Research Article

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Vitamin D And Liver Cirrhosis ; Relation To Liver Dysfunction And Etiology: A Retrospective Case Control Study

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1. Abstract :

1.1. Background :
There is evidence that vitamin D (VD) metabolism is related to the pathophysiology of cirrhosis. The objectives of the study are primarily to identify the association between serum VD level and etiology/pattern of liver cirrhosis in Yemen .The secondary aim is to identify the association between level of VD and severity of liver dysfunction, sex, and age.

1.2. Methods and Materials:
This retrospective study was conducted between April 2007 and April 2014, on patients with liver cirrhosis , both cholestatic and non-cholestatic (Cirrhosis-C, Cirrhosis-NC). Severity of liver disease was assessed using Child-Pugh score. Correlation between serum VD level and etiology/ pattern of liver cirrhosis and severity of liver dysfunction were analyzed. A multiple regression was run to predict serum VD from liver disease status, severity of liver disease, gender, and age.

1.3. Results:
135 patients were included in this study of which 90 (66.7%) patients with liver cirrhosis and 45 (33.3%) patients without cirrhosis . There was no correlation between VD deficiency status and patients with liver cirrhosis status (r=0.15, p=0.076). Additionally, no correlation between VD level and severity of liver cirrhosis (r= 0.10, p=0.288) was observed. Serum VD was slightly higher in male patients, but not statistically significant (r=0.1, p=0.241). In the multiple regression model, all four variables did not add statistical significance to the prediction, p = 0.658.

1.4. Conclusion:
We found no association between VD deficiency and degree of hepatic dysfunction. Minimal association with etiology/pattern (cholestatic or non-cholestatic) of liver cirrhosis patients, and sex was noted.

2. Keywords:
Vitamin D3, Liver, Dysfunction, Etiology, Yemen ,

3. Introduction

Vitamin D insufficiency and deficiency are prevalent in almost half the healthy population of developed countries [1] Several studies have shown that VD deficiency is a common feature.in those suffering from advanced chronic liver disease, independent of the etiology [1]. Vitamin D is a hormone with numerous and important biological properties that influence host physiology by regulating epigenetic regulation of more than 2000 genes throughout the body. VD is best known for its role in maintaining bone mineralization but also has diverse and profound influences which can determine disease development and outcome. [2]. Regarding patients with chronic liver disease of varying etiologies, VD deficiency has been associated with increased mortality [3] Patients with chronic liver disease (CLD) have an increased risk for the development of osteoporosis and fractures, reduced muscle strength, an impaired inflammatory response, and malignancy. These conditions have also been associated with VD deficiency [4]. Adverse outcomes of VD deficiency such as osteoporosis, osteomalacia and increased fracture risk is well known [5].

However, because the liver plays an important role in the metabolism and pleomorphic functions of VD the question is whether VD deficiency is a consequence of liver disease or a contributor to the liver dysfunction [1], The main source of vitamin D in humans is the exposure of skin to sunlight. For further activation, VD is hydroxylated in the liver to form 25-hydroxyvitamin D (25-(OH)D) and in the kidneys to form the active metabolite 1,25(OH)2 vitamin D. The body stores of VD are best reflected by the serum levels of 25-(OH)D. [6] Cholestasis is an impairment of bile formation and/or bile flow which may clinically present with fatigue, pruritus and, in its most overt form, jaundice. Early biochemical markers in often asymptomatic patients include increase alkaline phosphatase (AP), and Gamma glutamyl transpeptidase (GGT) followed by conjugated hyperbilirubinemia at more advanced stages

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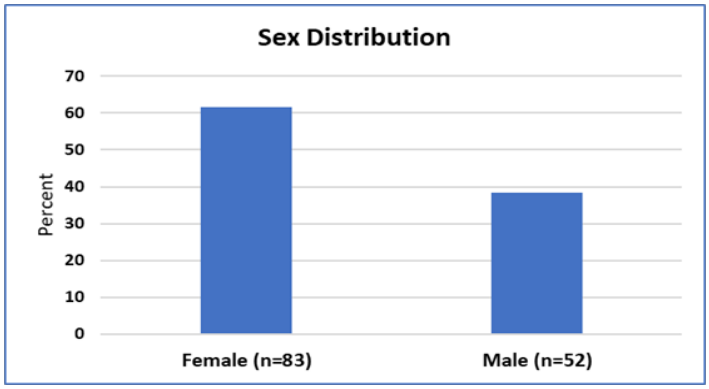
[7]. Given the crucial role of VD in metabolic homeostasis, monitoring VD levels and treatment of patients with documented deficiency is of paramount importance. For patients with CLD, 25-OH, VD level should be at or above 30 ng/mL. [8]. Currently, the VD level status is categorized as normal (≥30 ng/ml), insufficiency (20-29.9 ng/ml), deficient (10-19 ng/ml) and severely deficient (> 10 ng/ml) . [9] Nevertheless, the VD deficiency in chronic liver disease is only partly the result of a synthetic dysfunction of the liver, as enhanced by the fact that VD deficiency is highly prevalent in non-cirrhotic patients. [10] The primary aim of this study is to identify any association between VD level and etiology and / or pattern of liver cirrhosis .The secondary aim is to identify any association between level of VD and grade of liver dysfunction (Child-Pugh score), sex and age .

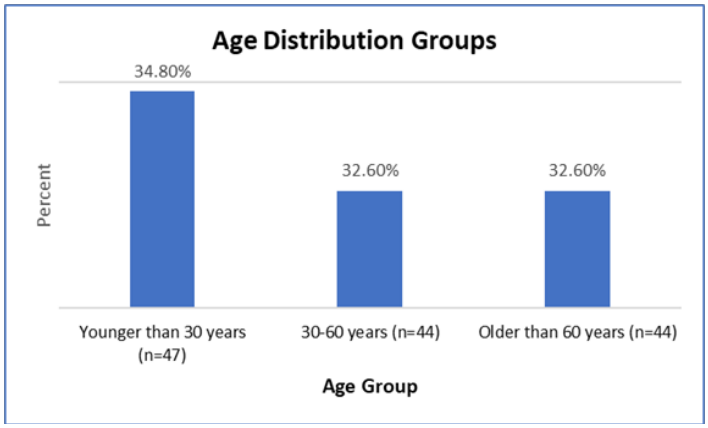
Figure 1A: Demographics of Study Population- Sex



4. Patients and Methods

This retrospective study is registered at Research Registry . The study was conducted in the Specialized Research Center for Hepatology and Gastroenterology in Sana"a , Yemen. between April 2007 and April 2014 on patients with liver cirrhosis (CLD), both cholestatic and non-cholestatic diseases. The included patients are from different regions in Yemen and referred for treatment in our center. This study was approved by the committee of the Specialized Research Center for Hepatology and Gastroenterology and is reported according to the STROCSS guidelines [11]. Cirrhosis was diagnosed on the basis of any of the clinical features such as , hepatomegaly or shrunken liver, splenomegaly, or biochemical abnormality especially reduced synthetic function of the liver as hypoalbuminemia or prolonged INR, In addition to positive abdominal ultrasound for irregular liver margins , dilated portal vein , presence of ascites, as well as endoscopic findings as presence of esophageal varices or portal hypertensive gastropathy. While liver biopsy remains an important diagnostic test, all patients in this cohort refused to undergo liver biopsy. On other hand, Schistosomiasis cases were diagnosed based on combination of bilharzial urinary antigen and positive rectal snip for Shistosomiasis. Cholestasis is defined by elevated levels of alkaline phosphatase , plasma gamma glutamyl transferase. In late stages, hyperbilirubinemia and clinical manifestations such as pruritis and jaundice develop. hyperbilirubinemia , jaundice and pruritis. [12]. To assess the severity of liver disease, the Child-Pugh scoring system was utilized. This score is based on the degree of encephalopathy, the presence of ascites, prothrombin time, and the serum levels of bilirubin, and albumin. Accordingly, the patients had either compensated liver disease (Class A, 5-6 points), moderate liver disease (Class B, 7-9 points), or severe liver disease (Class C, 10-15 points).

Figure 1B: Demographics of Study Population- Age Groups



4.1 Inclusion Criteria

- Case – Patients with Liver cirrhosis both cholestatic or non-cholestatic.
- Control : (Non cirrhotic) .They are selected from patients treated in our center and complaining of non-specific complains such as fatigue dyspepsia , or abdominal distension or , The are matched with the cases for age and sex.

4.2 Exclusion Criteria

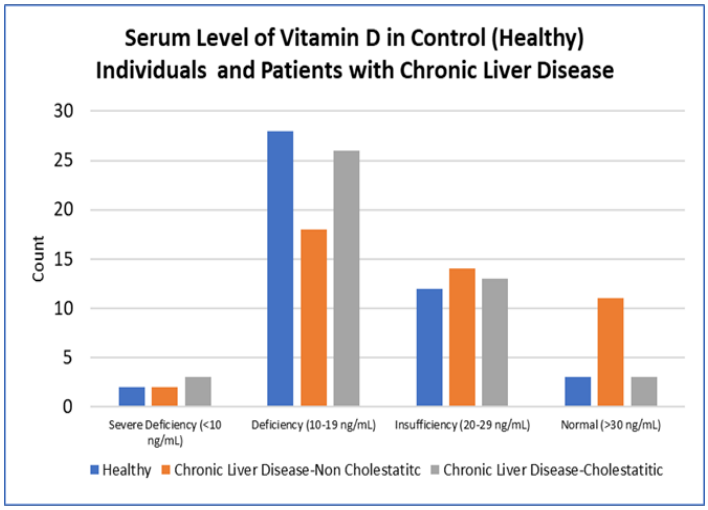
- History of previous treatment with vitamin D3
- History of new fracture or acute arthritis or rheumatoid arthritis which may affect level of VD.

4.3 Vitamin D measurement

Blood (2ml) was drawn from the patients to check for vitamin D3. Serum 25(OH) D3 was analyzed by Electrochemiluminescence method . Reagent and standards :The 25(OH)D was measured using The Cobas analyzer and the Elecsys Vitamin D3 Kit (Roch). The kit includes polyclonal anti-25(OH)D3 antibody labeled with ruthenium comples 1.5 mg/l, biotinylated 25(OH)D 0.15 mg/l, reaction buffer (acetate buffer 220 mmol/l, pH 3.9, albumin 2 g/l). and streptavidin-coated microparticles (0.72 mg./mi). Before using the Elecsys Vitamin D3 kit was kept upright in order to insure that the microparticles were throughly mixed. The kit's reagents remain stable at measured using a Hitachi Cobas e 411 electrochemiluminescence instrument. The assay has a two-step, eighteen-minute incubation period. In step 1, 25(OH)D3 in a 35-microl sample complex contained in the biotin-vitamin D/ polyclonal 25(OH)D-specific ruthenium-labeled antibody. Step 2, involves adding

streppavidine-coated microparticles, and through the interaction between biotin and streptavidin, the complex adheres to solid phase. After aliquoting he reaction mixture into the measurement cell, , procell is used to remove any loose material. Lastly , a photomultiplier is used to induce and measure chemiluminescent emission. The results are obtained using a master curve made using the standard reagent and instrument-generated calibration curve created by 2-point calibration.

Figure 2: Serum Level of Vitamin D in Conrol (Healthy) Individuals and Patients with Chronic Liver Disease based on Chronicity of Disease.



5. Statistical analysis

Quantitative variables were presented as mean and standard deviation. Frequency and percentage were used for qualitative measures and were analyzed using the $\chi 2$ test . Correlation between serum vitamin D levels and severity of liver disease (Child Pugh scores), chronicity of liver disease, age and sex, were analyzed. Differences in proportions were assessed by Pearson Chi-Square. Post hoc analysis involved pairwise comparisons with a Bonferroni correction. Data were analyzed using SPSS Version 26 software (USA). Statistical significance was established at $p< 0.05$. To determine predictors of serum VD, a multiple regression analysis was performed.

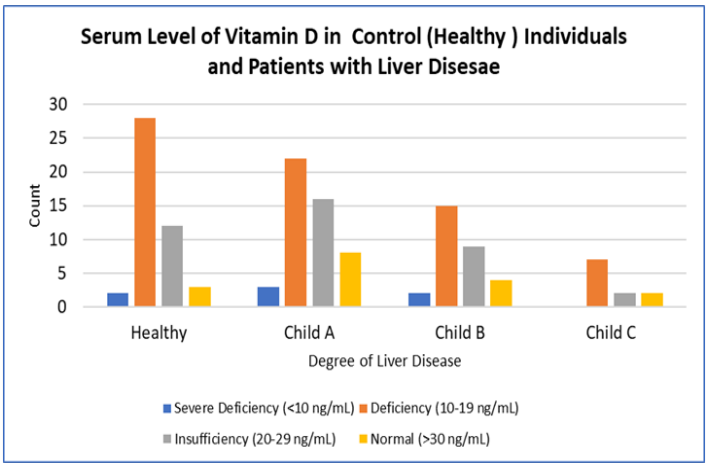


Figure 3: Serum Level of Vitamin D in Control (Healthy) Individuals and Patients with Chronic Liver Disease based on Severity of Liver Disease

5.1 Sample size calculation:

While power analysis is an integral part of planning clinical research studies, our study is retrospective in nature and is based on existing data and including 135 patients (45 in the control group and 90 in the studied group), therefore, giving the controversy of performing a post-hoc power analysis among most of researchers and biostatisticians, a sample size calculation was not performed in our study. Additionally, calculating power once the p-value associated with a statistic is known adds no new information and in fact, is considered the logic underlying post-hoc power analysis is fundamentally flawed [13]

6. Results

Patient demographics characteristics are shown in Table 1. There were 52 (38.4%) males and 83 (61.5%) females. Forty-seven (34.8%) patients were younger than 30 years-old), 44 (32.6%) patients (between 30-60 years-old) and 44 patients (older than 60 years old). In this cohort, approximately 80% of liver cirrhosis etiology distributed as follows; 35.5% hepatitis C virus/hepatitis B virus (n= 32), 28.9% autoimmune hepatitis (AIH, n=26), and 15.6% Schistosomiasis (n=14) . The remaining 18 (20%) patients included 4 patients with Wilson disease, eight patients with combined schistosomiasis and AIH, four patients with combined HCV and schistosomiasis, and two patients with HC and AIH, and two patients with idiopathic liver disease . Overall, there was no correlation between serum VD level and severity of liver diseases ($r= 0.10$, $p=0.288$). Serum VD was slightly higher in male patients than female, but not statistically significant ($r=0.1$, $p=0.241$). In the multiple regression model, all four variables (chronicity of liver disease, severity of liver disease, sex, and age) did not add statistically significance to the prediction, $p = 0.658$. Although weak, and non-statistically significant, there was a positive correlation between VD deficiency status and CLD status ($r=0.15$, $p=0.076$).

Table 1: Demographic Patients characteristics

Characteristics	Control group	Cirrhosis -cholestatic	Cirrhosis	Total
Sex, n (%)	(n=45)	(n=45)	-non-cholestatic (n=45)	(N=135)
Male	11 (24.4)	24 (53.3)	17 (37.8)	52 (38.5)
Female	34 (75.6)	21 (46.7)	28 (62.2)	83 (61.5)
Age				
Younger than 30 years	6 (13.3)	24 (53.3)	17 (37.8)	47 (34.8)
30-60 years	17 (37.8)	14 (31.1)	13 (28.9)	44 (32.6)

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Older than 60	22 (48.9)	7 (15.6)	15 (33.3)	44 (32.6)
BMI (Kg/m2)*				
<25	9 (20.0)	13 (28.9)	9 (20.0)	31 (23.0)
25 to 29	32 (71.1)	26 (57.8)	32 (71.1)	90 (66.7)
>29	4 (8.9)	6 (13.3)	4 (8.9)	14 (10.4)

No statistically significant differences were observed in serum level of VD between control group of patients and patients with liver cirrhosis (cholestatic versus non-cholestatic). Additionally, no association was observed between serum level of VD and severity of liver disease as assessed by Child-Pugh score. Table 2 and 3. Proportion of VD deficiency was noted to be statistically significantly higher in control group of patients compared to patients with cholestatic (62.2% vs. 40.0%, $p<0.05$) and compared to patients with non-cholestatic chronic liver disease (62.2% vs 57.8%, $p>0.05$). When evaluating serum level of VD based on severity of liver disease, patients with Child C have higher percentage of VD deficiency compared to patients with Child A and Child B disease, although not statistically significant.

Table 2: Serum Level of Vitamin D in Patients with Liver cirrhosis.

Serum Level of Vitamin D	**Control group**	**Cirrhosis-cholestatic**	**Cirrhosis -non-cholestatic**	**p-value**
Severe Deficiency (<10 ng/mL), n (%)	2 (4.4)	2 (4.4)	3 (6.7)	0.112
Deficiency (10-19 ng/mL), n (%)	28 (62.2)	18 (40.0)	26 (57.8)	
Insufficiency (20-29 ng/mL),n (%)	12 (26.7)	14 (31.1)	13 (28.9)	
Normal (>30 ng/mL), n (%)	3 (6.7)	11 (24.4)	3 (6.7)	
ng,nanogram; mL, milliliter				

Table 3: Serum Level of Vitamin D in Patients with Liver Cirrhosis based on Severity as Assessed by Child-Pugh Score.

Serum Level of Vitamin D	**Control group**	**Cirrhosis-cholestatic**	**Cirrhosis -non-cholestatic**	**p-value**
Severe Deficiency (<10 ng/mL), n (%)	2 (4.4)	2 (4.4)	3 (6.7)	0.112
Deficiency (10-19 ng/mL), n (%)	28 (62.2)	18 (40.0)	26 (57.8)	
Insufficiency (20-29 ng/mL),n (%)	12 (26.7)	14 (31.1)	13 (28.9)	
Normal (>30 ng/mL), n (%)	3 (6.7)	11 (24.4)	3 (6.7)	
ng,nanogram; mL, milliliter				

To predict serum level of VD (dependent variable), four variables were used in a multiple regression model. We used the actual serum VD level as a continuous variable. These predictors (variables) included liver disease status (i.e., healthy, cholestatic liver disease, non-cholestatic liver disease), severity of liver disease (i.e., healthy, Child A, Child B, Child C), patient sex, and patients age group. In the multiple regression model, all four variables did not add statistical significance to the prediction, $p = 0.658$. However, age and sex of the patients have a higher coefficient in predicting serum VD. Table 4.

Table 4: Multiple Linear Regression Results of Serum Level of Vitamin D.

a Dependent Variable:	**B**	**95% CI for B**		**Beta***	**Sig.**
Level (ng/mL)		LB	UB		
(Constant)	13.598	2.817	24.38		0.014
Group: Control =1, Cirrhosis -C=2, Cirrhosis -NC=3)	0.173	-2.055	2.4	0.017	0.878
Severity of CLD Control =0, Child A=1, Child B=2, Child C=3	0.638	-1.379	2.656	0.072	0.532
Age: <30y=1, 30-60y=2, >60y=3	1.066	-2.01	4.142	0.105	0.494
Sex: Female=1, Male=2	2.822	-2.266	7.91	0.165	0.275

B, Unstandardized Coefficients, CI, Confidence Interval, LB, lower bound, UB, upper bound, Beta, Standardized Coefficients, Cirrhosis C =Cirrhosis -cholestatic, Cirrhosis-NC,= Cirrhosis-non-cholestatic.

*status of liver disease explains 1.7% of variability in the serum Vitamin D level, severity of liver disease explains 7.2%, while age and sex of the patient explain 10.5% and 16.5% of variability in serum level of vitamin D.

7. Discussion

In patients with CLD, the prevalence of VD deficits is much higher and practically universal. Up to 93% of patients with chronic liver disease have insufficient vitamin D levels, and almost one-third of these show severe deficiency [1]. In the United States, between 25% and 50% of the adult population has VD deficiency. In our study we found no association between level of VD and severity of liver disease (Child-Pugh class). Also, we found no association between level of VD and etiology of CLD. However, Putz-Bankuti et al showed that VD deficiency is highly prevalent in a cohort of 75 consecutive

advanced chronic liver disease patients and that low 25(OH) D levels are associated with liver dysfunction as assessed by Child-Pugh score [14]. On the other hand , Kumar et al analyzed the correlation between VD deficiency and hepatic encephalopathy versus the control group. They conducted a cross-sectional study in a cohort of 100 subjects of North Indian population, which demonstrated that the mean level of 25(OH) D was significantly lower in subjects of hepatic encephalopathy [15]. As reported in previous studies, we believe that the observed deficiency in VD may be related to several causes: an impaired hepatic hydroxylation of VD, dietary insufficiency, malabsorption, reduced hepatic production of VD binding protein, and an impaired cutaneous production due to either reduced exposure to sunlight or jaundice [16]. Mikkel et. al found that VD deficiency in cirrhosis relates to liver dysfunction (Child-Pugh class) rather than the etiology of chronic liver disease [4]. The relationship between VD and AIH has been discussed. Vitamin D may have a beneficial role in AIH [17]. Genetic studies have provided the opportunity to determine what proteins link VD to AIH pathology. VD also exerts its effect on AIH through non-genomic mechanisms. Calcitriol is useful in treating AIH, because it is an active form of a VD3 metabolite, and its receptors are present in the sinusoidal endothelial cells, Kupffer cells, and stellate cells of normal livers, and the biliary cell line.[17]. VD deficiency is common among patients with chronic hepatitis B (CHB) and is associated with adverse clinical outcomes. [18]. As in case of chronic hepatitis C (CHC), VD levels are lower in patients with nonalcoholic fatty liver disease (NAFLD) compared with controls. [1]. AIH patients have low VD levels compared with control group [16]. Previous study showed that plasma 25(OH)D was significantly lower in the patients with primary biliary cirrhosis (PBC) not receiving supplementary vitamin D compared with the controls ($p < 0.05$).[15] In the patients with extra hepatic obstructive jaundice and those with primary biliary cirrhosis (PBC) receiving supplementary VD, the plasma 250HD levels were similar to those of controls. [10]. Both cholestatic and non-cholestatic liver disease are associated with suboptimal vitamin D stores. Cholestasis reduces the intestinal availability of bile salts which are needed for the absorption of fat-soluble vitamins such as VD. Among 6 subjects (mean age 12.1 years) with cholestasis since infancy, most displayed a significantly blunted absorption response to enteral vitamin D2 as compared to healthy children, and baseline serum 25-OHD values were undetectable in five out of the six subjects [18].

Non-cholestatic diseases may also result in abnormalities of VD physiology, with the burden on patients with cirrhosis. Impaired conversion of VD to the 25 hydroxylated form in the liver is the major mechanism for the resulting VD insufficiency, since photo conversion in the skin is normal in patients with liver disease [17] . Lean Fisher and Alexander Fisher concluded that VD inadequacy is very common in non-cholestatic chronic liver disease patients and correlates with the severity of the disease. [21]. In 100 adult subjects (1/3 women; mean age 49 years) with non-cholestatic chronic liver disease, Fisher L, and Fisher et al. reported serum levels of 25-OHD <50nmol/L (20ng/mL) in 86% of the cirrhotic versus 49% of the non-cirrhotic patients ($p=0.001$), and this level correlated inversely with the international normalized ratio (INR), suggesting that VD status may be determined in part by chronic liver disease severity [22]. Metabolic bone diseases such as osteomalacia and osteopenia is relatively common in patients with liver disease, particularly cholestatic liver diseases. Potential mechanisms for this include inadequate calcium intake, and suboptimal VD status. Other non-vitamin D related factors may be important, such as hypogonadism [23] , vitamin K deficiency [24], alcohol intake in adults, and medications (25]. Our study has several limitations: First, it is a retrospective study with all inherent limitations to this type of study. Second, the small sample size, from a single institution, with its effect on the power of the study. Third, the study evaluated only four factors that could affect VD level; however, potential other factors were not evaluated in this study. Additionally, while most patients refused liver biopsy, using a transient elastography as a validated non-invasive assessment method for diagnosing chronic liver disease would be appropriate. However, this was not performed in our cohort. Despite these limitations, this study sheds some lights on the association between serum VD level, and chronic liver diseases in Yemen. It also shows that patient's sex, and age are additive factors that affects serum VD.

8. Conclusion:

We found no significant association between VD deficiency and etiology or pattern (cholestatic or non-cholestatic) of liver cirrhosis , and also with degree of hepatic dysfunction (Child-Pugh score).

9. Recommendations:

Further multi-institutional research is needed to study other potential factors that contribute to VD deficiency in patients with liver cirrhosis.

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