

Renal angina: an emerging paradigm to identify children at risk for acute kidney injury

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Abstract Acute kidney injury (AKI) leads to high rates of morbidity and independently increases mortality risk. Therapy for AKI is likely limited by the inability to reliably diagnose AKI in its early stages, and, importantly, small changes in serum creatinine may be associated with poor outcomes and severe AKI. Whereas AKI biomarker research seeks to identify more sensitive and timely indices of kidney dysfunction, AKI lacks physical signs and symptoms to trigger biomarker assessment in at-risk patients, limiting biomarker efficacy. Accurate models of AKI prediction are unavailable. Severity of illness (SOI) scoring systems and organ dysfunction scores (OD), which stratify patients by prediction of mortality risk, are AKI reactive, not predictive. Kidney-specific severity scores do not account for AKI progression, and stratification models of AKI severity are not predictive of AKI. Thus, there is a need for a kidney scoring system that can help predict the development of AKI. This review highlights the concept of renal angina, a combination of patient risk factors and subtle AKI, as a methodology to predict AKI progression. Fulfillment of renal angina criteria will improve the efficiency of AKI prediction by biomarkers, in turn

expediting early therapy and assisting in creation of AKI-predictive scoring systems.

Keywords Renal angina · Acute kidney injury · Scoring systems

Introduction

Acute kidney injury (AKI) is a significant problem in critical illness. Approximately 5–6% of all hospitalized adults and 10% of children suffer from varying degrees of AKI [1]. AKI is known to worsen mortality rates, increase duration of mechanical ventilation, and prolong hospital stays in critically ill adults and children [2, 3]. The presence of AKI in critical illness occurs at a rate of 10–15% and carries a 50% mortality rate in children requiring dialysis [4–6]. AKI survivors are also at risk for progression to chronic kidney disease (CKD) [7]. Cross-talk between the kidney and other vital organs has also been demonstrated to harbor deleterious consequences on end organ function and in-hospital morbidity and mortality rates [8, 9], suggesting that AKI-associated mortality is not solely secondary to standard sequelae (e.g., hyperkalemia, acidosis, or uremia). Consistently effective AKI therapy to prevent or limit the disease intensity is lacking, potentially due to delayed recognition of existing and/or ongoing injury. AKI diagnosis is traditionally dependent on changes in serum creatinine (SCr), a marker with limitations involving time, body habitus, sex, age, steady-state measurement, and patient condition. Primarily due to the lag in the rise of SCr, the diagnosis of AKI is often delayed, which creates a significant barrier to effective early intervention. Notably, small increases in SCr (0.3 mg/dl) may reflect significant kidney damage and is associated with poor patient outcomes [10, 11]. As a result, an intensive research effort has been expended to identify novel AKI biomarkers to determine therapy to be instituted prior to a rise in SCr.

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AKI researchers have termed the effort to identify AKI biomarkers as a quest for the “renal troponin” equivalent. Treatment for acute myocardial infarction (MI) was transformed by the use of troponin I measurements in patients with signs and symptoms of a cardiac angina. Sensitivity and specificity of troponin elevations and electrocardiographic changes for MI have allowed practitioners to institute early and life-saving therapy. However, whereas the novel AKI biomarkers recently discovered may serve well as a renal troponin equivalent, AKI lacks an important parallel to MI. Simply put, AKI does not hurt. Thus, whereas many different AKI biomarkers can be used across a broad swath of critically ill patients, their ability to improve patient care and outcomes may be limited by the relatively nonspecific manner in which they are tested [12]. In order to optimize the utility of AKI biomarkers, screening systems are needed to identify patients who are at high risk of developing AKI.

Scoring systems are important to epidemiologic study in critical illness. These scoring systems [severity of illness (SOI), organ-specific illness scores (OD), and AKI stratification scores] provide objective SOI information, allowing comparisons between therapies, units, and hospitals by juxtaposing expected versus observed outcomes. However, the scoring systems are broad-based population comparisons; individual patient risk of either mortality or organ failure is not well assessed. Collectively, these scores, even those that are kidney centric, are reactive to existing AKI and predictive of neither AKI nor its severity. Given the remarkably deleterious contribution of AKI to morbidity and mortality in critical illness [2, 13], a kidney-injury screening system predictive of AKI severity and disease progression is needed.

In this educational review, we present our recently proposed empiric concept of renal angina (RA), a methodology to enhance AKI prediction [12] to guide AKI biomarker assessment. We provide descriptive overviews of the existing scoring systems for critical illness, kidney-specific severity scoring systems, and kidney injury stratification scores, all of which have limited ability to predict AKI. We highlight the need for improvement in AKI biomarker efficiency. The description of RA is then used to demonstrate that the diagnosis of AKI may be made in more real time by expediting AKI-biomarker efficiency and making the prediction of AKI progression more possible

The necessity of early AKI prediction

AKI increases overall mortality rates, independent of disease severity. AKI is an independent risk factor for mortality, with odds ratios (ORs) as high as 4.8, and independently increases hospital costs, length of stay, and ventilator days [2, 13–15]. In a study of nearly 4,000 critically ill children, AKI increased mortality rates and

lengthened intensive care unit (ICU) stay fourfold [16]. AKI increases mortality rates in adults and children with multiorgan failure, hematopoietic stem-cell or solid-organ transplant, extracorporeal membrane oxygenation (ECMO), or acute respiratory distress syndrome (ARDS) anywhere from 10% to 57.1% [17–19]. AKI carries a high risk of death in children independent of illness severity [5]. AKI occurs in between 2.7% and 28% of children following cardiopulmonary bypass (CPB) and carries a notable increased morbidity risk, including longer duration of mechanical ventilation and hospital stay [20, 21], and higher risk of mortality [22]. For these children, a creatinine rise of $\geq 25\%$ is a significant risk factor for increased length of stay and mechanical ventilation, but even a small initial rise in creatinine leads to an increased risk of subsequently developing AKI [11]. Finally, at 3- to 5-year follow-up, 40–50% of pediatric patients with AKI showed signs of chronic renal insufficiency [23]. Collectively, these studies strongly suggest that AKI represents a serious burden to the pediatric patient population and to the health care system at large.

Effective therapeutic measures for AKI are lacking. Managing AKI is segmented into optimization of renal perfusion pressure through preload or vasopressor therapy, treating oxidative and inflammatory injury, and preventing or reducing fluid overload (FO) [24–26]. None of these measures, however, have proven effective at ameliorating AKI. Augmentation of renal perfusion using volume modification and vasopressor support has not been shown to improve mortality rates in patients with AKI. Neither dopamine [27] nor fenoldopam lessen their risk of mortality [28]. Therapy for oxidative and inflammatory kidney injury is largely speculative and has yet to be demonstrated as efficacious in large studies [29]. The use of renal replacement therapy (RRT) for inflammatory mediators in AKI is not globally supported [30]. Notably, positive fluid balance has a direct correlation with mortality in adults with AKI [31]. The Prospective Pediatric Continuous Renal Replacement Therapy Registry Group (ppCRRT) repeatedly demonstrated in retrospective studies that increased fluid administration is independently associated with mortality in children started on CRRT [32, 33]. Interestingly, in the sum of AKI management literature, proven and reliable therapies for existing AKI or for halting the progression of AKI from mild to severe, do not exist. The state of the art for AKI therapy is preventative measures aimed at maintaining adequate renal perfusion pressure, avoiding nephrotoxic agents, treating sepsis, limiting hypoxia, and ensuring adequate nutrition [24, 25]. All of these data beg the question: Why are all of these therapies seemingly ineffective?

Delayed recognition likely contributes greatly to the poor outcome. At diagnosis, AKI has often progressed to a state of damage that may not be amenable to acute

intervention. This paradigm has been created by outdated detection modalities based on creatinine and urine output, which have limitations hindering early diagnosis. As even small elevations in SCr are reflective of significant kidney damage, creatinine is clearly a late marker of AKI [10, 11]. As is discussed later, appreciating the contribution of AKI to mortality is evident in the evolution of SOI and OD scores over time. The increasing weighted contribution of AKI to the overall scores mirrors abundant clinical evidence of the impact of AKI; patients are now recognized as dying from and not just with AKI [34, 35]. AKI biomarker research emphasizes the limitations in creatinine as a marker and has aggressively sought out new indices of AKI [36–40]. Proper use and analysis of such biomarkers would allow for earlier intervention, potentially leading to amelioration, or possibly prevention, of AKI progression to overt kidney failure and the associated extrarenal sequelae of host morbidity and mortality.

Severity of Illness scores do not adequately predict AKI

SOI scores are used to characterize and stratify adult and pediatric critical illness. The initial SOI systems were developed to benchmark, or compare, critical care units against one another, to monitor resource use, evaluate therapies, and improve quality assessment [41, 42]. They were not intended to predict SOI in individual patients but, rather, to group patients together in strata of illness, which would allow group-wide mortality or SOI prediction. Iteration of SOI scores reflect adjustments made over time to weight variables of illness for their retrospectively appreciated effects on mortality rates. For example, the weighted contribution of AKI to the SOI score (and thus the prediction of mortality) has increased in all iterations of all SOI scores reported to date. SOI scores can be broken down into three main categories: admission, outcome-prediction scores, and admission organ-failure scores. Interestingly, neither category adequately predicts progression of individual organ failure (i.e., kidney) but, rather, treats the contribution from AKI to the SOI scores as a binary variable (present or absent) (Tables 1 and 2).

The admission SOI outcome prediction scores do not offer prognostication. These survival prediction models were devised to provide an indication of the risk of death of groups of ICU patients. Also, these scores do not generally consider SOI related to organ dysfunction after the first 24–36 h. Illness in the ICU is commonly an aggregate consequence of progressive organ dysfunction that occurs down a continuum. Further, wide variations exist for the mortality rate predicted in groups of patients with AKI [43], potentially due to limited sampling of AKI patients. The major adult SOI outcome prediction models are: The Acute Physiology and Chronic Health Evaluation (APACHE), the

Simplified Acute Physiology (SAPS), and the Mortality Probability Model (MPM). APACHE II [44] (Table 1) is the most widely used SOI for adults. Interestingly, comparison of sequential iterations of the APACHE II and III scores illustrates the increasing weight given to AKI (point increase for elevated creatinine and inclusion of points for oliguria and azotemia: a smaller increase in creatinine was required for points, and those points contributed a higher percentage toward overall mortality rates (Table 1). SAPS scores, as with those of APACHE, cannot be used to track disease progression [45]. The MPM models (not depicted) use a binary system (disease absent or present) [46, 47]. The pediatric SOI models are the Pediatric Risk of Mortality (PRISM) and the Pediatric Index of Mortality (PIM). The initial version of PRISM did not include any contribution to illness from kidney disease [48]. Subsequent versions of PRISM accounted for AKI and have led to the most recent version, PRISM III [49]; however, it is notable that the weighted contribution of severe AKI ($SCr \geq 200\%$ for selected age) is the same as a serum glucose of 201, a pH of 7.28, or a platelet count of 200,000. This relatively low estimation of the contribution of AKI to mortality is likely explained by the date of PRISM III publication (1996) before the onslaught of literature noting the tremendously deleterious impact of AKI on critical illness. The PIM score has criticisms, including selection and timing biases [50]. In summary, besides often being cumbersome to calculate and not always being available in the public domain (e.g., APACHE III, PRISM III), APACHE, SAPS, and PRISM, the major SOI scores, have been useful in critical care units for comparison of mortality prediction based on illness severity, but none can be used to predict AKI progression.

Organ dysfunction scores do not adequately predict AKI

OD scores were developed to describe but not predict the degree of organ dysfunction. The key difference between the OD and SOI scores is that specific OD is assessed over time and severity rather than as a snapshot in isolation. The primary OD scores are the Multiple Organ Dysfunction Score (MODS), the Logistic Organ Dysfunction Score (LODS), and the Sequential Organ Failure Assessment (SOFA) (Table 2). The SOFA [51] scores organ injury independent of therapy and accounts for escalating AKI severity but does not function as a predictive tool for progression. MODS incorporates the worst parameter of OD for a patient's entire ICU stay and also does not offer a prediction for development of kidney injury. The PELOD score is the pediatric-organ-specific injury score [52] that has been validated in pediatric intensive care units (PICUs) in Europe and Canada. Patients with high PELOD scores and increased number of ODs have the highest probability

Table 1 Selected Severity of Illness (SOI) scoring systems

System	Temperature	CV	Resp	Metabolic	Heme	GCS	Hepatic	Kidney
APACHE II	<30, >41=4 30–32, 39–41=3 32–34=2 34–36, 38.5–39=1	MAP: <50 or >160=4 130–160=3 50–70, 110–130=2 HR: <40, >180=4 40–54, 140–180=3 55–70, 110–140=2	RR: <5, > 50=4 35–50=3 10–11, 25–34=2 AvDO ₂ : > 500=4 350–500=3 200–350=2 pO ₂ : <55=4 55–60=3 61–70=2	Art pH: <7.15, >7.7=4 7.15–7.24, 7.6–7.7=3 7.25–7.32=2 7.5–7.6=1 Serum HCO ₃ : <15, >52=4 (mEq/L) 15–18, 41–52=3 18–23=2 32–41=1 Sodium: <110, > 180=4 (mEq/L) 111–119, 160–180=3 120–129, 155–159=2 150–154=1 Potassium: <2.5, > 7=4 (mEq/L) 6–6.9=3 2.5–2.9=2 3–3.4, 5.5–5.9=1 Sodium: >155=4 <119=3 120–134=2 Glucose: <40=8 (mg/dl) 40–59=6 >350=5 200–349=3 350–499=11 250–349=9 100–249=7 40–49, 110–119=5 100–109=1	Hct: <20, >60=4 (%) 20–30, 50–60=2 46–50=1 WBC: <1, >40=4 1–3, 20–40=2 15–20=1			Creatinine: >3.5=4 (mg/dl) 2–3, 4=3 <0.6, 1.5–1.9=2
APACHE III	<33=20 33–34=16 33.5–33.9=13 34–35=8 >40=4 35–36=2	MAP: 40–59=15 >140=10 130–139=9 60–69, 120–129=7 70–79=6 100–119=4 HR: >155=17 140–154=13 <40=8 120–139=7 40–49, 110–119=5 100–109=1	RR: >50=18 <5=17 35–39=9 6–11=8 12–13=7 25–34=6 Av DO ₂ : >500=13 350–499=11 250–349=9 100–249=7 pO ₂ : <50=15 50–69=5 70–79=2	Sodium: >155=4 <119=3 120–134=2 Glucose: <40=8 (mg/dl) 40–59=6 >350=5 200–349=3 350–499=11 250–349=9 100–249=7 pO ₂ : <50=15 50–69=5 70–79=2	Hct: >50 = 3 <40.9=3 WBC: <1=19 1–3, >25=5 20–24.9=1 >350=5 200–349=3 350–499=11 250–349=9 100–249=7 pO ₂ : <50=15 50–69=5 70–79=2		Albumin: <2=11 2–2.4=6 >4.5=4 Bili: >6=16 (mg/dl) 3–5=6 2–3=5	^a Creatinine: >1.5=10 ^b Creatinine: >1.95=7 >1.5–1.94=4 <0.4=3 UOP: <400=15 (ml/day) 400–599=8 500–899=7 900–1499=5 1500–1999=4 >4000=1 BUN >80=12 40–79=11 20–39=7 17–19=2 UOP: <500=11 500–1000=4 BUN 28–83=6 >84=10
SAPS II (Chronic Dz age admit status also included)	>39=3	SBP: <70=13 70–99=5 >200=2 HR: <40=11 >160=7 120–160=4 40–69=2	P/F: <100=11 100–200=9 MV=6	Sodium: <125=5 (mEq/L) >145=1 Potassium: <3, > 5=3 (mEq/L) HCO ₃ : <15=6 (mEq/L) 15–19=3	WBC: <1=12 >20=3		Bili: >6=9 (mg/dl) 4–6=4 9–10=7 11–13=5	
PRISM I		SBP: Infant 130–160, Child 150–200=2 Infant 55–65, Child 65–75=2	RR: Infant 61–90=1 Child 51–70=1	Potassium: 6.5–7.5=1 (mEq/L) 3–3.5=1 <3=5	PTT: × 1.5 norm=2	<8=6 Pupils 4, 10	PT: × 1.5 norm=2 Bili>3.5=6	

Table 1 (continued)

System	Temperature	CV	Resp	Metabolic	Heme	GCS	Hepatic	Kidney
		Infant >160, Child >200=6 Infant <40, Child <50=7 DBP: all ages>110=6 HR:Infant >160, Child >150=4 Infant <90, Child<80=4	Infant>90=5 Child>70=5 Apnea=5 P/F 200–300=2 <200=3 PaCO2 51–65=1 >65=5	>7.5=5 Calcium: 7–8=2 (mg/dldl) 12–15=2 <7=6 >15=6 Glucose: 40–60=4 (mg/dldl) 250–400=4 <40=8 >400=8 Bicarbonate <16, >30=3				
PRISM III	<33, >40=3	SBP: Neonate 40–55=4, <40=7 Infant 45–65=3, <45=7 Child 55–75=3, <55=7 Adolescent 65–85=3, <65=7	pHi: <7=6 7.2–7.28=2 pCO2: >75=3 50–75=1 pO2: <42=6 42–49=3	Glucose: >200=2 Sodium: <110, >180=4 (mEq/L) 111–119, 160–180=3 120–129, 155–159=2 150–154=1 Potassium: >6.9=3 (mEq/L)	Plt: <50=5 50–90=4 100–200 =2 WBC: <3=4 PTT Neonate>85=3 All other>57=3	<8=5 Pupils=11 Neonate>22=3 All other>22=3	PT Neonate>22=3 All other>22=3	Creatinine: (mg/dldl) Neonate >0.85=2 Infant >0.9=2 Child >0.9=2 Adolescent >1.3=2 BUN (mg/dldl): Neonate >11.9=3 All other: >14.9=3

APACHE Acute Physiology and Chronic Health Evaluation, *SAPS* Simplified Acute Physiological Score, *PRISM* Pediatric Risk of Mortality, *Dz* disease, *CV* cardiovascular, *Resp* respiration, *GCS* Glasgow Coma Scale, *MAP* mean arterial pressure, *HR* heart rate, *RR* respiratory rate, *AVDO2* arteriovenous oxygen content difference, *pO2* oxygen partial pressure, *Art* arterial, *HCO₃⁻* bicarbonate, *HCT* hematocrit, *WBC* white blood cells, *Bili* bilirubin, *UOP* urine output, *BUN* blood urea nitrogen, *SBP* systolic blood pressure, *P/F* partial pressure of arterial oxygen/fraction of inspired oxygen, *MV* mechanical ventilation, *DBP* diastolic blood pressure, *PACO₂* partial pressure of carbon dioxide in the blood, *PTT* partial prothrombin time, *PT* prothrombin time

^a No renal failure

^b Renal failure

Table 2 Organ dysfunction scores

System	CV	Resp	Heme	GCS	Hepatic	Kidney
SOFA	Dopa>15, Norepi>0.1=4	P/F : <100=4	Platelets (103/mm ³): <20=4	<6=4	Bili (mg/dl): >12=4	Creatinine (mg/dl):>5=4
	Dopa>5, Norepi 0–0.1=3	<200=3	<50=3	6–9=3	6–12=3	3.5–5=3
	Dopa<5, Dobutamine=2	<300=2	<100=2	10–12=2	2–6=2	2–3.5=2
	MAP<70=1	<400=1	<150=1	13–14=1	1.2–2=1	1.2–2=1
		S/F: <67=4 67–141=3 142–220=2 221–301=1				UOP (ml/day): <200=4 <500=3
MODS	PAR >30=4	P/F : <75=4	Platelet: <20=4	< 6=4	Bili: >240=4	^a Creatinine: >500=4
	21–30=3	76–150=3	21–50=3	7–9=3	121–240=3	351–500=3
	15–20=2	151 – 225=2	51–80=2	10–12=2	61–120=2	201–350=2
	10–15=1	226 – 300=1	81–120=1	13–14=1	21–60=1	101–200=1
PELOD	HR:	P/F: <70=10	WBC: <1.5=10	3=20	ALT>950=1	Creatinine
	<12 years >195=10	pCO ₂ : >90=10	1.5–4.4=1	4–6 =10	INR>1.4=1	<7 days >1.59=10
	>12 years >150=10	MV=1	Platelet: <35=1	7–11=1	Pupils=10	7 days – 1 year >0.62=10
	SBP:		PTT>60=1			1–12 years >1.13=10
	<1 month <35=20 35–65=10					>12 years >1.59=10
	1 month–1 year <35=20					
	35–75=10					
	1–12 yr <45=20					
	45–85=10					
	>12 <55=20					
55–95=10						

SOFA Sequential Organ Failure Assessment, MODS Multiple Organ Dysfunction Score, PELOD Pediatric Logistic Organ Dysfunction score, CV cardiovascular, Resp respiration, GCS Glasgow Coma Scale, Dopa dopamine, Norepi norepinephrine, P/F partial pressure of arterial oxygen/fraction of inspired oxygen, MAP mean arterial pressure, PAR pressure-adjusted heart rate, HR heart rate, RR respiratory rate, pO₂ oxygen partial pressure, Art arterial, HCO₃⁻ bicarbonate, HCT hematocrit, WBC white blood cells, Bili bilirubin, UOP urine output, ALT alanine transferase, INR International Normalized Ratio, BUN blood urea nitrogen, SBP systolic blood pressure, MV mechanical ventilation, PTT partial prothrombin time

^a Micromol/liter

of death [53]. Additionally, each organ system accounted for in the PELOD score has been independently associated with increased mortality risk. However, the contribution of AKI to the PELOD score does not enable a practitioner to predict progression and, as Table 2 illustrates, this contribution, while significant, is only based on a present/absent dichotomization. In summary, whereas OD scores are intended to assess disease severity based on specific OD and can be assessed on a continual basis, they do not allow for study of the time course of OD. OD scores on day X do not predict the degree of OD on day X+2^o or X+3 for individual organs. Given the contribution of specific OD to critical illnesses, such as AKI, having an organ-specific scoring system that would allow prediction of progression would be highly useful for the bedside practitioner.

Kidney-specific severity scores do not predict AKI

Kidney-specific severity scores are used to analyze risk factors for mortality in patients with existing kidney failure. As they are complex and not facile to calculate at the bedside, kidney-

specific severity scores are used by kidney-disease epidemiologists to analyze the effect of comorbidities on mortality in patients with AKI (Tables 3 and 4). Table 3 demonstrates that inclusion criteria for each scoring system require a patient's SCr to be significantly elevated. Table 4 describes numerous

Table 3 Definition of acute renal failure (ARF) in kidney-specific severity scores

Score	Creatinine (mg/dl)	BUN (mg/dl)	Chronic disease Δ creatinine (mg/dl) over baseline
Bullock	≥ 2.5	≥100	≥2.5
Liano	≥ 2	Not used	Patients not included
Mehta	≥ 2	≥40	≥1
SHARF-II _o	≥ 2	Not used	≥50%
PICARD	≥ 0.5 rise in those with baseline <1.5	Not used	≥1 in those with baseline >1.5, baseline >5 not included

BUN blood urea nitrogen, SHARF Stuivenberg Hospital Acute Renal Failure, PICARD Program to Improve Care in Acute Renal Disease

Table 4 Log odds of death or probability of death given acute renal failure (ARF) in kidney-specific severity scores

Score	Log odds of death=sum of variables
Bullock (Log)	-1.765-0.687 (CP1+.037)+0.822 (CP2+0.1)+1.053 ([pulmonary complications]-.087)+0.05 (age 61.1)+0.7 ([jaundice]+.143)+0.608 ([CV complications]-.247)+0.365 ([hypercatabolism]+.0303)
Liano (Prob)	0.32 (age in decades) - 0.086 (male) - 0.109 (nephrotoxic)+0.109 (oliguric)+0.116 (hypotensive)+0.122 (jaundice)+0.15 (coma) -0.154 (conscious)+0.182 (assisted ventilation)+0.210
Mehta	0.17 (age)+0.8605 (male)+0.0144 (BUN) -0.3398 (creatinine)+1.2242 (hematologic failure)+1.1183 (liver failure)+0.9637 (respiratory failure)+.0119 (heart rate) -0.4432 (log[UOP]) -0.7207
SHARF-II _o	3 (age in decades)+2.6 (albumin category)+1.3 (prothrombin category)+16.8 (mechanical ventilation)+3.9 (heart failure)+2.8 (bilirubin)+27 (sepsis)+21 (hypotension) -17
PICARD	0.1241 (age in decades) - .2063 (log UOP)+.69 (serum creatinine<2)+0.0828 (BUN per 10)+0.4811 (liver failure)+0.58 (ARDS)+0.5074 (platelet count<150)+0.4803 (sepsis) -1.2563

SHARF Stuivenberg Hospital Acute Renal Failure, PICARD Program to Improve Care in Acute Renal Disease, Anuria CP1=0, CP2=1, Nonoliguria CP1=1, CP2=0, CV cardiovascular, BUN blood urea nitrogen, UOP urine output, ARDS acute respiratory distress syndrome

logistic and linear regression models derived using variables from several other organ systems but illustrates the inapplicability of bedside use of such scoring models. Kidney-specific severity scores have several limitations: they were almost exclusively derived in single centers, they lack discriminatory ability to predict mortality [supported by low area under the curve–receiver operating characteristics (AUC-ROC)] [54], and are inadequate for AKI prediction or progression modeling. Also, the use of RRT is not included in the kidney-specific severity scores. This deliberate exclusion is secondary to the knowledge that a significant proportion the sickest critically ill patients are not offered CRRT or are too unstable to be placed on CRRT. Accordingly, the kidney-specific severity scores offer no information about AKI disease severity and CRRT use. The a priori requirement of a marked creatinine elevation for inclusion in the initial derivation studies eliminates the possibility of analyzing the effect of AKI progression on disease severity and mortality. There are no published kidney-specific severity scores in children. In summary, the benefits of the kidney-specific severity scores for the bedside practitioner, especially the pediatric practitioner, are limited, and none of the scores allow for progressive AKI prediction. However, the use of these scores has highlighted comorbidities commonly associated with increased mortality risk in AKI: age, mechanical ventilation, sepsis, and hypotension with concurrent vasopressor use being the most cited. Combining these comorbidities with early AKI to predict AKI progression may be a valuable tool for the pediatric bedside practitioner but has not as yet been studied.

Stratification scores and AKI

Scores to stratify single-organ disease do not carry predictive power for disease progression in that particular organ. For instance, the Glasgow Coma Scale (GCS), used to assess impaired consciousness in traumatic brain injury,

does not give internal prediction for progression of neurologic injury. Similarly, the Ranson criteria, devised to assess pancreatitis, do not predict progression or resolution of pancreatic injury. To amend the variability within AKI diagnosis [55], in 2002, the Acute Dialysis Quality Initiative Group standardized the definition of AKI using the RIFLE (a mnemonic for three levels of severity: Risk, Injury, and Failure, and two outcomes, Loss and End-stage kidney disease) criteria [56]. Based on glomerular filtration rate (GFR), SCr values, and urine output plotted against time of admission, RIFLE marks progressive degrees of injury in both ICU and non-ICU adult patients. In 2004, the Acute Kidney Injury Network (AKIN) devised strata to define AKI based on time in relation to absolute creatinine increase, percentage increase, or documented oliguria, broadening the window for time of AKI diagnosis and creating an automatic “failure” designation for any patient placed on RRT [57]. In 2007, the pediatric amendment to RIFLE was adopted (pRIFLE) [5], which incorporates changes in creatinine clearance rather than absolute creatinine values. Validation studies of RIFLE and AKIN in adults [15, 58, 59], RIFLE in pediatrics [16], and pRIFLE criteria [60–62] have been published.

Whereas kidney-injury stratification scores describe and quantify AKI progression, they do not predict AKI (Table 5). Several large retrospectively studies have described AKI progression using RIFLE and AKIN, but they do not describe risk factors for progression or offer a methodology for predicting that progression. Patients with the RIFLE subclasses of injury and failure (I and F) have higher mortality rates than patients without AKI or who are in the AKI-R (risk) class [63], so the ability to predict AKI progression would be of great utility to bedside practitioners [15, 16]. In a confirmatory study of regression models used to predict progression of in-hospital AKI to CKD, whereas 5,351/11,589 adults admitted for MI or pneumonia demon-

Table 5 Stratification of kidney injury

Scheme	Stage	Creatinine criteria	Urine output criteria
RIFLE	R – Risk	$\uparrow \geq 1.5x$ or $\downarrow \text{GFR} \geq 25\%$	< 0.5 ml/kg/h for 6 h
	I – Injury	$\uparrow \geq 2x$ or $\downarrow \text{GFR} \geq 50\%$	< 0.5 ml/kg/h for 12 h
	F – Failure	$\uparrow \geq 3x$ or $[\text{Cr}] > 350 \mu\text{mol/L}$	< 0.3 ml/kg/h for 24 h or anuria for 12 h
	L – Loss	Persistent failure > 4 weeks	
	E – End stage	Persistent failure > 3 months	
Pediatric RIFLE (pRIFLE)	R – Risk	$e\text{CrCl} \downarrow \geq 25\%$	< 0.5 ml/kg/h for 8 h
	I – Injury	$e\text{CrCl} \downarrow \geq 50\%$	< 0.5 ml/kg/h for 16 h
	F – Failure	$e\text{CrCl} \downarrow \geq 75\%$ or $e\text{CrCl} < 35$ ml/min/1.73 m ²	< 0.3 ml/kg/h for 24 h or anuria for 12 h
	L – Loss	Persistent failure > 4 weeks	
	E – End stage	Persistent failure > 3 months	
AKIN	Stage 1	$\uparrow \geq 0.3$ mg/dl or \uparrow to 150–200% baseline	< 0.5 ml/kg/h for 6 h
	Stage 2	\uparrow to 200–300% baseline	< 0.5 ml/kg/h for 12 h
	Stage 3	\uparrow to $\geq 300\%$ baseline or ≥ 4.0 mg/dl with an acute \uparrow of 0.5 mg/dl	< 0.3 ml/kg/h for 24 h or anuria for 12 h

GFR glomerular filtration rate, *Cr* creatinine, *eCrCl* estimated creatinine clearance

strated some degree of AKI by RIFLE, models were not developed to predict progression of AKI severity during the actual hospital stay [7]. Progression from R to I to F in pediatrics has been described, though in descriptive fashion and not using methodology that analyzed the risks of progression [16]. A useful methodology for predicting AKI progression, which could immediately aid the bedside clinician, has not adequately been described.

Biomarkers for AKI

AKI researchers have sought novel early, sensitive, and specific biomarkers for AKI. As depicted in Table 6, a

plethora of biochemical markers are under study in both serum and urine of ill patients for established AKI and early detection, prognosis, and association of AKI with death. A recent review of AKI biomarkers illustrates that whereas prospective studies have been performed and several biomarkers perform well for recognition of established AKI [most notably, cystatin C, neutrophil-gelatinase-associated lipocalin (NGAL), and interleukin (IL)-18], very few demonstrate reliable discriminatory ability for predicting AKI severity (by AUC-ROC) [39]. In fact, serum NGAL was unable to identify children who would require RRT, whereas serum cystatin C showed modest discriminatory ability (AUC 0.76). Similarly, in several

Table 6 Biomarkers under study for acute kidney injury (AKI)

Time frame	Established AKI	Early detection	Prognosis	Death	
Serum	NGAL	NGAL	NGAL	NGAL	
	Cystatin C	Cystatin C	Cystatin C	Cystatin C	
	Carb-Hb	Pro-ANP neutrophil-CD11b		IL-6, IL-8, IL-10	
Urine	NGAL	NGAL	NGAL	NGAL	
	IL-18	IL-18	Cystatin C aprotinin	IL-18	
	GST	GST, α -GST	α -GST	KIM-1	
	NAG	NAG	NAG	NAG	
	α -1 microglobulin KIM-1	γ -GT	α -1 microglobulin		
	NHE-3	KIM-1	KIM-1		
	MMP-9		π -GST	β -2-microglobulin	
			MMP-9	GGT	
		AP	LDH		
		LDH			

NGAL neutrophil gelatinase-associated lipocalin, *Carb-Hb* carbamylated hemoglobin, *Pro-ANP* pro-atrial natriuretic peptide, *IL* interleukin, *GST* glutathione S-transferase, *NAG* N-acetyl-glucosamine, γ -*GT* gamma-glutamyltranspeptidase, *MMP* matrix metalloproteinase, *AP* aminopeptidase, *LDH* lactate dehydrogenase, *KIM-1* kidney injury molecule-1

studies, urinary biomarkers were ineffective at predicting AKI progressing to the need for RRT [38, 64]. Neither serum nor urine biomarkers have impressive statistical performance in predicting AKI-associated death [65–67]. Additionally, almost all biomarker studies have analyzed specific biomarker levels (plasma or urine) as cutoffs for rule-in/rule-out analyses (e.g., urine NGAL level 50 ng/ml for AKI in children post-CPB [68]); interpreting exact biomarker values for specific AKI-causing disease processes is thoroughly unexplored. A recent review of biomarker studies performed in children with AKI demonstrates several truths that temper the encouraging results to date for AKI diagnosis or prediction: diagnosis is often based on a SCr change >50% (which, as stated earlier, may be an overestimate of significant injury and may contribute to the high sensitivities reported), cutoff values often sacrifice specificity for high sensitivity, and nearly all derivation studies have been performed in extremely high-risk patients (postkidney transplant or CPB) [69]. Implementation of AKI biomarkers to the general pediatric population, or even the critically ill pediatric population, will continue to demonstrate such statistical bias, and therefore dampen enthusiasm for results, until a structured methodology for identifying tiers of at-risk children is developed.

Renal angina: more than risk stratification

Given the limitations of the SOI and AKI classification systems noted above, we sought to use the available evidence to formulate a concept of RA to identify critically ill patients at-risk for AKI [12]. Risk is informed by baseline and contextual risk factors (e.g., diabetes, high-risk procedures such as CPB), and evidence of injury (FO, oliguria, increased SCr). In short, RA is a clinical guide that identifies patients at high risk for AKI by integrating baseline, contextual, and clinical evidence of kidney injury. For example, patients undergoing CPB and bone marrow transplantation (BMT) are at high risk for AKI, but there is little utility in measuring biomarkers every 6 h in every patient every day. Similarly, patients with sub-RIFLE changes in estimated creatinine clearance (eCrCl) and increases in FO are at risk for progression to more severe AKI, but many do not progress. Furthermore, many patients may present with acutely elevated SCr levels, which may be easily reversible with hydration (prerenal azotemia or fluid-responsive AKI). Thus, RA, which combines baseline and contextual risk factors with various thresholds of evidence of acute kidney dysfunction, from sub-RIFLE to RIFLE changes, should improve the prediction of clinically significant AKI and direct novel biomarker assessment. More importantly, combining RA with biomarkers should improve the positive predictive value of biomarkers to detect AKI development and severity.

RA can be thought of in terms of a simple equation:

$$\text{Renal Angina Threshold} = \text{Risk of AKI} \times \text{Evidence of AKI}$$

Thus, as the AKI risk increases (e.g., BMT patient on vasopressors and mechanical ventilation), less evidence of AKI is needed (small changes in SCr) to meet the threshold for RA. Conversely, a patient with few risk factors of AKI (a young child admitted to ICU for bronchiolitis but not intubated) would require more evidence of AKI in order to achieve the RA threshold. Once patients achieve that threshold, then the task of the clinician is to rule out AKI using AKI biomarkers and other clinical investigations. We believe that this diagnostic framework is consistent with other clinical syndromes and provides an approach that nonnephrology clinicians can use. We proposed three strata of risk groups by tranches (Table 7). As the risk of AKI increases by tranche, the clinical evidence of kidney injury required to achieve RA is decreased. Thus, fulfilling pediatric RA criteria is based on the combination of an initial risk stratification emanating from the underlying clinical state (ICU admission, BMT, or a patient receiving invasive mechanical intubation), with early signs of renal dysfunction (small, sub-RIFLE) changes in SCr, or positive, or mild degrees of positive, fluid accumulation. Admittedly, the availability and ease of calculating changes in eCrCl for a given patient is not universal, especially in pediatric patients without previous illness (and documented baseline SCr levels). Accordingly, we propose that absolute changes in SCr may also be used: very high risk (any change in SCr from baseline for patient of similar age and size per standard reference values), high risk (change in

Table 7 Pediatric renal angina criteria

Hazard tranche	Renal angina threshold
Moderate-risk patients	Doubling of SCr ^a
Patients admitted to PICU ^a	OR
	eCrCl decrease >50%
	OR
	ICU fluid overload >15%
High-risk patients	Serum Cr increase ≥0.3 mg/dl*
• Acute decompensated heart failure	OR
• Stem-cell-transplant recipient	eCrCl decrease 25-50%
	OR
	ICU fluid overload >10%
Very-high-risk patients	Any Serum Cr increase*
Receiving mechanical ventilation	OR
and one or more vasoactive	eCrCl decrease >25%
medications	OR
	ICU fluid overload >5%

PICU pediatric intensive care unit, SCr serum creatinine, OR odds ratio, eCrCl estimated creatinine clearance, ICU intensive care unit

SCr of at least 0.3 mg/dl), and moderate risk (doubling of SCr, which would correlate to an estimated decrease in CrCl of ~50%). Patients who fulfill features of both the risk stratification and the associated threshold for clinical signs of kidney dysfunction are akin to the cardiac angina paradigm to guide troponin assessment. For instance, troponin would not be expected to function well for predicting myocardial ischemia in an otherwise healthy 25-year-old who experienced chest pain after eating a fatty meal. Likewise, troponin should not be drawn on every 85-year-old seen in an emergency room, irrespective of the presence of chest pain just because MIs are more prevalent in older individuals. In fact, when troponin is tested in critically ill patients without signs and symptoms of acute coronary syndrome, it loses its diagnostic capacity.

The three-tiered clinical risk stratification scheme was based on observed AKI rates (defined as pRIFLE-I, or a 50% rise in SCr) in a number of pediatric epidemiological studies. For all ICU patients, AKI rates were reported as 4–10% [16, 70], pediatric BMT recipients had a reported rate of 11–21% [71, 72], and critically ill patients receiving mechanical ventilation had a reported rate of 50% [5, 60]. We termed these strata moderate, high, and very high risk, respectively. The tiers were based on available clinical data with demonstrated risk for developing AKI. Other patients, such as general oncology patients, solid-organ transplant recipients, and immunosuppressed patients, also carry increased AKI risk, but they were grouped together in the moderate-risk groups (ICU admission) for simplicity. With increasing risk strata, thresholds for the corresponding clinical sign (SCr change or percent fluid accumulation) to fulfill RA criteria decreases accordingly. Numerous retrospective pediatric studies demonstrated the potential negative implication of excessive FO. Based on aggregate analysis of data and consensus opinion within the ppCRRT, an estimated 10–15% FO at time of CRRT initiation is associated with increased risk of mortality. Using the 10% number as a median, we established initial thresholds for RA FO to reflect standard intervals above and below based on AKI risk (e.g., 5%, 10%, 15%) [73]. To further relate RA to the troponin-MI paradigm, if a patient has diabetes, hypertension, and smokes, the amount of chest pain or dyspnea required to raise suspicion of acute coronary syndrome is much less than in a thin patient without any of these risk factors. Additionally, we designed criteria with the intent that the negative predictive value should be extremely high in patients who do not fulfill the RA criteria, thus precluding capricious biomarker testing/assessment in patients who will not likely develop AKI.

We must be clear that this point to state that RA as we have conceived it remains an empiric concept, although we are actively testing it in our pediatric ICU population. Once validated and—likely—refined, we hope that RA can serve to optimize biomarker assessment in critically ill children.

Questions: (answers are provided following the reference list)

- Of the following, the recommended therapy for improving mortality rates of AKI is
 - Optimizing renal perfusion with fluid or vasopressors
 - Optimizing nutrition
 - Early recognition and elimination of ongoing agents leading to AKI
 - Diuretics
- Which of the following pediatric illness scores has a weighted contribution for increasing creatinine values?
 - PELOD
 - PRISM I
 - PRISM III
 - SOFA
 - None of the above
- Which AKI stratification levels have been demonstrated to be associated with increased mortality risk in children?
 - pRIFLE R, I, and F
 - pRIFLE I and F
 - AKIN stage 2
 - pRIFLE F only
- The current incidence of AKI in ventilated pediatric ICU patients is:
 - <1%
 - 45–55%
 - 11–20%
 - 4–10%
- To fulfill RA, a mechanically ventilated child on inotropy requires an eCrCl change or an FO of:
 - Decrease by >50% or FO >15%
 - Decrease by >25%, FO >15%
 - Decrease by >50%, no FO requirement
 - Decrease by >25%, no FO requirement
 - Decrease by >25%, FO >5%

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Answers:

1. c
2. e
3. b
4. c
5. e