DISCUSSION

1. Patients with advanced liver disease (Ascites cirrhosis), would, definitely, suffer from Renal dysfunction, was the hypothesis, and

It was proved, as indicated by the Anova F score and tukey’s post host test as shown in tables 4A, 4B, 8A and 8B, conducted for mean eGFR and mean serum creatinine of four groups.

Glomerular filtration rate is a very useful general index for the assessment of the severity of renal damage. The eGFR is a simple technique of estimation of creatinine clearance and thereby, glomerular filtration rate. This method would eliminate the need for timed urine collection (Vasudevan et al., 2011).
A highly significant (p<0.001), decline in estimated glomerular filtration rate was observed in Group 3 patients of ascites cirrhosis, as confirmed by one sample t test between mean eGFR of Group 3 and hypothetical cut off value.

The creatinine is the freely filtered non protein nitrogen and its serum level depends on the GFR. Therefor, the use of single value of serum creatinine to estimate GFR, is attractive and many problems inherent in measurement of creatinine clearance by 24 hours urine collection, can be avoided (Smith, 1990). The renal dysfunction in ascites cirrhosis patients was also proved by a significantly (p<0.001), elevated mean serum creatinine value of Group 3, when compared with hypothetical cut off value of serum creatinine.

Renal dysfunction is a common and serious problem in patients with advanced liver disease and advanced cirrhosis, can precipitate functional type of renal dysfunction, called hepato renal syndrome. First description of functional renal failure in cirrhosis was given by Hecker and Sherlock in 1956. Renal dysfunction was found in 37 patients of ascites cirrhosis in Group 3, out of total 67 patients of cirrhosis (non ascites, n=30 & ascites cirrhosis, n=37).

The data of present study showed a prevalence of 56% for renal dysfunction. Another study was conducted by (Prakash et al.,2011) on the 404 patients of cirrhosis. The renal disease was found in 44% of patients. The higher prevalence of renal disease in cirrhotics as found in the present study, may be attributed to comparatively smaller sample size (67 cirrhotics) against the 404 patients. But the study done by Prakash et al., and the present study, validated the prevalence of renal dysfunction in ascites cirrhotics.

In advanced cirrhosis, when patients are symptomatic, circulatory dysfunction take place, that are characterized by low systemic vascular resistance, reduced effective arterial blood volume leading to activation of sympathetic nervous system and ensuring renal vasoconstriction and renal failure (Sola & Gines, 2010).
2. **Glomerular Filtration Rate in renal dysfunction, would, definitely, show correlation with serum Albumin and serum Sodium, was the hypothesis.**

This was proved as shown by pearson coefficient of correlation values \((r=+0.57, p<.002)\), \((r=+0.53, p<.007)\) \((r=+0.65, p<.001)\) between \((\text{GFR, Albumin})\), \((\text{Albumin, Sodium})\) and \((\text{GFR, Sodium})\) respectively.

The positives values of Pearson’s coefficient of correlation, indicate direct correlation between Glomerular filtration rate and Serum Albumin & Serum Sodium. In decompensated cirrhosis, intense renal vasoconstriction occurs due partly to decreased effective circulatory blood volume and also due to activation of sympathetic nervous system and release of epinephrine from adrenal medulla. This leads to renal ischemia, consequently, the glomerular filtration rate is decreased.

Further, activation of Renin Angiotensinogen Aldosterone System, and non osmotic release of Anti diuretic hormone, from neurohypophysis, result in renal sodium and water retention. This consequences into hypervolumic hyponatremia (Gines & Guevara, 2008). The hypoalbuminemia, being multifactorial in cirrhosis, mainly results from increased volume of distribution for albumin in ascites cirrhosis. Therefore, the decline in GFR is followed by a decrease in serum sodium and serum albumin values.

3. **Hepatorenal syndrome, Spontaneous bacterial peritonitis and Acute tubular necrosis, would emerge as the major causes of renal dysfunction in ascites cirrhosis in Group 3, was the hypothesis,** It had been proved as 9 out of 37 (24%) patients in ascites cirrhosis group had polymorphonuclear neutrophil count more than 250/mm3. The (6/9) 66% of the SBP patients had culture positive, whereas, remaining patients had culture negative despite the presence of PMN count > 250cumm. This frequency of SBP in ascites cirrhotics in the present study, almost matches with that of (18-30% in hospitalised patients) as described by (Syed et al., 2007).

Although, SBP infection responds to antibiotic therapy, but still, it has high incidence to progress into renal failure. It is due to exaggerated inflammatory response to sepsis in
ascites patients. Bacterial endotoxins do not produce any change in the systemic haemodynamics in healthy rats as studied by (Sugano, 1992), but produces arterial hypotension and increased levels of cytokines in cirrhotics rats. The plasma levels of cytokines in sepsis in ascites in humans, were recorded to be as 20 folds higher than individuals in sepsis (Follo, 1994). Cytokines aggravates vasodilation, leading to renal failure.

Another, 16 patients out of 37 (43%) showed renal tubules epithelial casts as revealed in the analysis of urine sediment while remaining 12 patients out of 37 (33%) in ascites cirrhosis in Group 3, found suffering from HRS. The present data showed that Acute tubular necrosis emerged as the major cause of renal dysfunction with a prevalence of 43% (16/37). The patients with hepatorenal syndrome had the frequency of 33%(12/37), whereas the spontaneous bacterial peritonitis was the least prevalent (24%(9/37), cause of renal dysfunction in ascites cirrhotics. Similar findings were observed by (Madan et al., 2004) in their study.

4. Hypoalbuminemia and Hyponatremia (determined by serum concentrations), would, definitely, appear in renal dysfunction, was the hypothesis, it had been also proved, as indicated by serum Albumin Anova score, F (217.5), (p<0.0005), post hoc test score (q.05=27.8) between controls in Group 4 and ascites cirrhotic in Group 3 and further, one sample t test score (t=13), p <0.001) between ascites cirrhosis in Group 3 and serum Albumin cut off value, which showed significant hypoalbuminemia.

Further, Anova test score, F (97), (p<0.0005) and post hoc test score (q=20.64) was obtained in four groups for serum sodium and one sample t score (t=9.60, p<0.001) was obtained between ascites cirrhosis patients in Group 3 and serum sodium cut off, indicated significant hyponatremia in ascites cirrhosis patients.

There is decreased effective circulatory volume as a consequence of splanchnic vasodilation, thereby inducing renal hypoperfusion. There is activation of RAAS, causing
impaired renal excretion of sodium and free water. The total body water exceeds total body sodium, hence producing hypervolumic hyponatremia (Gines, 2008) and a decrease in plasma osmolarity. The hypervolemia, so produced, would cause dilution of cells and solid components of plasma, along with dilution of electrolytes (Steele, 1997; Kumar & Berl, 1998). This is one of the causes of hypoalbuminemia in ascites cirrhosis.

The other causes of hypoalbuminemia in cirrhosis can be attributed to poor dietary intake, reduced synthesis, increased loss and increased volume of distribution as in ascites cirrhosis (Throop et al., 2004).

5. Anemia (as determined by decline in haemoglobin value), would be observed in renal dysfunction, was the hypothesis. It was proved by one way Anova score F, post hoc test score as shown in tables 15A, 15B, between ascites cirrhosis and control groups and one sample t test score (t=11, p<.0001) with cut off point of 13 mg/dl. Progressive decline in renal function induces gradual decrease in total haemoglobin. The reason behind can be the RAAS activity induced hypervolemia, that causes haemodilution, in advanced cirrhosis (Clyne et al., 1994). Therefore, the hypervolemia and haemodilution can be the important causes of anemia in renal dysfunction.

The Anemia was also found in patients, who suffered from non ascites cirrhosis in Group 2, although, renal function was normal. But the decline in haemoglobin value was significantly more in ascites cirrhosis patients as compared to non ascites patients. This fact proposes the multifactorial cause of Anemia in cirrhosis patients. These factors can be poor dietary intake, leading to deficiency of vitamin B12, folic acid and iron. But the Anemia increases in ascites cirrhosis patients. This can be due to haemodilution, blood loss via GIT and decreased RBC production, as a result of reduced level of erythropoietin in renal dysfunction (Lewis et al., 2007).

6. Glomerular Filtration Rate
It is the important renal parameter to assess the health of kidneys. According to National kidney foundation, the reference range of GFR is 90-120 ml/min/1.73 m2.

Glomerular filtration rates of all the Groups showed significant difference as dictated by one way Anova results (tables 4a,4b), but the Groups 1 and 2 had mean GFR values within reference range and well above the GFR cut off value, whereas, only the Group 3 (ascites cirrhosis) exhibited the mean GFR value significantly below the cut off, hence showed renal dysfunction in patients with advanced liver disease (Bellomo et al., 2004).

The result obtained in the present study, pertaining to mean GFR, had also been observed by (Esrailian & Runyon, 2003) in their study on the patients of alcoholic cirrhosis with ascites. The researchers (Lau et al., 2011), also authenticate the findings obtained in present study by their work on end stage liver disease patients, awaiting orthotopic liver transplantation.

The mean value of GFR in cirrhotic ascites patients obtained in the present study, was further, supplemented by the retrospective study on 152 cirrhotic ascites by (Warner et al., 2011).

7. Estimation of Serum Creatinine in advanced liver disease patients

It is an important, easy and cheaper method to assess renal function and to predict survival of patients in end stage liver disease (Aband et al., 1993).

Mean serum creatinine obtained in Group1 and Group 2 were within reference range except the Group 3, which showed significant elevation (p<0.0001) in serum creatinine when compared with the cut off value, that showed renal dysfunction in cirrhotic ascites.

In early 2000, MELD score, emerged as the more objective and reliable alternative to Child pugh score. The MELD score utilises the bilirubin and INR as the liver markers along with Creatinine as the renal marker.
The very fact that serum creatinine is present along with two other variables in MELD score, authenticate the findings obtained in this study, pertaining to serum creatinine (Malinchoc et al., 2000; Kremor et al., 2001; Chenn et al., 2011). The value of serum creatinine has high impact on MELD score (Francoz et al., 2010).

8. Blood Urea Nitrogen alone is not a reliable indicator of renal function in cirrhosis because it is affected by factors like high protein intake, GIT bleeding and fever. These factors raise the BUN, while, malnutrition and hypovolemeia, are the factors that depress BUN.

On the contrary, BUN/Creatinine ratio is the important indicator of Azotemia in cirrhosis ascites patients (Hosten, 1990). This fact proves the findings obtained in present study related to BUN/CRT. ratio which was significant (p=0.03), in Group 3 when compared to cut off value.

9. Sodium is an important mineral of the extracellular fluid. Electrolyte balance of the body is maintained by kidneys.

In the present study, serum sodium showed significant difference in all four groups, but only the Group 3 with cirrhosis ascites patients had exhibited significant (t=9.5, p<0.001) decline in serum sodium level when compared with cut off, thus, suffered with the hyponatremia.

These results have been supported by (Lindsay, 2010), in his report on alcoholic cirrhosis patients. Advanced cirrhosis leads to a state of chronic hypervolumic hyponatremia (Ellis, 1995). The explanation is the ↓ systemic vascular resistance and activation of RAAS (Martin et al., 2006).

The hyponatremia in cirrhosis, further, worsens in patients with habitual consumption of alcohol due to intake of large amount of fluid with little sodium (Hilden & Svendgen, 1980).
This fact is further supplemented by the prevalence of 67% of the cirrhotic ascites patients in Group 3, in the present study, had the habit of alcoholic consumption.

A prevalence of hyponatremia with 17/37 (46%), 10/37 (27%), 10/37(27%) with sodium cut offs (130-134), (125-129), (<129) meq/L, were observed in ascites cirrhosis patients in Group3.

Hyponatremia in cirrhosis is a severe complication and it can be an independent predictor of mortality in patients awaiting liver transplantation (Biggins et al., 2005; Angeli et al., 2006; Sterns et al., 2009). The serum sodium level in cirrhosis can have important prognostic value and can be used along with other parameters in MELD to predict the survival of patients.

10. A positive, direct and significant correlation was observed between eGFR and Albumin in cirrhotic ascites in Group 3 as shown in (Graph3, Table 20). This result has been validated by the work of (Georgopoulo, et al., 2005), in his study on 16 patients of advanced cirrhosis, and 12 patients exhibited hypoalbuminemia.

This declining value of albumin in cirrhosis is attributed to many factors, involving malnutrition, vitamin deficiency, and impaired protein synthesis.

11. Positive, direct and significant correlation was observed between sodium and albumin in ascites cirrhotic patients in Group 3 as shown in graph 5, table 20.

Similar results were obtained by (Cunha et al., 1999), in their work on the 142 hypoalbuminemic hospitalised patients. They obtained a direct correlation between hypoalbuminemia and hyponatremia as exhibited by (r= 0.40) value of pearson’s coefficient of correlation. However, in the present study, a direct and higher magnitude, (r=+0.530, p<0.0007), of correlation was achieved between hypoalbuminemia and hyponatremia in ascites cirrhotics in Group 3.

The advanced cirrhosis impairs renal ability to excrete sodium and free water from body due to hyperdynamic circulation. The sodium and water retention leads to haemodilution.
The dilution of blood cells and solid components of plasma (Gines et al., 2005) along with electrolytes occur. Therefore, the hypoalbuminemia and hyponatremia covariates in advanced cirrhosis.

The hypoalbuminemia in advanced cirrhosis is multifactorial, mainly attributed to increased area of albumin distribution (Kumar & Berl, 1998). Hypoalbuminemia, in advanced cirrhosis, thus, results in decreased colloidal oncotic pressure in the vascular compartment, thereby, leading to the fluid leakage into the interstitial space. This happens due to change in vascular permeability (systemic leaky capillary syndrome).

There is fluid retension in interstitial spaces and hypovolumia, hence, activation of RAAS and non osmotic release of ADH take place and further, deterioration of the renal ability to excrete sodium and free water from body. This RAAS activity due to hypoalbuminemia would augment the similar activity due to hyperdynamic circulation in cirrhosis. This state manifests as hyponatremia covariating with hypoalbuminemia in ascites cirrhosis (Kumar & Berl, 1998; Steele, 1997).

12. **The significant hyperkalemia** was found in ascites cirrhotics in Group 3. Hyperkalemia is a frequent complication in ascites cirrhotic in renal failure. The main etiology is impaired excretion of ingested and or infused potassium and the potassium that is released by the injury of tissues (Brady & Brenner, 2005). The finding of present study was confirmed by the study of (Milionis & Elisaf, 1999) on ascites cirrhosis patient of 53 year, found to be hyperkalemic. They attributed the hyperkalemia due to increased potassium intake through oral and parenteral routes, movement of potassium from cellular to ECF and decreased potassium urinary excretion due to impaired renal function.

13. **Significant, hypolbuminemia and hyperkalemia** were observed in the ascites cirrhosis patients in Group 3, and these two conditions, significantly, covaried in an inverse relationship, as shown in table 20B, graph 7.
The possible explanation is the hyperdynamic circulation in decompensated cirrhosis. This leads to impairment of ability of kidneys to excrete sodium and water, causing plasma volume expansion. Further, due to reduced GFR, the excretion of potassium from body is decreased, along with enhancement in the release of potassium from injured cells to ECF.