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Etiological Factors and Clinical Profile of Acute Kidney Injury

in Medical Intensive Care Unit

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ABSTRACT

Background and Objectives: Data on the etiology, management practices and outcome in patients admitted to intensive care units in Kerala has not been studied in depth. The present study was undertaken to identify the etiologic factors and outcome of patients with Acute Kidney Injury admitted in the Medical Intensive Care Unit. **Methods:** Cross sectional study, done in 150 consecutive patients admitted to MICU, Government Medical College, Kottayam meeting the AKIN creatinine criteria for AKI over a period of 12 months.

Results and Discussion: The most common diagnosis in the patients admitted with AKI in MICU was Leptospirosis (22%) followed by undifferentiated fever (21%) and sepsis seen in 17%. 45% of the patients required dialysis, among which 24% underwent CRRT while the 76% underwent hemodialysis. Out of 150 cases 59% survived and 41% expired. Mortality was more in the patients in this study with undifferentiated acute febrile illness (43.8%) and leptospirosis (36.4%).

Conclusion: The most common etiology for AKI was leptospirosis (22%) followed by undifferentiated fever (21%). Mortality was 41% in the patients in the study group. Requirement of ventilator support and inotropic supports were independent predictors of mortality.

Key words: Leptospira; AKI; MICU

1 INTRODUCTION:

Acute kidney injury (AKI) complicates 5–7% of acute care hospital admissions and up to 30% of admissions to the intensive care unit. [1] The tropical zone which is geographically limited by the Tropics of Cancer and Capricorn, is an area with extreme heterogeneity in terms of ethnic composition, as well as the socioeconomic and developmental status. Acute kidney injury remains one of the most enigmatic problems in these regions with high incidence rates (25% - 80%) especially in the intensive care units.

There are very few studies on the etiologic factors of acute kidney injury in the intensive care units in South India. Unlike in the developed nations, were sepsis is a predominant etiologic factor; in high rainfall receiving regions of the tropics - like Kerala, infections like leptospirosis form a major cause of AKI.

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2 OBJECTIVE:

To study the etiologic factors, clinical profile and outcome of patients with Acute Kidney Injury admitted in Medical intensive care unit.

3 MATERIAL AND METHODS:

Study Design : Cross sectional analytical study
Study Setting : Medical Intensive Care Unit,
Government Medical College, Kottayam
Duration of Study : 12 Months

Study Population : Patients with AKI diagnosed by AKIN Creatinine Criteria

Sample Size

n = (Z $\alpha)$ 2 pq/d²

- Z α = 1.96 for α at 5% level of significance
- $\mathbf{p}=\mathbf{prevalence}$ of sepsis causing AKI- 38.6%

(Based on Eswarappa et al on spectrum of AKI in critically ill patients [2]

q = 100 - p

d = absolute precision [3]

(4x38.6x61.4)/8x8=148

Minimum required sample size - 150

Study Tool : Performa based on case records

Inclusion Criteria : atients admitted to MICU within the study period with diagnosis of Acute Kidney Injury by AKIN creatinine criteria

Exclusion Criteria : Patients with Chronic Kidney disease

Study Procedure : 150 consecutive patients admitted to Medical Intensive Care Unit during my study period meeting the AKIN creatinine criteria for acute kidney injury was included in this study. All patients or their relatives were interviewed as per the prepared performa and then complete clinical examination was done.

The following investigations were performed: blood routine, random blood sugar, renal function tests, liver function tests, serum electrolytes, serum uric acid, INR, blood pH, urine analysis, ECG, chest X ray, ultrasonography of abdomen for all cases and specific tests for diagnosis in special cases. The data collected was entered in Microsoft excel and analyzed using SPSS software. Associations between various factors were assessed using chi square test for qualitative variables and t test/ANOVA for quantitative variables. Appropriate non parametric tests were applied wherever required. The level of statistical significance was taken as p value less than 0.05.

Ethical consideration: The above mentioned study was conducted in this institution after obtaining due ethical clearance from the Ethical Committee of Government Medical College, Kottayam. Informed consent was obtained from cases in the study.

4 **THEORY:**

AKI affects patients worldwide, leading to decreased survival, and sometimes to new onset of CKD. Outcomes in AKI are influenced by the underlying disease, the severity and duration of renal impairment and by the baseline characteristics of the patient. The cause of AKI is often multi-factorial.

The role of sepsis in AKI has been well documented in western literature, causing nearly 50% of the AKI cases in few studies. [4–6] Sepsis is associated with high burden of illness, greater abnormality in acute physiology & laboratory findings & greater non-renal organ failure [1–3]. Approximately 25-35% of patients with severe sepsis and 40-55% of patients with septic shock die within 30 days [1, 2].

Other causes include acute gastroenteritis, nephrotoxic drugs, cardiac causes and hepatic causes. Hypertension, diabetes and coronary artery disease are predominant comorbid conditions. Fidel Barrantes et al concluded that the Acute Kidney Injury Network (AKIN) definition of acute kidney injury predicts hospital mortality, need for renal replacement therapy and prolonged hospital stay in critically ill patients. [4]

The true picture of AKI in the tropics is poorly understood due to the late presentation of patients to tertiary centres. Tropical infectious diseases are an important cause of admission to ICU in Kerala, and diseases like leptospirosis have a high propensity to cause AKI.

CASE DEFINITIONS Acute Kidney Injury:

Defined by AKIN Creatinine Criteria

Stage 1: Increase of S Cr ${\geq}0.3$ mg/dl / increase of S Cr ${\geq}150\%$ to 200% over 48 hrs

Oliguria urine output <0.5 ml/ kg / hr over 6 hrs Stage 2: Increase of S Cr \geq 200% to 300% over 48 hours Oliguria urine output <0.5 ml/ kg / hr over 12 hrs Stage 3: Increase of S Cr \geq 300% S Cr \geq 4 mg/dl and acute rise \geq 0.5mg/dl Initiation of RRT [7]

A diagnosis of sepsis/septic shock was made where the primary reason for admission was a sepsis related illness, and included sepsis associated with pneumonia, gastrointestinal disease, urinary tract infections, central nervous system infections, soft tissue infections and sepsis of undetermined source based on a qSOFA score >2 in presence of documented infection. A cardiac diagnosis was made where the primary reason for admission was cardiogenic shock, cardiac arrest, congestive cardiac and acute myocardial infarction.

A respiratory diagnosis encompassed aspiration syndrome, exacerbations of chronic obstructive pulmonary disease or asthma. A diagnosis of gastrointestinal diagnosis included chronic liver disease, pancreatitis and acute diarrheal disease. Metabolic/poisoning diagnoses included causes of metabolic coma, diabetic ketoacidosis, drug overdose or other endocrinopathies. Primary neurologic diagnoses included stroke or other neurological causes for coma. A diagnosis of Dengue by IgM Dengue ELISA test. A diagnosis of probable Leptospirosis based on System of scoring using the Modified Faine's Criteria [8]

5 **RESULTS:**

1. Gender distribution

73.3% of the patients in the study group were males and 26.7% were females.

2. Age distributionTable 1

Mean age was 49.6 years with a standard deviation of 16.5. Youngest and the oldest of the study population had 15 and 88 years of age respectively.

3. Presenting symptomsFigure 1

Fever was the most common presenting symptom seen in 108 (72%) patients, decreased urine output in 72 (48%) patients, breathlessness in 68 (45%) patients, and myalgia in 64(43%) patients.

Other common presenting symptoms were headache, cough, altered sensorium and abdominal pain seen in 35 (23%), 30 (20%), 28 (19%) and 28 (19%) respectively.

4. Nephrotoxic drug intakeTable 2

Only 10 patients that accounts for 7 % had h/o nephrotoxic drug usage. NSAID (2.7%) was the most common one implicated used by 4 patients prior to development of AKI.

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Age group	SEX		Total
(years.)	Male	Female	Total
$<\!\!24$	11 (10.0%)	2(5.0%)	$13 \ (8.7\%)$
25 - 34	14 (12.7%)	5(12.5%)	19(12.7%)
35-44	20~(18.2%)	4(10.0%)	24~(16.0%)
45-54	20(18.2%)	10(25.0%)	30(20.0%)
55-64	22(20.0%)	9(22.5%)	31(20.7%)
65-74	15(13.6%)	8(20.0%)	23(15.3%)
75 &above	8(7.3%)	2(5.0%)	10(6.7%)
Total	110(100.0%)	40(100.0%)	150(100.0%)





Figure 1. Presenting symptoms

Table	2.	Nephrotoxic	drug	intake
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Drugs	Frequency	Percentage
No	140	93.3~%
NSAID	4	$2.7 \ \%$
Lithium	2	1.3~%
ARB	2	1.3~%
Herbal	1	0.7~%
Cocaine	1	0.7~%
Total	150	$100 \ \%$

Etiologic factors	Frequency	Percentage
Leptospirosis	33	22 %
Undifferentiated acute febrile illness	32	21.3~%
Sepsis	26	17.3~%
Respiratory diagnosis	17	11.3~%
Cardiac diagnosis	14	$9.3 \ \%$
Gastrointestinal	13	8.7 %
Metabolic/poisoning diagnoses	7	4.7 %
Primary neurologic diagnoses	3	2 %
Dengue	3	2 %
Drug	1	$0.7 \ \%$
Snake bite	1	$0.7 \ \%$
Total	150	100.0~%

Table 3. Etiologic factors



Figure 2. Etiologic factors

5. Etiologic factorsTable 3Figure 2

The most common etiology of AKI in the patients in this study group was leptospirosis seen in 33 patients which accounts to 22% followed by undifferentiated fever seen in 32 patients (21%) and sepsis seen in 26 patients (17%).

6. Stage of acute kidney injury by the AKIN creatinine criteria Figure ${\bf 3}$

The most common stage of AKI in the patients in this study group on admission to the medical intensive care unit was stage 3 seen in 97 patients which accounts to 64.7%.

7. Dialysis RequirementFigure 4

68 out of the 150 patients in the study group required dialysis, which accounts to 45%. Among the patients in the study group who underwent dialysis 52 patients (76.5%) underwent intermittent hemodialysis while 16 patients (23.5%) underwent CRRT.

8. Indication For DialysisTable 4

The predominant indication for dialysis in the patients in the study group was metabolic acidosis and anuria in 52.9%



Figure 3. Stage of acute kidney injury



Figure 4. Dialysis type

Table 4	. Indie	cation	\mathbf{for}	dialysis
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	Frequency	Percentage
Metabolic acidosis alone	9	13.2%
Hyperkalemia	1	1.5%
Anuria alone	22	32.4%
Metabolic acidosis and anuria	36	52.9%
Total	68	100.00%

of the patients.

9. Ventilation RequirementFigure 5

66 out of the 150 patients which accounts to 56% required invasive ventilation.

10. Inotrope RequirementTable 5

125 of the 150 patients in the study group which accounts for 83% required inotropic support.

11. Mortality Figure 6

Mortality was 41% in the patients in the study group, 62 patients out of 150 expired.

12. Association Between Aki Stage And MortalityTable 6

53% of those with stage 3 AKI expired compared to no mortality in the stage 1or2.

13. Association Between Inotrope Use And MortalityTable 7

Mortality was more in the patients in this study requiring inotrope support. 48% of those with inotropic support expired.

14. Association Between Ventilation And MortalityTable 8

Mortality was more in the patients in this study requiring ventilator support.

15. Association Between Diagnosis And OutcomeTable 9Figure 7

Mortality was more in the patients in this study with undifferentiated acute febrile illness, 43.8% and leptospirosis, 36.4%.

16. Association Between Diagnosis And Stage Of AKITable 10Figure 8



Figure 8. Association between diagnosis and stage of AKI

90.9% of those with leptospirosis and 87.5% of those with undifferentiated febrile illness presented in AKI stage 3.

17. Logistic Regression Analysis Of Outcome PredictorsTable 11

By logistic regression analysis of the factors having association with mortality, requirement of ventilator support and inotropic supports were independent predictors of mortality.

6 DISCUSSION:

AGE AND GENDER

A trend towards an increasing number of AKI cases among male patients was observed compared to female patients [73% and 27 % respectively] in this study.

Compared with all ICU admissions, patients with AKI were found in male gender in Basu et al, Cruz et al and Daher et al [9-11]. The reasons for such gender differences are unclear but are likely associated with work activities.

Majority of patients in this study belonged to 55-65 years (21%) followed by 45-55 years (20%). Mean age was 49.6 years with standard deviation 16.5. The population of patients with AKI in developing tropical countries is younger (30-40 years of age) than that reported in developed temperate countries (60-70 years of age) like Angus et al [12]

CLINICAL FEATURES

Fever was the most common presenting symptom (72%) followed by decreased urine output (48%), breathlessness (45%), and myalgia (43%). Predominant presenting features included fever (89.6%), oliguria (70.4%), and breathlessness (40.4%) as in Mehta et al [13].

Only 7 % of the patients in this study had h/o nephrotoxic drug usage. NSAID (2%) being the most common one implicated.

The most common general examination finding in the patients in this study was icterus (52%) followed by conjunctival congestion (22%). The most common systemic examination finding in patients in this study was basal crepitations (40%). In Eswarappa et al, edema was seen in 28.0%, pallor in 20.0% and icterus in 21.0% of the patients [6]

The mean serum creatinine in the patients in this study on admission to the Medical ICU was 3.72 mg/dL with a standard deviation of 1.65. Mean serum creatinine was 3.64 with SD of 3.1 in a study by Maulita et and 10.18 ± 5.19 mg/dl in a study by Ahmed et al [14]

DIAGNOSIS

The most common diagnosis in the patients in this study was leptospirosis (22%) followed by undifferentiated fever (21%) and sepsis seen in 17%.

In contrast to sepsis, drugs and cardiogenic shock in the developed world, acute tubular necrosis (ATN) due to community-acquired infections remains the commonest cause of AKI in the tropics. Chug, Medve and Angus et al [15-17]

The main causes of ICU hospitalization were acquired immunodeficiency syndrome (AIDS)-related diseases (28.6%), pneumonia 13%), leptospirosis (11.6%) in Daher et al [16] It was scrub typhus (51.2%), falciparum malaria (10.4%), and enteric fever (8.7%) in study by Basu et al [14]. Unlike in our study the predominant cause of AKI in most studies in tropical areas was due to malaria.

90.9% of those with leptospirosis and 87.5% of those with undifferentiated febrile illness presented in AKI stage 3. Significant association was identified between the etiology of AKI and the stage of presentation on admission to the medical intensive care unit.

Significant association was identified between etiology of AKI and the need for dialysis. Dialysis was required in



Figure 5. Ventilation requirement

Table 5	. Inotrope	Inotrope requirement		
	Frequency	Percentage		
No	25	16.70%		
Yes	125	83.30%		
Tota	l 150	100.00%		



Figure 6. Mortality

Table 6. Association between AKI stage and mortality

		Outcome	
		Survived	Expired
		5	0
	Stage 1	100.0%	0
	Stage 2	28	0
AKI stage		100.0%	0
	Stage 3	55	62
		47.0%	53.0%
Total		Number	62
		%	41.3%

Pearson Chi-Square Value - 29.808

p value - 0.000

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Table 7. Association between inotrope use and mortality

	Outcome		-	
	Survived	Expired	Total	
	23	2	25	
Inotropic support absent	92.0%	8.0%	100.0%	
2 AA	65	60	125	
Inotrope support present	52.0%	48.0%	100.0%	
	88	62	150	
Total	58.7%	41.3%	100.0%	

Pearson chi-square Value - 13.746

P value - 0.000

P value - 0.000

	Outcome			
	Survived	Expired	Total	
	63	3	66	
Ventilator support absent	95.5%	4.5%	- 00	
	25	59	0.4	
Ventilator support present	29.8%	70.2%	84	
Total	88	62	150	
	58.7%	41.3%	150	

Pearson chi-square - 65.777

Table 9. Association between diagnosis and Outcome

		Outcome	
	14.01 × 1	Survived	Expired
	Sepsis	16	10
	251.C	61.50%	38.50%
	Cardiac diagnosis	7	7
	Cardiac diagnosis	50.00%	50.00%
	Respiratory diagnosis	11	6
		64.70%	35.30%
	Gastrointestinal	9	4
		69.20%	30.80%
	Metabolic/poisoning Diagnoses	3	4
	18 - 2875 - 1895 - 1	42.90%	57.10%
Diagnosis	Primary neurologic Diagnoses	1	2
		33.30%	66.70%
	Undifferentiated acute Febrile illness	18	14
		56.30%	43.80%
	Leptospirosis	21	12
		63.60%	36.40%
	Dengue	2	1
	673	66.70%	33.30%
	Drug	0	1
	-	0.00%	100.00%
	Snake bite	0	1
		0.00%	100.00%
	•	88	62
lotal		58.70%	41.30%

81.3% among those with undifferentiated febrile illness and 78.8% among those with leptospirosis and the association was significant by Chi square test.

Leptospirosis with AKI admitted to ICU had a significantly higher frequency of severe AKI 73.2 % and a higher prevalence of dialysis requirement (57.3 %) in a study by De Francesco et al [18]

MANAGEMENT

The most common stage of AKI in the patients in this study group on admission to the medical intensive care unit was stage 3 in 64.7%. Unlike in a study by lopes et al in which AKI occurred in 50.4% of patients – 21.1% with Stage 1, 10.1% with Stage 2 and 19.2% with Stage 3.

45% of the patients in the study group required dialysis, among which 24% underwent CRRT while the 76% underwent hemodialysis.

In a study conducted by Bernieh b et al. 58% of patients were managed conservatively while 42% patient were managed with dialysis which is comparable with present study [12]

The predominant indication for dialysis in the patients in this study group was metabolic acidosis with anuria. The most common indication for dialysis was refractory fluid overload (89.4 %), followed by uremic signs and symptoms (61.1 %) in study by Ibrahim et al [19], probably because CKD patients were also included.



Figure 7. Association between diagnosis and Outcome

		AKI stage				
	CMR	1	2	3		
DIAGNOSIS	Sepsis	1	8	17		
		3.8%	30.8%	65.4%		
	Cardiac diagnosis	2	10	2		
		14.3%	71.4%	14.3%		
	Respiratory diagnosis	2	7	8		
		11.8%	41.2%	47.1%		
	Gastrointestinal	0	5	8		
			38.5%	61.5%		
	Metabolic/poisoning Diagnoses	0	5	2		
			71.4%	28.6%		
	Primary neurologic Diagnoses	1	2	0		
		33.3%	66.7%	0.0%		
	Undifferentiated acute	1	3	28		
	Febrile illness	3.1%	9.4%	87.5%		
	Leptospirosis	0	3	30		
			9.1%	90.9%		
	Dengue	0	2	1		
			66.7%	33.3%		
	Drug	0	0	1		
				100.0%		
	Snaka hita	0	1	0		
	Shake one		100.0%			
Total		7	46	97		
		4.7%	30.7%	64.7%		

Table 10. Association between diagnosis and stage of AKI

Pearson Chi-Square Value- 56.27

P value - 0.000

		S.E.	Wald	df	Sig.	Exp(B)
Basal crepitations	416	.654	.405	1	.525	.660
Breathlessness	.989	.643	2.364	1	.124	2.687
AKI stage	20.905	5237.667	.000	1	.997	1199225957.801
Ventilation	3.535	.726	23.717	1	.000	34.291
Inotrope	2.102	1.043	4.059	1	.044	8.186
Indication for dialysis	170	.118	2.050	1	.152	.844
Constant	-66.870	15713.000	.000	1	.997	.000

Table 11. Logistic regression analysis of outcome predictors

MORTALITY

Mortality was 41% in the patients in the study group. The ICU mortality rate was 39.3% (44/112) in study by Medve et al [18] which is comparable with our study.

Maximum mortality was seen in the age group 55-65years - 22.6% and 45-55 years. - 17.7%. Mortality was more, 72.6% in the male patients in this study group compared to females. However, no significant association was identified between age group, gender, patients with comorbidities, and mortality. Age, gender or the presence of co-morbidities was not associated with a higher risk of AKI as in Wijikerma et al [13]

Among those with breathlessness as presenting symptom, 58.8% expired compared to only 26.8% among those with no breathlessness on admission to the Medical ICU. Significant association was identified mortality and breathlessness as the presenting symptom. Among those with Basal Crepitations, 53.3% expired compared to only 33.3% among those with no Basal Crepitations on admission to the Medical ICU. Significant association was identified.

Respiratory involvement, along with AKI had statistically significant chances of poor outcome (p<0.05) in a study by Bhadade et al [20]

Mortality was more in the patients in this study with undifferentiated acute febrile illness, 43.8% and leptospirosis, 36.4%. No significant association was identified between the etiology of AKI and mortality unlike in study by Eswarappa et al which identified significant difference in mortality due to medical versus surgical etiology of AKI.

53% of those with stage 3 AKI expired compared to no mortality in the stage 1 or 2. Significant association could be identified between stage of AKI and mortality. *AKIN* stages based on creatinine criteria predicted mortality as in a study by Lopez et al. [21]

Mortality was more in the patients in this study who underwent dialysis 48.5% compared to those who did not require it. This may be because of the fact that they are more hemodynamically compromised. But no significant association was identified between dialysis and mortality.

The need for dialysis treatment has been associated with a higher mortality rate (50-70%) than among patients with AKI who did not require RRT in study by Bhadade et al [22]

Significant association was identified between indication for dialysis and mortality. 60% of the patients who underwent dialysis and died had both metabolic acidosis and anuria. Significant association was identified between patients with metabolic acidosis and anuria and mortality in Kumar et al. [23] Mortality was more in the patients in this study requiring inotrope support (48%) and ventilator support (70.2%). Significant association was identified between inotropic and ventilator support; and mortality. Vasopressor support and assisted ventilation were predictors for mortality in a study by Mathew George et al. [24]

By multivariate logistic regression analysis of the factors having association with mortality, requirement of ventilator support and inotropic supports were independent predictors of mortality. Significant association was identified between patients with ventilator support and mortality in Saxena et al ⁴⁷ and Liano et al. [25]

7 CONCLUSION:

150 consecutive patients diagnosed to have acute kidney injury admitted to the medical ICU of a tertiary care center in Kerala were studied. The main burden of diseases were due to infective etiologies. The most common was leptospirosis (22%) followed by undifferentiated fever (21%) and sepsis (17%). This is unlike studies done in developed countries. This reflects mainly the trend in tropical regions with higher rainfall. Mortality was 41% in the study and requirement of ventilator support and inotropic supports were independent predictors of mortality.

In the tropics, diseases like leptospirosis have a high propensity to be the cause of AKI. So a high degree of suspicion should be kept to aid in the diagnosis and early referral to centers with intensive care facilities.

Appendix-1 LIST OF ABBREVIATION

- 1. AKI Acute Kidney Injury
- 2. AKIN Acute Kidney Injury Network
- 3. CKD Chronic kidney disease
- 4. CRRT Continuous renal replacement therapy
- 5. ECG Electro Cardio Gram
- 6. ELISA Enzyme Linked Immunosorbant Assay
- $_{7}\,$ ICU Intensive care unit
- 8. INR International Normalized Ratio
- 9. KDIGO Kidney Disease Improving Global Outcome

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- 10. qSOFA Score Quick Sequential Organ Failure Assessment
- 11. RIFLE Risk of renal failure, Injury to kidney, Failure of kidney function, Loss of kidney function, and Endstage kidney disease
- 12. RRT Renal Replacement Therapy
- 13. S Cr Serum creatinine
- 14. SD Standard deviation

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