CLINICO-LABORATORY CHARACTERISTICS, RISK FACTORS AND OUTCOME OF ACUTE KIDNEY INJURY

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ABSTRACT

OBJECTIVE: To determine the clinico-laboratory characteristics, risk factors and outcome related to acute kidney injury (AKI) in hospitalized patients.

METHODS: This prospective study on 101 consecutive patients admitted to the Northwest General Hospital & Research Centre, Peshawar, Pakistan was carried out from January-March 2019. Patients were staged according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines and outcomes were measured in terms of in-hospital mortality and change in KDIGO staging.

RESULTS: Majority (n=57/101; 56.43%) were males. Mean age of patients was 57.90±16.93 years. Twenty-seven (26.73%) patients were in AKI stage-I, 29 (28.71%) in stage-2 and 45 (44.55%) were in stage-3. Hypertension (n=74/101; 73.27%) was the commonest co-morbid recovery. In-hospital mortality was 6.9% (n=7/101) and 57.1% (n=4/7) of these patients had KDIGO stage-3. Serum creatinine levels declined in 22 (21.78%) cases, remained static in 23 (22.8%) and worsened in 06 (5.9%) cases. Male gender and presence of hypovolemia (p<0.05) significantly differed in survivors compared to non-survivors. Furthermore, factors associated with decline in serum creatinine included stage-II AKI and length of hospital stay, while stage-II and III AKI on admission, absence of oliguria crude odd ratio (cOR: 2.681, p=0.027, 95% CI: 1.12-6.44) and serum creatinine levels on admission (cOR: 0.668, p<0.001, 95% CI: 0.54-0.83) were associated with complete recovery.

CONCLUSION: Sepsis and hypovolemia constituted the major risk factors. Gender and hypovolemia were the significant factors between the survivors and non-survivors.

KEYWORDS: Acute Kidney Injury (MeSH); Patient Outcome Assessment (MeSH); KDIGO (Non-MeSH); Fatal Outcome (MeSH); Mortality (MeSH); Sepsis (MeSH); Oliguria (MeSH).

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TABLE I: PATIENTS CHARACTERISTICS AMONG BETWEEN SURVIVORS AND NON-SURVIVORS

| Variable                      | Total (n=101) | Survivors (n=94) N (%) | Non-survivors (n=7) N (%) | p-value |
|-------------------------------|---------------|------------------------|---------------------------|---------|
| Gender                        |               |                        |                           |         |
| Male                          | 57 (56.43)    | 50 (87.71)             | 7 (12.28)                 | 0.018*  |
| Female                        | 44 (43.56)    | 44 (100)               | 0 (0)                     |         |
| KDIGO stage on admission      |               |                        |                           |         |
| Stage 1                       | 27 (26.73)    | 26 (96.30)             | 1 (3.70)                  | 0.703*  |
| Stage 2                       | 29 (28.71)    | 27 (93.1)              | 2 (6.9)                   |         |
| Stage 3                       | 45 (44.55)    | 41 (91.1)              | 4 (8.89)                  |         |
| Co-morbid conditions          |               |                        |                           |         |
| Hypertension                  | 74 (73.27)    | 69 (93.24)             | 5 (6.76)                  | 1.000*  |
| Diabetes mellitus             | 58 (57.43)    | 53 (91.30)             | 5 (8.62)                  | 0.696*  |
| Coronary artery disease       | 41 (40.59)    | 39 (95.12)             | 2 (4.88)                  | 0.698*  |
| Congestive heart failure      | 34 (33.66)    | 33 (97.06)             | 1 (2.94)                  | 0.418*  |
| Chronic Kidney disease        | 21 (20.79)    | 20 (94.23)             | 1 (4.76)                  |         |
| Previous hospitalization      |               |                        |                           |         |
| Yes                           | 61 (60.39)    | 58 (95.08)             | 3 (4.92)                  | 1.000*  |
| No                            | 40 (39.60)    | 36 (90)                | 4 (10)                    |         |
| Dialysis                      |               |                        |                           |         |
| Yes                           | 83 (82.8)     | 77 (92.77)             | 6 (7.23)                  | 1.000*  |
| No                            | 18 (17.82)    | 17 (94.44)             | 1 (5.56)                  |         |
| Oliguria                      |               |                        |                           |         |
| Yes                           | 36 (35.64)    | 31 (86.11)             | 5 (13.89)                 | 0.094*  |
| No                            | 65 (64.36)    | 63 (96.92)             | 2 (3.08)                  |         |
| Risk factors for acute kidney disease | | | | |
| Sepsis                        | 39 (38.61)    | 35 (89.74)             | 4 (10.26)                 | 0.033*  |
| Hypovolemia                   | 21 (20.79)    | 17 (80.95)             | 4 (19.05)                 | 0.425*  |
| Acute fluid overload          | 18 (17.82)    | 17 (94.44)             | 1 (5.56)                  | 1.000*  |
| Acute Coronary Syndrome       | 10 (9.91)     | 9 (90)                 | 1 (10)                    | 0.529*  |
| Obstructive Uropathy          | 09 (8.91)     | 9 (100)                | 0 (0)                     | 1.000*  |
| Drugs                         | 07 (6.93)     | 7 (100)                | 0 (0)                     | 1.000*  |
| Glomerulonephritis            | 04 (3.96)     | 4 (100)                | 0 (0)                     | 1.000*  |
| Respiratory failure           | 04 (3.96)     | 4 (100)                | 0 (0)                     | 1.000*  |
| Pigment nephropathy           | 01 (0.99)     | 1 (100)                | 0 (0)                     | 1.000*  |
| Contrast induced              | 02 (1.98)     | 2 (100)                | 0 (0)                     | 1.000*  |
| Reasons for admission         |               |                        |                           |         |
| Infectious Disease            | 23 (22.8)     | 21 (22.3)              | 2 (28.6)                  | 0.480*  |
| Cardiovascular disorders      | 21 (20.79)    | 20 (95.24)             | 1 (4.76)                  |         |
| Chronic kidney disease        | 18 (17.82)    | 17 (94.44)             | 1 (5.56)                  |         |
| Neurological diseases         | 15 (14.85)    | 15 (100)               | 0                        |         |
| Obstructive uropathy          | 5 (4.95)      | 5 (100)                | 0                        |         |
| Liver disorders               | 04 (3.96)     | 4 (100)                | 0                        |         |
| Gastrointestinal disorders    | 04 (3.96)     | 3 (75)                 | 1 (25)                    |         |
| Obstructive related acute kidney injury | 2 (1.98) | 2 (100) | 0 | |

* Student independent t test. # Mann whitney test. † Chi square test. & Fisher exact test.

Operational Definitions

1. AKI was defined as per KDIGO guidelines as follow:
   - Stage 1: 1.5–1.9 times baseline odds ratio (or) = 0.3mg/dL (=26.5 mol/L) increase in the serum creatinine, (and/or) urine output, 0.5 mL/kg/h for 6-12 hour.
   - Stage 2: 2.0–2.9 times baseline in the serum creatinine (and/or) urine output <0.5 mL/kg/h for = 12 hr.
   - Stage 3: 3.0 times baseline increase in the serum creatinine to = 4.0mg/dL (=353.6 mol/L) (and/or) urine output of <0.3 mL/kg/h for = 24h, or anuria for = 12h or the initiation of renal replacement therapy or in patients, 18 years, decrease in estimated GFR to <35 mL/min/1.73 m².

2. Obstructive uropathy was defined as the cause of AKI with radiological evidence and improvement after the relief of obstruction.

3. Drugs were labeled as the cause of AKI where there was clinical relation in the absence of other factors causing AKI.

4. Contrast-induced nephropathy was defined as a rise in serum creatinine of 25% or an absolute increase in serum creatinine of 0.5 mg/dl within 48 hours after the procedure.

5. Sepsis was defined as patients with suspected or confirmed bacterial infection and presence of ≥2 of the following variables:
   - a) Glasgow Coma Scale <15 or Altered mental status
   - b) Respiratory rate >22/minute
   - c) Systolic BP <100mmHg
   - d) White cell count >12000/µL or <4000/µL.

6. Hypovolemia is defined as:
   - a) Decrease in blood pressure less than 90/60mmHg
   - b) Delayed capillary refill
   - c) Improvement after normalization of blood flow

7. CKD was defined as patients persistent reduction in eGFR of less...
than 60 mL/min per 1.73 m² or with radiological and biochemical evidence of chronic kidney disease for more than 3 months.13

### RESULTS

All patients were classified as per KDIGO guidelines. Twenty seven (26.73%) patients were in AKI stage I, 29 (28.71%) patients were in stage II and 45 (44.55%) patients were in stage III (Table I). Hypertension (n=74/101; 73.27%) was the most common co-morbid condition followed by diabetes mellitus (n=58/101; 57.43%). Of the total, 36 (35.64%) cases of hypovolemia (n=21/101; 20.8%) were among hospitalized patients that also require dialysis, 7 (38.88%) had sepsis, 5 (27.77%) had hypovolemia and 3 (16.66%) had acute circulatory overload (Table III).

The mean serum creatinine on admission was 4.50±3.10 mg/dL in all patients with 4.35±2.96 mg/dL and 6.46±4.56 mg/dL in survivors and non-survivors respectively (p=0.085). Baseline median (IQR) serum K⁺ was 4.71 (4.72) mmol/L, 4.65 (1.68) mmol/L and 4.99 (1.55) mmol/L in all patients, survivors and non-survivors respectively (p=0.211).

Mean (SD) length of hospital stay was 5.37±3.37, 5.49±3.356 and 3.71±3.302 days in all patients, survivors and non-survivors respectively (p=0.180). Data regarding the outcome showed that 43 (42.57%) patients completely recovered from AKI at the time of discharge. Serum creatinine levels declined in 22 (21.78%) cases, remained static in 23 (22.8%) cases and worsened in 06 (5.9%) cases. The outcome was good in 77.78% (n=21/27) cases of KDIGO stage I. Out of 43 cases with fully recovery, 21 (48.8%) cases were in KDIGO stage I.

### DISCUSSION

The term of AKI has been described from time to time using various criteria. Most of the times in literature, serum creatinine level is the most frequently used marker by the researchers in defining and staging AKI. It can also be defined based on urinary output. The criterion implemented in our study was based on the KDIGO guidelines 2012, stating that an increase in serum creatinine of ≥ 0.3 mg/dl (= 26.5 mol/l) within 48 hours.14

It has been observed that a slight increase in Cr level can increase the relative mortality. AKI is a common cause of an increase in morbidity and mortality among hospitalized patients that also results in an increased hospital stay and a financial burden.15 Patients with AKI have three to seven times higher odds for deaths compared to non-AKI admissions.16 The presence of CKD and other concomitant condition raises the risk of AKI.

Studies have been done to predict the possible causes and outcomes of patients having AKI.2-4 To our knowledge, it is the first study in this area conducted outside ICU settings to estimate the risk factors and outcomes in AKI patients, using KDIGO definitions.

Hypertension followed by diabetes was the most common co-morbid in our study population. A previous study described the same medical co-morbidities in their hospital-acquired acute kidney injury patients. In patients requiring hospitalization for acute health associated problems, several factors such as age-linked changes and accompanied co-morbidity renders elder population prone to develop AKI.17

Primary reasons for admission of the study patients to the hospital included infectious diseases (n=23, 22.8%), cardiovascular disease (n=21, 20.8%), chronic kidney disease (n=18, 17.8%), neurological disease (n=15, 14.9%) and respiratory disease (n=9, 8.9%). Park et al. reported pulmonary disease, gastrointestinal disease, and malignancies to be the primary reason for admission in their study patients.18 Previous hospitalization was higher in non-survivors (75%) as compared to survivors (61.7%). Previous health status was normal in 39.6% of patients which is similar to a study conducted in an ICU setting (41%).17

Studies from India reported that the

### TABLE II: OUTCOME OF ACUTE KIDNEY INJURY IN TERMS OF KDIGO STAGING AND IN-HOSPITAL MORTALITY

| KDIGO stage on admission | Outcome in terms of KDIGO staging |
|--------------------------|----------------------------------|
|                          | Declined (n=22) | Static (n=23) | Resolved (n=43) | Worsened (n=6) | Death (n=7) | Total (n=121) |
| Stage 1                  | I (3.70)       | 2 (7.40)      | 21 (77.78)     | 2 (7.40)       | 1 (3.70)    | 27 (26.73)    |
| Stage 2                  | 8 (27.59)      | 5 (17.24)     | 11 (37.93)     | 3 (10.35)      | 2 (6.89)    | 29 (28.71)    |
| Stage 3                  | 13 (28.89)     | 16 (35.56)    | 11 (24.44)     | 1 (2.22)       | 4 (8.89)    | 45 (44.56)    |

KDIG: Kidney Disease Improving Global Outcomes
etiology of the AKI has changed in recent times from drug-induced to sepsis and volume depletion.\textsuperscript{12,19} In these studies, sepsis was the most frequently associated factor (n = 39, 38.6%) found among AKI patients, which was 48% and 34.88% in other studies.\textsuperscript{3,13} This high incidence of sepsis in our patients may be because most of our patients were from medical units. It is well documented that sepsis attributed to AKI carries high mortality.\textsuperscript{1,3} The presence of AKI is an independent risk factor in these patents corresponds to in-hospital mortality. Rangel-Frausto et al described that in culture-positive patients, AKI was recorded in 51% with septic shock, 23% with severe sepsis, and 19% with mild to moderate sepsis.\textsuperscript{15} Despite medical advancement the death ratio of severe sepsis has continued to spike.\textsuperscript{16} Compared to non-septic (45%) AKI, sepsis-related AKI has a very high mortality (74%).\textsuperscript{16} Mortality noted in present study was 6.9%, which is less than the reported 10.8%\textsuperscript{12,19} 42.8% globally.\textsuperscript{12,21,22} The reason could be the low number and non-ICU status of the patients in this study. The other possible reasons include a decreased number of days spent in the hospital, the high number of patients in stage I and II AKI according to KDIGO and relatively young population with absence of multiple comorbidities. Sepsis was followed by intravascular volume depletion (21, 20.8%) and acute fluid overload (18, 17.8%) as the most frequently associated factors among our AKI patients. The likelihood of the progression of hospital-acquired AKI increases from 9.2 to 9.4 times in the presence of factors such as volume depletion and congestive cardiac failure.\textsuperscript{23} Poor prognosis was seen in these patients.

Thirty six patients were oliguric of whom, 5 patients died in our study. Such patient tends to have longer hospitalization and need more regular dialysis sessions. Oliguria has been recognized as a poor prognostic sign in AKI. Oliguria and high creatinine levels when combined have been performed to estimate the highest mortality in a sample of 32,000 patients.\textsuperscript{24}

According to KDIGO staging, the majority of patients (45, 44.55%) progressed to Stage III and mortality was also highest in stage III (4, 57.1%). Among those who recovered completely most of them (21, 48.8%) belonged to stage I according to KDIGO guidelines. These results resemble the one concluded in data collected from Asia-Africa.\textsuperscript{13}

Gender was found to be associated with in-hospital mortality in AKI patients in our results, all of them were males which supported results of a meta-analysis of studies providing sex-stratified incidence of hospital-acquired acute kidney injury (HAAKI) demonstrates that female sex is associated with protection from AKI. It also concluded that it is male sex that is associated with HAAKI.\textsuperscript{1}

Factors affecting the outcome [change in serum creatinine] were determined. Stage II AKI and length of hospital stay were the factors associated with decline in serum creatinine. On the other hand, patients with stage II, III AKI on admission, absence of oliguria, and lower serum creatinine on admission were associated with complete recovery in terms of serum creatinine. Stage II had a significant decline in serum creatinine levels than stage III which may be due to early approach in the management of progressing AKI patients. Similarly, an increase in hospital stay also had a significant decline in serum creatinine levels which support a prolonged monitored approach for AKI patients inside the hospital... Keeping stage I as a reference, the odds ratio of stage II and stage III was 0.175 and 0.092 respectively. These results can be due to low baseline serum creatinine levels and early renal replacement therapy to these patients. Patients who had mildly functioning kidneys initially with urinary output >500ml/24hr had significant recovery than those with oliguria at the time of presentation which shows oliguria a bad prognostic sign. Lower serum creatinine levels on admission were statistically significant regarding complete recovery among AKI patients which means lower baseline serum creatinine can be used as a good prognostic marker among AKI patients.

Strength and Limitation of the Study

To our knowledge, it is the first study in this region using KDIGO guidelines and estimating in-hospital mortality. The limitation of this study is single center and lack of follow up after discharge from the hospital. Moreover, we acknowledge that our sample size is small, large sample would yield more meaningful insight.

| Cause and Management of Acute Kidney Injury | Need for Dialysis | Death |
|-------------------------------------------|------------------|-------|
|                                           | (n=103)          | (n=7) |
|                                           | No N | % | Yes N | % | No N | % |
| Hypovolemia (n=25)                        | 16   | 16.2 | 13  | 13.9 | 4   | 57.1 |
| Sepsis (n=43)                             | 32   | 38.5 | 7   | 8.8  | 4   | 57.1 |
| Acute circulatory overload (n=19)         | 15   | 16.0 | 3   | 66.7 | 1   | 14.2 |
| Acute coronary syndrome (n=11)            | 9    | 8.1  | 1   | 11.1 | 1   | 14.2 |
| Obstructive uropathy (n=9)                | 9    | 9.9  | 1   | 11.1 | 0   | 0.0  |
| Drugs (n=7)                               | 6    | 6.7  | 1   | 11.1 | 0   | 0.0  |
| Glomerulonephropathies (n=4)              | 2    | 2.0  | 1   | 11.1 | 0   | 0.0  |
| Respiratory Failure (n=4)                 | 4    | 4.1  | 0   | 0.0  | 0   | 0.0  |
| Contrast induced (n=2)                    | 2    | 2.0  | 0   | 0.0  | 0   | 0.0  |
| Pigment nephropathy (n=1)                 | 1    | 1.0  | 0   | 0.0  | 0   | 0.0  |

**TABLE III: CAUSES AND MANAGEMENT OF ACUTE KIDNEY INJURY**
TABLE IV: FACTOR PREDICTING OUTCOME (CHANGES IN SERUM CREATINE)

| Parameters                          | Crude Odd Ratios (95% CI) | p-value |
|-------------------------------------|---------------------------|---------|
| Factors affecting decline in serum creatinine |                           |         |
| KIDGO stage on admission            |                           |         |
| Stage 1                             | 0.095 (0.01-0.77)         | 0.028   |
| Stage 2                             | 0.935 (0.33-2.65)         | 0.903   |
| Length of hospital stay             | 1.152 (1.01-1.32)         | 0.039   |
| Respiratory failure                 |                           |         |
| Yes                                 | 1                         |         |
| No                                  | 0.81 (0.01-0.83)          | 0.340   |
| Factors affecting good outcome [Recovery] |                           |         |
| Chronic Kidney Disease              |                           |         |
| Yes                                 | 0.100 (0.02-0.46)         | 0.003   |
| No                                  | 1                         |         |
| Kidney Disease on admission         |                           |         |
| Stage 1                             | 0.175 (0.54-0.57)         | 0.004   |
| Stage 2                             | 0.092 (0.03-0.29)         | <0.001  |
| Oliguria                            | 2.681 (1.12-6.44)         | 0.027   |
| Baseline serum Creatinine           | 0.668 (0.54-0.83)         | <0.001  |

CONCLUSION

The majority of our study patients were in KIDGO stage III and sepsis and hypovolemia constituted the major risk factor. AKI demonstrated a significant association with in-hospital mortality of 6.9%. Male gender and presence of hypovolemia were the significant factors between survivors and non-survivors. Stage II and III AKI on admission, absence of oliguria, and lower serum creatinine levels on admission were associated with complete recovery.

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AUTHOR’S CONTRIBUTION

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

**NS:** Analysis and interpretation of data, drafting the manuscript, critical review, approval of final version to be published

**SA & ANA:** Conception and study design, critical review, approval of final version to be published

**RS & KH:** Acquisition of data, drafting the manuscript, approval of final version to be published

**AH:** Analysis and interpretation of data, critical review, approval of 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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