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RESEARCH ARTICLE

"STUDY OF SERUM AMMONIA IN HEPATIC ENCEPHALOPATHY AND ITS CORRELATION WITH SEVERITY"

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Abstract

Background and objectives: Hepatic encephalopathy (HE) encompasses a spectrum of manifestations ranging confusion and coma. Data on correlation of serum ammonia levels with grades of HE is inconsistent. This study was undertaken to find the correlation between serum ammonia levels and grades of HE.

Methodology: This hospital based descriptive cross-sectional study was undertaken in the Department of General Medicine, from a tertiary care hospital situated in South Karnataka from November 2018 to May 2020. A total of 86 patients with HE were included in the study.

Results: Majority of the patients (83.72%) were males and the male to female ratio was 5.14:1. The mean age was 54.01±11.55 years and most of the patients (36.05%) were aged from 51 to 60 years. Most of the patients had lack of awareness (47.67%) followed by disorientation (24.42%). According to West heaven criteria, most of the patients (47.67%) had grade 1 HE followed by grade 2 (24.42%), grade 3 (23.26%) and grade 4 (4.65%). The mean serum ammonia levels were 105.43±49.66 and 88.65 µg/dl. Majority of the patients (96.51%) had serum ammonia levels of >60 µg/dl. There was strong positive correlation between HE grades and serum ammonia levels (ρ=0.752; R^2=0.455; $p<0.001$). Also, mean serum ammonia levels in grade 4 HE (203.50±107.87 µg/dl) were significantly high compared to grade 3 (139.20±41.48µg/dl), 2 (112.57±36.91µg/dl) and 1 (75.75±20.20µg/dl) ($p<0.001$).

Conclusion and Interpretation: The serum ammonia level were elevated in patients with HE. There is strong positive correlation between HE grades and serum ammonia levels which corresponds to the severity of HE.

Introduction:-

Hepatic encephalopathy (HE) is brain dysfunction caused by liver insufficiency and/or porto-systemic shunting manifesting as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.[1] It refers to a complex, potentially reversible or progressive syndrome of cerebral dysfunction, which consists of neuropsychiatric, cognitive and motor disturbances, characterized by a broad etiological spectrum".[2] It is one of

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the most serious complications of liver failure, either chronic or fulminant. It can either be acute and reversible, or chronic and progressive leading to coma and death.[3]

It is difficult to establish the incidence and prevalence of hepatic encephalopathy due to differences in etiology and severity of HE. Therefore, a true picture of HE is not fully known. The precipitating factors for developing encephalopathy in cirrhotic are electrolyte abnormalities, medications, gastrointestinal bleeding and infections. The acute form of HE can lead to fulminant hepatic failure [FHF] which manifests as seizures, coma, de-cerebrate posturing and death. The pathophysiology of HE is multifactorial with several circulating neurotoxins, however ammonia is strongly considered as a central factor in the pathogenesis of HE.[3]

Ammonia can alter the excitatory and inhibitory neurotransmission, affecting the glutaminergic, γ-aminobutyric acid [GABA]-ergic and dopaminergic systems[4,5] Other proposed mechanisms of neuronal dysfunction include ammonia-induced RNA oxidation, activation of mitogen-activated protein kinases and of nuclear factor-Kb. Even though few studies have shown the correlation of serum ammonia levels with grades of encephalopathy in CLD and in ALF,[3] the available data is inconsistent.[6,7] This study examined the relation between serum ammonia levels in HE and its correlation with severity of HE.

Methodology:-

This hospital based descriptive cross sectional study was conducted for a period of 18 months from November 2018 to May 2020 in the Department of General Medicine from a tertiary care hospital situated in South Karnataka. Prior to the commencement, ethical clearance was obtained from the Institutional Ethics committee.

Based on a study by Ong JP. et al.[8] (2003) for correlation between ammonia levels and the severity of HE with Spearman rank correlation coefficient, at 95% confidence interval (CI), and probability value (p value) of ≤ 0.05 as statistically significant, the optimal sample size required to determine the objective was 86.

Adult patients aged upto 80 years with diagnosis of CLD having signs of HE were included in the study. Patients with ALD, septic, uremic of encephalopathy were excluded from the study. Prior to the commencement, the study was approved by the Institutional Ethics Committee. Patients who fulfilled the selection criteria their next of kin (Since the patients are in HE, a state of disturbed consciousness) was briefed about the nature of the study and a written informed consent was obtained prior to the enrollment. Patient's next of kin was interviewed and demographic information like age, gender and clinical presentation was noted. Detailed history of other associated medical conditions along with treatment history and personal history were recorded. A thorough general physical examination was conducted to evaluate vitals and the signs of liver failure were noted. The mental status was assessed and graded by West Haven criteria[9,10] as follows.

1. Grade 0-No signs and symptoms.
2. Grade 1–Lack of awareness, shortened attention span, anxiety, and impaired performance of addition.
3. Grade 2–Lethargy or apathy, minimal disorientation for time or place subtle personality change inappropriate behaviour, impaired performance of subtraction.
4. Grade 3–Somnolence to semistupor, but responsive to verbal stimuli, confusion, gross disorientation.
5. Grade 4–Coma (unresponsive to verbal or noxious stimuli).

Apart from routine investigations patients were investigated for serum ammonia levels by enzymatic kinetic method using cobast 6000 machine. Those who had serum ammonia levels greater than 60 µg/dl were classified as hyperammonemia.[11]

Statistical analysis

The data obtained was coded, entered into Microsoft Excel Worksheet and analyzed using statistical software SPSS version 20.0. Continuous variables were presented as mean±standard deviation (SD) and analyzed for normality by the Shapiro-Wilk test. Categorical variables were compared using the Chi-square or Fisher's exact test while continuous variables with normal distribution were compared using Independent t-test and those did not follow normal distribution were tested using Mann-Whitney U tests. The comparison of serum ammonia levels with severity of HE was done by one way analysis of variance (ANOVA) and for the data that was not normally distributed, Kruskal Wallis Test was used to compare more than two median values. Spearman's rank correlation coefficient was used to determine correlation between serum ammonia levels severity of HE. At 95% CI, a 'p' value of ≤0.050 was considered as statistically significant.

Results:-

The clinical profile of the study population is as show in the table 1. The serum ammonia levels ranged between 52 to 362.70 µg/dl. The mean and median serum ammonia levels were 105.43±49.66 and 88.65 µg/dl (Table 1). Further, 96.51% of the patients had serum ammonia levels of >60 µg/dl (Graph 1). Overall, 83.72% of the patients were males and 16.28% were females the male to female ratio was 5.14:1. Although, 83.13% of the males had raised serum ammonia levels (>60 µg/dl) compared to 16.87% of the females, the difference was statistically not significant. (p=0.583). Age of the patients ranged between 28 to 77 years. The mean and median age was 54.01±11.55 and 54 years. 36.05% of the patients were aged from 51 to 60 years (p=0.488) and majority of patients (36.14%) in this age group 51 to 60 years had raised serum ammonia levels (>60 µg/dl). However no association was found between raised serum ammonia levels (>60 µg/dl) with age (p=0.488). The clinical presentations, medical and personal history of the patients and its association with serum ammonia levels is as shown in table 2. On examination, 74.42% of the patients had icterus and 60.47% had asterixis. However, no association was found between raised serum ammonia levels (>60µg/dl) with signs of liver failure (p>0.050) (Table 2). Spleen was palpable in 95.35% of the patients and liver was not palpable in 94.19% of the patients. Shortened memory was noted in 55.81% of the patients. Further significantly higher number of patients with shortened memory (57.83%) had raised serum ammonia levels (>60µg/dl) (p=0.004). with regard to manifestations of altered mental status, 47.67% had lack of awareness, 24.42% had disorientation, 23.26% had somnolence to semi stupor and 4.65% had coma. No statistically significant association was noted between severity of HE and serum ammonia levels (p=0.503) (Table 3). There was strong positive correlation between HE grades and serum ammonia levels (ρ=0.752;R^2=0.455;p<0.001) (Graph 2). The mean and median serum ammonia levels significantly increased with higher HE grades (p<0.001) (Table 4).

Discussion:-

In the present study majority of the patients (96.50%) had raised serum ammonia levels (>60 µg/dl) with elevated mean and median serum ammonia levels suggesting that HE is associated with hyperammonia. These observations were similar to a study done by Sharma T. et al.[12] (2016) who reported elevated ammonia levels (100%) in all the patients with HE. However this study did not mention about the average serum ammonia levels in the population studied.

In this study the severity of HE based on West haven criteria, showed grade one to be common (47.67%) followed by grade two (24.42%), three (23.26%) and least being grade four (4.65%). These observations were consistent with the observations reported by a study by Sharma T. et al.[13] (2016) where 30% of the patients had grade one HE, 13.75% had grade two HE, 28.75% had grade three HE, 21.25% had grade four HE, and 6.25% of the patients had grade zero HE. In contrast, Brar R. et al.[14] (2016) reported 58.62% of the patients with grade four HE.

In the present study, no statistically significant association was found between elevated serum ammonia levels and grade of HE but, there was strong positive correlation between HE grades and serum ammonia levels (ρ=0.752; R^2=0.455; p<0.001). Furthermore, the mean serum ammonia levels significantly increased with higher HE grades that is, the mean serum ammonia levels in grade four HE were significantly high compared to grade three, grade two and grade one. Due to the wide variation in the serum ammonia levels suggesting multimodal distribution the median serum ammonia levels were considered rather than mean and the difference across the different grades of HE were tested using both median and IQR also using Kruskal Wallis test which is reliable test for the data with multimodal distribution. Even the comparison of median value showed significant stepwise increase in the median serum ammonia levels with higher HE grades that is, the median serum ammonia levels in grade four HE were significantly high compared to grade three, two and one. This difference between the stepwise increase in serum ammonia levels was statistically significant (p<0.001). These observations not only hypothesize significant correlation between grades of HE with serum ammonia levels but confirm that, increase in serum ammonia levels with severity of HE based on West Haven criteria. These observations were consistent with findings reported by previous studies in the literature. Earlier, Ong et al.[8] (2003) compared four different measurements of ammonia concentration (arterial and venous total, arterial and venous partial pressure) in 121 patients with cirrhosis and grade 0 - 4 HE and showed a moderate correlation between all four measurements and grade of HE. Recently, Qureshi MO et al.[15] (2016) measured serum ammonia levels in 135 patients with liver cirrhosis with HE and reported that ammonia levels correlated with the severity of HE. Brar R. et al.[14] (2016) also reported that, serum ammonia level was 23-64 in grade one and two, while serum ammonia level was 65-148 in grade three and four, suggesting that serum ammonia level increases with high grade of HE a finding consistent with the present study. Another study by

Sharma T. et al.[12] (2016) demonstrated that, the arterial ammonia level correlated with the grades of HE. Higher grades of encephalopathy being associated with higher levels of ammonia. On comparing the values of the milder grades of HE (zero, one, two) with those of the severe grades (three, four) it was seen that in the milder grades the mean ammonia level was low compared to the severe grades.

In contrast to the observations from the present study, Khan WM et al.[16] (2017) reported that increasing serum ammonia levels were not related to higher grades of HE. However the observations reported by Khan WM et al.[16] (2017) were based on 100 patients with viral HE and most of the patients with grade two HE followed by grade three, four and one. The serum ammonia levels of these patients widely ranged between 14 and 178 mcg/dl, at the mean values of 74.17 mcg/dl in grade I, 57.79 mcg/dl in grade II, 71.88 mcg/dl in grade III, and 81.13 mcg/dl in grade four HE. The spearman correlation was 0.097. In a smaller study of 20 patients with CLF, Kundra A et al.[17] (2005) found no statistically significant correlation in the patients with elevated ammonia levels and the presence of HE.

Overall the findings of the present study is consistent with several previous studies,[3,,8,12,14] that favor ammonia in the causation of HE. Also, the data showed that serum ammonia levels have a good correlation with clinical grades of HE. Ammonia neurotoxicity is an important component of cerebral dysfunction in liver failure patients, but still there is much debate on the underlying mechanisms and also in understanding the better type of ammonia measurement.[3]

In the present study majority of the patients were males (male to female ratio 5.14:1) suggesting occurrence of HE in males five times more than the females (p=0.583). These observations were consistent with the observations reported by Sharma T. et al.[12] (2016) where majority of patients were males (76.25%) with the male:female ratio being 3.2:1. The male preponderance noted in the present study was also consistent with the reports by Khan WM et al.[16] (2017) (63%) and Ong JP. et al.[8] (2003) (64%) on the contrary, Qureshi MO et al.[15] (2016) reported 45.9% of the males and 54.07% of the females.

In the present study most of the patients (36.05%) of the patients were aged from 51 to 60 years and maximum patients (36.14%) had raised serum ammonia levels. These observations suggest occurrence of HE common in sixth decade of life (p=0.488). The age distribution pattern observed in the present study was comparable with a study by Brar R. et al.[14] (2016) who reported that, 38% of the patients were in the 48-58 age group. On the contrary, Sharma T. et al.[12] (2016) reported that, most of the patients with HE were found in the third decade of life. The mean age noted in the present study was similar to the study by Khan WM et al.[16] (2017).

In this study with regard to clinical profile, reported history of altered sleep (38.37%), alcohol intake (60.47%), yellowish discoloration of eyes (37.2%), hematemesis (16.28%) and previous episodes of HE (47.67%). On examination with respect to signs of liver failure, majority of the patients (74.42%) had icterus followed by asterixis (60.47%) and ascites (59.30%). However, no association was found between clinical signs of liver cell failure, symptoms as well as past medical history with elevated serum ammonia levels (p>0.050). On systemic examination, majority of the patients had palpable spleen (95.35%), altered mental status, liver was not palpable in 94.19% of the patients each, shortened memory (55.81%). Further, shortened memory was significantly associated with elevated serum ammonia levels (p=0.004). With regard to altered mental status in line with HE severity, most of the patients had lack of awareness (47.67%), disorientation (24.42%), somnolence to stupor (23.26%), and coma (4.65%). Sharma T. et al.[12] (2016) also noted most common symptoms as neuropsychiatric manifestations like disorientation, drowsiness, mood fluctuations, lack of concentration, and sleep disorders (100%).

Overall, the serum ammonia levels are elevated in patients with HE. There is strong positive correlation between HE grades and serum ammonia levels which corresponds to the severity of HE. Hence, serum ammonia estimation could be useful additive so as to identify patients with higher grade HE. However, these observations require further validation due to potential limitations of this study. The strength of the study was that the present study enrolled patients with HE and also assessed the correlation between serum ammonia and grades of HE assuming that the data is having multimodal distribution which makes the results of this study more reliable and valid in patient with chronic liver disease. The limitation of the study was that, the findings in this study were based on the data having relatively smaller sample size from a single centre. Further, multicentric studies involving large sample size with age and sex specific serum ammonia levels considering outcomes may provide the true relationship between serum ammonia and grade HE.

Table 1:- Clinical profile of the study population.

Parameters	Mean (n=86)		Median	Range	
	Mean	SD		Min	Max
Age (Years)	54.01	11.55	54.00	28.00	77.00
Duration of yellowish discolouration of eyes (Days)	12.03	6.47	10.50	7.00	28.00
Duration of altered sleep rhythm (Days)	9.18	4.68	7.00	2.00	28.00
Duration of altered mental status (Days)	3.19	2.58	2.00	1.00	14.00
Duration of hemetemesis (Days)	2.00	0.68	2.00	1.00	3.00
Duration of malaena (Days)	7.82	5.69	7.00	1.00	21.00
Duration of fever (Days)	4.40	2.55	4.50	1.00	7.00
Duration of abdominal distension (Days)	10.86	7.88	7.00	1.00	30.00
Duration of abdominal pain (Days)	5.47	3.70	5.00	1.00	14.00
Pulse rate (per minute)	77.15	11.34	74.00	52.00	129.00
Respiratory rate (per minute)	20.53	4.43	20.00	14.00	30.00
Systolic blood pressure (mm Hg)	129.70	21.36	128.00	80.00	190.00
Diastolic blood pressure (mm Hg)	81.35	12.13	81.00	60.00	110.00
SGOT (IU/L)	114.56	138.85	80.00	28.00	1187.00
serum alkaline phosphatase(U/L)	147.63	68.58	132.00	17.00	442.00
SGPT (IU/L)	57.79	112.39	33.50	11.00	1040.00
Total bilirubin (mg/dl)	6.24	4.88	4.85	0.66	19.53
Direct bilirubin (mg/dl)	3.65	3.19	2.37	0.26	14.55
Indirect bilirubin (mg/dl)	1.80	1.58	1.29	0.11	7.56
Serum albumin (mg/dl)	2.47	0.61	2.50	1.20	5.36
Serum Globulin (mg/dl)	3.97	0.91	3.90	0.80	5.80
serum total protein (mg/dl)	6.38	0.90	6.30	4.30	8.89
A/G ratio (mg/dl)	0.63	0.27	0.60	0.10	1.90
Serum urea (mg/dl)	48.26	34.05	37.00	8.00	186.00
Serum creatinine (mg/dl)	1.56	1.27	1.22	0.36	9.51
serum sodium (meq/L)	132.65	6.41	132.00	115.00	147.00
Serum Potassium (mEq/L)	4.08	0.80	4.15	1.39	6.24
Serum Ammonia (µg/dl)	105.43	49.66	88.65	52.00	362.70

Table 2:- Distribution of patients according to the clinical presentation and history and its association with serum ammonia levels.

Parameters	Clinical presentation	Serum Ammonia levels (µg/dl)				Total		p value
		11 to 60 (n=3)		>60 (n=83)				
		No.	%	No.	%	No.	%	
Clinical presentation	Yellowish discoloration of eyes	0	0.00	32	38.55	32	37.21	0.242
	Altered sleep rhythm	1	33.33	32	38.55	33	38.37	0.673
	Altered mental status	2	66.67	79	95.18	81	94.19	0.166
	Hematemesis	0	0.00	14	16.87	14	16.28	0.583
	Malena	1	33.33	16	19.28	17	19.77	0.488
	Fever	0	0.00	10	12.05	10	11.63	0.687
	Abdominal distension	3	100.00	28	33.73	31	36.05	**0.044**
	Abdominal pain	0	0.00	19	22.89	19	22.09	0.468
Past medical and personal history	Previous episodes of HE	1	33.33	40	48.19	41	47.67	0.535
	Mixed diet	2	66.67	54	65.06	56	65.12	0.722
	Altered sleep	2	66.67	63	75.90	65	75.58	0.573
	Alcohol intake	0	0.00	52	62.65	52	60.47	0.058

	Family history of liver disease	0	0.00	0	0.00	0	0.00	-
Signs of liver failure	Asterixis	3	100.00	49	59.04	52	60.47	0.216
	Icterus	2	66.67	62	74.70	64	74.42	0.593
	Parotid swelling	0	0.00	12	14.46	12	13.95	0.633
	Spider naevi	0	0.00	3	3.61	3	3.49	0.898
	Gynaecomastia	0	0.00	8	9.64	8	9.30	0.743
	Loss of axillary hair	0	0.00	16	19.28	16	18.60	0.535
	Fetor hepaticus	0	0.00	1	1.20	1	1.16	0.965
	Ascites	1	33.33	50	60.24	51	59.30	0.360
	Palmar erythema	0	0.00	1	1.20	1	1.16	0.965
	Muscle wasting	0	0.00	0	0.00	0	0.00	-

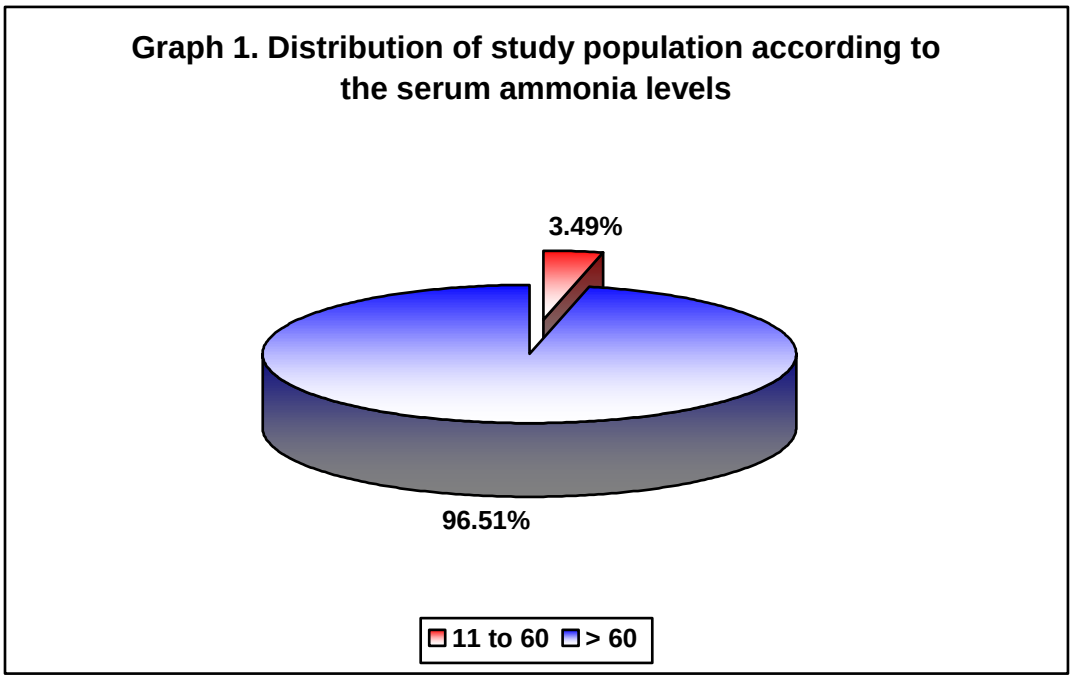
Table 3:- Distribution of study population according to the HE severity and its correlation with serum ammonia levels.

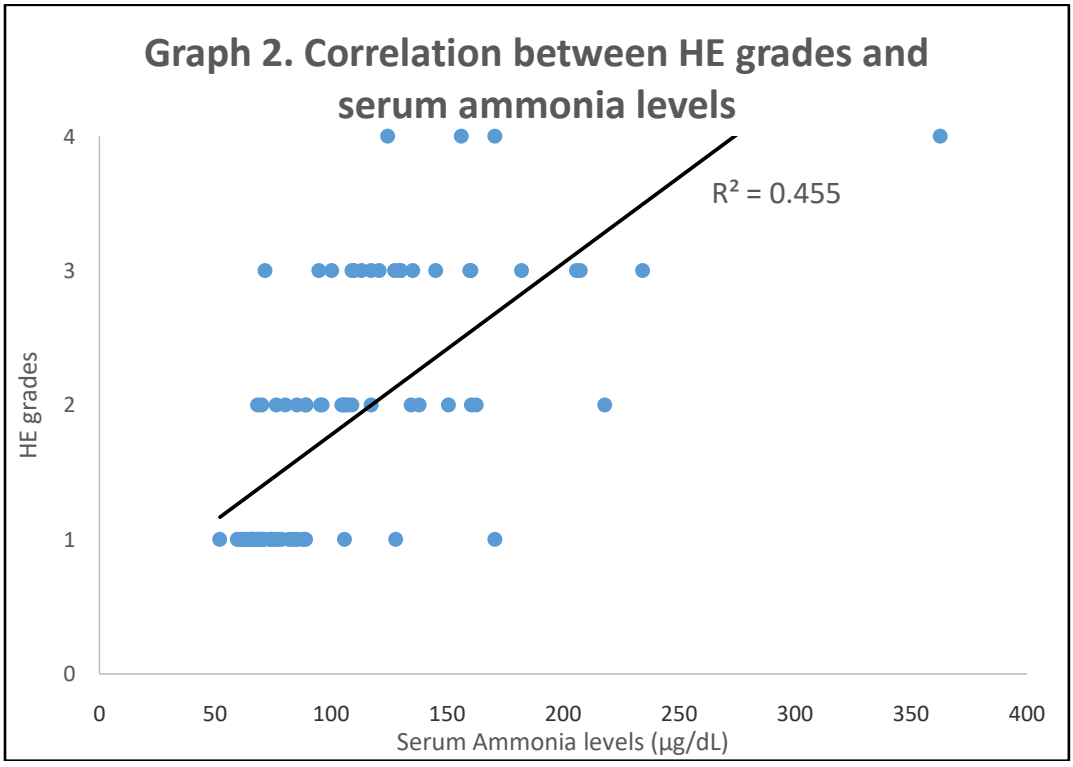
HE severity (West haven criteria grade)	**Serum Ammonia levels (µg/dl)**				**Total**	
	11 to 60		**>60**			
	No.	**%**	**No.**	**%**	**No.**	**%**
0	0	0.00	0	0.00	0	0.00
1	3	7.31	38	92.68	41	47.67
2	0	0.00	21	100.00	21	24.42
3	0	0.00	20	100.00	20	23.26
4	0	0.00	4	100.00	4	4.65
Total	**3**	**3.49**	**83**	**96.51**	**86**	**100.00**

p = 0.503

Table 4:- Comparison of mean serum ammonia levels with HE severity.

HE severity (West haven criteria grade)	**n**	**Serum Ammonia levels (µg/dl)**			
		Mean	**SD**	**Median**	**IQR**
0	00	-	-	-	-
1	41	75.75	20.20	70.20	14.75
2	21	112.57	36.91	105.30	49.05
3	20	139.20	41.48	129.85	49.30
4	4	203.50	107.87	163.40	182.25
F value	24.213			-	
p value	**<0.001**			**<0.001**	





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