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Capillary microvascular function in patients with liver cirrhosis: A nailfold video-capillaroscopy study

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Abstract

Background Liver cirrhosis is characterized by major circulatory dysregulation, related to an imbalance between several vasoactive agents. Although alterations in intrahepatic and systemic vasculature have been rather well described, the peripheral microcirculation and endothelial function are less well studied. Our aim was to evaluate peripheral microcirculatory function in patients with cirrhosis via nailfold video-capillaroscopy.

Methods We enrolled 60 patients with cirrhosis and 20 controls. All participants underwent nailfold video-capillaroscopy. Capillary density was measured at rest (baseline), after 4-min arterial occlusion (post-occlusive reactive hyperemia) and after 2-min venous congestion.

Results Cirrhotic patients presented lower capillary density than controls at baseline (35.8±3.6 vs. 38±1.1 capillaries/mm^2, P=0.01), during post-occlusive reactive hyperemia (40.0±4.4 vs. 45.3±1.5 capillaries/mm^2, P<0.001), and after venous congestion (43.3±4.2 vs. 47.2±1.5 capillaries/mm^2, P<0.001). Capillary density decreased significantly with deterioration of Child-Pugh class at baseline (Child-Pugh A: 38.0±3.9 vs. Child-Pugh B: 35.6±2.7 vs. Child-Pugh C: 33.9±3.2 capillaries/mm^2, P<0.001), during post-occlusive reactive hyperemia (43.5±3.4 vs. 39.8±3.0 vs. 36.8±3.9 capillaries/mm^2, respectively, P<0.001), and after venous congestion (46.7±3.1 vs. 43.0±2.7 vs. 40.1±3.8 capillaries/mm^2, respectively, P<0.001).

Conclusions Capillary density in all phases was significantly lower in cirrhotic patients compared to controls. Moreover, a lower capillary density was associated with deteriorating Child-Pugh stages, suggesting that increasing severity of cirrhosis is associated with more impaired peripheral microcirculatory function.

Keywords Cirrhosis, peripheral microcirculation, nailfold video-capillaroscopy

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Conflict of Interest: None

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Introduction

Liver cirrhosis represents a major public health issue and a significant factor in morbidity and mortality worldwide [1,2]. Since its early stages are asymptomatic, the prevalence of cirrhosis is underestimated; population-based studies reported a prevalence of 0.3%, but autopsy studies from the general population have found rates up to 4.5-9.5% [1,3,4]. In developed countries, the main causes of cirrhosis are viral hepatitis and misuse of alcohol, while more recently, non-alcoholic liver disease, an entity strongly associated with cardiovascular disease, is increasingly recognized as a major cause of cirrhosis [1,5].

Endothelial dysfunction refers to a state of imbalance between vasodilating and vasoconstricting factors, inappropriately favoring the latter [6]. Nitric oxide (NO) is directly associated with endothelial function, as decreased bioavailability of NO is the hallmark of endothelial dysfunction [7]. In liver cirrhosis, a major dysregulation of the circulatory systems is observed,

characterized by alterations in both intrahepatic and systematic vasculature; these are associated with imbalance of vasoactive agents, including mainly NO [8]. In particular, reduced NO bioavailability, oxidative stress, and endothelial dysfunction in the intrahepatic circulation result in significant intrahepatic vasoconstriction and increased vascular resistance, leading to portal hypertension [8]. On the other hand, NO overproduction is observed in systematic vascular beds, causing arterial vasodilation and hyperdynamic circulatory syndrome [8]. Although alterations in the intrahepatic circulation and the systematic microcirculation have both been well described, the peripheral microcirculation in cirrhosis is less well studied. There are a few studies describing peripheral microvascular alterations in the literature, but with conflicting results [9,10]. Armentano *et al*, in a small pilot study, found that flow-mediated dilatation (FMD) was higher in Child-Pugh C than Child-Pugh B and Child-Pugh A, suggesting an increased peripheral vasodilatory response with the progression of the disease [11]. Similarly, Berzigotti *et al* indicated that FMD increased in parallel with Child-Pugh score [12]. On the other hand, Ponziani *et al* found that FMD was lower in patients with cirrhosis than in healthy controls, while Marcacci *et al* suggested that FMD, and consequently peripheral endothelial function, was reduced in worsening cirrhosis [13,14].

During the last decades, several methods have been developed to assess endothelial and microvascular function in humans [9,15]. Nailfold capillaroscopy is a noninvasive method that provides a detailed examination of the number and the morphology of the nailfold capillaries, giving valuable information about microcirculatory derangement [9]. Nailfold video-capillaroscopy (NVC), a development of the aforementioned method, offers the opportunity to evaluate capillaries' functional alterations—and consequently microvascular function—by measuring capillary density during different vascular phases (baseline, post-arterial occlusion and after venous congestion) [16]. NVC has been used to assess peripheral microcirculation function in patients with hypertension, diabetes mellitus, rheumatoid arthritis and chronic kidney disease [16-19]. To the best of our knowledge, no study has examined microvascular endothelial function in individuals with cirrhosis using NVC and employing the standard methodology.

The aim of the present study was to evaluate microvascular function with the use of NVC in patients with cirrhosis versus controls, as well as at different stages of cirrhosis by evaluating differences between the various Child-Pugh classes. As secondary objective, we examined possible associations between microvascular function and markers of macrovascular function, including parameters such pulse wave velocity (PWV), wave reflection indices and carotid intima–media thickness (cIMT).

Patients and methods

Study population

This observational study included patients followed at the outpatient liver clinics of the 4th Department of Internal Medicine, Hippokration Hospital, Thessaloniki, Greece. Inclusion criteria were: 1) age >18 years; and 2) patients with cirrhosis, diagnosed either by biopsy or by a combination of clinical, laboratory and imaging features. We excluded patients with: 1) pregnancy; 2) hepatocellular carcinoma or other active malignant disease; 3) liver transplantation; 4) myocardial infarction or unstable angina during the past 3 months; 5) congestive heart failure class III-IV according to the New York Heart Association criteria (NYHA III-IV); 6) chronic atrial fibrillation or other arrhythmias that could affect the recording of blood pressure; and 7) chronic kidney disease according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines [20]. A blinded member of our team matched eligible participants within each study group (controls, Child-Pugh A, Child-Pugh B and Child-Pugh C) for age (±5 years, with reference group Child-Pugh C) and sex in a 1:1 ratio. Age- and sex-matched controls without cirrhosis were also included (i.e., healthy controls and patients with dyslipidemia or well-controlled hypertension). The protocol was approved by the Ethics Committee of School of Medicine, Aristotle University of Thessaloniki, and all participants provided informed written consent prior to study enrollment. The study was performed according to the Declaration of Helsinki (2013 Amendment).

Study procedures

Participants who met the inclusion and exclusion criteria were scheduled to visit our research unit, after a 12-h fast and without using caffeine, alcohol or tobacco. Demographic and anthropometric characteristics, past medical history and concomitant medication were recorded. A physical examination was performed, and venous blood samples were obtained for routine laboratory tests. After 10 min of seated rest, 3 blood pressure (BP) measurements were performed at the level of the brachial artery, according to recommendations [21]. Subsequently, NVC was performed, and arterial stiffness indexes and cIMT were measured, as described in detail below. All the measurements were performed in a quiet room with a temperature of 23-24°C.

NVC

NVC was performed using a OptiPix Capillaroscopy Clinic 1.7.x device (magnification 200×). Using digital video, capillaries were depicted on the dorsal skin of the distal phalanx of the third and fourth fingers of the right hand. The imaging was performed in the middle of the nailfold, ~4.5 mm from the terminal capillary line. The researcher chose a visual field of 1 mm^2 and the number of capillaries was counted offline from a freeze-framed reproduction of the video. The capillary density was measured (as the mean of the 2 fingers) in 3 different phases, as previously described in the literature (Fig. 1) [16,22]. Baseline capillary density was measured during a period of 15 sec, and only continuously erythrocyte-perfused capillaries

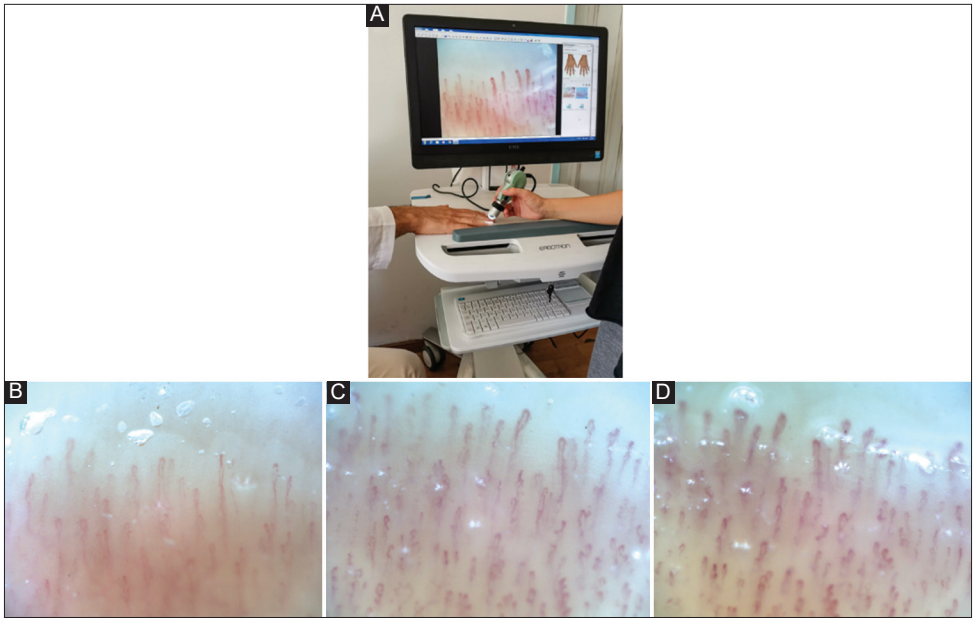

Figure 1 Images of (A) the nailfold video-capillaroscopy device, and capillary density in a patient with cirrhosis at (B) baseline, (C) post-occlusive hyperemia, and (D) venous congestion

were counted. Subsequently, arterial occlusion was applied, using a small cuff at the base of the studied finger that was inflated to 260 mmHg for 4 min. Capillary density during post-occlusive reactive hyperemia was defined as the number of all (continuously and intermittently perfused) capillaries that were counted during 15 sec immediately after the release of the cuff. Fifteen min following the post-occlusive reactive hyperemia phase, venous congestion was induced by inflating the cuff to 60 mmHg for 2 min. Immediately after that, all (continuously and intermittently perfused) capillaries were counted for 15 sec and the capillary density after venous congestion was recorded. In addition, the absolute increase in capillary density from baseline to the post-occlusive reactive hyperemia phase was calculated by subtracting the baseline capillary density from the post-occlusive reactive hyperemia capillary density. The % capillary recruitment was also determined by dividing the absolute increase in capillary density in post-occlusive reactive hyperemia by baseline capillary density and multiplying the result by 100.

Arterial stiffness and carotid intima–media thickness

Arterial stiffness and wave reflection parameters were measured with the using a Sphygmocor XCEL device (AtCor Medical, Sydney, Australia). The Sphygmocor XCEL system is designed to derive the aortic pressure waveform by capturing cuff pulsation from the brachial artery, using a validated generalized transfer function to reconstruct the aortic pulse waveform [23]. A pneumatic cuff was fitted on the participant's upper arm and, after 5-min rest, the brachial cuff was automatically inflated to measure brachial BP; it was then deflated and automatically re-inflated after 5 sec to capture a PWV waveform. Augmentation pressure (AP) was defined as the difference of aortic pressures between the second and first systolic peaks. Augmentation index (AIx) was calculated by dividing AP by aortic pulse pressure (PP), and was expressed as a percentage (%). AIx(75) was derived by the Sphygmocor software, adjusting AIx at an inverse rate of 4.8% for each 10 beats/min elevation in heart rate.

Arterial stiffness was assessed by measuring carotid–femoral PWV in accordance with the established recommendations [24]. Applanation tonometry with a high-fidelity pencil-type probe (SPTtransducer, Millar instruments, Houston, Texas, USA) was used to record the carotid pulse. The femoral pulse was evaluated using volumetric displacement within a cuff fitted around the thigh. PWV was calculated by dividing the distance between the carotid and femoral recording sites in meters to the pulse transit time in sec.

cIMT was evaluated with a 2D ultrasound device (GE Healthcare Ultrasound, Vivid S5, 8L-RS probe, USA) in both right and left common carotid arteries (CCA). Three measurements were made, and the mean was calculated for each CCA. The total cIMT was calculated as the average of the means of the right and left CCA. The procedure was performed as described previously in the literature [25].

Statistical analysis

The statistical analysis was performed using SPSS software version 25.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of distributions. Continuous variables were presented as mean ± standard deviation or median (25^{th}, 75^{th} percentile), according to the normality of the distribution.

Categorical variables were expressed as absolute frequencies and percentages (n, %). Between-groups comparisons for continuous variables were performed with the independent *t*-test or the Mann-Whitney test, where applicable. For comparisons of more than 2 groups, the 1-way ANOVA or the Kruskal-Wallis test was used, according to the normality of the distribution. Categorical variables were compared using the chi-square or Fisher's exact test. Bivariate correlation coefficients (r) were calculated using Pearson's product formula to assess the associations between NVC parameters and PWV and cIMT. Statistical significance was considered as a 2-sided P-value <0.05.

Results

Participant characteristics

Fig. 2 presents the study flowchart. A total of 80 participants were included in the study: 60 patients with cirrhosis (20 in each group for Child-Pugh classes A, B and C) and 20 controls. Demographic, clinical and laboratory characteristics of the study population are presented in Table 1. For patients with cirrhosis, the primary liver disease was alcohol-related liver disease in 28 patients (46.7%), metabolic dysfunction-associated steatotic liver disease in 13 patients (21.7%), autoimmune hepatitis in 9 patients (15%), chronic hepatitis B in 8 patients (13.3%), and unknown/cryptogenic in 2 patients (3.3%). Twenty patients (33.3%) had compensated cirrhosis and 40 decompensated cirrhosis (66.7%). There were no significant differences between groups in age, sex or body mass index. As expected, model for end-stage liver disease (MELD) score and MELD-Na score were progressively larger, while platelet count, hemoglobin levels and albumin levels were lower in more advanced Child-Pugh classes.

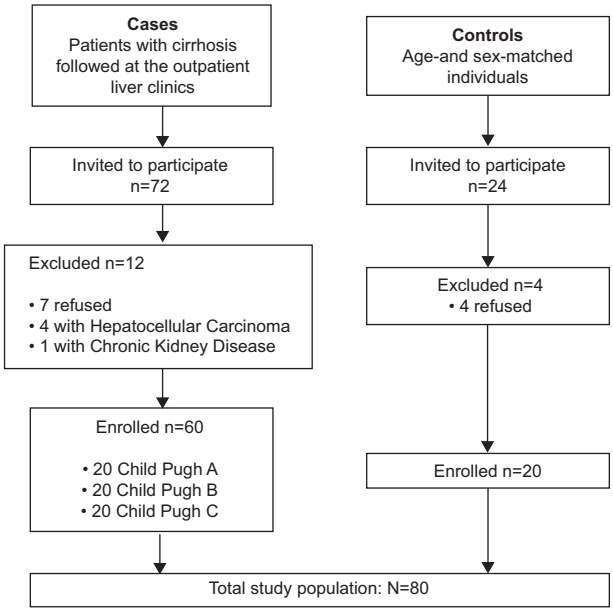

Figure 2 Study flowchart

NVC parameters in cirrhotic patients and controls

Table 2 presents the differences in NVC parameters between patients with cirrhosis and controls. Baseline capillary density was lower in patients with cirrhosis than in controls (35.8±3.6 vs. 38±1.1 capillaries/mm^2, P=0.01). Similarly, cirrhotic patients presented significantly lower capillary density both during post-occlusive reactive hyperemia (40.0±4.4 vs. 45.3±1.5 capillaries/mm^2, P<0.001) and after venous congestion (43.3±4.2 vs. 47.2±1.5 capillaries/mm^2, P<0.001). Capillary recruitment was significantly lower in patients with cirrhosis compared to controls (11.8±4.6% vs. 19.1±2.6%, P<0.001).

NVC parameters in different Child-Pugh classes

Fig. 3 presents the differences in NVC parameters between patients with different Child-Pugh classes. Capillary density in all phases (baseline, during post-occlusive reactive hyperemia and after venous congestion) decreased significantly with deterioration of Child-Pugh class (Fig. 3). Similarly, capillary recruitment became significantly lower as the Child-Pugh class increased (controls: 19.1±2.6%, Child-Pugh A: 15.1±5.1%, Child-Pugh B: 11.9±2.9, Child-Pugh C: 8.3±2.7%, P<0.001).

Arterial stiffness, wave reflections and cIMT in cirrhotic patients and controls, and in different Child-Pugh classes

Supplementary Table 1 presents the differences in central blood pressure, wave reflection parameters, arterial stiffness and cIMT between cirrhotic patients and controls. No significant differences were detected in aortic SBP or DBP pressure levels between the 2 groups. Similarly, wave reflection parameters (AP, AIx, AIx75), PWV and cIMT were similar between the groups.

Aortic SBP and aortic DBP decreased with deterioration of Child-Pugh class (Child-Pugh A: 122.4±16.8/79.6±12.6 mmHg, Child-Pugh B: 118.2±12.9/73.4±9.8 mmHg, Child-Pugh C: 104.7±12.2/68.7±6.1 mmHg, P=0.001 and P=0.002, respectively). No significant differences were detected in wave reflections, PWV or cIMT among different Child-Pugh classes (Table 3).

Associations of NVC parameters with laboratory tests, PWV and cIMT in cirrhotic patients

The capillary density during post-occlusive reactive hyperemia was negatively associated with MELD score (r=-0.602, P<0.001), MELD-Na score (r=-0.610, P<0.001), total bilirubin (r=-0.473, P<0.001), international normalized ratio (INR) (r=-0.504, P<0.001) and C-reactive protein (CRP) (r=-0.357, P=0.005). A positive association was observed

Table 1 Demographic, anthropometric and clinical characteristics of the study participants

Characteristics	Controls	Child-Pugh A	Child-Pugh B	Child-Pugh C	P-value
N	20	20	20	20	
Age (years)	59.4±9.8	56.4±12.1	61.1±9.9	57.1±12.6	0.537
Males	11 (55%)	11 (55%)	11 (55%)	11 (55%)	>0.99
BMI (kg/m^2)	27.2±2.7	27.2±5.4	25.9±3.7	26.4±4.1	0.364
Etiology	-	ALD 7 (35%)	ALD 12 (60%)	ALD 9 (45%)	0.728
		MASLD 6 (30%)	MASLD 2 (10%)	MASLD 5 (25%)	
		AIH 4 (20%)	AIH 3 (15%)	AIH 2 (10%)	
		HBV 3 (15%)	HBV 2 (10%)	HBV 3 (15%)	
		Cryptogenic 0	Cryptogenic 1 (5%)	Cryptogenic 1 (5%)	
Ascites	-	0	17 (85%)	20 (100%)	<0.001
HE	-	0	8 (40%)	11 (55%)	0.001
Variceal bleeding	-	0	6 (30%)	5 (25%)	0.521
Active smokers	6 (30%)	8 (40%)	10 (50%)	7 (35%)	0.606
Hypertension	12 (60%)	6 (30%)	5 (25%)	2 (10%)	0.006
Diabetes	0	6 (30%)	4 (20%)	5 (25%)	0.078
Dyslipidemia	5 (25%)	5 (25%)	1 (5%)	2 (10%)	0.095
CAD	0	1 (5%)	1 (5%)	2 (10%)	0.551
Office SBP (mmHg)	127.5±8.9	132.6±19.2	127.8±14.3	114.3±15.3	0.002
Office DBP (mmHg)	77.8±7.1	79.2±12	73.3±10.7	67.7±5.8	0.001
Hemoglobin (g/dL)	13.6±1.1	13.1±2.1	11.1±2	10.3±1.9	<0.001
Platelet count (10^3/μL)	262.8±48.1	126.9±68.6	112.4±62.1	87.9±48.1	<0.001
Creatinine (mg/dL)	0.91±0.15	0.79±0.17	0.98±0.28	0.93±0.28	0.78
AST (U/L)	22.7±5.2	41.9±20.8	44.5±22.1	60.4±38.9	<0.001
ALT (U/L)	19.3±5.9	39.1±24.1	36.6±16.5	37.7±17.7	0.114
ALP (U/L)	67.5±14.2	109.8±43.4	112.8±51.9	122.1±58.2	0.001
gGT (U/L)	27.9±16.5	59.4±35.7	70.9±44.4	59.3±50.2	0.006
Total bilirubin (mg/dL)	0.83±0.30	1.15±0.42	1.88±0.91	3.82±1.88	<0.001
Albumin (g/dL)	4.2±0.2	4.1±0.4	3.4±0.5	3±0.4	<0.001
INR	0.98±0.06	1.22±0.26	1.26±0.15	1.69±0.37	<0.001
hs-CRP (mg/L)	2.88±1.62	5.24±2.28	11.01±8.17	12.52±5.21	<0.001
MELD	-	9.1±2.3	12.1±2.4	17.5±3.9	<0.001
MELD-Na	-	9.5±3.1	12.7±3.3	18.9±4.2	<0.001

Values are mean ± standard deviation, or n (%) for categorical variables

BMI, body mass index; ALD, alcohol-related liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; AIH, autoimmune hepatitis; HBV, hepatitis B virus; HE, hepatic encephalopathy; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; gGT, gamma-glutamyl transferase; hs-CRP, high-sensitivity C-reactive protein; MELD, model for end-stage liver disease

between capillary density during post-occlusive hyperemia and albumin (r=0.679, P<0.001). No association was observed between capillary density during post-occlusive hyperemia and PWV (r=-0.022, P=0.873), while it was moderately and inversely associated with cIMT (r=-0.344, P=0.007). Similarly, the capillary density after venous congestion was inversely associated with MELD score (r=-0.574, P<0.001), MELD-Na score (r=-0.580, P<0.001), total bilirubin (r=-0.456, P<0.001), INR (r=-0.480, P<0.001), and CRP (r=-0.306, P=0.017), while it was positively correlated with albumin (r=0.641, P<0.001). There was no correlation between capillary density after venous congestion and PWV (r=-0.005, P=0.969). A moderate inverse association was detected between capillary density after venous congestion and cIMT (r=-0.360, P=0.005). Capillary recruitment was inversely correlated with MELD score (r=-0.431, P=0.001), MELD-Na score (r=-0.426, P=0.001),

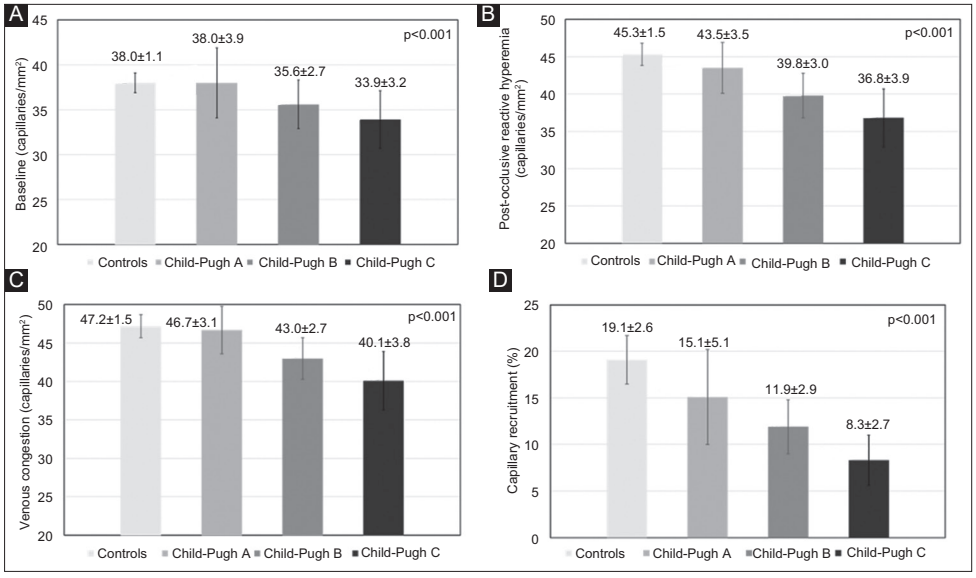

Figure 3 Capillary density at baseline (A), during post-occlusive reactive hyperemia (B), after venous congestion (C) and capillary recruitment (D) in different study subgroups

Table 2 Nailfold video-capillaroscopy parameters in patients with cirrhosis and controls

Parameters	Cirrhosis (n=60)	Controls (n=20)	P-value
Baseline capillary density (capillaries/mm²)	35.8±3.6	38±1.1	0.010
Capillary density during post-occlusive reactive hyperemia (capillaries/mm²)	40.0±4.4	45.3±1.5	<0.001
Capillary density after venous congestion (capillaries/mm²)	43.3±4.2	47.2±1.5	<0.001
Absolute increase in capillary density from baseline to post-occlusive reactive hyperemia (capillaries/mm²)	4.2±1.8	7.3±1	<0.001
Capillary recruitment (%)	11.8±4.6	19.1±2.6	<0.001

Values are mean ± standard deviation

total bilirubin (r=-0.394, P=0.002), INR (r=-0.275, P<0.033), and CRP (r=-0.303, P=0.019). Capillary recruitment was positively associated with albumin (r=0.416, P=0.001). No associations were observed between capillary recruitment and PWV (r=-0.037, P=0.789) or cIMT (r=-0.037, P=0.777).

Discussion

This study used NVC to compare microvascular function between patients with cirrhosis and controls, as well as among different stages of cirrhosis, and evaluated capillary density at rest, during post-occlusive reactive hyperemia and after venous congestion. Capillary density was significantly lower in cirrhotic patients compared to controls in all phases of NVC. Moreover, capillary density decreased with the deterioration of Child-Pugh stages. Similarly, capillary recruitment became progressively lower with worsening stages of cirrhosis, suggesting that increasing severity of cirrhosis is associated with more impaired peripheral microcirculatory function. This observation was also reinforced by the fact that capillary density and capillary recruitment were inversely correlated with MELD/MELD-Na score, total bilirubin and INR, whereas they were positively associated with albumin.

The endothelium is the inner cellular lining of blood vessels, which serves an important role in many vascular functions [26]. It is critically involved in the control of vasomotor tone and vascular permeability, procoagulant and anticoagulant activity, angiogenesis, inflammatory processes, and innate and acquired immunity [26]. Endothelial dysfunction refers to a state of imbalance between vasodilating and vasoconstricting factors, inappropriately favoring the latter [6]. It is considered as an early sign of microcirculation disruption and is associated with adverse cardiovascular outcomes [27-29]. Over the years, several methods have been used to assess peripheral endothelial and microvascular function in human studies, including venous occlusion plethysmography, flow-mediated dilatation (FMD), laser Doppler flowmetry, laser-speckle contrast imaging analysis and NVC [9]. The aforementioned methods have also been used in patients with cirrhosis with conflicting results [9,10]. A few studies found that FMD was lower in the early stages of cirrhosis, indicating a heightened vasodilatory response with the progression of the disease [11,12,30]. On the other hand, a number of studies have shown that peripheral endothelial function deteriorates progressively towards the advanced stages of cirrhosis [13,14,31]. In a recent meta-

Table 3 Arterial stiffness, wave reflection parameters and cIMT in the different study sub-groups

Parameters	Controls (n=20)	Child-Pugh A (n=20)	Child-Pugh B (n=20)	Child-Pugh C (n=20)	P-value
Arterial stiffness and wave reflections					
Aortic SBP (mmHg)	118.7±10.4	122.4±16.8	118.2±12.9	104.7±12.2	0.001
Aortic DBP (mmHg)	78±7.6	79.6±12.6	73.4±9.8	68.7±6.1	0.002
AP (mmHg)	13.6±6.3	16.4±8.7	18.2±8.1	11.6±7.2	0.052
AIx (%)	32.1±11	35.8±13.1	37.8±14.1	30.7±13.9	0.333
AIx(75) (%)	28.4±10.9	34.8±12.1	35.5±16.4	29±13.9	0.225
PWV (m/s)	7.9±1.3	7.9±2.2	7.7±1.4	7.1±1.7	0.417
cIMT					
Right (mm)	0.69±0.13	0.71±0.11	0.74±0.07	0.73±0.09	0.527
Left (mm)	0.71±0.14	0.70±0.10	0.74±0.07	0.72±0.09	0.713
Average (mm)	0.70±0.13	0.71±0.10	0.74±0.06	0.73±0.08	0.606

Values are mean ± standard deviation

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; AP, augmentation pressure; AIx, augmentation index; PWV, pulse wave velocity; cIMT, carotid intima–media thickness

analysis by our group, we found no difference in peripheral endothelial function, evaluated with semi-invasive or noninvasive methods, between patients with cirrhosis and controls, suggesting that the heterogeneous design of the included studies and potential confounding variables, such as the presence of cardiovascular risk factors, could have contributed to the above result [10].

NVC is a simple, noninvasive, dynamic method that can be used to evaluate endothelial function and microcirculation [16]. Capillary rarefaction refers to the reduction of capillary density in any given visual field, and can be divided into structural/anatomical, defined as a decrease in the overall number of capillaries, and functional, defined as a reduction in the number of perfused capillaries [32]. NVC, using post-occlusive reactive hyperemia and venous congestion, can provide information on both types of capillary rarefaction, offering important advantages compared to simple capillaroscopy. In particular, capillary density after venous congestion is considered to objectively determine the anatomic capillary number, as it can reveal non-perfused capillaries that may be overlooked through simple capillaroscopy [16]. Additionally, capillary density during post-occlusive reactive hyperemia evaluates the functional recruitment of initially non-perfused capillaries, being an indicator of both structural and functional integrity [16]. To the best of our knowledge, only 1 study has used NVC in patients with cirrhosis [33]. Brito-Azevedo *et al* used NVC to evaluate the microcirculation in cirrhotic patients and compare it with inflammatory parameters [33]. However, the authors did not apply the standardized methodology, as previously described in the literature, to assess the microcirculatory function, and they did not provide information about capillary density during post-occlusive reactive hyperemia and after venous congestion, which could be compared with our results [33].

Our study had a different scope: to evaluate peripheral microvascular function and to examine potential correlations with macrovascular parameters, in order to achieve a more accurate approach to changes in the peripheral circulation in patients with cirrhosis. First, we showed that baseline capillary rarefaction is greater in cirrhotic patients than in controls, and deteriorates with progressing Child-Pugh stages. In addition, patients with cirrhosis exhibited lower capillary density than controls, both during post-occlusive reactive hyperemia and after venous congestion, a difference that becomes progressively worse as the disease deteriorates, suggesting that cirrhosis impairs both structural and functional capillary integrity, while the severity of the disease exacerbates this impairment.

NVC has already been implemented in the evaluation of patients with various conditions, mainly patients with rheumatologic disorders; however, an increasing body of research now extends its application to hypertension, diabetes mellitus and chronic kidney disease [16-19]. Based on our findings, this technique could also be valuable in cirrhosis, potentially identifying patients with more advanced clinical status, impaired peripheral microcirculation and a worse prognosis. In this context, and given the simple, noninvasive nature of the methodology, NVC may represent a promising tool for bedside risk stratification. Furthermore, integrating NVC into routine hepatology practice could enable noninvasive monitoring of microvascular health over time, providing additional information beyond conventional biochemical and hemodynamic parameters. Serial NVC assessments might, for example, help track the progression of microvascular dysfunction, or evaluate responses to therapeutic interventions. Nevertheless, evidence in this area remains limited, and further research is needed to standardize protocols, validate prognostic thresholds, and determine the feasibility of incorporating this methodology into everyday clinical practice.

Regarding the macrocirculation, PWV, the gold-standard measure of arterial stiffness [34], and cIMT, a common measure of atherosclerosis [35], we found no significant differences between cirrhotic patients and controls, or between different stages of cirrhosis. Our findings are in partial agreement with existing studies. Novo *et al* found that PWV was

significantly higher in patients with hepatitis C virus (HCV) cirrhosis compared to controls, suggesting that HCV leads to subclinical vascular damage [36]. Huang *et al* measured PWV and demonstrated that cirrhotic patients had higher values than controls, while they found no disparities among different etiologies of cirrhosis, or between compensated and decompensated disease [37]. The absence of such differences (between patients and controls) in our study could probably be associated with the sample size. However, we demonstrated a mild reverse correlation between cIMT and capillary density, both during post-occlusive reactive hyperemia and after venous congestion, suggesting that microcirculatory dysfunction may be associated with macrovascular impairment in cirrhotic patients.

This study has several strengths. It is the first to examine the full spectrum of peripheral circulation alterations in patients with different stages of cirrhosis, including valid methods for evaluating both microcirculation (NVC) and macrocirculation (arterial stiffness, cIMT). We applied a strict and detailed protocol to assess microcirculation with NVC, adhering to the standardized methodology in the literature. The main limitation of the study is its observational character, which prevents the establishment of cause-and-effect relations. Although this is the largest study in the field, the sample was insufficient for conducting subgroup analyses that would have enabled us to examine the influence of additional factors on the differences we demonstrated. Finally, our findings regarding microvascular function should be interpreted with caution when extrapolating to other vascular beds. Endothelial cells throughout the vascular tree display considerable phenotypic heterogeneity in both structure and function; therefore, observations derived from one arterial or microvascular bed cannot be directly generalized to others [26]. Combining NVC with additional noninvasive techniques, such as the assessment of skin microvascular function using laser Doppler flowmetry and intradermal microdialysis, may offer a more comprehensive characterization of the peripheral microcirculation in patients with cirrhosis. While NVC provides high-resolution structural information on capillary density and recruitment, laser Doppler flowmetry can dynamically quantify cutaneous blood flow responses, while intradermal microdialysis allows a localized assessment of the release of endothelial mediators, such as nitric oxide or acetylcholine-induced vasodilation [9]. Future studies may therefore benefit from protocols that incorporate more than 1 complementary technique.

In conclusion, this study showed that capillary density at rest, during post-occlusive reactive hyperemia and after venous congestion, was lower in cirrhotic patients compared to controls, while it further deteriorated with advanced disease, as indicated by progressive Child-Pugh stages, suggesting that cirrhosis is characterized by impaired peripheral microvascular function, and that disease severity contributes to further microcirculation dysfunction. As endothelial dysfunction and microcirculatory disturbances are associated with adverse outcomes in different populations, further studies are needed to explore the potential effects of these findings on morbidity and mortality in patients with cirrhosis.

Summary Box

What is already known:

- Cirrhosis is characterized by dysregulation in both intrahepatic and systematic vasculature
- Peripheral microcirculation in cirrhosis is less well studied
- Endothelial dysfunction and microcirculation disruption are associated with cardiovascular risk
- Nailfold video-capillaroscopy evaluates functional alterations in capillaries and consequently microvascular function

What the new findings are:

- Capillary density in all functional phases decreases as cirrhosis progresses
- Capillary recruitment is significantly reduced in cirrhotic patients compared to controls, and progressively worsens with advanced Child-Pugh class
- Increasing severity of cirrhosis is associated with more impaired peripheral microcirculatory function
- Nailfold video-capillaroscopy, employing the standardized methodology, emerges as a simple, noninvasive tool for assessing peripheral microcirculation in patients with cirrhosis

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Supplementary material

Supplementary Table 1 Arterial stiffness, wave reflection parameters and cIMT in patients with cirrhosis and controls

Parameters	Cirrhosis (n=60)	Controls (n=20)	P-value
Arterial stiffness and wave reflections			
Aortic SBP (mmHg)	114.9±15.9	118.7±10.4	0.332
Aortic DBP (mmHg)	73.9±1.7	78.0±7.6	0.121
AP (mmHg)	15.3±8.3	13.6±6.3	0.405
AIx (%)	34.7±13.8	32.1±11	0.446
AIx(75) (%)	33.0±14.2	28.4±10.9	0.189
PWV (m/s)	7.6±1.8	7.9±1.3	0.511
cIMT			
Right (mm)	0.73±0.09	0.69±0.13	0.220
Left (mm)	0.72±0.09	0.71±0.14	0.596
Average (mm)	0.73±0.08	0.70±0.13	0.350

Values are mean ± standard deviation

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; AP, augmentation pressure; AIx, augmentation index; PWV, pulse wave velocity; cIMT, carotid intima–media thickness