Fragmented QRS is associated with cirrhotic cardiomyopathy in patients with decompensated cirrhosis

Mehmet Demir[1], Mustafa Kurt[2], Adnan Burak Akçay[2]

(1) Department of Gastroenterology, (2) Department of Cardiology, Mustafa Kemal University Faculty of Medicine, Hatay, Turkey.

Abstract

Background/Aim : **It has been reported that the fragmented QRS (fQRS) is related to left ventricular systolic dysfunction and diastolic dysfunction.The aim of this study was to determine the frequency of fragmented QRS (fQRS) in patients with decompensated cirrhosis and to evaluate the relationship between the presence of fQRS and systolic and diastolic dysfunction.**

Methods : **The study included consecutive 189 patients with decompensated cirrhosis. fQRS pattern was described as presence of RSR' manifested as existence of additional R wave and notching in either R or S waves in ECG recordings. Conventional echocardiography and tissue doppler echocardiography were performed in all patients.**

Results : **The prevalence of fQRS was 31% (59/189) in patients with decompensated cirrhosis. The patients with fQRS had worse diastolic and systolic functions in comparison to the patients without fQRS. In addition, multivariate analysis revealed that the presence of an fQRS, Na levels < 125 mEq/L, the Child-Pugh score and the MELD score were independent predictive factors for mortality (respectively, $p < 0.001$, $p < 0.001$, $p < 0.001$ and $p < 0.001$).**

Conclusions : **In conclusion,this study showed a relationship between the presence of an fQRS and cardiac dysfunction. In addition, the fQRS appeared to act as an independent predictor of mortality in patients with decompensated cirrhosis. These data suggest that the fQRS may represent a novel noninvasive marker for cardiac involvement and for predicting mortality in patients with decompensated cirrhosis.** (Acta gastroenterol. belg., **2016**, 79, **191-196**).

Key words : cirrhotic cardiomyopathy, fragmented QRS, tissue Doppler imaging.

Introduction

Cirrhotic cardiomyopathy (CCM) is associated with increased morbidity and mortality in patients with advanced cirrhosis (1). CCM is defined by an impaired contractile responsiveness to stress, as well as by a resting ejection fraction < 55% (systolic dysfunction), diastolic dysfunction and electrophysiological abnormalities in the absence of known cardiac disease (2). Hyperdynamic circulation, a well-known clinical state in patients with advanced cirrhosis, is characterised by raised cardiac output (CO) and heart rate (HR) and decreased systemic vascular resistance and blood arterial pressure (1). This type of circulation may lead to the development of cardiovascular complications such as cirrhotic cardiomyopathy (1). The literature on the prevalence of CCM is limited because diagnosis of CCM is difficult and its clinical presentation is silent. Recent studies have shown that approximately half the patients undergoing liver transplantation have cardiac problems and about 7-21% of patients die from heart failure (3,4). These data suggest that CCM may, in fact, be very prevalent.

The pathogenesis of CCM is not clear, but some studies have shown pathological findings such as cardiomyocyte hypertrophy, patchy fibrosis, altered pigmentation, myofibril vacuolisation and subendothelial oedema in the myocardium (5-7). One interesting finding is that a fragmented QRS (fQRS) observed on a 12-lead routine ECG can be a marker of myocardial fibrosis (8). An fQRS associated with left ventricular systolic and diastolic dysfunctions has also been associated with other diseases, such as metabolic syndrome, chronic kidney disease and obstructive sleep apnoea (9-11). These findings suggest a relationship between the fQRS and cirrhotic cardiomyopathy, but no data are presently available in the literature to support a relationship between the fQRS and cardiovascular dysfunction in patients with liver cirrhosis. The aim of this study was to determine the frequency of the fQRS in patients with decompensated cirrhosis and to evaluate the relationship between the presence of an fQRS and systolic and diastolic dysfunction.

Patients and Methods

Study Design and Patients

The study included consecutive 228 patients with decompensated cirrhosis admitted to the Mustafa Kemal University department of gastroenterology between January 2012 and January 2015. The diagnosis of liver cirrhosis was made by liver biopsy findings or, if biopsy was unavailable, the combination of clinical, biochemical, and radiological findings of hepatic failure and portal hypertension. In addition, the FIB-4 score was calculated for all patients ; patients with FIB-4 scores> 3.25 were included in the study (12).

Decompensated cirrhosis was defined as the presence of ascites, a total bilirubin level > 2 mg/dl, variceal bleeding (gastric or oesophageal) and encephalopathy (West Haven Criteria > 2) (13). The MELD scores of all

Correspondence to : Mehmet Demir, M.D., Department of Gastroenterology, Mustafa Kemal University Faculty of Medicine, Hatay, Center 31000, Turkey. E-mail : drmehmetdemir@yahoo.com

Submission date : 15/09/2015
Acceptance date : 11/12/2015

cirrhotic patients were calculated as suggested by the United Network for Organ Sharing (UNOS) (www http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/meld-model-unos-modification).

Patients with organic valvular heart disease, chronic atrial fibrillation, typical bundle branch block pattern (QRS ≥ 120 ms), incomplete right bundle branch block, pulmonary artery systolic pressure > 50 mmHg, renal failure, cardiac medications usage, pregnancy, coronary artery disease, chronic obstructive pulmonary disease, TIPS and hepatoma or other malignancy were excluded from this study.

Measurement of the fragmented QRS

A 12-lead ECG (filter range 0.15-100 Hz ; 25 mm/s, 10 mm/mV) test was performed on all patients. All the ECG results were analysed by two independent cardiologists (M.K. and A.B.A.) blinded to the patient characteristics. An fQRS was defined as different QRS morphologies with varying RSR' patterns, including the presence of an additional R wave (R'), notching in the nadir of the R or S wave, or > 1 R' (fragmentation) in 2 contiguous leads (Fig. 1).

Echocardiographic data

The study population underwent conventional echocardiography and tissue Doppler echocardiography. The patient was placed in the left lateral decubitus position and the images were obtained using a standard 2D transducer device (Vingmed System Vivid 7, GE Vingmed Ultrasound, Horten, Norway). Pulse wave Doppler from the apical four-chamber view was used to evaluate left ventricular filling and the tissue Doppler imaging sample volume was placed sequentially, from a four-chamber view, at the septal and lateral sides of the valvular ring. Measurements included the deceleration time (DT), the isovolumic relaxation time (IVRT), the E-wave and the early (E) and late (A) diastolic velocities.

Tissue Doppler imaging utilises a modified wall filter and reduced gain in order to display myocardial velocity while avoiding blood flow detection. The mean early diastolic (Em), late diastolic (Am) and systolic myocardial velocities (Sm) were recorded and the E/Em ratio was calculated. All the measurements were obtained at 50 m/s at the end of the expiration. The left ventricular ejection fraction was calculated using M-mode echocardiography.

Statistical Analyses

Data were analysed using SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc., Chicago, IL, USA). The results are expressed as mean ± standard deviation (SD). Parametric continuous variables were compared by an independent Student's t test or the Mann-Whitney U test and categorical variables were analysed by chi-squared and Fisher's exact tests. Univariate and multivariate logistic regression analysis models were used to identify independent, significant and predictive factors of death. P values below 0.05 were considered statistically significant in all analyses.

Ethics and Consent

The local ethics committee of Mustafa Kemal University approved the study and each patient provided written informed consent in accordance with the latest updated version of Helsinki Declaration.

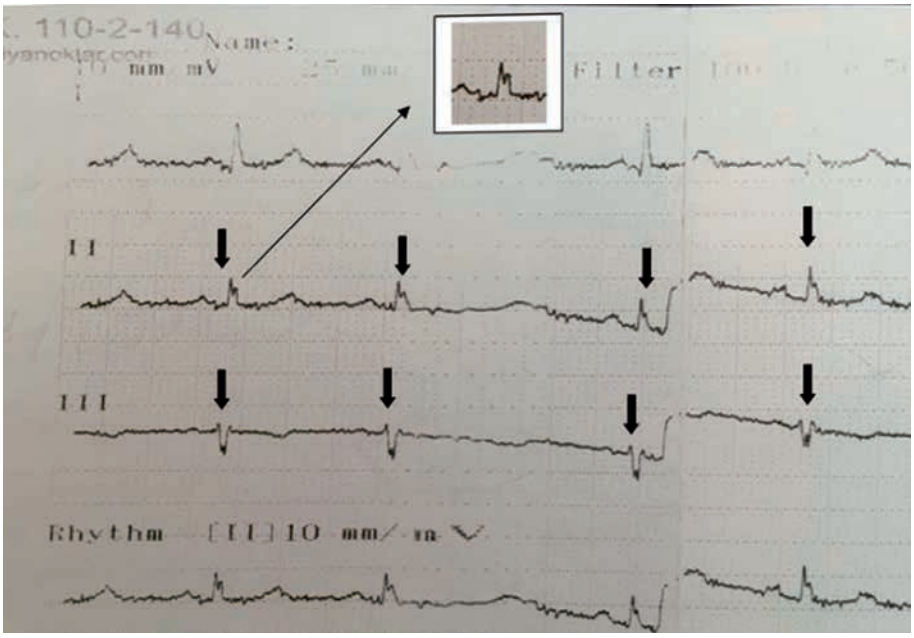

Fig. 1. — Fragmented QRS in a patient (arrows)

Table 1. — **Clinical and epidemiological characteristics of patients with decompensated cirrhosis according to fragmanted QRS status**

Variable	Patients with cirrhosis with fQRS n = 59	Patients with cirrhosis without fQRS n = 130	p
Age (year)	67.24 ± 9.12	62.89 ± 8.53	< 0.01
Male/Female (n)	28/31	62/68	NS
SBP (mm Hg)	89 ± 11	88 ± 14	NS
DBP (mm Hg)	66 ± 7	69 ± 9	NS
HR(beats/min)	91 ± 9	90 ± 12	NS
ALT (IU/L)	63 ± 11	59 ± 15	NS
Albumin (gr/dl)	2.9 ± 0.3	3.3 ± 0.5	< 0.01
Bilirubin	3.4 ± 0.7	3.5 ± 0.5	NS
INR	1.8 ± 0.4	1.7 ± 0.5	NS
Creatinine	1.2 ± 0.3	0.9 ± 0.6	NS
Na (mEq/L)	126.3 ± 3.4	129.1 ± 4.1	< 0.001
Hb	11.3 ± 2.2	11.1 ± 4.1	NS
WBC	6487 ± 2011	6504 ± 1867	NS
Platelets, mm3	149000 ± 32000	155000 ± 18500	NS
MELD score	22.7 ± 3.7	19.2 ± 4.1	< 0.001
CTP score	11.11 ± 1.6	9.9 ± 3.4	< 0.001
Mortality n (%)	24 (40.7%)	24 (18.5%)	< 0.001

SBP, systolic blood pressure ; DBP, diastolic blood pressure ; Hb, hemoglobin ; WBC, white blood cell HR, heart rate ; ALT, alanine aminotransferase ; INR, international normalized ratio ; Na, Sodium ; MELD, the model for end-stage liver disease ; CTP, Child-Turcotte-Pugh.

Results

The study included 189 patients with decompensated cirrhosis (99 female, 90 male) aged 45 to 82 years (63.8 ± 7.3 years, mean ± SD) with different etiologies (viral etiology in 101 patients, alcoholic in 39 patients, cryptogenic in 28 patients and others in 21 patients) who were admitted to the Mustafa Kemal University department of gastroenterology. Liver cirrhosis was diagnosed only in 8 patients by liver biopsy. Of the patients with decompensated cirrhosis, 61 (32.3%) were Child-Turcotte-Pugh (CTP) class B and 128 (67.7%) were CTP class C. No patient was CTP class A. During a mean follow-up of 21 ± 5 months, 25.4% (48/189) of the patients died.

The prevalence of fQRS was 31% (59/189) in patients with decompensated cirrhosis. Of the patients with an fQRS, 28 (47.5%) were male and 31 (52.5%) were female, with a mean age of 67.24 ± 9.12 years. Of the patients without an fQRS, 62 (47.7%) were male and 85 (51.9%) were female, with a mean age of 62.89 ± 8.53 years. Gender was not significantly associated with the fQRS status ($p > 0.05$), but patients with an fQRS were older ($p < 0.05$). Systolic, diastolic and mean blood pressures, heart rate, alanine aminotransferase (ALT), bilirubin, international normalised ratio (INR), creatinine, haemoglobin and white blood cell(WBC) counts did not differ significantly between the patients with an fQRS and patients without an fQRS. Serum sodium (Na) (126.3 ± 3.4 versus 129.1 ± 4.1 $p < 0.001$) and albumin (2.9 ± 0.3 versus 3.3 ± 0.5 $p < 0.001$) levels were significantly lower and MELD scores (22.7 ± 3.7 versus 19.2 ± 4.1 $p < 0.001$) and CTP scores (11.11 ± 1.6 versus 9.9 ± 3.4 $p < 0.001$) were significantly higher in patients with an fQRS than in those without an fQRS. All-cause mortality was higher in patients with an fQRS than without an fQRS (40.7% versus 18.5% $p < 0.001$). The demographic and clinical data of the patients with and without an fQRS are presented in Table 1.

Univariate analysis showed that age > 60 years old ($p = 0.028$), the presence of an fQRS ($p = 0.011$), creatine levels > 2 mg/dl ($p < 0.023$), albumin levels < 2.5 mg/dl ($p = 0.046$), total bilirubin levels > 4 mg/dl ($p = 0.044$), Na levels < 125 mEq/L ($p < 0.001$), a Child-Pugh score > 10 ($p < 0.001$) and a MELD score > 20 ($p < 0.001$) were risk factors for mortality in patients with decompensated cirrhosis. Multivariate analysis revealed that the presence of an fQRS, Na levels < 125 mEq/L, the Child-Pugh score and the MELD score were independent predictive factors for mortality (respectively, $p < 0.001$, $p < 0.001$, $p < 0.001$ and $p < 0.001$).

Of all the patients, 134 (70.9%) were using nonselective β-blockers (the NSBB group). The prevalence of an fQRS was 30.6% (41/134) and 32.7% (18/55), respectively, in the NSBB group and the non-NSBB group, and the difference between the groups was not statistically significant ($p > 0.05$).The NSBB and non-NSBB groups also showed no significant differences in left atrial diameter (LAD), left ventricular diastolic diameter (LVDD), left ventricular ejection fraction (LVEF), pulmonary artery pressure (PAB), IVRT, DT, E/A, Sm, Em, Am and E/Em. Table 2 shows the electrocardiography (ECG) and echocardiographic related characteristics of the NSBB and non-NSBB groups.

The groups with and without an fQRS showed no differences in left atrial diameter (LAD), left ventricular diastolic diameter (LVDD), left ventricular ejection fraction (LVEF), pulmonary artery pressure (PAB) and late

Table 2. — **ECG and Echocardiographic parameters of patients with decompensated cirrhosis according to NSBB use**

Conventional Doppler	NSBB group n = 134	Non-NSBB group n = 55	P
LAD (cm)	2.7 ± 0.9	2.8 ± 0.5	NS
LVDD (cm)	4.4 ± 1.8	4.4 ± 1.6	NS
LVEF (%)	58.9 ± 4.1	59.5 ± 6.3	NS
PAB (mm Hg)	18 ± 5	19 ± 4	NS
IVRT (msec)	86 ± 24	82 ± 15	NS
DT (msec)	191 ± 65	186 ± 78	NS
E/A	1.07 ± 0.37	1.26 ± 0.75	NS
Tissue Doppler			
Sm (cm/s)	11.16 ± 1.6	11.98 ± 2.3	NS
Em (cm/s)	11.4 ± 2.5	10.6 ± 4.1	NS
Am (cm/s)	7.2 ± 1.4	7.4 ± 1.1	NS
E/Em	12 ± 28	11 ± 26	NS
ECG			
fQRS	41 (30.6%)	18 (32.7%)	NS

ECG, electrocardiography ; fQRS, fragmented QRS ; LAD: left atrial diameter ; LVDD, left ventricular diastolic diameter ; LVEF, left ventricular ejection fraction ; PAB, pulmonary artery pressure ; IVRT, Isovolumetric relaxksation time ; DT, deceleration time ; E, early diastolic mitral inflow velocity ; A, late diastolic mitral inflow velocity ; Sm, peak systolic mitral annular velocity ; Em, early diastolic mitral annular velocity ; Am, late diastolic mitral annular velocity.

diastolic mitral annular velocity (Am). The patients with an fQRS had worse diastolic functions than the patients without an fQRS (IVRT, 98 ± 42 versus 73 ± 26 msec, $p < 0.01$; DT, 233 ± 75 versus 181 ± 84 msec, $p < 0.01$; E/A, 0.85 ± 0.47 versus 1.38 ± 0.79, $p < 0.01$; Em, 8.3 ± 3.6 versus 12.2 ± 3.9 cm/s, $p < 0.01$; E/Em ratio, 11 ± 08 versus 8 ± 22, $p < 0.05$). In addition, the systolic functions were worse in the patients with an fQRS than in the patients without an fQRS (Sm, 8.1 ± 1.3versus 10.9 ± 1.7 $p < 0.01$). Table 3 shows the conventional echocardiography-related and tissue Doppler echocardiography-related characteristics of the patients with and without an fQRS.

Discussion

Cirrhotic cardiomyopathy may influence the prognosis and worsen the course of cirrhosis during invasive procedures, such as insertion of a transjugular intrahepatic portosystemic shunt and liver transplantation (1). In addition, CCM is an important factor in the pathogenesis of the hepatorenal syndrome (14). A recent study showed that diastolic dysfunction in cirrhotic patients is independently associated with both death and a combined endpoint of death or liver transplantation (15). Therefore, diagnosis of CMM is very important, but this disorder is often overlooked in clinical practice because it is clinically silent unless the patients are exposed to stress (1). If clinically suspected in patients with cirrhosis, CCM can be diagnosed by physical stress (physical exercise) or pharmacological (dobutamine stress echocardiography) tests. Tissue-Doppler and speckle tracking echocardiography can detect systolic and diastolic dysfunctions when the patient is at rest (1). Nevertheless, at present, no standardised criteria are available for the diagnosis of CCM.

The diastolic dysfunction observed in patients with cirrhosis is the result of increased stiffness of the myocardial wall (1). The pathological background of the increased stiffness is most likely cardiac hypertrophy, patchy fibrosis and subendothelial oedema (5-7). Some recent studies reported that the presence of an fQRS is associated with myocardial scars and myocardial fibrosis (8). In addition, previous studies have reported the fQRS as a marker of cardiac involvement in several diseases, including sarcoidosis, familial Mediterranean fever, rheumatoid arthritis, beta thalassaemia major and systemic sclerosis (15-20). Moreover, a study has recently reported that the fQRS is significantly associated with systolic and diastolic dysfunction in patients with metabolic syndrome (10). Adar *et al*. suggested that the fQRS is an independent predictor of subclinical left ventricular dysfunction in patients with obstructive sleep apnoea (11). Another study of 39 kidney transplant patients reported that the presence of an fQRS is associated with systolic and diastolic dysfunction (9). These findings suggest a relationship between the fQRS and cardiovascular dysfunction in patients with liver cirrhosis. Indeed, in our study, the DT, IVRT and E/Em ratio were significantly higher in patients with fQRS than in patients without fQRS and E/A ratio was significantly lower in patients with an fQRS. In addition, Sm was significantly lower in patients with an fQRS than without an fQRS. In light of these results, our opinion is that the presence of fQRS can serve as a novel noninvasive marker for cardiac involvement in patients with decompensated cirrhosis.

No clear mechanism for the development of the fQRS has been established. However, the fQRS could arise from the non-homogeneous activation of the ventricles due to myocardial scars, fibrosis or ischaemia (8). The

Table 3. — **Echocardiographic parameters of patients with decompensated cirrhosis according to fragmanted QRS status**

Conventional Doppler	Patients with cirrhosis with fQRS n = 59	Patients with cirrhosis without fQRS n = 130	p
LAD (cm)	2.8 ± 0.4	2.8 ± 0.6	NS
LVDD (cm)	4.2 ± 1.7	4.1 ± 2.4	NS
LVEF (%)	58.1 ± 3.3	59.7 ± 4.2	NS
PAB (mm Hg)	19 ± 5	19 ± 4	NS
IVRT (msec)	98 ± 42	73 ± 26	< 0.01
DT (msec)	233 ± 75	181 ± 84	< 0.001
E/A	0.85 ± 0.47	1.38 ± 0.79	< 0.001
Tissue Doppler			
Sm (cm/s)	8.1 ± 1.3	10.9 ± 1.7	< 0.01
Em (cm/s)	8.3 ± 3.6	12.2 ± 3.9	< 0.01
Am (cm/s)	7.2 ± 1.9	7.3 ± 1.4	NS
E/Em	11 ± 38	8 ± 33	< 0.05

fQRS, fragmented QRS ; LAD, left atrial diameter ; LVDD, left ventricular diastolic diameter ; LVEF, left ventricular ejection fraction ; PAB, pulmonary artery pressure ; IVRT, Isovolumetric relaxksation time ; DT, deceleration time ; E, early diastolic mitral inflow velocity ; A, late diastolic mitral inflow velocity ; Sm, peak systolic mitral annular velocity ; Em, early diastolic mitral annular velocity ; Am, late diastolic mitral annular velocity.

fQRS may represent an inexpensive and easily obtainable electrocardiographic marker of myocardial fibrosis. The fQRS can also be detected in healthy individuals, with a prevalence of 9.2% reported in healthy subjects (21). In addition, a high prevalence of the fQRS has been found in some diseases, such as familial Mediterranean fever (56%), rheumatoid arthritis (37.5%) and systemic sclerosis (55%) (18-20). In the present study, the frequency of an fQRS in patients with decompensated cirrhosis was 31%. Unfortunately, this study did not include a control group for comparison.

Interestingly, the MELD and CTP scores were significantly higher in patients with decompensated cirrhosis with an fQRS than without an fQRS. In addition, albumin and Na levels were significantly reduced in patients with decompensated cirrhosis with an fQRS. High MELD scores, high CTP scores and low Na levels have well-known associations with reduced survival in patients with cirrhosis. In the present study, the fQRS served as an independent predictor of mortality in patients with decompensated cirrhosis. The fQRS therefore appears to have potential as a noninvasive marker for predicting mortality in patients with decompensated cirrhosis. Additional studies are needed in this regard.

Oral administration of non selective β-blockers (NSBB), such as propranolol, is well known to decrease cardiac output, heart rate and portal venous pressure gradient in cirrhotic patients and NSBB have been associated with beneficial effects for prophylaxis of variceal bleeding in cirrhotic patients (22). In addition, Kim YK *et al*. suggested that the use of propranolol is associated with beneficial effects on perioperative mortality in cirrhotic patients awaiting liver transplantation (23). Nevertheless, another study suggested that the use of NSBB is associated with poor survival and should be contraindicated in cirrhotic patients with refractory ascites (24). In our study, no correlation was noted between the prevalence of the fQRS and the use of NSBB ($P > 0.05$) and no effects were observed on the echocardiographic parameters due to NSBB use in patients with decompensated cirrhosis.

We believe that the results of this study are very important because they show, for the first time in the literature, that a relationship exists between the presence of an fQRS and diastolic and systolic dysfunction in patients with decompensated cirrhosis. However, the lack of a control group, the relatively small number of subjects and the absence of stress tests for systolic dysfunction are the important limitations to the present study. In addition, the absence of liver biopsies in many patients is another important limitation because patients with noncirrhotic portal hypertension were not fully excluded from the present study. Nevertheless, we regard the possibility of their inclusion as very small, because the FIB-4 scores were calculated for all patients and those patients with FIB-4 scores < 3.25 patients were excluded from this study.

In conclusion, this study showed a relationship between the presence of an fQRS and diastolic and systolic dysfunction in patients with decompensated cirrhosis. In addition, the fQRS appeared to act as an independent predictor of mortality in patients with decompensated cirrhosis. These data suggest that the fQRS may represent a novel noninvasive marker for cardiac involvement and for predicting mortality in patients with decompensated cirrhosis. Further studies will be needed to confirm these findings.

References

1. LICATA A., NOVO G., COLOMBA D., TUTTOLOMONDO A., GALIA M., CAMMA' C. Cardiac involvement in patients with cirrhosis : a focus on clinical features and diagnosis. *J. Cardiovasc. Med. (Hagerstown)*, 2015, **61** : 646-664.
2. MOLLER S., HENRIKSEN J.H. Cirrhotic cardiomyopathy. *J. Hepatol.*, 2010, **53** : 179-190.

3. ZARDI E.M., ABBATE A., ZARDI D.M., DOBRINA A., MARGIOTTA D., VANTASSELL B.W. *et al*. Cirrhotic cardiomyopathy. *J. Am. Coll. Cardiol*., 2010, **56** : 539-549.
4. MYERS R.P., LEE S.S. Cirrhotic cardiomyopathy and liver transplantation. *Liver Transpl*., 2000, **6** : 44-52.
5. LUNSETH J.H., OLMSTEAD E.G., FORKS G. *et al*. A study of heart disease in one hundred and eight hospitalized patients dying with portal cirrhosis. *AMA Arch. Intern. Med*., 1958, **102** : 405-413.
6. SCHENK E.A., COHEN J. The heart in chronic alcoholism. Clinical and pathologic findings. *Pathol. Microbiol. (Basel)*, 1970, **35** : 96-104.
7. MØLLER S., HENRIKSEN J.H. Cardiovascular dysfunction in cirrhosis. Pathophysiological evidence of a cirrhotic cardiomyopathy. *Scand. J. Gastroenterol*., 2001, **36** : 785-794.
8. DAS M.K., ZIPES D.P. Fragmented QRS : a predictor of mortality and sudden cardiac death. *Heart Rhythm*., 2009, **6** : 8-14.
9. ULUSOY S., OZKAN G., ADAR A., BEKTAŞ H., KIRIŞ A., CELIK S. Relationship between fragmented QRS complex and left ventricular systolic and diastolic function in kidney transplant patients. *Prog. Transplant*., 2014, **24** : 146-151.
10. ONER E., ERTURK M., BIRANT A., KALKAN A.K., UZUN F., AVCI Y., GÜRDOGAN M., PUSUROGLU H., YILDIRIM A. Fragmented QRS complexes are associated with left ventricular systolic and diastolic dysfunctions in patients with metabolic syndrome. *Cardiol. J*., 2015 Jul 23. doi : 10.5603/CJ.a2015.0045. [Epub ahead of print]
11. SAYIN M.R., ALTUNTAS M., AKTOP Z., OZ I.I., YAVUZ N., AKPINAR I., SAGATLI E., KARABAG T., AYDIN M. Presence of Fragmented QRS Complexes in Patients with Obstructive Sleep Apnea Syndrome. *Chin. Med. J. (Engl.)*, 2015, **128** : 2141-2146.
12. STERLING RK., LISSEN E., CLUMECK N. *et al*. Development of a simple noninvasive index to predict significant fibrosis patients with HIV/HCV co-infection. *Hepatology*, 2006, **43** (6) : 1317-1325.
13. GARCIA-TSAO G., FRIEDMAN S., IREDALE J., PINZANI M. Now there are many (stages) where before there was one : In search of a pathophysiological classification of cirrhosis. *Hepatology*, 2010, **51** : 1445-1449.
14. KRAG A., BENDTSEN F., HENRIKSEN J.H., MOLLER S. Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. *Gut*, 2010, **59** : 105-110.
15. KARAGIANNAKIS D.S., VLACHOGIANNAKOS J., ANASTASIADIS G., VAFIADIS-ZOUBOULIS I., LADAS S.D. Diastolic cardiac dysfunction is a predictor of dismal prognosis in patients with liver cirrhosis. *Hepatol. Int*., 2014, **8** : 588-594.
16. HOMSI M. *et al*. Fragmented QRS complexes on 12-lead ECG : a marker of cardiac sarcoidosis as detected by gadolinium cardiac magnetic resonance imaging. *Ann. Noninvasive Electrocardiol*., 2009, **14** (4) : 319-326.
17. BUYUKKAYA E. *et al*. The relation of fragmented QRS with tissue Doppler derived parameters in patients with b-thalassaemia major. *Clin. Invest. Med*., 2012, **35** (5) : E334.
18. CELIK M.M., BUYUKKAYA E., USTUN N., NACAR A.B., KURT M., KARAKAS M.F., BILEN P., DURU M., SEN N., AKCAY A.B. Relation of fragmented QRS to tissue Doppler-derived parametersin patients with familial Mediterranean fever. *Wien Klin. Wochenschr*., 2015, **127** : 185-190.
19. KADI H., INANIR A., HABIBOGLU A. *et al*. Frequency of fragmented QRS on ECG is increased in patients with rheumatoid arthritis without cardiovascular disease : A pilot study. *Mod. Rheumatol*., 2011. DOI : 10.1007/s10165-011-0493-9.
20. BAYAR N., ÇAY H.F., ERKAL Z., SEZER İ., ARSLAN Ş., ÇAĞIRCI G., ÇAY S., YÜKSEL İ.Ö., KÖKLÜ E. The importance of fragmented QRS in the early detection of cardiac involvement in patients with systemic sclerosis. *Anatol. J. Cardiol*., 2015, **15** : 209-212.
21. TERHO H.K., TIKKANEN J.T., JUNTTILA J.M., ANTTONEN O., KENTTÄ TV., ARO A.L., KEROLA T., RISSANEN H.A., REUNANEN A., HUIKURI H.V. Prevalence and prognostic significance of fragmented QRS complex in middle-aged subjects with and without clinical or electrocardiographic evidence of cardiac disease. *Am. J. Cardiol*., 2014 Jul 1, **114** (1) : 141-147.
22. BOSCH J., GROSZMANN R.J., SHAH V.H. Evolution in the understanding of the pathophysiological basis of portal hypertension : How changes in paradigm are leading to successful new treatments. *J. Hepatol*., 2015, **62** (1 Suppl) : S121-S130.
23. KIM Y.K., HWANG G.S., SHIN W.J., BANG J.Y., CHO S.K., HAN S.M. Effect of propranolol on the relationship between QT interval and vagal modulation of heart rate variability in cirrhotic patients awaiting liver transplantation. *Transplant. Proc*., 2011, **43** : 1654-1659.
24. SERSTE T., MELOT C., FRANCOZ C. *et al*. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. *Hepatology*, 2010, **52** : 1017-1022.