DISCUSSION

Acute kidney injury (AKI) is one of the most feared complications in septic critically ill patients because it further worsens prognosis and increases cost of care. In addition, sepsis and septic shock are the dominant causes of AKI, accounting for nearly 50 % of episodes of AKI. [89, 90]

The incidence of acute kidney injury proportionally rises with the severity of sepsis, occurring in 19 % of patients with sepsis, 23 % patients with severe sepsis and 51 % patients with septic shock. [90, 91]

Over the last few years, several new markers have been developed to identify kidney injury, such as NGAL, KIM-1, IL-18 and L-FABP, among others. [55] An early biomarker might have prognostic implications, given the immense impact of AKI associated mortality on global disease-related mortality. [122]

Two recent studies have reported an unadjusted AUC values for prediction of AKI outcomes, between 0.58 and 0.71, suggesting that the diagnostic AKI biomarkers are of less predictive value among patients who already established AKI. [123,124] Therefore prognostic biomarkers are required to predict outcomes in patients with established AKI.

One of those early biomarkers with possible diagnostic and prognostic power was Urinary angiotensinogen, which has been previously identified as a prognostic biomarker of AKI after cardiac surgery. However, at the time of its discovery it was unclear if its prognostic significance was generalizable to AKI secondary to causes other than cardiac surgery. [119]

We conducted a prospective observational study during the period from March 2014 to December 2014 on 100 adult patients of both sexes who suffered from severe sepsis. Patients were categorized into two groups according to AKI development; Non AKI group which consisted of 30 patients (Group I), and AKI group which consisted of 70 patients (Group II). The patients included in the study are those who were admitted to the units of Critical Care Medicine Department in Alexandria Main University Hospital and who fulfilled the diagnostic criteria for severe sepsis arrival to ICU according to the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. [87,125] the aim of the present study was to evaluate the possible rule of urinary angiotensinogen in predicting AKI in critically ill patients with severe sepsis.

Demographic data

In the present study, Group I and Group II were homogeneous in terms of size and demographic characteristics with no statistically significant difference between them regarding gender and age (p=0.160, and p=0.462, respectively). Most of the patients enrolled in the present study were over 60 years old; the mean age was 60.50 for Group I and 61.69 for Group II.

Similar to the present study, the mean age of patients with severe sepsis in most epidemiological studies ranged between 55 and 64 years.[83,126,127,128,129] Martin et al[126] which studied the effect of age on the development of adult sepsis on 10,422,301 adult

sepsis patients hospitalized over 24 years, from 1978 to 2002, found that there was a direct relationship between advanced age and the incidence of severe sepsis, with a sharp increase in incidence in elderly people.[126]

In this study Males accounted for 18 patients (60%) in Group I and 50 patients (71.43%) in Group II while females accounted for 12 patients (40%) in Group I and 20 patients (28.57%) in Group II. Martin et al. [127] also studied the epidemiology of sepsis in the United States from 1979 through 2000 found that men were more likely than women to develop sepsis. However, it was not clear whether this difference was due to higher prevalence of comorbidities in men, or whether women are protected against the inflammatory changes that occur in severe sepsis.

Although we did not find a statistically significant difference between Group I and Group II regarding preexisting conditions. It is well known that patients with severe sepsis frequently have underlying comorbidities that predispose them to infections and may have an additive contribution to mortality.[130] In the present study diabetes mellitus and hypertension were the most common preexisting conditions found in both groups accounting for 19 patients (63.33%) and 16 patients (53.33%) in Group I, respectively, while they accounted for 22 patients (31.43%) and 20 patients (28.57%) in Group II, respectively.

In agreement with our findings, Karlsson et al. [131] found during their prospective observational study that investigated the incidence, treatment, and outcome of severe sepsis in ICU-treated adults in Finland that the most frequent preexisting conditions in patients with severe sepsis were diabetes mellitus (34.9%) and hypertension (21.5%), This was also found by other authors who found diabetic patients have an increased risk of developing infections and sepsis, [132,133] and constitute 20.1% - 22.7% of all sepsis patients.[134,135]

In the current study, the lungs and bacteremia were the most common sites of infection in both groups accounting for 14 patients (46.67%) and10 patients (33.33%) in Group I respectively, while they accounted for 33 patients (47.14%) and 23 patients (32.86%) in Group II respectively.

Similar to the present study, Mayr et al. [136] in international surveillance of epidemiology of severe sepsis, they found that lungs and bacteremia were the commonest sites of infection in patients with severe sepsis with percentages in orders (76%) and (41%) respectively.

Prediction of AKI

In our study, the patients were observed along hospital stay for consecutive 7 days with daily analysis of kidney function. Then they were compared according to urinary Ang. / Cr. Ratio and creatinine level on admission. We found a significant difference between the two studied groups regarding urinary Ang. / Cr. Ratio, whereas this difference was not statistically significant regarding creatinine level on admission; all patient had a normal creatinine level on admission while urinary Ang. /Cr. Ratio was elevated on admission in patients who developed AKI later in the study versus those who did not, this raise up the urinary angiotensinogen as an earlier predictor of AKI.

The cutoff value of urinary Ang. /Cr. Ratio on admission to predict later occurrence of AKI during ICU stay was 52.24ng/mg: at this level, sensitivity and specificity were 88.57 percent and 53.30 percent, respectively

To clarify this potential concept a step further, we investigated the correlation between urinary Ang. /Cr. Ratio with daily AKIN staging and S.Cr. level, There was a statistically significant correlation for each day between AKIN staging & urinary Ang./ Cr. Ratio with the highest correlation on day 5 after admission. The same regarding significant correlation was present between daily S.Cr. & urinary Ang. /Cr. Ratio and the highest correlation fifth day. The spermann coefficient respectively Rs=0.669, Rs=0.607

Alge et al. 2011 [119] studied urinary Ang. /Cr. Ratio on patients after cardiac surgery as a predictor of severe AKI development, the cutoff value was 33.27ng/mg with sensitivity and specificity 75 percent and 66.1 percent respectively, As he classified the studied patient according to AKI development. All patients had AKIN stage1 at the time of sample collection with follow up progression of AKIN staging during hospital stay.

Outcomes of AKI patients

In the present study, the studied groups are followed up for 7 days during ICU stay with different outcomes developed ranged between (vasopressor requirement, prolonged ICU stay > 7days, renal replacement therapy need, death and discharge after recovery).

These outcomes were firstly categorized regarding this cutoff value on admission (group≤52.24) (N=22) and (group > 52.24) (N=78), then these outcomes were correlated with our cutoff value; we did not find any positive correlation between this cutoff value and any of these outcomes (p=0.431) which means that urinary Ang./Cr. Ratio with cutoff value(52.24ng/mg) did not predict any of these outcomes.

To find another cutoff values to predict AKI outcomes, we categorized patients` outcomes again according to development of AKI; Non AKI group which consisted of 30patients (group I), and AKI group which consisted of 70 patients & correlated the AKI group`s outcomes with urinary Ang./Cr. Ratio.

AKI group outcomes were (vasopressor requirement, prolonged ICU stay > 7 days, RRT and death), as there was no patient discharged from this group.

Then the prediction power of urinary Angiotensinogen for AKI outcomes was estimated and found to have a statistically significant value (p< 0.001).

On further sub analysis for the four mentioned outcomes, there was a significant correlation with prediction of outcomes each of RRT requirement and mortality (p=0.040), (p=0.020), while there was not any correlation in prediction of each of vasopressor requirement or prolonged ICU stay > 7 days (p=0.291).

In the two studies by Alge et al.2013, [137] which studied Urinary angiotensinogen / creatinine ratio as a predictor of adverse outcomes among acute kidney injury patients in the intensive care unit and Alge et al. 2011[119], and in the contrary to our findings, there were a positive correlation with length of ICU stay prediction, we anticipate that,

the difference between his & ours study results is due to the difference in number of follow up days in the ICU by 7 days in ours and 22 days in his 2013 study and 60 days in 2011 study.

On any account, although we did not find the positive correlation with length of ICU stay, we did find as previously mentioned the positive correlation with other AKI outcomes regarding (RRT requirement and mortality prediction) the same way as Alge et al. found.

Renal replacement therapy requirement

In the present study there was a positive correlation between urinary Ang. /Cr. Ratio and prediction of RRT requirement (AUC=0.744) (p=0.040) with cutoff value 75.24ng/mg with sensitivity and specificity 81.25 percent and 60 percent respectively.

In agreement with this study, Alge et al. 2013[137] founded a significant correlation between studied Urinary angiotensinogen / creatinine ratio and RRT requirement in AKI patients. (p<0.001)

Also in his second study, Alge et al. 2011 [119] demonstrated that urinary angiotensinogen discriminated with 100% accuracy between patients who required RRT after development of AKI and those who did not, so a positive correlation between urinary Ang. /Cr. ratio and RRT requirement in patients who developed AKI after cardiac surgery developed with cutoff value 34.33ng/mg with sensitivity and specificity 75 percent and 73.4 percent respectively.

Mortality prediction in AKI patients

In our study, we found also a strong predictive power of urinary Ang. /Cr. Ratio in predicting mortality among AKI patients (AUC=0.694) (p=0.020) with cutoff value 84.8ng/mg with sensitivity and specificity 68.75 percent and 40 percent respectively.

In agreement with this study, Alge et al. 2013[137] founded a significant correlation between studied Urinary angiotensinogen / creatinine ratio and mortality prediction in AKI patients. (p<0.001)

Also In agreement with this study, Alge et al. 2011 [119] founded also a positive correlation between urinary Ang. /Cr. Ratio and prediction of mortality in patients who developed AKI after cardiac surgery with cutoff value 58.63ng/mg with sensitivity and specificity 70 percent and 78.3 percent respectively.

Although we did not directly compare the prognostic predictive power of angiotensinogen to that of other biomarkers, our results are comparable with what has been reported in the literature for previously described AKI biomarkers. For example, Hall et al. [123] reported unadjusted AUCs of 0.71, 0.64, and 0.63 for the prediction of the composite outcome of worsening of AKI or death for urine NGAL, kidney injury molecule-1, and IL-18, respectively. Koyner et al. [124] recently reported unadjusted AUCs of 0.58, 0.63, and 0.74 for urine NGAL, urine IL-18, and plasma NGAL, respectively, for the outcome of worsening of AKI. Thus, uAnCR, alone or in combination with other biomarkers could improve risk classification models in these patients.

SUMMARY

AKI is a frequent and serious complication of sepsis in ICU patients, Moreover, there is strong evidence that sepsis and septic shock are the most important causes of AKI in critically ill patients, account for 50% or more of cases of AKI in ICUs.

So, Early recognition of AKI in the ICU setting is crucial..by using early biomarkers like urinary angiotensinogen level which correlates with intrarenal angiotensinogen and AngII levels that play a major role in molecular mechanisms of AKI,

The aim of this work was to evaluate the possible role of the urinary angiotensinogen as a predictor of AKI in patients with severe sepsis.

We conducted a prospective observational study during the period from January 2014 to December 2014 on 100 adult patients of both sexes who suffered from severe sepsis. Patients were categorized into two groups according to AKI development; non AKI group which consisted of 30 patients (Group I), and AKI group which consisted of 70 patients (Group II). Patients were included in the study if they have the criteria of severe sepsis and excluded if they Have chronic kidney disease, started RRT or septically shocked.

Group I and Group II were homogeneous in terms of size, demographic characteristics, preexisting conditions, and site of infection with no statistically significant difference between them.

After taking an informed consent from every patient or from his/her next of kin, All the cases were subjected to detailed history taking, Full clinical examination and laboratory organ survey to confirm the diagnosis of sever sepsis. Urinary angiotensinogen and creatnine was withdrawn once from each patient on the day of admission to calculate Urinary angiotensinogen / creatinine ratio (uAnCR, ng/mg) and to be correlated with serum creatinine which withdrawn daily..

The results of this study demonstrated that:

There was a significant correlation between the studied groups and uAng. /Cr. Ratio on admission, while there was not any statistically significance between the studied groups and serum Cr. Level on admission.

Moreover, there was a positive correlation between uAng./Cr. Ratio on admission and AKIN staging and serum creatinine level of the all studied patient in the follow up days, with highest correlation in the fifth day of follow up.

In Group II (who developed AKI) the uAng. / Cr. Ratio did not predict vasopressor requirement or predict increased length of hospital stay > 7 days, but it positively predict RRT requirement and mortality among AKI patients.

By the end of the present study, we reached a conclusion that urinary angiotensinogen not only a new promising biomarker in early prediction of AKI in patients with severe sepsis but also it can be used to predict the outcomes among those patients.

CONCLUSION

From the results of the present study, we can conclude that:

- Angiotensinogen is a new promising biomarker for predicting AKI in patients with severe sepsis.
- Urinary angiotensinogen predicts adverse outcomes in patients with AKI and could be used in clinical trial design to enrich the study population with patients who might benefit from intervention.