RESEARCH

SERUM PROLACTIN AS A MARKER OF SEVERITY OF HEPATIC ENCEPHALOPATHY IN CIRRHOSIS

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Abstract

Background: Hepatic encephalopathy is a serious complication of chronic liver disease. From the epidemiological perspective, it has become clear that HE is probably the most frequent complication of cirrhosis that leads to hospitalisations and higher rates of mortality. Therefore the present study aimed to study of role of biomarkers such as prolactin as a marker of severity of hepatic encephalopathy, The aim is to study the role of serum prolactin levels as a marker of severity of hepatic encephalopathy. **Materials and Methods:** This was an observational cross-sectional study conducted among patients with cirrhosis of liver in hepatic encephalopathy admitted in Gandhi hospital. Total 100 patients were included in the study after obtaining the informed consent and appropriated investigations were done. **Result:** In our study we found that males were predominantly affected with 95% of study population and females accounting to 5%. Mean age of population is 47.13 years. Alcohol was found to be the most common etiological factor causing cirrhosis of liver accounting to 68% of study population followed by HBV infection (12%). Among the precipitating factors of HE constipation (48%) was most common precipitating factor followed by upper GI Bleed (41%), hyponatremia (38%) and infection (36%) and most of them were found to be in Grade 2 (32%) and Grade 1(23%). Of the study population 43% were observed to be in class C , 40% in child pugh class B , 17% % were in class A .Total 56% patients recovered during the course of hospital stay. There was a significant increase in serum prolactin levels with increasing severity of grade of hepatic encephalopathy from grade 1 to grade 4, with mean of 17.05 ± 3.70 in grade 1 HE, 24.76 ±4.64 in grade 2 HE, 30.57 ± 3.19 in HE grade 3, and 32.73±2.20 in HE grade 4 and serum prolactin levels almost being in normal range in MHE with a P Value of < 0.001. **Conclusion:** Serum prolactin can be used as a biochemical marker of severity of hepatic encephalopathy.

INTRODUCTION

The burden of liver cirrhosis is soaring worldwide, Cirrhosis is defined as irreversible change in the normal liver tissue that results in the degeneration of functioning liver cells and their replacement with fibrous connective tissue.[1] There are close to 10.6 million cases (2017) of decompensated cirrhosis and 112 million prevalent cases of compensated cirrhosis globally. 1It is estimated that with the given population burden, India accounts for approximately 18.3% of all cirrhosis deaths globally.[2] According to studies, patients with liver cirrhosis do not pursue hospital treatment when in compensated state. It is only when the patient becomes decompensated that is when they develop abdominal distension (ascites), jaundice, altered sensorium (Hepatic encephalopathy), gastrointestinal bleed they seek medical attention.

Hepatic encephalopathy is a serious complication of both chronic liver disease and Acute liver failure and is broadly defined as an alteration in mental status and cognitive function occurring in presence of liver failure. The clinical and economic burden of HE is considerable, and it contributes greatly to impaired quality of life, morbidity and mortality. The incidence of HE is 11.6 per 100 person years which increases to 40% by 5 Years.[3] The prevalence of overt HE at the time of diagnosis of cirrhosis is 10–14%, 16–21% in decompensated cirrhosis.[4,5,6] From the epidemiological perspective, it has become clear that HE is probably the most frequent complication of cirrhosis that leads to hospitalisations and repeated re- admissions affecting approximately 20% of patients with liver cirrhosis each year.[7] Therefore, the healthcare burden and costs associated with the management of HE are extensive and increasing.

More importantly, it has been demonstrated that HE is associated with high rates of mortality, with a survival of only 23% at three years from onset

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irrespective of the severity of liver disease, indicating that HE is not merely a symptom of liver failure, but that it may have independent pathophysiological and prognostic implications.[8] The West Haven criteria (WHC) is the most frequently used for grading HE. Hormonal disorders and circadian rhythm abnormalities are often associated with liver disease, and the severity of these disorders is related to liver disease severity and duration.[9] The hypothalamic-pituitary-gonadal axis is affected in most patients, but also other hormones are altered by hepatic insufficiency such as thyroid hormones and growth hormone.

Normally prolactin is associated with characteristic nocturnal rise, and a Characteristic circadian rhythm. Loss of circadian rhythm is characteristic of Cirrhotic Patients. 76 Until recently it was thought that these hormonal disturbances were caused mainly by ineffective elimination of hormones by the diseased liver. It is now known that the pathogenesis of disturbed hormonal function in liver cirrhosis is rather more complex, as it frequently involves disrupted secretion and feedback pathways. Increased level of serum prolactin is associated with increased risk of hepatic encephalopathy and progression of severity of hepatic disease The main goal of this study is to evaluate the role of serum prolactin levels as a marker of severity of Hepatic Encephalopathy in patients with cirrhosis based on west haven criteria.[10]

MATERIALS AND METHODS

This was a hospital based observational study that was conducted in patients admitted with cirrhosis of liver presented with hepatic encephalopathy or complicating into hepatic encephalopathy in Gandhi Hospital. A total of 100 patients who were fulfilling the inclusion and exclusion criteria were included in the study from 10/1/2021 to 31/12/21 after taking informed consent.

Inclusion Criteria

All patients with cirrhosis of liver with hepatic encephalopathy.

Exclusion Criteria

History of chest wall trauma. cranial surgery/ irradiation, pituitary or hypothalamic disease, chronic renal failure, herpes zoster, seizure disorder, patient on medication known to elevate prolactin levels and pregnancy

Procedure

Informed consent will be obtained from all the patients enrolled in the study. For data collection, a questionnaire was developed. A detailed clinical history of the patient was taken regarding the present and past illnesses. Questions were asked about gastrointestinal bleeding, including hematemesis and melena, constipation, vomiting, diarrhoea, oliguria, fever, bleeding manifestation, high protein diet, paracentesis and any trauma or surgery. Personal history about alcohol consumption was noted in along with smoking and i.v drug abuse Use of any sedatives, diuretics, tranquilizers, analgesics and cough syrups was also inquired in detail. All patients were carefully examined with special attention to jaundice, anaemia, fever, asterixis, hydration, pedal edema, and ascites. Detailed per abdominal and neurological examination was done on all patients and patients with hepatic encephalopathy were identified and graded according to West Haven Criteria Clinical Grades of hepatic encephalopathy including MHE.

For each patient investigation like full blood count, liver function tests, renal function tests, random blood sugar, serum electrolytes, serum ammonia serum albumin and coagulation profile, serum prolactin was carried out. An abdominal ultrasound was done to look for liver and splenic size, parenchymal echogenicity, portal vein diameter, and ascites. In case of ascites, an ascites tap was also done to look for spontaneous bacterial peritonitis

Serum prolactin was measured quantitatively by chemiluminescence assay using ROSH reagent and HITACHI E411 analyser with assay range (4.04-15.2 ng/ml). Any evidence of the presence of other co-existent complications of cirrhosis liver was also recorded and Child's score was assessed for each patient based on following parameters.

Table 1: Child Pugh Score

Parameters	Numerical Score		
	1	2	3
Ascites	none	slight	moderate to severe
Encephalopathy	none	slight to Moderate	moderate to severe
Serum bilirubin (mg/dl)	<2	2-3	>3
Albumin (gm/dl)	>3.5	2.8-3.5	<2.8
Prothrombin time	1-3	4-6	>6

Child Pugh class A – 5 to 6
Child Pugh class B – 7 to 9
Child Pugh class C – 10 to 15

All patients were followed for the duration of their stay in hospital and whether they survived or died at the end of the stay was also recorded.

Data was entered into Microsoft Excel (Windows 10) and analyses were done using the Statistical Package for Social Sciences (SPSS) for Windows software (version 22.0; SPSS Inc, Chicago). Descriptive statistics such as mean and standard deviation (SD) for continuous variables, frequencies and percentages were calculated for categorical Variables were determined. Comparison of mean of quantitative variables were analysed using unpaired t test and ANOVA (Analysis of Variance) for variables having 2 and more than 2 categories respectively. Bar charts and Pie charts were used for visual representation of the analysed data. Level of significance was set at 0.05.

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RESULTS

In the present study of 100 patients the mean age of population was 47.13 ± 9.16. Majority of cases belonged to age group between 31 to 49 years (65%) followed by age group more than or equal to 50 years (33%). In our study majority of patients were males accounting to 95% and females accounting to 5%. In our study mortality of 44% of patients in hepatic encephalopathy during course of hospital stay.

Table 2: Distribution of study subjects according to the age

Age (Years)	No.	Percent
≥ 50	33	33.0
31-49	65	65.0
<30	2	2.0
Mean (SD)	47.13 (9.16)	
Range	30-69	
Gender		
Male	95	95.0
Female	5	5.0
Outcome		
Recovered	56	56.0
Death	44	44.0

Table 3: Distribution of study subjects according to the aetiology. Complaints and precipitating factors

Aetiology	No.	Percent
Alcohol	68	68.0
Alcohol & HBV	2	2.0
HBV	12	12.0
HCV	6	6.0
NASH	8	8.0
Others	4	4.0
Complaints		
Fever	38	38
Pain Abdomen	47	47
Vomiting	16	16
Diarrhoea	9	9
Constipation	46	46
Ascites	97	97
UGI Bleeding	41	41
Icterus	91	91
Precipitating Factors		
Infection	36	36.0
UGI Bleed	41	41.0
Constipation	48	48.0
Diarrhoea	9	9.0
Hyponatremia	38	38.0
Hypokalaemia	17	17.0
Toxins and Drugs	6	6.0

In our study alcohol (68%) was found to be most common etiological factor followed by HBV infection (12%). In the our study more than 1 precipitating factor was found to cause hepatic encephalopathy of which constipation (48) was found to be most common presenting factor followed by UGI Bleed (41), hyponatremia (38), infection (36).

Table 4: Mortality among precipitating factors

	Total number of patients	Death	Recovered
Ugi Bleed	41	20	21
Infection	36	30	6
Constipation	48	22	26
Hyponatremia	38	20	18
Hypokalaemia	17	4	13
Drugs	6	3	3
Diarrhoea	9	1	8

In our study mortality was more in patients with infection, hyponatremia and UGI Bleed as a precipitating factor

Table 5: Distribution of Study Subjects according to the Laboratory Investigations

Investigations	No.	Percent
Anaemia	73	73.0
Leucocytosis	35	35.0
Thrombocytopenia	60	60.0

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Elevated AST	56	56.0
Elevated ALT	49	49.0
Elevated ALP	48	48.0
Elevated Blood Urea	30	30.0
Elevated Serum Creatinine	20	20.0
Prolonged PT/INR	38	38.0
Serum Albumin	No.	Percent
Normal	17	17.0
2.5-3.5	40	40.0
<2.5	43	43.0
Serum Sodium	No.	Percent
<135	38	38.0
135-150	57	57.0
>150	5	5.0
Serum Potassium	No.	Percent
<3.5	17	17.0
3.5-5.5	72	72.0
>5.5	11	11.0

Table 6: Distribution of Study Subjects according to the GRADE OF VARICES

UGIE Grade of Varices	No.	Percent
0	9	9.0
1	36	36.0
2	25	25.0
3	25	25.0
4	5	5.0
Grades of Hepatic Encephalopathy		
MHE	9	9.0
Grade 1	23	23.0
Grade 2	32	32.0
Grade 3	21	21.0
Grade 4	15	15.0
Childs Pugh Classification		
Class A	17	17.0
Class B	40	40.0
Class C	43	43.0

In our study, majority patients were found to have grade 1 varices (36%) followed by grade 2 and grade 3 varices (25%) 5% of patients had grade 4 varices while 9% of patients had no varices. In our study 32% were found to be in HE grade 2, 23% were in HE Grade 1, 21% were in HE grade 3, 15 % were in HE grade 4, 9% in MHE. In our study, 43% of patients were in Class C, 40% were in class B, 17% were in class A.

Table 7: Mean Serum Prolactin Levels in different Grades of Hepatic Encephalopathy

Prolactin Level	MHE	Grade 1	Grade 2	Grade 3	Grade 4
Mean	12.44	17.05	24.76	30.57	32.73
SD	2.60	3.70	4.64	3.19	2.20
Median	12.20	16.90	25.30	31.70	32.70
ANOVA, P Value <0.001, Significant					

In our study there was a statistically significant difference were found in serum prolactin levels in different grades of hepatic encephalopathy. There was a significant increase in serum prolactin levels with increasing severity of grade of hepatic encephalopathy from grade 1 to grade 4, with a p value of <0.001 and serum prolactin levels being normal in MHE.

Table 8: Serum Prolactin Levels in classes of Child Pugh (N=100)

Prolactin Level	Class A	Class B	Class C
Mean	14.75	22.26	29.96
SD	3.73	6.33	4.32
Median	14.1	21.35	31.30
ANOVA, P Value <0.001, Significant			

There was a significant increase of prolactin level in Child Pugh Class B and C when compared to Class A . In our study the ammonia level in MHE was found to be within normal range with mean of 51.6 mcg/dl with standard deviation of 19.04

The ammonia levels were elevated in all other grades of hepatic encephalopathy with mean of 89.5 mcg/dl with standard deviation of 17.05mcg/dl in Hepatic encephalopathy grade1 and 90.96 mcg/dl with standard deviation of 11.51 in HE Grade 2, 91.96 mcg/dl with standard deviation of 7.71 in HE Grade 3 and 92.4 mcg/dl with standard

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deviation of 4.41 in HE grade 4. In our study we found a positive correlation of 0.375 between mean ammonia levels in different grades of HE and mean.

Table 9: Comparison of results of clinical profile among various studies in hepatic encephalopathy

Study	Mean Age	Sex	Etiology	Precipitating Factors of HE	Grades Of HE	CPC
Vinoth Kumar senthirama n et al,[11]	49.58 ± 12.26	92.23% males, 7.77% females	Alcohol (88.3%) HBV (4.85%)	Dehydration (78.64%), diuretics (46.60%), hypokalaemia (35.3%), constipation (33.1%), Infection (30.1%) and UGI Bleed (30.9%)	39.8% in grade 3 HE, 36.89% in grade 2, 19.42% in grade 4 and 3.88% in grade 1 HE	87.38% class C, 7.65% class B, 0.97% class A
Nayak M et al,[12]	40.48 ± 11.38	Males (86%) Female s (14%)	Alcohol (76%), HBV (16%), HCV (4%) and others (4%).	Upper GI bleed (86.1%), constipation (34%), hyponatremia (24%), hypokalaemia (14%), infection (26%), drugs (18%)	Grade 4 36% , grade 3 (30%)), grade 2 (10%) , grade 1(24%)	CPC Class C (60%), Class A (24%), Class B (16%).
Handady et al,[13]	50.32 ± 16.2	Male (75.8%) Female s (24.2%)	Viral hepatitis (41.7%), alcoholism (12.5%), autoimmune disease(10.8%), unknown aetiology(31.6 %)	Infection (41.7%), constipation (36.4%), hypokalaemia (27.5%), UGI Bleed (26.7%), hyponatremia (21.7%).	Grade 2 (43.3%), grade 4 (13.3%), grade 1 HE (11.7%), grade 3 (31.7%)	CPC class B (68.3%) class C (31.7%).
Nandu S Poudyal et al	49.2 ± 10.2 years	Males (79%) females (21%)	Alcohol (86%) HBV (7%) HCV (5%)	Infection (49.2%) imbalance (41%), constipation (33%), upper GI bleed (16%)	grade2 (57.5%), grade 1 (22%), grade 3 (16%) grade 4 (4.5%)	Class C(71.2%), Class B(28.8%)
Present Study	47.13 ± 9.16	Males (95%) Female (5%)	Alcohol (68%) HBV (12%) NASH (8%) HCV (6%)	Constipation (48%) Upper GI Bleed (41%) Hyponatremia (38%) Infection (36%0	Grade 2 (32%) Grade 1 (23%) Grade 3 (21%) Grade 4 (15%)	Class C (43%) Class B (40%)

DISCUSSION

This was a cross sectional study of 100 patients diagnosed with decompensated chronic liver disease in hepatic encephalopathy conducted at Gandhi hospital, secunderabad over a period of 1 year. In our study we found that males were predominantly affected with 95% of study population and females accounting to 5%. Mean age of population is 47.13 with standard deviation of 9.16. Most of the cases belong to the age group between 31 to 49 years of age. Alcohol was found to be the most common etiological factor causing cirrhosis of liver accounting to 68% of study population followed by HBV infection (12%). Most of the patients presenting complaints were ascites, jaundice and pedal edema. Among the precipitating factors of HE constipation was found to be most common precipitating factor accounting to 48% followed by upper GI Bleed (41%), hyponatremia (38%) and infection (36%) and most of them were found to be in Grade 2 (32%) and Grade 1(23%). Of the study population 43% were observed to be in class C, 40% in child pugh class B, 17% % were in class A. In our study 56% patients recovered during the course of hospital stay. In a study by Vinoth Kumar Seetharaman et al,[11] a total of 103 patients were studied, mean age of population was found to be 49.58 ± 12.26, 92.23% of the study population were males, and rest 7.77% were females. Alcohol is the most common etiological factor accounting to 88.35% and HBV (4.85%). Among the precipitating factors Dehydration was most common (78.64%), diuretics (46.60%), hypokelmia (35.3%), constipation (33.1%), Infection (30.1%) and GI Bleed (30.9%).87.38% belonged to child Pugh class C, 7.65% Belonged to class B, 0.97% were in class A. 39.8% of cases were in grade 3 HE, 36.89% were in grade 2, 19.42% in grade 4 and rest 3.88% in grade 1 HE.

In study conducted by Nayak M et al,[12] a total of 50 patients were studied, mean age of study population was 40.48 ± 11.38, majority of patients were in age group of 20 – 40 years. 86% were males and 14% were females. Alcohol was found to be the most common etiological factor accounting to 76%, HBV (16%), HCV (4%) and others (4%). Pedal edema was found to be the most common presenting feature. 60 % belonged to CPC Class C, Class A (24%), Class B (16%). Among precipitating factors upper GI bleed (86.1%) was most common precipitating factor, followed by constipation (34%), hyponatremia (24%), hypokalaemia (14%), infection (26%), drugs (18%). 36% were in grade 4, 30% were in grade 3, 10% in grade 2, 24% in grade-1.

In a study conducted by Handady et al,[13] a total of 120 patients were studied, in which mean population age is 50.32 ± 16.2, 75.8% patients were male and rest 24.2% were female. Among the etiological factors 41.7% were viral hepatitis, 12.5% were due to alcoholism, 10.8% were due to autoimmune disease, and rest 31.6% are of unknown aetiology. 43.3% of patients were in grade 2 HE, 13.3% were in grade 4

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HE, 11.7% were in grade 1 HE, 31.7% were in grade 3 HE. According to CPC 68.3% belonged to class B and the rest 31.7% to class C. Among the precipitating factors infection (41.7%) was found to be most common precipitating factor, constipation (36.4%), hypokalaemia (27.5%), UGI Bleed (26.7%), hyponatremia (21.7%). In a study by Maqsood et al 116a total of 50 patients were studied, 25% were male and 25% were female. 86% of patients were above 40 years of age, 12% between 20 – 40 years and 2% less than 20 years of age. Infection (42%) was the most common precipitating factor followed by UGI Bleed (38%), constipation (38%).

In a study by Nandu S Poudyal et al,[14] comprising of 132 patients, with mean age of 49.2 ± 10.2 years, 79% of them were males and 21% were females. Alcohol (86%) was found to be most common etiological factor with HBV and HCV contributing 7% and 5% respectively, and rest 2% were cryptogenic. The most common precipitating factor of HE in the study was infection (49.2%) followed by electrolyte imbalance (41%), constipation (33%), upper GI bleed (16%).57.5% of patients were in grade 2 HE, 22% were in grade 1 HE, 16% were in grade 3 HE and the rest 4.5% were in grade 4 HE.71.2% of patients were found to be in CPC Class C, and 28.8% were in CPC Class B

The findings in the study were similar to study conducted by Chaitanya H Balakrishna et al,[14] Including 60 patients with cirrhosis of liver of which 10% in CPC Class A, 40% in Class B and 50% in class C and serum prolactin was elevated in 73.33% of patients and higher prolactin levels were found in Class C and B, with highest levels of serum prolactin (value >35 ng/ml) were seen in patients of Class C [normal value for serum prolactin noted in the study was 3-19 ng/ml.].[15] Patients in the study were in hepatic encephalopathy and all of them had elevated serum Prolactin including the highest reading noted in their study of 60 ng/ml In a study conducted by T.K Rajasekarpandian et al,[16] among the 100 study patients, there was a statistically significant difference in relation to child pugh score status between elevated prolactin group(majority were class B – 35.16%) and normal prolactin group (majority were Class A – 55.56%). In a study conducted by Zietz et al,[17] where 52 male cirrhotic were compared to 50 age matched controls basal prolactin levels were significantly different within the various child pugh classes (CPC Class A 6.6 ±0.4 µg/l; CPC Class B 10.2 ±1.8µg/l; CPC class C 16.1 ±3.2 µg/l)

In our study there was a statistically significant difference were found in serum prolactin levels in different grades of hepatic encephalopathy. There was a significant increase in serum prolactin levels with increasing severity of grade of hepatic encephalopathy from grade 1 to grade 4, with mean of 17.05 ± 3.70 in grade 1 HE, 24.76 ±4.64 in grade 2 HE, 30.57 ± 3.19 in HE grade 3, and 32.73±2.20 in HE grade 4 and serum prolactin levels almost being in normal range in MHE with a P Value of < 0.001. In a study conducted by Mona Arfa et al,[18] prolactin concentration in cirrhotic patients with HE was significantly increased compared to patients without HE and its cut-off value was more than 18.85 ng/dl could predict HE in cirrhotic patients showing a sensitivity of 88% and a specificity of 90.3%. The study results were similar to the study done by Fawzy M Khalil et al which included a study population 50 patients where there was a statistically significant difference in Child Pugh class C and B (mean value of 20.69 ± 7.41 ,19.35 ±10.6 respectively) when compared to Child Pugh class A (mean value of 13.84 ±8.99) and also there was statistically significant increase in prolactin levels in grade 3 and 4 (with a maximum value of 39 ng/ml). McClain et al,[19] in his study observed that 21 patients of alcoholic liver disease with Porto Systemic Encephalopathy were divisible into two groups, 12 patients were having mildly increased serum prolactin values and 9 patients were having markedly increased level of serum prolactin. Patients of latter group not only had greater derangement of liver functions but also higher mortality. Mukherjee et al.[20] Analysed the prolactin levels in patients with hepatic cirrhosis and found a higher levels in both patients with encephalopathy and mortality.

As serum prolactin can be regarded as a sensitive indicator of functional dopamine activity in brain, and dopamine is a hypothalamic prolactin inhibitor factor. Increased prolactin levels indicate depletion of dopamine. Decompensated liver function also leads to an alteration in the type of amino acids entering the central nervous system, with an increase in circulating aromatic amino acids leading to an increase in the synthesis of false neurotransmitters such as octopamine and phenyl ethanolamine. These false neurotransmitters may inhibit the dopamine release which in turn cause increased prolactin secretion. As these levels of neurotransmitters are also related to the severity of liver disease. So, lesser the level of these neurotransmitters, (i.e., more the level of serum prolactin), more is the severity of liver disease, and hence more the mortality.

CONCLUSION

Since the dopamine level cannot be directly measured in the body fluids, we used prolactin to measure the severity of hepatic encephalopathy. In our study we found that Serum Prolactin levels significantly increased with increasing severity of hepatic encephalopathy and with severity of liver disease. There was a significant increase in serum prolactin levels with increasing severity of grade of hepatic encephalopathy from grade 1 to grade 4, with mean of 17.05 ± 3.70 in grade 1 HE, 24.76 ±4.64 in grade 2 HE, 30.57 ± 3.19 in HE grade 3, and 32.73±2.20 in HE grade 4 and serum prolactin levels almost being in normal range in MHE with a P Value of < 0.001. Therefore, serum prolactin can be used as a marker of severity of hepatic encephalopathy and can be used to monitor treatment. As the study included only 100

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patient's further studies are needed to establish the role of serum prolactin in severity of grade hepatic encephalopathy.

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