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RESEARCH ARTICLE

ACUTE KIDNEY INJURY OUTCOME IN CRITICALLY ILL PATIENTS

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ABSTRACT

Background : The incidence of ICU related AKI has increased over the last few decades This is probably related to the rising incidence of sepsis related hospital admissions, increased prevalence of risk factors for AKI, including chronic kidney disease (CKD), diabetes mellitus, and congestive heart failure, and expanded use of intravenous radio-contrast agents. ICU patients with AKI have higher morbidity, mortality, and health care costs compared to ICU patients without AKI.

Objective: To study indicators of acute kidney injury that might affect the outcome of critically ill patients.

Design: Prospective study.

Setting: ICU units of Menoufiya University Hospitals- *Egypt*.

Patients: All patients with acute kidney injury (AKI) were prospectively enrolled in the study from their admission in ICU till discharge. AKI was defined by RIFLE and AKIN classification systems. All patients are critically ill assessed by APACHE III score, excluding those patients with CKD stage IV and ESRD patients.

Measurements : Age, sex, cause of admission to ICU ,preexisting organ dysfunction ,DM ,HTN , type and mechanism of acute kidney injury were recorded. The Acute Physiology and Chronic Health Evaluation (APACHE III) score, was recorded at admission. The most severe RIFLE class and AKIN stage that the patient reached were recorded. Investigations including Complete blood count, Liver functions {Serum albumin, Prothrombin time, Total and direct bilirubin} Liver enzymes (AST – ALT) Renal functions (Blood urea and Serum creatinine), Serum electrolytes (Serum sodium, Serum potassium, Serum calcium, Serum phosphorus), Lipid profile (Serum Cholesterol and Triglycerides) were done to the patients and recorded. Resting electrocardiogram was done and its results were recorded. There were 51 patients in the study; all patients were enrolled in the study at the time of ICU admission.

Results: 55.9% of patients were in good health 3 months before ICU entry. The reason for admission was medical in 86, 3 % of cases. The type of acute kidney injury was prerenal (45.1%), renal (52.9%), or postrenal (2%). Renal replacement therapy was used in 23.5 % of patients. Twenty six (51.0%) patients died during the hospital stay. Six variables were predictive of death. These variables were male gender, severity of RIFLE class, AKIN stage, hypocalcaemia, hypertriglyceridemia and severity of illness as assessed at the time of ICU admission by APACHE III score.

Conclusions: In our study the indicators of AKI that are associated with worse outcome of critically ill patients with AKI in ICU included: male gender, Cardiac cause at admission to ICU, abnormal ECG changes, severe class/stage of AKI according to RIFLE and AKIN classifications and high APACHE III score at ICU admission. On the other hand, a cutoff value of APACHE III score < 73 is a good predictor of recovery of critically ill patients with AKI at time of admission.

INTRODUCTION

Acute kidney injury (AKI), is defined as abrupt, persisting and theoretically reversible worsening or loss of renal function associated with a decline in diuresis and increase in serum creatinine and urea) (Haase *et al.*, 2011). Following long advocacy and persistent work, the RIFLE system, was ultimately developed, involving a broad consensus of experts (Mehta *et al.*, 2007). The AKI Network, a somewhat larger, multidisciplinary, international group, subsequently proposed some small modifications to the RIFLE criteria. Studies validating RIFLE/AKI Network criteria have now included more than 500,000 patients (Kai Singbartl' and John A Kellum 2012). Several studies have demonstrated that the RIFLE criteria have clinical relevance for the diagnosis of AKI, classifying the severity of AKI and for monitoring the progression of AKI, as well as having predictive ability for mortality in hospitalized patients in general, and patients in the intensive care unit (ICU) setting in particular. (Lopes *et al.*, 2008) There is now substantial evidence from clinical studies that both short-term and long-term outcomes are adversely affected by AKI. Hospital mortality increases in association with AKI stage. Furthermore, survival appears to be affected for at least 1 year and may be longer (Murugan *et al.*, 2010). The incidence of ICU related AKI has increased over the last few decades This is probably related to the rising incidence of sepsis related hospital admissions, increased prevalence of risk factors for AKI, including chronic kidney disease (CKD), diabetes mellitus, and congestive heart failure, and expanded use of intravenous radio-contrast

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agents. ICU patients with AKI have higher morbidity, mortality, and health care costs compared to ICU patients without AKI (Waikar *et al.,* 2008). Categorization of a patient's illness into grades of severity occurs frequently in the ICU. Numerous severity-of-illness scoring systems have been developed and validated over the past two decades. Although these scoring systems have been validated as tools to accurately assess populations of critically ill patients, their utility in predicting individual patient outcomes is not clear). The scoring systems most commonly used in critically ill adults are APACHE II, APACHE III, MPM II, SAPS II, and SOFA score systems (Holme *et al.,* 2011). The aim of the study was to evaluate the predictors of AKI that may affect the outcome of critically ill patients, as assessed by: a) Hospital outcome; b) RIFLE and AKIN classification systems for diagnosing AKI. c) Analysis of prognostic factors using the following variables: APACHE III score computed at admission, age, sex, preexisting chronic disease, mechanism and type of AKI, initial or delayed inclusion in the study, need for renal replacement therapy, Investigations results.

MATERIALS AND METHODS

All patients with acute kidney injury admitted to Intensive Care units (ICU) in Menoufia University Hospitals were prospectively enrolled during 15 months period from April 2010 to December 2011. All patients are critically ill classified by APCHAE III score. Critical illness comprises a wide spectrum of life- threatening medical or surgical conditions usually requiring ICU-level care. Most critically ill patients exhibit at least severe single organ failure and require active therapeutic support (Winkler Marion 2012). All patients have acute kidney injury diagnosed by Acute Kidney Injury Net Work Classification and RIFLE classification. When no true baseline serum creatinine was available: hospital admission creatinine, ICU admission creatinine, or MDRD estimated creatinine was used. Modification of Diet in Renal Disease (MDRD) equation for assessment of kidney function, assuming a GFR of 75 ml/min per 1.73m2 was used to determine basal serum creatinine in absence of a known history of chronic renal disease when ICU or hospital serum creatinine level was elevated (Bellomo *et al.,* 2008). Patients with CKD stage IV and ESRD patients were excluded.

Patients were classified as follow: according to the cause of ICU admission, into Surgical, Medical and Oncology. Medical was subdivided into Cardiac illness, Respiratory illness, Hepatic illness, Neurological illness, renal illness and Multisystem illness. According to the type of AKI into three groups: Prerenal, Renal and Postrenal. According to mechanism of AKI (cause) into: Toxic (contrast, aminoglycosides and other drugs). Hemodynamic, Septic/ SIRS. (The criteria used for the diagnosis of sepsis and/or septic shock were those criteria proposed by The American College of Chest Physicians and the Society of Critical care Medicine) (Members of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee: American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: 1992) and other causes (EX: autoimmune diseases: SlE, TTP, severe UTI). According to the time of onset of AKI in relation to ICU admission ``initial" if the patient meets the inclusion criteria at the time of ICU admission, and as ``delayed" if the criteria are fulfilled during the ICU stay. Investigations include Complete blood count, Liver functions (Serum albumin, Prothrombin time, Total and direct bilirubin, Liver enzymes {AST – ALT}), Renal functions (Blood urea and Serum creatinine), Serum electrolytes (Serum sodium, Serum potassium, Serum calcium, Serum phosphorus), Lipid profile (Serum Cholesterol and Triglycerides), abdominal ultrasound and Resting electrocardiogram (12-lead). During hospital stay in ICU patients were monitored for the need for renal replacement therapy (RRT). The Outcome of patients was assessed on discharge to be recovery, renal impairment or death.

Statistical Analysis

Two types of statistical analysis were done: Descriptive statistics: was expressed in: Number (No), percentage (%), mean ($\bar{X}$) and standard deviation (SD). And Analytic statistics: Qualitative data was analyzed by chi square and whenever one cell of the expected was equal or less than 5; Fisher's exact test was done. Normally distributed quantitative data was analyzed by t-test (for comparison between 2 groups) .ANOVA (for comparison between more than 2 groups) with LSD as post- HOC test whenever ANOVA test is significant. Not normally distributed data was analyzed by Mann- Whitney test (for comparison between 2 groups). Kruskal-Wallis test (for comparison of more than two groups). P- Value of < 0.05 was considered statistically significant. ROC curve was used to detect the cutoff point (point with best value of sensitivity and specificity) for APACHAE III score between the recovery group on one side and the renal impairment and death groups on the other side (Fawcett, Tom 2006).

RESULTS

Patient Population

Fifty one patients are our study group. Mean age was 48.5 plus minus 17.5 yrs. The male was 29. Female was: 22. Forty five (45.1%) of patients had Previous organ dysfunction/ failure. Twenty three (23.5%) of patients had DM. The reason for admission was medical and oncologic in44 (86,3%) of patients and surgical in the remaining 7(13,4%) patients. The type of acute kidney injury was prerenal in 23 (45.1%), renal in 27 (52.9%), and postrenal in 1patient (2.0%). The mechanism of acute kidney injury was septic in 12 (23.5%) patients, hemodynamic (excluding sepsis) in 26 (51%), toxic in3 (5.9%), and of other origins in 10 patients (19.6%). Forty five (88.2%) of patients had initial AKI. Delayed AKI occurred in 6 (11.8%) of patients .Renal replacement therapy was needed in 12 patients (23.5%). 38(74.5%) patients had normal renal ultrasound .The remaining had grade I – II medical nephropathy. 32(62.7%) patients had normal ECG. The remaining had abnormal ECG changes. According to the RIFLE classification: Forty one (80.4%) patients had maximally reached F class, Eight (15.7%) patients had maximally reached I class and two (3.9%) patients had maximally reached R class. According to the AKIN classification:Forty one (80.4%) patients had maximally

reached stage III, Eight (15.7%) patients had maximally reached stage II and two (3.9%) patients had maximally reached stage I. Severity was assessed at the time of admission by: APACHE III score (with mean 79.4 plus minus 20.4). According to the laboratory characteristics of studied patients: mean serum creatinine was 6.1 plus minus 4.0. Mean blood urea was 159.7 plus minus159.7. Mean blood calcium was 7.8 plus minus 1.0 mean serum triglycerides 110.5 plus minus 79.4. Twenty six (51.0%) of patients died during ICU stay, Twenty one (41.5%) of patients discharged fully recovered. Four (7.8%) of patients discharged after recovery with renal impairment.

Onset of Acute kidney injury

According to the relation of onset of AKI whether initial or delayed with the mean age and gender, the type of co-morbidity (Previous organ failure – HTN – DM), the US findings, the ECG findings, the lab characteristics and different grades of the APACHE III scoring system of the studied group, our study showed that there is no Significant difference between these variables and type of onset of AKI.

Outcome of critically ill patients with AKI

According to the relation of outcome of studied patients whether recovery, renal impairment or death with clinical and laboratory variables, our study showed that: there is no significant difference between the 3 groups of outcome regarding the mean age. While the female gender was significantly higher among the recovery group: female: (n: 13 (61.9%), male (n: 8) (38.1%) and male gender was significantly higher among the death group: male (n: 10 ((73.1%). Female (n: 7(26.9%), Figure 1.

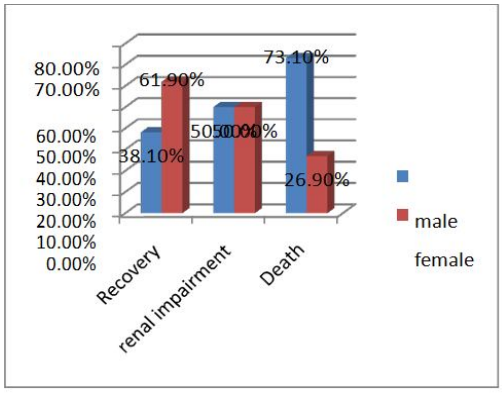

Figure 1. Distribution of gender regarding the outcome among the studied group

There is no significant difference between the 3 groups of outcome of AKI regarding the type of co-morbidity :(Previous organ dysfunction, DM, HTN). No significant difference between the 3 groups of outcome of patients regarding the onset of AKI. No significant difference as regard causes of ICU admission between the 3 groups of outcome of studied patients except there is significant increase in cardiac patients in renal impairment group. No significant difference between the 3 groups of outcome of studied patients regarding the cause (mechanism) of AKI. The type of AKI or presence of nephropathy in ultrasound abnormal ECG findings is significantly higher among renal impairment group.

According to the relation of RIFLE classification system to outcome: class I of RIFFLE classification is significantly higher among the recovery group while class F is significantly lower among the same group than renal impairment and death groups, Figure 2

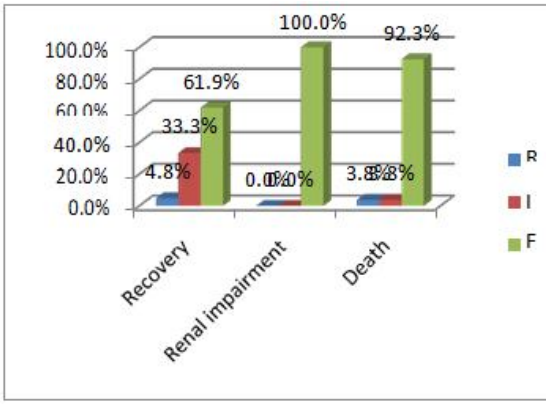

Figure 2. Distribution of the classes of RIFFLE classification regarding the outcome among the studied group

Table 1. Comparison between the 3 groups of outcome of studied patients and classifications of AKI

Type of Classification	Outcome on discharge						Test of sig.	P value
	Recovery (n= 21)		Renal impairment (n=4)		Death (n=26)			
	No	(%)	No	(%)	No	(%)		
RIFLE classification R: I: F:	17 13	(4.8) (33.3) (61.9)	0 0 4	(0.0) (0.0) (100.0)	1 1 24	(3.8) (3.8) (92.3)	0.23 7.31 6.79	>0.05 <0.05 <0.05
AKIN classification: I: II	17 13	(4.8) (33.3) (66.7)	0 0 4	(0.0) (0.0) (100.0	1 1 24	(3.8) (3.8) (92.3)	0.82 7.31 6.79	>0.05 <0.05 <0.05

According to the relation of AKIN classification system to outcome: stage II of AKIN classification is significantly higher among the recovery group while stage III is significantly

lower among the same group than renal impairment and death groups, Figure 3

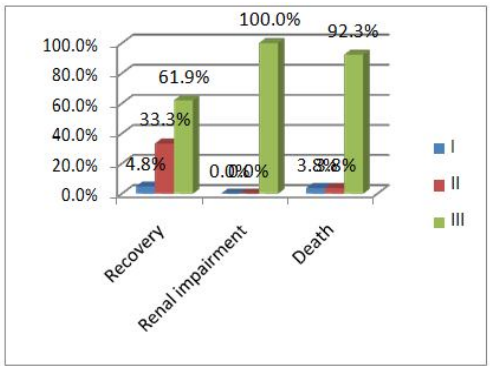

Figure 3. Distribution of the stages of AKIN classification regarding the outcome among the studied group

According to Comparison between the 3 groups of outcome of studied patients regarding the laboratory characteristics of the patients, our study showed that: Serum calcium is significantly lower in death group than recovery group. Figure 4

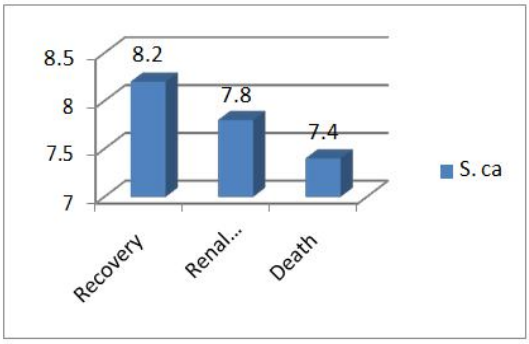

Figure 4. Mean values of serum calcium regarding the outcome among the studied group

Serum triglycerides are significantly higher in death group than recovery group. Figure 5

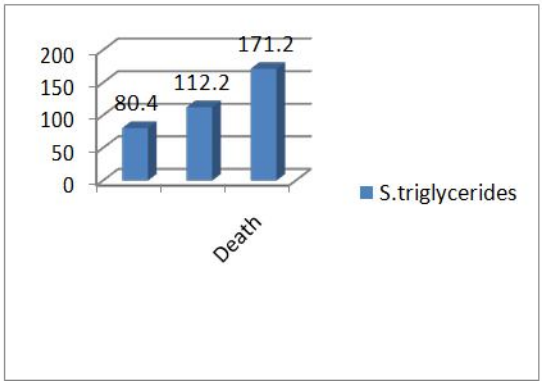

Figure 5. Mean values of serum triglycerides regarding the outcome among the studied group

No significant difference between serum creatinine, blood urea and other laboratory investigations with outcome. According to the comparison of severity of APACHE III score with the outcome: there is highly significant difference between the 3 groups of outcome regarding APACHE III score. Figure 6

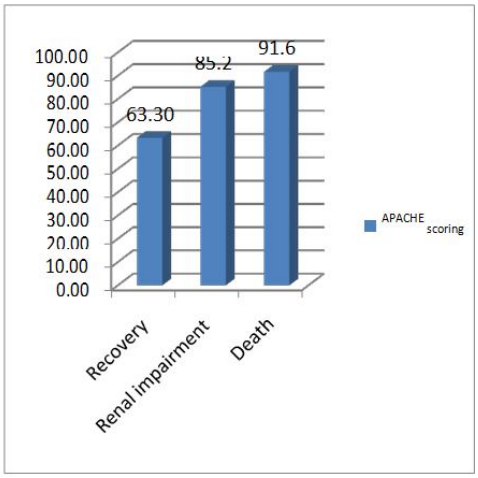

Figure 6. Mean values of APACHE scoring regarding the outcome among the studied group

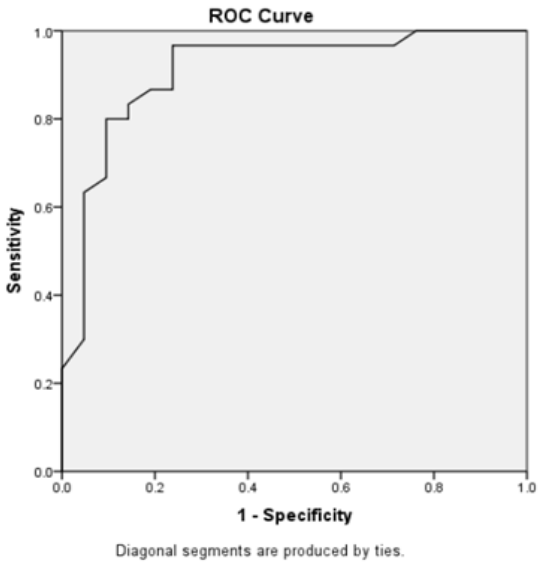

Figure 7. Cutoff point between recovery group from one side and renal impairment and death groups from the other side

Cutoff point between recovery group from one side and renal impairment and death groups from the other side.

DISCUSSION

It is now well known that AKI affects a large number of patients (although the exact incidence is variable). AKI is associated with an increased risk of death. Patients who need renal replacement therapy (RRT) have a higher risk of death. (Uchino *et al.*, 2005) The aim of the study was to

evaluate the indicators of AKI that may affect the outcome of critically ill patients. No significant difference between serum creatinine, blood urea and other laboratory investigations with outcome. According to the comparison of severity of APACHE III score with the outcome: there is highly significant difference between the 3 groups of outcome regarding APACHE III score. Figure 6 According to the relation of outcome of studied patients whether recovery, renal impairment or death with the mean age and gender of the studied group, our study showed that there is no significant relation between the 3 groups of outcome of patients regarding the mean age, while the female gender was significantly higher among the recovery group and male gender was significantly higher among the death group. This means that male gender is a risk factor for death in critically ill patients with AKI. Comparing this observation to previous studies we founded that : Liano and coworkers (Liano *et al.,* 1993), using a multiple linear regression model derived from a series of 228 patients and validated in a control sample of 100 patients, showed that age and sex had a significant influence on mortality. Male gender and increasing age is associated with increased mortality. This study confirm our observation regarding gender but against our observation regarding age. Other studies supported the observation of Liano and coworkers regarding age. (Rasmussen *et al.,* 1985; Schaefer *et al.,* 1991; Cioffi *et al.,* 1984; Gentric and Cledes 1991; Brivet *et al.,* 1983; Turney *et al.,* 1991; Groeneveld *et al.,* 1991; Degaichia *et al.,* 1981; Brivet *et al.,* 1996).

The difference between our study and previous studies regarding age may be due to the less number of studied groups in our study in comparison with number of studied patients in these previous studies. According to the relation of outcome of studied patients with onset of AKI our study showed that there is no significant relation between the 3 groups of outcome of patients regarding the onset of AKI. This observation was supported by Morris JA and coworkers 1991(Morris *et al.,* 1991), In their retrospective study showed no difference in outcome between the early and late renal failure subgroups. Another study did not agree with us; Brivet and coworkers 1996 (Brivet *et al.,* 1983), in their prospective, multicenter study of 360 patients showed that delayed occurrence of acute renal failure during ICU stay represents a bad prognostic factor in critically ill patients with ARF. This result may be due to a worsening in clinical condition despite supportive therapy, as suggested by the higher values of severity scores at the time of inclusion than at admission in late acute renal failure patients. According to the relation of outcome of studied patients with the two classification systems of AKI (RIFLE and AKIN) the maximum RIFLE class (class R, class I or class F) and the maximum AKIN stage (I , II , III) reached during ICU stay, our study showed that class I of RIFFLE classification is significantly higher among the recovery group while class F is significantly lower among the same group than renal impairment and death groups. It shows also that stage II of AKIN classification is significantly higher among the recovery group while stage III is significantly lower among the same group than renal impairment and death groups. This means that class F in RIFLE classification and stage III in AKIN classification of AKI are both predictor of death in critically ill. This result is supported by many other study results: One of the earliest studies evaluating the epidemiology of AKI was by Abosaif and coworkers 2005(Abosaif *et al.,* 2005), who studied 247 patients admitted to ICU with a serum creatinine 1 150 mol/l. The investigators found that the ICU mortality was greatest among patients classified as RIFLE F. Hoste and coworkers, 2006 (Hoste *et al.,* 2006), studied 5,383 critically ill patients. RIFLE I and RIFLE F were independent predictors of hospital mortality after controlling for other variables known to predict outcome in critically ill patients. Cruz DN and coworkers 2007 (Cruz *et al.,* 2007), in their prospective multicenter observational study Of 2164 ICU patients with AKI showed that RIFLE classification was independent risk factors for mortality and mortality was highest among those in RIFLE class F. José António Lopes and coworkers 2008 (José António *et al.,* 2008), in their retrospective study of 662 patients showed that AKIN classification and RIFLE classification can predict mortality in critically ill patients. Daher EF and coworkers 2008 (Daher *et al.,* 2008), in their a retrospective study of 722 patients who were admitted to the infectious disease ICU showed that, according to RIFLE, Patients in "Failure" showed a higher mortality than risk and injury. Tina Palmieria and Athena Lavrentievab (Tina Palmieria and Athina Lavrentievab. 2010), in Retrospective, descriptive cohort study showed that the association of Failure class (in RIFLE classification) of acute kidney injury with high mortality. Barrantes F and coworkers (Barrantes *et al.,* 2008), in their, Retrospective cohort study of 471 patients with no recent history of renal replacement therapy who were admitted to the medical intensive care unit during 1 yr showed that The Acute Kidney Injury Network definition (classification) of acute kidney injury predicts hospital mortality in critically ill patients. Mandelbaum Tal and coworkers (Mandelbaum Tal *et al.,* 2011), in their Retrospective cohort study of 19,677 adult patient records showed that critically ill patients who developed some stage, staged by (AKIN) classification, of acute kidney injury resulting in a stage wise increased mortality risk. However, the mortality risk associated with acute kidney injury stages 1 and 2 does not differ significantly. Karim Lakhal and coworkers (Karim Lakhal *et al.,* 2011), In their retrospective study of 299 patients showed that Contrast media–associated AKI, defined by the AKIN stage 1 classification, was independently associated with ICU mortality. Chen YC and coworkers (Chen *et al.,* 2009), in their prospective study of 121 sepsis patients were admitted to ICU showed that RIFLE classification is accurately predicting in-hospital mortality in ICU sepsis patients. Yuan F and coworkers (Yuan *et al.,* 2009), in their retrospective study of 3,945 post traumatic critically ill patients showed that RIFLE provides a well-balanced classification system for determining AKI and predicting its outcome in this population.

According to the relation of outcome of studied patients with the laboratory characteristics of the studied patients, our study showed that No relation between serum creatinine and blood urea and outcome of studied patients. Previous study founded a relation between serum creatinine and blood urea outcome: Ostermann M and Chang RW (Ostermann and Chang

2009), in their Retrospective study showed that serum creatinine and urea levels only had a weak correlation with outcome after RRT. Serum calcium is significantly lower in death group than recovery group. Serum triglycerides are significantly higher in death group than recovery group. which means that hypocalcemia and hypertriglyceridemia predicts mortality in critically ill patients with AKI .This results was supported by the following studies: Andreas Link and coworkers 2012 (Andreas Link *et al.*, 2012), in their prospective observational study on 208 critically ill patients with acute kidney injury (AKI) showed that The total to ionized (T/I) Ca2+ ratio was determined as an independent predictor for 28-day mortality in critically ill patients with AKI on CRRT- citrate dialysis machine .Numerous studies over the past several decades have shown that ionized hypocalcemia is common in illness. In some of these studies, severity of hypocalcemia has correlated directly with severity of illness. (Chernow *et al.*, 1982; Desai *et al.*, 1988; Burchard *et al.*, 1990; Zaloga 1992; Muller *et al.*, 2000; Zivin *et al.*, 2001; Hästbacka and Pettilä 2003; Schetz *et al.*, 2008). Schetz M and coworkers 2008(43), in post hoc analysis of the Leuven studies suggests that an improved lipid profile might contribute to the renoprotective effect. This is supported by an animal model of renal ischaemia-reperfusion, administering HDL before ischaemia. Reduced endothelial activation and protection against oxidative stress might play a role (Hästbacka and Pettilä 2003).

According to the relation between outcome of the studied patients and APACHE III score , our study showed that highly significant relation between the 3 groups of outcome regarding APACHE III score .There is positive correlation between the increase in APACHE III score and outcome of patients so APACHE III score is good predictor of ICU outcome . This result is in line with studies done before: Li G and coworkers 2009 (Li *et al.*, 2009), in their retrospective cohort study of 111 critically ill patients with confirmed influenza virus infection. Showed that: APACHE III predicted mortality in critically ill patients with confirmed influenza virus infection. Wang IK and coworkers 2005(Wang *et al.*, 2005), in their prospective study showed that the mortality rates increase as the APACHE II score increases. Daher EF and coworkers 2008 (José António Lopes 2008), in their a retrospective study of 722 patients who were admitted to the infectious disease ICU showed that APACHE II score was a dependent risk factor for mortality in ICU. Rordorf G and coworkers 2000 (Rordorf *et al.*, 2000), in their Retrospective study of 63 consecutive ischemic stroke patients in Neurology/neurosurgery intensive care unit showed that APACHE II score can predict mortality in these patients. Our study showed that Cutoff point between recovery group from one side and renal impairment and death groups from the other side is: 73

Conclusion

In our study AKI indicators which are associated with worse outcome of critically ill patients in ICU included: male gender, cardiac cause at admission to ICU, abnormal ECG changes, severe class/stage of AKI according to RIFLE and AKIN classifications and high APACHE III score at ICU admission. Cutoff value of APACHE III score < 73 at time of admission is a good predictor of recovery of critically ill patients with AKI.

Recommendations

- Further studies on larger number of patients to be done.
- Critically ill patients with severe AKI degree (RIFLE class F and AKIN stage III) and APACHE III score (<73) need special care and perfect supportive management to improve their outcome.
- Other possible modifiable predictors such as cardiac problems and hypocalcaemia should be carefully assessed and managed.
- What we found in our study is just a tiny amount of the vast majority and the need for evolving new biomarkers that can predict the outcome of AKI in critically ill patients in ICU is crucial.

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