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Comparative evaluation of cardiac health in patients with chronic liver disease secondary to HCV, HBV, and NASH

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Abstract---Background: There is a documented relationship between chronic liver disease and cardiac dysfunction. The current investigation aims to compare the cardiac health in patients with chronic liver disease secondary to HCV, HBV, and NASH. Patients and Methods: This prospective study included 150 patients divided into three groups; Group I (50 HCV cases), Group II (50 HBV cases), and Group III (50 NASH cases). Each group was subdivided into two equal subgroups; the A subgroup included patients without liver cirrhosis, and the B subgroup included patients with liver cirrhosis. The assessment included laboratory biomarkers, transabdominal ultrasound, fibroscan, echocardiography, and carotid doppler. Results: EF had mean values of 62.58, 62.8, and 64.14%, whereas prolonged QT interval was noted in

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30%, 40%, and 37% of patients in the three groups, respectively. E/A ratios > 1 were detected in 70%, 66%, and 72% of patients, while carotid atherosclerosis was detected in 28%, 28%, and 32% in the same three groups, respectively. All of the previous parameters were comparable between the three main groups. On comparing subgroups A to B, prolonged QT intervals, carotid atherosclerosis, and decreased EF were more noticed in the latter. Nonetheless, the E/A ratio did not express significant differences between the previous subgroups. Conclusion: The three aetiologies of chronic liver disease had considerable cardiovascular effects, including EF, E/A ratio, prolonged QT interval, and carotid atherosclerosis. Liver cirrhosis was associated with poor cardiac function manifested by decreased EF, prolonged QT interval, and increased incidence of carotid atherosclerosis.

Keywords---cardiac health, chronic liver disease, cirrhosis.

Introduction

Patients with liver disease often have hemodynamic disorders, including fluid redistribution, decreased peripheral vascular resistance, and decreased cardiac performance status. Similarly, uncontrolled heart disease could also lead to hepatic damage [1, 2]. The presence of synchronous cardiac and hepatic diseases is a documented predictor of mortality, as it was previously reported that about 25% of cirrhotic patients died of poor cardiac function [3]. The hepatitis C virus (HCV) is the main cause of liver disease in Egypt [4]. It can lead to cirrhosis of the hepatic parenchyma as well as extra-hepatic manifestations like steatosis and insulin resistance. Previous trials have documented the negative impact of HCV infection on cardiac performance status, which was markedly improved after HCV elimination [5, 6]. The hepatitis B virus (HBV) is also an important viral pathogen causing liver cirrhosis. HBV patients with either compensated or decompensated hepatic disease could present with multiple manifestations, including cardiac disease [3, 7]. Non-alcoholic steatohepatitis (NASH) represents a special type of chronic liver disease that is linked to metabolic syndrome and insulin resistance [8, 9]. Accumulating data support the association between NASH and cardiovascular disorders, including carotid atherosclerosis and ischemic heart disease [10-12]. After intensive literature research, a clear paucity can be noted regarding the cardiac performance in cirrhotic individuals with different aetiologies. Therefore, we conducted the current investigation to evaluate and compare the cardiac health in patients with chronic liver disease secondary to HCV, HBV, and NASH.

Patients and Methods

The current prospective comparative trial was conducted at the National Liver Institute, Menoufia Governorate, Egypt, after obtaining approval from the local scientific and ethical committee of our institute. The study was conducted over a two-year period, from December 2019 to December 2021. The study was designed for adult patients aged between 18 and 65 years who presented with chronic liver disease at our outpatient clinic during the previous period. On the other hand, we

excluded subjects with primary cardiovascular diseases, pregnancy, intra or extra-hepatic malignancy, concomitant HCV and HBV infection, decompensated cirrhosis, history of alcohol abuse, or anemia.

The included participants were allocated into three equal groups based on the etiology of cirrhosis; Group I included 50 chronic liver disease patients secondary to HCV (positive HCV antibodies, positive HCV RNA by polymerase chain reaction PCR for > six months, previous HCV treatment whatever the PCR status at the time of inclusion, with no other evident etiology of cirrhosis), Group II included 50 patients secondary to HBV infection (established by positive HBsAg, positive PCR for HBV DNA for > six months, previous treatment of HBV infection whatever PCR status at the inclusion time, and absent other aetiologies of cirrhosis), and Group III included the remaining 50 patients who had liver disease secondary to NASH (confirmed by fibroscan when the hepatic controlled attenuation parameter ≥ the reading representing steatosis grade I, with absent other aetiologies of cirrhosis).

All patients received the standard evaluation starting with proper and detailed history taking, general examination (including heart examination), and local abdominal examination. Laboratory work-up included complete blood count (CBC), liver biochemistry (including hepatic transaminases, bilirubin, albumin, gamma-glutamyl transferase GGT, alkaline phosphatase, and international normalized ratio INR). Other laboratory investigations included glycated hemoglobin (HbA1C), lipid profile, and alpha-fetoprotein (AFP). Investigations to identify the etiology of cirrhosis included HCVAb, HBsAg, and markers for autoimmune liver disease (for exclusion).

Other investigations included 12-lead electrocardiography, transabdominal ultrasonography, liver fibroscan, transthoracic echocardiography, and carotid doppler ultrasound. The QT interval was estimated and corrected via Bazett's formula [13]. The echocardiography procedure was performed via a Vivid 3N device (General Electric) provided with 2.5- and 3.5-MHz transducers. Two-dimensional and M-mode were performed for all patients. The former was done in parasternal and apical views, while the latter was done to assess cardiac chamber dimensions. The ejection fraction (EF) and E/A ratio were calculated. Systolic dysfunction was diagnosed when EF was < 55% [14], whereas the presence of an E/A ratio of < 1 was taken as an indicator of diastolic dysfunction [15].

Regarding the assessment of carotid atherosclerosis, it was done via the Xario machine (Toshiba) using a 7.5 MHz transducer. Measurement of the carotid intimal medial thickness (IMT) was done by an experienced radiologist, two cm proximal to the bifurcation of the common carotid artery. Carotid atherosclerosis was diagnosed when IMT > 1mm [16, 17]. Each of the previous three groups was subdivided into two equal subgroups (25 patients in each subgroup); subgroup A included patients without liver cirrhosis, while subgroup B included patients with compensated liver cirrhosis. The presence of cirrhosis was established by US and fibroscan when the liver stiffness corresponded to stage-4 fibrosis in the latter diagnostic modality. Our main outcome was to compare the different cardiac parameters between the evaluated three different aetiologies of cirrhosis.

The collected data were tabulated and analyzed using the SPSS software for windows. Categorical data were expressed as numbers and percentages, and then using the Chi-Square test, Fischer Exact test, or Monte Carlo test. For quantitative data, they were expressed as mean (with standard deviation) or median (and range and interquartile range). These data were compared using either the independent student-t or one-way Anova tests when two or three groups were compared, respectively. For any of the previous tests, a p-value less than 0.05 was considered statistically significant.

Results

For all patients included, their ages ranged between 44 and 64 years (mean = 55.38 years). Men represented 52.7% of the included total patient sample, while the remaining patients were women (Not shown in the tables). When comparing the main three study groups, their age had mean values of 56.22, 54.78, and 55.14 years in Groups I, II, and III, which was statistically comparable between the study groups. However, the same groups expressed significant statistical differences regarding their gender (p = 0.029), with an increased male predominance in Group I (68% vs. 46% and 44% in Groups II and III, respectively) (Table 1).

Table 1
Demographic data of the study groups

Demographic data	Group I (n = 50)		Group II (n = 50)		Group III (n = 50)		p
	No.	%	No.	%	No.	%	
Sex Male Female	 34 16	 68.0 32.0	 23 27	 46.0 54.0	 22 28	 44.0 56.0	0.029*
Age (years) Min. – Max.	47.0 – 64.0		44.0 – 62.0		45.0 – 62.0		
Mean ± SD.	56.22 ± 4.18		54.78 ± 4.87		55.14 ± 4.64		0.264
Median (IQR)	56.0 (53.0 – 60.0)		55.5 (51.0 – 59.0)		57.0 (51.0 – 59.0)		

On comparing the subgroups regarding liver biochemistry, subgroups B in the three study groups expressed significantly elevated serum bilirubin, GGT, and AFP. However, the same group showed a marked decrease in serum albumin and hepatic transaminase levels. Other laboratory parameters are shown in Table 2.

Table 2
Liver biochemistry in the study subgroups

Liver profile	Group I (n = 50)		Group II (n = 50)		Group III (n = 50)	
	Subgroup A (n = 25)	Subgroup B (n = 25)	Subgroup A (n = 25)	Subgroup B (n = 25)	Subgroup A (n = 25)	Subgroup B (n = 25)
total Bilirubin Min. – Max.	0.30 – 1.80	0.40 – 2.10	0.30 – 1.70	0.70 – 2.20	0.30 – 1.0	0.80 – 2.20

Mean ± SD.	0.70 ± 0.42	1.25 ± 0.48	0.80 ± 0.36	1.50 ± 0.48	0.63 ± 0.20	1.48 ± 0.47
Median (IQR)	0.50 (0.40 – 0.90)	1.30 (0.80 – 1.60)	0.80 (0.50 – 1.0)	1.70 (1.1 – 1.9)	0.60 (0.50 – 0.80)	1.60 (1.1 – 1.9)
P	<0.001*		<0.001*		<0.001*	
direct Bilirubin						
Min. – Max.	0.08 – 0.90	0.20 – 0.90	0.10 – 0.50	0.20 – 0.70	0.10 – 0.40	0.20 – 0.70
Mean ± SD.	0.25 ± 0.18	0.50 ± 0.18	0.30 ± 0.11	0.46 ± 0.13	0.22 ± 0.10	0.46 ± 0.18
Median (IQR)	0.20 (0.10 – 0.30)	0.50 (0.40 – 0.60)	0.30 (0.20 – 0.40)	0.40 (0.40 – 0.60)	0.20 (0.20 – 0.30)	0.40 (0.30 – 0.60)
P	<0.001*		<0.001*		<0.001*	
Albumin						
Min. – Max.	3.30 – 4.50	3.30 – 4.20	3.40 – 4.30	3.30 – 4.10	3.60 – 4.80	3.40 – 3.90
Mean ± SD.	3.92 ± 0.32	3.74 ± 0.26	3.84 ± 0.27	3.63 ± 0.21	4.17 ± 0.34	3.62 ± 0.14
Median (IQR)	3.90 (3.7 – 4.2)	3.70 (3.6 – 4.0)	3.80 (3.6 – 4.1)	3.60 (3.5 – 3.7)	4.20 (3.9 – 4.5)	3.60 (3.5 – 3.7)
P	0.037*		0.004*		<0.001*	
AST						
Min. – Max.	9.0 – 41.0	9.0 – 59.0	18.0 – 65.0	15.0 – 55.0	35.0 – 85.0	27.0 – 55.0
Mean ± SD.	25.48 ± 9.67	27.56 ± 12.58	39.04 ± 11.69	29.44 ± 10.60	55.40 ± 12.44	39.92 ± 7.93
Median (IQR)	25.0 (18.0 – 32.0)	28.0 (16.0 – 33.0)	42.0 (30.0 – 46.0)	26.0 (22.0 – 35.0)	52.0 (46.0 – 63.0)	40.0 (35.0 – 47.0)
P	0.515		0.004*		<0.001*	
ALT						
Min. – Max.	9.0 – 64.0	9.0 – 82.0	20.0 – 90.0	14.0 – 60.0	45.0 – 95.0	38.0 – 65.0
Mean ± SD.	26.52 ± 11.51	28.12 ± 19.30	48.52 ± 16.56	35.76 ± 13.29	67.20 ± 12.09	47.28 ± 8.17
Median (IQR)	25.0 (20.0 – 30.0)	18.0 (16.0 – 40.0)	46.0 (38.0 – 60.0)	32.0 (28.0 – 40.0)	65.0 (62.0 – 75.0)	45.0 (41.0 – 52.0)
P	0724		0.004*		<0.001*	
Alkaline phosphatase						
Min. – Max.	45.0 – 110.0	35.0 – 107.0	35.0 – 110.0	49.0 – 115.0	57.0 – 120.0	57.0 – 120.0
Mean ± SD.	74.72 ± 15.11	75.64 ± 22.43	60.32 ± 20.35	84.84 ± 16.54	86.12 ± 15.88	92.32 ± 16.45
Median (IQR)	75.0 (65.0 – 82.0)	80.0 (70.0 – 93.0)	60.0 (40.0 – 75.0)	85.0 (72.0 – 96.0)	83.0 (75.0 – 93.0)	95.0 (83.0 – 103.0)
P	0.866		<0.001*		0.182	
GGT						
Min. – Max.	11.0 – 35.0	13.0 – 38.0	12.0 – 40.0	18.0 – 45.0	12.0 – 24.0	18.0 – 45.0
Mean ± SD.	20.56 ± 6.49	22.12 ± 6.55	26.36 ± 7.92	31.56 ± 8.23	17.16 ± 3.47	29.28 ± 7.84
Median (IQR)	19.0 (16.0 – 23.0)	21.0	28.0	31.0	18.0	28.0

		(18.0 – 25.0)	(20.0 – 30.0)	(25.0 – 40.0)	(15.0 – 20.0)	(24.0 – 35.0)
P	0.402		0.027*		<0.001*	
INR Min. – Max. Mean ± SD. Median (IQR)	1.0 – 1.20 1.08 ± 0.07 1.10(1.0 – 1.1)	1.10 – 1.30 1.17 ± 0.08 1.20(1.1 – 1.2)	1.0 – 1.30 1.14 ± 0.09 1.10(1.1 – 1.2)	1.0 – 1.30 1.14 ± 0.08 1.10(1.1 – 1.2)	1.04 – 1.20 1.11 ± 0.04 1.10(1.1 – 1.1)	1.0 – 1.20 1.10 ± 0.06 1.10(1.1 – 1.1)
P	<0.001*		0.961		0.590	
AFP Min. – Max. Mean ± SD. Median (IQR)	11.0 – 75.0 25.04 ± 15.07 20.0 (16.0 – 28.0)	11.0 – 75.0 37.24 ± 20.44 30.0 (20.0 – 55.0)	6.0 – 29.0 16.84 ± 5.11 17.0 (13.0 – 20.0)	2.0 – 4020.0 197.7 ± 796.6 32.0 (22.0 – 60.0)	7.0 – 25.0 15.40 ± 4.43 15.0 (12.0 – 18.0)	11.0 – 75.0 35.12 ± 19.36 30.0 (19.0 – 45.0)
P	0.019*		<0.001*		<0.001*	

HbA1C showed a significant difference between the three groups (p > 0.01), as it had mean values of 5.65%, 5.33%, and 6.45% in Groups I, II, and III, respectively (Table 3).

Table 3
Glycosylated hemoglobin in the three study groups

HbA1c (%)	Group I (n = 50)	Group II (n = 50)	Group III (n = 50)	F	p
Min. – Max. Mean ± SD. Median (IQR)	4.90 – 6.60 5.65 ± 0.40 5.60 (5.3 – 6.0)	5.0 – 6.40 5.33 ± 0.23 5.30 (5.2 – 5.4)	5.10 – 8.0 6.45 ± 0.91 6.55 (5.7 – 7.2)	47.368*	<0.01*
Sig. bet. groups.	p_1=0.021*, p_2<0.01*, p_3<0.01*				

Regarding lipid profile in the three study groups, serum triglycerides showed a significant elevation in Group III (144.6 mg/dl vs. 129.5 and 114.8 mg/dl in Groups I and Group II, respectively. The remaining three lipid profile parameters, including cholesterol, and high-and low-density lipoproteins, were statistically comparable between the three study groups (Table 4).

Table 4
Lipid profile in the main three study groups

Lipid profile	Group I (n = 50)	Group II (n = 50)	Group III (n = 50)	P
Triglycerides Min. – Max. Mean ± SD.	70.0 – 240.0 129.5 ± 37.34	71.0 – 210.0 114.8 ± 26.95	60.0 – 239.0 144.6 ± 44.10	<0.001*

Median (IQR)	129.0(95.0 – 158.0)	110.0(95.0 – 130.0)	150.0(117.0– 170.0)	
Sig. bet. groups.	p_1=0.117, p_2= 0.104, p_3<0.001*			
Cholesterol Min. – Max. Mean ± SD. Median (IQR)	 101.0 – 225.0 171.0 ± 30.97 173.0(158.0 – 192.0)	 95.0 – 264.0 167.3 ± 35.45 160.0(145.0 – 180.0)	 106.0 – 244.0 179.6 ± 36.87 181.5(160.0 – 205.0)	0.195
Low-density lipoprotein (LDL) Min. – Max. Mean ± SD. Median (IQR)	 46.0 – 144.0 91.12 ± 25.40 90.0(70.0 – 107.0)	 50.0 – 197.0 88.24 ± 29.84 85.0(70.0 – 101.0)	 45.0 – 175.0 93.76 ± 28.15 90.0(70.0 – 110.0)	0.613
high-density lipoprotein (HDL) Min. – Max. Mean ± SD. Median (IQR)	 30.0 – 70.0 49.70 ± 9.13 50.0(44.0 – 55.0)	 31.0 – 84.0 51.22 ± 9.11 50.0(46.0 – 55.0)	 35.0 – 66.0 47.42 ± 8.13 50.0(40.0 – 53.0)	0.098

EF had mean values of 62.58%, 62.8%, and 64.14% in Groups I, II, and III, respectively. In the same groups, an E/A ratio of more than one was detected in 30%, 34%, and 28% of patients, respectively, whereas the remaining cases had an E/A ratio < 1 (Table 5).

Table 5
Echocardiographic findings in the three main study groups

Echo	Group I (n = 50)	Group II (n = 50)	Group III (n = 50)	P
EF % Min. – Max. Mean ± SD. Median (IQR)	 55.0 – 69.0 62.58 ± 4.15 63.0(59.0 – 66.0)	 56.0 – 72.0 62.80 ± 4.26 63.0(59.0 – 66.0)	 56.0 – 78.0 64.14 ± 4.40 64.0(61.0 – 67.0)	0.145
E/A ratio <1 >1	 15(30.0%) 35(70.0%)	 17(34.0%) 33(66.0%)	 14(28.0%) 36(72.0%)	0.803

EF showed a significant decline in association with cirrhosis in Groups II and III when compared to non-cirrhotic ones. Nonetheless, that significant decline was not observed in Group I. Likewise, the E/A ratio did not show any significant difference between the cirrhotic and non-cirrhotic subgroups in Groups I and III. In contrast, the E/A ratio ≥1 was more detected in association with cirrhosis (p = 0.037) (Table 6).

Table 6
Echocardiographic findings in the study subgroups

Echo	Group I (n = 50)		Group II (n = 50)		Group III (n = 50)	
	Subgroup A (n = 25)	Subgroup B (n = 25)	Subgroup A (n = 25)	Subgroup B (n = 25)	Subgroup A (n = 25)	Subgroup B (n = 25)
Ejection fraction(EF %)						
Min. – Max.	56.0 – 69.0	55.0 – 69.0	56.0 – 72.0	56.0 – 67.0	57.0 – 78.0	56.0 – 67.0
Mean ± SD.	63.68 ± 3.56	61.48 ± 4.46	64.04 ± 4.72	61.56 ± 3.40	65.52 ± 5.13	62.76 ± 3.05
Median (IQR)	64.0 (62.0 – 66.0)	60.0 (58.0 – 64.0)	64.0 (62.0 – 67.0)	62.0 (59.0 – 64.0)	65.0 (63.0 – 68.0)	63.0 (61.0 – 65.0)
P	0.060		0.038*		0.026*	
E/A ratio						
<1	5(20.0%)	10(40.0%)	12(48.0%)	5(20.0%)	4(16.0%)	10(40.0%)
≥1	20(80.0%)	15(60.0%)	13(52.0%)	20(80.0%)	21(84.0%)	15(60.0%)
P	0.123		0.037*		0.059	

Prolonged QT interval was noted in 30%, 40%, and 37% of patients in Groups I, II, and III, respectively, which was comparable on statistical analysis (p = 0.572) (Table 7).

Table 7
QT interval in the main three study groups

QT	Group I (n = 50)		Group II (n = 50)		Group III (n = 50)		P
	No.	%	No.	%	No.	%	
Normal	35	70.0	30	60.0	33	66.0	0.572
Prolonged	15	30.0	20	40.0	17	37.0	

According to Table 8, there was a significant increase in QT interval prolongation in association with cirrhosis in Groups I and II. However, that change was not noticed in Group III.

Table 8
QT interval in the study subgroups

QT	Group I (n = 50)				Group II (n = 50)				Group III (n = 50)			
	Subgroup A (n = 25)		Subgroup B (n = 25)		Subgroup A (n = 25)		Subgroup B (n = 25)		Subgroup A (n = 25)		Subgroup B (n = 25)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%

Normal	22	88.0	13	52.0	19	76.0	11	44.0	18	72.0	15	60.0
Prolonged	3	12.0	12	48.0	6	24.0	14	56.0	7	28.0	10	40.0
P	0.005*				0.021*				0.370			

Carotid atherosclerosis was detected in 28%, 28%, and 32% of cases in Groups I, II, and III, respectively, which was insignificant on statistical analysis (p = 0.879) (Table 9).

Table 9
Carotid IMT in the main three study groups

IMT in carotid doppler	Group I (n = 50)		Group II (n = 50)		Group III (n = 50)		P
	No.	%	No.	%	No.	%	
Normal	36	72.0	36	72.0	34	68.0	0.879
Atherosclerosis	14	28.0	14	28.0	16	32.0	

The presence of cirrhosis did not have any significant impact on the incidence of carotid atherosclerosis, as shown in Table 10.

Table 10
Carotid IMT in the study subgroups

IMT inCarotid doppler	Group I (n = 50)				Group II (n = 50)				Group III (n = 50)			
	Subgroup A (n = 25)		Subgroup B (n = 25)		Subgroup A (n = 25)		Subgroup B (n = 25)		Subgroup A (n = 25)		Subgroup B (n = 25)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Normal	21	84.0	15	60.0	19	76.0	17	68.0	20	80.0	14	56.0
Atherosclerosis	4	16.0	10	40.0	6	24.0	8	32.0	5	20.0	11	44.0
P	0.059				0.529				0.069			

There was no significant difference between the cirrhotic subgroups as well as non-cirrhotic groups regarding the incidence of carotid atherosclerosis (Table 11).

Table 11
Comparison between the three studied groups according to IMT in Carotid doppler in each subgroup

IMT inCarotid doppler	Subgroup A (n = 75)						Subgroup B (n = 75)					
	Group I (n = 25)		Group II (n = 25)		Group III (n = 25)		Group I (n = 25)		Group II (n = 25)		Group III (n = 25)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Normal	21	84.0	19	76.0	20	80.0	15	60.0	17	68.0	14	56.0
Atherosclerosis	4	16.0	6	24.0	5	20.0	10	40.0	8	32.0	11	44.0
P	0.779						0.675					

As illustrated in Table 12, the cirrhotic subgroups tended to have a higher incidence of QT prolongation, carotid atherosclerosis, and low EF.

Table 12
Comparison between the two studied groups according to different parameters

	Subgroup A (n = 75)		Subgroup B (n = 75)		Test of sig.	P
	No.	%	No.	%		
E/A ratio <1 ≥1	 21 54	 28.0 72.0	 25 50	 33.3 66.7	 0.502	0.479
QT Normal Prolonged	 59 16	 78.7 21.3	 39 36	 52.0 48.0	 11.774*	0.001*
IMT inCarotid doppler Normal Atherosclerosis	 60 15	 80.0 20.0	 46 29	 61.3 38.7	 6.304*	0.012*
EF % Min. – Max. Mean ± SD. Median (IQR)	 56.0 – 78.0 64.41 ± 4.53 64.0(62.0 – 67.0)		 55.0 – 69.0 61.93 ± 3.68 62.0(59.0 – 64.50)		 t= 3.678*	 <0.001*

Discussion

Nowadays, little data is known regarding the accurate incidence of cardiac dysfunction in patients with liver cirrhosis. The impact of the etiology and severity of liver disease on cardiac performance is also understudied. That is why we conducted the current study to evaluate cardiac functional status in patients with different aetiologies of cirrhosis (HCV, HBV, and NASH). Few studies have handled that comparison, and that poses an advantageous point in favor of our study. Our findings showed no significant difference between the three main study groups regarding the QT interval. Nevertheless, the cirrhotic subgroups had significant prolongation of the same parameter compared to the non-cirrhotic subgroups. Moaref and his colleagues confirmed our findings regarding the prolongation of QT interval in association with cirrhosis [18]. Multiple factors contribute to QT interval prolongation in cirrhotic individuals, including delayed cardiac repolarization, downregulation of adrenergic receptors secondary to chronic norepinephrine exposure, increased bile salts levels, and increased serum uric acid [18-20].

Li et al. also reported normalization of the QT interval in 85% of cirrhotic individuals after undergoing liver transplantation. This indicates the strong association between liver disease and QT interval prolongation [21]. In the current study, we found that systolic function was within normal ranges in the cirrhotic and non-cirrhotic subgroups. Moreover, left ventricular EF showed no significant difference between the different groups. In agreement with our findings, many previous

studies reported normal EF ranges in patients with cirrhosis, indicating normal systolic function [22-25]. Contrarily, other researchers noted a significant increase in the incidence of systolic dysfunction, especially when the individuals were exposed to stress, including sodium load, erect posture, or exercise [22, 24, 26, 27]. The decreased myocardial reserve, weakened heart rate response to stress, and impaired oxygen extraction at cardiac muscle could explain the previous dysfunction [22, 28].

Our findings showed no significant difference between the three groups regarding the E/A ratio. However, there was a statically significant difference in HBV subgroups between non-cirrhotic and compensated cirrhotic subgroups. The incidence of diastolic dysfunction was significantly increased in association with HBV cirrhosis. Yuan et al. agreed with our findings, as they reported that impaired relaxation was more noticed in patients with chronic HBV infection compared to patients with compensated liver disease [3]. The previous difference in E/A ratio detected in HBV subgroups was not observed in subgroups of HCV and NASH groups. In the NASH group, patients with diastolic dysfunction represented 40% and 16% of subgroups B and A, respectively, implying the increased incidence of dysfunction with cirrhosis despite the absence of any statistical significance. In the same context, Byrne and Targher confirmed the association between NASH severity and cardiac remodeling [29].

In the HCV group in our study, diastolic dysfunction was present in 40% and 20% in subgroups B and A, respectively. The incidence was higher in association with cirrhosis, although no statistical significance was reached. A previous study conducted in Egypt highlighted the significant association between HCV cirrhosis and diastolic cardiac dysfunction. The authors attributed these cardiac changes to chronic cardiac inflammation and subsequent fibrosis [30]. In our study, when comparing the cirrhotic population to the non-cirrhotic ones, there was a significant elevation in the incidence of diastolic dysfunction. That coincides with previous publications, which stated that the E/A ratio is significantly decreased in association with cirrhosis, especially when ascites is present [31, 32]. The impaired diastolic function with cirrhosis could be explained by cardiac fibrosis, hypertrophy, and subendothelial edema [33].

In our study, the three main groups did not show any significant differences in the incidence of carotid atherosclerosis ($p = 0.879$). Nonetheless, the incidence was relatively higher in association with NASH. This is in accordance with previous studies which confirmed the association between NASH and atherosclerotic cardiovascular disease [34-36]. Our findings showed an increased incidence of carotid atherosclerosis in the cirrhotic than the non-cirrhotic subgroups, regardless of the cause. Previous studies have established the association between severe liver disease and increased carotid IMT [37, 38]. In the current study, HbA1C showed a significant increase in group III compared to the other two groups. This is in agreement with Chen et al., who reported that increased HbA1C levels might play a crucial role in the pathogenesis of NASH [39].

Our findings showed increased levels of triglycerides in association with NASH compared to the other two groups. As dyslipidemia is another feature of the metabolic syndrome, which is the main criminal of NASH pathogenesis, it is

reasonable to detect high triglyceride levels in such patients [40]. Our study has some limitations; first of all, we included a relatively small sample size. Additionally, all patients were collected from a single hepatology center. Thus, more studies, including more patients from different centers, should be conducted in the near future.

Conclusion

Based on the preceding findings, the three evaluated aetiologies of chronic liver disease had considerable cardiovascular effects, including EF, E/A ratio, prolonged QT interval, and incidence of carotid atherosclerosis. Liver cirrhosis was associated with poor cardiac function manifested by decreased EF, prolonged QT interval, and increased incidence of carotid atherosclerosis.

Conflict of interest: Nil.

References

1. Arai T, Atsukawa M, Tsubota A, Kato K, Abe H, Ono H, et al. Liver fibrosis is associated with carotid atherosclerosis in patients with liver biopsy-proven nonalcoholic fatty liver disease. Sci Rep. 2021;11(1):15938.https://doi.org/10.1038/s41598-021-95581-8.
2. Barakat AAE-K, Nasr FM, Metwaly AA, Morsy S, Eldamarawy M. Atherosclerosis in chronic hepatitis C virus patients with and without liver cirrhosis. The Egyptian Heart Journal. 2017;69(2):139-47.https://doi.org/https://doi.org/10.1016/j.ehj.2016.10.004.
3. Baratta F, D'Erasmo L, Bini S, Pastori D, Angelico F, Del Ben M, et al. Heterogeneity of non-alcoholic fatty liver disease (NAFLD): Implication for cardiovascular risk stratification. Atherosclerosis. 2022;357:51-9.https://doi.org/10.1016/j.atherosclerosis.2022.08.011.
4. Bergström A, Andersson B, Edner M, Nylander E, Persson H, Dahlström U. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC). Eur J Heart Fail. 2004;6(4):453-61.https://doi.org/10.1016/j.ejheart.2004.02.003.
5. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism. 2016;65(8):1038-48.https://doi.org/10.1016/j.metabol.2015.12.012.
6. Byrne CD, Targher G. Non-alcoholic fatty liver disease-related risk of cardiovascular disease and other cardiac complications. Diabetes Obes Metab. 2022;24 Suppl 2:28-43.https://doi.org/10.1111/dom.14484.
7. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. Bmj. 2000;321(7255):215-8.https://doi.org/10.1136/bmj.321.7255.215.
8. Chen C, Zhu Z, Mao Y, Xu Y, Du J, Tang X, et al. HbA1c may contribute to the development of non-alcoholic fatty liver disease even at normal-range levels. Biosci Rep. 2020;40(1).https://doi.org/10.1042/bsr20193996.

9. Demir M, Demir C. Effect of hepatitis B virus infection on right and left ventricular functions. Med Sci Monit. 2012;18(9):Cr587-91.https://doi.org/10.12659/msm.883356.
10. Domont F, Cacoub P. Chronic hepatitis C virus infection, a new cardiovascular risk factor? Liver Int. 2016;36(5):621-7. https://doi.org/10.1111/liv.13064.
11. Dongiovanni P, Paolini E, Corsini A, Sirtori CR, Ruscica M. Nonalcoholic fatty liver disease or metabolic dysfunction-associated fatty liver disease diagnoses and cardiovascular diseases: From epidemiology to drug approaches. Eur J Clin Invest. 2021;51(7): e13519.https://doi.org/10.1111/eci.13519.
12. Enany B, El Zohiery AK, Elhilaly R, Badr T. Carotid intima-media thickness and serum leptin in psoriasis. Herz. 2012;37(5):527-33.https://doi.org/10.1007/s00059-011-3547-z.
13. Epstein SK, Ciubotaru RL, Zilberberg MD, Kaplan LM, Jacoby C, Freeman R, et al. Analysis of impaired exercise capacity in patients with cirrhosis. Dig Dis Sci. 1998;43(8):1701-7.https://doi.org/10.1023/a:1018867232562.
14. Genovesi S, Prata Pizzala DM, Pozzi M, Ratti L, Milanese M, Pieruzzi F, et al. QT interval prolongation and decreased heart rate variability in cirrhotic patients: relevance of hepatic venous pressure gradient and serum calcium. Clin Sci (Lond). 2009;116(12):851-9.https://doi.org/10.1042/cs20080325.
15. Grose RD, Nolan J, Dillon JF, Errington M, Hannan WJ, Bouchier IA, et al. Exercise-induced left ventricular dysfunction in alcoholic and non-alcoholic cirrhosis. J Hepatol. 1995;22(3):326-32.https://doi.org/10.1016/0168-8278(95)80286-x.
16. Kablak-Ziembicka A, Tracz W, Przewlocki T, Pieniazek P, Sokolowski A, Konieczynska M. Association of increased carotid intima-media thickness with the extent of coronary artery disease. Heart. 2004;90(11):1286-90.https://doi.org/10.1136/hrt.2003.025080.
17. Kelbaek H, Eriksen J, Brynjolf I, Raboel A, Lund JO, Munck O, et al. Cardiac performance in patients with asymptomatic alcoholic cirrhosis of the liver. Am J Cardiol. 1984;54(7):852-5.https://doi.org/10.1016/s0002-9149(84)80220-9.
18. Kelbaek H, Rabøl A, Brynjolf I, Eriksen J, Bonnevie O, Godtfredsen J, et al. Haemodynamic response to exercise in patients with alcoholic liver cirrhosis. Clin Physiol. 1987;7(1):35-41.https://doi.org/10.1111/j.1475-097x.1987.tb00631.x.
19. Keller H, Bezjak V, Stegaru B, Buss J, Holm E, Heene DL. Ventricular function in cirrhosis and portasystemic shunt: a two-dimensional echocardiographic study. Hepatology. 1988;8(3):658-62.https://doi.org/10.1002/hep.1840080337.
20. Kouyoumjian SP, Chemaitelly H, Abu-Raddad LJ. Characterizing hepatitis C virus epidemiology in Egypt: systematic reviews, meta-analyses, and meta-regressions. Sci Rep. 2018;8(1):1661.https://doi.org/10.1038/s41598-017-17936-4.
21. Li L, Liu HR, Shu JL, Xi XP, Wang Y. [Clinical investigation of Q-T prolongation in hepatic cirrhosis]. Zhonghua Yi Xue Za Zhi. 2007;87(38):2717-8
22. Maslennikov R, Ivashkin V, Efremova I, Poluektova E, Shirokova E. Gut-liver axis in cirrhosis: Are hemodynamic changes a missing link? World J Clin Cases. 2021;9(31):9320-32.https://doi.org/10.12998/wjcc.v9.i31.9320.
23. Matyas C, Haskó G, Liaudet L, Trojnar E, Pacher P. Interplay of cardiovascular mediators, oxidative stress and inflammation in liver disease and its

complications. Nat Rev Cardiol. 2021;18(2):117-35.https://doi.org/10.1038/s41569-020-0433-5.
24. Mishra S, Yadav D, Gupta M, Mishra H, Sharma P. A Study of Carotid Atherosclerosis in Patients with Non-alcoholic Fatty Liver Disease. Indian J Clin Biochem. 2013;28(1):79-83.https://doi.org/10.1007/s12291-012-0286-8.
25. Moaref A, Zamirian M, Yazdani M, Salehi O, Sayadi M, Aghasadeghi K. The Correlation between Echocardiographic Findings and QT Interval in Cirrhotic Patients. Int Cardiovasc Res J. 2014;8(2):39-43
26. Møller S, Henriksen JH. Cardiovascular complications of cirrhosis. Gut. 2008;57(2):268-78.https://doi.org/10.1136/gut.2006.112177.
27. Nasr FM, Metwaly A, Khalik AA, Darwish H. Cardiac dysfunction in liver cirrhosis: A tissue Doppler imaging study from Egypt. Electron Physician. 2015;7(4):1135-43.https://doi.org/10.14661/2015.1135-1143.
28. Ogawa Y, Imajo K, Yoneda M, Nakajima A. [Pathophysiology of NAsh/NAFLD associated with high levels of serum triglycerides]. Nihon Rinsho. 2013;71(9):1623-9
29. Oni ET, Agatston AS, Blaha MJ, Fialkow J, Cury R, Sposito A, et al. A systematic review: burden and severity of subclinical cardiovascular disease among those with nonalcoholic fatty liver; should we care? Atherosclerosis. 2013;230(2):258-67.https://doi.org/10.1016/j.atherosclerosis.2013.07.052.
30. Petta S. Hepatitis C virus and cardiovascular: A review. J Adv Res. 2017;8(2):161-8.https://doi.org/10.1016/j.jare.2016.06.001.
31. Pozzi M, Carugo S, Boari G, Pecci V, de Ceglia S, Maggiolini S, et al. Evidence of functional and structural cardiac abnormalities in cirrhotic patients with and without ascites. Hepatology. 1997;26(5):1131-7.https://doi.org/10.1002/hep.510260507.
32. Sia CH, Ngiam JN, Chew N, Beh DLL, Poh KK. Educational case series of electrocardiographs during the COVID-19 pandemic and the implications for therapy. Singapore Med J. 2020;61(8):406-12.https://doi.org/10.11622/smedj.2020087.
33. Sookoian S, Pirola CJ. Non-alcoholic fatty liver disease is strongly associated with carotid atherosclerosis: a systematic review. J Hepatol. 2008;49(4):600-7.https://doi.org/10.1016/j.jhep.2008.06.012.
34. Tacke F, Weiskirchen R. Non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH)-related liver fibrosis: mechanisms, treatment and prevention. Ann Transl Med. 2021;9(8):729.https://doi.org/10.21037/atm-20-4354.
35. Tana C, Ballestri S, Ricci F, Di Vincenzo A, Ticinesi A, Gallina S, et al. Cardiovascular Risk in Non-Alcoholic Fatty Liver Disease: Mechanisms and Therapeutic Implications. Int J Environ Res Public Health. 2019;16(17).https://doi.org/10.3390/ijerph16173104.
36. Țieranu E, Donoiu I, Istrătoaie O, Găman AE, Țieranu LM, Gheonea DI, et al. Q-T Interval Prolongation in Patients with Liver Cirrhosis. Curr Health Sci J. 2018;44(3):274-9.https://doi.org/10.12865/chsj.44.03.11.
37. Wong F, Girgrah N, Graba J, Allidina Y, Liu P, Blendis L. The cardiac response to exercise in cirrhosis. Gut. 2001;49(2):268-75.https://doi.org/10.1136/gut.49.2.268.

38. Wong F, Liu P, Lilly L, Bomzon A, Blendis L. Role of cardiac structural and functional abnormalities in the pathogenesis of hyperdynamic circulation and renal sodium retention in cirrhosis. Clin Sci (Lond). 1999;97(3):259-67
39. Wong F. Cirrhotic cardiomyopathy. Hepatol Int. 2009;3(1):294-304.https://doi.org/10.1007/s12072-008-9109-7.
40. Yuan W, Lu HZ, Mei X, Zhang YY, Zhang ZG, Zou Y, et al. Cardiac health in patients with hepatitis B virus-related cirrhosis. Medicine (Baltimore). 2019;98(13):e14961.https://doi.org/10.1097/md.0000000000014961.