Original Paper

A Comparison of Traditional and Novel Definitions (RIFLE, AKIN, and KDIGO) of Acute Kidney Injury for the Prediction of Outcomes in Acute Decompensated Heart Failure

Andrew K. Roy[a, b]   Catherine Mc Gorrian[a, b]   Cecelia Treacy[a]
Edel Kavanaugh[a]   Alice Brennan[b]   Niall G. Mahon[a, b]   Patrick T. Murray[a, b]

[a]Mater Misericordiae University Hospital, and [b]University College Dublin, Dublin, Ireland

Abstract

Aims: To determine if newer criteria for diagnosing and staging acute kidney injury (AKI) during heart failure (HF) admission are more predictive of clinical outcomes at 30 days and 1 year than the traditional worsening renal function (WRF) definition. *Methods:* We analyzed prospectively collected clinical data on 637 HF admissions with 30-day and 1-year follow-up. The incidence, stages, and outcomes of AKI were determined using the following four definitions: KDIGO, RIFLE, AKIN, and WRF (serum creatinine rise ≥0.3 mg/dl). Receiver operating curves were used to compare the predictive ability of each AKI definition for the occurrence of adverse outcomes (death, rehospitalization, dialysis). *Results:* AKI by any definition occurred in 38.3% (244/637) of cases and was associated with an increased incidence of 30-day (32.3 vs. 6.9%, $\chi^2 = 70.1$; p < 0.001) and 1-year adverse outcomes (67.5 vs. 31.0%, $\chi^2 = 81.4$; p < 0.001). Most importantly, there was a stepwise increase in primary outcome with increasing stages of AKI severity using RIFLE, KDIGO, or AKIN (p < 0.001). In direct comparison, there were only small differences in predictive abilities between RIFLE and KDIGO and WRF concerning clinical outcomes at 30 days (AUC 0.76 and 0.74 vs. 0.72, $\chi^2 = 5.6$; p = 0.02) as well as for KDIGO and WRF at 1 year (AUC 0.67 vs. 0.65, $\chi^2 = 4.8$; p = 0.03). *Conclusion:* During admission for HF, the benefits of using newer AKI classification systems (RIFLE, AKIN, KDIGO) lie with the ability to identify those patients with more severe degrees of AKI who will go on to experience adverse events at 30 days and 1 year. The differences in terms of predictive abilities were only marginal.

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Patrick T. Murray
Clinical Research Center
Mater Misericordiae University Hospital
Dublin 7 (Ireland)
E-Mail patrick.murray @ucd.ie

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Introduction

Acute kidney injury (AKI) occurring during admission for acute decompensated heart failure (ADHF) has a major impact on prognosis and management and may also increase the risk of subsequent development of chronic kidney disease. Traditionally, AKI in ADHF patients is defined by worsening renal function (WRF; ≥0.3–0.5 mg/dl increase in serum creatinine) during hospitalization; however, some studies have demonstrated that even smaller increases in serum creatinine may also be associated with an increased length of stay and adverse in-hospital outcomes [1]. The use of varying definitions for AKI in ADHF populations, as well as the heterogeneity seen between different populations, has meant that described rates of AKI can range from 10 to 40%, with outcome data such as in-hospital mortality and heart failure (HF)-related readmission rates varying significantly between studies [2–5]. Furthermore, the degree of AKI severity, which may represent differing degrees of renal insult (from pre-renal azotaemia to acute tubular necrosis), and the time period within which AKI occurs may also have significant impact on clinical outcomes. Improving the accuracy for detecting AKI stages and severity in ADHF may thus highlight subgroups of patients who may benefit from earlier initiation of renal-sparing therapies, prevention of contrast nephropathies for those potentially undergoing interventions, or to aid in identifying those patients who may require more intensive follow-up in the early post-discharge period.

In recent years, interdisciplinary consensus groups have proposed standardized systems to define and stage AKI. Both the RIFLE (Risk, Injury, Failure, Loss of Kidney Function, and End-stage Kidney Disease) [5, 6] and Acute Kidney Injury Network (AKIN) criteria [7] were designed for the purpose of accurately diagnosing and assessing the severity and progression of AKI in critically ill patients as well as of providing some predictive ability for mortality. Both systems rely on changes in creatinine or glomerular filtration rate (GFR) while also incorporating urine output criteria. The RIFLE criteria have been validated in over 555,000 patients, mostly in the setting of cardiac surgery, intensive care, or sepsis-related syndromes [5, 8]. To date, there have been no studies of HF populations comparing the predictive ability of WRF to that of the RIFLE, AKIN, or the novel KDIGO (Kidney Disease: Improving Global Outcomes) [9] classification systems for AKI, thus applying pre-specified creatinine changes within standardized time frames in patients receiving acute and chronic therapies (diuretics, inotropes, vasodilators, ACE inhibitors). This study therefore aims to provide further insight into the epidemiology of AKI in ADHF using newer definitions and to examine the association between AKI severity and major clinical outcomes of this syndrome at 30 days and 1 year.

Methods

Study Population
We performed a review of prospectively collected admission data in a single tertiary referral centre. Demographic and clinical data were analyzed to determine the occurrence of AKI using any definition in patients presenting with a primary diagnosis of ADHF and requiring admission for more than 24 h. Using electronic records, all patients under the care of the HF service from 2002 to 2009 were identified and analyzed. These included new referrals as well as patients already known to the service, whereby the first admission (index) with ADHF during the study time window (2002–2009) was included for analysis. The study period then consisted of 1 year from the index admission, during which time data were extracted for the occurrence of primary outcomes. The study was approved by our Institutional Research Ethics Committee and complies with the Declaration of Helsinki research study protocol.

Inclusion and Exclusion Criteria
Patients with both systolic and diastolic HF (HF with preserved ejection fraction, EF) were included in the study. ADHF was defined according to ESC guidelines [10, 11]: clinical parameters included signs (such

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as elevated jugular venous pulsation, hepatojugular reflux, third heart sound, peripheral oedema, and pulmonary crepitations) as well as symptoms (such as breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, and reduced exercise tolerance) typical of HF. Echocardiography was used to define systolic (reduced left ventricular EF) and diastolic (normal or only mildly reduced EF in the setting of non-dilated left ventricle and diastolic dysfunction/left ventricular hypertrophy/left atrial enlargement) HF. Patients were excluded from the analysis if there was a history of pre-existing renal replacement therapy (RRT), renal allograft, age <16 years, or if serum creatinine data were not available either during the pre-specified time windows for AKI or during the pre-admission period (in the case of abnormal serum creatinine at presentation). Patients admitted electively for cardiac transplant evaluation or in-patients transferred from other centres were excluded.

Serum Creatinine Measurements

Serial measurements of serum creatinine values were analyzed for every day of admission from baseline admission date until discharge. All creatinine assays were carried out in a single laboratory using Beckman Coulter platform analyzers.

Definition of Baseline and 1-Year Renal Function Using Estimated GFR

Estimated GFR (eGFR; in ml/min/1.73 m^2) at baseline and 1 year was calculated using the Modification of Diet in Renal Disease formula: $186.3 \times (\text{serum creatinine (mg/dl)})^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) [12–14].

Definitions of AKI

The incidence, stages, and outcomes of AKI were determined using the four definitions from KDIGO, RIFLE, AKIN, and WRF and are described in table 1. The cut-off point of ≥0.3 mg/dl for WRF was chosen based on the observations from multiple prior HF studies [1, 2, 4, 15–17]. Peak serum creatinine was defined as the highest value in µmol/l during the admission within pre-specified time points as required for the application of the four AKI criteria (table 1). Baseline serum creatinine was estimated from either the admission value (if this was within the normal range) or from another value within 6 months, whichever was lowest, in keeping with consensus practice in other large-scale AKI studies in different populations (intensive care, cardiac surgery, paediatric populations) [18]. This caveat was designed to detect 'true' baseline creatinine measurements as serum creatinine is often already raised at HF presentation. The definitions applied to diagnose AKI (RIFLE, AKIN, and the novel KDIGO criteria) all vary in both the degree of change in serum creatinine required (table 1) and the time period within which the change must occur. For the dichotomized AKI versus non-AKI population, AKI was considered to have occurred if the patient satisfied any of the four criteria (RIFLE, KDIGO, AKIN, WRF). We then compared individual classification systems as a whole (e.g. satisfying any stage, allowing for comparison of the AKI time periods) as well as stage by stage to examine the severity of AKI within the appropriate time periods (48 h, 7 days, etc.). A graded change in urine output can also be used as an alternative to serum creatinine for AKI diagnosis; however, given the physiologic responses expected from diuretic therapy, its application and utility in this ADHF cohort was not studied.

Study Outcomes

The primary outcome (for 30 days and 1 year) was a composite of HF-related readmission, RRT, and all-cause mortality, and was recorded and verified using hospital electronic records and cross-referenced with our centre's prospective HF database.

Statistical Analysis

For differences in the baseline characteristics of the patients (AKI vs. non-AKI), we used Student's t test or Mann-Whitney U test for continuous variables and Pearson's χ^2 test for dichotomous variables. Logistic regression analysis, using 30-day and 1-year events as outcome variables, was used to compare each definition by stage of disease severity of AKI patients to patients with no evidence of AKI. Areas under the receiver operating characteristic curves (AUC) were then used to compare the performance of each AKI definition in predicting the primary outcome. Data are presented as AUC and odds ratios (OR) with 95% confidence intervals (CI). A p value of <0.05 was considered statistically significant. The predictive ability of all four definitions was examined in simple logistic regression models adjusted for age and gender.

Classification tables were derived using the optimal predicted probability of an event occurring in patients with AKI as a cut-off and were then identified using sensitivity/specificity plotted against the

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Table 1. RIFLE, AKIN, KDIGO, and WRF criteria for definition of AKI

	Serum creatinine criteria	Minimum time period for AKI to occur
RIFLE [5, 6]		
Risk	Increase in serum creatinine ≥1.5 times baseline or decrease in eGFR ≥25%	Serum creatinine changes over 1–7 days, sustained for more than 24 h
Injury	Increase in serum creatinine ≥2.0 times baseline or decrease in eGFR ≥50%	
Failure	Increase in serum creatinine ≥3.0 times baseline or decrease in eGFR ≥75% or an absolute serum creatinine ≥354 µmol/l with an acute rise of at least 44 µmol/l	
AKIN [7]		
Stage 1	Increase in serum creatinine of ≥26.2 µmol/l or increase to ≥150–199% (1.5- to 1.9-fold) from baseline	Acute serum creatinine changes occur within a 48-hour period during hospitalization
Stage 2	Increase in serum creatinine to 200–299% (>2- to 2.9-fold) from baseline	
Stage 3	Increase in serum creatinine to 300% (≥3-fold) from baseline or serum creatinine ≥354 µmol/l with an acute rise of at least 44 µmol/l or initiation of RRT	
KDIGO [9]		
Stage 1	≥1.5 times baseline* or 0.3-mg/dl increase**	* Defintion of AKI requires serum creatinine changes ≥1.5 times baseline to have occurred within 7 days, or ** a 0.3-mg/dl increase in serum creatinine must occur within a 48-hour time period
Stage 2	≥2 times baseline	
Stage 3	≥3 times baseline or increase in creatinine to ≥4.0 mg/dl	
WRF [2–5]		
	Increase in serum creatinine from baseline of ≥0.3 mg/dl (26.5 µmol/l)	Serum creatinine change can occur at any time during admission
	For conversion from SI Units, divide by 88.4 for mg/dl.	

predicted probability. With ROC curves from the nested logistic models, we used the method of DeLong et al. [19] to compare the AUC for each AKI definition. Statistical analyses were carried out using Intercooled STATA 9.0 (Stat Corp., College Station, Tex., USA) and PASW (SPSS Inc., Chicago, Ill., USA).

Results

Study Population

The total study population consisted of 637 participants (table 2). The mean age ± SD of the study population was 64.6 ± 14.4 years, and 70.6% were male. The commonest aetiology of HF was ischaemic heart disease (60.7%, 387/637). Baseline demographics are described in table 2. The mean eGFR was 72.4 ± 28.4 ml/min at baseline and 62.2 ± 25.6 ml/min at 1 year. In terms of baseline renal function, 41% (261/637) of the patients had stage 3 or higher chronic kidney disease (eGFR <60 ml/min). In patients hospitalized with ADHF and sustain-

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Table 2. Baseline characteristics of study population (n = 637), where AKI is defined using any definition

	Total population	AKI (n = 244)	No AKI (n = 391)	p value
Male gender, n (%)	453 (71.1)	175 (71.7)	280 (71.6)	0.90
Mean age ± SD, years	64.6±14.3	64.0±15.1	65.0±13.8	0.40
Atrial fibrillation, n (%)	295 (46.3)	131 (58.0)	164 (46.7)	0.01
ICD, %	17.6	17.9	17.4	0.85
Diabetes, n (%)	151 (23.7)	75 (30.5)	76 (19.5)	0.001
Median EF (IQR), %	25 (25)	25 (20)	25 (20)	0.14
EF ≥50%, n (%)	61 (9.6)	18 (7.3)	43 (11.1)	0.12
Baseline eGFR, ml/min/1.73 m^2	72.4±28.4	65.3±26.5	77.5±28.6	<0.001
GFR <60 on admission, n (%)	230 (36.1)	114 (46.3)	132 (53.7)	<0.001
Median length of stay, days [IQR]	10 [10]	14 [12]	9 [7]	<0.001

ing AKI, the median hospital lengths of stay were longer, but there was no significant difference in cardiac function by EF, with both groups having a median EF of 25% (table 2).

Incidence of AKI Using Different Definitions

AKI by any definition occurred in 38.3% (244/637) of ADHF admissions. Using the different criteria, the incidence for AKI was 36.7% (234/637) for KDIGO, 25.6% (163/637) for RIFLE, 27.9% (178/637) for AKIN, and 33.0% (210/637) for WRF. Patients with AKI by any definition were more likely to have diabetes mellitus (p = 0.001) and atrial fibrillation (p = 0.01). Patients with AKI had a lower mean eGFR compared to those without AKI by any definition (65.3 ± 26.5 vs. 77.5 ± 28.6 ml/min, p < 0.001). Among the patients who developed AKI, 46.3% had an abnormal eGFR at baseline (table 2). The incidences of individual stages of AKI are summarized in online supplementary table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000347037).

Primary Outcomes for AKI
30-Day Outcomes

AKI by any definition was also associated with an increased incidence of 30-day adverse outcomes (32.3 vs. 6.9%, χ^2 = 70.1; p < 0.001). This primary outcome composite consisted of 21.5% (n = 53) HF readmissions, 7.3% (n = 18) deaths, and 2.4% (n = 6) patients requiring RRT. Among patients with AKI defined by the RIFLE criteria, 11.6% (74/637) had 30-day adverse outcomes compared to 6.0% (38/637) of the patients experiencing primary outcome without AKI. Using AKIN, there were 9.9% (63/637) versus 6.8% (43/637) of patients without AKI. For the 30-day outcome using KDIGO, there were 11.9% (74/637) versus 4.7% (30/637) patients without AKI, and for WRF 11.6% (74/637) versus 5.0% (32/637). There was a stepwise increase in the 30-day primary outcome with increasing AKI stages using RIFLE, KDIGO, or AKIN, which remained robust when adjusted for age and gender (p < 0.001). In direct comparison, both RIFLE and KDIGO had only marginally superior AUC values to WRF for the prediction of adverse outcomes at 30-days (AUC 0.76 and 0.74 vs. 0.72, χ^2 = 5.6; p = 0.02; table 3).

1-Year Outcomes

AKI by any definition was also associated with an increased incidence of 1-year adverse outcomes (67.5 vs. 31.0%, χ^2 = 81.4; p < 0.001). The predictive ability of the KDIGO criteria at 1 year was only marginally superior to that of WRF (AUC 0.67 vs. 0.65, χ^2 = 4.8; p = 0.03), as

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Table 3. Performance of the four AKI definitions for predicting primary outcomes at 30 days in 637 AKI patients with ADHF

	AUC (95% CI)	Sensitivity %	Specificity %	Positive predictive value, %	Negative predictive value, %
KDIGO [2010]	0.74 (0.69–0.79)	39.6	89.2	42.4	88.1
RIFLE [2007]	0.76 (0.71–0.81)	44.4	92.8	55.30	89.3
AKIN [2007]	0.72 (0.66–0.77)	34.0	95.5	60.0	87.8
WRF [2000]	0.72 (0.67–0.77)	69.8	74.3	35.2	92.5

Table 4. Performance of the four AKI definitions for predicting primary outcomes at 1 year in 637 AKI patients with ADHF

	AUC (95% CI)	Sensitivity %	Specificity %	Positive predictive value, %	Negative predictive value, %
KDIGO [2010]	0.66 (0.63–0.70)	54.4	77.1	66.1	67.3
RIFLE [2007]	0.64 (0.60–0.68)	40.1	86.0	70.1	63.6
AKIN [2007]	0.64 (0.61–0.68)	42.5	83.7	68.2	64.0
WRF [2000]	0.65 (0.62–0.69)	49.5	80.0	67.0	65.9

Table 5. Subgroups of primary outcomes at 30 days and 1 year according to occurrence of AKI by any definition

	Total (n = 637)	30-day AKI	30-day no AKI	1-year AKI	1-year no AKI
RRT, n (%)	14 (2.2)	6 (2.4)	1 (0.3)	11 (4.5)	3 (0.7)
HF readmission, n (%)	215 (33.8)	53 (21.5)	19 (4.9)	120 (48.8)	95 (24.3)
Mortality, n (%)	52 (8.2)	18 (7.3)	5 (1.3)	31 (12.6)	21 (5.4)

seen in table 4. Similar to 30-day outcomes, there was also a stepwise increase in primary outcome at 1 year according to the severity of AKI by stage using RIFLE, KDIGO, or AKIN (p < 0.001). Age, male gender, presence of diabetes, and ICD implantation were also all associated with significant renal dysfunction (eGFR <60 ml/min) at 1 year. Among the patients with AKI defined by the RIFLE criteria, 18.1% (115/637) had 1-year adverse outcomes in comparison to 27% (172/637) of those experiencing primary outcome without AKI. Using AKIN, there were 19.1% (122/637) versus 26.0% (165/637) patients without AKI. For the 1-year outcome using KDIGO, there were 24.5% (156/637) versus 20.6% (131/637) patients without AKI, and for WRF 22.3% (142/637) versus 22.8% (145/637). Table 5 demonstrates the types of clinical events (comprising the primary outcome) experienced by the study population at 30 days and 1 year.

Effect of Severity/Stage of AKI on Clinical Outcomes
Using a logistic regression model comparing individual stages of AKI to no AKI, table 6 highlights the marked increase in risk of primary adverse outcome at 30 days as stage of AKI increases, particularly beyond stage 1 (in the AKIN and KDIGO systems) or stage R (in the

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Table 6. Logistic regression analysis examining the primary outcome at 30 days according to AKI severity using the RIFLE, KDIGO, and AKIN criteria for patients with AKI

	Stage	OR	95% CI	z	p value
RIFLE	Stage 1 (risk) vs. 0	4.2	2.4–7.3	5.1	<0.001
	Stage 2 (injury) vs. 0	17.7	8.1–38.4	7.3	<0.001
	Stage 3 (failure) vs. 0	47.8	16.8–135.6	7.3	<0.001
KDIGO	Stage 1 vs. 0	3.9	2.3–6.4	5.3	<0.001
	Stage 2 vs. 0	19.4	7.6–48.6	6.3	<0.001
	Stage 3 vs. 0	101.6	22.2–466.0	5.9	<0.001
AKIN	Stage 1 vs. 0	2.9	1.7–4.8	4.0	<0.001
	Stage 2 vs. 0	17.6	7.0–44.1	6.1	<0.001
	Stage 3 vs. 0	45.3	14.5–141.1	6.6	<0.001

0 indicates no AKI according to definition applied, i.e. stage 0.

RIFLE system). The risk of adverse outcomes for any patient with stage 2 AKI, as defined by RIFLE (OR 17.7, 95% CI 8.1–38.4), KDIGO (OR 19.4, 95% CI 7.6–48.6), or AKIN (OR 17.6, 95% CI 7.0–44.1), is approximately four to five times higher than for those who experience stage 1 AKI. For patients with stage 3 AKI, the risk of primary outcome is over ten times higher than for those with stage 1 AKI.

Effect of Known Chronic Kidney Disease on Clinical Outcomes

Abnormal renal function at baseline in patients with known chronic kidney disease (≥stage 3) was also significantly associated with the occurrence of primary outcomes at 30 days and 1 year (p < 0.001). When baseline impaired renal function (eGFR <60 ml/min) was examined for the predictive ability for the 30-day and 1-year outcomes, it was found to be inferior to any of the other definitions of AKI (WRF, RIFLE, AKIN, or KDIGO), with an AUC of 0.57 and 0.59, respectively (supplementary tables).

Discussion

This study demonstrates that in patients presenting with ADHF, classifying AKI using any of the newer definitions (RIFLE, AKIN, KDIGO) offers only marginally improved outcome prediction when compared to the traditional WRF definition. More importantly, we have shown that the value of using any of the new classification systems lies in the ability to provide prognostic information and risk discrimination between AKI severity stages. Similar to the systematic review by Damman et al. [20] and the recent study by Zhou et al. [21], our findings demonstrate exponential increases in risk for mortality and HF readmissions according to AKI severity as well as increased duration of hospitalization for those with AKI. To our knowledge, this is the first study to examine the performance of the recent consensus KDIGO definitions in an acute HF cohort.

Incidence and Time to AKI Development

The variation in AKI incidences between the different classification systems highlights the challenges in optimizing sensitivity and specificity for providing accurate prognostic information, as demonstrated in table 7. Examining the performance of incremental changes

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Table 7. Overview of studies using specific serum creatinine criteria applied to patients admitted with acute HF

First author [Ref.]	Patient population	Definition of AKI	AKI	Study criteria	Outcomes
Cowie [2]	299 patients; prospective study, with 6 months of follow-up	>26.5 µmol/l (0.3 mg/dl) occurring up to day 15 only	29%	Systolic dysfunction only (EF ≤40%)	Length of stay longer in AKI group (median 11 vs. 9 days, p = 0.006); no difference in mortality or rehospitalization rates
Metra [16]	318 patients; prospective study	≥25% incr and 0.3 mg/dl	34% WRF-Abs%, 42% WRF	HF admission requiring intravenous (diuretic or vasodilator) therapy, excluding recipients of contrast or dialysis	WRF-Abs% is an independent predictor of death or HF rehospitalization (HR 1.47, 95% CI 1.13–1.81, p = 0.024)
Krumholz [25]	Retrospective study of 1,681 patients >65 years of age (average 79 ± 8)	>26.5 µmol/l (0.3 mg/dl)	28%	HF admission	Increased length of stay, hospital cost, and hospital mortality; WRF occurs in 90% of cases within 7 days
Akhter [28]	Retrospective study of 481 patients from the VMAC trial	>0.5 mg/dl increase in serum creatinine	25%	Analysis of outcomes with (i) WRF and (ii) baseline renal insufficiency (serum creatinine >1.5mg/dl)	(i) WRF is an independent risk factor for 6-month mortality (RR 1.61, 95% CI 1.09–2.37, p = 0.02); (ii) baseline renal impairment is the most significant independent predictor of 6-month mortality (RR 2.72, 95% CI 1.76–4.21, p < 0.001)
Kociol [29]	Retrospective study of 20,063 patients, OPTIME-HF registry	0.3-mg/dl difference between admission and discharge serum creatinine	17.8%	Study not designed to detect changes in serum creatinine that had normalized by discharge	WRF is independently associated with 1-year mortality (HR 1.12, 95% CI 1.04–1.20) but not with readmission
Verdiani [3]	Prospective study of 394 patients	WRF	11%	Independent predictors of WRF were age >75 years (p = 0.049), history of chronic kidney disease (p = 0.047), and admission HR ≥1.00 (p = 0.004)	No difference in length of stay, rehospitalization, and mortality
Smith [22]	Prospective study of 412 patients	>0.1 mg/dl >0.2 mg/dl >0.3 mg/dl >0.4 mg/dl >0.5 mg/dl	75% 58% 45% 32% 24%	Admission for HF, age >50 years, excluded high-output causes of HF	Using even >0.2 mg/dl, risk of death increased by 20%, whereas using >0.5 mg/dl, mortality risk is increased by 2–3 times
Hata [30]	Retrospective study where n = 376	RIFLE	73%	HF admission	In-hospital mortality for risk = 0%, injury = 4.3%, and failure = 49.1%
Zhou [21]]	Retrospective study where n = 1,005	RIFLE	44.3%	HF admission	In-hospital mortality for risk = 7.4%, injury = 25.4%, and failure = 66.7%

VMAC = Vasodilation in the Management of Acute Congestive Heart Failure trial; OPTIME-HF = Organized Program to Initiate Life-saving Treatment in Hospitalized Patients with Heart Failure; incr = increase; Abs% = absolute percent.

in creatinine ranging from 0.1 to 0.5 mg/dl, Smith et al. [22], using the higher definition of a ≥0.5-mg/dl increase in creatinine, were able to predict a two to three times increased risk of mortality after hospital discharge. Investigating a similar HF cohort, Gottlieb et al. [1] concluded that both a 0.3-mg/dl increase plus the requirement of a final creatinine of >1.5 mg/dl provided a higher prognostic sensitivity and specificity, exceeding 60%. The study by

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Smith et al. [22] highlights the variations seen in both sensitivity and specificity for detecting mortality according to the definition of WRF used. When the lowest definition (0.1) is applied, the unadjusted HR for mortality approaches 1.0 (HR 1.10, 95% CI 0.91–1.11), with a sensitivity of 75% and a specificity of 25%. This compares with the alternative definition used (≥25%, serum creatinine >2.0 mg/dl), which markedly improves specificity for occurrence of mortality to 91%, at the expense of poor sensitivity. The incorporation of percentage definitions (RIFLE, AKIN, and KDIGO, but not WRF) is designed to include those with baseline or admission creatinine levels that may already be raised. The AKIN and KDIGO criteria were also designed to incorporate smaller incremental changes in creatinine level. Using a relative creatinine change of ≥1.5 times (or absolute increase by 26.2 μmol/l) improves sensitivity for the AKIN criteria when compared to the RIFLE criteria, but the restrictive time window of AKI occurring during any 48-hour period adversely impacts specificity and predictive ability, as seen in our study. Thus, the time to development of AKI is important as creatinine changes at different stages of admission may also reflect different pathophysiologic processes. During the first few days of admission for ADHF, fluctuations in serum creatinine most likely reflect type 1 cardiorenal syndrome [23], characterized by renal hypoperfusion, renal venous congestion, and associated activation of cytokine and neurohormonal axes [24]. This is in contrast to the changes in serum creatinine which may occur later during the admission and may be more related to iatrogenic factors such as the initiation of ACE inhibitors, interventional procedures, or prolonged use of or resistance to higher-dose diuretics. In the POSH study, the median time to WRF was 4 days (range 1–12), with 70% of patients experiencing WRF by 7 days [2]. Similarly, in studies by Krumholz et al. [25] and Forman et al. [26], WRF rates at 7 days were 90 and 80%, respectively. The AKIN criteria, requiring a 48-hour window for an acute creatinine change to occur, are the most restrictive of all definitions applied in this study but still highlight the adverse impact that an abrupt change in serum creatinine can have, with an AKI incidence of 27.9% seen in this population.

Impact on Prognosis at 30 Days and 1 Year

Our results demonstrate that the RIFLE and KDIGO classification systems have only marginally superior prognostic ability when compared to WRF (and AKIN) to predict the composite of mortality, need for RRT, and HF-associated rehospitalization at 30 days. Thus, for the RIFLE criteria, a minimum increase of ≥1.5 times the baseline creatinine level over 7 days may have a slightly better predictive ability (AUC 0.76) than a ≥0.3-mg/dl creatinine change throughout the admission, as seen using the WRF criteria (AUC 0.72). This is in contrast to our findings at 1 year, where only the novel KDIGO criteria have marginally better predictive ability for outcomes. Whether these small differences hold significant clinical value remains to be seen and will require further validation in different HF populations.

The reduced long-term predictive ability at 1 year may be due to small secondary event rates or may suggest the cardiorenal and systemic disturbances that occur with AKI may either resolve or progress to a chronic pathophysiologic state [27] where adverse outcomes may be driven by other factors (comorbidities, impaired functional status, poor social support).

Severity of AKI Predicts Risk for Adverse Events

Further differences encountered when comparing definitions for AKI are highlighted in online supplementary tables 1 and 2. The high sensitivity for both WRF and stage 1 KDIGO in detecting AKI (106 and 46 patients, respectively) is offset by the increased risk of events (primary outcome, HF admission) experienced as severity of AKI increases. Using the RIFLE criteria, there are more patients classified into higher classes (severity) of AKI, which in turn increases both their risk of events occurring and the ability to predict those events. Compared

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CardioRenal Medicine

Cardiorenal Med 2013;3:26–37

DOI: 10.1159/000347037

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to WRF at 30 days, 58.9% of the AKI cases defined by the RIFLE criteria are injury class (stage 2) or higher, thus being subsets of patients with more severe AKI, higher risk of primary outcome, mortality, and HF readmission. This is similar to the results found with the KDIGO (39.5%) and AKIN (52.4%) criteria.

Thus, the ability to further classify patients at risk of events by stage of AKI severity underscores one of the major advantages of using these newer classification systems over the traditional WRF definition. Furthermore, when we analyze the association between AKI stage and outcome, it becomes apparent that the 30-day primary outcomes are largely driven by those patients with worsening severity of AKI (e.g. stages 2 and 3), with the incidence for outcome in stage 1 ranging from 22 to 26% (35% for WRF). This is in contrast to outcomes at 1 year, where the incidence has almost tripled to 63–67%, suggesting that while the small incremental changes in creatinine during admission may not be the only factor in predicting short-term event rates, their significance becomes apparent at long-term follow-up.

Clinical Implications

Using the RIFLE, KDIGO, or AKIN classification systems for AKI occurring during admission for ADHF allows the clinician to prognostically stratify patients depending on the stage of AKI reached. The incidence rates and prognostic information provide a more accurate standard for diagnosing AKI in ADHF, thus allowing for qualitative interpretation when significant injury has occurred as well as for the quantitatively assessment of the stage and severity of that injury, above and beyond that offered by WRF. The subgroup analysis clearly indicated that those patients with AKI are at higher risk of readmission, with risk doubling or tripling depending on severity of AKI (stages 2 and 3). Thus, these patients are identified as a subgroup with higher demand on health-care resources and worsening outcomes, and may represent a target group for renal-sparing interventions as well as early post-discharge follow-up or telemonitoring programs. Applying these criteria also provide a clinically useful epidemiologic framework for benchmarking further cardiorenal studies involving novel biomarkers of renal injury, stressing the importance and applicability of time periods to assess AKI.

Limitations

There are several potential limitations to this study, in particular the single-centre HF population with potential towards selection bias (particularly in the early years of data collection) where patients managed under specialist care tended to have lower EF as well as the relatively small sample size necessitating the use of a composite endpoint. We used serum creatinine measurements for the application of the different AKI definitions as there have been no studies validating the use of urine output criteria for patients with ADHF and receiving diuretic or vasodilator therapy. There is the potential for further reclassification of some AKI patients if urine outputs were to be used. The assumption of baseline serum creatinine taken from admission or within 6 months is also a source of potential error as there may be fluctuations in renal function that have not been detected during that period. Furthermore, similar to other studies, eGFR estimation using serum creatinine in conditions of altered renal haemodynamics (diuretics, systemic hypotension) does have inherent limitations [13].

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Conclusion

During admission for ADHF, the major benefit of using any novel AKI classification system (KDIGO, RIFLE, or AKIN) over WRF is the increased ability to identify those patients with more severe AKI who will go on to experience adverse events at 30 days and at 1 year. From a predictive point of view, the individual differences between the newer classification systems in this study are small and require application in much larger ADHF populations to further elucidate whether significant changes exist. This study highlights the importance of identifying clinically meaningful changes in serum creatinine during admission for ADHF using newer AKI definition systems that include staging criteria to stratify severity.

Acknowledgements

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