Failure vs non-AKI | 3 | 9.3 | 6.09, 14.20 | <0.0001 | 0.61 |
| Injury vs Risk | 3 | 4.16 | 1.62, 10.66 | 0.003 | 0.39 |
| Failure vs Risk | 3 | 7.48 | 3.41, 16.43 | <0.0001 | 0.93 |
| Failure vs Injury | 3 | 1.56 | 0.78, 3.11 | 0.2 | 0.1 |
| *ICU treated with CRRT* | | | | | |
| Injury vs Risk | 2 | 1.09 | 0.89, 1.34 | 0.41 | 0.74 |
| Failure vs Risk | 2 | 1.48 | 0.57, 3.84 | 0.42 | 0.03 |
| Failure vs Injury | 2 | 1.55 | 0.44, 5.41 | 0.49 | <0.0001 |
| *Not confined to ICU* | | | | | |
| Risk vs non-AKI | 1 | 3.43 | 3.01, 3.90 | <0.0001 | NA |
| Injury vs non-AKI | 1 | 6.64 | 5.90, 7.48 | <0.0001 | NA |
| Failure vs non-AKI | 1 | 9.34 | 8.35, 10.44 | <0.0001 | NA |
| Injury vs Risk | 2 | 1.55 | 0.95, 2.53 | 0.08 | 0.01 |
| Failure vs Risk | 2 | 2.11 | 1.22, 3.64 | 0.008 | 0.003 |
| Failure vs Injury | 2 | 1.39 | 1.24, 1.56 | <0.0001 | 0.69 |

AKI, acute kidney injury; CI, confidence interval; Cr, creatinine; CRRT, continuous renal replacement therapy; ICU, intensive care unit; RR, relative risk.
[a]Includes ref. nos. 3–15.
[b]Includes ref. nos. 16, 17, and 19 in addition to all references mentioned in footnote a.

have been published in indexed journals.[3–28] Most of these studies are epidemiological and evaluated mortality of critically ill patients with AKI comparing subjects in the R, I, and F classes to verify if outcome progressively worsened with increasing severity of AKI. Although most deal with adults, one study tried to validate for the first time the RIFLE criteria in a cohort of critically ill pediatric patients.[21] Aside from this, studies have also used the RIFLE criteria to validate cystatin C[23] and an instrumental Doppler index[20] for detecting AKI in critically ill patients. A number of epidemiologic studies have tried to quantify the performance of the RIFLE classification with receiver operator characteristic curves,[3,4,7,10,11,13] some comparing it with other scoring systems. Some of these studies are discussed in detail below. Although the findings are interesting, this type of analysis is inherently somewhat flawed. As RIFLE focuses on only the

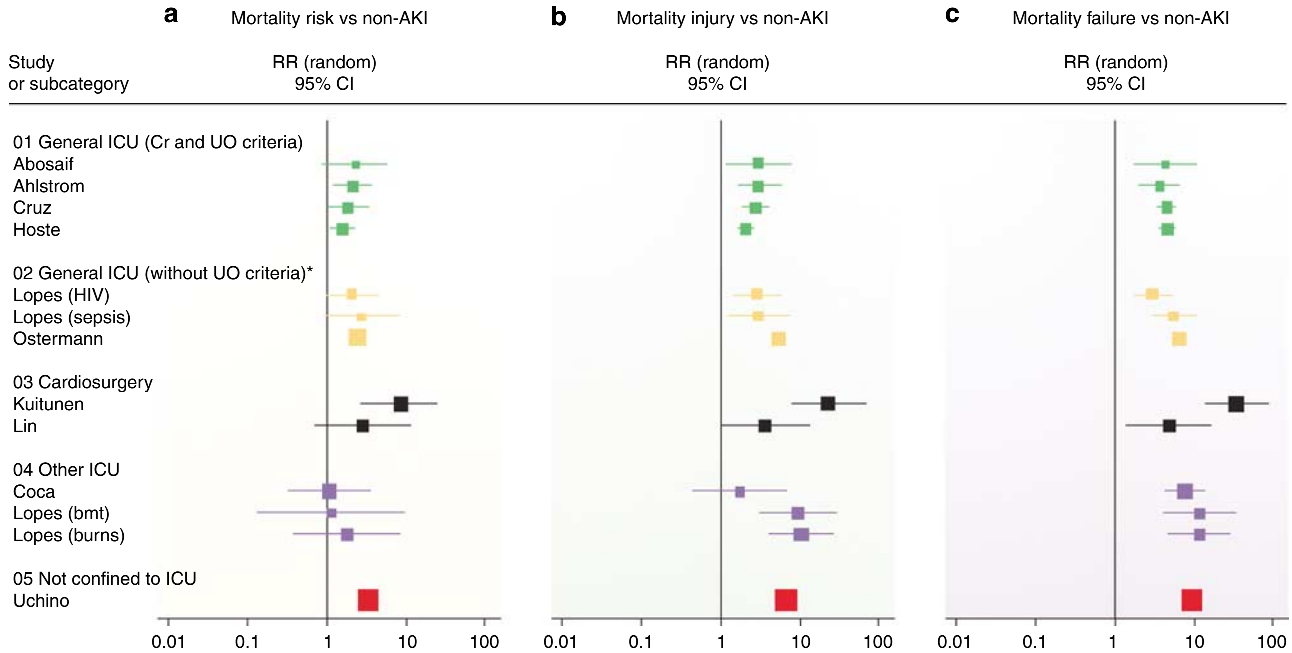


**Figure 2 | Forrest plot showing RR for death with respect to non-AKI patients.**[3–15] (**a**) Risk (RR = 2.40; 58 073 participants included in meta-analysis), (**b**) Injury (RR = 4.15; 55 351 participants included in meta-analysis), and (**c**) Failure (RR = 6.37; 53 758 participants included in meta-analysis). Cr, creatinine; UO, urine output. See Table 2 for details.

renal aspect of the patient's illness, its predictive ability is expected to be inferior to that of general illness severity scores.[34] The RIFLE classification was originally intended to standardize the definition and severity of AKI, rather than be a tool which would predict mortality. Nevertheless, such a system should carry some overall predictive value to be clinically meaningful. This systematic review clearly supports this concept. With respect to non-AKI patients, there clearly appears to be a stepwise increase in RR for death going from Risk to Failure: this trend was confirmed in different patient populations (ICU, hospital, cardiac surgery, and pediatric). The only interesting exception was in RRT patients,[16,17] wherein the RIFLE criteria appeared to be less effective in predicting risk of death (Table 2). One possible explanation is that these patients are already gravely ill, such that RIFLE is no longer able to further discriminate between the R-I-F classes. However, future studies with larger sample sizes are needed to make more definitive conclusions on this subgroup.

Although clinically very useful, the RIFLE classification has its limitations. In a number of studies, the urine output criteria were not used, or its use was not specified (Table 1). Although decreased urine output has a high specificity and sensitivity for AKI, the urine output criteria also pose certain issues.[27] First, sensitivity and specificity may be lost when diuretics are used, and this issue is not specifically addressed in the RIFLE criteria. Second, the urine output criteria can only be accurately assessed in patients with a urinary catheter, which is more likely to occur in the ICU and less likely in the wards. These data are also more difficult to retrieve in retrospective studies, as was seen in this review.[7,8,13,14,15,18,19,23] Third, it is possible that the urine output criteria for Risk, Injury, and Failure are not well-balanced with the respective creatinine criteria, and are too sensitive. In other words, Risk patients defined by creatinine criteria are more severely ill compared with Risk patients defined on urine output criteria. This may be an explanation for the different impact of RIFLE class on mortality among studies in which urine criteria were used or not used (Figure 2; Table 2). This finding is in agreement with two earlier studies. In the series of Hoste *et al.*,[6] patients with RIFLE-F based on GFR criteria had a slightly higher mortality than patients in the same class based on urine output criteria. Cruz *et al.*[5] specifically compared the predictive value of the serum creatinine and urine output criteria. In their analysis, the serum creatinine criteria appeared to be a better predictor of mortality than urine output. However, they also noted that the predictive value of the 'true' RIFLE class (using the worse of either creatinine or urine output) was statistically more stable. This finding supports the clinical utility of using the composite criteria as it had been originally proposed by ADQI.[1] Another limitation of RIFLE is the need for a baseline creatinine, which may not always be available. Although a provision has been made by ADQI to use an estimated baseline creatinine based on the modification of diet in renal disease equation,[1,2] the validity of this assumed creatinine has been questioned.[27] The limitations of these current criteria may be helped by the use of emerging biomarkers for AKI, such as cystatin C and neutrophil gelatinase-associated lipocalin.[25,35] These can be used to further refine the criteria, or be used in conjunction with traditional AKI markers, such as creatinine and diuresis.

Lastly, RIFLE does not take into account the etiology of AKI, nor the need for RRT. A subsequent modification of the classification has taken the latter point into consideration.[28]

Below, we briefly review the studies separated into three broad headings: RIFLE in the general ICU, RIFLE in cardiac surgery, and RIFLE in the non-ICU population. Aside from these, two studies also looked at RIFLE in adult patients with severe burns,[12,15] and one in pediatric patients.[21] A brief synopsis of all published studies can be found in Table 1.

**RIFLE in the general ICU**

Abosaif *et al.*[3] retrospectively applied the RIFLE classification of AKI to evaluate its sensitivity and specificity to predict renal and patient outcomes in 183 critically ill patients with AKI. Subjects were divided into four groups (non-AKI, R, I, and F), and demographic, biochemical, hematologic, clinical, and long-term health status were compared among these groups. The predictive value of the RIFLE classification for mortality in the ICU was examined by logistic regression and receiver operator characteristic curve analysis. The RIFLE-F group showed the worst parameters with regard to Acute Physiology and Chronic Health Evaluation (APACHE) II score, pH, lowest and highest mean arterial pressures, and Glasgow Coma Scale. Mortality rate in the ICU (60 days, 74.4%) and 6-month mortality rate (86%) were significantly greater in the RIFLE-F group compared with all other groups. Receiver operator characteristic curve analysis showed that Simplified Acute Physiology Score II was more sensitive than APACHE II score for prediction of patient death in the Risk and Injury groups compared with the Failure and control groups. The authors concluded that RIFLE classification might improve the ability of such older and established ICU scoring systems as APACHE II and Simplified Acute Physiology Score II in predicting outcome of ICU patients with AKI.

Åhlström *et al.*[4] described rather different findings with respect to the above-described report. They evaluated the ability to predict hospital mortality in two AKI-specific severity-of-illness scoring methods, the RIFLE score and the score presented by Bellomo *et al.*[36] in 2001. The study included 668 consecutive patients. AKI prevalence was classified according to the RIFLE and Bellomo scores. As a measure of control, the authors evaluated two general severity-of-illness scoring systems, the admission APACHE II and Sequential Organ Failure Assessment scores.

Admission Sequential Organ Failure Assessment scores and maximum RIFLE scores for the first 3 days in the ICU were independent predictors of hospital mortality. In receiver operator characteristic curve analysis, Sequential Organ Failure Assessment and APACHE II scores performed better than AKI-specific scores, and discriminative powers for hospital mortality were only moderate for the RIFLE and Bellomo scores: areas under the curve were 0.653 and 0.587, respectively. Neither of the AKI-specific scoring methods presented good discriminative power regarding hospital mortality. However, maximum RIFLE score for the first 3 days in the ICU was found to be an independent predictor of hospital mortality, along with admission Sequential Organ Failure Assessment score. Cruz *et al.*[5] conducted the first prospective multicenter study to estimate the AKI incidence in critically ill patients in 19 ICUs in northeastern Italy. Clinical characteristics and outcomes of patients with AKI on the basis of their RIFLE class were described. Of 2164 ICU patients who were admitted during the study period, 234 (10.8%) developed AKI, while 3.3% were treated with RRT. Of the AKI patients, 19% were classified as Risk, 35% as Injury, and 46% as Failure. Preexisting kidney disease was present in 36.8%. The most common causes of AKI were prerenal causes (38.9%) and sepsis (25.6%). At the diagnosis of AKI, median serum creatinine and urine output were 2.0 mg per 100 ml and 1100 ml day$^{-1}$, respectively. Overall ICU mortality in the cohort was between 30 and 42%, and was highest among those in RIFLE class F (mortality: 20% in R, 29.3% in I, and 49.5% in F). Independent risk factors for mortality included RIFLE class, sepsis, and need for RRT, whereas a postsurgical cause of AKI, exposure to nephrotoxins, higher serum creatinine, and higher urine output were associated with lower mortality risk.

Hoste *et al.*[6] performed a retrospective single study on 5383 patients in seven ICUs admitted during a 1-year period. AKI occurred in 67% of ICU admissions, and 28, 27, and 12% reached a maximum RIFLE class of Risk, Injury, and Failure, respectively. Of the patients that reached a level of R, 56% progressed to either I or F. Patients with maximum RIFLE class R, I, and F had hospital mortality rates of 8.8, 11.4, and 26.3%, respectively, in contrast to 5.5% in non-AKI patients. RIFLE classes were still associated with hospital mortality after adjusting for multiple covariates (baseline severity of illness, case mix, race, gender, and age). Their findings showed that patients with RIFLE-R are indeed at significant risk of progression to more severe AKI. Patients with RIFLE class I or F incur a significantly increased length of stay and an increased risk of in-hospital mortality compared with those who do not progress past class R or those who never develop AKI. Osterman and Chang[8] performed a retrospective analysis of a database of 41 972 patients admitted to 22 ICUs in the UK and Germany between 1989 and 1999. The authors found that AKI as defined by RIFLE occurred in 35.8% of patients: 17.2% R, 11% I, and 7.6% F. Patients with Risk, Injury, and Failure had a hospital mortality of 20.9, 45.6, and 56.8%, respectively, compared to 8.4% among non-AKI patients. Independent risk factors for hospital mortality were age, APACHE II score on admission to ICU, presence of preexisting end-stage disease, mechanical ventilation, RIFLE class, maximum number of failed organs, admission after emergency surgery, and nonsurgical admission. Interestingly, RRT was not an independent risk factor for hospital mortality. The authors concluded that there was an association between AKI and hospital outcome, but associated organ failure, nonsurgical admission, and admission after emergency surgery had a greater impact on prognosis than severity of AKI.

Two studies looked specifically at AKI patients treated with RRT in the ICU.[16,17] Bell *et al.*[16] wanted to determine the optimal duration of follow-up for patients with AKI treated with continuous renal replacement therapy (CRRT) and to test the hypothesis that a 6-month follow-up would be sufficient to catch most of the mortalities. In addition, they looked at the association between mortality and the RIFLE classification. Out of 8152 consecutive patients who were admitted to the ICU, 207 patients were treated with CRRT. ICU mortality in this cohort was 34.8%, while 30-day and in-hospital mortalities were 45.9 and 50.2%, respectively. The cohort's all-cause mortality 6 months after inclusion was 59.9, but 54.6% died as early as 60 days. Patients in RIFLE-F had a 30-day mortality of 57.9% compared with 23.5% for those in the R category and 22.0% for I patients. The authors showed that a 60-day follow-up is adequate to catch the majority of deaths in AKI patients treated with CRRT.

Maccarello *et al.*[17] evaluated the association of RIFLE classification with the outcomes of critically ill patients with AKI who required RRT. They conducted a prospective cohort study in three medical–surgical ICUs: 214 patients (mean age: 71.4 ± 15.8 years) were analyzed. Continuous renal replacement therapy was used in 179 (84%) patients, classified as R (25%), I (27%), or F (48%). Overall mortality was 76%. There were no significant differences in mortality according to RIFLE class (R, 72%; I, 79%; and F, 76%). Independent predictors of mortality were older age, presence of comorbidity, poor chronic health status, number of associated organ dysfunctions, and start of RRT after the first day of ICU. RIFLE classification was forced into the model and was not selected. A subgroup analysis of 150 patients who received mechanical ventilation and vasopressors found RIFLE-F level to be associated with increased mortality. This is the only study thus far in which no difference in mortality is seen among the different RIFLE categories. However, this center had a high rate of RRT use in the ICU, and an overall mortality higher than any of the other studies, including that of Bell discussed above.[16] The reasons for the different results seen in these two studies on RRT patients are not clear.

### RIFLE in cardiac surgery

Three reports were published presenting results from cardiac surgical populations. The identification and early treatment of AKI in this setting appears very important. Postoperative AKI affects about 30% of all patients and significantly increases risk of death after cardiac surgery.[37]

Kuitunen *et al.*[10] sought to determine the prevalence of postoperative renal impairment according to RIFLE criteria in 813 cardiac surgical patients. The RIFLE classification discriminated 90-day mortality quite well (area under the curve, 0.824) compared with the change of plasma creatinine and the change of GFR (areas under the curve, 0.849 and 0.829, respectively). The results of the multivariate forward stepwise logistic regression analysis confirmed that RIFLE classification was an independent risk factor for 90-day mortality.

Extracorporeal membrane oxygenation (ECMO) is indicated in critically ill patients with postcardiotomy cardiogenic shock or life-threatening respiratory failure. Lin *et al.*[11] conducted a retrospective study, examining the outcome of 46 patients supported by ECMO, and described the association between mortality and RIFLE class. This investigation confirmed that the prognosis for critically ill patients supported by ECMO is poor. Cumulative survival rates at 6 months follow-up following hospital discharge differed significantly for non-AKI vs RIFLE-I and -F, and RIFLE-R vs -F. The RIFLE classification also appeared to be clinically useful in ECMO patients. Heringlake *et al.*[22] prospectively collected quality management data on different cardiac surgery population characteristics from 51 German centers, including different renal outcomes. They found that RIFLE-R, -I, and -F levels were reached by 9, 5, and 2% of the evaluated population, respectively. Interestingly, centers with a low incidence (9%) of new onset renal dysfunction significantly differed from those with a high incidence (50%) by being more liberal with fluid administration, preferentially using noradrenaline for hemodynamic support. Case mix, urgent cases, and the use of loop diuretics were not different among these centers.

### RIFLE outside the ICU

Uchino *et al.*[14] sought to assess, in a retrospective study, the ability of the RIFLE criteria to predict mortality in hospital patients. Patients were excluded if they were younger than 15 years old, were on chronic dialysis, had kidney transplant, or if their length of hospital stay was <24 h. The authors evaluated 20 126 patients, of whom 14.7% required ICU admission. According to the RIFLE criteria, 9.1% of all patients were in Risk, 5.2% were in Injury, and 3.7% were in the Failure category. Hospital mortality was 8.0% for the entire cohort, but there was an increase in hospital mortality from non-AKI to Failure (non-AKI, 4.4%; R, 15.1%; I, 29.2%; and F, 41.1%). Multivariate logistic regression analysis showed that RIFLE was a significant predictive factor for hospital mortality, with an almost linear increase in odds ratios from Risk to Failure.

Ali *et al.*[19] examined the incidence of AKI in a population base of more than 500 000 people, regardless of whether they required RRT and irrespective of the hospital setting in which they were treated. They also tested the hypothesis that the RIFLE classification predicts outcomes. All case records of patients with serum creatinine concentrations >1.7 mg per 100 ml (male) or >1.5 mg per 100 ml (female) over a 6-month period and their clinical outcomes were obtained. The incidences of AKI and Acute on Chronic Renal Failure were 1811 and 336 per million population, respectively. Median age was 76 years for AKI and 80.5 years for Acute on Chronic Renal Failure. Sepsis was a contributing factor in 47% of patients. The RIFLE classification was useful for predicting full recovery of renal function, RRT requirement, length of hospital stay among survivors, and in-hospital mortality. However, RIFLE did not predict mortality at 90 days or 6 months.

In summary, we presented the results of recent studies that utilized RIFLE criteria to correlate AKI diagnosis and prognosis. Most of these studies showed strikingly similar results, and, from our pooled analysis, there appears to be a stepwise increase in RR for death going from Risk to Failure with respect to non-AKI patients. In this light, the RIFLE classification appears to be a simple and useful clinical tool, using readily available clinical data, to detect and stratify the severity of AKI, and possibly predict outcome. Future research might be directed to specify which kind of intervention (medical therapy, experimental therapy, and extracorporeal renal replacement) should be applied at the different levels of AKI: the timing of different therapeutic approaches is as fundamental as the efficacy of the treatment itself. In this regard, biomarkers of AKI such as cystatin C and neutrophil gelatinase-associated lipocalin would be useful and important adjuncts to clinical criteria such as the RIFLE classification. Moreover, it would be interesting to further understand which component of the RIFLE classification (rise in serum creatinine or fall in urine output) is more predictive of patient outcome. A recent revision of RIFLE nomenclature and classification has been endorsed by participating societies representing critical care and nephrology societies worldwide, and is expected to simplify and further refine AKI classification: RIFLE criteria was modified into a staging classification system with stages I, II, and III resembling R, I, and F levels, respectively, and with L and E levels being removed and remaining solely as clinical outcomes.[28]

In conclusion, we now have a common classification of AKI that may help researchers determine the appropriate study population and optimal timing for trials on medical or extracorporeal therapies, and eventually help clinicians to easily follow evidence-based guidelines.

## MATERIALS AND METHODS

### Study selection, data abstraction, and validity assessment

We performed a literature search without language restriction in PubMed using the terms (acute renal failure or AKI) and (Risk or Injury or Failure or RIFLE) from 2004 through June 2007, bibliographies of review articles, and consulted with experts in the field. Since the first report on ADQI, we identified 24 full-text original investigations in which the RIFLE classification was used to define AKI (Table 1).[3–26] Two authors reviewed all citations. In an effort to summarize the results of the remaining studies in a comprehensive manner, their data were combined in a meta-analysis. Eight of the twenty-four studies were not included (Figure 3). One study was a practice pattern survey of 81 hospitals and patient level data were not available.[22] Two studies reported the use of RIFLE in orthotopic liver transplant patients; the first combined non-AKI and Risk patients in a single category,[18] while the second grouped Risk and Injury patients together in a single category.[23] One study was performed in the pediatric setting.[21] One study used RIFLE criteria to validate an instrumental Doppler index for detecting AKI in a cohort of critically ill patients.[20] One study used the RIFLE classification to examine the value of cystatin C as a predictor of AKI,[25] while another used cystatin C values in a modified RIFLE classification to describe the incidence of AKI after

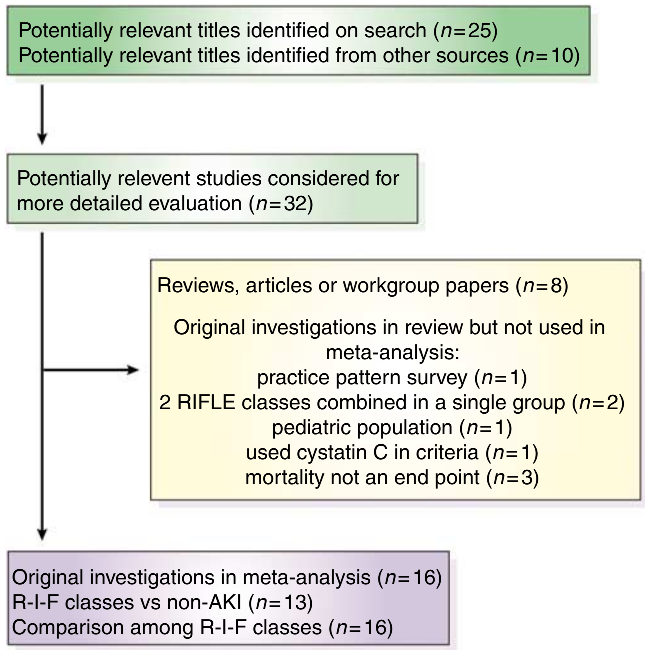


**Figure 3 | Details of included and excluded studies.**

elective abdominal surgery.[26] One study used the outcome classes Loss and end-stage renal disease to evaluate renal outcome in patients with nosocomial bloodstream infection.[24] Sixteen studies were available for analysis of mortality (Figure 3). In 13 studies (designated with A in Table 1), patient level data on mortality was available for Risk, Injury, and Failure patients, as well as those without AKI (non-AKI).[3–15] One author reported the use of RIFLE in four different patient populations in separate letters.[7,9,12,13] In three additional studies, mortality was reported only for AKI patients (designated with B in Table 1).[16,17,19] Death was reported at ICU discharge,[3,5,8,16,17] hospital discharge,[4,6,11,14,15,16,17,19,21] 28 days,[21] 30 days,[16,18] 60 days,[3,7,13] 90 days,[10,19] 1-year post liver transplant,[20,23] and not stated in two studies.[9,12] To summarize the association between RIFLE class and mortality in published studies in adults, we looked at the pooled estimate of the mortality RR for patients with RIFLE class Risk, Injury, or Failure compared to non-AKI patients as reported in 13 studies.[3–15] We also looked at the RRs comparing mortality among the three RIFLE classes R, I, and F, in which three additional studies were included.[16,17,19] Mortality data at hospital discharge were used when available. Data were combined using a random effects model. Intertrial heterogeneity was estimated by $\chi^2$-test. Analyses were performed with Review Manager version 4.2 (RevMan; The Nordic Cochrane Centre, The Cochrane Collaboration 2003, Copenhagen, Denmark). The level of statistical significance is set at $P$ less than 0.05. Values for RR are expressed as a point estimate with 95% confidence intervals and $P$-value.

## DISCLOSURE

The authors declare that they do not have any financial interest with the information contained in this paper.

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