ASSESSMENT OF RENAL ANGINA INDEX AND CYSTATIN C AS PREDICTIVE MARKERS OF SEVERE ACUTE KIDNEY INJURY IN CHILDREN WITH SEPTIC SHOCK: A PROSPECTIVE OBSERVATIONAL STUDY

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(DECLARATION BY THE CANDIDATE)

DECLARATION

I hereby declare that the thesis titled **"Assessment of Renal Angina Index and Cystatin C as Predictive Markers of Severe Acute Kidney Injury in Children with Septic Shock: A Prospective Observational Study."** embodies the original work carried by the undersigned in the All India Institute of Medical Sciences Jodhpur, (Rajasthan)

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CERTIFICATE

This is to certify that the thesis titled "**Assessment of Renal Angina Index and Cystatin C as Predictive Markers of Severe Acute Kidney Injury in Children with Septic Shock: A Prospective Observational Study.**" is carried out by **Dr. Anil Kumar J S**, a post graduate student in the Department of Pediatrics, AIIMS Jodhpur, in partial fulfilment of the requirement for the degree of **M.D. PEDIATRICS**, is a bonafide work done by him under our direct supervision and guidance.

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LIST OF ABBREVIATIONS

AKI	Acute kidney injury
PICU	Paediatric intensive care unit
SCr	Serum Creatinine
GFR	Glomerular filtration rate
RAI	Renal angina index
CKD	Chronic kidney disease
RRT	Renal replacement therapy
CAKUT	Congenital anomalies of the kidney and urinary tract
KDIGO	Kidney disease improving global outcomes
pRIFLE	Pediatric Risk, Injury, Failure, Loss of kidney function, End-stage renal disease
AKIN	Acute Kidney Injury Network
pROCK	Pediatric reference change value optimized for AKI
AuROC	Area under the receiver operating characteristic
KIM-1	Kidney injury molecule-1
NGAL	Neutrophil gelatinase-associated lipocalin
NAG	N-acetyl-D-glucosaminidase
L-FABP	Liver fatty-acid binding protein
IGFBP	Insulin like growth factor binding protein
TIMP-2	Tissue inhibitor of metalloproteinase-2
ADQI	Acute Dialysis Quality Initiative
eCCl	Estimated creatinine clearance
AWARE	Assessment of Worldwide AKI, Renal Angina and Epidemiology
ATN	Acute tubular necrosis
AGN	Acute glomerulonephritis
HUS	Hemolytic uremic syndrome
TTP	Thrombotic thrombocytopenia purpura
ATP	Adenosine triphosphate
PPAR	Peroxisome Proliferator Activated Receptors
CysC	Cystatin C

FST	Furosemide stress test
hOAT	Human organic acid transporter
UFR	Urinary flow rate
CRP	C- reactive protein
PCT	Procalcitonin
TLC	Total Leucocyte Count
CHF	Congestive cardiac failure
MODS	Multi organ dysfunction syndrome
IQR	Interquartile range
RCT	Randomized control trial
UTI	Urinary tract infection
ACE	Angiotensin converting enzyme
CI	Confidence interval
ECrcl	Estimated creatinine clearance
Psofa	Paediatric sequential organ failure assessment
Max	Maximum

SUMMARY

Background

Acute kidney injury, the leading cause of increased morbidity and mortality in paediatric intensive care units (PICU), requires prompt identification and treatment to avoid further renal damage and progression to chronic kidney disease (CKD). Out of many methods for evaluation of acute kidney injury (AKI), novel methods like use of renal biomarkers and Renal angina index (RAI) are notable one. Renal angina index is a simple, safe, non- invasive, low-cost tool for early prediction of progressive renal impairment. Cystatin- C is an established biomarker for early assessment of renal dysfunction. As there are limited studies on RAI in septic shock children for prediction of severe AKI and lack of comparative tests on RAI and renal biomarkers, present study aims at assessment of RAI and comparison of diagnostic accuracy of RAI and cystatin C for predicting progression to severe AKI in septic shock children.

Objectives

- The primary objective was to validate the use of the Renal angina index in pediatric critical care setup as a predictive marker of severe acute kidney injury (KDIGO stage$\geq$2) in children with septic shock within 7 days of admission.
- The secondary objectives were to evaluate the association between RAI(+) and need of renal replacement therapy, need and duration of mechanical ventilation, duration of PICU stay, mortality and to compare the predictive values of RAI and cystatin C in progression to severe AKI.

Methods

In this prospective cohort study, children between 1 month to 18 years admitted in PICU with septic shock were enrolled. Renal angina index was assessed at 8–12 h after a patient of septic shock was admitted and was used for prediction of severe acute kidney injury within 7 days after admission.Sample for serum and urinary Cystatin C were collected within 12 hours of PICU admission and analysed later after storing at -80 degree Celsius. Urine output monitoring was done and KFT was repeated daily to look for development of severe AKI and children were classified as

AKI according to KDIGO criteria. The need for renal replacement therapy, duration of PICU stay and need and duration of mechanical ventilation and mortality in the enrolled subjects were analysed.

Results

60 patients were enrolled. 55% were males, the median age was 69.2 months (IQR 21-117). 29/60(48.3%) had a positive renal angina index (RAI). Among these, 27/29 (93.1%) patients developed severe AKI (stage 2/3). Among those with negative RAI, 6/31(19.3%) patients progressed to severe AKI. Positive RAI at 8-12 hours of admission showed sensitivity of 93.1%, specificity of 80.6%, PPV 81.8% and NPV of 92.59% with AUROC of 0.82 (95% CI 0.69 to 0.90) in predicting severe AKI within 7 days of PICU admission. Serum cystatin C performed at 12 hours of admission showed good predicting ability for severe AKI with AUROC of 0.89 (95% CI 0.86-0.98). Serum cystatin C demonstrated excellent sensitivity (100%) and good specificity of 90% at cutoff of 1 mg/L, in predicting development of severe AKI.

Diagnostic accuracy of urine cystatin C performed at 12 hours of admission in predicting severe AKI was fair as suggested by AUROC 0.72 (95% CI: 0.60-0.83). Urine cystatin C showed sensitivity of 74.3%, specificity of 80.9 %, PPV 87.8 % and NPV of 62.9% in predicting severe AKI (stage 2 or 3). Fifteen percent children required RRT. RAI showed good diagnostic accuracy in predicting requirement of RRT , AUROC 0.80 (95%CI 0.67-0.89).

17/60 (28.33%) patients died during PICU stay. RAI showed average predicting ability for mortality AUROC 0.65 (95% CI 0.51-0.76). Among RAI positive patients, 26/29 (89.67%) required mechanical ventilation (MV). Diagnostic accuracy of RAI in predicting need of MV was average with AUROC 0.66 (95% CI 0.53-0.78).

Conclusion

Renal angina index serves as a simple bedside tool which has robust predictive value in detecting renal impairment progression in children and also in determining the requirement for renal replacement therapy. The diagnostic value of RAI is comparable with that of serum cystatin C, which has the best diagnostic accuracy in our study. Urine cystatin C has a lower predictive ability than RAI. To conclude , RAI can be used in paediatric ICU for the prediction of severe AKI in septic shock children. Further larger studies are needed to validate these results.

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INTRODUCTION

Acute kidney injury (AKI) often occurs early after paedatric intensive care unit (PICU) admission in patients with septic shock and the incidence is 59–72% [1–3]. During septic shock, decreased cortical renal perfusion is observed by renal contrast-enhanced ultrasound [4]. AKI is independently associated with increased morbidity and mortality [1]. Current management guidelines for patients with AKI recommend that early recognition of AKI risks and augmentation of supportive care will limit AKI progression [5].

Notably, small increases in serum creatinine (0.3 mg/dl) may reflect significant kidney damage and are associated with poor patient outcomes. Primarily due to the lag in the rise of serum creatinine, the diagnosis of AKI is often delayed, which creates a significant barrier to effective early intervention [6, 7]. The serum creatinine (Cr) levels can be affected by many factors, including age, gender, drug, diet, muscle mass, metabolic rate, inflammatory illness, or hepatic disease which can influence serum Cr leading to an inaccurate estimation of renal function impairment. Also, it does not detect renal function impairment until more than 50 % of GFR (glomerular filtration rate) is decreased [8]. One of the ways to solve this problem is to combine other indicators to alleviate the uncertainty of creatinine and urine volume in judging renal function. Extensive research efforts and technological advancements have led to the discovery and validation of biomarkers that diagnose AKI before functional indicators alter and predict AKI severity.

AKI is one of several disorders that impair the structure and function of the kidney. AKI is described as a sudden drop in kidney function, which includes, but is not limited to, ARF. AKI is an intricate clinical syndrome described as the abrupt loss of kidney function, which results in the retention of nitrogenous wastes and the inability of the kidney to regulate fluid and electrolyte homeostasis (9). It is a broad clinical syndrome encompassing various etiologies including specific kidney diseases (e.g., acute interstitial nephritis, acute glomerular and renal vascular diseases); non-specific conditions (e.g., ischemia, toxic injury); as well as extra renal pathology (e.g., pre renal azotemia, and acute post renal obstructive nephropathy). Even mild and reversible AKI has significant clinical implications, including an increased risk of Mortality. As a result, AKI can be compared to acute lung injury or acute coronary syndrome.

Prospective studies in India indicate that AKI affects 4 to 6% of paedatric inpatients in normal wards and up to 40% in PICUs (9). Acute kidney injury is associated with a very poor outcome in critically ill children. Early detection and treatment of AKI reduces morbidity and prevents further renal damage and progression to CKD (chronic kidney disease).

Proteomic technology advancement has prompted substantial research into novel protein markers that may aid in characterizing AKI etiology, easing clinical judgment, and improving risk classification and therapy response tracking (10). As a result, numerous potential markers have been discovered in recent years, such as kidney injury molecule-1 (KIM-1) (11,12) cystatin C (13), neutrophil gelatinase-associated lipocalin (NGAL)(14, 15), uromodulin (16), N-acetyl-D-glucosaminidase (NAG) (17), urinary IL-18 (18), liver fatty-acid binding protein (L-FABP)(19), IGF binding protein-7(20), Tissue inhibitor of metalloproteinase-2 (TIMP-2) (21), etc.

Cystatin C is a small, non-glycosylated (13-kDa) endogenous protein produced in all nucleated human cells at a constant production rate and is unaffected by inflammation (22). Cystatin C is filtered freely through the glomerular membrane and is neither secreted by the tubule, and nor gets reabsorbed back into the serum. It is catabolized in the proximal tubule. As a result, its serum levels depict glomerular filtration rate (GFR). It has been suggested as a substitute for serum creatinine to determine GFR with a higher diagnostic value (23, 24). It can detect renal dysfunction 24–48 h before creatinine (25). Cystatin C plasma level is independent of muscle mass; thus, it is a superior marker of renal function compared to serum Cr in children and patients with muscle loss.

Several previous investigations have shown that serum cystatin C is an early predictor of AKI and an effective predictor of mortality (22). Urinary cystatin C concentration rises with renal tubular damage, regardless of GFR variations. Following AKI, serum cystatin C levels rise earlier than urine levels (26).

Treatment for acute myocardial infarction (MI) was transformed by using troponin I measurements in patients with signs and symptoms of cardiac angina. The sensitivity and specificity of troponin elevations and electrocardiographic changes for MI have allowed practitioners to institute early and life-saving therapy. The clinical and laboratory equivalents of cardiac angina (pain and troponin I) do not exist in the course

of AKI, so the renal angina index (RAI, a product of risk factors and renal injury) was conceptualized. The concept of renal angina index (RAI) combines risk factors and early signs of injury, intending to stratify patients at risk to avoid subsequent AKI. According to reports, RAI can improve the accuracy of the prediction of AKI in critically ill children and young adults. The aim of this study was to evaluate the predicting ability of RAI in predicting subsequent AKI within 7 days after PICU admission in children with septic shock by comparing it with serum and urine cystatin C and serum creatinine elevation.

Table 1: Renal angina index

RENAL ANGINA INDEX	**Score**
Acute kidney injury- risk strata	
Moderate risk: PICU admission	**1**
High risk: History of bone marrow or solid organ transplantation	**3**
Very high risk: Ventilation and inotrope use	**5**
Injury strata	
5% fluid overload or no change in eCrCl	**1**
5% to <10% fluid overload or decrease in eCrCl by 0%-24%	**2**
10% to <15% fluid overload or decrease in eCrCl by 25%-49%	**4**
≥15% fluid overload or decrease in eCrCl by ≥50%	**8**
Total Score = Risk*Injury.	

eCrCl: Estimated creatinine clearance, PICU: Paedatric intensive care unit.

However, there are only a few studies that have assessed the use of renal angina index and cystatin C in early prediction of severe AKI in children and only one study in children with septic shock. Therefore we planned to do this study and also compare renal angina index with other renal biomarkers (cystatin C) to understand the predictive ability of renal angina index.

REVIEW OF LITERATURE

Acute kidney injury in children

AKI is defined as a decrease in glomerular filtration rate (GFR), which is generally characterized by an elevation in serum creatinine from baseline and/or a reduction in urine output.

AKI is a global disease that occurs in the community or in the hospital setting, where it is common in ICUs, medical, surgical, paedatric, and oncology wards. AKI, regardless of its source, is a predictor of both immediate and long-term negative effects (27).

Definition and staging

Recognizing the need for a more standard definition, the Acute Dialysis Quality Initiative (ADQI) Group, which comprised of professionals in adult and paedatric nephrology and critical care, proposed the RIFLE criteria (28), for assessing the severity of acute renal failure in critically ill adult patients. Patients are classified as RIFLE (Risk of Renal Dysfunction, Injury to the Kidney, Failure of Kidney Function, Loss of Kidney Function, and End-Stage Renal Disease) based on increases in blood creatinine levels and/or a decrease in urine output from baseline.

Ackan-Arikan et al. developed pRIFLE (29), a modified version of the RIFLE criteria for paedatric patients, in the year 2000. Instead of variations in serum creatinine concentrations, pRIFLE uses changes in estimated creatinine clearance (eCrCl) and urine output depending on weight. Ackan-Arikan et al. found AKI in 82% of the 150 mechanically ventilated paedatric patients in their study, with the majority of cases occurring within the first week of admission to the Paedatric Intensive Care Unit (PICU). Children with AKI had a mortality rate of 14.6%, compared to 11.1% for those with normal renal function. Table 2 describes the pRIFLE criteria for AKI.

Table 2: pRIFLE criteria of Acute Kidney Injury

	Estimated Creatinine Clearance*	Urine Output
Risk (R)	Decrease by 25%	< 0.5 mL/kg/hr for 8 h
Injury (I)	Decrease by 50%	< 0.5 mL/kg/hr for 16 h
Failure (F)	Decrease by 75% or < 35 mL/min/1.73 m^2	< 0.3 mL/kg/hr for 24 hr or anuric for 12 h
Loss (L)	Loss of renal function for > 4 weeks	
End Stage (E)	End Stage Renal Disease (persistent failure for >3 months)	

*Calculated with Schwartz equation: Length (cm) × K (constant) / serum creatinine

According to additional research, smaller fluctuations in serum creatinine than those addressed by the RIFLE criterion may be associated with unfavorable outcomes. The AKIN criteria proposed a new definition by taking into account these minor changes in serum creatinine values and establishing a period of 48 hours to determine the change in creatinine with no need to first correlate with a baseline value. Additionally, the need for renal replacement therapy (RRT) was taken into account. As a result, the Acute Kidney Injury Network (AKIN) classification was issued in March 2007 (30), which is a modified version of RIFLE based on the following changes: The AKIN classification includes only serum creatinine (SCr) changes, not GFR changes; baseline SCr is not necessary, and at least two SCr values must be obtained within 48 hours. Table 3A shows the AKIN classification.

Table 3A: AKIN Classification of AKI

Stage	Serum Creatinine criteria	Urine output Criteria
1	Increase in SCr ≥26.5 μmol/L (≥0.3 mg/dL) or increase in SCr ≥150 to 200% (1.5- 2×) from baseline	<0.5 mL/kg/h (>6 h)
2	Increase in SCr >200 a 300% (>2 - 3×) from baseline	<0.5 mL/kg/h (>12 h)
3	Increase in Cr >300% (>3×) from baseline or SCr ≥353.6 μmol/L (≥4 mg/dL) with an acute rise in SCr ≥44.2 μmol/L (≥0.5 mg/dL)	<0.3 mL/kg/h (24 h) or anuria (12 h)

The Kidney Disease Improving Global Outcomes (KDIGO) AKI Work Group developed AKI diagnostic and staging criteria in 2012 (31), recognizing the need for a unified diagnosis for practice, research, and public health. Despite differences in incidence and staging due to the use of different categories, all three exhibited similar relationships with patient morbidity and mortality in a comparison study on AKI epidemiology and associated outcomes in hospitalized children using pRIFLE , AKIN, and KDIGO. It also concluded that "KDIGO is applicable to both paedatric and adult populations," citing the "need for a consistent AKI definition" as a benefit. KDIGO criteria for AKI were used in two large, prospective, multinational studies to analyze epidemiology and outcomes in critically ill adults, children the AKI-EPI study (32), and the Assessment of Worldwide AKI, Renal Angina, and Epidemiology [AWARE] study (33). Both studies discovered that AKI, as defined by the KDIGO criteria, increases patients' morbidity and mortality risk. As a result, the current study uses the KDIGO criteria to categorize AKI. Table 3B details the KDIGO criteria for AKI.

Table 3B: KDIGO classification of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥0.3 mg/dl (X26.5 mmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 mmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥24 hours OR Anuria for ≥12 hours

Abbreviation: eGFR- Estimated GFR

pROCK (Paedatric reference change value optimized criterion for AKI in children)

The serum creatinine reference change value is used to calculate pROCK, a new criterion for paedatric AKI. Children with pROCK-defined AKI had a significantly higher risk of mortality when compared to children without AKI (hazard ratio, 3.56; 95% confidence interval, 3.15 to 4.04).

In an issue of the Journal of the American Society of Nephrology, Hou et al. presented their invention of a unique paedatric-specific creatinine-based AKI diagnostic tool called the paedatric reference change value optimal criterion for AKI in children (pROCK) (34). The creation of this classification was motivated by the concern that pRIFLE and KDIGO are problematic in people with low and highly fluctuating blood creatinine levels, which are common in young children. The pROCK AKI diagnostic criteria were bi dimensional.

According to the pROCK AKI diagnostic criteria, paedatric AKI is defined as a serum creatinine elevation of 20mmol/L (0.23 mg/dl) and a 30% increase over baseline. AKI

stage 2 is defined by a serum creatinine increase of 40mmol/L (0.45 mg/dl) and a 60% increase over baseline, while AKI stage 3 is defined by an increase of 80mmol/L (0.91 mg/dl) and a 120% increase over baseline.

Global Incidence:

The prevalence of AKI in children appears to be increasing, and the etiology of AKI has shifted from primary renal disease to multifactorial reasons, particularly in hospitalized children, over the last several decades. Genetic factors can predispose some children to AKI.

Sutherland et al. used the pRIFLE, AKIN, and KDIGO criteria to assess AKI incidence and outcomes in ICU and non-ICU paedatric patients in an observational study of 14,795 hospitalizations between 2006 and 2010. According to pRIFLE, AKIN, and KDIGO, the incidences of AKI in the cohort were 51.1%, 37.3%, and 40.3%, respectively. Patients with AKI had a higher mortality rate across all classes (pRIFLE 2.3%, AKIN 2.7%, and KDIGO 2.5% vs. no AKI (0.8-1.0%)). The prevalence of Stage 3 AKI was 10.8%, 6.7%, and 11.7%, respectively (35).

Rheault et al. (2015) discovered that 336 children with nephrotic syndrome had a 58.6% incidence of AKI when they examined medical data from 17 paedatric nephrology facilities across North America using the pRIFLE criteria (36).

In a single-center study of 8260 ICU patients (37) by Sanchez-Pinto et al., 529 (6.4%) had AKI according to KDIGO criteria at the time of ICU admission, while 974 (11.8%) developed AKI during their ICU stay. Patients without AKI had a 2.7% 28-day ICU mortality rate, while those with AKI had a 25.3% mortality rate. While AKI recovery was associated with a stepwise decline in mortality, AKI progression was independently associated with increased mortality.

A team of researchers affiliated with the American Society of Nephrology's Acute Kidney Injury Advisory Group conducted an extensive review of large cohort studies from 2004 to 2012 to determine the global prevalence of adult and paedatric AKI (38). There were 24 studies involving children among the 312 total studies (n = 49,147,878 patients) found. The rates of AKI incidence and AKI-related mortality in children were 33.7% (95% CI 26.9-41.3%) and 13.8% (95% CI 8.8-21.0%), respectively, according to the study**.**

Indian incidence

AKI was diagnosed in 108 critically ill patients (36.1%) and 34 of 378 non-critically ill patients (9.0%) who were studied prospectively at AIIMS Delhi between February and September 2008 (P=0.001) (39). The most common stages were stage 1 in 48 (65.8%) patients, stage 2 in 13 (17.8%), and stage 3 in 12 (16.4%); dialysis was required in 11 (15%) patients. AKI patients had significantly longer hospital stays (9 days vs 7 days, P = 0.02) and higher fatality rates (37% vs 8.7%; HR 2.73; 95% CI 1.64-4.54).

Table 4: Etiology of AKI

Category	**Abnormality**	**Possible causes**
Pre renal	Hypovolaemia	Haemorrhage Volume depletion Renal fluid loss (over-diuresis) Third space (burns, peritonitis, muscle trauma)
	Systemic vasodilation	Anti-hypertensive medications Gram negative bacteraemia Cirrhosis Anaphylaxis
	Impaired cardiac function	Congestive heart failure Acute myocardial infarction Massive pulmonary embolism
	Increased vascular resistance	Anaesthesia Surgery Hepatorenal syndrome NSAID medications Drugs that cause renal vasoconstriction (i.e. cyclosporine)
	Tubular	Renal ischaemia (*shock, haemorrhage, trauma, perioperative loss, pancreatitis, bacteraemia*)

Intrinsic		Nephrotoxic drugs (*antibiotics, contrast media, antineoplastic drugs, anaesthetic drugs, organic solvents, heavy metals*) Endogenous toxins (*myoglobin, haemoglobin, uric acid*)
	Glomerular	Acute post-infectious glomerulonephritis Lupus nephritis IgA glomerulonephritis Infective endocarditis Goodpasture syndrome Wegener disease
	Interstitium	Infections (*bacterial, viral*) Medications (*antibiotics, diuretics, NSAIDs, and many more drugs*)
	Vascular	Large vessels (*bilateral renal artery stenosis or renal vein thrombosis*) Small vessels (*vasculitis, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, malignant hypertension, thrombotic emboli*)
	Intrarenal obstruction	Nephrolithiasis Blood clots Papillary necrosis
	Extrarenal obstruction	Prostate hypertrophy Improperly placed catheter Bladder, prostate or cervical cancer Retroperitoneal fibrosis

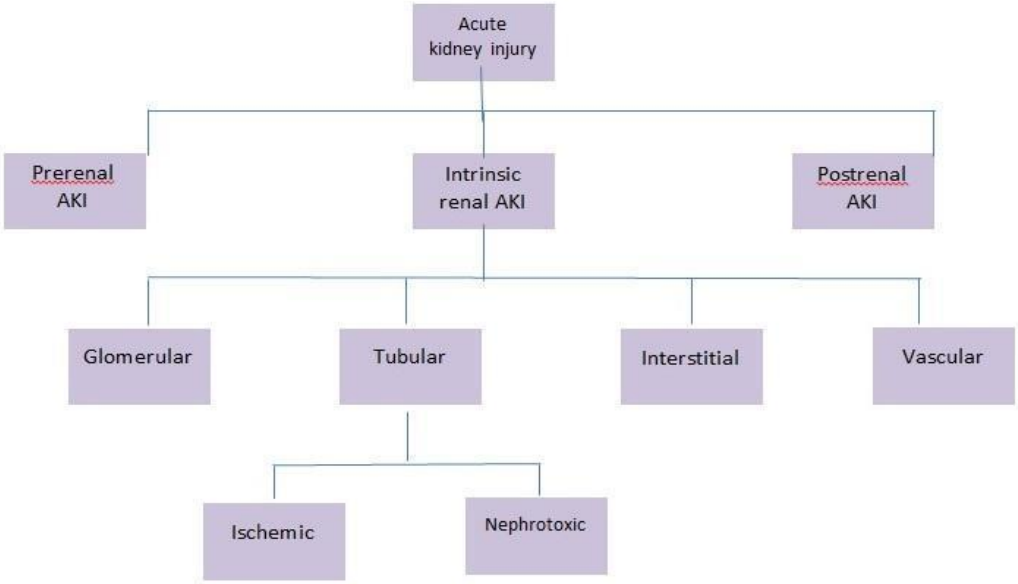

Figure 1: Classification of AKI

AKI is caused by a focal mismatch between oxygen and nutrient delivery to the nephrons (due to compromised microcirculation) and increased energy demands (due to cellular stress). Table 4 describes the various etiologies of AKI.

The three primary groups on which AKI management is based are pre-renal, intrinsic, and post-renal. Figure 1 depicts the classification of AKI.

Pre-renal AKI: Renal hypo perfusion causes a lower GFR as an adaptive response to numerous extra-renal stressors (without harming the renal parenchyma). Because the kidneys receive up to 25% of cardiac output, any systematic or isolated failure of the intra renal circulation can significantly reduce renal perfusion.

Post-renal AKI occurs after an acute obstruction of urinary flow, which raises intra tubular pressure and thus reduces GFR. Acute urinary tract obstruction can also cause decreased renal blood flow and inflammatory processes, which both lower GFR.

A blockage above the bladder must affect both kidneys, and just one kidney in the case of a patient with one functioning kidney, to cause significant renal failure. A patient with pre-existing renal impairment, on the other hand, may develop AKI with only one kidney obstructed.

Intrinsic renal AKI

Glomerular Damage

Acute glomerulonephritis (AGN) can be caused by systemic diseases such as systemic lupus erythematous, bacterial endocarditis, or Wegener's granulomatosis or it can be caused by a primary renal disease such as idiopathic rapidly progressive GN (40).

Tubular Damage

AKI caused by tubular damage is referred to as acute tubular necrosis (ATN). It could be because of:

1. Ischemic - caused by a significant or prolonged decrease in renal perfusion.

2. Nephrotoxic - caused by a variety of renal toxic endogenous (hemoglobin in hemolysis and myoglobin in rhabdomyolysis) and exogenous (aminoglycosides, amphotericin B, cisplatin, radio contrast medium) substances.

Historically, classic ATN goes through a 1-2 week oliguria phase, a 10-14 day non-oliguria phase, and then renal function returns (40).

Interstitial Injury

It can be caused by an allergic reaction to a variety of medications (penicillin, cephalosporin, and sulphonamides) or by an infection (41).

Vascular Damage

When the intra renal arteries are damaged, renal perfusion and GFR are reduced. Some of the conditions that can cause vascular damage (TTP) are malignant hypertension, aeroembolism disease, preeclampsia/eclampsia, and haemolytic uremic syndrome (HUS)/ thrombotic thrombocytopenic purpura (41).

PATHOGENESIS

Tubular Epithelial Cell Apoptosis

Toxin and ischemic insults to the kidney primarily cause tubular epithelial cell Mortality, resulting in decreased kidney function.

1) A high requirement for oxygen and ATP to drive transport functions makes tubular epithelial cells extremely vulnerable.

2) A low oxygen tension environment.

3) The concentration of harmful chemicals inside these cells as they pass through the urine.

Apoptosis is the most common type of cell Mortality in the kidney after ischemia or toxic insults (42, 43).

Immune Mechanisms of AKI

To demonstrate immune mechanisms, an ischemia-reperfusion injury model was used. Because of the low oxygen tension in the renal medulla, the S3 portion of the proximal tubule is more vulnerable to injury (44, 45).

Innate immunological leukocytes, endothelial cells, and epithelial cells cause early ischemia-reperfusion injury and subsequent inflammation. During the early immune response, dendritic cells and macrophages are activated and release cytokines and chemokine's that cause an influx of leukocytes. Later, regulatory T cells and macrophage subsets suppress renal ischemia-reperfusion damage or initiate repair mechanisms (46).

The complement system, which includes the C3 and C5 subunits, influences the pathophysiology of AKI (47).

Peroxisome Proliferator-Activated Receptors

They are nuclear hormone receptors that regulate gene expression and, as a result, a wide range of physiological processes such as lipid metabolism, cellular differentiation, inflammatory reactions, and cell survival.

In response to insults such as ischemia and cisplatin, many enzymes involved in cellular metabolism and homeostasis become less active. PPAR-ligand administration or proximal tubule-specific PPAR overexpression prevents the loss of these enzymes (48).

Pathophysiology of sepsis-induced AKI

Sepsis-related endothelial dysfunction, inflammation, coagulation issues, and adaptive cell responses to injury all contribute to clinical AKI.

Sepsis reduces functional capillary density by decreasing peripheral vascular resistance, redistributing tissue blood flow, and interfering with microcirculatory perfusion.

Even if global renal blood flow is normal or even increased during the early hyper dynamic stage of sepsis, changes in the microcirculation in the renal cortex or renal medulla may occur, increasing renal vascular resistance.

Platelets, fibrin, stiff red blood cells, leukocytes, and endothelial cell edema all contribute to capillary occlusion. Sepsis causes increased renal micro vascular permeability, which causes interstitial edema and fluid retention. As an encapsulated organ, fluid accumulation reduces renal microcirculatory perfusion by altering trans mural pressures and worsening venous congestion (49).

An imbalance between vasoconstrictors, vasodilators, and oxidative stress at the endothelial level with a heterogeneous expression of inducible nitrogen synthase results in augmented vasoconstriction and small vessel occlusion. This locally compromises the microcirculation and causes regional ischemia due to the interaction of leukocytes with activated endothelial cells and activation of the coagulation system.

The cytokine storm that occurs during the early stages of severe sepsis causes leukocyte and platelet activation, micro vascular dysfunction, hypoxia, and tissue destruction. Pro-inflammatory mediators stimulate endothelial cells and increase vascular permeability (50).

Sepsis-related AKI is characterized by oxidative stress. Tubular cells exposed to inflammation adjust to their new tubular environment. Furthermore, they may act in a paracrine manner to spread this signal and shut down additional tubular cells, worsening the already existing AKI (51).

There is a need for specific markers or tests to aid in the early prediction of the development and progression of renal dysfunction, which would aid in the early initiation of treatment to avoid further complications, as delayed diagnosis of acute

kidney injury can result in poor outcomes such as increased morbidity, the development of systemic complications, and high mortality.

Renal biomarkers in AKI

Early detection and treatment of AKI prevents further renal damage and CKD progression, lowering morbidity and mortality. Serum creatinine measurement remains the most practical and widely used method for assessing renal function impairment. However, it is influenced by a number of factors such as age, gender, medication, food, nutritional status, metabolic rate, inflammatory illness, level of hydration, hepatic disease, and others, resulting in an inaccurate assessment of renal function. It is neither sensitive nor specific in response to small changes in GFR and becomes apparent only after the kidneys have lost 50% of their functional capacity (52). As a result, as creatinine accumulates over time, serum Cr detects GFR changes after the injury has occurred. As a result, a better biomarker of renal function was required.

The ideal biomarker should be inexpensive, dynamic, non-toxic, and easy to measure with a quick test using a readily available sample, such as serum or urine. The assay must have high sensitivity, specificity, and prognostic value. The renal biomarker should be freely filtered at the glomerulus without any tubular secretion, reabsorption, or metabolism. It should be unaffected by exogenous substances (53). Table 5 describes the various mechanisms of renal biomarkers.

Proteomic technology's advancement has sparked intense research into new protein markers that could aid in the early detection of renal failure, improve risk stratification, simplify clinical evaluation, and track therapy response. Based on the various mechanisms of new biomarkers (54), it is divided into the following categories:

Table 5: Mechanism of various renal biomarkers

Category	**Example**
Cellular injury-associated protein	Neutrophil gelatinase-associated lipocalin Kidney injury molecule-1 Liver-type fatty-acid-binding protein Tissue inhibitor of metalloproteinase 2 Insulin-like growth factor binding protein 7
Functional biomarker	Cystatin C Proenkephalin
Urinary low-molecular-weight proteins	α1-microglobulin β2-microglobulin Retinol-binding protein Adenosine-deaminase-binding protein Cystatin C
Urinary tubular enzyme	α-glutathione S-transferase pi-glutathione S-transferase γ-glutamyltranspeptidase Alanine aminopeptidase Lactate dehydrogenase N-acetyl-beta-glucosaminidase Alkaline phosphatase
Inflammatory mediators	Interleukin-18

Cystatin C (Cys C)

The CST3 gene encodes the protein cystatin C, which has several properties that make it an ideal surrogate marker of kidney function and thus a better substitute for serum creatinine. All nucleated cells in the human body produce cystatin C, a 13-kDa endogenous cysteine proteinase inhibitor, and it is released into plasma at a relatively constant rate. The glomeruli filter out 99% of protein with little to no protein binding. After glomerular filtration, it is fully catabolized in the proximal renal tubule and is not returned to blood. It is neither reabsorbed nor actively secreted into the lumen of the tubule (55).

It is crucial for the intracellular breakdown of different peptides. Elevated cystatin C levels may be a sign of impending AKI because they represent damage to the tubular epithelium. Compared to serum creatinine, the generation of cystatin C is less affected by age, sex, muscle mass or nutrition. A few studies suggested that increased CRP and interleukin-6 (IL-6) could reduce cystatin C expression when there is inflammation.

Nakhjavan-Shahraki et al. (56) assembled the databases of Medline, Embase, ISI Web of Science, Cochrane library, and Scopus until the end of 2015 for a systematic review and meta-analysis that included 24 publications [1948 children (1302 non-AKI children and 645 AKI cases)]. The performance parameters of cystatin C for predicting AKI were investigated. Children with AKI had significantly higher levels of cystatin C in their urine (SMD = 0.54; 95% CI: 0.34-0.75; p 0.0001) and serum (SMD = 0.96; 95% CI: 0.68-1.24; p 0.0001). The overall area under the curve for serum cystatin C and urine cystatin C in predicting AKI was 0.83 (95% CI: 0.80-0.86) and 0.85 (95% CI: 0.81-0.88), respectively.

The sensitivity and specificity were 0.85 (95% confidence interval: 0.78-0.90) and 0.61 (95% CI: 0.48-0.73), respectively. It was concluded that cystatin C is a good prognostic marker for AKI in children.

Bagheri et al. (2018) conducted a prospective study to assess the efficacy of serum creatinine and serum cystatin C levels in the early detection of AKI (57). The study included 54 participants, 13 of whom had AKI. It was found that patients with AKI had more pronounced changes in cystatin C levels than patients with normal renal function.

The rate of serum cystatin C elevation was higher in AKI patients than the rate of serum creatinine elevation (p 0.05).

Murty et al. conducted a two-year comparison study at a tertiary care hospital in 2013 with 200 healthy volunteers and 130 AKI patients (55). Blood creatinine and serum cystatin C levels were measured in patients with early AKI using RIFLE criteria. While all patients had high blood cystatin C levels at the same time, only 56.2% of patients in the AKI group had normal early serum creatinine levels. According to multiple logistic regression analysis, cystatin C-based GFR predicted worsening AKI more accurately than creatinine-based GFR. As a result, serum cystatin C is a better indicator of renal function in the early stages of AKI.

Safdar et al conducted a prospective cohort study in 2016 to determine the value of using cystatin C in PICU settings for diagnosing AKI progression using pRIFLE criteria (58). Serum creatinine and cystatin C levels in 62 patients were measured at the time of admission (0 h), as well as 6, 12, and 24 h later. AKI affected 32 (51.4%) of these patients. The area under the ROC curve for serum cystatin for the diagnosis of AKI at 0, 6, 12, and 24 h revealed sensitivities of 78, 94, 94, and 83%, respectively. However, the specificities of serum cystatin C at 0, 6, 12, and 24 h were 57, 57, 60, and 50%, respectively. At 0 h, 6 h, 12 h, and 24 h, serum creatinine sensitivity was 50, 65.4, 69.2, and 57.7%, while specificity was 67.7, 70, 60, and 70%. At 12 hours, serum cystatin C was found to be more effective than serum creatinine in the diagnosis of AKI ($p = 0.03$), but no differences were found at 0, 6, or 24 hours. According to the study's findings, serum cystatin is a sensitive but non-specific diagnostic test for AKI in critically ill children. Our study analyzed cystatin C levels at 12 hours, as it has better predictability at 12 hours as described in the above study with sensitivity and specificity of 94% and 60% respectively at 12 hours.

In a 2019 observational study conducted by Ziegelasch et al(59) to establish age and gender-specific cystatin C (Cys C) reference values for healthy infants, children, and adolescents and to relate them to the pubertal stage, height, weight, and body mass index (BMI), it was discovered that during the first two years of life, median cystatin C levels decrease depending on height and weight (from 11 to 14 years old, in males median cystatin C levels rise to 0.98 mg/l, while in females median cystatin C levels fall

to 0.86 mg/l. As a result, in our study, the average cut-off for serum cystatin C positivity was taken as 1.0mg/l.

In their 2019 prospective cohort study, Siddiqua et al discovered a positive relationship between cystatin C and serum creatinine in evaluating the progression of AKI in 34 critically ill children (60). The cut-off for urine cystatin C was taken as 0.1mg/l, as at this cut-off, it had maximum sensitivity and specificity.

Renal Angina Index

Small increases in serum creatinine may indicate severe kidney impairment and be linked to unfavorable patient outcomes, making creatinine a late measure of acute kidney injury (AKI). Researchers studying AKI refer to the search for AKI biomarkers as the "search for the renal troponin I," meaning that earlier detection of AKI biomarkers would enable earlier management. Unlike myocardial infarction, AKI does not hurt. Thus, there is no validated equivalent of chest pain or angina equivalent to increasing suspicion of AKI presence on the part of the clinician. Troponin's performance in detecting a heart attack is marginal in the absence of proper context. Renal angina was proposed as an empirical concept for developing an AKI risk threshold to identify patients who would benefit the most from a confirmatory AKI biomarker test. In short, renal angina is a clinical tool that identifies patients at high risk for AKI by integrating baseline, contextual, and clinical evidence of kidney injury. When criteria for fulfilling renal angina are met, an AKI biomarker (a renal troponin) is optimally used (Figure 1 - Renal Angina Index Thresholds).

The AKI risk factors used for renal angina criteria were derived from population literature on AKI in adults and children. The most common risk factors are sepsis, mechanical ventilation, and the use of inotropic or vasopressor support. Relatively common co-morbid risk factors can also be age specific (for example, diabetes in adults and bone marrow transplantation (BMT) in children) (61).

Early signs of kidney injury used to determine renal angina are changes in serum creatinine and the degree of fluid overload (FO). Small changes in serum creatinine levels have been linked to a high rate of progression to severe AKI and worsened in-hospital morbidity and mortality.

Fluid overload (FO) is calculated as

FO = [(Fluid IN – Fluid OUT (L)) / (Admit weight in kilograms)] * 100 (62).

The RAI was created to put renal angina construct into action. The equation's logic dictates that as a patient's risk increases, they require less "clinical sign of AKI" early on to fulfill renal angina. Similarly, if a patient is at lower risk but exhibits more overt signs of clinical AKI, renal angina is met. According to the epidemiology of AKI, the risk of AKI multiplies with increased risk factors. For higher-risk patients, the incidence of AKI increases by a factor of five to ten to fifty percent. In the case of fluid overload, the same increase is observed retrospectively. The risk of Mortality in AKI patients increases in a similar manner with increasing AKI severity. Thus, the concept renal angina index was done by multiplication of risk and injury signs.

The RAI score is a combination of risk factors and clinical signs. Risk strata were assigned point values of 5 (very high risk), 3 (high risk), and 1 (low risk). Changes in estimated creatinine clearance (eCrCl) or percentage fluid overload (% FO) are used to diagnose the injury. The point values assigned are as follows: 1 (ICU status with no decrease in eCrCl or 5% FO), 2 (> 5% FO or eCrCl decrease of 0-25%), 4 (>10% FO or eCrCl decrease of 25-50%), or 8 (>15% FO or eCrCl decrease of > 50%). The RAI's composite range is thus: 1, 2, 3, 4, 5, 6, 8, 10, 12, 20, 24, and 40.

Table 6: Review of literature

Sl no.	Author and year	Study	Outcome
01	Nejat et al. 2010 (63)	Urinary cystatin C is diagnostic of acute kidney injury and sepsis, and predicts mortality in the intensive care unit.	AUCs for diagnosis by using Urine Cys C were as follows: sepsis, 0.80, (95% confidence interval (CI), 0.74 to 0.87); AKI, 0.70 (CI, 0.64 to 0.75); and death within 30 days, 0.64 (CI, 0.56 to 0.72). urine Cys C remained independently associated with sepsis, AKI, and mortality with odds ratios (CI) of 3.43 (2.46 to 4.78), 1.49 (1.14 to 1.95), and 1.60 (1.16 to 2.21), respectively.
02	Zhang et al 2011(64)	Cystatin C in prediction of acute kidney injury: A systemic review and meta-analysis	Across all settings, the diagnostic OR for serum Cys C level to predict AKI was 23.5 (95% CI, 14.2-38.9), with sensitivity and specificity of 0.84 and 0.82, respectively. The area under the receiver operating characteristic curve (AUROC) of serum Cys C level to predict AKI was 0.96 (95% CI, 0.95-0.97)
03	Basu et al 2013 (65)	Derivation and validation of the renal angina index to improve the prediction of acute kidney injury in critically ill children	Incidence rates for a Day 0 RAI of 8 or more were 15–68% and Day-3 AKI was 13–21%. In all cohorts, Day-3 AKI rates were higher in patients with an RAI of 8 or more with the area under the curve of RAI for predicting Day-3 AKI of 0.74–0.81. An RAI under 8 had high negative predictive values (92–99%) for Day-3 AKI.
04	Basu et al 2014 (66)	Incorporation of biomarkers with the renal angina index for prediction	Individual biomarkers demonstrated marginal discrimination for severe AKI (area under curve [AUC]: NGAL, 0.72;

		of severe AKI in critically ill children	MMP-8, 0.68; Ela-2, 0.72), inferior to prediction by the clinical model of the RAI (AUC=0.80). The inclusion of each biomarker with the RAI demonstrated NRI (0.512,0.428, and 0.545 for NGAL, MMP-8, and Ela-2, respectively; all P,0.03) and IDI (0.075 for Ela-2). The inclusion of both Ela-2 and NGAL with RAI demonstrated an NRI of 0.871 (P,0.001) and an IDI of 0.1 (P=0.01).
05	Basu et al(67) 2016	Sepsis-associated acute kidney injury- is it possible to move the needle against this syndrome?	Reported data on the predictive factors of death in patients with sepsis-associated AKI. In their retrospective evaluation of 77 children with sepsis and AKI, the rate of severe AKI (pRIFLE stage I---F and/or stage 2---3 were both over 75%) and the overall mortality was substantial (33.7%).
06	Basu et al (68) 2017	Assessment of a renal angina index for prediction of severe acute kidney injury in critically ill children: a multicentre, multinational, prospective observational study	The primary outcome was the presence of severe acute kidney injury on day 3 after ICU admission. Patients with severe acute kidney injury before day 3 or after day 3 were not included as positive for severe acute kidney injury. The primary analyses tested the diagnostic utility of the renal angina index for the prediction of this outcome compared with serum creatinine concentration relative to baseline.
07	Kaur et al (69)2018	Utilization of the renal angina index in PICU of a developing country for	RAI could be used as a simple and important bedside tool to predict patients at risk of severe AKI.

		prediction of subsequent severe acute kidney injury	
08	Sundararaju, et al (70) 2019	Renal Angina Index in the prediction of acute kidney injury in critically ill children	RAI usefully predicts the development of subsequent severe AKI on days 3 and 7, and is associated with duration of mechanical ventilation and hospital stay. A higher RAI threshold (≥12 or ≥20) is more discriminatory than RAI ≥8.
09	Gawadia, et al (71)2019	Prediction of severe acute kidney Injury using renal angina index in a paedatric intensive care unit.	Day 0 Renal angina index positivity is a promising tool to identify critically ill children with impending severe AKI.
10	Abbasi et al 2020 (72)	Discriminatory precision of renal angina index in predicting acute kidney injury in children; a systematic review and meta-analysis	The study showed area under the ROC curve of RAI in prediction of AKI was 0.88 [95% (CI): 0.85 to 0.91]. Sensitivity and specificity of this tool in predicting AKI were 0.85% (95% CI: 0.74% to 0.92%) and 0.79% (95% CI: 0.69% to 0.89%), respectively. The diagnostic odds ratio of RAI was 20.40 (95% CI: 9.62 to 43.25).
11	Huang et al (73) 2020	Assessment of early renal angina index for prediction of subsequent severe acute kidney injury during septic shock in children.	Early RAI could be used as a more convenient and effective index to predict the risk of AKI in children with septic shock within 3 days. Early RAI combined with serum lactate improved the predictive performance for assessing AKI.
12	Budi et al (74) 2020	Renal angina index in paedatric septic patients as a predictor of acute kidney injury in a remote area.	In this prospective observational study, they have found that the use of RAI as a predictor for the occur-rence of severe AKI in paedatric septic patients was

			reliable compared to using serum creatinine increase based on KDIGO criteria.
13	Francisco et al 2021(75)	Assessment of the renal angina index for the prediction of acute kidney injury in patients admitted to a European paedatric intensive care unit.	RAI presented a sensitivity of 87.5% and a specificity of 88.1%. Prediction of day 3 all-stage AKI by RAI had an AUC=0.878; its performance increased for severe AKI (AUC = 0.93).
14	Meena et al 2022 (76)	Diagnostic accuracy of renal angina index alone or in combination with biomarkers for predicting acute kidney injury in children	RAI + had sensitivity 86% specificity 77%, and AUC of 0.88 (0.85–0.91) for prediction of severe AKI on day 3.
15	Goldstein et al 2022 (77)	Integration of the renal angina index and urine neutrophil gelatinase-associated lipocalin improves severe acute kidney injury prediction in critically ill children and young adults	RAI was ≥8. RAI <8 had negative predictive value (NPV) of 0.98 (95% CI 0.97-0.99); RAI ≥ 8 had positive predictive value (PPV) of 0.37 (95% CI 0.30-0.46) to predict days 2 to 4 sAKI (area under the receiver operating characteristic curve [AUC-ROC] 0.88 [95% CI 0.84-0.92]). Of 147 RAI+ patients, 89 had NGAL available. RAI/NGAL combination improved PPV (0.64, 95% CI 0.50-0.79) without decrement in NPV (0.98, 95% CI 0.97-0.98).

LACUNAE IN LITERATURE

- Lack of studies on assessment of renal angina index in predicting AKI in children with septic shock, especially in developing countries.
- Lack of comparative studies of RAI and other renal biomarkers among children with septic shock for prediction of AK

AIM AND OBJECTIVES

Primary objective

- To validate the use of the renal angina index in paedatric critical care setup as a predictive tool for severe acute kidney injury (KDIGO stage≥2) in children with septic shock within 7 days of admission.

Secondary objectives

- To assess the predicting ability of RAI for the need of renal replacement therapy.
- To compare the predictive values of RAI and Cystatin C in the early detection of AKI.
- To assess the predicting ability of RAI for the need and duration of mechanical ventilation and the duration of PICU stay.
- To assess the predicting ability of RAI for the mortality.

MATERIALS AND METHODS

Setting: PICU and Paedatric emergency of AIIMS, Jodhpur.

Study design: Prospective cohort study

Sample Size- Convenience sampling was taken

Inclusion criteria:

- All consecutively hospitalized patients aged 1 month to 18 years' old who were admitted with septic shock.
- Those whose parents gave written informed consent.

Exclusion criteria:

- Children with CKD.
- Children with obstructive uropathy.
- Children with KDIGO stage-2 and 3 AKI at admission

Methodology

1. This prospective cohort study was conducted in children from one month of age to 18 years admitted with septic shock to the paedatric intensive care unit.
2. All children fulfilling the inclusion criteria had their demographic data and anthropometric values recorded along with their primary diagnosis, duration of illness, and duration of stay in PICU/ Paedatric emergency. Baseline vitals, urine output, GFR, baseline urea, creatinine and albumin, CBC, CRP, PCT, and blood culture were recorded. Daily p SOFA, Vasoactive inotropic scores were calculated. Serum lactate was recorded. Ultrasound KUB records were reviewed, to rule out obstructive uropathy.
3. All children fulfilling the inclusion criteria was assessed for the presence of other co-morbidities like HTN, CHF, DM, and cirrhosis. Use of nephrotoxic drugs, history of cardiac surgery, and presence of sepsis were documented.

4. Baseline data at admission comprised of demographic information, including age, sex, primary diagnosis, the system involved, renal dysfunction using KDIGO (kidney disease improving global outcomes) staging, and baseline serum creatinine measurement (SCr).

5. Renal angina index calculation for the fulfillment of renal angina was assessed 8–12 h after a patient was admitted to the PICU and was used for prediction of severe acute kidney injury within 7 days of PICU admission. Risk factors were assigned a score: of 1, 3, or 5 (where 1 denotes the lowest risk and 5 denote the highest risk). Mechanical ventilation and vasoactive support was used within the 12-h time point but were not required simultaneously for a patient to be scored 5 points.

6. Injury score was assigned to a patient on the basis of fluid overload percentage and estimated glomerular filtration rate (eGFR) reduction. Percentage fluid overload (FO %) was calculated by [Fluid in (ml) − fluid out (ml)] ÷ Patient Weight (gm)} × 100) [15]. eGFR was based on estimated creatinine clearance (eCrCl) calculated by the Schwartz equation, for the determination of RAI. Renal angina index (range 1 to 40) was calculated by multiplication of the risk and injury scores assigned (risk score × FO% score or risk score × GFR score), whichever of the two was worse. The index RAI ≥ 8 was considered renal angina positive (RA+). A score of < 8 was denoted renal angina negative (RA−). The components of renal angina are presented in Table 1.

7. The primary outcome was the presence of severe AKI within 7 days of admission. Severe AKI is defined by the KDIGO stage ≥ 2: serum creatinine of 200% baseline (a decrease in eCrCl of ≥ 50% from baseline). Secondary outcomes included the use of renal replacement therapy (RRT), the need and duration of mechanical ventilation, length of PICU stay (LOS), and incidence of mortality.

8. Urine output monitoring was continued and daily serum urea and creatinine were sent to look for progression into AKI KDIGO Stage 2 (Increase in serum creatinine by 2-2.9 times the baseline OR urine output less than 0.5 mL/kg/h for ≥12 hours) or stage 3 (Increase in serum creatinine by ≥3 times the baseline OR

Increase to ≥4 mg/dL OR Urine output less than 0.3 mL/kg/h for 24 hours OR Anuria for ≥12 hours).

9. The additional serum and urine samples collected for biomarker assay (cystatin C) 12 hours after admission were transported using frozen ice packs. Samples were centrifuged at 3000 rpm for 15 minutes at room temperature and were aliquoted in cryovials and stored at −80 degree C.
10. Once the adequate numbers of samples were collected, the samples were analyzed using the Human Cystatin C ELISA kit and read using a micro plate reader with a 450 nm filter. Values >1mg/L were considered serum Cystatin C positive.
11. Vasoactive inotropic score (VIS) was calculated daily.
12. VIS= dopamine dose (mcg/kg/min) + dobutamine dose (mcg/kg/min) + 100 x epinephrine dose (mcg/kg/min) + 10 x milrinone dose (mcg/kg/min) + 10,000 x vasopressin dose (units/kg/min) + 100 x norepinephrine dose (mcg/kg/min).
13. Paediatric sequential organ failure assessment (pSOFA) score was calculated daily. The score is detailed in Table 7 (80).

Table 7: p SOFA score (paedatric sequential organ failure assessment) (80)

	Score[a]				
Variables	**0**	**1**	**2**	**3**	**4**
Respiratory					
$Pao_2:Fio_2$[b] or $Spo_2:Fio_2$[c]	≥400	300-399	200-299	100-199 With respiratory support	<100 With respiratory support
	≥292	264-291	221-264	148-220 With respiratory support	<148 With respiratory support
Coagulation					
Platelet count, $\times 10^3/\mu L$	≥150	100-149	50-99	20-49	<20
Hepatic					
Bilirubin, mg/dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular					
MAP by age group or vasoactive infusion, mm Hg or µg/kg/min[d]					
<1 mo	≥46	<46	Dopamine hydrochloride ≤5 or dobutamine hydrochloride (any)	Dopamine hydrochloride >5 or epinephrine ≤0.1 or norepinephrine bitartrate ≤0.1	Dopamine hydrochloride >15 or epinephrine >0.1 or norepinephrine bitartrate >0.1
1-11 mo	≥55	<55			
12-23 mo	≥60	<60			
24-59 mo	≥62	<62			
60-143 mo	≥65	<65			
144-216 mo	≥67	<67			
>216 mo[e]	≥70	<70			
Neurologic					
Glasgow Coma Score[f]	15	13-14	10-12	6-9	<6
Renal					
Creatinine by age group, mg/dL					
<1 mo	<0.8	0.8-0.9	1.0-1.1	1.2-1.5	≥1.6
1-11 mo	<0.3	0.3-0.4	0.5-0.7	0.8-1.1	≥1.2
12-23 mo	<0.4	0.4-0.5	0.6-1.0	1.1-1.4	≥1.5
24-59 mo	<0.6	0.6-0.8	0.9-1.5	1.6-2.2	≥2.3
60-143 mo	<0.7	0.7-1.0	1.1-1.7	1.8-2.5	≥2.6
144-216 mo	<1.0	1.0-1.6	1.7-2.8	2.9-4.1	≥4.2
>216 mo[e]	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	≥5

14. Statistical analysis of the predicting ability of RAI and serum cystatin C, urine cystatin C for severe AKI were done. The standard curve of cystatin C is shown in fig 2.

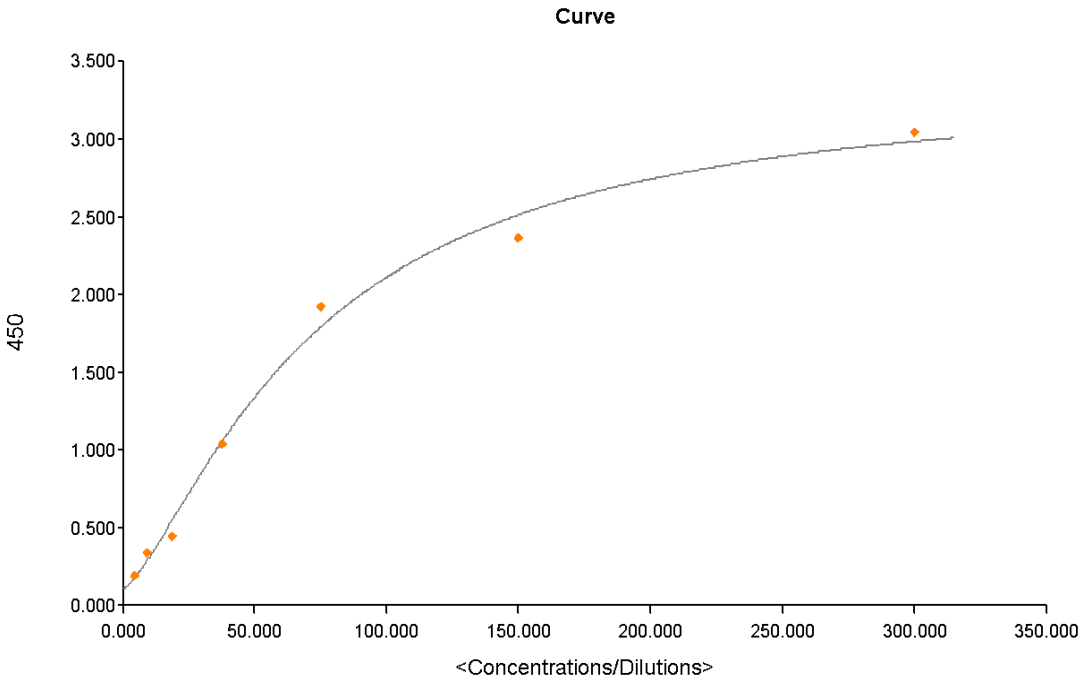

Figure 2: Standard curve of Cystatin-C

Definitions

- **Systemic inflammatory response syndrome (SIRS)** (78) is defined by two or more of the following of which one has to be fever or abnormal peripheral WBC count:

• Temperature >38.4°C or > 36°C

• Heart rate >160/min in infants and >150/min in children

• Respiratory rate >60/min in infants and >50/min in older children

• Peripheral white blood cell count <4000/mm3 or > 12,000/mm3 or >10% band forms

- **Sepsis:** SIRS due to infection (78)

Septic shock (79): Suspected or confirmed sepsis with cardiovascular dysfunction (clinical signs of inadequate tissue perfusion including any of the following criteria - capillary refill time >2 seconds or <1 second, cool extremities (as compared to core temperature over the sternum), feeble or bounding peripheral pulses, hypotension (systolic BP <5th centile as per PALS guidelines) and decreased urine output.

KDIGO defines **AKI** as any of the following:

Stage 1: Increase in serum creatinine by 1.5-1.9 times the baseline within 7 days or increase by ≥0.3 mg/dL (26.5 µmol/L) within 48 hours.

OR

Urine output less than 0.5 mL/kg/h for 6-12 hours

Stage 2: Increase in serum creatinine by 2-2.9 times the baseline

OR

Urine output less than 0.5 mL/kg/h for ≥12 hours

Stage3: Increase in serum creatinine by ≥3 times the baseline OR Increase to ≥4 mg/dL (353.6 µmol/L) OR Renal replacement therapy initiation OR decrease in estimated GFR to <35 mL/min/m^2

OR

Urine output less than 0.3 mL/kg/h for 24 hours OR Anuria for ≥12 hours

Sample Size calculation

Convenient sample size was taken. All the consequent patients meeting eligibility criteria were enrolled in the study between March 2021 to September 2022.

Statistical analysis:

Data was analyzed using IBM-SPSS (IBM SPSS Statistics for Windows, version 23.0, released in 2011; IBM Corp., Armonk, NY, USA). Categorical data was expressed as a percentage, and compared using Chi-square or Fisher's exact test and/or relative risk (RR) (95% CI). Continuous data was expressed as mean ± standard deviation (SD) or median (interquartile range) and compared using parametric or nonparametric tests, as appropriate, and mean difference (95% CI); $P \leq 0.05$ was considered statistically significant. The diagnostic utility of RAI and serum cystatin C in predicting various outcomes was assessed, using receiver operating characteristic curve (sensitivity, specificity, negative and positive predictive values and estimates of area under the curve (AUC).

Ethical considerations:

Research ethics approval: The study was undertaken after the ethical clearance from the institute`s ethical committee.

Consent:

1. Informed written consent was obtained by the candidate.

2. The purpose and information regarding the study was explained to the child's parents.

3. The parents or consenting guardian was informed that they can ask to withdraw from the study at any time without having reasons for the same.

Confidentiality:

The confidentiality of information obtained was maintained and revealed only to the doctor/auditor involved in the study and if required to regulatory authorities.

OBSERVATIONS AND RESULTS

Total of 941 children admitted to Paediatric emergency were assessed for eligibility during the study period, out of which 140 (14.8%) children developed septic shock. Out of 140 children, 43 children were diagnosed with cases of chronic kidney disease (CKD), 27 children were already in stage 2/3 of AKI at the time of enrolment and 10 patients didn't give informed consent, and hence were excluded. 60 children fulfilled the eligibility criteria and were enrolled after taking informed consent. The study flow chart is given in figure 3.

Out of the 60 enrolled children, 33 (55%) were males and 27 (45%) were females. 22(36.67%) of them were infants, 13 (21.67%) children were between the age group of 1-5 years, and 25(41.67%) belonged to the age group of 6 years to 18 years, with the median age being 69.23 (IQR 21-117) months. The age-wise and gender distribution of the participants are given in figure 5 and figure 6 respectively. Among the recruited patients, etiologically, 10 (16.67%) had primarily central nervous system (CNS) involvement, 13 (21.67%) had underlying respiratory system disorders, 8 (13.33%) had cardiovascular system (CVS) pathology, 1(1.67%) had renal involvement primarily,8 (13.33%) hemat-oncology system involvement, 5 (8.33%) had trauma, accidents and poisoning, 6 (10%) were infectious disease patients, 2(3.33%) endocrinology disorders, 7 (11.67%) children had abdomen as the primary system involvement. The diagnosis at admission is detailed in figure 7.

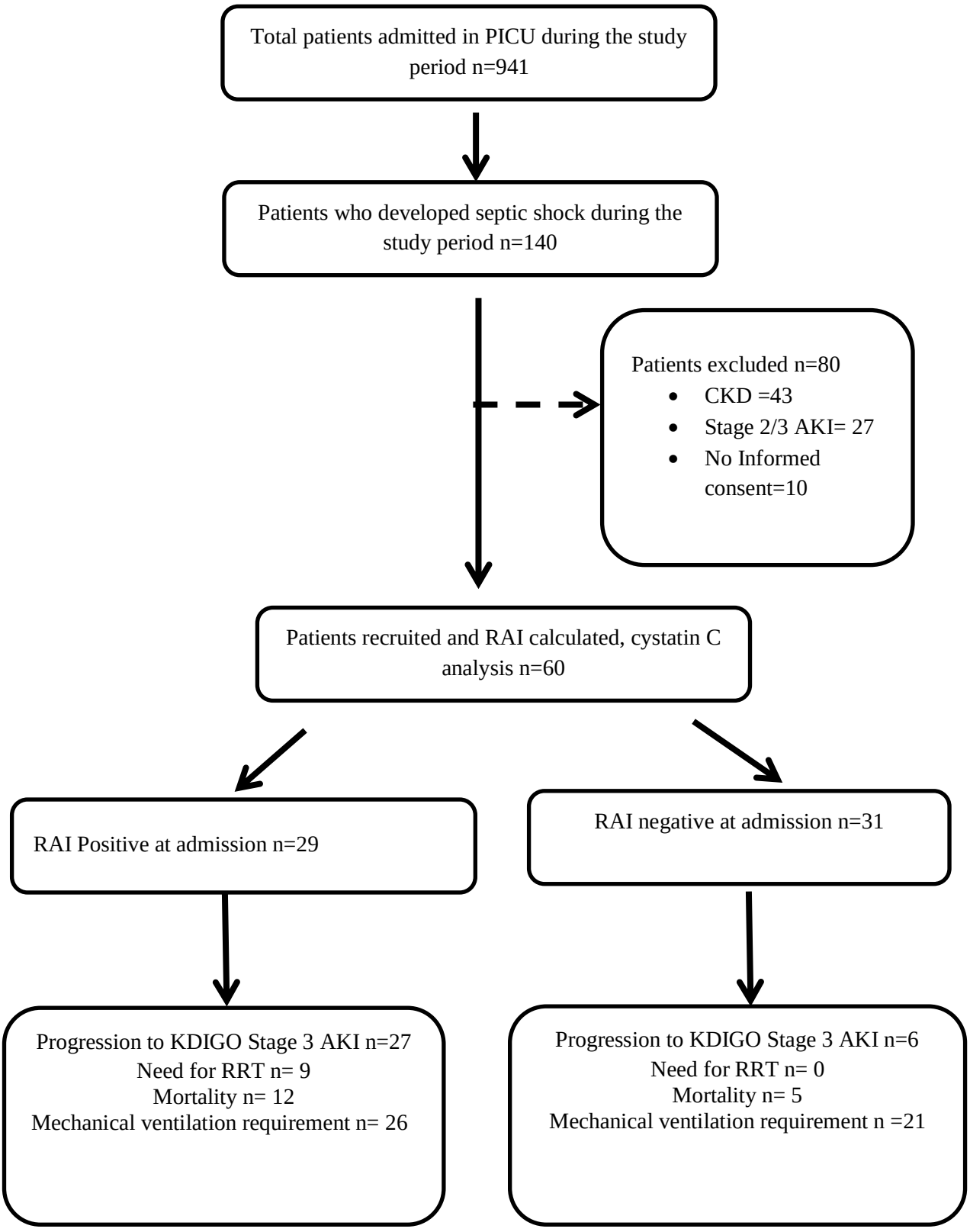

Figure 3: Study flow diagram

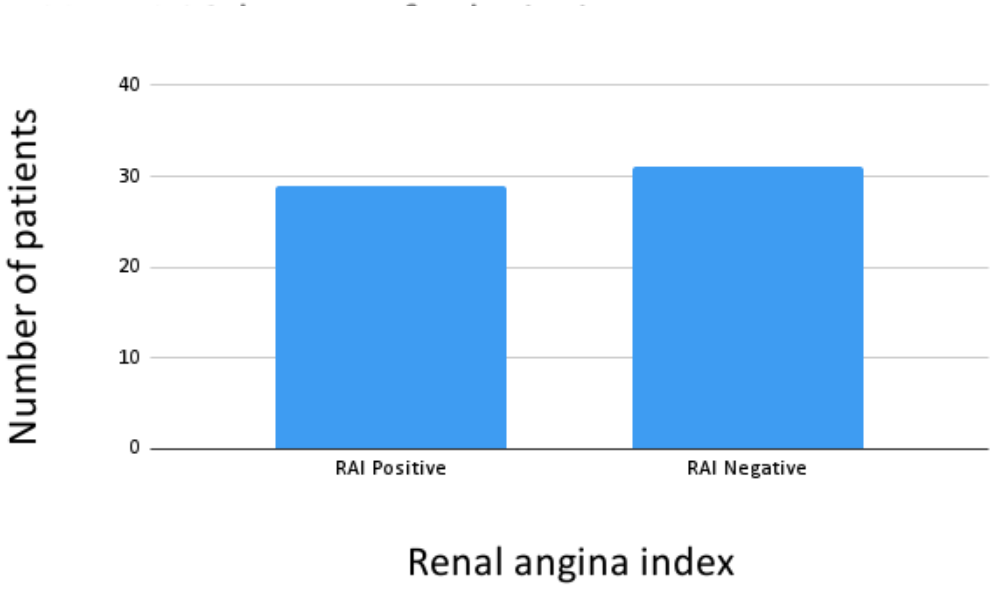

Figure 4: RAI at 12 hours of admission

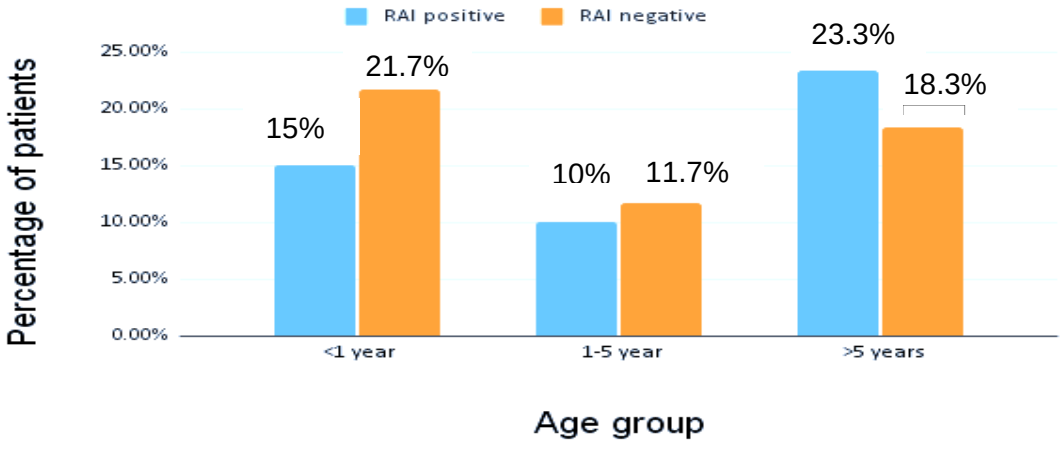

Figure 5: Age-wise distribution of patients

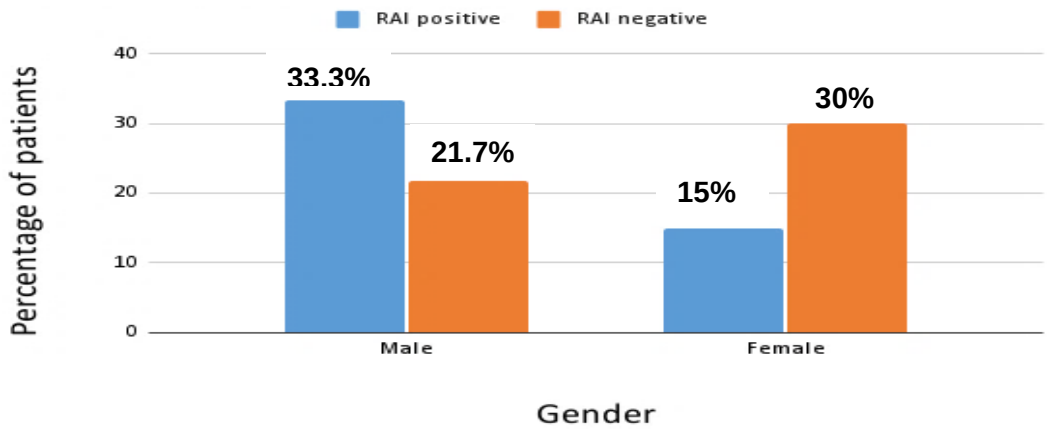

Figure 6: Gender-wise distribution patients

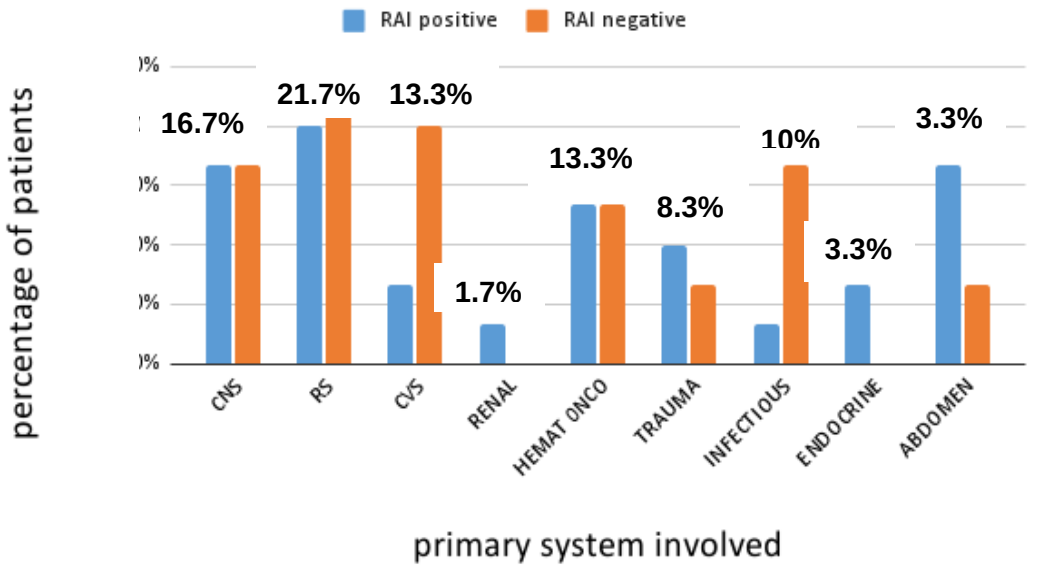

Figure 7: System wise distributions patients

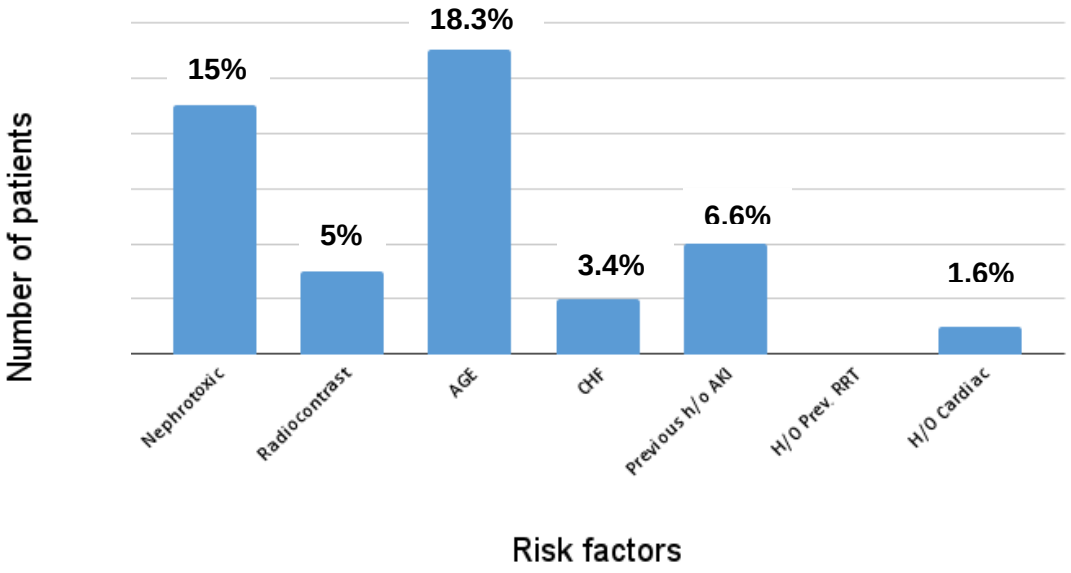

Figure 8: Risk factors for AKI

On evaluating risk factors for developing AKI among enrolled subjects, 9 (15%) patients had exposure to nephrotoxic drugs. 3 (5%) children had exposure to radio-contrast agents and acute gastroenteritis in 11 (18.3%) children, h/o previous AKI in 4 (6.6%) children, CHF in 2(3.3%) children, h/o cardiac surgery (1.6%) children. None of the participants had a significant family history of renal dysfunction and none had a previous history of renal replacement therapy. Risk factors for AKI have been described in figure 8.

Patients were distributed into two groups (Table 8) according to the RAI score (negative vs. positive) at 12 hours of admission. In total, 48.3% of patients had an RAI ≥ 8. The patient demographics characteristics among RAI positive and negative groups are depicted in table 8.

Table 8: Patient characteristics

Demographics		Positive	Negative	Total
		N (%)	N (%)	N (%)
Age (years)	<1	9(15%)	13(21.7%)	22(36.7%)
	1-5	6(10%)	7(11.7%)	13(21.7%)
	6-18	14(23.3%)	11(18.3%)	25(41.7%)
Gender	Male	20(33.3%)	13(21.7%)	33(55%)
	Female	9(15%)	18(30%)	27(45%)
Primary system involvement	Central nervous	5(8.3%)	5(8.3%)	10(16.7%)
	Respiratory	6(10%)	7(11.7%)	13(21.7%)
	Cardiovascular	2(3.3%)	6(10%)	8(13.3%)
	Renal	1(1.7%)	-	1(1.7%)
	Hematoncology	4(6.7%)	4(6.7%)	8(13.3%)
	Trauma and accidents, Poisoning	3(5%)	2(3.3%)	5(8.3%)
	Infectious Disease	1(1.7%)	5(8.3%)	6(10%)
	Endocrinology	2(3.4%)	-	2(3.3%)
	Abdomen	5(8.3%)	2(3.3%)	7(11.7%)
Nephrotoxic drug usage	Present	4(6.7%)	5(8.3%)	9(15%)
	Absent	25(41.7%)	26(43.3%)	51(85%)
Radio-contrast usage	Yes	0	3(5%)	3(5%)
	No	29(48.3%)	28(46.7%)	57(95%)
Envenomation	Positive	0	0	0
	Negative	29(48.3%)	31(51.7%)	60(100%)
Acute gastroenteritis	Present	8(13.3%)	3(5%)	11(18.3%)
	Absent	21(35%)	28(46.7%)	55(91.7%)
H/O AKI in Previous admission	Present	4(6.7%)	0	4(6.7%)
	Absent	25(41.7%)	31(51.7%)	56(93.3%)
H/O renal replacement therapy in past	Present	0	0	0

	Absent	29(48.3%)	31(51.7%)	60(100%)
H/O Cardiac surgery	Present	0	1(1.7%)	0
	Absent	29(48.3%)	30(50%)	59(98.3%)
H/O Significant family history AKI	Yes	0	0	0%
	No	29(48.3%)	31(51.7%)	60(100%)
Previous ultrasound abnormal	Not Available	26(43.3%)	24(40%)	50(83.3%)
	Present	1(1.7%)	1(1.7%)	2(3.3%)
	Absent	2(3.3%)	6(10%)	8(13.3%)
AKI at admission	No	27(45%)	31(51.7%)	58(96.7%)
	Stage 1	2(3.3%)	0	2(3.3%)
Comorbidities	Hypertension	1(1.7%)	0	1(1.7%)
	Diabetes mellitus	1(1.7%)	0	1(1.7%)
	Congestive heart failure	2(3.4%)	0	0
	Cirrhosis	0	0	0

Diagnostic accuracy of RAI in predicting severe AKI

TABLE 9: Association between Renal angina index positivity at 12 hours and progression to severe AKI

		RAI Positive	RAI Negative	Total Patients
		N (%)	N (%)	N (%)
Progression to severe AKI	Present	27(45%)	6(10%)	33(55%)
	Absent	2(3.3%)	25(41.7%)	27(45%)
Total		29(48.3%)	31(51.7%)	60(100%)

AUC=0.81, P=0.05, (95% CI 0.70 - 0.90)

Patients were distributed into two groups (Table 8) according to the RAI score (negative vs. positive) at 12 hours of admission. In total, 48.3% of patients had an RAI ≥ 8. Urine output monitoring was continued and daily serum urea and creatinine were sent to look for progression into AKI KDIGO Stage 2.

29/60 (48.33%) of enrolled subjects were Renal angina index positive. Among Renal angina index positive, 27/29(93.1%) patients developed severe AKI (stage 2/3). Among Renal angina index negative, 6/31(19.3%) patients progressed to severe AKI. Renal angina index positivity at 12 hours and progression into KDIGO severe AKI within 7 days of PICU admission had a sensitivity of 93.1%, specificity of 80.6%, and \ PPV of 81.8%, and NPV of 92.59% with AUC of 0.82(95% confidence interval 0.70 to 0.90) with P=0.05 and hence statistically significant. The association of RAI positivity at 12 hours and progression to severe AKI is given in Table 9 and figure 8 and 9.

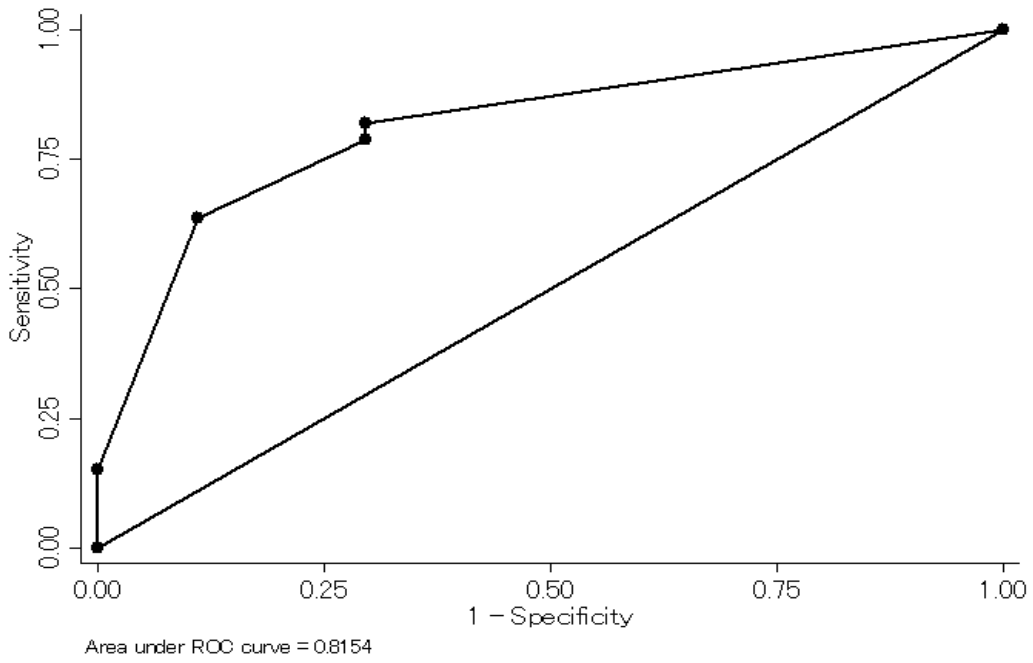

Figure 8: AUROC for the renal angina index result at 12 hours for prediction of severe AKI within 7 days after PICU admission. AUROC 0.82 (95%CI 0.70-0.90).

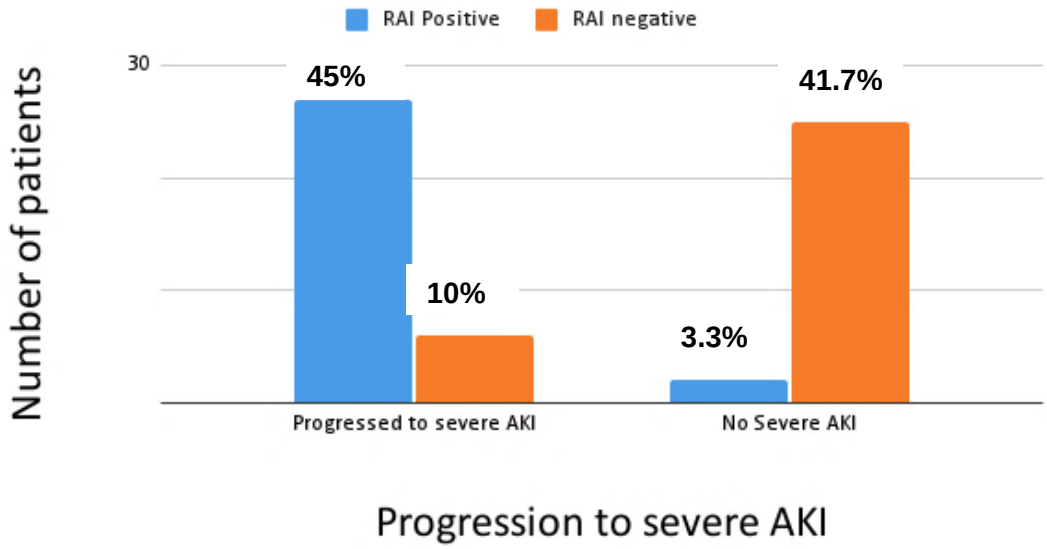

Fig 9: Renal angina index result at hours and progression to severe AKI

Diagnostic accuracy of RAI in predicting severe AKI

Table 10: Association between serum cystatin C positivity at 12 hours and progression to severe AKI

		S.cystatin-C positive	S.cystatin-C negative	Total patients
		N (%)	N (%)	N (%)
Progression to severe AKI	Present	30(50%)	3(5%)	33(55%)
	Absent	0	27(45%)	27(45%)
Total		30(50%)	30(50%)	60(100%)

AUC=0.89 P=0.002(95%CI 0.86 -0.99)

Patients were distributed into two groups (Table 10) according to the serum cystatin C (negative vs. positive) at 12 hours of the admission. Urine output monitoring was continued and daily serum urea and creatinine were sent to look for progression into severe AKI.

30/60 (50%) of enrolled subjects had serum cystatin c positive. Among serum cystatin C positive, 30/30(100%) patients developed severe AKI (stage 2 or 3). Among serum Cystatin C negative, 3/30(10%) patients had progressed to severe AKI. Hence there was a significant association between serum cystatin C positivity and progression to severe AKI. Serum cystatin C positivity at 12 hours and progression into KDIGO severe AKI (within 7 days of PICU admission) had a sensitivity of 100%, specificity of 90% and PPV of 90.9%, and NPV of 100% with AUC of 0.89 with (95% confidence interval 0.86-0.99), P=0.002 and hence statistically significant. The association of serum cystatin C positivity at 12 hours and progression to severe AKI is given in Table 10 and figure 10A and B.

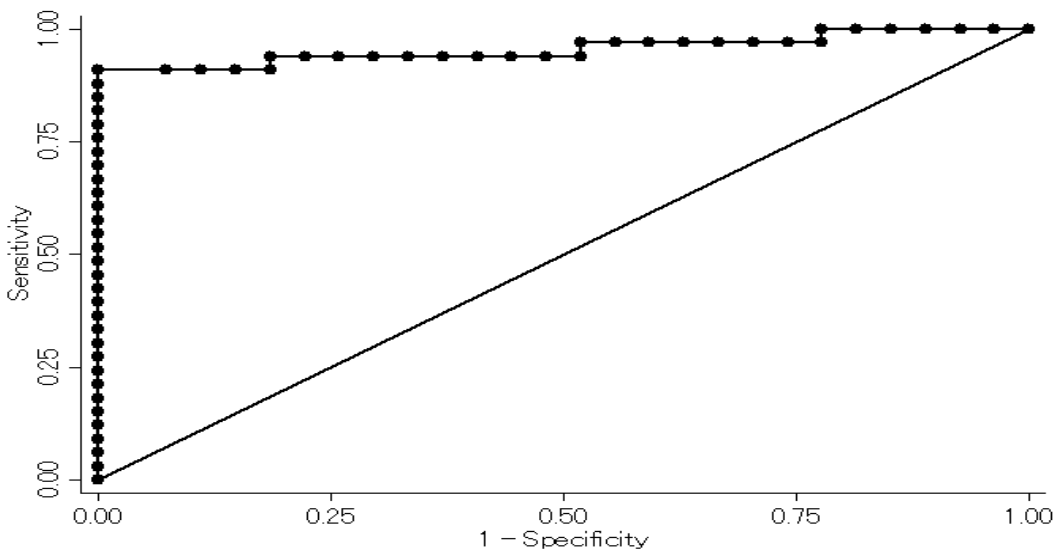

Figure 10 A: AUROC for serum cystatin C result at 12 hours for prediction of severe AKI within 7 days after PICU admission. AUC-ROC 0.89 with (95%CI 0.86-0.99)

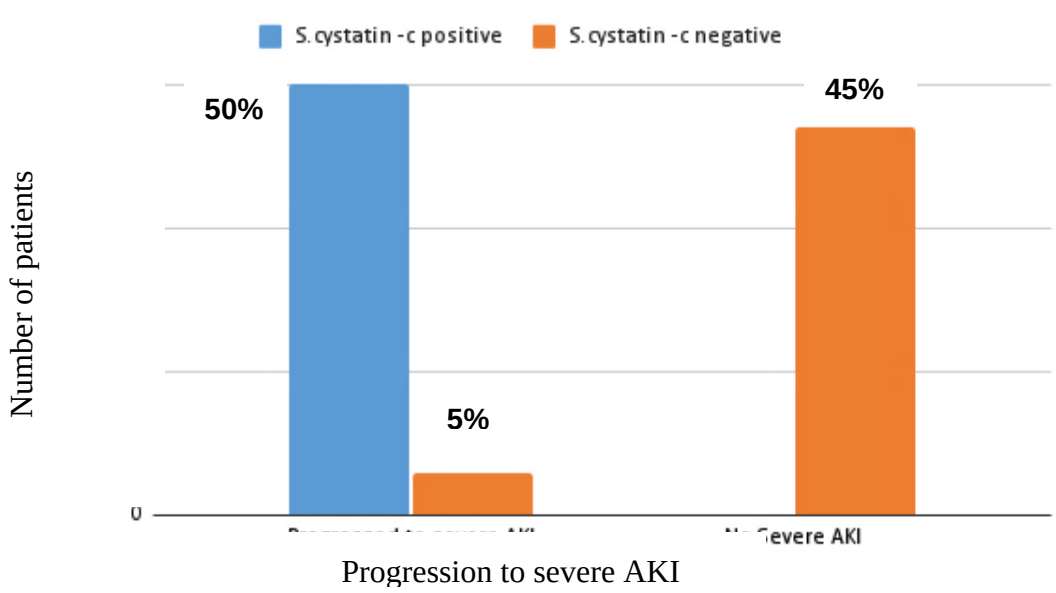

Figure 10 B: Serum cystatin C result at 12 hours and progression to severe AKI.

Diagnostic accuracy of RAI in predicting severe AKI

Table 11: Association between Urine cystatin C positivity at 12 hours and progression to severe AKI

		U. cystatin-c positive	U. cystatin-c negative	Total Patients
		N (%)	N (%)	N (%)
Progression to severe AKI	Present	29(48.3%)	4(6.7%)	33 (55%)
	Absent	10(16.7%)	12(28.3%)	27 (45%)
Total		39(65%)	16(35%)	60 (100%)

AUC=0.72, P=0.07, (95% CI 0.60 - 0.84)

Patients were distributed into two groups (Table 11) according to the urine cystatin C (negative vs, positive) at 12 hours of admission. In total, 65% had urine cystatin C positive. Urine output monitoring was continued and daily serum urea and creatinine were sent to look for progression into AKI KDIGO Stage 2 and 3.

39/60 (65%) of enrolled subjects were urine cystatin C positive. Among urine cystatin C positive patients, 29/39(74.3%) developed severe AKI (stage 2 or 3). Among serum cystatin C negative patients, 4/16(25%) progressed to severe AKI. Urine cystatin C positivity at 12 hours had a sensitivity of 74.3%, specificity of 80.9 %, PPV of 87.8 %, and NPV of 62.9% with AUC of 0.71, P=0.0726, (95% CI 0.60 to 0.84) for prediction of progression into KDIGO severe AKI (within 7days) and hence statistically not significant. The association of urine cystatin C positivity at 12 hours and progression to severe AKI is given in Table 11 and figure 11A and B.

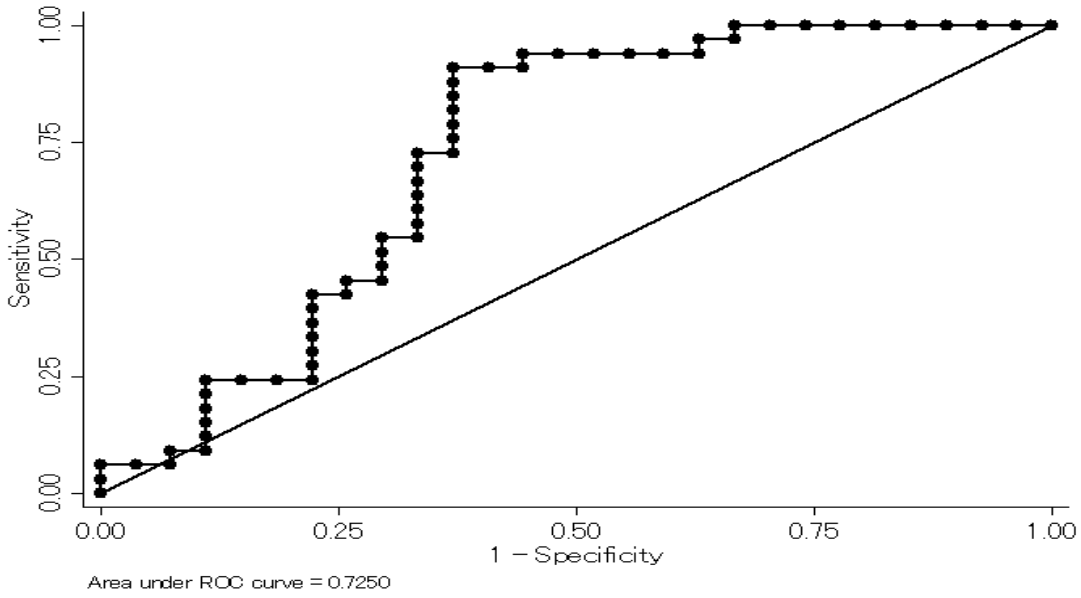

Figure 11 A: AUROC for urine cystatin C result at 12 hours for prediction of severe AKI within 7 days after PICU admission. AUC of 0.72 (95%CI 0.60 - 0.84).

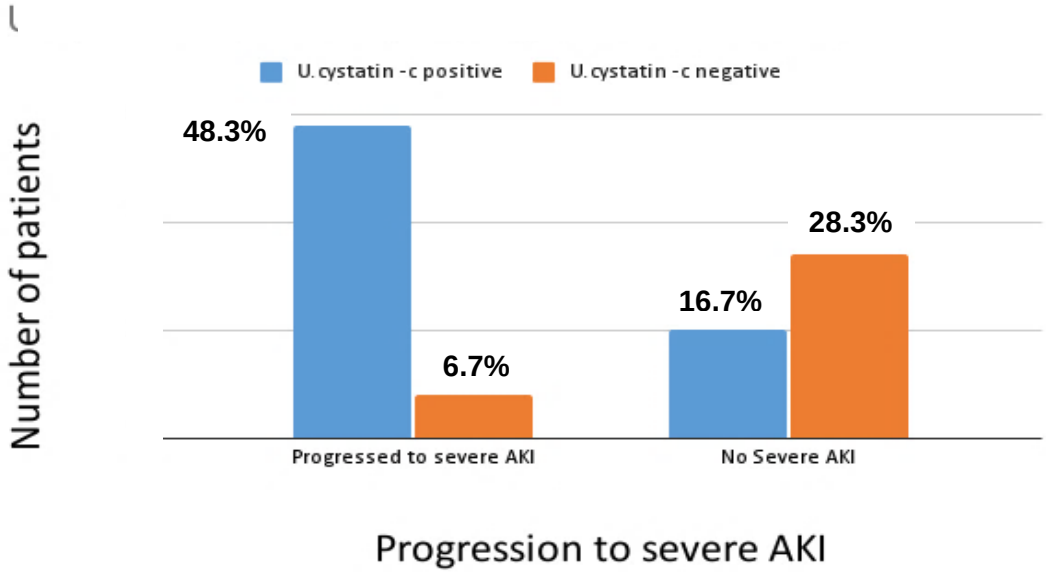

Figure 11 B: Urine cystatin C result at 12 hours and progression to severe AKI

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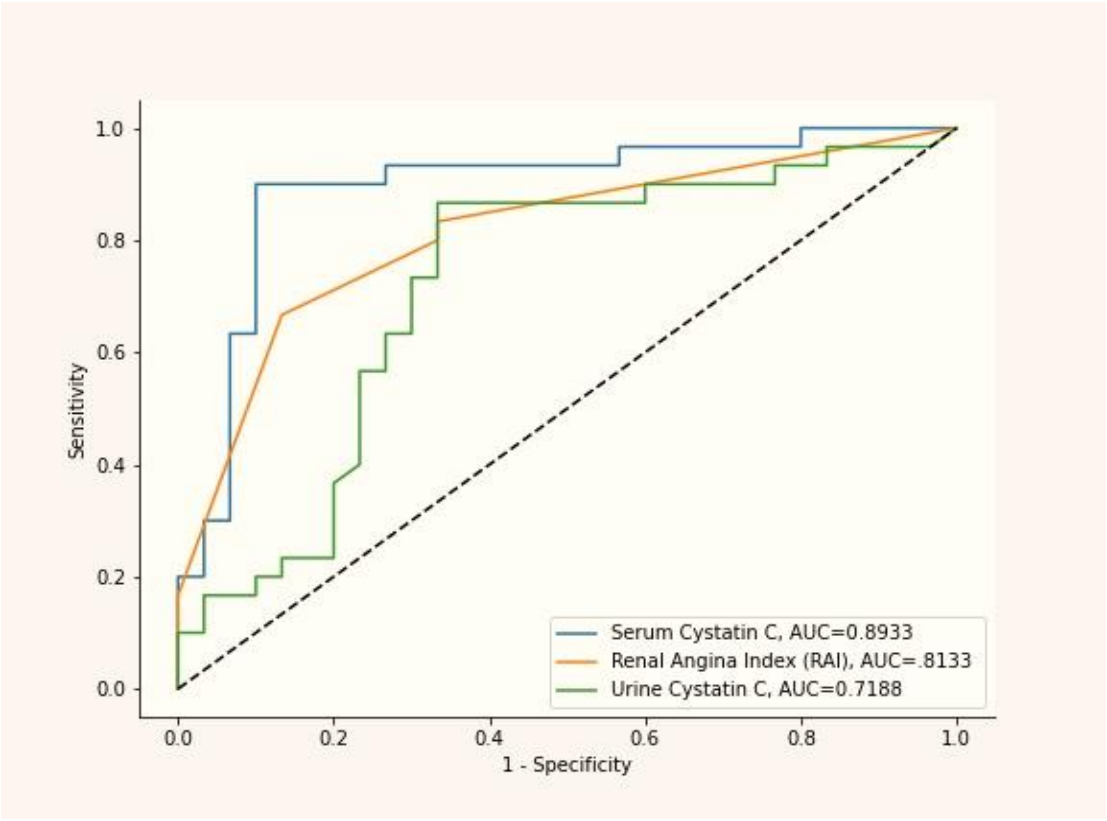

Fig 11C: Comparison of AUROC of renal angina index, serum cystatin C and urine cystatin C at 12 hours for prediction of severe AKI

Table12. Association between RAI positivity at 12 hours and the need for RRT

		RAI Positive	RAI Negative	Total Patients
		N(%)	N(%)	N (%)
RRT Requirement	Present	9(15%)	0	9(15%)
	Absent	20(33.3%)	31(51.7%)	51(85%)
Total		29(48.3%)	31(51.7%)	60(100%)

P = 0.001

Patients were divided into two groups (Table 8) according to the RAI score (negative vs positive) at 12 hours of admission. In total, 48.3% had an RAI ≥ 8. Urine output monitoring was continued and daily serum urea and creatinine were sent to look for progression into AKI KDIGO Stage 2.

29/60 (48.33%) of enrolled subjects were Renal angina index positive. Total of 9/60(15%) underwent Renal replacement therapy (RRT). Among Renal angina index positive 9/29(31.03%) patients required RRT. All of them required peritoneal dialysis as the mode of RRT. Among Renal angina index-negative patients none of them required RRT. Hence there was a significant association between Renal angina index positivity and the need for RRT. Renal angina index positivity at 12 hours and need for RRT had a sensitivity of 31.03%%, specificity of 100% PPV of 100%, and NPV of 60.7% with P=0.001 and hence statistically significant. The association of RAI positivity at 12 hours and the need for RRT is given in Table 12 and figure 12.

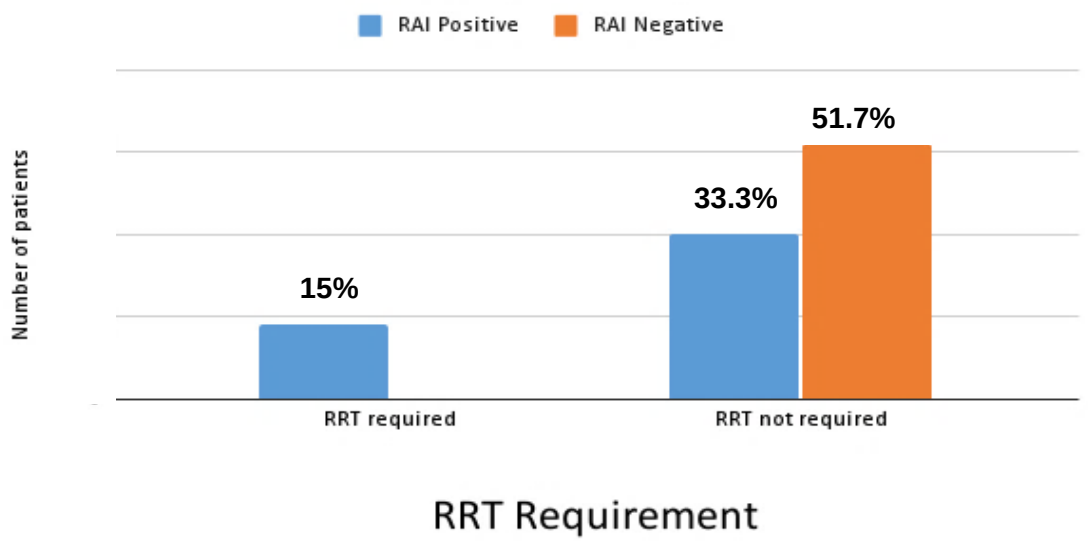

Figure12: RAI Positivity and need for RRT

Table13. Association between RAI positivity and mortality

		RAI Positive	RAI Negative	Total Patients
		N (%)	N	N
Mortality	Present	12(20%)	5(8.3%)	17(28.3%)
	Absent	17(28.3%)	26(43.3%)	43(71.7%)

P = 0.030

Out of 60 enrolled children, 17/60 (28.33%) children died during their stay in PICU. 12/29 (41.33%) RAI positive patients died during their hospital stay. All-cause mortality among children who were RAI-negative was 5/31 (16.1%). RAI showed average predicting ability for mortality AUROC 0.65 (95% CI 0.51-0.76). A significant association between RAI Positivity at 12 hours with all-cause mortality was noticed in the study {Pearson chi^2 (RAI positive) = 4.7046, P = 0.030} and hence statistically significant. Mortality among the enrolled is depicted in Table 13 and figure 13.

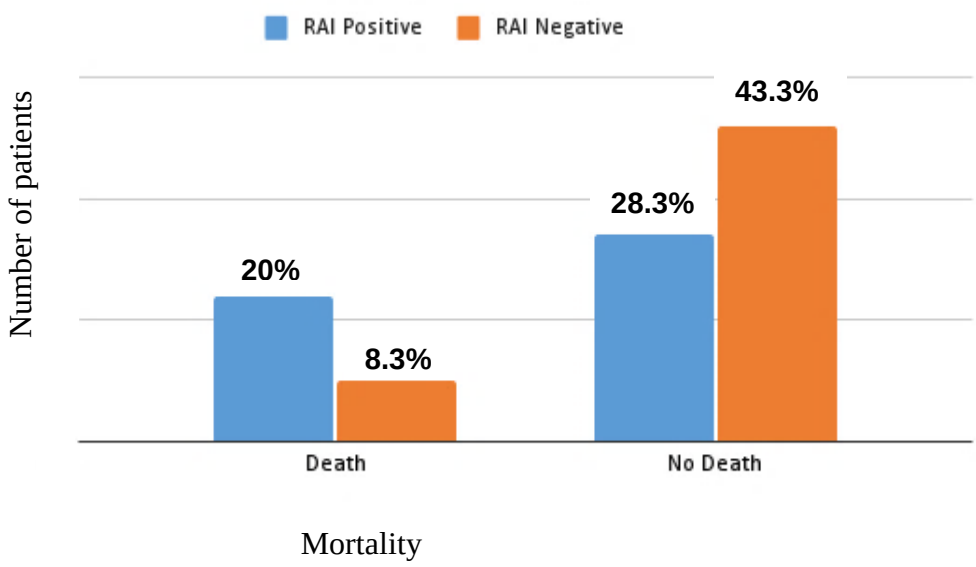

Figure13: RAI Positivity vs mortality

Table 14: **Association between Progression to severe AKI and mortality**

		Progression to severe AKI	NO AKI/ Non severe AKI	Total Patients
		N (%)	N (%)	N(%)
Mortality	Present	13(21.7%)	4(6.7%)	17 (28.3%)
	Absent	20(33.3%)	23(38.3%)	43 (71.7%)
Total		33(55%)	27(45%)	60 (100%)

P= 0.036

13/33 (39.33%) children who progressed to severe AKI died during their hospital stay. Among those who did not progress to severe AKI, 4/27(14.8%) died during the hospital stay with P=0.036 and hence statistically significant. So there is an association between severe AKI progression and Mortality. Mortality among those who progressed to severe AKI is depicted below in Figure 14 and Table 14.

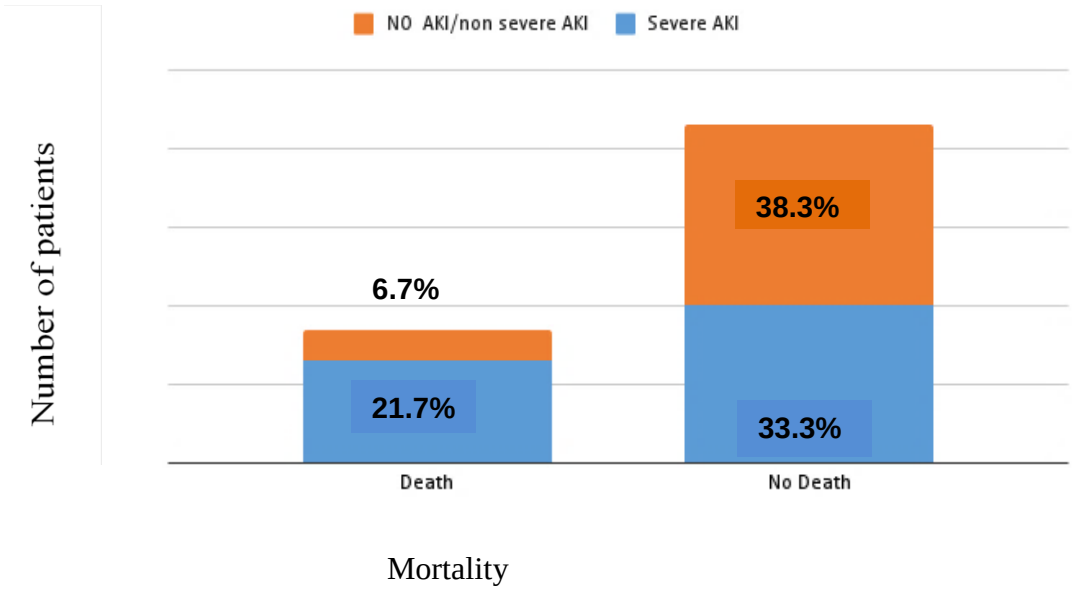

Figure 14: Progression to severe AKI vs Mortality

Table 15: **Association of RAI positivity and need of mechanical ventilation**

		RAI positive	RAI negative	Total Patients
		N (%)	N (%)	N (%)
Mechanical Ventilation required	Present	26(43.3%)	21(35%)	47(78.3%)
	Absent	3(5%)	10(16.7%)	13(21.7%)
Total		29(48.3%)	31(51.7%)	60(100%)

P = 0.040

29/60 (48.33%) of enrolled subjects were renal angina index positive. A total of 47/60(87.33%) required mechanical ventilation (MV). Among renal angina index positive 26/29(89.67%) patients required MV. Among renal angina index-negative patients 21/31(67.7%) required MV. Hence there was a significant association between Renal angina index positivity and the need for mechanical ventilation. Renal angina index positivity at 12 hours and need for MV had a sensitivity of 89.6%%, specificity of

32.2%, PPV of 55.5%, and NPV of 51.67% with p=0.04 and hence statistically significant. The association of RAI positivity at 12 hours and the need for RRT is given in Table 15 and figure 15.

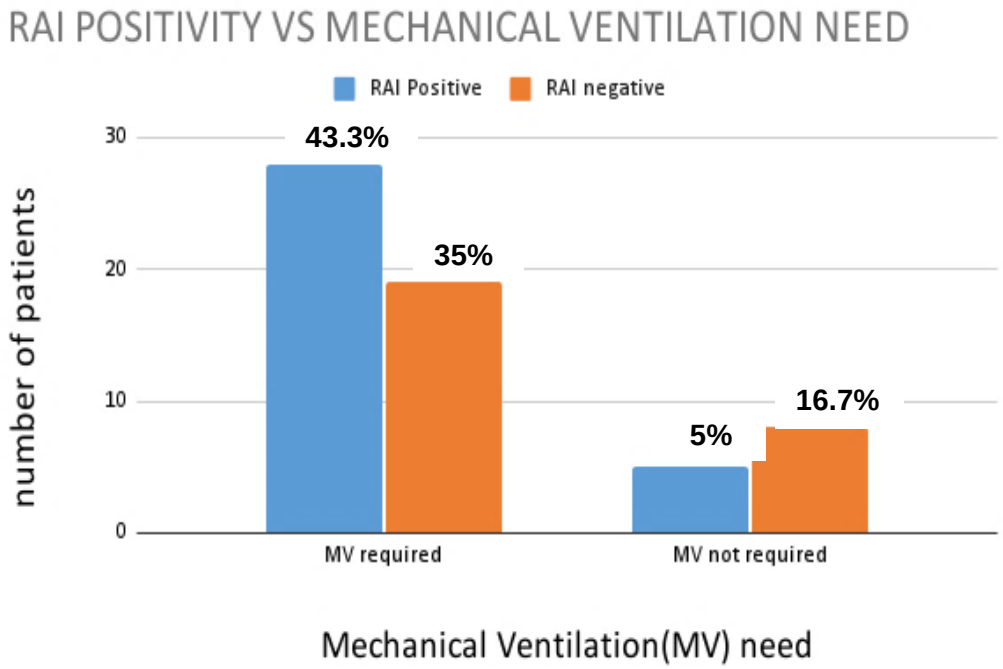

Fig 15: RAI positivity and need for mechanical ventilation

RAI positivity association with duration of MV

The association between RAI positivity and duration of MV was studied which showed a p-value of 0.0877 and hence statistically not significant.

Duration of mechanical ventilation and progression to severe AKI

The association between the duration of MV and progression to severe AKI was studied which showed a p-value of 0.40 and hence statistically not significant.

RAI positivity association with duration of the PICU stay

The association between RAI positivity and duration of PICU stay was studied which showed a p-value of 0.4629 and hence statistically not significant.

Duration of PICU stay and progression to severe AKI

The association between the duration of PICU stay and progression to severe AKI was studied which showed a p-value of 0.03 and hence statistically significant. Interestingly we found that the duration of PICU stay was lesser among patients who progressed to severe AKI. This could probably be explained by the fact that mortality was higher among the children with severe AKI.

Association between max pSOFA and mortality

The association between max pSOFA and mortality was studied, which showed higher the p SOFA score more the Mortality. 17/60(28.3%) patients died during the PICU stay, out of them 11.7% had scores of 8-11, 41.1% had scores of 12-15, and 47% had scores> 16. There was no Mortality observed when the score was less than 8. The association between max pSOFA and mortality is presented in figure 16.

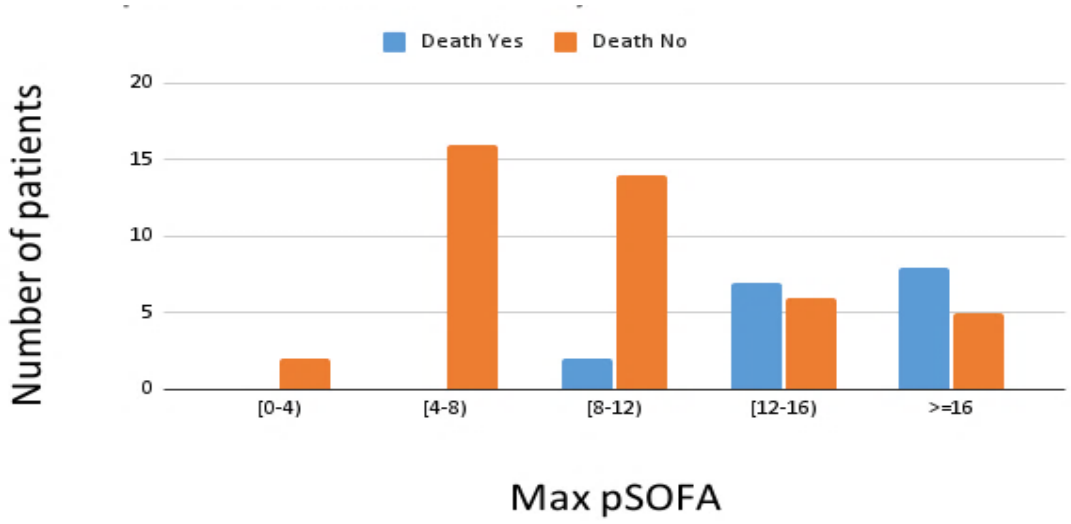

Fig 16: Max p SOFA and mortality association

Max p-SOFA and progression to severe AKI

The association between Maximum (Max) p-SOFA and progression to severe AKI was studied which showed a p-value of 0.023 and hence statistically significant.

Association between max VIS score and mortality

The association between max vasoinotropic score (VIS) and mortality was studied, which showed higher the VIS score, more the mortality. 17/60(28.3%) patients died during the PICU stay, out of them 11.7% had scores of 0-40, 17.6% had scores of 40-80, 5.8% had scores of 80-120, 64.7% had scores>120. The association between max pSOFA and mortality is presented in figure 17

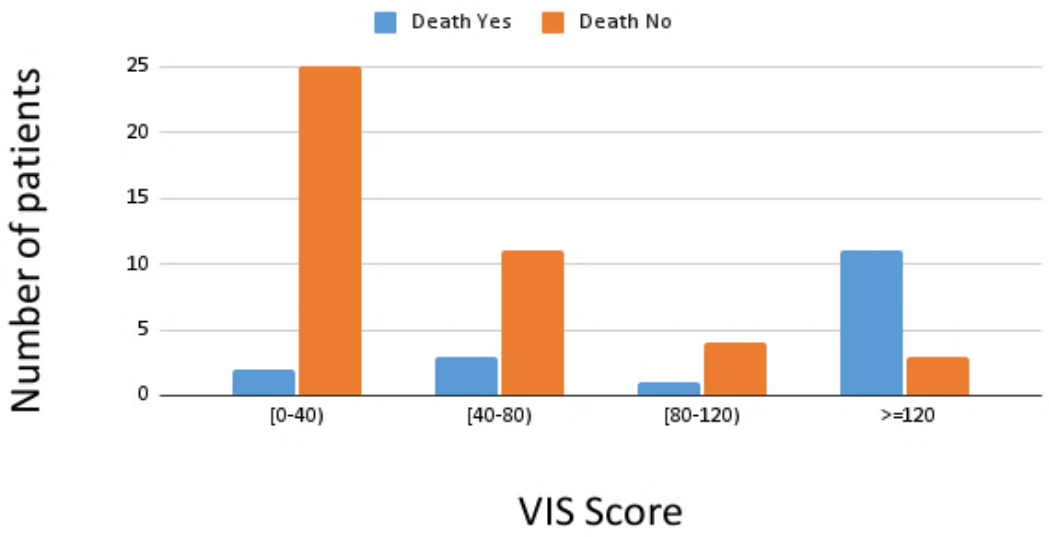

Fig 17: Maximum vasoactive inotrope score (VIS score) and Mortality

VIS score and progression to severe AKI

The association between VIS score and progression to severe AKI was studied which showed a p-value of 0.02 and hence statistically significant.

Association between Lactate levels and Mortality

The association between lactate levels and mortality was studied, which showed higher the lactate levels more the mortality. 17/60(28.3%) patients died during the PICU stay, out of them 5.88% had lactate of 2 to 4, and 94.1% had lactate of >4. The association between lactate level and mortality is presented in figure 18

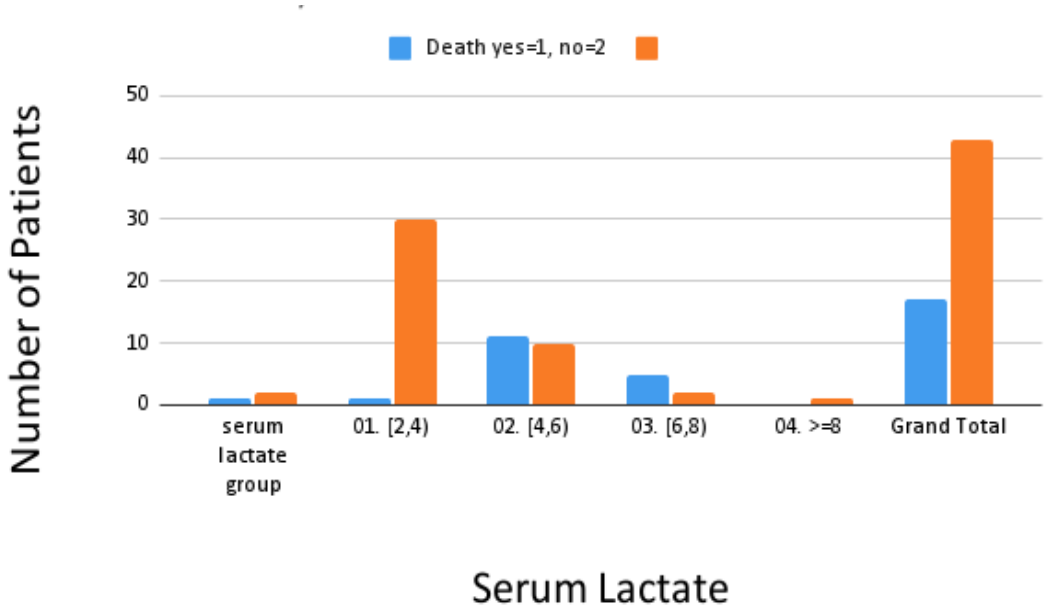

Fig 18: Association between serum lactate and mortality

Association between Lactate levels and progression to severe AKI

The association between serum lactate and progression to severe AKI was studied which showed a p-value of 0.00001 and is hence statistically significant.

Table 16: Table –Outcome characteristics

		RAI positive	RAI Negative	Total Patients
		N (%)	N (%)	N (%)
Progression to severe AKI	Present	27(45%)	6(10%)	33 (55%)
	Absent	2(3.3%)	25(41.7%)	27945%)
RRT Requirement	Present	9(15%)	0	9(15%)
	Absent	20(33.3%)	31(51.7%)	51(85%)
Mortality	Present	12(20%)	5(8.3%)	17(28.3%)
	Absent	17(28.3%)	26(43.3%)	43(71.7%)
Mechanical Ventilation required	Present	26(43.3%)	21(35%)	47(78.3%)
	Absent	3(5%)	10(16.7%)	13(21.7%)

		S.cystatin-C positive	S.cystatin-C negative	Total Patients
		N (%)	N (%)	N (%)
Progression to severe AKI	Present	30(50%)	3 (5%)	33 (55%)
	Absent	0	27 (45%)	13 (21.7%)

		U.cystatin- C positive	U.cystatin- C negative	Total patients
		N (%)	N (%)	N (%)
Progression to severe AKI	Present	29 (48.3%)	4 (6.7%)	33 (55%)

DISCUSSION

The efficacy of the renal angina index in predicting progression to severe AKI has already been established by various studies. However, similar studies in septic shock children are lacking. We could find only one retrospective study from China by Huang et al (63). Our study aims to assess the diagnostic accuracy of renal angina index in predicting severe AKI in septic shock children.

In contrast, to the study by Huang et al (73) where 84 patients were admitted with septic shock out of which 66 patients were enrolled, in our study 140 patients were admitted with septic shock to PICU and among them 60 patients met the eligibility criteria of this study and there was no missing data. Patients aged 1 month to 16 years old were enrolled in a study by Huang et al, (73) whereas in our study we included patients aged 1 month to 18 years of age.

In contrast to the retrospective study by Huang et al 2020 (73) where the mean age was 58 (8.50–131.75) months, 44(66.70%) were male, 36(54.50%) developed AKI within 3 days after PICU admission, in our study the mean age was 69.2(IQR 21-117) months, 55% were male, and 55% developed AKI within days 7 of PICU admission.

A study by Francisco et al in 2021 (70), included participants between the ages of 1 month and 18 years, had a mean age of 55(IQR 11-151) months, 56% were male and 17% had positive RAI. In our study 22(36.67%) of them were infants, 13 (21.67%) children were between the age group of 1-5 years, and 25(41.67%) belonged to the age group of 6 years to 18 years. A total of 55% of patients were RAI-positive.

The respiratory system (21.67%) followed by the central nervous system (16.67%) was the major system involved in our study .This was similar to a study by Gawadia et al (71) in which predominantly respiratory (76%) followed by central nervous system was involved (23%).

On evaluating risk factors for developing AKI among enrolled subjects, acute gastroenteritis in 22 (36.7%) and 21 (35%) patients had exposure to nephrotoxic drugs, 6 (10%) children had exposure to radio-contrast agents and a previous history of AKI was found in 8 (13.33%) patients. According to a number of research studies (61-62), exposure to nephrotoxic medications is associated with the development of AKI in the

adult population in 16–25% of cases. For each patient who receives a nephrotoxic drug, the likelihood of developing AKI increases by 53% in the same population (62). About one-quarter of patients hospitalized for AGE may suffer from AKI with a longer stay for patients with more severe AKI (81).

In our study 29/60 (48.33%) of enrolled subjects were Renal angina index positive. Among Renal angina index positive 27/29(93.1%) patients developed severe AKI (stage 2/3), which had a sensitivity of 93.1%, specificity of 80.6%, and PPV of 81.8%, and NPV of 92.59% with AUC of 0.8154(95% CI 0.69 to 0.90) with P=0.05. Similarly study by Huang et al (73) showed early RAI+ occurred in 38/66 (57.57%) of patients. The proportion of AKI in the early RAI+ group (78.94%) was higher than that in the RAI negative group (21.42%) (p = 0.04).

In a systemic review and meta-analysis by Meena et al (76) to assess the diagnostic accuracy of RAI, overall, 22 studies (24 reports, 14,001 participants) were included. RAI ≥ 8 on day 0 had summary sensitivity, specificity, and AUC of 0.86 (95% CI, 0.77–0.92), 0.77 (0.68–0.83), and 0.88 (0.85–0.91) respectively for prediction of severe AKI on day 3(71) which is comparable to our study.

30/60 (50%) of enrolled subjects in our study were serum cystatin c positive. Among serum cystatin c positive 30/30(100%) patients developed severe AKI (stage 2 or 3) and which had a sensitivity of 100%, specificity of 90% and PPV of 90.9%, and NPV of 100% with AUC of 0.89 with (95% CI 0.86-0.99).

Zhang et al. (64) analyzed data from 19 studies and 11 countries involving 3,336 patients. Of these studies, 13 were included in the meta-analysis. Across all settings, the diagnostic odds ratio (OR) for serum Cys C level to predict AKI was 23.5 (95% CI, 14.2-38.9), with sensitivity and specificity of 0.84 and 0.82, respectively. The area under the receiver operating characteristic curve (AUROC) of serum Cys C level to predict AKI was 0.96 (95% CI, 0.95-0.97). Subgroup analysis showed that serum Cys C was of diagnostic value when measured early (within 24 hours after renal insult or intensive care unit admission).

A total of 24 articles were included in the meta-analysis by Nakhjavan-Shahraki et al. (82) [1948 children (1302 non-AKI children and 645 AKI cases)]. Serum (SMD = 0.96; 95% CI: 0.68-1.24; $p < 0.0001$) and urine (SMD = 0.54; 95% CI: 0.34-0.75; $p < 0.0001$)

levels of cystatin C were significantly higher in children with AKI. The overall area under the curve of serum cystatin C and urine cystatin C in the prediction of AKI was 0.83 (95% CI: 0.80-0.86) and 0.85 (95% CI: 0.81-0.88), respectively. It concluded that cystatin C has an acceptable prognostic value for the prediction of AKI in children. Since the serum level of cystatin C raises within the first 24 h of admission in patients with AKI, this biomarker can be a suitable alternative for traditional diagnostic measures. The predictive ability of serum cystatin C in the above study is comparable with our study. In our study 39/60 (65%) of enrolled subjects were urine cystatin C positive. Among urine cystatin C positive 29/39(74.3%) patients developed severe AKI (stage 2 or 3) which had a sensitivity of 74.3%, specificity of 80.9 %, PPV of 87.8 %, and NPV of 62.9% with AUC of 0.71, P=0.0726, (95% CI 0.60to 0.84), which was statistically not significant.

A prospective observational study by Nejat et al (63) in 2010 involving 81 adult patients admitted to ICU showed an AUROC curve of 0.70 of urine cystatin C in the prediction of AKI among the enrolled. The predictive ability of urine cystatin C, when analyzed with the findings of our study, is equivalent to those of the above-mentioned study.

29/60 (48.33%) of enrolled subjects were RAI positive. Total of 9/60(15%) underwent RRT. Among Renal angina index positive 9/29(31.03%) patients required RRT, which had a sensitivity of 31.03%, specificity of 100 % and PPV of 100%, and NPV of 60.7% with P=0.001 and hence statistically significant. The early RAI+ group was associated with a higher incidence of RRT (34.21% vs.10.71%, p = 0.02) in the study by Huang et al (73).

A systemic review and meta-analysis were done by Meena et al. (76) with the objective to evaluate the performance of RAI alone or in combination with biomarkers in predicting severe AKI (KDIGO stage 2 and 3 or equivalent) and receipt of kidney replacement therapy (KRT) in critically ill children. The sensitivity, specificity, and AUC of RAI for predicting receipt of KRT were 0.82 (0.71-0.90), 0.74 (0.66-0.81), and 0.85 (0.81-0.88) respectively.

In our study out of 60 enrolled children, 17/60 (28.33%) children died during their stay in PICU. Among RAI positive patients 12/29 (41.33%) died during PICU stay. A significant association between RAI Positivity and mortality was noticed in our study (P

= 0.03) and hence statistically significant. Huang et al (73) also observed a significant association between RAI+ and increased mortality (57.89% vs. 17.85%, p < 0.01).

A total of 47/60(87.33%) required mechanical ventilation (MV) in our study. Among Renal angina index positive 26/29(89.67%) patients required MV, which had a sensitivity of 89.6%%, specificity of 32.2% PPV of 55.5%, and NPV of 51.67% with p=0.04 and hence statistically significant. The early RAI+ group was associated with a higher incidence of MV (73.68% vs.32.14%, p < 0.01) in the study by Huang et al (73).

The association between RAI + and duration of MV (p=0.08) and the association between RAI + and duration of PICU stay (p=0.46) were not significant in our study.

The study by Huang et al (73) showed that the AUC of serum lactate for predicting AKI was 0.69 (95% CI 0.57–0.82, p = 0.01) with an optimal cut-off of 4.80 mmol/L. In our study 17/60(28.3%) patients died during the PICU stay, out of them 5.88% had lactate of 2 to 4, and 94.1% had lactate of >4.

A prospective, observational study by Radovic M et al (83) in 2019 included 100 adult elective cardiac surgery patients assessed as low-risk for developing cardiac surgery-associated AKI (CSA-AKI). UNGAL, KIM-1, and lactate were measured preoperatively, at the end of cardiopulmonary bypass (CPB) and 3, 12, 24, and 48 h later. Patients with CSA-AKI had significantly higher lactate but similar UNGAL and KIM-1 levels compared to patients without CSA-AKI. Unlike UNGAL and KIM-1, postoperative lactate was a good biomarker of CSA-AKI with the highest odds ratio (OR) of 2.7 [1.4–4.9] 24 h after CPB. Peak lactate concentration ≥ 4 mmol/L carried a dramatically higher risk of developing CSA-AKI (OR 6.3 [1.9–20.5]).

The association between max p SOFA and mortality was studied, mortality increased progressively across patient subgroups from lower to higher P SOFA scores. 17/60(28.3%) patients died during the PICU stay, out of them 11.7% had scores of 8-11, 41.1% had scores of 12-15, and 47% had scores> 16. There was no Mortality observed when the score was less than 8.

In a study by Ghada et al in 2019(84) the p SOFA score was higher in non survivors (*P* < .001) and mortality increased progressively across patient subgroups from lower to higher SOFA scores. The ROC curve analysis revealed that the AUC of the p SOFA score for predicting 30-day mortality was 0.89.

This study by Wang H et al (85) found that the SOFA score was associated with 28- and 90-d mortality of patients with AKI undergoing CRRT and that as the SOFA score increased, the 28- and 90-d mortality of patients with AKI undergoing CRRT increased.

The association between VIS and mortality was studied, which showed that higher the VIS score more the mortality.17/60(28.3%) patients died during the PICU stay, out of them 11.7% had scores of 0-40, 17.6% had scores of 40-80, 5.8% had scores of 80-120, 64.7% had scores>120. A retrospective study was done by Anwarul H et al in 2015 (86) to find the association between vasoactive-inotropic score and mortality in paedatric septic shock. It divided the cohort into two groups based on the cut-off value of 20. VIS 21 on two or more readings was considered as 'High VIS' (Group-H), and all others (1-20) were considered as 'Low VIS' (Group-L). The median VIS was 13 (IQR 10 – 22.8). Group-L had 52 (73.2%) children. The overall mortality rate of PICU admissions was 12% and case-specific mortality was 59.2%; 23 (38.9%) and 19 (100%) children expired from Group-L and Group-H, respectively (95% CI 1.049 – 1.230; *P*=0.002). So, higher score has a progressive increase in mortality.

In a retrospective study by Hou K et al (87)1935 patients were included, 291 patients (15.0%) developed postoperative AKI among which VIS-max was associated with postoperative AKI (odds ratio [OR]: 1.19, 95% confidence interval [CI]: 1.11-1.34, P < 0.001) and the need for RRT in AKI patients (OR: 1.29, 95%CI: 1.01-1.83, P = 0.007). In our study association between VIS score and progression to severe AKI was studied which showed a p-value of 0.02.

CONCLUSION

The diagnostic value of RAI is comparable with that of serum cystatin C, which has the best diagnostic accuracy in our study. Urine cystatin C has a lower predictive ability than RAI. To conclude, RAI can be used in paediatric ICU for the prediction of development of severe AKI in septic shock children. Further larger studies are needed to validate these results.

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PARTICIPANT INFORMED CONSENT FORM (PICF) (English)

Protocol / Study number: _____

Participant identification number for this study: _____

Title of project: Assessment of renal angina index and cystatin C as predictive markers in severe acute kidney injury in children with septic shock: a prospective cohort study

Name of Principal Investigator: Dr. Anil Kumar J S, Telephone No. 9008515133

The contents of the information sheet dated that was provided have been read carefully by me/ explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions. The nature and purpose of the study and its potential risks / benefits and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected. I understand that the information collected about me from my participation in this research and sections of any of my medical notes may be looked at by responsible individuals from AIIMS, Jodhpur. I give permission for these individuals to have access to my records. I agree to take part in the above study.

(Signatures / Left Thumb Impression)

Date:

Place:

Name of the Participant: _____

Son / Daughter / Spouse of: _____

Complete postal address: _____

This is to certify that the above consent has been obtained in my presence.

_____

Signature of the Principal Investigator

Place:

Date:

1) Witness – 1	2) Witness – 2
Name: ----------	Name: ----------
Signature	Signature
Name/ Address:	Name/ Address:

अनुलग्नक-1

आंशिक सूचित सहमति फार्म (PICF) (हिन्दी)

प्रोटोकॉल / अध्ययन संख्या: _____

इस अध्ययन के लिए प्रतिभागी की पहचान संख्या: _____

परियोजना का शीर्षक: **सेप्टिक शॉक वाले बच्चों में एक्यूट कि**
गंभीर डनी की चोट के रूप में रीनल एनजाइना इंडेक्स और सिस्टैटिन सी का पूर्वानुमान सूचक

प्रधान अन्वेषक का नाम: डॉ। डेज़ी खेरा, Tel.No. 8003996913

उपलब्ध कराई गई सूचना पत्र की सामग्री को मेरे द्वारा ध्यान से पढ़ा गया है / मुझे विस्तार से समझाया गया है, जिस भाषा में मैं समझता हूं, और मैंने सामग्री को पूरी तरह से समझ लिया है। मैं पुष्टि करता हूं कि मुझे सवाल पूछने का अवसर मिला है। अध्ययन की प्रकृति और उद्देश्य और इसके संभावित जोखिम / लाभ और अध्ययन की अपेक्षित अवधि, और अध्ययन के अन्य प्रासंगिक विवरण मुझे विस्तार से बताए गए हैं। मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और मैं बिना किसी कारण के किसी भी समय वापस लेने के लिए स्वतंत्र हूं, बिना मेरी चिकित्सा देखभाल या कानूनी अधिकार प्रभावित हुए बिना। मैं समझता हूं कि इस शोध में मेरी भागीदारी और मेरे किसी भी मेडिकल नोट के वर्गों के बारे में मेरे द्वारा एकत्रित जानकारी को एम्स, जोधपुर के जिम्मेदार व्यक्तियों द्वारा देखा जा सकता है। मैं इन व्यक्तियों को अपने रिकॉर्ड तक पहुंचने की अनुमति देता हूं। मैं उपरोक्त अध्ययन में भाग लेने के लिए सहमत हूं।

(हस्ताक्षर / बाएं अंगूठे का निशान)

दिनांक:

स्थान:

प्रतिभागी का नाम: _____

पुत्र / पुत्री / पति / पत्नी: _____

पूरा डाक पता: _____

यह प्रमाणित करना है कि मेरी उपस्थिति में उपरोक्त सहमति प्राप्त हुई है।

_____

प्रधान अन्वेषक का हस्ताक्षर:

स्थान:

दिनांक:

1) गवाह – 1

नाम: ----------

हस्ताक्षर

नाम / पता:

2) गवाह - 2

नाम:----------

हस्ताक्षर

नाम / पता:

ANNEXURE 2

PATIENT INFORMATION SHEET

Title: Assessment of renal angina index and cystatin C as predictive markers of severe acute kidney injury in children with septic shock: a prospective observational study.

Introduction: This statement describes the purpose, procedures, benefits, risks and discomforts of the study and your right to withdraw from the study at any point of time.

Purpose: To assess the use of RAI and Cystatin C in early prediction of acute kidney injury, so that early intervention can be planned which would prevent further renal damage.

Study Procedure: Your relevant clinical history was recorded, followed by clinical examination. Serum and urine samples were collected at 0hours and 6hours. Renal angina index was calculated at 8 to 12 hours after PICU admission and Child was monitored for progression of acute kidney injury. Serum and urine cystatin C values were noted.

Benefits: No monetary benefits were given to you. However, any new information that can come to light regarding any findings in the study will help in further management of the disease and help all other ailing patients suffering from this problem.

Confidentiality: Records of your study participation was kept confidential, under safe custody. Any publication of data will not identify you by name. By signing the consent form you authorize the sharing of your study related medical records to the regulatory authorities and the Institutional Ethical Committee.

Information regarding withdrawal: You have the right to withdraw yourself from the study at any time during the course of the study.

Contact for additional information: Any time during or after the study, you can obtain further information about the study from Dr. Anil kumar J S, Phone no.-9008515133, All India Institute of Medical Science, Jodhpur, Rajasthan.

अनुलग्नक २

रोगी सूचना पत्र

शीर्षक: सेप्टिक शॉक वाले बच्चों में गंभीर एक्यूट
किडनी की चोट के रूप में रीनल एनजाइना इंडेक्स और सिस्टैटिन सी का पूर्वानुमान सूचक के रूप में आकलन: एक संभावित कोहोर्ट अध्ययन।

परिचय: यह कथन अध्ययन के उद्देश्य, प्रक्रियाओं, लाभों, जोखिमों और असुविधाओं और किसी भी समय अध्ययन से हटने के आपके अधिकार का वर्णन करता है।
उद्देश्य: तीव्र गुर्दे की चोट की प्रारंभिक भविष्यवाणी में आरएआई और सिस्टैटिन सी के उपयोग का आकलन करने के लिए, ताकि शुरुआती हस्तक्षेप की योजना बनाई जा सके जिससे आगे गुर्दे की क्षति को रोका जा सके।
अध्ययन प्रक्रिया: आपका प्रासंगिक नैदानिक इतिहास दर्ज किया जाएगा, इसके बाद नैदानिक परीक्षा होगी। सीरम और मूत्र के नमूने 0 घंटे और 6 घंटे पर एकत्र किए जाएंगे। PICU में प्रवेश के बाद 8 से 12 घंटे में गुर्दे के कोण की गणना की जाएगी और बच्चे को तीव्र गुर्दे की चोट की प्रगति के लिए निगरानी की जाएगी। सीरम और मूत्र सिस्टैटिन सी मूल्यों को नोट किया जाएगा।
लाभ: कोई मौद्रिक लाभ आपको नहीं दिया जाएगा। हालांकि, किसी भी नई जानकारी जो अध्ययन में किसी भी निष्कर्ष के बारे में प्रकाश में आ सकती है, बीमारी के आगे प्रबंधन में मदद करेगी और इस समस्या से पीड़ित अन्य सभी बीमार रोगियों की मदद करेगी।
गोपनीयता: सुरक्षित अभिरक्षा के तहत, आपके अध्ययन की भागीदारी के रिकॉर्ड को गोपनीय रखा जाएगा। डेटा का कोई भी प्रकाशन आपको नाम से नहीं पहचानेगा। सहमति पत्र पर हस्ताक्षर करके आप नियामक अधिकारियों और संस्थागत नैतिक समिति को अपने अध्ययन से संबंधित मेडिकल रिकॉर्ड को साझा करने को अधिकृत करते हैं।
वापसी के बारे में जानकारी: आपको अध्ययन के दौरान किसी भी समय अध्ययन से खुद को वापस लेने का अधिकार है।
अतिरिक्त जानकारी के लिए संपर्क करें: अध्ययन के दौरान या बाद में किसी भी समय, आप डॉ.अनिल कुमार जे एस, फोन नंबर। 9008515133, अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर, राजस्थान से अध्ययन के बारे में अधिक जानकारी प्राप्त कर सकते हैं।

CASE RECORD FORM

Name- Age/Sex-

Date of Birth-

Fathers name-

Mothers name-

Address -

Phone no. 1-

Phone no. 2-

Date of admission to Paedatric emergency-

Date of admission to Paedatric Intensive Care Unit-

Diagnosis-

Time and date of diagnosing SEPTIC SHOCK

H/o Drug usage:

- Aminoglycosides YES NO
- Sulphonamides YES NO
- Amphotericin B YES NO
- Acyclovir/ Ribavirin YES NO
- Cisplatin/ Ifosfamide YES NO
- Cyclosporine/ tacrolimus YES NO
- ACE inhibitors YES NO

H/o exposure to radiocontrast agents: YES NO

H/o envenomation: YES NO

H/o acute gastroenteritis/ blood loss YES NO

H/o fever YES NO

H/o Hypertension/ Diabetes mellitus/ Congestive heart failure/ Cirrhosis:

YES NO

H/o AKI in previous hospitalization: YES NO

H/o Renal replacement therapy in past: YES NO

H/o Cardiac Surgery in past: YES NO

Significant family history: YES. NO

Baseline values (hospital database or outside records within past 6 months):

- Urea
- Creatinine
- GFR
- $Na^+/K^+/Ca^{2+}$
- Albumin*
- TLC
- CRP*
- Procalcitonin*
- Hb%
- Lactate

Previous Ultrasound abdomen/ KUB (if obstructive uropathy):

Nutritional status- Average Thin Overweight Obese

Height:_____cms Weight:_____kg BSA:_____kg/m^2

GCS:

Vitals:

- Pulse rate/ volume/ character:
- Blood pressure:
- Temperature:
- Respiratory rate:
- Saturation:

Per abdomen examination:

Genital examination:

Cardiovascular system examination:

Respiratory system examination:

Central nervous system examination

	Baseline	**0hours**	**6hours**	**12hours**	**Day 2**	**Day 3**	**Day 7**
Urine output (ml/kg/hr)							
GFR ($ml/min/1.73m^2$)							
Daily Urea (mg/dl)							
Daily Creatinine (mg/dl)							
Daily $Na^+/K^+/Ca^{2+}$ (mEq/dl)							
Blood pressure (mm of Hg)							
Serum lactate							
Daily p SOFA							
Vasoactive inotropic score							

RENAL ANGINA INDEX	
Score	
Acute kidney injury risk strata	
Moderate risk: PICU admission	**1**
High risk: History of bone marrow or solid organ transplantation	**3**
Very high risk: Ventilation and inotrope use	**5**
Clinical injury signs	
<5% fluid overload or no change in eCrCl	**1**
5% to <10% fluid overload or decrease in eCrCl by 0%-24%	**2**
10% to <15% fluid overload or decrease in eCrCl by 25%-49%	**4**
≥15% fluid overload or decrease in eCrCl by ≥50%	**8**
Total Score	

eCrCl: Estimated creatinine clearance, PICU: Paedatric intensive care unit

Outcomes:

Progression into KDIGO AKI Stage ≥2: **Present** **Absent**

Cystatin C values:

- **Serum:_____ mg/L**
- **Urine:_____mg/L**

Urine R/M:

Urine for active sediment:

Urine culture

Duration of PICU stay:

Need for RRT (before discharge):

Need and duration of mechanical ventilation:

Blood culture:

ETHICAL CLEARANCE CERTIFICATE

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/3528 Date: 12/03/2021

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3363**

Project title: **"Assessment of renal angina index and cystatin C as predictive markers of severe acute kidney injury in children with septic shock: A prospective observational study"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr. Anil Kumar J S**
Guide:	**Dr. Daisy Khera**
Co-Guide:	**Dr. Kuldeep Singh, Dr. Mithu Banerjee, Dr. Aliza Mittal, Dr. Bharat Choudhary & Dr. Siyaram Didel**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary
Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Basni Phase-2, Jodhpur, Rajasthan-342005; **Website:** www.aiimsjodhpur.edu.in; **Phone:** 0291-2740741 Extn. 3109
E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com

S. No.	Name	AIIMS ID	Diagnosis
1	Manisha	AIIMS/JDH/2021/04/015768	Acute Leukemia (pre B cell ALL, CNS negative) in induction phase with Pancytopenia withVery Severe Febrile Neutropenia with Skull lytic lesions with intracranial venolymphatic malformation with Coagulopathy with Compensated Shock (septic) AKI Stage 3
2	DIKSHIT GEHLOT	AIIMS/JDH/2021/05/003859	Acute encephalopathy with biphasic seizures and late diffusion restriction with Anicteric hepatic failure ?Reye's / Reye like syndrome with coagulopathy and septic shock with ventilator associated pneumonia (Acinetobacter) with bradyarrythmia ?sinus arrhythmia with non oliguriic KI Stage 1
3	ABHINANDINI	AIIMS/JDH/2021/08/004341	Non fatal drowning with sptic shock with respiratory failure
4	SHAKTIPAL SINGH	AIIMS/JDH/2021/07/007964	Seizure disorder ?neurometabolic disorder? Immune mediated with vit D insufficiency with respiratory failure with Health associated infection (ventilator associated pneumonia) with septic shock (R) moderate malnutrion.
5	ISHAN	AIIMS/JDH/2021/07/010878	A/H/O fall from height with severe Traumatic brain injury with status epilepticus with multiple base of skull fracture with Left IVH with EDH with septic shock (Resolved) with dyselectrolytemia (resolved) with tongue laceration repaired with VAP(Acinetobacter, Pseudomonas) with Choreoathetoid movements with Dystonia.
6	ROCKY KUMAR	AIIMS/JDH/2021/07/018108	Community acquired pneumoniae with respiratory failure with septic shock
7	AJAY PAL SINGH	AIIMS/JDH/2021/08/017634	A/H/O FALL FROM HEIGHT WITH SEPTIC SHOCK WITH MODS WITH MRSA In SEPTICAEMIA
8	JYOTI	AIIMS/JDH/2021/10/008106	Scrub typhus encephalitis with vasculitis with decompensated shock ® with raised ICP ® with Respiratory failure ® with pre renal AKI
9	DARSHAN	AIIMS/JDH/2021/10/007017	Acute febrile encephalopathy with septic shock with scrub typhus with respiratory failure
10	RAMA	AIIMS/JDH/2021/09/006812	preterm with IUGR with Lateonset sepsis with meningitis with septic shock
11	VIMLA	AIIMS/JDH/2021/02/007123	TEF REPAIR WITH PDA LIGATION WITH SEPTIC SHOCK WITH VAP
12	B/o Samira	AIIMS/JDH/2021/11/003876	Cystic fibrosis with acute exacerbation with VAP with SEPTIC SHOCK
13	Sakshi	AIIMS/JDH/2022/05/000933	SEVERE DKA WITH SEPTIC SHOCK RESPIRATORY FAILURE
14	Pooja	AIIMS/JDH/2022/05/001287	Acute Febrile encepalopathy with rash ? Rickketsial infection
15	Bhavya Bhandari	AIIIMS/JDH/2019/05/020925	Down syndrome with ASD with hypothyroidism with respiratory failure with septic shock with severe pneumonia with ARDS
16	jeevika	AIIMS/JDH/2021/09/003931	YELLOW NAIL SYNDROME WITH RECURRENT PNEUMONIA WITH ACUTE SEVERE EXACERBATION WITH SEVERE CAP WITH SEPTIC SHOCK
17	Priyansh	AIIMS/JDH/2021/09/000674	SEVERE TRAUMATIC BRAIN INJURY WITH RIGHT FRONTO TEMPORAL AREA BLEED WITH PARIETAL BONE FRACTURE WITH SEPTIC SHOCK
18	Sagar	AIIMS/2022/08/004268	AML WITH HYPERLEUCOCYTOSIS WITH ACUTE GASTRO ENTERITIS WITH DAUNORUBUCIN INDUCED HYPERSENSITIVITY REACTION WITH SEPTIC SHOCK
19	MEHAK	AIIMS/JDH/2022/02/003201	COMMUNITY ACQUIRED PNEUMONIA WITH RESPIRATORY FAILURE WITH SEPTIC SHOCK WITH AKI STAGE 3
20	MUKESH	AIIMS/JDH/2022/01/027849	COMMUNITY ACQUIRED PNEUMONIA WITH SEPTIC SHOCK WITH VAP WITH CHYLOTHORAX ITH LEFT THYROID ARTERY RUPTURE WITH EXTENDED MEDIASTINAL ABSCESS
21	SWAROOP	AIIMS/JDH/2022/02/000695	T1DM SEVERE DKA WITH SEPTIC SHOCK WITH COVID PNEUMONIA
22	NITISH KUMAR	AIIMS/JDH/2022/01/027930	Viral pneumoniae ith Respiratory failure with suspected airway anomaly with septic shock with meningitis
23	ABDUL RAZAQ	AIIMS/JDH/2022/01/032751	ACYANOTIC CONGENITAL HEART DISEASE WITH CCF WITH CMV WITH SEPTIC SHOCK WITH MULTIPLE BOWEL PERFORATION
24	Praveen Prajapat	AIIMS/JDH/2021/03/014252	CYSTIC ILD WITH ACUTE EXACERBATION WITH SEPTIC SHOCK WITH DYSELECTROLYTEMIA
25	SAHIRA	AIIMS/JDH/2022/05/001917	CHRONIC DIARRHEA WITH SEPTIC SHOCK WITH MYOCARDITIS
26	MAHESH	AIIMS/JDH/2022/01/026608	ANORECTAL MALFORMATION WITH BLADDER INVOLVEMENT WITH SEPTIC SHOCK WITH UROSEPSIS
27	NIDHI	AIIMS/JDH/2022/07/016778	CYANOTIC CONGENITAL HEART DISEASE WITH RTA WITH SEVERE TBI WITH MULTIPLE INFARCTS WITH SEPTIC SHOCK
28	BO POOJA	AIIMS/JDH/2022/01/032715	PERSISTENT PNEUMONIAE WITH RESPIRATORY FAILURE WITH SEPTIC SHOCK
29	REYANSHI	AIIMS/JDH/2022/11/014105	DOWN PHENOTYPE WITH ACHD WITH SEPTIC SHOCK WITH RESPIRATORY FAILURE WITH STAGE 2 AKI
30	BO SONU	AIIMS/JDH/2022/03/006030	VLBW WITH FTT WITH PNEUMONAIE(HAI) WITH SEPTIC SHOCK WITH AKI STAGE 2
31	NEERAJ	AIIMS/JDH/2022/03/009194	CV JUNCTION ABNORMALITY WITH ASPIRATION PNEUMONIA WITH SEPTIC SHOCK
32	JAI	AIIMS/JDH/2022/03/009383	SINGLE VENTICULAR PHYSIOLOGY WITH CCF WITH PNEUMONIAE WITH SEPTIC SHOCK
33	KHUSHI	AIIMS/JDH/2022/03/013210	scrub typhus encephalitis with septic shock with AKI Stage 3 with Dyselectrolytemia with VAP
34	PREM PRAKASH	AIIMS/JDH/2022/03/012337	HYpernatremic dehydration secondary to faulty feeding with septic shock with hyperkalemia with anemia with coagulopathy with seizures
35	NIKITA	AIIMS/JDH/2022/03/020943	Complex Congenital heart disease with infectove sendocarditis with septic shock with respiratory failure
36	FALAK	AIIMS/JDH/2022/03/021771	Ulcerative colitis with severe activity with refractory catecholamine resistant septic shock with MODS with pancytopenia
37	MAHIKA	AIIMS/JDH/2022/02/017076	Acyanotic congental heart disease with septic shock with SAM
38	NANDINI	AIIMS/JDH/2022/04/06719	Meningo encephalitis ? viral with sptic shock
39	AASHNA	AIIMS/JDH/2021/10/016775	B cell ALL ON INDUCTION PHASE OF CHEMOTHERAPHY WITH FEBRILE NEUTROPENIA WITH SEPTIC SHOCK WITH IC BLEED WITH PNEUMONIA
40	MONALI	AIIMS/JDH/2022/04/006703	K/c/o Post hypoxic sequelae with pneumonia with sepsis with acute gastroenteritis with hypernatremic dehydration with non-oliguric AKI with septic shock® with hypoglycaemia®
41	SHIVNIYA	AIIMS/JDH/2022/04/008670	Obstructive hydrocephalus with VP Shunt insitu with spiration pneumonia with septic shock
42	KHUSVEER	AIIMS/JDH/2021/11/008851	B CELL ALL CNS 1 IN INTERIM MAINTENANCE PHASE WITH PROFOUND FEBRILE NEUTROPENIA WITH SEPTIC SHOCK
43	KANIKA	AIIMS/JDH/2022/05/007122	Dengue encephalitis WITH SEPTIC SHOCK
44	LALIT	AIIMS/JDH/2022/04/011578	Newly diagnosed Primary systemic Anaplastic Large cell lymphoma - High risk, Bone marrow negative, CNS? with SMA + SVC syndrome(?) with cutaneous manifestations completed Cycle A1 and Cycle BM1 of ALCL99 protocol with Pancytopenia with Profound febrile neutropenia with compensated septic shock with Ifosphamide induced reticulate skin hyperpigmentation with hypokalemia(drug induced)(?)
45	Kavita	AIIMS/JDH/2022/06/005662	Acute gastroenteritis with moderate dehydration septic shock
46	Ravina Kanwar	AIIMS/JDH/2022/07/004432	B ALL WITH FEVRILE NEUTROPENIA
47	Dinesh	AIIMS/JDH/2022/05/008347	Fraser type 1 floating knee Left side with posterior fasciotomy with sever traumatic brain injury WITH SEPTIC AHOCK with AKI
48	RENUKA	AIIMS/JDH/2022/05/015470	Bronchiectasis with Septic shock (resolved) and Respiratory failure (Resolved) under evaluation with Reactive Airway Disease with FTT with
49	KUSUM	AIIMS/JDH/2022/06/000786	Case of Microbiologically confirmed MDR (Rifampicin resistant) ? (Disseminated TB-Pulmonary, CNS, Abdominal) with respiratory failure with flaccid quadriparesiswith septic shock
50	Sawai	AIIMS/JDH/2022/06/014114	Case of FIRES with super refractory status epilepticus with VAP with refractory septic shock with coagulopathy with Acute liver Failure with Hypokalemia (Passive) with Pancytopenia, Suspected HLH with Post cardiac arrest ROSC
51	Hirendra	AIIMS/JDH/2022/05/020802	ALL WITH B/L PNEUMONIA WITH RIGHT FRONTOTEMPORAL BLEED WITH SEPTIC SHOCK WITH ARDS
52	Varma Kanwar	AIIMS/JDH/2022/03/022273	ALL With febrile neutropenia with septic shock
53	MOHIT	AIIMS/JDH/2022/07/001008	SPneumonoa with septic shock with AKI
54	ARAVIND	AIIMS/JDH/2022/08/000221	Advanced Nodular lymhocyte predominant lymhoma with febrile neutropenia
55	ABHIJEET	AIIMS/JDH/2021/12/011293	Steroid sensitive nephrotic syndrome (infrequently relapser) with enteric fever with MIS-C with MODS (transaminitis with myocarditis with sepsis induced myocardial
56	PRIYANSHI	AIIMS/JDH/2022/08/013525	Complicated SAM with MODS with perforation peritonitis with Right Pneumothorax with Right ICD INSITU with septic shock.
57	ANUJ	AIIMS/JDH/2022/09/003934	Acute encephalitis syndrome with severe ARDS with septic shock with hypoglycemia
58	MANISHA	AIIMS/JDH/2021/10/011898	Case of acute necrotising encephalitis secondary to ?HSV with AKI stage3 (on peritoneal dialysis day 4) with overt DIC with purpura fulminans with septic shock ® with stage 2 hypertension with acute liver failure with vitamin D deficiency with hyperphosphatemia with ROSC status post CPR
59	khushbu		IBD(Ulcerative colitis) with pancytopenia with febrile neutropenia with septic shock with acute encepalopathy with non oliguric AKI
60	Rudrapal	AIIMS/JDH/2022/04/001260	Menke`s disease (genetically confirmed ATP7A gene frameshift mutation) with GDD with FTT with SAM with Microcephaly with operated cystic hygroma with left amputated upper limb with respiratory failure pneumonia (viral) with status epilepticus with acute gastroenteritis without shock with extubation failure with VAP (pseudomonas) with septic shock with Dystonia.

S. No.	Age	Gender M=1,F=2	SYSTEM INVOLVED CNS=1 RS =2 CVS=3 Renal= 4 Hemato onco=5 Trauma and accidents= 6 Infectiou sdiseases =7 ENDOCRINOLOGY=8 abdominal =9	Nephrotoxic drug usage, Y=1, N=2	Radiocontrast, Y=1, N=2	Envenomation, Y=1, N=2	AGE, YES=1 NO=2	h/o Nil=0 HTN=1, DM=2, CHF=3, Cirrhosis=4	Previous h/o AKI Y=1, N=2	H/o RRT, Y=1, N=2	Cardiac surgery Y=1, N=2	Family history Y=1, N=2	Baseline urea	Baseline Creatinine	weight(kg)	height(cm)	Baseline GFR	Pulse rate Normal=1, Tachycardia=2, bradycardia+3	BP, Normotensive=1, Hypotensive=2, Hypertensive 3	Temperature Normal=1, Hyperthermia/fever=2 Hypothermia	RR Normal=1, tachpnea=2 , Bradypnea=3	Spo2 Normal=1 desaturation=2	Per abdomen Normal=1, Abnormal=2	CVS normal=1 abnormal=2	RS normal=1, abnormal=2	CNS Normal=1, Abnormal=2	Current stage of AKI stage NO=0 STAGE =1 STAGE =2
1	9 year	2	5	2	2	2	2	0	2	2	2	2	12	0.41	21	121	121.8853659	2	2	2	2	1	2	1	1	1	0
2	4 year	1	1	1	2	2	2	0	2	2	2	2	17	0.55	12.5	102	76.59272727	3	2	2	2	2	2	2	2	2	0
3	9 Month	2	6	2	2	2	2	0	2	2	2	2	18	0.43	7	67	64.35116279	1	2	2	3	2	1	2	2	2	0
4	4 1/2 month	1	1	2	2	2	2	0	2	2	2	2	7	0.42	5.4	63	61.95	2	2	2	1	2	1	1	2	2	0
5	2 year	1	6	2	2	2	1	0	2	2	2	2	19	0.51	13	93	75.31176471	2	2	2	1	2	1	2	1	2	0
6	1 1/2 Month	1	2	2	2	2	2	0	2	2	2	2	9	0.34	4	55	66.80882353	2	2	2	1	2	1	2	2	2	0
7	5 year	1	6	2	2	2	1	0	2	2	2	2	12	0.5	17	105	86.73	2	2	2	2	2	2	2	1	2	0
8	2 Year	2	7	1	2	2	2	0	2	2	2	2	11	0.6	25	142	97.74333333	2	2	2	1	2	2	2	1	2	0
9	2 YEAR	1	7	2	2	2	2	0	2	2	2	2	13	0.34	10	80	97.17647059	2	2	2	1	1	2	2	1	2	0
10	1.5 month	1	1	2	2	2	2	0	2	2	2	2	14	0.31	1.25	46	61.28387097	2	2	2	3	2	1	1	1	1	0
11	9 Year	2	3	2	2	2	2	0	2	2	1	2	14	0.48	20	125	107.5520833	2	2	2	1	1	1	2	2	1	0
12	5month	2	2	2	2	2	2	0	1	2	2	2	13	0.29	3.8	61	86.87241379	2	2	2	2	2	1	2	2	1	0
13	15 year	2	8	2	2	2	2	2	2	2	2	2	17	0.65	46	164	104.2030769	2	2	2	2	2	1	2	1	2	0
14	12 year	2	7	2	2	2	2	0	2	2	2	2	12	0.61	40	159	107.6508197	2	2	2	2	2	1	2	1	1	0
15	10 YEAR	1	3	2	2	2	2	0	2	2	2	2	12	0.62	16	114	75.93870968	2	2	2	2	2	2	1	1	2	0
16	2 year	1	2	2	2	2	2	0	2	2	2	2	16	0.41	8	82	82.6	2	1	2	2	2	1	2	2	1	0
17	1 year	1	6	2	2	2	1	0	1	2	2	2	12	0.46	10	83	74.51956522	2	2	2	2	2	1	2	2	2	0
18	1 YEAR	1	5	1	2	2	2	0	2	2	2	2	12	0.36	9.8	76	87.18888889	1	2	2	2	2	1	1	2	1	0
19	2 YERA	1	2	2	2	2	1	0	2	2	2	2	30	0.54	12.5	90	68.83333333	2	2	2	1	1	1	1	2	1	0
20	16 YEAR	1	2	2	2	2	2	0	2	2	2	2	49	0.81	60	172	87.69876543	1	2	2	2	2	1	1	2	1	0
21	12 YEAR	1	8	2	2	2	2	0	2	2	2	2	14	0.58	40	140	99.68965517	2	2	2	2	2	1	1	2	2	0
22	1 MONTH	1	2	2	2	2	2	0	2	2	2	2	12	0.31	3.4	52	69.27741935	2	2	2	2	1	1	1	2	1	0
23	4 1/2 MONTH	1	3	2	2	2	2	3	2	2	2	2	8	0.28	3.5	54	79.65	2	2	2	2	2	1	2	2	2	0
24	18 YEAR	1	2	2	2	2	2	0	2	2	2	2	9	0.57	31.3	166	120.277193	2	2	2	2	2	1	1	2	2	0
25	6 YEAR	2	9	2	2	2	2	0	2	2	2	2	12	0.45	14	114	104.6266667	2	2	2	2	2	2	1	1	2	0
26	9 YEAR	1	9	2	2	2	2	0	2	2	2	2	15	0.43	20	127	121.9790698	2	2	2	1	1	2	1	1	1	0
27	17 YEAR	2	3	2	1	2	2	3	2	2	2	2	13	0.56	45	154	113.575	2	2	2	2	2	1	2	1	2	0
28	6 MONTH	2	2	2	2	2	2	0	2	2	2	2	14	0.32	2.3	45	58.078125	2	2	2	2	2	1	1	2	2	0
29	8 MONTH	2	3	2	2	2	2	0	2	2	2	2	14	0.41	5.4	60	60.43902439	2	2	2	2	2	1	2	2	2	0
30	1 1/2 month	1	2	2	2	2	2	0	2	2	2	2	15	0.35	1.65	44	51.92	2	2	2	2	1	1	2	2	2	0
31	3 YEAR	1	2	2	2	2	2	0	2	2	2	2	12	0.29	12	102	145.262069	2	2	2	2	2	1	2	2	1	0
32	4 MONTH	1	3	2	2	2	2	0	2	2	2	2	11	0.34	4.1	63	76.52647059	2	2	2	2	2	1	2	2	1	0
33	5 YEAR	2	7	2	2	2	2	0	2	2	2	2	13	0.29	20	94	133.8689655	2	2	2	2	2	1	2	2	2	0
34	2 MONTH	1	9	1	2	2	2	0	2	2	2	2	19	0.4	3.4	52	53.69	2	2	2	1	1	2	2	1	2	1
35	16 YEAR	2	3	2	2	2	2	0	2	2	2	2	15	0.58	45	154	109.6586207	2	2	2	2	2	1	2	2	1	0
36	16 YEAR	2	9	2	2	2	2	0	2	2	2	2	18	0.78	40	150	79.42307692	2	2	2	2	2	2	2	2	2	0
37	5.5 MONTH	2	3	2	2	2	2	0	2	2	2	2	21	0.56	4.8	67	49.4125	2	2	2	2	1	1	2	1	1	0
38	17 YEAR	2	1	1	1	2	2	0	2	2	2	2	16	0.6	75	176	121.1466667	2	2	2	2	1	1	2	1	2	0
39	3 YEAR	2	5	1	2	2	1	0	2	2	2	2	31	0.39	13.7	104	110.1333333	2	2	2	2	2	1	2	2	2	0
40	10 MONTH	2	1	2	2	2	1	0	2	2	2	2	7	0.3	7.4	68	93.61333333	2	2	2	1	1	1	2	1	1	0
41	2 YEAR	2	1	2	2	2	2	0	2	2	2	2	12	0.43	7	74	71.0744186	2	2	2	2	2	1	1	2	2	0
42	2 YEAR	1	5	1	2	2	1	0	2	2	2	2	10	0.41	9.5	83	83.60731707	2	2	2	1	1	1	1	1	1	0
43	11 YEAR	2	7	2	2	2	2	0	2	2	2	2	11	0.6	27	133	91.54833333	2	2	2	1	1	2	1	1	2	1
44	7 YEAR	1	5	1	1	2	2	0	2	2	2	2	9	0.44	33	136	127.6545455	2	2	2	2	1	1	1	1	1	0
45	2month	2	9	2	2	2	1	0	2	2	2	2	11	0.38	3.2	55	59.77631579	2	2	2	1	1	2	1	1	1	0
46	17 year	1	5	2	2	2	2	0	2	2	2	2	14	0.65	48	168	106.7446154	2	2	2	2	1	1	1	1	1	0
47	11 YEAR	1	6	2	2	2	2	0	2	2	2	2	16	0.45	38	136	124.8177778	2	2	2	2	1	1	1	1	1	0
48	10 YEAR	2	2	2	2	2	2	0	2	2	2	2	12	0.48	39	145	124.7604167	2	2	2	2	2	1	1	1	1	0
49	15 YEAR	2	7	2	2	2	2	0	2	2	2	2	9	0.6	45	158	108.7566667	2	2	2	2	2	1	1	1	1	0
50	9 year	1	1	2	2	2	2	0	2	2	2	2	13	0.5	28	120	99.12	2	2	2	1	2	1	1	1	2	0
51	7 year	1	2	2	2	2	1	0	2	2	2	2	11	0.48	24	116	99.80833333	2	2	2	2	2	1	1	2	2	0
52	12 year	2	5	2	2	2	2	0	2	2	2	2	19	0.51	41	146	118.2313725	2	2	2	2	2	2	2	2	2	0
53	3 MONTHS	1	2	1	2	2	2	0	2	2	2	2	18	0.4	4.5	56	57.82	2	2	2	2	2	3	2	2	2	0
54	7 YEAR	1	5	2	2	2	2	0	1	2	2	2	18	0.53	25	116	90.39245283	2	2	2	2	2	2	2	2	2	0
55	7 YEAR	1	4	2	2	2	2	1	1	2	2	2	10	0.42	33	118	116.0333333	2	2	2	1	1	2	1	1	1	0
56	3 MONTHS	2	9	2	2	2	1	0	2	2	2	2	8	0.4	3.8	61	62.9825	2	2	1	2	1	2	1	1	1	0
57	3 YEAR	1	1	2	2	2	2	0	2	2	2	2	7	0.68	13	93	56.48382353	2	2	2	1	1	1	1	2	2	0
58	5 months	2	1	2	2	2	2	0	2	2	2	2	12	0.28	4.8	65	95.875	2	2	2	1	1	1	1	1	2	0
59	17 year	2	9	2	2	2	1	0	2	2	2	2	12	0.62	58	170	113.2419355	2	2	2	2	1	2	2	1	2	0
60	7 mon ths	1	1	2	2	2	2	0	2	2	2	2	11	0.34	6	68	82.6	2	2	2	2	1	1	1	1	2	0

S. No.	U/O 0 hr	U/O 6 hr	U/O 12 hr	u/o 24-48 hour	U/O 48-72 hours	U/0 72-96 Hours	U/0 96-120 Hours	U/O 120-144 Hours	U/0 day 6 (144-168 hours)	urea day 0(0 to 24 hour)	Urea day 1 (24-48hour)	urea day 2 (48 to 72 hr)	urea day 3 (72 to 96 hour)	Urea Day 4 (96-120 hrs)	urea Day 5(120 to 144 hr)	urea day 6(144 to 168 hrs)	Creatinine day 0 (O hr 24 hr)	Creatinine Day1 (24-48 hrs)	Creatinine day 2(24-48hrs)	Creatinine day 3 (72-96hrs)	Creatinine day 4(96-120hrs)	Creatinine day 5 (120-144hrs)	Creat day 6(144-168hrs)
1	2.3	2.1	1.2	0.9	2.15	2.15	1.8	2.1	2.5	12	9	24	24	20	22	36	0.43	0.68	0.75	0.91	1.21	1.4	1.98
2	2.6	2.1	2.8	1.7	2.8	3.2	2.1	1.9	2.4	68	52	46	39	41	45		0.74	0.68	0.8	0.82	0.93	1.01	0.9
3	2.8	1.6	2.6	2.2	3.1	2.8	2.2	2.6	3.1	23	20	21	27	22	27	24	0.45	0.54	0.47	0.54	0.59	0.47	0.42
4	3.3	2.1	2.8	1.6	1.2	2.2	1.4	1.7	1.8	7	6	12	14	18	16	21	0.35	0.38	0.56	0.76	0.79	0.82	0.76
5	2.9	2.1	2.7	1.2	1.65	2.6	1.4	1.8	3.06	19	15	8	12	17	19	17	0.51	0.49	0.49	0.51	0.47	0.4	0.42
6	1.6	1.3	1.2	1.8	2.1	-	-	-	-	15	23	31	27	-	-	-	0.46	0.52	0.48	0.56	-	-	-
7	0.9	0.6	0.6	0.4	0.2	0.4	-	-	-	54	51	48	38	-	-	-	0.5	0.76	1.08	1.4	-	-	-
8	2.1	1.4	1.6	1.3	2.1	2.8	1.7	1.9	2.6	77	6	50	39	34	30	20	1.15	0.99	1.16	0.83	0.74	0.62	0.45
9	3.4	2.1	2.6	1.8	2.2	1.7	1.1	1.7	1.8	14	16	18	16	16	12	13	0.5	0.52	0.47	0.52	0.54	0.44	0.38
10	2.8	2.4	2.61	2.87	3.9	1.8	-	-	-	21	56	110	98	-	-	-	0.83	1.57	1.97	2.3	-	-	-
11	2.1	1.8	1.8	2.2	2.6	1.9	1.8	2.4	1.6	25	24	25	35	27	37	40	0.52	0.51	0.6	0.55	0.61	0.64	0.51
12	2.5	2.3	1.4	2.6	1.8	3.8	2.4	1.9	1.6	13	14	17	13	17	21	17	0.29	0.41	0.44	0.43	O.43	0.29	0.34
13	2.2	1.3	1.8	2.6	2.7	2.3	1.8	1.6	1.7	15	26	58	32	21	75	73	1.1	1.3	1.74	2.47	2.3	1.8	1.18
14	1.2	1.5	1.6	1.1	0.6	0.3	-	-	-	17	28	48	46	-	-	-	0.89	1.34	1.18	3.34	-	-	-
15	0.85	0.7	0.94	1.6	1.8	1.5	1.2	1.6	1.9	44	40	40	49	62	79	86	0.67	0.74	0.71	1.35	1.5	1.71	2.45
16	2.1	1.7	1.8	1.47	1.04	1.71	1.4	1.7	2.86	23	56	65	56	45	50	47	0.5	0.67	0.75	0.8	0.67	0.6	0.65
17	1.4	1.5	1.6	1.2	1.5	1.4	1.2	1.1	1.3	12	32	42	47	35	38	32	0.46	0.59	0.67	1.04	1.3	1.1	0.9
18	2.5	2.1	2.2	1.4	1.8	1.5	1.1	1.7	1.5	11	16	20	36	34	56	88	0.4	0.32	0.32	0.42	0.54	0.87	1.14
19	2.2	2.4	0.9	0.6	0.3	0.5	0.3	0.2	0.45	30	47	78	117	90	127	142	0.54	1.18	1.67	2.46	2.8	3.27	3.09
20	1.1	1.4	1.5	0.9	0.8	1.2	1.3	1.5	1.7	12	21	27	24	21	14	24	0.74	0.86	0.57	0.76	0.82	0.78	0.8
21	1.8	1.3	2.2	2.5	2.3	2.8	1.7	1.6	1.5	18	26	42	83	81	86	91	1.03	1.43	1.75	2.86	2.6	2.71	2.62
22	1.8	2.1	1.6	2.1	2.94	2.3	1.8	1.5	1.8	10	15	19	6	7	8	8	0.41	0.42	0.59	0.35	0.42	0.47	0.49
23	2.8	1.3	1.6	1.4	1.06	2.7	2.5	1.9	1.8	29	26	27	22	11	21	22	0.33	0.31	0.31	0.3	0.35	0.3	0.43
24	1.2	1.4	1.8	0.9	0.7	1.1	1.4	-	-	29	28	32	25	21	-	-	0.51	0.64	1.14	0.92	1.2	-	-
25	1.8	1.3	2.1	1.6	1.2	1.3	1.6	-	-	38	36	35	33	36	-	-	0.43	0.4	0.36	0.36	0.31	-	-
26	3.2	2.3	3.8	3.3	4.2	2.8	2.1	1.8	2.6	37	27	23	29	28	30	34	0.6	0.43	0.48	0.52	0.54	0.62	0.43
27	1.8	1.4	1.5	1.1	2.7	1.6	1.5	2.1	0.9	24	22	23	14	12	13	15	0.7	0.8	0.54	0.8	0.76	0.74	0.67
28	2.3	2.1	2.8	1.6	2.8	1.8	1.9	2.1	2.2	11	9	14	21	18	16	14	0.37	0.35	0.43	0.48	0.53	0.43	0.4
29	1.8	1.3	2.1	1.6	1.3	1.2	1.4	1.7	2.1	23	32	52	48	52	30	24	0.38	0.38	0.97	0.7	0.65	0.51	0.42
30	1.3	1.4	1.5	1.8	1.2	2	2.1	2.3	1.8	19	16	21	23	24	29	39	0.36	0.42	0.77	1.16	1.02	1	0.95
31	1.8	2.1	1.6	2.3	3.2	2.1	2.3	1.8	1.9	39	43	69	82	86	68	56	0.39	0.72	0.91	1.24	1.3	1.2	1.01
32	1.2	1.1	1.5	1.3	1.9	1.6	1.8	2.1	2.6	38	76	167	152	123	96	62	0.74	0.8	1.3	-	-	-	-
33	0.3	0.6	1.1	1.6	1.2	1.1	1.2	1.4	1	19	9	22	33	21	18	20	0.85	0.86	0.88	0.65	0.51	0.45	0.3
34	0.4	0.6	0.7	0	0	0.3	0.6	1	1.4	297	256	261	201	150	122	35	0.78	1.03	1.7	3.2	3.36	2.6	0.51
35	1.6	1.2	0.8	0.4	0.3	1.2	1.1	1.5	1.2	21	40	45	54	65	97	176	0.9	1.3	1.6	1.8	2.13	2.12	4.53
36	1.2	0.6	0.5	0	-	-	-	-	-	23	45	-	-	-	-	-	0.71	1.23	1.7	-	-	-	-
37	1.2	1.6	2.2	2.6	1.8	1.6	1.6	1.5	1.6	24	21	18	14	12	11	9	0.53	0.48	0.46	0.46	0.46	0.42	0.43
38	1.6	2	1.8	1.2	1.3	1.2	2.2	1.7	1.7	19	19	29	45	34	40	35	0.6	0.63	0.67	1.08	0.82	0.61	0.58
39	1.2	1.8	2.1	1.6	2.7	1.6	1.8	1.4	1.2	14	6	15	31	23	15	24	0.44	0.39	0.35	0.29	0.38	0.29	0.26
40	1.3	1.2	1.7	1.8	2.1	1.6	1.3	1.6	1.1	243	185	102	45	26	9	7	0.57	0.89	1.29	0.71	0.49	0.33	0.3
41	2.7	1.9	1.4	1.2	1.3	1.5	1.3	2.2	1.8	20	20	5	8	6	11	9	0.32	0.34	0.38	0.35	0.42	0.47	0.42
42	1.2	1.5	1.4	2.8	1.6	1.8	1.4	1.6	1.8	9	10	10	7	15	20	20	0.42	0.41	0.37	0.34	0.33	0.69	0.67
43	1.7	2.08	0.3	0.24	0	0	0	-	-	25	123	132	130	-	-	-	0.82	0.96	1.1	1.98	2.27	-	-
44	1.3	1.4	2.1	1.5	1.3	1.6	1.2	1.1	1.4	11	13	18	22	30	14	9	0.38	0.36	0.35	0.41	0.37	0.43	0.53
45	0.6	0.4	0.3	0.5	1.2	2.3	3.6	2.7	1.2	12	20	95	85	61	12	9	0.4	0.51	0.53	1.04	0.79	0.42	0.3
46	1.2	1.4	2.1	1.6	1.7	1.1	2.1	1.1	1.5	14	12	8	9	21	13	16	0.7	0.71	0.8	1.1	1.2	1.5	1.1
47	1.2	1.4	1.5	1.5	2.3	1.5	1.4	1.3	2.1	12	11	21	21	11	13	13	0.6	0.61	0.72	1.2	1.3	1.2	1.1
48	2.1	1.5	2.1	2.1	1.4	2.1	2.2	2.1	1.4	11	16	14	13	13	14	16	0.51	0.53	0.61	0.62	0.62	0.71	0.61
49	1.4	1.7	1.6	1.4	1.5	1.4	2.1	1.4	2.1	14	17	18	16	11	17	17	0.54	0.52	0.57	0.63	0.67	0.72	0.74
50	1.2	1.6	1.9	2.2	1.9	2.6	1.7	1.4	1.5	38	36	76	41	-	64	54	0.43	0.44	0.48	1.01	0.9	0.95	0.81
51	1.3	1.8	1.6	1.2	2.2	2.1	1.3	1.4	1.2	27	19	20	36	-	21	37	0.31	0.36	0.65	0.78	0.99	0.61	0.62
52	1.4	`1.4	2.1	1.2	1.6	2.1	1.4	1.1	1.2	2.1	12	9	11	12	19	21	0.56	0.58	0.62	0.58	0.52	0.55	0.61
53	1.2	1.3	1.2	1.6	1.8	1.4	1.2	2.1	1.3	46	48	52	54	32	12	11	0.54	0.63	0.86	0.92	0.82	0.54	0.52
54	1.9	2.1	0.45	0.3	0.3	0	-	-	-	52	49	64	68	-	-	-	0.42	0.57	0.86	1.1	-	-	-
55	1.9	0.45	0.3	0.4	1.2	2.4	1.8	2.6	3	52	49	64	119	-	190	179	0.47	0.44	0.82	1.23	1.86	1.71	1.29
56	1.4	1.7	2.7	1.9	2.2	1.8	1.9	2.4	1.8	47	56	26	19	15	37	62	0.4	0.9	1.06	1.47	1.5	1.55	1.89
57	2.7	1.8	1.6	2.1	1.5	2.4	1.8	1.4	2.2	7	47	60	64	56	53	58	0.4	0.68	0.87	10.92	0.74	0.86	0.81
58	1.2	1.7	2.1	2.5	1.7	1.1	1.8	1.3	1.2	123	32	34	37	41	26	22	0.32	0.4	0.68	0.82	1.33	1.2	0.9
59	1.2	1.3	2.1	2.3	1.3	1.5	1.8	1.9	1.2	12	15	21	21	11	10	8	11	0.72	0.82	1.2	1.3	1.4	1.2
60	1.2	2.7	2.4	2.3	2.2	1.9	2.4	2.1	1.4	22	24	12	11	9	8	10	0.36	0.43	0.52	0.41	0.37	0.39	0.32

S. No.	Na Day 0	Na day 1	Na day 2	NA DAY 3	Na day 4	Na day 5	Na day 6	K Day 0	KDAY 1	k DAY 2	K DAY 3	K day 4	K DAY 5	K DAY 6	BP(0 HR)	BP day 1	BP day 2	BP day3	BP day 4	BP day 5	BP day 6
1	132	134	136	135	137	136	131	4.45	5.06	4.78	4.27	4.2	5.29	4.2	116/60	92/42	113/64	102/54	104/74	120/87	114/76
2	152	158	165	152	136	152	148	4.7	3.1	4.1	4.1	3.7	4.9	3.4	68/72	106/72	14/68	116/72	114/78	118/62	106/62
3	142	145	145	140	137	145	132	3	4.2	4.13	4.21	4.1	4.05	4.3	93/58	96/52	98/66	96/58	94/68	99/58	101/74
4	138	136	138	141	137	137	135	3.88	3.26	3.8	3.88	4.5	4.19	4.93	70/36	68/38	76/32	98/64	102/74	110/69	96/63
5	135	133	134	136	139	137	136	3.63	3.5	4.05	4.3	3.65	4.07	4.32	92/57	98/58	98/60	102/56	98/68	94/62	97/55
6	132	129	130	136	-	-	-	5.1	5.6	7.2	4.2	-	-	-	68/42	76/48	66/42	64/42	-	-	-
7	124	130	135	135	-	-	-	3.9	4.72	4.67	4.9	-	-	-	86/42	80/46	78/48	76/56	-	-	-
8	141	143	156	153	147	145	146	3.15	4.1	-	4.6	4.7	4.1	4.28	78/52	92/61	96/68	102/74	98/72	108/72	-
9	128	134	136	136	136	139	136	3.94	4.85	3.8	4.2	4.7	3.87	3.67	78/48	98/56	102/68	98/72	102/82	96/72	104/72
10	141	139	135	143	-	-	-	0.2	6.39	4.56	3.76	-	-	-	56/32	53/32	58/62	64/42	-	-	-
11	135	149	148	141	142	143	143	4.51	4.2	4.15	4.11	4.32	3.65	4.58	78/46	96/62	94/48	80/45	84/56	102/46	102/76
12	132	139	136	142	145	137	136	4.68	5.05	4.8	3.36	3.87	5.5	3.6	62/42	66/48	76/48	78/52	86/56	79/54	76/52
13	136	145	143	159	154	157	145	3.76	3.78	4.2	3.05	4.7	4.09	4.32	85/52	96/52	86/62	102/75	96/72	110/68	118/74
14	137	136	138	137	-	-	-	3.68	3.76	3.8	3.51	-	-	-	76/42	102/62	88/62	78/42	-	-	-
15	141	149	150	145	143	143	140	4.84	4.4	3.64	5.3	3.65	5.41	4.09	81/72	92/52	102/72	105/86	102/69	106/82	106/86
16	141	136	135	134	136	130	137	4.79	4.2	3.65	4.8	4.2	3.77	4.07	68/38	66/36	86/48	94/62	102/86	94/62	102/68
17	135	137	138	143	142	137	136	4.7	4.6	4.56	3.45	3.43	4.23	4.32	98/62	88/48	48/66	66/46	78/62	83/62	76/56
18	133	144	143	147	142	144	137	4.63	3.2	3.61	3.87	3.87	3.8	3.83	106/72	104/96	98/72	98/68	96/63	102/72	104/78
19	137	140	142	134	144	138	137	5.91	3.69	3.14	3.55	3.45	4.16	3.41	74/48	102/76	98/68	98/62	102/68	97/42	96/58
20	134	128	130	125	136	132	138	4.18	4.91	4.84	0.64	4.32	4.73	3.98	78/52	116/78	114/78	118/82	116/88	116/72	121/84
21	150	150	157	155	137	153	146	3.43	4.3	4.25	3.37	4.3	3.21	3.7	82/46	106/72	102/76	106/66	102/76	104/78	110/78
22	135	131	135	133	136	132	136	5.59	4.51	5.24	5.4	3.7	5.16	5.2	68/42	106/72	98/86	106/72	98/68	102/74	108/82
23	145	143	143	142	142	142	138	3.88	3.07	3.65	3.28	3.6	4.21	3.78	56/42	68/48	98/72	88/56	82/62	102/80	94/72
24	131	146	143	147	143	-	-	6.23	3.23	3.53	4.55	4.2	-	-	82/46	98/76	106/86	88/58	82/60	-	-
25	154	154	152	142	143	-	-	3.01	3.62	4.1	3.73	3.74	-	-	86/62	96/68	107/72	106/68	106/72	-	-
26	135	132	133	132	137	132	128	3.48	4.32	4.39	4.39	4.2	4.36	3.77	78/54	98/68	102/76	92/62	92/62	102/76	108/84
27	142	144	144	143	142	140	140	3.92	4.27	3.8	3.46	3.65	4.22	3.59	68/42	92/68	102/68	108/72	98/62	108/82	108/78
28	89	134	136	137	142	137	142	65	3.8	4.2	3.7	4.2	4.2	3.6	88/62	83/65	80/62	88/42	89/66	92/74	96/62
29	130	136	136	144	136	135	134	4.79	5.9	4.7	4.48	4.5	3.93	4.2	62/42	78/62	76/62	74/64	74/54	78/63	76/62
30	130	147	140	147	142	140	138	4.59	3.34	4.08	3.43	4.5	4.22	4.08	62/48	68/42	72/52	66/42	68/45	72/52	66/48
31	129	145	1343	142	143	142	143	4.38	3.89	4.2	3.8	4.2	3.7	4.2	70/48	82/56	84/62	82/60	82/62	86/62	84/61
32	141	144	132	132	146	147	145	3.2	4.2	4.6	4	4.2	4.1	4.1	64/44	72/54	70/52	74/66	72/61	74/62	76/60
33	136	144	151	155	147	141	143	144	3.7	3.8	4.2	4.7	3.8	3.6	70/52	68/42	82/48	86/62	88/62	88/62	96/72
34	175	175	173	170	164	162	156	7.39	6.1	6.6	7.3	5.2	4.3	4.5	66/42	68/48	72/52	76/54	74/60	76/62	74/62
35	132	132	126	136	136	137	139	5.1	5.2	4.6	2.8	4.1	3.8	3.9	78/54	74/62	84/62	90/68	92/66	94/68	98/68
36	136	139	-	-	-	-	-	-	4.1	-	-	-	-	-	76/62	62/40	-	-	-	-	-
37	135	134	136	139	137	139	134	133.4	2.9	4.68	2.63	3.63	4.15	4.2	62/46	68/48	70/52	74/54	72/62	78/56	76/60
38	138	139	142	142	138	136	137	4.7	4.23	4.85	4.26	4.2	4.1	3.7	82/62	96/72	102/82	104/78	98/76	102/78	100/68
39	137	136	138	134	142	135	136	4.33	3.8	3.31	3.68	3.7	4.12	3.96	110/74	102/68	98/68	94/72	98/76	102/68	106/76
40	152	156	155	147	150	142	142	4.33	3.71	2.78	3.87	3.9	4.95	3.99	62/42	76/56	74/54	80/60	74/58	76/56	74/58
41	132	128	142	141	137	135	143	4.7	3.57	4.53	4.31	4.2	4.1	3.8	68/42	76/62	78/54	76/52	82/58	84/56	82/62
42	137	135	139	135	142	136	141	4.04	4.08	3.7	2.93	3.1	5.61	4.8	106/68	96/66	98/62	91/60	98/72	102/76	104/76
43	129	126	134	132	136	-	-	3.96	3.6	3.8	4.2	4.3	-	-	78/61	72/60	74/82	68/48	78/48	-	-
44	0.4	136	135	139	142	141	136	3.4	3.5	3.7	4.2	4.4	4.6	4.8	4.2	106/78	102/66	106/76	98/69	94/68	94/68
45	146	147	144	137	144	136	133	4.31	4.9	3.9	3.6	3.5	3.18	3.7	68/46	78/64	82/64	86/64	78/68	82/64	84/64
46	143	138	141	138	143	137	135	3.6	4.2	4.5	4.2	4.1	3.8	3.8	102/78	92/64	104/72	98/62	102/67	98/67	102/74
47	136	141	146	135	143	143	136	4.1	4.5	3.6	4.2	4.3	3.8	3.6	98/66	102/68	98/64	102/82	98/68	102/72	98/64
48	137	141	141	136	141	136	135	3.6	3.7	3.6	3.8	4.1	4.5	4.2	92/68	102/72	102/76	104/74	102/68	104/76	104/82
49	142	142	141	136	136	137	142	14	4.2	3.6	3.6	3.6	4.2	3.6	102/68	98/62	102/68	98/62	102/72	98/68	106/72
50	136	138	139	132	137	142	136	4.43	4.1	3.7	3.9	4.1	4.6	4.12	72/66	92/64	98/68	102/72	106/80	106/83	98/72
51	135	131	137	158	158	160	154	4.3	3.8	5.06	5.07	5.2	5.2	4.9	80/62	94/64	102/74	104/76	102/74	108/76	102/82
52	142	141	139	141	143	138	138	4.2	3.7	4.2	4.2	3.7	4.2	3.6	92/62	104/66	96/62	102/76	86/62	98/66	104/68
53	138	136	133	136	135	144	139	4.1	3.7	3.5	3.6	4.1	4.9	3.9	56/36	64/44	68/42	66/52	66/46	68/56	68/52
54	128	125	125	126	-	-	-	3.7	4.1	4.2	4.6	-	-	-	80/65	102/52	86/66	76/42	-	-	-
55	128	125	127	117	126	123	129	5.12	4.84	5.16	3.67	4.1	4.55	3.89	80/65	102/58	86/66	92/68	98/72	98/72	94/68
56	135	137	136	138	141	147	145	136	4.01	3.91	3.71	3.8	4.21	3.62	78/56	76/62	82/64	90/62	92/66	86/64	88/62
57	135	138	152	159	148	145	139	141	4.6	4.5	4.2	4.2	4.8	3.4	94/62	92/53	96/56	102/64	102/68	92/60	104/64
58	136	138	141	137	136	138	139	3.5	4.8	4.6	4.2	3.8	3.1	3.8	66/43	72/60	76/52	78/50	82/58	82/62	88/52
59	134	136	138	139	132	139	141	3.53	3.6	4.1	4.3	4.4	4.6	4.3	78/56	92/63	102/62	98/62	102/72	104/72	98/62
60	132	136	142	141	137	139	141	3.2	3.9	3.9	4.7	4.3	4.9	4.2	66/44	72/56	70/62	74/58	76/58	84/52	88/50

S. No.	serum Lactate	pSOFA day 0	pSOFA day 1	pSOFA day 2	p SOFA day 3	pSOFA day 4	pSOFA day 5	pSOFA day 6	max pSOFA	Vasoactive inotropic score day 0	Vasoactive inotropic score day 1	Vasoactive inotropic score day 2	Vasoactive inotropic score day 3	Vasoactive ionotropic score Day 4	Vasoactive inotropic score day 5	Vasoactive inotropic score day 6	max Vasocactive	RAI score positive=1 negative=2	RAI score	Progression to severe AKI Day 3 Positive=1, negative=2	Progression to severe aki d3-7, positive =1, negative =2	Serum cystatin c postive=1, negative=2	Urine cystatin c positive=1, negative=2	Urine R/M 1= NORMAL 2= ABNORMAL	Urine culture 1= sterile 2= growth	Duration of PICU stay	Neet for RRT Present=1 absent=2	mechanical ventilation required ,yes=1,no=2	Need and duration of mechanical ventilation :	Mortality yes=1, no=2	Blood culture 1= sterile 2= growth
1	2.9	6	8	10	10	9	8	4	10	10	30	40	30	20	10	0	40	1	20	1	1	2	1	1	1	10	2	1	6	2	1
2	2.2	5	6	7	5	5	5	5	7	10	20	10	0	0	0	0	20	2	5	2	2	1	2	1	1	12	2	1	10	2	2
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