Increased incidence of abnormal reflux flow in lower extremity veins of cirrhotic patients by Doppler ultrasonography

Nevbahar A. Degirmenci, MD, Aysegul H. Ozakyol, MD, Sahinde Atlanoglu, MD, Esra Akcan, MD, Salim Susuz, MD.

ABSTRACT

الأهداف: تحديد معدل حدوث انسياب الدم الغير طبيعي لدى أرجل المرضى المصابين بتليف الكبد بواسطة أشعة الدوبلر.

الطريقة: أجريت دراسة استطلاعية على 100 مريض و56 شخص من مجموعة الشاهد من كلية الطب، اسكهير، تركيا خلال الفترة من يناير 2010م و ديسمبر 2011م. قمنا بتصنيف الأرجل طبقاً لدرجات تصنيف الأسباب الاكلينيكية الحيوية. تم فحص الأعصاب الطرفيه السفليه والأعصاب في موضع الاستلقاء بواسطة أشعة الدوبلر لانسياب الدم. تم اعتبارتدفق الدم أكثر من 1000 غير طبيعي. تم تصنيف تدفق الدم إلى 3 أنواع سطحي، عميق، أو سطحي و/أو عميق. تم إجراء أشعة دوبلر للبطن أيضاً لفحص أعصاب البطن العلوية والعصب المجاور للسرة. أجري الاختبار الإحصائي باستخدام اختبار الانوفا واختبار تكي وتحليل العلاقة.

النتائج: أظهرت النتائج أنه 56% من المرضى مصابين بإصابة سطحية 56%، وعميقة 52%، وسطحي و/أو عميق 58%. كانت هنالك علاقة بين حدوث انسياب الدم ودرجته وتليف الكبد (p=0.002, p=0.000, p=0.001). كما تم توزيع المرضى إلى درجات من 1 إلى 4. كانت هنالك علاقة بين درجة التدفق 1 ودرجة التصنيف السطحية والعميقه (p=0.007, p=0.000) ودرجة التدفق 2 (p=0.004, p=0.041) ودرجة التدفق 4 (p=0.022, p=0.90). لم تظهر أي علاقة بين درجة التدفق 3 ودرجة التصنيف السطحية والعميقه. كما وجدت علاقة بين عصب السرة الجانبي ودرجة التصنيف السطحية (p=0.015).

خاتمة: تزداد الإصابة بحدوث انسياب الدم في أعصاب الأطراف السفلية لدى المرضى المصابين بتليف الكبد وتصنيفها يعطي معلومات مهمة.

Objectives: To determine incidence of abnormal reflux flow (ARF) in legs of cirrhotic patients by Doppler ultrasonography (DUS).

Methods: We prospectively studied 100 patients and 56 controls from the Faculty of Medicine, Eskişehir Osmangazi University Eskişehir, Turkey, between January 2010 and December 2011. We classified the legs according to the Clinical Etiology Anatomy Pathophysiology (CEAP) scores. Lower extremity superficial and deep veins were examined in supine position by DUS for ARF. Reflux flows more than 1000 msec were considered as abnormal. Abnormal reflux flow was classified in 3 categories as superficial (SARF), deep (DARF), and SARF and/or DARF (ARF). We also performed abdominal DUS to depict anterior abdominal collateral and paraumbilical vein. Statistical analysis was carried out by using analysis of variance with Tukey test, t-test, and correlation coefficient analysis.

Results: Percentages of SARF in patients were 56%, DARF 52%, and ARF 58%. Correlation analysis showed association between SARF or DARF or ARF and cirrhosis (p=0.002, p=0.000, p=0.001). Patients were distributed within CEAP 1 to CEAP 4. There was an association between SARF or DARF and CEAP 1 (p=0.007, p=0.000) or CEAP 2 (p=0.004, p=0.041) or CEAP 4 (p=0.022, p=0.90). We showed no correlation between CEAP 3 and SARF or DARF. There were also correlation between paraumbilical vein and SARF (p=0.015).

Conclusion: Cirrhotic patients increased incidence of ARF at lower extremity veins and CEAP classification creates and provides essential information.

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From the Departments of Radiology (Degirmenci, Atlanoglu, Akcan), Gastroenterology (Ozakyol), Internal Medicine (Susuz), Faculty of Medicine, Eskisehir Osmangazi University, Meselik Eskisehir, Turkey.

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Address correspondence and reprint request to: Dr. Nevbahar A. Degirmenci, Department of Radiology, Faculty of Medicine, Eskisehir Osmangazi University, Meselik Eskisehir, Turkey. E-mail: nakcar@ogu.edu.tr

Cirrhosis, the most evolved stage of liver fibrosis, is a systemic disease which brings some clinical complications such as portal hypertension, varices, variceal hemorrhages, ascites, and portosystemic encephalopathy.[1-3] Varices in cirrhotic patients, which are usually intra-abdominal, probably develops as a result of increased portal venous tension. We know that portal hypertension leads to collateralization, which are in communication with systemic circulation at special places. Varicose veins of lower extremities are seen in people aged 30-70 years in frequency of 10-40% usually secondary to venous insufficiency (VI),[4,5] which may develop due to valvular incompetence, that is the most common cause, primary muscle pump failure, or venous obstruction. Congenitally weak veins or abnormal valves may also dilate under normal hydrostatic pressure. Multiple pregnancies, old age, and white race are known risk factors.[4-7] On inspection, lower extremity of patients with VI shows varicosities, edema, color changes and even ulceration that could be categorized by Clinical-Etiology-Anatomy-Pathophysiology (CEAP) scoring system.[8] It is known that legs of the cirrhotic patients are also frequently edematous and have some changes in their skin. We thought that VI might be additional finding in cirrhotic patients and clinical findings of VI should be differentiated from the changes related to cirrhosis itself. As far as we know there are no report on this topic.

Diagnostic Doppler criteria of VI is ARF, which means reflux flow lasting more than 500 ms in standing position.[4-7] Portal hypertension could also be evaluated by Doppler ultrasonography. According to our experience, the most important limitation of Doppler ultrasonography (DUS) is difficulty in examination of deeply placed small vessels with slow flow. Additionally, it depends on patient cooperation and radiologist experience. It might be valuable to know the collaterals, that are placed other than abdomen of cirrhotic patients whose abdominal Doppler examinations are rather difficult and might need more expensive or invasive imaging methods such as computed tomography, magnetic resonance, or angiography.[2] It is known that lower extremity venous Doppler US is relatively an easy one. For this reason, we decided to evaluate cirrhotic patients legs for abnormal reflux flow (ARF) by DUS. Cirrhotic legs was also categorized according to CEAP scoring system.

Methods. We prospectively studied 100 patients and 56 healthy volunteers with cirrhosis recruited from the Gastroenterology Department, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey, between January 2010 and December 2010 prospectively. The study was approved by the local research ethics committee, and was carried out according to the principles of the Helsinki Declaration. Written informed consent was obtained from all participants.

Inclusion and exclusion criteria. Cirrhosis was diagnosed on the basis of protocol used in our gastroenterology department and the control group was included volunteers with no known disease and no leg problem. There were no patients with abdominal disease other than problems related to cirrhosis. We excluded patients with cavernous transformation, which might developed as a result of any other diseases. We did not include patients with primary leg problem such as lymph edema, arterial insufficiency, and with primary leg varices seen before diagnosis of cirrhosis. We also exclude patients with thrombosis in lower extremity veins. While forming control group, we excluded people from the study having potential of ARF by examining their legs according to CEAP scores.

All gray-scale, spectral and color DUSexaminations were carried out by a radiologist with 15 years experience. We used the same scanner (a Toshiba SSA 770A, Toshiba, Tokyo, Japan) and a 3-5 MHz convex (Toshiba, Tokyo, Japan) and 7.5 MHz lineer transducer (Toshiba, Tokyo, Japan). Examinations were performed in the mornings after fasting over night. The legs were inspected, and telengiectasia, varicosities, edema, and skin lesions were noted to make clinical classification (C) as part of the CEAP classification from 1 to 6.[8] We compared the findings with ARF at leg veins. We performed all the examinations in supine position because most of the patients were exhausted. We started with lower extremity venous Doppler ultrasonography. Then continued with abdominal gray-scale ultrasonography for presence of ascites. Although it was not possible to depict all the collateral, we tried to observed the abdominal varicosities by color Doppler ultrasonography. Spectral waveforms were optimized by using the lowest pulse repetition frequency (PRF) possible without aliasing, the greatest gain possible without background noise, a low wall-filter (50 Hz), and 2-4 mm Doppler gate.

Each limb was examined for ARF at 18 venous sites, including external pudendal vein, inferior epigastric vein, greater saphenous vein at the 4 region (saphenofemoral junction, thigh, upper calf, and lower calf), and lesser saphenous vein at the 2 region (saphenopopliteal junction and mid-calf). The deep veins were the common femoral, deep femoral, and femoral veins (proximal and distal), popliteal veins (proximal and distal), gastrocnemial vein, anterior and posterior tibial veins, peroneal vein, and perforating

veins. The main calf veins were examined in the midcalf. The gastrocnemial veins were evaluated within 2 cm before their union with the popliteal vein. We used rapid-inflation pneumatic cuffs with maximum pressure of 80 mm Hg to augment flow. These were placed distal to the venous segment under investigation. Time to inflation was 0.3 seconds, inflation was maintained for one second, and deflation was achieved in less than one second. For groin and proximal thigh vein measurements, the cuff was placed on the lower thigh, and for the other veins it was placed on the lower calf. Reflux flow for more than 1000 milliseconds after the release of pressure-cuff was considered. We summarized the lower extremity veins as SFJ, SPJ, GSV, SSV, deep veins including common femoral vein, femoral vein, deep femoral vein, popliteal vein and its branches, inferior epigastric or external pudendal vein (**Table 1**). Findings grouped as superficial ARF (SARF), deep ARF (DARF) and patients with ARF either with SARF or DARF (ARF). Superficial ARF included superficial veins of leg, DARF included deep veins of leg (**Table 2**).

Sonographically, ascites appeared anechoic, and in a different amount. Collateral depicted readily were paraumbilical and anterior abdominal collaterals.

Table 1 - Summary of patients and healthy volunteers with abnormal reflux flow.

Abnormal reflux flow	Patients (%)	Control (%)
Saphenousfemoral junction	44 (44)	9 (16)
Saphenouspopliteal junction	24 (24)	1 (2)
Deep veins	60 (60)	6 (11)
Great saphenous vein	16 (16)	4 (7)
Small saphenous vein	8 (8)	2 (4)
Popliteal vein and its branches	24 (24)	4 (7)
Epig. and pud.	16 (16)	2 (4)

Deep veins - Common femoral, femoral, deep femoral, popliteal veins and its branches, Epig. and pud. - Inferior epigastric vein and external pudendal veins

Table 2 - Patients and healthy volunteers according to the group of abnormal reflux flow (ARF).

Abnormal reflux flow	Patients (%)	Control (%)
SARF	56 (56)	10 (18)
DARF	52 (52)	6 (11)
ARF	58 (58)	10 (18)

SARF included saphenofemoral junction, saphenopopliteal junction, great saphenous vein, small saphenous vein inferior epigastric, and external pudendal veins. DARF - included common femoral, deep femoral, femoral, popliteal veins and its branches. ARF included either SARF or DARF

Correlation analysis was performed between findings related to lower extremity DUS and presence of cirrhosis and paraumbilical vein, stage of cirrhosis (child Pugh classification as A, B, and C), age of patients, duration of disease, and CEAP score of cirrhotic legs.

Statistical analysis. We sued the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) Version 15.0 software for all analyses. Continuous variables were compared across groups with one-way analysis of variance (ANOVA) with Tukey HSD multiple comparison test, and t test. The associations among the categorical variables were determined with Spearman's correlation coefficient analysis. P values less than 0.05 were accepted as significant. Power of the statistics was given.

Results. There were 41 cirrhotic women (with the age range of 29-71 years, mean age was 57 years) and 59 cirrhotic men (age range: 41-65 years, mean: 55 years). The control group included 26 women (age range: 35-69 years, mean: 50 years) and 30 men (age range: 35-75 years, mean 55 years). Cirrhosis was due to hepatitis B viruses (33 cases), hepatitis C viruses (40 cases), alcohol (12 cases), and Wilson disease (3 case). The reason was unknown (cryptogenic liver fibrosis) in 9 cases. We could not reach file follow up data in 3 cases during statistical analysis. Liver function tests are known to be useful diagnostic parameters and used in staging cirrhosis (child Pugh classification).[9] Distribution of patients according to stage of cirrhosis (child Pugh) was as follows: 36 patients were in stage A, 20 patients were in stage B, and 44 patients were in stage C. The mean duration of disease in cirrhotic patients was 5.2±5.5 years (ranging between a few days to 21 years). Disease duration, age of patients, stage of cirrhosis was not associated with ARF (p=0.123, p=356, p=549). Abnormal reflux flow was diagnosed when defined criteria were found.[4] The number and percentage of patients and healthy volunteers with ARF were summarized in **Table 1**.

Table 2 shows the numbers and percentages of ARF in different groups namely SARF, DARF, or ARF. On inspection, we detected CEAP 1 (telengiectasia) in 72 patients (72%), CEAP 2 (varicosities) in 22 patients (22%), CEAP 3 (edema) in 46 patients (46%), and CEAP 4 (color changes in skin) in 10 patients. There were no patients with CEAP 5 or CEAP 6. As patients were cirrhotic, etiological classification was not applied as we were not sure on the reason of ARF. In general, we observed abdominal collaterals in 74 patients (74%). Paraumbilical vein was detected in 24% patients. We noticed that large, patent paraumbilical vein almost

always accompanied by ARF in superficial or deep veins (**Figures 1A, 1B, 2A, 2B**). Abnormal reflux flow in deep veins was shown in **Figures 3A and 3B**. There were SARF in 22 of 24 patients with paraumbilical veins. We also observed that there were inferior epigastric ARF in 22 patients with paraumbilical vein. Ascites were seen in 52 patients. Correlation analysis between type of ARF and variables, which were presence of cirrhosis, paraumbilical vein, ascites, age and CEAP score including power of the tests were given in **Table 3**.

Discussion. Although there are various reports on collateralization in chronic hepatic diseases,[1-3,10-14] in this study we evaluate the lower extremity venous structures in cirrhotic patients by Doppler ultrasonography. Abnormal reflux flow was found to be more frequent in cirrhotic patients (56%) than healthy volunteers (18%). A prolonged VI characterized by some clinical signs,[6] which were classified with CEAP scoring system.[8] When we applied this scoring system to cirrhotic patients, we found association between type 1 to type 3 ARF and CEAP 1 (telengiectasia), or CEAP 2 (varicosities), or CEAP 4 (skin changes) but not with CEAP 3 (edema), as these patients might already have edematous legs due to complications of cirrhosis. We also observed that ARF at deep veins were more frequent in cirrhotic patients when compared with healthy volunteers (52% versus 11%). As it is known that ARF in deep venous system plays a significant role in the progression of venous insufficiency. Deep system reflux increases as clinical changes become more severe.[15]

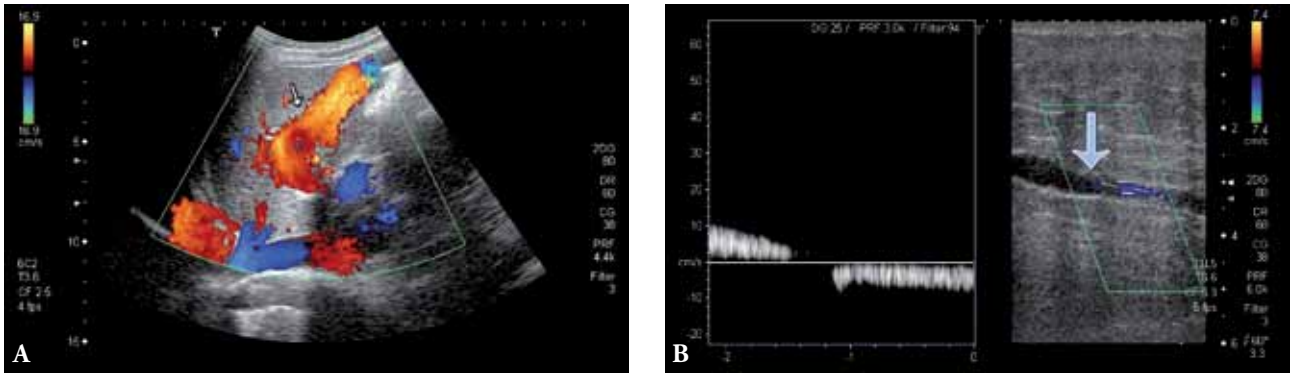

Figure 1 - A 29-year-old women with cryptogenic cirrhosis. Doppler ultrasonography showing **A)** Color Doppler image of liver shows vein with large diameter, red in color (white arrow). It originates from the left portal vein and courses, antero-inferiorly. Paraumbilical vein extends inferiorly towards umbilicus (not shown). The patient had also ascites (grade 2), not shown. Posteriorly, inferior vena cava and hepatic branches are seen, there is color overwrite artefact, red in color, around them. **B)** Spectral Doppler image related to lower extremity shows abnormal reflux flow in great saphenous vein (blue arrow).

Table 3 - Correlation analysis between variables related to cirrhotic patients and venous Doppler ultrasonography of lower extremities.

Variables	SARF		DARF		ARF	
	P-values	Correlation coefficients	*P*-values	Correlation coefficients	*P*-values	Correlation coefficients
Cirrhosis	0.002*	0.411*	0.000*	0.461*	0.001*	0.449*
Paraumbilical vein	0.015*	0.423*	0.082	0.297	0.082	0.297
Ascites	0.544	-0.111	0.180	-0.243	0.517	-0.119
Age	0.439	0.142	0.729	0.064	0.754	0.158
CEAP 1	0.007*	0.596*	0.000*	0.615*	0.000*	0.596*
CEAP 2	0.004*	0.498*	0.041*	0.393*	0.002*	0.522*
CEAP 3	0.699	0.071	0.320	0.181	0.595	0.098
CEAP 4	0.022*	-0.402*	0.242	-0.213	0.104	-0.293

SARF - abnormal reflux flow in superficial veins of lower extremities, DARF - abnormal reflux flow in deep veins of lower extremities, ARF -abnormal reflux flow either in superficial or deep veins. CEAP - Clinical-Etiology-Anatomy-Pathophysiology . *statistically significant *p*-values. Power of the tests ranged between 0.99 to 1.

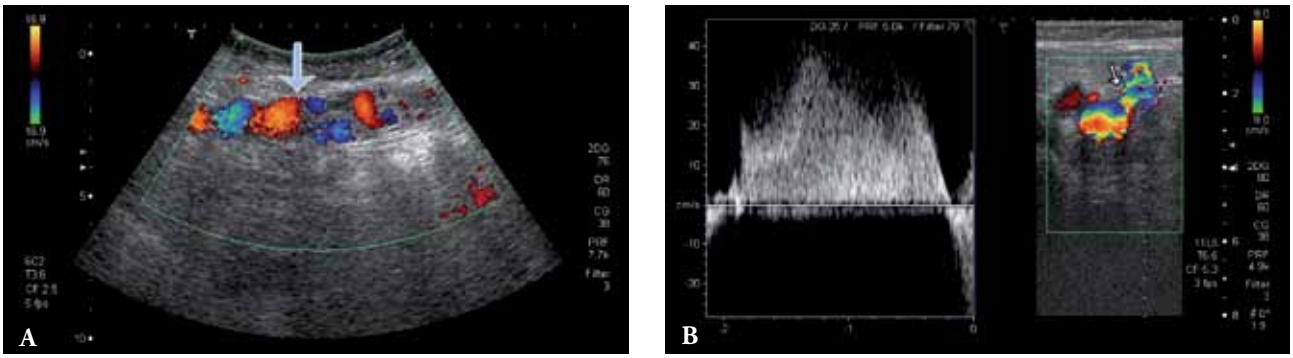

Figure 2 - Doppler ultrasonography of a 50-year-old women with primary biliary cirrhosis. **A)** Color Doppler image shows collateral vein just behind the anterior abdominal wall suggesting paraumbilical vein (blue arrow). **B)** Spectral Doppler image related to lower extremity shows abnormal reflux flow in saphenofemoral junction (white arrow).

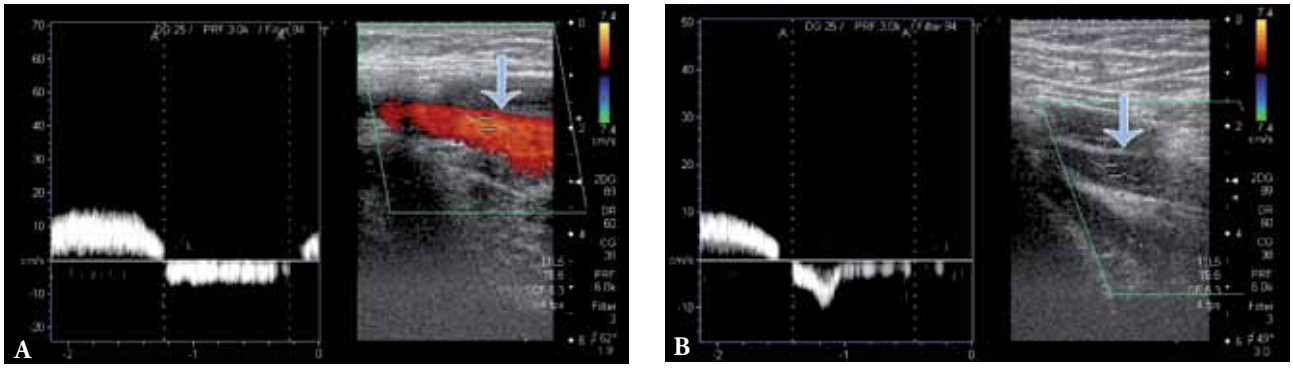

Figure 3 - A 44-year-old cirrhotic men with unknown etiology. Figures related to lower extremity venous Doppler ultrasonography. Spectral Doppler image shows reflux flow at **A)** common femoral and **B)** at femoral veins (blue arrows).

A dilated paraumbilical vein, reported to be seen in 10-43% of patients, is sensitive finding for diagnosis of portal hypertension. The vast majority of paraumbilical flow returns to the systemic circulation via one of the 2 inferior epigastric veins.[16] We showed correlation between inferior epigastric and external pudendal veins ARF and saphenofemoral junction incompetence in the present study. We noticed that almost all patients with inferior epigastric ARF had patent paraumbilical vein. We thought that increased hydrostatic pressure within these lower abdominal veins, which drains the paraumbilical vein, could play an important role in the development of valvular incompetence in lower extremities. Whenever we saw paraumbilical veins they were also accompanied by ARF in the legs of the patients. Depending on this result we thought that paraumbilical veins, even though not found in every patients, could play an important role in the development of ARF in cirrhotic patients. In the present study, the mean duration of disease was 5.2 years which was too short for normal people to developed severe ARF. We observed that there were no correlation between duration of disease or age of patients and ARF. Thus, we exclude the role of aging in development of ARF in cirrhotic patients in contrast to normal population.[4] As it was surprising to find no correlation between ascites and ARF. As it was known that multiple pregnancy, which causes increase in intra-abdominal pressure as well as hormonal alteration, could be a predisposing factor for VI. Probably the presence of intra-abdominal collaterals is more powerful predisposing factor than ascites.

The present study has some limitations. First, the sample size is small; however, one of the diagnostic parameter related to cirrhosis is collaterals. We observed that it was not possible to show all type of collaterals such as esophageal, splenorenal, retroperitoneal collaterals with accuracy of Doppler ultrasonography. For this reason, we included the anterior abdominal collaterals and paraumbilical vein that were shown readily by Doppler ultrasonography. It is known that detection of varices in the abdomen by DUS depends

on the user experience, patient's habitus and also quality of ultrasonography equipment. Additional small vessels and collaterals with slow flow are rather difficult to depict by Doppler ultrasonography. More powerful imaging methods such as computed tomography, magnetic resonance imagings, and endoscopic ultrasonography could be more valuable in evaluation of intra-abdominal collaterals.[2,16-18] Patient's clinical status might also affect quality of ultrasonographic imaging. In the present study, most patients were debilitated due to the complications of cirrhosis, which were esophageal hemorrhage, hepatic encephalopathy, or whatever else that was other limitation.

In conclusion, cirrhotic patients had increased tendency to developed ARF in their legs. As these patients are prone to develop many complications it would be better for physicians to be in alert of this condition, too. DUS is a noninvasive and practical method to follow up these patients. But sometimes it becomes difficult to perform abdominal DUS in condition such as abdominal distention, uncooperative patients, obesity, deeply placed vessels, small vessels, vessels with slow flow, and so forth. Probably, in this study, a smooth path for this difficulties frequently seen in cirrhotic patients as lower extremity varices are rather superficial which are readily seen by Doppler ultrasonography.

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