Comparison of B Type Natriuretic Peptide and Echocardiographic Findings among Patients with Various Stages of Liver Diseases

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Background and study aim: Cirrhotic cardiomyopathy of cirrhotic patients without heart diseases is a chronic cardiac disorder with impaired cardiac contractility, responding to stress as well as altered diastolic relaxation. More studies are required to address unanswered questions, including consensus definition, particular diagnostic tests, exact prevalence of such syndrome in addition to proper management approaches. Herein, we aimed at determining prevalence regarding cirrhotic cardiomyopathy in our patients and improving early diagnosis of this syndrome.

Patients and methods: 72 chronic liver disease (CLD) patients were recruited from gastroenterology department of Suez Canal University Hospital, Ismailia, Egypt. The patients were then divided into three main groups according to Child-Pugh criteria, and each group included 24 patients. All patients underwent a medical history assessment and clinical examination, laboratory investigations involving BNP levels, ECG in addition to echocardiography .

Results: QTc interval prolongation was present in 56% of our decompensated cirrhotic patients. Diastolic dysfunction exhibiting different grades (grade I- II) was found in most cirrhotic patients (82%) in this study, while LT atrial dilatation with different grades (mild to severe) was found in 69% of patients. Increased Child-Pugh class was significantly associated (p-value <0.05) with cirrhotic patients holding ECG abnormalities, diastolic dysfunction, in addition to increased BNP levels and left atrial diameter.

Conclusion: Herein, we demonstrated a statistically significant correlation in patients with cirrhosis between cardiac dysfunction and cirrhosis severity. BNP may be an early marker to identify cirrhotic cardiomyopathy's latent entity.

INTRODUCTION

In the past, liver cirrhosis caused cardiovascular abnormalities were believed to be a result of alcohol in the blood rather than a consequence of cirrhosis, even though cirrhotic patients typically present with hyper-dynamic circulation, resting tachycardia, bounding pulse, warm peripheries, and wide pulse pressure **[1,2]**. During the late 1980s, increasing interest in investigating cirrhosis associated cardiovascular complications was found due to increased cardiac-related mortalities (heart failure) following liver transplantation **[2]**, trans-jugular intrahepatic portosystemic stent shunt (TIPS) insertion **[3]**, and surgical portocaval shunts **[4]**. Past evidence suggests that, regardless of the cause, cirrhosis affords significant cardiovascular complications. Similar cardiac manifestations, including weakened myocardium contractility responding to stress and electrophysiological and diastolic dysfunction, were demonstrated in human as well as animal models of non-alcoholic cirrhosis **[5]**.

Liver cirrhosis associated cardiovascular abnormalities are commonly known as "cirrhotic cardiomyopathy," and until now, no method of diagnosis exists for such a condition **[6]**. Møller et al. found that cardiac markers (for stress and volume overload), including

Troponin-I, atrial natriuretic peptide (ANP), and B type natriuretic peptide (BNP), were elevated in cirrhotic patients, which may be explained by the hyperactivity of the renin-angiotensin-aldosterone system resulting in indirect diastolic dysfunction **[6]**. There is limited information regarding the exact definition, prevalence, diagnosis, and management of this syndrome, which requires more robust research **[7]**. Our study aims to determine prevalence of cirrhotic cardiomyopathy among Egyptian chronic liver disease patients as well as to identify the best methods for early diagnosis.

PATIENTS AND METHODS

This cross-sectional research involved 72 chronic liver disease (CLD) patients recruited from the gastroenterology department of Suez Canal University Hospital Ismailia, Egypt. Typically, the included patients were then divided into three groups of 24 according to the Child-Pugh criteria. Diagnosing cirrhosis was determined by means of clinical, laboratory, in addition to ultrasonography findings. Patients were excluded if they had a preexisting condition that affects cardiac function, such as critically ill patients, cardiovascular disease history, arrhythmias, diabetes mellitus, severe anaemia (Hb <7 gm/dL), renal failure (serum creatinine >1.5 mg/dL), alcohol consumption, and hypertension. Written informed consent was provided by all included patients agreeing to participate in this research.

The Hospital's independent Ethics committee evaluated and accepted both the protocol and the informed consent.

A full workup was done for all patients, which included a detailed medical history, clinical examination, laboratory investigation (complete blood count, liver function tests, serum electrolytes, blood glucose, serum creatinine, and BNP), abdominal ultrasound, ECG and echocardiography. Prior to echocardiogram, all subjects were subjected to 12-lead surface EGG in supine position.

All patients underwent a cardiac examination at the Suez Canal University Hospital Department of Cardiology. Cardiac assessment included transthoracic echocardiography performed with the patients at rest, as well as a Doppler echocardiography. Transthoracic Echo was performed using the machine model vivid 7 from the general electric health care company, with TDI mode and a 2.5 MHz phased array probe. One of the examiners was blinded to the patient's characteristics.

Statistical Analysis:

After collecting data, they were subjected to organization, followed by statistical analysis utilizing SPSS software statistical package version 12. Regarding quantitative groups, univariate parametric, as well as non-parametric analysis of variance, were utilized. Besides, T-test, as well as ANOVA tests, were utilized in order to compare the means of two groups. Pearson Product Correlation analysis was utilized for determining relationships between cardiac parameters as well as natriuretic peptide levels. Sensitivity and specificity were done by receiver operator characteristic (ROC). P values <0.05 were a measure of statistical significance.

RESULTS

The present study contains patients holding 54.65±9.34 years as mean age, exhibiting a range of 27-76 years. Patients were predominantly males (n=46, 63.89%). About 75% of patients reside in urban areas, while 25% of patients reside in rural areas. Hepatitis C was the most frequent reason toward liver disease, found in 75% of patients (Table 1). BNP level, prolonged QT, diastolic dysfunction, and LT atrial dilatation were increased in Child B and C patients in comparison to Child A patients, Table 2.

Electrophysiological abnormalities:

A longer QTc interval was documented in 56% of our decompensated patients and had a significant strong positive correlation with advanced Child class ($r = 0.6$, $p < 0.0001$). We found that diagnostic accuracy of QTc duration for discrimination between compensated patients (Child A) and decompensated patients (child B + C) revealed an AUC of 0.81 (95% confidence interval [CI], 0.707 – 0.897), with 91.6% sensitivity (95% CI, 80.0 – 97.7), and a specificity of 58.3% (95% CI, 36.6 – 77.9), Figure 1.

Diastolic function:

Diastolic function was diagnosed by conventional echocardiography and tissue Doppler imaging. Measurement of all relevant parameters included left atrial volume

measurements, peak early (E) and atrial (A) velocities of mitral inflow, A wave duration, septal mitral annular e' velocities was used.

Normal diastolic function E/A 0.8-1.5, E : e'< 9

Grade 1 diastolic dysfunction E/A <0.8, E: e' <9

Grade 2 diastolic dysfunction E/A 0.8-1.5, E: e' 9-12

Grade 3 diastolic dysfunction E/A >2 , E: e' >12 **[8]**.

Diastolic dysfunction exhibiting different grades (grade I- II) was seen in most cirrhotic patients (82%), with significant difference among patients in different Child groups (p <0.008), and was correlated with cirrhosis severity, Table 2.

Systolic function:

In all cirrhotic patients, a normal or increased systolic function (at rest) was observed. We found statistically significant differences in ejection fraction between Child A and Child B group patients (p-value = 0.028), Table 2.

Left atrium dilatation:

Left atrial dilatation with different grades (mild to severe) existed in 69% of our cirrhotic patients, with significant differences among patients in different Child groups and correlated with cirrhosis severity, Table 2.

In this study, we demonstrated that BNP represents a valid marker toward diastolic dysfunction in cirrhotic patients (p<0.002, 95% CI, 0.63–0.84) having 66.1% sensitivity as well as 84.6% specificity, at 78 pg./ml cutoff value.

The diagnostic accuracy of circulating BNP for discrimination of between compensated (Child A) and decompensated liver cirrhosis (Child B + C) revealed an AUC of 0.78 (95% confidence interval [CI], 0.671 - 0.872), with 79.1% sensitivity (95% CI, 65.0 - 89.5), and a specificity of 83.3% (95% CI, 62.6 - 95.3), Figure 2.

Table (1): Demographic and clinical characteristics of all cirrhotic patients.

Variable	Frequency (%)
Age (year)	
Median (range) – yr.	55 (27-76)
Mean±SD – yr.	54.65±9.34
≤50 yr. –no. (%)	24 (33.3%)
>50 yr. –no. (%)	48 (66.7%)
Gender	
Male	46 (63.89%)
Female	26 (36.11%)
Male-female ratio	1.7:1
Residence	
Rural	54 (75.00%)
Urban	18 (25.00%)
Etiology of Liver disease	
HCV	54 (75.00%)
HBV	3 (4.17%)
Bilharzias	11 (15.28%)
Others (! mixed)	4 (5.56%)

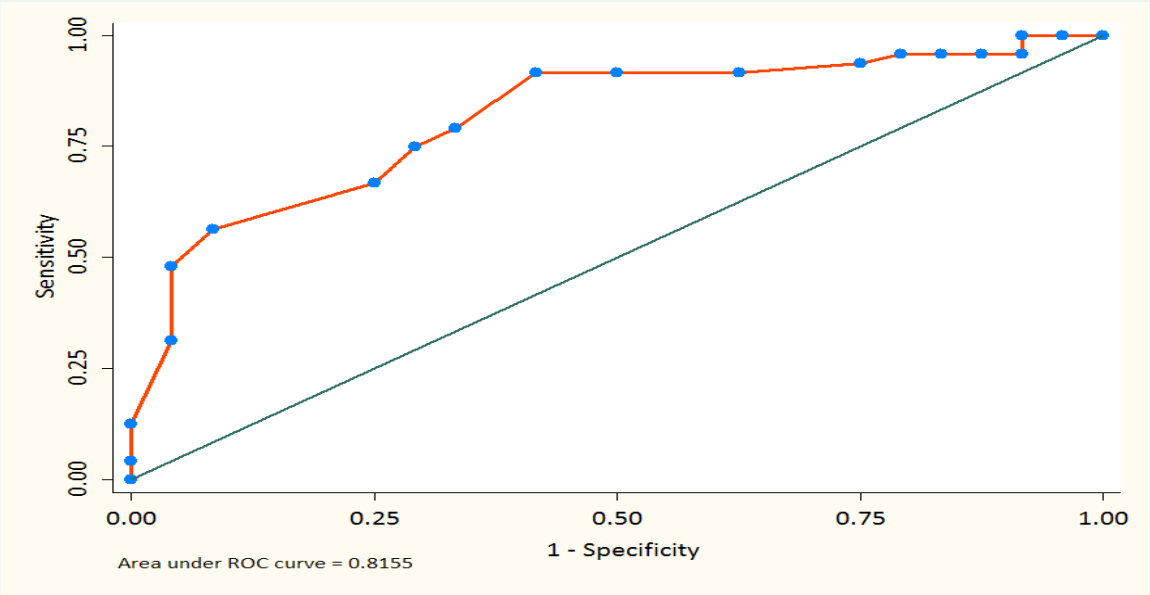
Table (2): Parameters of cardiac dysfunction of the cirrhotic patients according to Child class.

Variable	Child Classification			*p-value* [a]	*p-value* [b]	*p-value* [c]
	Class A (*n*=24)	**Class B** (*n*=24)	**Class C** (*n*=24)			
	No. (%)	No. (%)	No. (%)			
BNP level (cut off =)						
Normal	16 (66.7)	6 (25.0)	4 (16.7)	**0.004**	**<0.0001**	0.47
Increased	8 (33.3)	18 (75.0)	20 (83.3)			
Median (Range) – pg/ml	49.50 (18-110)	92.50 (10-110)	94.00 (42-250)	**0.003** ‡	**<0.0001** ‡	0.74 ‡
Mean ±S D – pg/ml	54.79±25.14	82.79±29.32	94.46±38.91			
QTc (cut off =)						
Normal	23 (95.8)	12 (50.0)	9 (37.5)	**<0.0001**	**<0.0001**	0.38
Prolonged	1 (4.2)	12 (50.0)	15 (62.5)			
Median (Range) – sec	0.385 (0.3-0.5)	0.425 (0.3-0.5)	0.460 (0.4-0.5)	**0.005** ‡	**<0.0001** ‡	**0.004** ‡
Mean±SD – sec	0.384±0.045	0.420±.046	0.446±0.023			
Ejection fraction (%)						
Median (Range)	65.5 (57-85)	73.5 (60-83)	70.0 (61-88)	**0.028** ‡	0.13 ‡	0.27 ‡
Mean±SD	68.0±7.15	72.50±7.36	70.71±6.84			
Diastolic Dysfunction						
Normal	9 (37.5%)	3 (12.5%)	1 (4.2%)	**0.046**	**0.004**	0.29 ●
Grade I-II	15 (62.5%)	21 (87.5)	23 (95.8%)			
LT atrium Diameter						
Normal	14 (58.3%)	4 (16.7%)	4 (16.7%)	**0.001** ●	**<0.0001**	0.95 ●
Mild	10 (41.7%)	11 (45.8%)	10 (41.7%)			
Moderate to severe	0 (0.0%)	9 (37.5%)	10 (41.7%)			

[a;]p-value for Child A vs. Child B
[b;]p-value for Child A vs. Child C
[c;] p-value for Child B vs. Child C
● corrected for community
‡ based on Mann-Whitnry U test

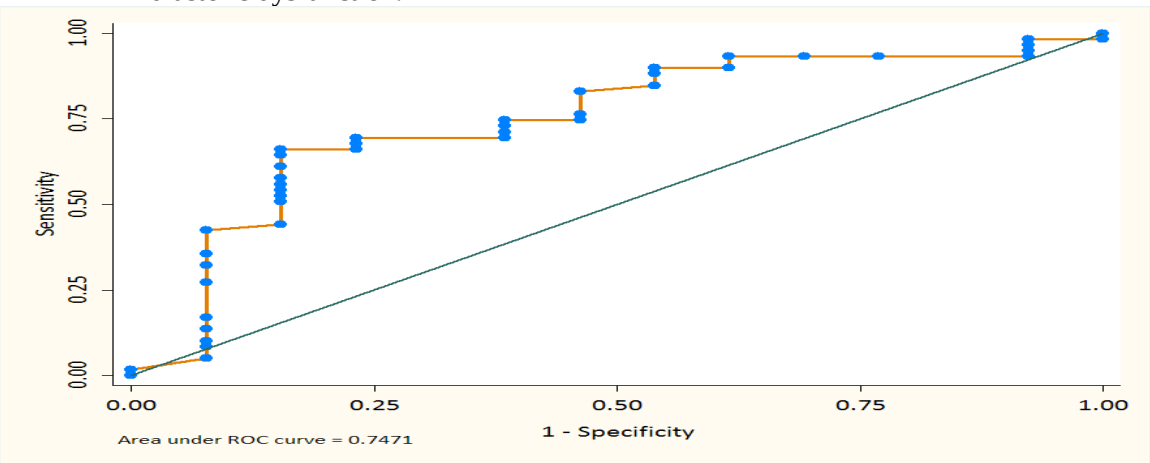
Class A : 5-6 point .
Class B : 7-9 .
Class C : 10-15 .
LA Vol/BSA
Normal 16-34 ml/m2
Mildly dilated 35-41ml/m^2
Moderately dilated 42-48ml/m^2
Severely dilated >48ml/m^2 [9].

Figure (1): ROC curve of QTc duration for discrimination between compensated (Child A) and decompensated liver cirrhosis (Child B + C).



	QTc
AUC	0.816
Standard error	0.0521
95% confidence interval	0.707 to 0.897
***p*-value**	**<0.0001**
Cut off value	>0.39
Sensitivity	91.67 (80.0 - 97.7)
Specificity	58.33 (36.6 - 77.9)

Figure (2): ROC curve of circulating BNP for discrimination between absence and presence of diastolic dysfunction.



	BNP
AUC	0.747
Standard error	0.0806
95% confidence interval	0.631 to 0.842
p-value	**0.0022***
Cut off value	>78
Sensitivity	66.10 (52.6 - 77.9)
Specificity	84.62 (54.6 - 98.1)

DISCUSSION

Patients having stable liver disease typically possess minor myocardial dysfunction that may not be obvious during a routine examination. However, a cardiac manifestation of liver cirrhosis may present either as the disease progresses or in the presence of physiological/ pharmacological stress **[7]**. During the last years, several studies have concentrated their attention on the existence of specific cardiac abnormalities in cirrhotic patients.

In this cross-sectional study, we evaluated cardiac functions of 72 cirrhotic patients using echocardiography and ECG in addition to serum BNP level.

In our study, liver cirrhosis was more prevalent in males holding 54.6 ± 9.3 years as mean age. This is comparable to studies done in other countries. Similarly, Kumar et al. reported that 78% of 90 cirrhotic patients were males having 46.2 ± 10.8 years as mean age **[10]**. Bhatti et al. stated that 58% of 166 cirrhosis patients were male, having a mean age of 57.05 ± 12.03 years **[11]**.

The Egyptian demographic health survey demonstrated an increased viremia prevalence with age and gender (particularly males) **[12]**. In Egypt, hepatitis C virus (HCV) is mostly prevalent among lower socioeconomic groups **[13]**. In our study, the most prevalent CLD etiology was hepatitis C infection, which was expected since hepatitis C is hyperendemic in Egypt. The majority of our patients resided in rural areas (75%), which may be associated with the higher prevalence of hepatitis C and bilharziasis in these areas. It should be noted that even though cirrhotic cardiomyopathy is clinically unremarkable at rest, during stressful conditions such as exercise, infections, specific medications, hemorrhage, as well as any intervention, such as the insertion of TIPS, and liver transplantation, which may result in the conversion of latent cirrhotic cardiomyopathy into heart failure **[14]**.

There is a need for more accurate and alternative screening tests in order to determine the severity of cirrhotic cardiomyopathy, which may prove useful in managing liver cirrhosis patients. Considering the gradual course of cirrhotic cardiomyopathy, there may be a benefit to using new laboratory markers, ECG, in addition to echocardiography, mainly in combination **[15]**.

One of the electrophysiological abnormalities found in cirrhotic patients is prolonged repolarization, which manifests as a prolonged QTc interval. This finding was demonstrated in our cirrhotic patients. A strong positive correlation existed between QTc and advanced Child class ($r = 0.6$, $p < 0.0001$), degree of diastolic dysfunction ($r = 0.373$, $p = 0.001$), and LT atrium diameter ($r = 0.312$, $p < 0.008$).

We found that diagnostic accuracy of QTc duration for discrimination between compensated (Child A) and decompensated liver cirrhosis (child B + C) revealed an AUC of 0.81 (95% confidence interval [CI], 0.707 – 0.897), with 91.6% sensitivity (95% CI, 80.0 - 97.7), and a specificity of 58.3% (95% CI, 36.6 – 77.9).

Our results are consistent with previously published studies, which found that QTc prolongation is prevalent among cirrhotic patients and directly correlated with liver dysfunction severity (Child-Pugh score), ascites, in addition to portal hypertension .

Prolonged QT interval and defective electromechanical coupling found in cirrhotic patients was linked to a volume overload **[16]**, as well as a combination of ion-channel dysfunction, autonomic dysfunction, plasma membrane abnormalities, in addition to receptor-related pathway defects **[17]**.

Diastolic dysfunction is defined as failure of left ventricular relaxation, which impedes blood flow through ventricle, thereby an increase in left ventricular end-diastolic pressure **[18]**.

Using conventional Doppler echo, we found that different grades (grade I- II) of diastolic dysfunction existed in most cirrhotic patients (82%). A significant difference existed among patients in different child groups ($p > 0.008$), correlated with cirrhosis severity.

Our study demonstrated that increased Lt atrium diameter (OR, 7.96; 95% CI, 2.11–30.07, $p = 0.002$), advanced Child class (OR, 13.80; 95% CI, 1.58–120.38, $p = 0.0017$), increased BNP level (OR, 5.56; 95% CI, 1.51–20.51, $p = 0.001$), and prolonged QTc duration (OR, 10.12; 95% CI, 1.24–82.96, $p = 0.03$) were significant predictors for diastolic dysfunction.

Møller and colleagues found that many patients with cirrhosis exhibited various diastolic dysfunction degrees. Diastolic dysfunction in cirrhosis patients may be explained by increased myocardial wall stiffness resulted from

myocardial hypertrophy, fibrosis, as well as subendothelial edema, which further results in elevated left heart (atrium and ventricle) filling pressures **[7]**. LV hypertrophy results in impaired diastolic relaxation, leading to lowered compliance and higher diastolic pressures **[19]**.

Another research assessed HCV cardiovascular impact on Egyptian patients and noticed a significant increase in diastolic dysfunction among patients **[20]**. This goes in accordance with our findings.

There is limited evidence that supports pathogenesis of cirrhosis induced diastolic dysfunction. It is suggested that the cardiac impairment may be as a result of collagen configuration alteration, sodium retention in addition to activation of renin aldosterone system **[21]**.

Diastolic dysfunction may progress to systolic dysfunction **[22]**. At rest, systolic function is either normal or increased in most cirrhotic patients, along with hyperdynamic circulation highlighted by elevated cardiac output as well as tachycardia. Stressors (pharmacological/ physiological) may exacerbate underlying systolic dysfunction in this patient group **[23]**.

Our study found statistically significant differences in Ejection fraction between Child A and Child B group patients (p-value = 0.028).

Pagourelias et al. found that EF was significantly higher in cirrhosis patients (77 men) in comparison to the controls (20 healthy), which was accounted for by increased blood volume and cardiac adaptation **[24]**.

Ziada and coworkers demonstrated that LVEF% has no difference among cirrhotic groups as well as controls **[25]**. Moreover, Eldeeb and coworkers stated that mean left ventricular systolic function parameters exhibited within normal range among the three Child groups' patients **[26]**. Systolic function is maintained in patients with cirrhosis with normal or even the presence of elevated ejection fraction at rest **[14]**, as reported by Baik et al.

Lt atrial dilatation was seen in most of our studied patients, with significant difference among patients in different Child groups (p-value = 0.001, <0.0001) between Child A and B, Child B and C, respectively. Dilation was linked to cirrhosis severity. These findings were in line with studies conducted by Wong et al. and Pozzi et al. **[23, 27]**.

Cardiac natriuretic peptides are considered markers of volume overload and cardiac dysfunction. Several researches have demonstrated that cirrhotic patients have elevated plasma concentrations of BNP as well as NT-pro-BNP, suggesting their use as markers of early cardiac dysfunction in cirrhotic patients **[28]**.

Regarding levels of BNP among the three study groups, a statistically significant difference was indicated and higher in Child C group patients (p<0.001). BNP levels augmented with cirrhosis severity.

In this study, BNP was found to be a valid marker toward diastolic dysfunction in patients with cirrhosis (p<0.002, 95% CI 0.63–0.84), exhibiting 66.1% sensitivity and 84.6% specificity, at 78 pg./ml cutoff value.

The diagnostic accuracy of circulating BNP for discrimination of between compensated (Child A) and decompensated liver cirrhosis (Child B + C) revealed an AUC of 0.78 (95% confidence interval [CI], 0.671 - 0.872), with 79.1% sensitivity (95% CI, 65.0 - 89.5), a specificity of 83.3% (95% CI, 62.6 - 95.3).

Our study demonstrated that HCV-related disease (OR = 0.24; 95%CI, 0.08–0.75, p = 0.013), diastolic dysfunction (OR, 5.56; 95% CI, 1.51–20.51, p = 0.01), increased LT atrium diameter (OR, 23.62; 95% CI, 6.30–88.54, p = 0.0001), and advanced child class (OR, 10.0; 95% CI, 2.54–39.29, p = 0.0009) are significant predictors for increased BNP level. Another study done in Egypt showed that BNP level was significantly higher in patients with cirrhosis than controls, but liver disease state, whether compensated or not, had no effect on its level **[29]**. Other researchers reported association between the level of BNP and pro-BNP and liver disease severity **[30]**.

In multivariate analysis, adjusted for diastolic dysfunction, liver disease etiology, and Child C, risk of increased BNP was 18 times higher in patients Grade I-II LT atrium diameter than patients with normal diameter (OR, 18.17; 95% CI, (3.93–84.05, p = 0.0002), table (3).

Our findings are consistent with those of preceding researches, indicating that BNP level was significantly elevated with liver cirrhosis degree, liver failure, in addition to portal hypertension **[30]**.

CONCLUSION

Our findings suggest that cardiac dysfunction is directly proportional to cirrhosis severity and linked to electrophysiological, echo-cardiographic, in addition to laboratory changes. Diastolic dysfunction, as well as Lt atrial dilatation, are mostly prevalent cardiac abnormalities, worsening with cirrhosis development. BNP is a highly specific and sensitive marker, and may be utilized toward the early detection of cardiac dysfunction in patients with cirrhosis.

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Conflict of interest: none declared.

Ethical considerations :

-confidentiality was assured.

-every individual was asked for a permission to do interview.

-examination steps of interview and examination was explained to the patient.

-patients faced no physical or psychological risks

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