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*RESEARCH ARTICLE*

# Frequency and Clinical Outcome of Hepatorenal Syndrome in Advanced Liver Cirrhosis in Medical Intensive Care Unit Zagazig University.

**Osama A. Khalil, Ahmed I. Elagrody, Ghada M. Samir, AlsayedAlnahal and Walid M. Afifi**
Internal Medicine Department, Zagazig University, Egypt.

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## *Abstract*

**Background:**Hepatorenal syndrome (HRS) develops in advanced liver cirrhosis duringthe first year of the diagnosis by 18% and increases to reachup to 40% at five years with two weeks median survival intype I HRS and four to six months intype II. **Aim of the work:**Frequency of HRS inpatients admitted to medical intensive care unit (ICU) ofZagazig University withadvanced cirrhotic,impact ofcirrhosis complications on the development of HRS, and itsclinical outcome. **Patients and Methods:**A cohort study on50patientswith the criteria of HRS in a period of six months and they were classified into type I and type II; withFull history, thorough clinical examination, routine investigations, APACHE II scorecalculationat admission, and mortality were followed at 2 weeks and 6 months.**Results:**Frequency of HRS was 9.4%mainly in type II.Spontaneous bacterial peritonitis (SBP) was higher in type I (p =0.03)with2.71 fold increase in relative risk.APACHEII score washigher in type I (p =0.02) with highermortality at 2 weeks (p =0.001). **Conclusion:**HRS type II was more common while type I had a more aggressive course.Morbidity and mortality increased significantly withSBP, HE and hematemesis, rapid and proper treatment especiallyfor SBP with early diagnosis and treatment of HRS, may improve the survival rate ofdiuretic resistant stage patients.



## Introduction:-

Hepatorenal syndrome (HRS) is a unique form of kidney injury resulting from renal vasoconstriction in the setting of systemic and splanchnic arterial vasodilatation in advancedcirrhotic patients. There are two types ofHRS: type I with rapid deterioration in kidney function in the form of risingin serum creatinine to greater than 2.5 mg/dl within a two-week period, whereas type II occurs in patients with refractory ascites with either a steady but moderate degree of functional renal failure (≥ 1.5 mg/dl) or a deterioration not fulfillingtype I criteria [(1)].

In patients with advanced cirrhosis, HRS is reported to occur in 18% within one year of diagnosis and up to 40% at five years. Untreated, median survival is two weeks for patients with type I and four to six months in patients with type II [(2)].

**Corresponding Author: - Ahmed I. Elagrody**
Address: -Internal Medicine Department, Zagazig University, Egypt.

**International Ascites Club** (IAC) (2007) has provided diagnostic criteria for HRS which are; cirrhosis with ascites, serum creatinine >1.5 mg/dL, no improvement of serum creatinine (decrease to a level ≤1.5 mg/dL after at least two days of diuretic withdrawal and volume expansion with albumin, blood or plasma), absence of shock, no current or recent treatment with nephrotoxic drugs, absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/day, microhematuria (> 50 red blood cells per high power field), and/or abnormal renal ultrasonography [(3)].

The last classification of the HRS was done by ***Santiago and Munoz, (2008)*** [(4)] *a*s following; Type I: cirrhosis with rapidly progressive acute renal failure, Type II: cirrhosis with subacute renal failure, Type III: cirrhosis with types I or II HRS superimposed on chronic kidney disease or acute renal injury, Type IV: fulminant liver failure with HRS.

HRS is a functional renal failure without significant histological changes, and therefore is potentially reversible. However, if left untreated, intense renal vasoconstriction precipitates irreversible renal damage. This explains as to why not all cases of HRS recover kidney function following liver transplantation.Untreated type I carries a bad prognosis, with mortality as high as 80% in 2 weeks, and only 10% of patients survive more than 3 months [(5)].Because of its poor prognosis and lack of effective therapy, the term "terminal functional renal failure" was synonymous with HRS [(6)].

This study was aiming to assess; the frequency of HRS and it types among patients who are admitted to medical intensive care unit in Zagazig University hospitals, the effect of some complications of the advanced liver cirrhosis on the development of HRS in those patients, and to study the clinical outcome of HRS.

## Patients and Methods:-

This work was carried out inthe period from March 2015 to Septemper 2015 in the form of cross sectional cohort study on 530 patients withchronic liver disease (according to the International Classification of Diseases, Ninth Revision, Clinical Modification,Code 571) who are admitted to hepato-gastroentrology subunit of medical intensive care unit within six months. Only 55 patients had advanced liver cirrhosis, ascites and with raised serum creatinine above 1.5 mg/dl, two patients died in the second day and three patients were excluded (2 patients had a decrease in serum creatinine after 2 days from admission to ICU after volume expansion, the other one had renal medical disease grade II in ultrasonography).So; 50 patients were included in the study andclassified into two types of HRS according to level and rising pattern of serum creatinine. In type I HRS there is doubling of serum creatinine reaching greater than 2.5 mg/dL in less than 2 weeks, and type II is characterized by moderate and slowly progressive renal failure with serum creatinine lower than 2.5 mg/dL[(7)].

**Inclusion criteria:-**

Cirrhotic patient with all of the following; ascites, both genders, above 18 years old, serum creatinine ≥ 1.5 mg/dL with no improvement after at least two days of diuretic withdrawal and volume expansion with albumin 1 g/kg of body weight per day up to a maximum of 100 g/day.

**Exclusion criteria:-**

cirrhotic patientabove 18 years old with ascites and serum creatinine above 1.5 mg/dL with any of the following;sepsis, shock, current or recent treatment with nephrotoxic drugs, parenchymal kidney disease (proteinuria >500 mg/day, microhematuria>50 red blood cells per high power field, and /or abnormal renal ultrasonography), and improvement of serum creatinine after diuretic withdrawal and volume expansion with albumin.

**Ethical clearance:-**

Written Informed consent was taken from the first degree relative to participate in the studyafter taking Institutional Review Board approval.

All patients were subjected to; full history and thorough clinical examination, Routine lab investigations (urine analysis, 24 hours urine protein, complete blood picture, serum creatinine in first and third day of admission [(9)], serum urea [(8)], liver function tests [(10)], prothrombin time (PT), INR and partial thromboplastin time (PTT), arterial blood gases (ABG), Na, K, C reactive protein, pelvi-abdominal ultrasonography and electrocardiography), and APACHE II Score[(11)].

All patients were followed during hospital stay and after discharge (by regular outpatient clinic visits or by telephone) for 6 months to determine the clinical outcome.

**Statistical Analysis:-**

The collected data were computerized and statistically analyzed using SPSS program version 18. Qualitative data were represented as frequencies and relative percentages. Chi square test was used to calculate difference between qualitative variables in different groups.Quantitative data were expressed as mean±SD.Independent T test was used to calculate difference between quantitative variables in 2 groups in normally distributed data. Mann Whitney test was used to calculate differences between quantitative variables in 2 groups in not normally distributed data. $p < 0.05$ was considered statistically significant (S), $p < 0.005$ was considered highly significant (HS), and $p \geq 0.05$ was considered non-significant (NS).

## Results:-

***Table (1)*** shows statistically significant increase in systolic and diastolic blood pressure (but within normal) and APACHE II score in type I HRS compared to type II. Also;highly significant increase in creatinine level in both 1st and 3rd day in type I compared to type II.

There was a significant increase in number of cases having SBP in type I HRS as compared to type II, withincrease of the relative risk of occurrence of type I HRS in SBP andhepatic encephalopathy by 2.71 and 1.85 fold respectively ***(table 2)***.

***After 2 weeks***, SBP increase the relative risk of death in type I and type II HRS by 1.5 and 1.4 fold respectively, hepatic encephalopathy increase the relative risk of death in type I and type IIHRS by 1.2 and 1.3 fold respectively, while; hematemesis increase the relative risk of death in type I HRS by 1.5 fold***(table 3)***.

Lastly; in ***table 4,*** there was a significant increase in the number of deceased cases in type I HRS compared to type II after 2 weeks.

**Table (1): Comparison of Mean±SD ofclinical and Laboratory data between Type I and Type II HRS cases**

| Variable | Type I(n=16) | Type II(n=34) | Test | p |
|---|---|---|---|---|
| | Mean ± SD | Mean ± SD | T | |
| Systolic BP:(mmHg) | 118.44 ± 16.3 | 107.06 ± 13.03 | 2.66 | 0.01 S |
| Diastolic BP: (mmHg) | 71.25 ± 9.57 | 64.56 ± 10.18 | 2.21 | 0.03 S |
| GCS | 10.82 ± 2.83 | 9.88 ± 2.58 | 1.14 | 0.26 NS |
| WBCs: ($x10^3$/uL) | 7.02 ± 1.88 | 6.99 ± 1.48 | 0.05 | 0.96 NS |
| Hb: (g/dL) | 8.86 ± 1.79 | 9.69 ± 1.91 | 1.46 | 0.15 NS |
| INR | 1.85 ± 0.41 | 1.77 ± 0.57 | 0.51 | 0.61 NS |
| Albumin: (g/dL) | 2.45 ± 0.67 | 2.37 ± 0.64 | 0.38 | 0.70 NS |
| BUN: (mg/dL) | 77.94 ± 20.05 | 67.35 ± 20.38 | 1.72 | 0.09 NS |
| Creatinine:1st day (mg/dL) | 3.3 ± 0.58 | 1.91 ± 0.26 | 11.73 | <0.001 HS |
| Creatinine:3rdday (mg/dL) | 2.59 ± 0.51 | 1.68 ± 0.18 | 9.18 | <0.001 HS |
| S. Na: (mmol/L) | 133.53 ± 5.48 | 133.56 ± 3.56 | 0.02 | 0.99 NS |
| S. K: (mmol/L) | 4.36 ± 0.83 | 4.68 ± 0.82 | 1.26 | 0.21 NS |
| | Mean ± SD | Mean ± SD | MW | |
| APACHE II score | 39.94 ± 15.23 | 29.26 ± 12.99 | 166 | 0.02 S |
| Platelets: ($x10^3$/uL) | 59.25 ± 19.77 | 69.53 ± 31.64 | 242 | 0.53 NS |
| Total bilirubin:(mg/dL) | 3.20 ± 2.32 | 3.04 ± 3.18 | 241 | 0.52 NS |
| Direct bilirubin: (mg/dL) | 2.01 ± 2.41 | 1.91 ± 1.45 | 247 | 0.60 NS |
| Urine RBCs: (Cell/HPF) | 3.35 ± 1.77 | 2.88 ± 1.14 | 271 | 0.98 NS |
| Urine protein: (mg/24h) | 23.17 ± 19.39 | 22.31 ± 14.64 | 241.5 | 0.52 NS |

**Table (2): Comparison of frequency and relative risk of some gastrointestinal complication between Type I and Type II HRS cases:**

| Variable | | Type I(n=16) | | Type II(n=34) | | Total | RR | $\chi^2$ | p |
|---|---|---|---|---|---|---|---|---|---|
| | | No | % | No | % | | | | |
| Encephalopathy | Yes | 13 | 81.2 | 22 | 64.7 | 35 | 1.85 | 1.42 | 0.23 |
| | No | 3 | 18.8 | 12 | 35.3 | 15 | | | NS |
| Hematemesis | Yes | 9 | 56.2 | 20 | 58.8 | 29 | 0.94 | 0.03 | 0.86 |
| | No | 7 | 43.8 | 14 | 41.2 | 21 | | | NS |
| SBP | Yes | 12 | 75 | 14 | 41.2 | 26 | 2.71 | 4.99 | 0.03 |
| | No | 4 | 25 | 20 | 58.8 | 24 | | | S |

**Table (3): The relative risk of some gastrointestinal complication on mortality among the types of heptorenal syndrome cases after 2 weeks**

| Variable | | | Deceased | Survived | Relative risk |
|---|---|---|---|---|---|
| SBP | Type I | Yes | 10 | 1 | 1.5 |
| | | No | 3 | 2 | |
| | Type II | Yes | 5 | 9 | 1.4 |
| | | No | 5 | 15 | |
| Encephalopathy | Type I | Yes | 11 | 2 | 1.2 |
| | | No | 2 | 1 | |
| | Type II | Yes | 7 | 15 | 1.3 |
| | | No | 3 | 9 | |
| Hematemesis | Type I | Yes | 8 | 1 | 1.5 |
| | | No | 4 | 3 | |
| | Type II | Yes | 6 | 14 | 0.8 |
| | | No | 5 | 9 | |

**Table (4): Comparison of outcome as regarded to mortality in relation to time between Type I and Type II HRS cases:**

| Outcome | | Type I | | Type II | | $\chi^2$ | p |
|---|---|---|---|---|---|---|---|
| | | No | % | No | % | | |
| 2 weeks | Deceased | 13 | 81.2 | 10 | 29.4 | 11.77 | 0.001 HS |
| | Survived | 3 | 18.8 | 24 | 70.6 | | |
| 6 months | Deceased | 2 | 66.7 | 15 | 62.5 | 0.02 | 0.89 NS |
| | Survived | 1 | 33.3 | 9 | 37.5 | | |

## Discussion:-

The current definition of HRS proposed by the International Ascites Club states that "HRS is a potentially reversible syndrome that occurs in patients with cirrhosis, ascites and liver failure that is characterized by impaired kidney function, marked alterations in cardiovascular function, and over-activity of the sympathetic nervous system and renin-angiotensin system. Severe renal vasoconstriction leads to a decrease of GFR [(3)].

HRS carries the worst survival among all causes of AKI in cirrhotic patients [(12)]. Prognosis of type II HRS patients is slightly better than type I, with a median survival of 6 months [(2)].

Therefore we tried to evaluate the frequency of HRS and its types, and to study the effect of some complications of the advanced liver cirrhosis on the occurrence and mortality of different types of hepatorenal syndrome in those subjects. Also; to detect the clinical outcome (morbidity and mortality) of hepatorenal syndrome.

In this study the frequency of HRS was 9.4% among 530 patients with advanced liver cirrhosis this was in line with***Moore et al., (2003)***[(13)] who reported that the incidence of HRS among hospitalized patients with cirrhosis and ascites in United States was 10%, . Also in another study conducted by ***Gines et al., (1993)*** [(15)] concluded that the estimated 1-year and 5-year probability of HRS was 8% and 39%, respectively in patients with cirrhosis with ascites. In another study, done by***Montoliu et al., (2010)*** [(14)] HRS was the cause of AKI in only 7.6% of 129 patients

with cirrhosis with ascites and AKI. In a study conducted by***Planas et al., (2006)***[16] that included 263 cirrhotic patients showed mush lower risk of HRS development with the cumulative 5 year probability of HRS development was only 11.4%.

On the other hand in a study conducted by***Wong et al., (2005)***[17]**,**they reported that the prevalence ofHRS in patients with cirrhosis having advanced liver disease waiting for liver transplantation is as high as 48%.in another study conducted by ***Salerno et al., (2011)***[18] ***and Martin –Liahi et al., (2011)***[19] the incidence of HRS among patients with liver cirrhosis was found (45.8%),(43%) respectively this may be due to the small sample size in their studies which was carried out on 62 , 55,52 patients only and to the elevated number of patients with end stage liver cirrhosis who are followed in their unit while good percentage of our patients was admitted to our unit by upper GIT bleeding and most of them had no ascitis.

The most frequent type of HRS in our study was type II HRS (68%) and type I was (32%) which is consistent with ***Runyon, (1998)***[20] who reported that type I HRS was 30% in patients with alcoholic hepatitis.

In contrast to the above study, ***Licata et al., (2013)***[21] found an equal prevalence of type I and type II HRS (45.5% vs 54.5%) respectively, this difference may be due to less number of patients who had SBP, from them (15) patient were type I HRS and (18) were type II HRS.

In this study, we found significant elevation in the mean ± SD values of serum creatinine, in type I HRS than in type II, while there was no significant difference between the 2 types of HRS in other clinical and laboratory findings.Similar results were obtained in a study by ***Licata et al.,(2013)*** [21] compared type I and type II HRS patients and showed no statistically significant differences between the two types, except for serum creatinine, creatinine clearance, INR values.

We found that SBP increase the relative risk of occurrence of type I HRS by 2.71 fold than those without SBP. This was in line with ***Navasa et al., (1998)*** [22] who reported that type I HRS develops in 25% of patients with SBP despite a rapid resolution of the infection. They suggested that SBP is associated with high risk of HRS is related to the role of the inflammatory response to SBP in HRS development. Another possible explanation is the development of septic cardiomyopathy with secondary deterioration in renal function ***Ruiz-del-Arbol et al., (2005)*** [23]**.**

Our study also finds that hepatic encephalopathy increase the relative risk of occurrence of type I HRS by 1.85 fold than those without hepatic encephalopathy; this can be explained by the presence of SBP in(45%) of hepatic encephalopathy patients, while upper GIT bleeding did not show any significant increase in relative risk of development of type I HRS.

In this cohort study we evaluate our patients for mortality during hospital stay for 2 weeks and after discharge during period of 6 month by telephone it was found that 13 patient with type I HRS deceased (81.2%)after 2 weeks and 10 patients with type II (29.4) while (66.7%)and (62.5%) of cases deceased after 6 months in type I and type IIrespectively with a Significant increase of mortality in type I HRS in comparison to type II HRS these results were consistent with ***Arroyo et al., (1996)*** [5] who reported that mortality is as high as 80% in 2 weeks, and only 10% of patients survive>3 months , another study conducted by ***Gines et al., (2003)*** [2]found that Patients with type II HRS have a much better median survival approximately 6 months, also; this was in line with a study conducted by***Stadlbauer et al., (2008)*** [24] who reported that the 3 month survival for HRS patients was 15% compared with 31% for patients with infection induced HRS. In contrast to ***Licata et al., (2013)*** [21] who found that the median survival was 30 day (range: 10-274) without significant difference between type I and type II HRS (p=0.2 by log –rank test) this may be explained by a relatively large number of patients with co-morbidities that adversely affected the prognosis, such as hepatocellular carcinoma in their study.

We can conclude that the frequency of HRS was high in our unit and it is a drastic complication of liver cirrhosis and is associated with significant morbidity and mortality specially those who are complicated by SBP.

So; we recommend the close monitoring of renal functions in patients with advanced liver cirrhosis may be of predictive value for the risk of morbidity and mortality in those subjects, and early diagnosis and treatment of thecomplications of advanced liver cirrhosis especially SBP may decrease the incidence of occurrence of HRS and

ameliorate the morbidity and mortality in those subjects thus improve the survival rate especially those with diuretic resistant stage.

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