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Original Article

Acute Renal Injury in Patients with ARDS: Presence and Associated Factors

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ABSTRACT

Objective: To determine the occurrence of Acute Renal Injury in Acute Respiratory Distress Syndrome patients along with contribution of co-morbidities and risk factors for the development of AKI.

Study Design: Comparative Cross Sectional study.

Place and Duration of Study: This study was done at medical ICU, Department of Medicine, Combined Military Hospital (CMH), Rawalpindi from Jan 2023 to Oct 2023.

Methodology: A total of 68 patients, with confirmed ARDS, 18yrs or above were included. The presence of co-morbidities in all patients was recorded. Patients BMI and SOFA score were calculated. Patients were divided as Group 1 (those who develop AKI) and Group 2 (those who did not develop AKI). On the basis of serum creatinine level group 1 patients were further categorized into three groups: stage I AKI, stage II AKI, and stage III AKI. The median (IQR) was calculated for non-normal variables. Chi-square test, unpaired t-test, and Mann-Whitney U test were applied and $p \leq 0.05$ was taken as statistically significant.

Results: Acute Kidney Injury was observed in 39(57.4%) patients (Group 1) while 29(42.6%) patients did not develop any AKI (Group 2). Group 1, had a significantly higher BMI, SOFA score, Comorbidities like Diabetes Mellitus (DM), Malignancies and liver Disease. Non-pulmonary sepsis was high in Group 2. There was a statistically significant association between AKI stages and specific characteristics.

Conclusion: AKI was quite common among ARDS individual. A Higher BMI, SOFA score, presence of DM, active malignancy, liver and cardiac illness showed strong association with the development of AKI.

Keywords: Acute Kidney injury, AKI, Acute Respiratory Distress Syndrome (ARDS), Sepsis.

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INTRODUCTION

Acute kidney injury (AKI) is a condition that is characterized by a decrease in glomerular filtration rate (GFR), resulting in the accumulation of various toxic substances & metabolic waste products in the body along with an inability to maintain the homeostatic balance of serum electrolytes and body fluids.[1] AKI may lead to significant short-term and long-term consequences, complicating pre-existing conditions, if any, and resulting in a considerably increased usage of medical resources and efforts. In intensive care units (ICUs), AKI is a commonly encountered complication occurring in about 50–70% of admitted patients and is associated with morbid outcomes, reaching devastating mortality rates of nearly 50%.[2]

Acute respiratory distress syndrome (ARDS) can be defined as an inflammatory and life-threatening acute respiratory condition, leading to severe morbidity and a significantly high mortality rate in patients that may reach up to 40%.[3] The common risk factors leading to the development of ARDS include pulmonary causes such as pneumonia which may be bacterial or non-bacterial in origin and non-pulmonary causes such as sepsis, liver & cardiac diseases, these are followed by less commonly encountered causes like gastric aspiration, trauma and transfusion of blood products.[4] In Pakistan researches on ARDS patients with COVID 19 infection showed that patient who developed AKI during their illnesses had worst outcome then non AKI patients.[5] AKI can be regarded as the most often extra-pulmonary organ dysfunction encountered by healthcare professionals in patients with ARDS, it can vary in its severity from mild to moderate and severe.[6] Although the mechanisms of co-existence are, the occurrence of both organ system dysfunction that adds to the burden of adverse patient outcomes

& increased mortality rates.[7] Several contributors are suggestive to be the cause of renal involvement, such as DM, malignancies, heart & liver diseases; biochemical irregularities like sepsis, hypovolemia,

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electrolyte imbalance, increase in various byproduct levels; and use of damaging nephrotoxic agents including NSAIDs, antimicrobials, contrast agents, ACEIs, etc.[8]

Amongst the critically ill patients admitted to medical ICUs, AKI has severely reduced their life span or otherwise lead to multi-organ dysfuction.[9] Furthermore, in the development of chronic kidney disease, AKI has been regarded as a major causative risk factor, worsening the long-term mental as well as physical well-being of the patients & adding to the burden on healthcare setups.[10]

Keeping in view the current clinical practices or facilities and paucity of local data, this study has been conducted to identify & categorize multiple variables such as age, gender, co-morbidities, and chronic diseases which may be associated with the development of AKI in patients of ARDS.

METHODOLOGY

This Comparative Cross Sectional study was performed at the Medical ICU, Department of Medicine, Combined Military Hospital (CMH), Rawalpindi from Jan 2023 to Oct 2023 after taking approval from Institutional Review Board (IRB), vide reference number 443. After a thorough literature search, we calculated a sample size of 34 via the WHO calculator, keeping the margin of error at 5%, a confidence level at 95%, and a prevalence of AKI at 2.2%.[11] Sampling was done using a non-probability consecutive sampling technique.

Inclusion Criteria: Adult patients with age 18 years or more admitted to the intensive care unit (ICU) of our hospital with a confirmed diagnosis of ARDS based on the Berlin definition,[12] were included in this study.

Exclusion Criteria: Any patient already suffering from a preexisting chronic kidney disease or having an AKI before being diagnosed with ARDS, or with an ICU admission of less than 24 hours were excluded from study.

A maximum number of available participants (68) during the study period were recruited. Written consent was obtained before enrolling all patients, and their confidentiality was ensured at all levels. Approval of the institutional ethical committee was also procured before starting the project.

AKI was determined by the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines ,using serum creatinine & urine output criteria.[13] Patients were divided as, Group 1 (who developed AKI) & Group 2 (who did not develop AKI). Demographic information encompassed age, gender, body mass index (BMI) of both groups. The presence of co-morbidities was documented such as Diabetes mellitus, active malignancies, lungs liver & heart disease. The severity of sepsis was graded by the sequential organ failure assessment (SOFA) score. The cause of ARDS was documented as pneumonia, aspiration, non-pulmonary sepsis & pancreatitis. On the basis of serum creatinine level Group 1 patients were further categorized into three groups: stage I AKI (upto 2.29mg/dl), stage II AKI (2.29-3.5mg/dl), and stage III AKI (higher than 3.5mg/dl).

Collected data were processed through SPSS 21, using standard protocol analysis. Baseline variables were analyzed descriptively using frequencies and percentages for qualitative variables and the mean with SD was calculated for continuous variables. Some variables like BMI, Sofa, and EF were found to be non-normally distributed. The median (IQR) was calculated for non-normal variables. Chi-square test (for comparison of qualitative variables), unpaired t-test (for comparison of quantitative variables), and Mann Whitney U test (for comparison of non-normal distributed variables) were applied and $p \leq 0.05$ was taken as statistically significant.

RESULTS

A total of sixty-eight (n=68) patients with a diagnosis of ARDS were included in the study, mean age was 52.69±7.15 yrs. Of the total, 40(58.8%) patients were male and 28(41.2%) were female. The details of demographic and clinical Characteristics of the Patients are shown in Table-I

The distribution of various characteristics among different stages of Acute Kidney Injury (AKI), categorized by BMI, SOFA score, presence of Diabetes Mellitus, occurrence of

Sepsis, presence of Liver Disease & Malignancy is shown in Table-II. The significant p-value indicated the statistical significance associations between AKI stages and the specified characteristics.

DISCUSSION

Our research results showed that approximately two-thirds of patients who were labeled as having ARDS developed AKI during their hospital stay with variable rates of progression to different stages of AKI. We deduced that in patients suffering from ARDS, having higher BMI, Co-morbidities like Diabetes mellitus (DM), any active malignancies, chronic

Table-I: Demographic and Clinical Characteristics of the Patients (n=68)

	Group 1 Acute Kidney Injury (n=39)	Group 2 No Acute Kidney Injury (n=29)	*p*-value
Age	51.8±6.9	53.7±7.4	0.292
Male	23(58.9%)	17(58.6%)	0.97
Female	16(41.1%)	12(41.4%)	
Patients Characteristics			
Baseline Serum Creatinine (mg/dl)	0.91±0.19	0.70±0.19	< 0.001**
BMI (kg/m²)	30.1(39.3 – 29.1)	28.3(34.7–26.0)	0.048*
Sofa	12.1±2.3	8.8±2.9	< 0.001**
Comorbidities			
lung Disease	15(38.5%)	9(31.0%)	0.526
Diabetes	18(46.7%)	6(20.7%)	0.030*
Active Malignancies	14(35.9%)	4(13.7%)	0.041*
Liver Disease	16(41.0%)	5(17.2%)	0.036*
Heart Failure	2(5.1%)	1(3.4%)	0.739
Etiologies leading to ARDS			
Pneumonia	32(82.1%)	22(75.9%)	0.532
Aspiration	8(20.5%)	5(17.2%)	0.734
Non-Pulmonary Sepsis	4(10.3%)	10(34.5%)	0.015*
Pancreatitis	2(5.1%)	1(3.4%)	0.739
Echocardiographic findings			
EF	60.0(65.1–55.1)	59.0(63.4–53.0)	0.761
Septic Shock	23(58.9%)	9(31.0%)	0.004
Nephrotoxic Agents			
Antimicrobial agents	34(87.2%)	26(89.6%)	0.754
ACEI	4(10.3%)	4(13.7%)	0.54
NSAIDS	2(5.1%)	1(3.4%)	0.739

Significant p-value, Highly significant p value***

diseases such as heart or liver disease, and a higher intensity of illness score, the Sequential Organ Failure Assessment score (SOFA) were found to be the significant contributors towards the occurrence of AKI. Patients having AKI demonstrated a higher rate of incidence of septic shock as compared to patients not having AKI.

Our study results showed a high percentage of patients with AKI 39(57.4%) than the non AKI patients 29(42.6%) patients with ARDS. A similar study by Aness *et al.*,[14] also revealed a high percentage of AKI patients with ARDS (51.1%) than non AKI patients.

Like the findings of Hsu *et al*, and Hoste *et al* study, our research study proved that AKI risk increases due to DM.[15] Since kidneys of a diabetic patients have an increased incidence of undergoing ischemic–hypoxic injuries, it is reasonable to believe that patients having ARDS and concomitant DM may have a greater risk of suffering from AKI. Although a limited number of patients from our study were harboring any history of cardiac disease, the presence of cardiac disease such as heart failure was found to be held by the development of AKI similar to a study conducted by Fuhram et al.[16]

A higher grade of illness as determined by the SOFA score had a strong relation to the occurence & severity of AKI as observed in our study patients. The probable explanation for this would be the hemodynamic derangements which would then aggravate the grades of illness scores. Respiratory acidosis occurring early in the development of ARDS was found to be a significant contributing factor towards the development as well as severity of AKI as observed in our study group. A similar association was found between a high SOFA score and the development of AKI in a study conducted in 2022 by Wang N. *et al.*,[17] and Anandh *et al.*,[18]

As observed in a couple of related studies, conducted by Soto GJ *et al.* and Cruz-Lagunas A *et al.*, we also found that obesity or increased BMI intensified the risk of development of AKI.[19]A plausible explanation for this phenomenon can be given by the fact that higher BMI leads to an increased release of pro-inflammatory markers and acute phase proteins which can be found to be much higher as compared to non-obese patients.

Primary diseases leading to ARDS as found in our study group included pneumonia followed by aspiration, non-pulmonary sepsis, and pancreatitis. We found pneumonia to

be the most contributory lung disease leading toward ARDS as well as AKI. The same observations were also highlighted in a study conducted by Chawla LS. *et al.*, defining pneumonia to be a leading factor in the development of AKI.[20] It was also observed in another study that the development of AKI in the settings of acute lung disease such as pneumonia may carry an overall mortality risk of 58% when it is compared to a 28% risk in patients of pneumonia not developing AKI.[21]

In our study group, the presence of an active malignancy was found to be increasingly associated with AKI. Patients already having ARDS along with the presence of significant co-morbidity such as cancer can have detrimental effects on the renal system. This

Table-II: Stratification of AKI staging with respect to BMI, Sofa, DM, Sepsis, Liver disease and Malignancy (n=68)

Characteristics		Stage				Total	*p*-value
		No AKI	Stage-I	Stage-II	Stage-III		
	20-25	14(73.7%)	1(5.3%)	2(10.5%)	2(10.5%)	19(27.9%)	
BMI	26-30	10(45.5%)	3(13.6%)	5(22.7%)	4(18.2%)	22(32.4%)	0.009
	>30	5(18.5%)	2(7.4%)	7(25.9%)	13(48.1%)	27(39.7%)	
Sofa	<10	23(74.1%)	3(9.7%)	3(9.7%)	2(6.5%)	31(45.6%)	<0.0001
	>10	6(16.2%)	3(8.1%)	11(29.7%)	17(45.9%)	37(54.4%)	
DM	Yes	6(25.0%)	1(4.2%)	2(8.3%)	15(62.5%)	24(35.3%)	<0.0001
	No	23(52.3%)	5(11.4%)	12(27.3%)	4(9.1%)	44(64.7%)	
Sepsis	Yes	(23.3%)	2(6.7%)	10(33.3%)	11(36.7%)	30(44.1%)	0.014
	No	22(57.9%)	4(10.5%)	4(10.5%)	8(21.1%)	38(55.9%)	
Liver Disease	Yes	5(25.0%)	0	5(25.0%)	10(50.0%)	20(29.4%)	0.021
	No	24(50.0%)	6(12.5%)	9(18.8%)	9(18.8%)	48(70.6%)	
Malignancy	Yes	4(22.1%)	1(5.6%)	3(16.7%)	10(55.6%)	18(26.5%)	0.023
	No	25(50.0%)	5(10.0%)	11(22.0%)	9(18.0%)	50(73.0%)	

observation was also highlighted by a study conducted by Luciano RL. *et al.*,[22] Another study conducted by Gallieni M. *et al.* defined active malignancy as one of the most commonly encountered co-morbid conditions leading to AKI amongst ICU patients. Various factors leading towards AKI as defined in this study included direct effects of malignancy, any complication resulting due to the malignancy, or the consequence or side effect of cytotoxic chemotherapy, targeted agents, or immune checkpoint inhibitors which are often severely nephrotoxic, and do account for a vast majority of cases.[23]

Patients suffering from liver diseases such as cirrhosis were also found to develop AKI in our study group . A study conducted by Chancharoenthana W et al, concluded that AKI is a common complication encountered in patients with liver disease and carries utmost significance concerning clinical and prognostic outcomes.[24] A similar conclusion was drawn in a study conducted by Deep A *et al*. The various reasons which may be contributory to the development of AKI in these patients were also categorized by this

study as pre-renal, acute tubular necrosis, post-renal, drug-induced renal failure, and hepatorenal syndrome (HRS).[25]

To our knowledge, this is the one of the first studies to explore different confounders such as various comorbidities and primary respiratory pathologies associated with the occurrence of AKI in ARDS patients.

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LIMITATIONS OF STUDY

The study was conducted at a single center with a single ethnic group of people. A more widespread study population and parameters needs to be included for further and more comprehensive analysis of AKI in ARDS patients.

CONCLUSION

In conclusion, a higher BMI score, and the co-morbidities such as DM, active malignancies, liver diseases, and heart failures in patients of ARDS were found to be contributory to the occurrence of AKI. Pneumonia was found to be the most common primary lung disease. A high sepsis severity score was also found to be a leading contributor to AKI Age and gender did not have any specific association with the occurrence of AKI.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SS & FAS: Data acquisition, data analysis, critical review, approval of the final version to be published.

IK& KAS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AE & AAC: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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