Internal and Emergency Medicine (2019) 14:705–711
https://doi.org/10.1007/s11739-019-02040-4

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Assessment of deep venous thrombosis in the lower extremity in Behçet's syndrome: MR venography versus Doppler ultrasonography

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Received: 9 October 2018 / Accepted: 18 January 2019 / Published online: 2 February 2019

Abstract

Lower extremity venous thrombosis (DVT) is the most common vascular manifestation of Behçet's syndrome (BS). Currently, Doppler ultrasonography (USG) is the most commonly preferred imaging modality in the diagnosis and follow-up of patients with acute and chronic DVT. Magnetic resonance (MR) venography, a quick and a non-invasive imaging modality, is successfully used to detect DVT in various settings. We had been unaware of studies with MR venography in BS. The aim of this study is to compare the diagnostic value of true fast imaging with steady-state precession magnetic resonance (True-FISP MR) venography and Doppler USG in the assessment of chronic DVT among patients with BS. 28 BS patients with chronic lower extremity DVT were studied. Common femoral (CFV) and femoral vein (FV) on both right and left sides were examined for the presence of thrombosis, recanalisation, collaterals and reflux. There are findings of chronic DVT in all Doppler USG images of 28 patients (45 of 56 FV and 35 of 56 CFV), while MR venography detects chronic thrombotic changes in 26/28 (93%) patients (43 of 52 FV and 28 of 52 CFV). Collateral veins are detected in 19 patients (19/28) with MR venography, whereas they are present in only 7 (7/28) with USG ($P=0.003$). Furthermore, patients with severe post-thrombotic syndrome are more likely to have collateral formation on the MR compared to those without (12/14 vs 7/14; $P=0.043$). Among patients with BS, MR venography might be an alternative or additional method to detect chronic thrombosis in the lower extremities.

Keywords Behçet's syndrome · Lower extremity venous thrombosis · MR venography · Color Doppler USG

Abbreviations

CFV	Common femoral vein
FV	Femoral vein
DVT	Deep-vein thrombosis
USG	Ultrasonography
MR	Magnetic resonance
BS	Behçet's syndrome
CV	Contrast venography
CDUS	Compression Doppler ultrasonography
USG	Ultrasonography
SFA	Superficial femoral artery
True-FISP MR	True fast imaging with steady-state precession (FISP) MR venography
VCSS	Venous clinical severity scoring
CEAP	Clinical, etiologic, anatomical, and by patho-physiological classification
PTS	Post-thrombotic syndrome

This article is part of the Topical Collection on Behcet disease.

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Introduction

Vascular involvement, an important cause of morbidity and mortality in Behçet's syndrome (BS) can be seen in up to 40% of the patients [1–3]. Lower extremity venous thrombosis (DVT) is the most common vascular manifestation [2–4]. Both deep and superficial veins as well as cerebral sinus veins can be affected [4, 5]. DVT occurs early through the course of the disease, runs a

relapsing–remitting course, and often precedes other major vascular involvement such as vena cava thrombosis, Budd–Chiari syndrome or pulmonary artery involvement [1–3, 6–8]. Severe post-thrombotic syndrome occurs in about half of the BS patients with DVT while venous claudication occurs in one-third [4, 5]. Both factors negatively affect the quality of life, and cause an increased rate of unemployment [4, 5].

Currently, compression Doppler ultrasound (CDUS) is the most commonly preferred imaging modality in the diagnosis and follow-up of patients with acute and chronic DVT [9]. Usually, the proximal veins are investigated, while compression is applied to the common femoral and the popliteal vein [9–11]. CDUS is quick, cost effective, practical, reproducible and provides anatomical data and hemodynamic evaluation. Nevertheless, its evaluation can be operator dependent, and its use might be limited in detecting thrombosis of proximal veins in the pelvis [10]. Additionally, it needs to be repeated in patients with normal findings [10]. The color Doppler ultrasonography (USG) on the other hand allows the evaluation of the entire deep venous system from the groin to the ankle [11]. Color flow artifacts are used to enhance small vessel visualization, nevertheless, compressibility still serves as the main element in diagnosis [10, 11]. With color Doppler USG, isolated calf DVT cannot be excluded; however, it needs high-quality equipment and experienced operators; therefore, it may not be available whenever it is needed for instance in the emergency setting [10, 11]. It has been shown that serial 2-point compression USG plus D-dimer is equivalent to color Doppler USG for the management of symptomatic outpatients with suspected DVT of lower extremities in non-Behçet cases [10]; thus, in routine clinical practice, one of the USG methods might be used [10].

Visualization of lower extremity veins have also been possible using computerized tomography (CT) and magnetic resonance (MR) venography. CT venography is semi-invasive, requires contrast material administration, and is associated with considerable radiation exposure [12, 13]. Furthermore, it may fail to depict some parts of the venous system due to the poor attenuation of deep veins in the limbs [13, 14]. MR venography on the other hand has the advantage of being quick, non-invasive and well tolerated, does not necessitate contrast injection or radiation exposure, and its interpretation is highly reproducible. It has been shown to be accurate when compared to contrast venography (CV) and color Doppler USG [15, 16]. It is less operator dependant and more advantageous for studying pelvic and lower limb veins, as the pelvic district cannot be assessed by compression evaluation alone.

We failed to find studies of MR venography in BS, and this study is designed to compare the diagnostic value of a non-contrast-enhanced MR venography to that of color Doppler USG in the assessment of DVT in patients with the diagnosis of BS.

Patients and methods

We studied all male 28 consecutive BS patients with DVT who attended the dedicated BS outpatient clinic at the Cerrahpasa Medical Faculty of University of Istanbul. All the BS patients had fulfilled the International Study Group Criteria [17]. By definition, all the patients had a documented thrombotic event in the lower extremities. DVT is defined as any (acute, subacute, or chronic) thrombotic event in any (superficial or deep) lower extremity vein demonstrated by a previous Doppler USG scan.

The disease duration for BS and age at DVT development was obtained from the charts. Demographic and clinical characteristics were surveyed by a standardized questionnaire. Clinical features of chronic venous disease were graded according to the venous clinical severity scoring (VCSS) and clinical, etiologic, anatomical, and by pathophysiologyical (CEAP) classification that had been used previously in BS [4]. Severe post-thrombotic syndrome (PTS) is defined as CEAP classes ≥ 4. Common femoral vein (CFV) and femoral vein (FV) on both the extremities were studied using both a repeat USG and non-contrast-enhanced MR venography. Sonographic images were interpreted without knowledge of MR venography data and MR images were interpreted by consensus of two radiologists (FK and BT) who were blinded to the USG examination.

Image analyzes of USG

Diameter and calibration of the venous lumen, fibrous septations, thrombus, Doppler flow signals, and reflux were evaluated using USG. The presence of collaterals adjacent to the FV or located in the deep muscular compartment or in the fascia was also evaluated. Images compatible with chronic venous thrombosis were divided into three groups defined as:

1. Chronic thrombosis with total occlusion: Lack of compression and augmentation response, the presence of echogenic thrombus in the lumen, lack of flow in Doppler examination or lack of color code in the lumen in color mode.
2. Chronic thrombosis with partial occlusion: Partial response to compression, the presence of weak Doppler signals and disorder in flow pattern, the presence of an area in the lumen which is not filled with color in color mode and the presence of echogenic thrombus in this area (Fig. 1a, b).

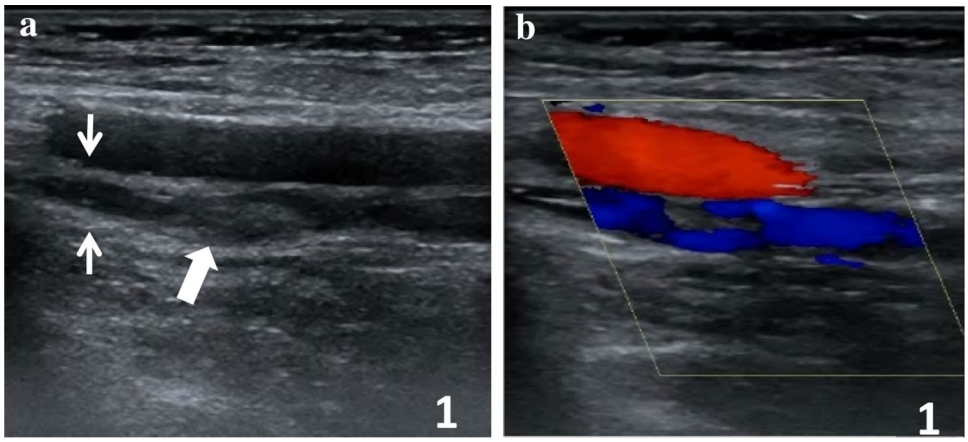

Fig. 1 **a** Gray scale US image in longitudinal plane: partial thrombus (thick arrow) and decrease in the lumen diameter of CFV (thin arrows). **b** Color Doppler US image at the same level of investigation. Weak thin flow pattern compatible with recanalization

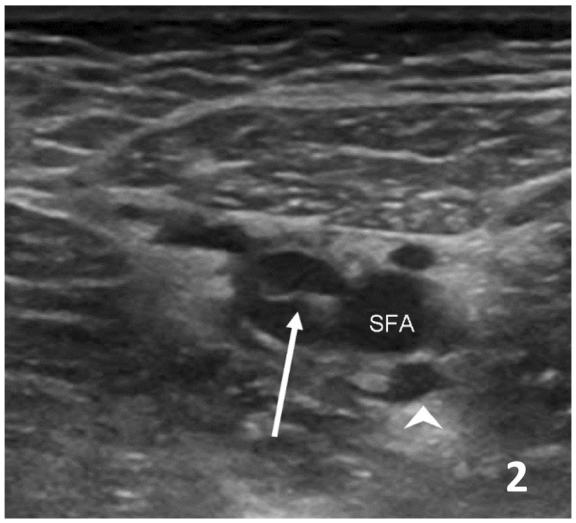

Fig. 2 Gray scale US image in axial plane. Fibrous septation in the lumen of FV (arrow). Large collateral venous structure near superficial femoral artery (SFA) (arrowhead)

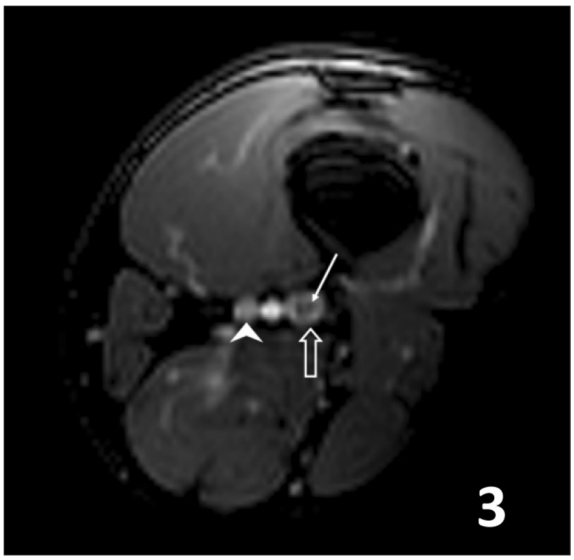

Fig. 3 Axial plane True-FISP MR venography. Fibrous septations (thin arrow) in the lumen of left FV (thick arrow). Large venous collateral structures near superficial femoral artery (SFA) (arrowhead)

3- Recanalized chronic thrombosis: Presence of hyperechogenic linear septation in the lumen and recanalization in the flow pattern (Fig. 2).

All these definitions are qualitatively based on the observations of the radiologists.

Image analyzes of true fast imaging with steady-state precession (FISP) MR venographies

True-FISP MR (1.5 T, Siemens Symphony) venography images were obtained using a multisection, two-dimensional, fast imaging and low-angle shot technique in axial and coronal planes from the femoral veins through the popliteal veins. DVT in chronic stage is defined as the presence of decreased vessel lumen diameter, hypointense fibrous linear septations (Figs. 3 and 4) within the lumen or a hypointense filling defects. The presence of collaterals adjacent to the FV, located in the deep muscular compartment or in the fascia is also assessed (Figs. 3, 4 and 5). Reflux could not be evaluated on MR venography.

The hospital local ethics committee approved the study protocol, and oral informed consent was obtained from all the patients.

Statistics

Categorical variables were compared using the Chi-square test or Fisher's exact tests, where appropriate. Comparisons of continuous variables were made using Student's *t* tests. Continuous variables with non-normal distributions were compared using Mann–Whitney *U* and

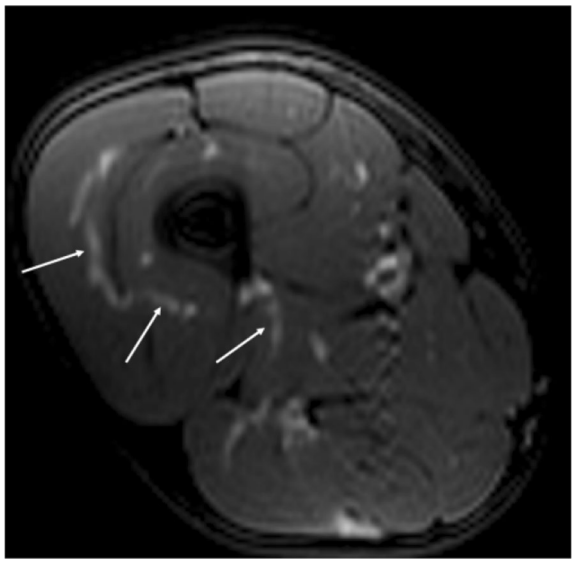

Fig. 4 Axial plane True-FISP MR venography. Dilated intramuscular collateral venous structures (arrows)

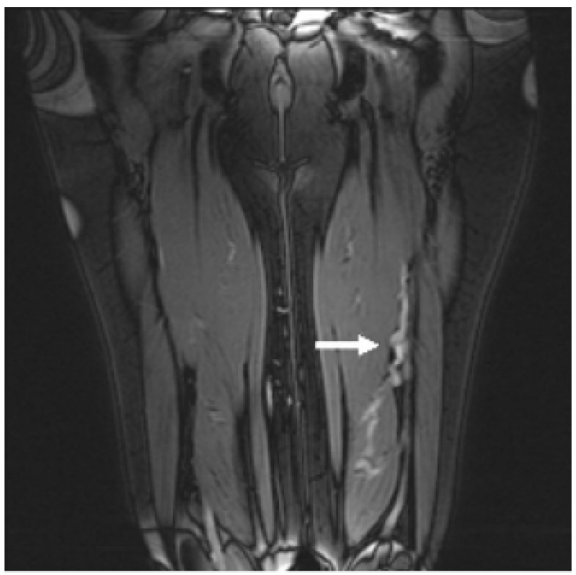

Fig. 5 Coronal plane True-FISP MR venography. Intramuscular dilated collateral vein on the left leg (arrows)

Kruskal–Wallis tests. The agreement between the two methods regarding the presence of thrombosis and collateral veins was evaluated using Kappa statistics.

All the tests were performed using version 18.0 of SPSS software for Windows (SPSS Inc, Chicago, IL).

Results

The mean age of the study subjects is 40.6 ± 12.4 years. The median [IQR] disease duration for BS and that for vascular disease are 10.4 [4.4–17.3] and 5.3 [1.5–8.5] years, respectively. The mean VCSS is 8.0 ± 4.7. Severe PTS is found in 14 patients (50%). All the patients were using immunosuppressive agents that was mostly azathioprine (25/28) and to a lesser degree colchicine (6/28), interferon (4/28) and corticosteroids (6/28).

Doppler USG findings (Table 1)

There are findings of DVT in chronic stage in all the Doppler USG images of 28 patients (45 of 56 FV and 35 of 56 CFV). DVT is bilateral in the majority (18/28, 64%). Chronic thrombosis with partial occlusion is the most common finding (32 FV and 27 CFV) compared to total occlusion (10 FV and 6 CFV) and recanalization (3 FV and 2 CFV). Additionally, there are changes compatible with subacute thrombosis in two patients. None of the patients had acute thrombosis. Reflux is identified in 41 FV and 34 CFV. Collaterals are detected in 7 patients (7 of 28 patients, 25%; 10 of 56 limbs). Three of these are observed on both legs. No intramuscular collateral formation is observed.

MR venography findings (Table 2)

MR venography is found to be normal in one patient, and inconclusive in another because of motion artifacts. Chronic thrombotic changes are identified in the remaining 26 patients (43 of 52 FV, 28 of 52 CFV) (Table 2). DVT is bilateral in 16/28 (57%).

The most common finding suggesting chronic thrombosis is the presence of hypointense linear fibrous septations within the vessel lumen. These are either solely present (22 FV and 16 CFV) (Fig. 3) or concomitant with a decrease in vessel diameter (7 FV and 5 CFV) (Fig. 4). In the remaining MR images, we observe a decrease in vessel diameter (12 FV and 5 CFV) or hypo-intense luminal filling defect (2 FV and 2 CFV). Changes suggesting subacute thrombosis such

Table 1 Doppler USG findings among 28 BS patients with LEVT

	FV, $n = 56$	CFV, $n = 56$
No thrombotic changes, *n* (%)	11 (20)	21 (37)
Chronic thrombus, *n* (%)	45 (80)	35 (63)
Partial	32 (57)	27 (48)
Total	10 (18)	6 (11)
Recanalized	3 (5)	2 (4)
Reflux	41 (73)	34 (61)

Table 2 MR venography findings among 28 BS patients with LEVT

	FV, $n=56$	CFV, $n=56$
Inconclusive MR venography[a], *n* (%)	2 (4)	2 (4)
No septae, normal luminal diameter, *n* (%)	11 (20)	26 (46)
Finding suggesting thrombotic changes, *n* (%)	43 (76)	28 (50)
Septae present, normal luminal diameter	22 (39)	16 (29)
Septae present, decreased luminal diameter	7 (13)	5 (9)
No septae, decreased luminal diameter	12 (21)	5 (9)
No septae, normal luminal diameter but intraluminal hypointense thrombus	2 (3)	2 (3)

[a]One patient had inconclusive findings

as increased vessel diameter, hypo-intense thrombus and increased signal within the adjacent fat tissue were observed in the same two patients in whom subacute changes were observed in Doppler US.

Collateral circulation is observed in 19 patients (19 of 28 patients, 68%; 31 of 56 limbs). These are bilateral in 12 patients. Collaterals adjacent to the FV are identified in both legs of five patients, while deep fascia or muscular collaterals are identified in 21 limbs of 28 patients.

USG MR correlation:

1. Side of thrombus: Color Doppler US and MR venography closely correlate with each other in the evaluation of the side of thrombus (USG: 24 R and 22 L; MR: 22 R and 20 L). The agreement with regard to detection of thrombosis is good (Kappa 0.77).
2. Collaterals: There is a significant difference between MR and Doppler in the evaluation of collateral circulation. MR venography allows an accurate view of collateral venous flow, and reveals more collateral vessels than Doppler does (19/28 vs 7/28) (Kappa 0.27). There is weak agreement in terms of collateral presence based per patient.

Clinical severity correlation with collateral presence on the MR:

VCSS values (14 ± 4.4 vs 5.0 ± 3.6; $P < 0.001$) are found to be significantly higher among patients with collateral formation on the MR than those without. Patients with severe PTS are more likely to have collateral formation on the MR compared to those without (12/14 vs 7/14; $P = 0.043$).

Discussion

We show that True-FISP MR venography and Doppler USG are comparable in the diagnosis of chronic DVT in patients with BS. MR venography identifies lesions compatible with chronic DVT in 26 of 28 patients who are shown to have evidence of chronic venous thrombosis based on USG. Collateral circulation is found to be significantly more apparent on MR venography compared to USG. Additionally, patients with collateral formation as indicated on the MR are found to have higher VCSS than those without, and patients with severe PTS are more likely to have collateral formation. On the other hand reflux can be observed only with USG.

In an early study that compares the diagnostic value of contrast venography (CV), MR venography and USG in 21 non-BS patients with either DVT or suspected pulmonary embolism, MR venography and USG are found to be comparable when compared with CV in diagnosing DVT above knee (MR: 100% sensitive and 100% specific; USG: 87% sensitive and 83% specific) [15]. In addition, MR venography reveals more collateral vessels than CV does [15].

MR venography has now become a valuable technique in detecting venous disease [15, 16]. Gadolinium-enhanced MR venography especially is considered to have superior accuracy to non-enhanced techniques [18]. Recent developments enable the acquisition of high-quality images of veins using fast MR imaging techniques [19, 20]. True-FISP MR venography emerges as a non-enhanced and non-invasive method that uses a very fast gradient-echo technique [19]. It has been proposed as an alternative to gadolinium-enhanced MR angiography in patients with suspected acute aortic dissection and aneurysm [20], lower extremity venous thrombosis [19, 21], mesenteric thrombosis [22] and the evaluation of the hepatic vasculature [23]. Although its use as a diagnostic modality may be limited because of the mixed T1/T2 contrast, it obtains good contrast in tissues that have different ratios of T1 and T2, such as blood and muscle [22]. Another important advantage of True-FISP imaging is that it requires only one short breath-hold and data acquisition time has considerably shortened [19]. Additionally, it may be repeated. Therefore, it may be suitable for the disabled, or for the patient in whom venous access can be a problem or cause vascular complications such as patients with BS. One further advantage of the MR venography over Doppler US, in any setting, is the lower inter- and intra-observer variability in the former [16].

In our study, we compare a non-invasive MR technique to Doppler USG rather than using gadolinium-enhanced method, to avoid possible vascular complications due to BS. Pathergy reaction that may result in thrombophlebitis, thrombosis or occlusions may be induced while doing venous punctures or venous canule/catheter insertions. This risk would be greater especially among male patients with vascular involvement.

Moreover, as shown in several studies, MR venography provides excellent visualization of the pelvic veins [16] contrary to Doppler US, which is often found to be unreliable in demonstrating thrombosis of the pelvic veins [15]. As

veins in BS are usually involved in a continuous and diffuse pattern, femoral veins are more likely to be affected together with the iliac veins and vena cava inferior [4]. Thus, MR venography can be effectively used to study the extent of venous involvement among patients with BS.

Venous circulation is usually maintained with the superficial and collateral vessels if the deep veins are totally occluded with thrombus. Cadaver studies have shown that an extensive system of veins provides communication between the distal FV and PV and the deep femoral vein [24]. Similarly, collaterals visualized with USG in the current study are found consistently parallel to the superficial femoral artery. As observed in our study, many of the deeper collateral pathways are not successfully imaged by the USG scan: collateral vessels are detected in 68% (19/28) of all the cases on MR venography, whereas they are detected in only 25% (7/28) on Doppler USG. As a result we confirm that True-FISP MR venography has a definite superiority over Doppler USG in detecting especially the deep collateral vessels. This superiority of MR venography might have an especially potential value in the management BS; as shown in the current study, patients with severe PTS or higher VCSS have significantly more collaterals. MR might also have a potential value in better determining the clinical severity, hence lead to a better management. It is well known that BS patients have increased tendency to form extensive venous and arterial collaterals, especially after thrombotic vascular events [4]. In a recent study done by our group, 78 (71 M, 7 F) patients with BS and 50 (29 M, 21 F) controls with idiopathic DVT were studied using CDUS [4]. Collateral formation is found to be significantly more common among BS patients compared to controls (31% vs 12%; $P=0.02$) [4]. Similarly, we had observed that there were extensive intra- and extra-hepatic venous collateral structures among BS patients with Budd–Chiari syndrome [25]. Finally, our group also indicates that bronchial arterial collaterals are an important cause of hemoptysis among patients with pulmonary artery involvement in the remission [26].

Limitations

Our study has some limitations. We studied only CFV and FV, although almost all deep and superficial veins can be involved in BS. All the patients had chronic DVT, and we could not include patients with an acute thrombotic attack. There were only two patients with subacute changes. The partial occlusion of a chronic thrombus was evaluated qualitatively rather than using a quantitative approach. It is well known that chronic thrombosis in non-BS patient population can show residual incompressibility in up to 50% of the cases after 1-year follow-up [27]. We did not evaluate the venous wall enhancement or measure the venous wall thickness. There were only male patients in our study. Since vascular involvement is more frequently seen among males in BS, we do not think that exclusion of females would cause substantial loss of information. Finally, it has to be noted that the sample size is rather small due to the explorative nature of this study.

Conclusions

Among BS patients, True-FISP MR venography might be an alternative or additional method to Doppler USG in detecting chronic thrombosis in the lower extremities, and has a definite superiority over Doppler USG in demonstrating the deep collateral vessels. This superiority of MR venography might especially have a potential value in the management of BS; as in the current study, patients with severe PTS or higher VCSS have significantly more collaterals.

Author contributions All the authors had access to the data and participated in writing of the manuscript.

Funding None.

Compliance with ethical standards

Conflict of interest Authors declare that they have no conflict of interest.

Statements on human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Oral informed consent was obtained from all the patients.

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