Original Article

Quantitative two-dimensional phase-contrast magnetic resonance imaging characterization of lower extremity venous disease: venous reflux versus venous obstruction

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Background: Lower extremity venous disease (LEVD) is a complex disorder, and determining the etiology of LEVD is paramount for treatment selection. Two-dimensional phase-contrast magnetic resonance imaging (2D PC-MRI) can provide an objective measure of hemodynamic status and may help differentiate between different etiologies of LEVD. A total of 271 participants, including 256 symptomatic patients with venous lower extremity disease and 15 healthy volunteers, were collected in this cohort study.

Methods: It is a single-center prospective observational study using 2D PC-MRI analysis to assess the hemodynamic characteristics of patients with LEVD among participants recruited between April 2017 and October 2021 at a tertiary hospital. The approval institutional review board number for this study were 201802137B0, 201901058B0, 202100938B0, and 202102344B0. Participants were classified as venous reflux (VR) and venous obstruction (VO) by standard ultrasonography. 2D PC-MRI by 1.5 T scanner revealed stroke volume (SV), forward flow volume (FFV), absolute stroke volume (ASV), mean flux (MF), velocity time integral (VTI), and mean velocity (MV) for each selected venous segments.

Results: 2D PC-MRI assessed 167 diseased legs from the 116 VR patients [mean age ± standard deviation (SD): 57.9±12.8 years; 39 males] and 113 diseased legs from the 95 VO patients (mean age ± SD: 66.4±12.8 years; 42 males). 2D PC-MRI analysis demonstrated discrimination ability to differentiate from VR to VO [SV, FFV, ASV, MF, VTI, and MV in the various venous segments, respectively, P≤0.001; area under the curve (AUC) =62–68.8%, P≤0.001 by Mann-Whitney *U* test]. The ratio data (morbid limb to normal limb) in the same individual with single-leg disease revealed differences between VR and VO (SV, FFV, ASV, and MF in the various venous segments, respectively; P<0.05; AUC =60.2–68.7%, P≤0.05

by Mann-Whitney *U* test). The most favorable differentiating variables of ratios were FFV in the great saphenous veins [AUC =68.7%, 95% confidence interval (CI): 59.8–77.6%] and ASV in the external iliac veins (AUC =67.4%, 95% CI: 58.7–76.2%).

Conclusions: Quantitative 2D PC-MRI analysis is capable of differentiating VR from VO. It also provides an important diagnostic capability for preoperative evaluation.

Keywords: Magnetic resonance imaging (MRI); non-contrast; phase contrast; reflux; obstruction; venous disease

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Introduction

Lower extremity venous disease (LEVD) covers morphological and functional abnormalities of the entire venous system. The clinical manifestations of LEVD range from utterly asymptomatic telangiectasia to symptomatic abnormalities such as edema, skin changes, itching, varicose veins, and venous leg ulcers. LEVD, mainly contributed by the pathophysiologic mechanism of venous reflux, reflux obstruction, or combined both, is a complex disease, responds slowly to treatment, and often requires repeated imaging assessments for the post-therapeutic response. Duplex ultrasonography (DUS), including grayscale B-mode and color Doppler, is considered the most reliable noninvasive method for diagnosing morphologic and hemodynamic abnormalities of LEVD (1). Distinguishing between venous reflux and venous obstruction is critical in determining treatment options. For example, saphenous vein ablation is recommended for patients with venous reflux, and endovascular stenting is recommended for patients with venous obstruction (2). However, the clinical utility of DUS is often limited in body habitus and bowel gas (3), which decline the visualization of iliac veins and inferior vena cava (IVC). In addition, the criteria of Doppler measurement used to define the severity of morphological stenosis are still being developed (2). Ultrasonography is known to be operator dependent. Thus, further evaluation using cross-sectional imaging modalities, such as contrast-enhanced magnetic resonance angiography (CE-MRA) and computed tomography angiography (CTA), is often required after a positive ultrasonography result. CE-MRA and CTA can provide more objective diagnoses and are more suited for evaluating the pelvic vessels and IVC. However, CE-MRA and CTA can only provide morphologic diagnoses without hemodynamic information. Although time-resolved magnetic resonance angiography can visualize the dynamic flow of contrast agents, it still lacks quantitative measurements.

Non-contrast magnetic resonance angiography (NC-MRA), including several different contrast mechanisms, has potential clinical utility in evaluating LEVD. The NC-MRA using a gated three-dimensional (3D) turbo spin-echo short tau inversion recovery (TSE-STIR) sequence has been used for diagnosing the LEVD from 2017 in our laboratory and was found to be efficacious in combination with DUS in a preliminary report (3,4). Under the 3D TSE sequence, arterial blood flows fast and leads to flow voids during the cardiac systolic phase. Thus, by 3D TSE-STIR sequence, the systolic-phased scan will acquire a dataset with only venous structures [magnetic resonance venography (MRV)] because STIR provides extra background (fat and bone) suppression. This noninvasive diagnostic method found correctable venous lesions in 15% of patients with negative ultrasonography results (5). The morphology of the whole venous anatomy of lower extremities, particularly the low-flow superficial venous system and pelvic collaterals in different diseases, could be clearly demonstrated through 3D imaging without the use of a contrast medium or radiation (6,7). In addition to the gated 3D TSE-STIR sequence for morphological evaluation, we also conduct quantitative analysis using the two-dimensional (2D) phase-contrast (PC) magnetic resonance imaging (MRI) sequence for hemodynamic measurement of various venous segments. This technique can quantify PC parameters of regions of interest drawn on a 2D plane, also known as quantitative PC-MRI. Currently, quantitative PC-MRI technology has been applied to cerebrospinal fluid, cardiovascular system, and aortic disease (8-10). However, rarely applied in peripheral vascular disease. The MRI protocol using gated 3D TSE-STIR MRV combined with quantitative 2D PC-MRI analysis has become the standard preoperative assessment for LEVD at our institution and works well (6,7,11-15). In this study, we focused on the

2D PC-MRI results and propose a noninvasive method to quantitatively define differences between venous pathologies of the lower extremity, especially for distinguishing venous reflux from venous obstruction. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1194/rc).

Methods

Participants

The Institutional Review Board of Chang Gung Memorial Hospital approved this study (institutional review board Nos. 201802137B0, 201901058B0, 202100938B0, and 202102344B0). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all participants. The study collected data from 271 participants using NC-MRA for evaluating lower extremities at a tertiary hospital between April 2017 and October 2021. All data were prospectively collected and retrospectively analyzed. Initially, 256 symptomatic patients with venous lower extremity disease were evaluated, and 21 patients were excluded. Exclusion criteria were pregnancy, restless legs, arrhythmia, morbid obesity, and devices not compatible with MRI. The remaining 235 patients were grouped by clinical presentation and then classified by DUS. According to the symptoms presented indication, we grouped the patients into the following: namely superficial venous varicose with venous reflux, stasis leg ulcers, swollen legs favoring venous obstruction, edema, and other presentation. The venous reflux patients were diseased in both the deep and superficial systems, however, the superficial systems were usually more obvious. The venous obstruction referred to the deep vein system. Before the scheduled MRI, the DUS was performed with patients in the supine position. The femoral vein (FV), great saphenous vein (GSV), popliteal vein (PV), and perforating vein in the calves were examined. Standard duplex sonography and color Doppler imaging were performed on the same device and reported by two sonographers (YK Huang, YH Tseng), using defined morphological and hemodynamic criteria. The two sonographers are specialized cardiovascular surgeons and have fourteen years of experience (YK Huang) and ten years of experience (YH Tseng) in the field of ultrasound examination, respectively. According to the ultrasonographic result, the venous pathologies were classified as follows: venous reflux, venous obstruction, and mixed or undetermined cause. All the patients have then evaluated by MRI. Besides, 15 healthy volunteers were enrolled for evaluating the venous condition using MRI. The inclusion criteria of the healthy controls were adult subjects without any lower extremity symptoms nor any known vascular disease of the lower extremity. All MRI images are reported by a radiologist (CW Chen) with 10 years of experience and specializing in vascular radiology. Although all subjects underwent MRI, only the interest groups (venous reflux, venous obstruction, healthy control) were analyzed using 2D PC-MRI data to compare differences between groups. *Figure 1* demonstrated the flow chart of the identification and exclusions of the study cohort.

MRI data acquisition

All data were collected using a 1.5-T MRI scanner (Philips Ingenia, Philips Healthcare, Best, The Netherlands). The dStream Whole Body coil was used for the inspection. It includes two dStream Torso anterior coils. Combined with the FlexCoverage posterior, it enables 200 cm coverage with a maximum of 108 channels. During scanning, the system will automatically detect the range of the scanning area and activate the corresponding part of the coils to receive signals. The examinee enters head first in a supine position with his hands placed overhead. Technicians stuck the electrocardiography (ECG) electrodes on the chest to detect the patient's heart rhythm and then use the heart synchronization method to obtain images. MRI protocol included gated 3D TSE-STIR MRV (*Figure 2*) for anatomic diagnosis and quantitative 2D PC-MRI for hemodynamic analysis. Under the TSE sequence, arterial blood flow is rapid and causes flow voids during systole. Therefore, using a 3D TSE-STIR sequence to trigger the imaging acquisition during systole, the collected 3D dataset will contain only venous structures, as STIR provides additional background (fat tissue) suppression. The total scan range includes the kidneys and ends at the feet. 3D TSE-STIR MRV images were acquired as scanning at four levels of coronal planes (abdomen, pelvis, thigh, and lower leg) using the following parameters: repetition time, 1 beat; echo time, 85 ms; inversion recovery delay time, 160 ms; voxel size, 1.7 mm × 1.7 mm × 4 mm; field of view, 360 mm × 320 mm. Quantitative 2D PC-MRI is scanning at four axial planes using the following parameters: repetition time, 16 ms; echo time, 8 ms; tilt angle, 10 degrees; 25 images/period; slice

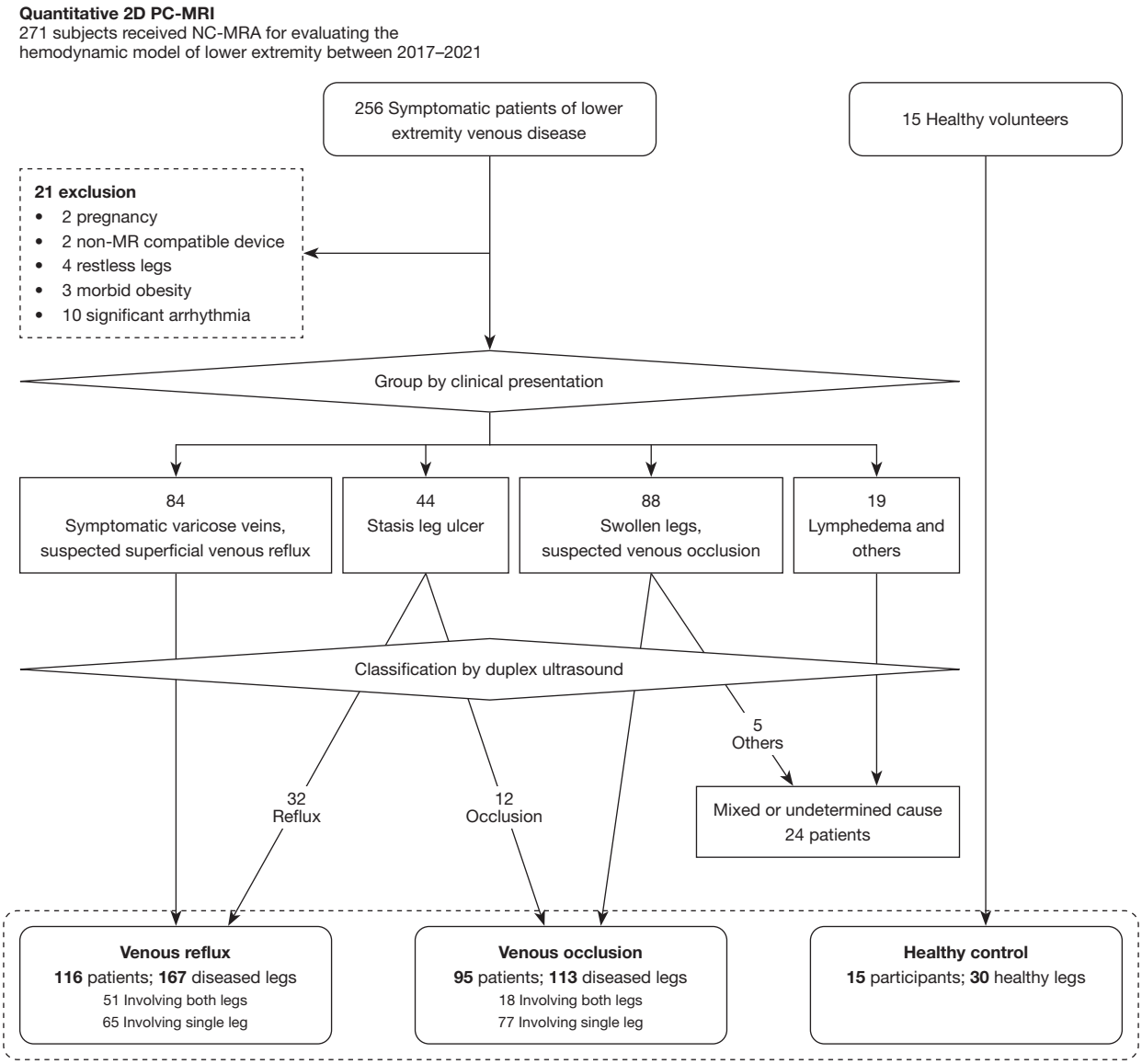

Figure 1 Cohorts of the study. 2D, two-dimensional; PC-MRI, phase-contrast magnetic resonance imaging; NC-MRA, non-contrast magnetic resonance angiography.

thickness, 5 mm; pixel size, 0.33 mm × 0.33 mm; velocity encoding, 80 cm/s. The whole process of MRI requires 25 minutes for imaging acquisition, imaging reconstruction, and 2D PC-MRI analysis.

Hemodynamic variables

By drawing the region of interest (ROI) on the vascular lumens (covering the whole lumen) at axial planes of the IVC, external iliac vein (EIV), FV, PV, and GSV (*Figure 3*) by an experienced medical radiation technologist (SC Wang), the variables will be generated by measuring the phase-shifting information of the voxels within the ROI. All of the eight variables are shown as follows: stroke volume (SV), the net volume of blood that passes through the lumen during one heartbeat; forward flow volume (FFV), the volume of blood that passes through the lumen in the positive direction (toward the head) during one heartbeat; backward flow

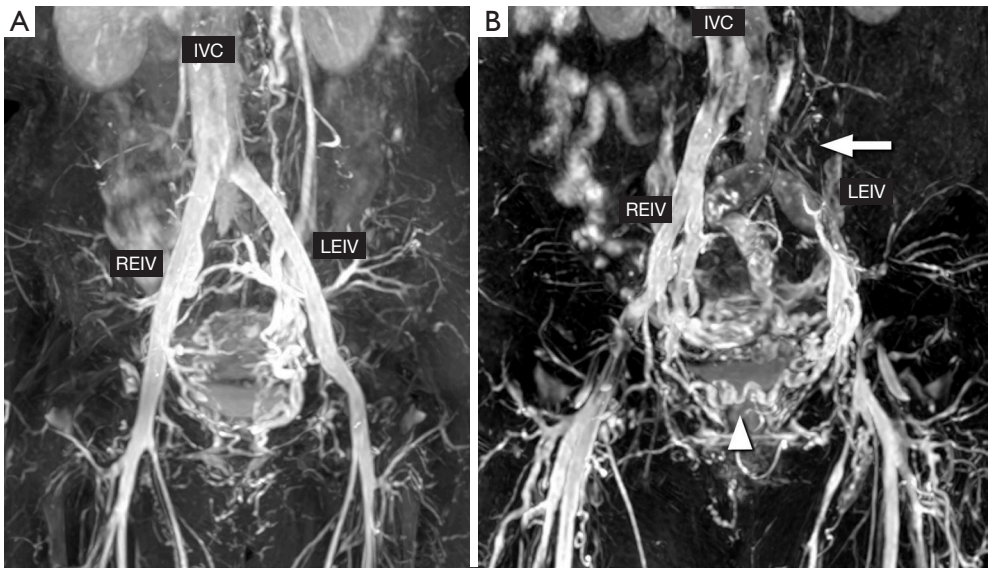

Figure 2 Pelvic image of three-dimensional magnetic resonance venography in two typical pathologies: venous reflux (A) and venous obstruction (B). (A) Patent pelvic veins with few transverse collaterals veins were noticed in venous reflux disease. (B) A gap (arrow) in the left external iliac vein and lots of transverse collateral veins (arrowhead) indicated the obstruction of the left external iliac vein. IVC, inferior vena cava; LEIV, left external iliac vein; REIV, right external iliac vein.

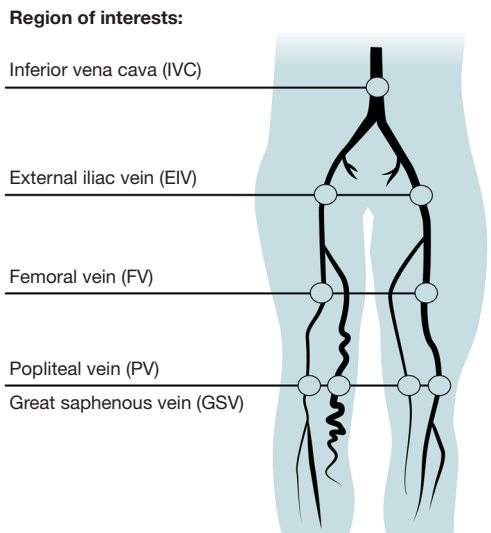

Figure 3 Drawing ROI for the hemodynamic analysis. Two-dimensional phase-contrast magnetic resonance imaging scanning is performed to obtain images containing phase shift information. By drawing 9 ROI covering vascular lumen in 4 axial planes, eight flow-related variables can be acquired for each ROI. ROI, region of interest.

volume (BFV), the volume of blood that passes through the lumen in the negative direction (toward the foot) during one heartbeat; regurgitant fraction (RF), the fraction of the BFV to FFV; absolute stroke volume (ASV), the absolute value of FFV plus the absolute value of BFV; mean flux (MF), stroke amount × heartbeat/60 × (1 – heartbeat); velocity time integral (VTI, also known as stroke distance), the net distance that blood proceeds in the vessel during one heartbeat; mean velocity (MV), stroke distance × heartbeat/60 × (1 – heartbeat).

Statistical analysis

Demographics characteristics of patients were compared using a one-way analysis of variance for continuous variables and Fisher's exact test for categorical variables. According to the primary diagnosis made using ultrasonography, we compared the clinical characteristics of patients with venous reflux and those with venous obstruction by using an independent sample *t*-test for age or Fisher's exact test for categorical variables. This study used both DUS and

Table 1 Demographic characteristics of patients with venous reflux and venous obstruction and healthy volunteers

Variables	Venous reflux (n=116)	Venous obstruction (n=95)	Healthy control (n=15)	P value
Age (years)	57.9±12.8	66.4±12.8	42.1±11.9	<0.001
Male	39 (33.6)	42 (44.2)	2 (13.3)	0.043
BMI (kg/m^2)	26.2±5.00	26.4±4.35	–	0.750
Family history of reflux	5 (4.3)	3 (3.2)	0 (0.0)	0.873
Smoke	15 (12.9)	22 (23.2)	0 (0.0)	0.028
Alcohol	12 (10.3)	17 (17.9)	0 (0.0)	0.081
Betel nuts	8 (6.9)	8 (8.4)	0 (0.0)	0.494
Hypertension	21 (18.1)	48 (50.5)	0 (0.0)	<0.001
Diabetes mellitus	14 (12.1)	19 (20.0)	1 (6.7)	0.093
Stroke	1 (0.9)	0 (0.0)	0 (0.0)	0.621
Coronary arterial disease	0 (0.0)	2 (2.1)	0 (0.0)	0.249
Deep vein thrombosis	2 (1.7)	21 (22.1)	0 (0.0)	<0.001
Cancer	5 (4.3)	23 (24.5)	1 (7.1)	<0.001

Data were presented as mean ± standard deviation or frequency (percentage). BMI, body mass index.

3D TSE-STIR MRV to detect venous obstruction. DUS (standard reference) examination results were considered the actual outcome to evaluate the comparative sensitivity, specificity, and accuracy of 3D TSE-STIR MRV. Cohen's kappa coefficient (k) was used to evaluate the inter-rater reliability between both tests. Due to the lack of normality, the data of 2D PC-MRI are expressed as median and interquartile range. The 2D PC-MRI data of diseased legs with different diagnoses (normal, reflux, and obstruction) were compared using Kruskal-Wallis test, with Bonferroni adjustment for post hoc comparison. The ability of 2D PC-MRI to discriminate different diagnoses (i.e., distinguish reflux from normal) was assessed through receiver operating characteristic curve analyses. The cutoff was determined using the Youden index. Patients with unilateral morbid leg were further identified and classified into reflux and obstruction groups. The 2D PC-MRI ratios of morbid and healthy limbs in the reflux and obstruction groups were compared using the Mann-Whitney *U* test. Lastly, the ability of 2D PC-MRI ratio data to distinguish between reflux and obstructive venous diseases was evaluated through receiver operating characteristic analysis. All tests were two-tailed, and P<0.05 was considered statistically significant. Data analyses were conducted using SPSS 25 (IBM SPSS Inc., Chicago, Illinois, USA).

Results

Participants characteristics

According to clinical presentations, the patients were grouped: varicose veins with leg soreness in 84 patients, stasis leg ulcers in 44 patients, cyanotic swollen legs in 88 patients, and atypical presentation (e.g., back pain) in 19 patients. Further classification by DUS identified that 116 and 95 patients had venous reflux and venous obstruction, respectively (*Figure 1*). Additionally, 15 volunteers were recruited as healthy controls. *Table 1* summarizes the demographic data of these 226 subjects. Patients with venous reflux were younger and had fewer comorbidities than those with venous obstruction, particularly regarding hypertension, malignant disease, and a history of deep venous thrombosis. There was no significant difference in body mass index (BMI) values between patients with venous reflux (26.2±5.00 kg/m^2) and venous obstruction (26.4±4.35 kg/m^2). The participants included both male and female, so we did not record the number of gravidity and parity. Data on BMI and parity in healthy controls were missing.

Venous obstruction detection by 3D TSE-STIR MRV

DUS detected cases of venous obstruction were compared

with the detected cases by 3D TSE-STIR MRV. Inter-rater reliability between 3D TSE-STIR MRV and DUS showed substantial agreement (k, 0.765). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 3D TSE-STIR MRV were 88.5%, 88.62%, 84.04%, 91.93% and 88.67%, respectively (Table S1).

2D PC-MRI analysis among reflux, occlusion, and controls

Table 2 shows the details of the 2D PC-MRI analysis including a total of 167 morbid legs with venous reflux, 113 morbid legs with venous obstruction, and 30 healthy legs. The SV, FFV, ASV, MF, VTI, and MV were broadly different among the legs with venous reflux, legs with venous obstruction, and healthy legs in most venous segments. The BFV, RF, VTI, and MV in the PV segment were similar in the three groups of legs (reflux, obstruction, and healthy). Comparison between the three groups showed that the venous obstruction legs had the lowest: (I) SV/FFV/ASV/MF in the IVC, EIV, FV, and GSV segments; (II) VTI in the IVC, FV, and GSV segments; (III) MV in the IVC and GSV segments. The venous reflux legs had higher SV, FFV, ASV, MF, VTI, and MV in GSV segments than did venous obstruction legs. The detailed comparison of 2D PC-MRI data of venous reflux, venous obstruction, and healthy legs is listed in the Table S2. The most differences were found between the venous obstruction and venous reflux legs; venous obstruction legs had lower SV, FFV, ASV, MF, VTI, and MV than did venous reflux legs, with a discriminating ability (P<0.005 in most venous segments, except the VTI and MV in the PV segment). The most favorable discriminating value for obstructive and reflux legs was found for ASV in GSV segment [area under the curve (AUC) =68.8%, 95% confidence interval (CI): 62.4–75.2%], SV in GSV segment [AUC =68.5%, 95% CI: 62.1–74.9%], and FFV in GSV segment (AUC =68.4%, 95% CI: 62.0–74.8%). Comparing venous obstructive and normal control legs, the SV, FFV, ASV, MF, VTI, and MV in the IVC segment (all P<0.05); SV, FFV, ASV, and MF in the EIV segment (all P<0.05); SV, FFV, ASV, MF, and VTI in the FV segment (all P<0.05); and SV, FFV, ASV, MF, VTI, and MV in the GSV segment (all P<0.05) were lower in venous obstructive legs than in healthy legs (*Figure 4*). Fewer differences between venous reflux and healthy legs were noticed.

Ratio of morbid limb to normal limb in the same individual

To minimize individual bias in the 2D PC-MRI analysis, we analyzed the ratios data of morbid limb to normal limb in the same patients: 65 and 77 patients had single-leg venous reflux and venous obstruction, respectively (*Figure 1*). The ratios of SV, FFV, ASV, MF in the EIV, FV, and GSV segments and the ratios of VTI and MV in the EIV segments were different between venous reflux and venous obstruction (*Table 3*, *Figure 5*).

Ability of 2D PC-MRI to discriminate reflux from obstruction

The AUC was then further calculated to determine the best cut-off point that were able to distinguish between venous reflux and venous obstruction, except for the variables that were not statistically significant in *Table 3* (*Table 4*). The most favorable differentiating variables for reflux and obstructive legs were FFV in the GSV segments (AUC =68.7%, 95% CI: 59.8–77.6%) and ASV in the EIV segments (AUC =67.4%, 95% CI: 58.7–76.2%).

Discussion

This study initially evaluated 271 participants using duplex ultrasound and NC-MRA and found that MRV using the gated 3D TSE-STIR sequence demonstrates substantial agreement (k, 0.765) to DUS for the diagnosis of lower extremity venous obstruction. Besides, MRV using the gated 3D TSE-STIR sequence also displayed excellent performance for the diagnostic tests (sensitivity, specificity, and accuracy were 88.5%, 88.62%, and 88.67%, respectively); these results were similar to our previous report (3,5). The study then applied 2D PC-MRI analysis to assess the hemodynamic models of 226 participants and 310 legs (*Figure 1*). The measured hemodynamic models were broadly different among the legs with venous reflux, legs with venous obstruction, and healthy legs (*Table 2*). The venous obstruction legs had the lowest flow measurements in almost all venous segments (SV, FFV, ASV, and MF in the IVC, EIV, FV, and GSV segments, respectively; P<0.001). The venous reflux legs had higher flow measurements in GSV segments than healthy legs and venous obstruction legs (SV, FFV, ASV, MF, VTI, and MV in the GSV segments, respectively; P<0.001). This finding is similar to that of Kim *et al.*, who evaluated 99 patients with venous insufficiency using ultrasonography and found that GSV with venous reflux was more prominent in diameter than those without venous reflux (16). That may be related to the development of GSV varicose veins due to venous

Table 2 Two-dimensional PC-MRI characteristics among diseased legs and healthy legs

Variables	Normal (n=30)	Venous reflux (n=167)	Venous obstruction (n=113)	P value
SV (mL)				
IVC	17.0 [12.4, 23.2]	11.27 [0.01, 17.10]*	0.01 [0.01, 14.72]*#	<0.001
EIV	4.18 [2.79, 4.71]	3.91 [2.15, 5.79]	1.81 [0.11, 4.17]*#	<0.001
FV	1.11 [0.84, 1.52]	1.18 [0.61, 1.80]	0.66 [0.04, 1.19]*#	<0.001
PV	0.58 [0.33, 0.85]	0.66 [0.27, 1.12]	0.48 [0.01, 0.89]#	0.021
GSV	0.29 [0.13, 0.57]	0.34 [0.05, 0.67]	0.05 [0.01, 0.25]*#	<0.001
FFV (mL)				
IVC	17.0 [12.4, 23.6]	11.56 [0.01, 17.18]*	0.01 [0.01, 14.82]*#	<0.001
EIV	4.18 [3.00, 5.09]	3.96 [2.15, 5.89]	1.50 [0.01, 4.20]*#	<0.001
FV	1.13 [0.84, 1.52]	1.19 [0.61, 1.80]	0.66 [0.10, 1.27]*#	<0.001
PV	0.60 [0.33, 0.86]	0.66 [0.27, 1.12]	0.48 [0.01, 0.89]#	0.021
GSV	0.30 [0.15, 0.57]	0.35 [0.08, 0.67]	0.06 [0.01, 0.28]*#	<0.001
BFV (mL)				
IVC	0.00 [0.00, 0.43]	0.00 [0.00, 0.01]	0.01 [0.00, 0.01]	0.094
EIV	0.00 [0.00, 0.25]	0.00 [0.00, 0.01]	0.00 [0.00, 0.01]	0.020
FV	0.00 [0.00, 0.01]	0.00 [0.00, 0.00]	0.00 [0.00, 0.01]	0.036
PV	0.00 [0.00, 0.00]	0.00 [0.00, 0.01]	0.00 [0.00, 0.01]	0.113
GSV	0.00 [0.00, 0.02]	0.00 [0.00, 0.01]	0.01 [0.00, 0.01]	0.019
RF (%)				
IVC	0.00 [0.00, 1.85]	0.00 [0.00, 0.01]	0.01 [0.00, 0.01]	0.095
EIV	0.00 [0.00, 6.02]	0.00 [0.00, 0.01]	0.00 [0.00, 0.01]	0.110
FV	0.00 [0.00, 1.84]	0.00 [0.00, 0.00]*	0.00 [0.00, 0.01]	0.019
PV	0.00 [0.00, 0.78]	0.00 [0.00, 0.01]	0.00 [0.00, 0.01]	0.106
GSV	0.00 [0.00, 15.31]	0.00 [0.00, 0.06]	0.01 [0.00, 0.01]	0.053
ASV (mL)				
IVC	18.4 [12.4, 24.4]	11.56 [0.01, 17.73]*	0.01 [0.01, 14.82]*#	<0.001
EIV	4.23 [3.16, 5.31]	3.97 [2.18, 5.98]	2.00 [0.18, 4.20]*#	<0.001
FV	1.14 [0.84, 1.54]	1.21 [0.61, 1.80]	0.66 [0.12, 1.27]*#	<0.001
PV	0.62 [0.34, 0.86]	0.66 [0.30, 1.12]	0.48 [0.07, 0.89]#	0.021
GSV	0.31 [0.17, 0.57]	0.36 [0.14, 0.67]	0.09 [0.01, 0.28]*#	<0.001
MF (mL)				
IVC	17.7 [14.9, 21.9]	13.08 [0.01, 19.39]*	0.01 [0.01, 16.55]*#	<0.001
EIV	4.24 [3.20, 4.89]	4.20 [2.48, 6.59]	1.97 [0.12, 4.74]*#	<0.001
FV	1.19 [0.91, 1.45]	1.36 [0.64, 1.96]	0.78 [0.05, 1.42]#	<0.001
PV	0.59 [0.33, 0.87]	0.75 [0.31, 1.27]	0.52 [0.01, 1.03]#	0.031
GSV	0.33 [0.13, 0.56]	0.36 [0.06, 0.82]	0.07 [0.01, 0.30]*#	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Normal (n=30)	Venous reflux (n=167)	Venous obstruction (n=113)	P value
VTI (cm)				
IVC	8.44 [7.13, 11.72]	7.25 [0.01, 10.54]*	0.01 [0.01, 8.15]*#	<0.001
EIV	3.72 [3.09, 4.35]	5.35 [3.57, 7.20]*	3.18 [0.01, 5.78]#	<0.001
FV	2.27 [1.74, 5.43]	2.94 [1.86, 4.22]	1.92 [0.01, 3.68]*#	<0.001
PV	0.97 [0.76, 1.22]	1.26 [0.60, 1.91]	1.20 [0.01, 2.11]	0.462
GSV	1.35 [0.86, 2.90]	1.60 [0.17, 3.03]	0.17 [0.01, 2.00]*#	<0.001
MV (cm)				
IVC	10.3 [7.8, 13.8]	8.05 [0.01, 13.25]*	0.01 [0.01, 8.93]*#	<0.001
EIV	3.96 [3.03, 4.69]	6.08 [3.89, 7.97]*	3.50 [0.01, 6.82]#	<0.001
FV	2.40 [1.71, 5.03]	3.18 [2.07, 4.81]	2.20 [0.01, 4.08]#	0.003
PV	0.97 [0.82, 1.40]	1.38 [0.58, 2.20]	1.39 [0.01, 2.45]	0.294
GSV	1.47 [0.82, 2.52]	1.74 [0.22, 3.27]	0.18 [0.01, 2.38]*#	<0.001

Data were presented as median [25th percentile, 75th percentile]. *, significance difference versus the normal; #, significance difference versus the reflux groups, respectively. PC-MRI, phase-contrast magnetic resonance imaging; SV, stroke volume; IVC, inferior vena cava; EIV, external iliac vein; FV, femoral vein; PV, popliteal vein; GSV, great saphenous vein; FFV, forward flow volume; BFV, backward flow volume; RF, regurgitant fraction; ASV, absolute stroke volume; MF, mean flux; VTI, velocity time integral; MV, mean velocity.

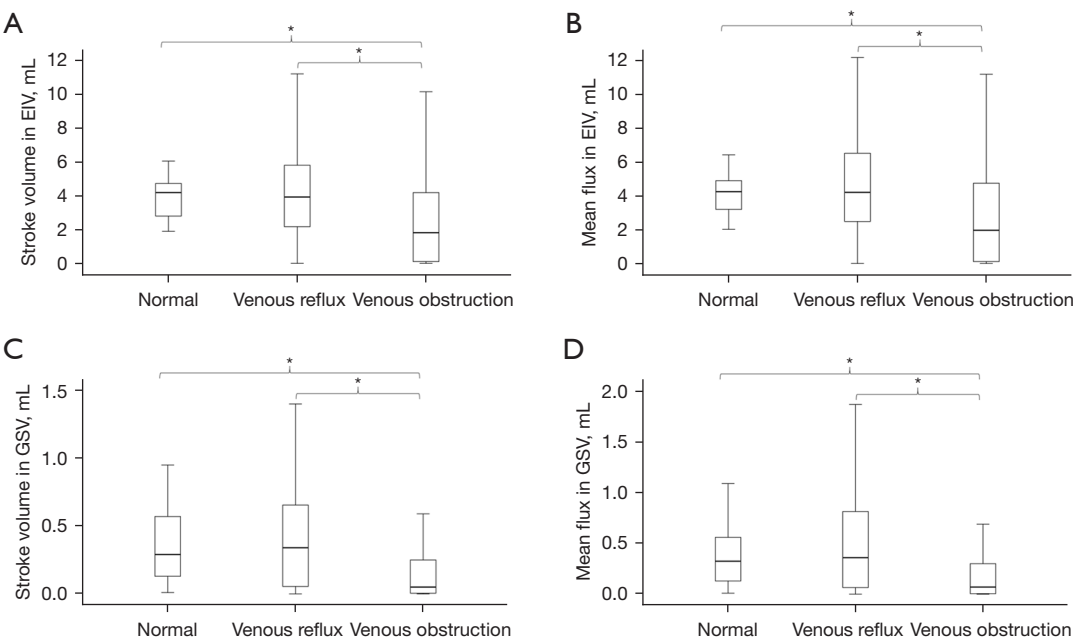

Figure 4 Box and whisker plots showing the comparison among the three groups (normal, venous reflux, and venous obstruction): (A) stroke volume in EIV segment; (B) mean flux in EIV segment; (C) stroke volume in GSV segment; (D) mean flux in GSV segment. *, the comparison between groups reaches a significant difference (P<0.05). EIV, external iliac vein; GSV, great saphenous vein.

Table 3 Two-dimensional PC-MRI characteristics (ratio of morbid limb to normal limb) in patients with single-leg venous disease

Variables	Reflux (n=65)	Obstruction (n=77)	P value
SV (mL)			
EIV	101.7 [92.3, 122.8]	100.0 [54.2, 100.0]	0.001
FV	100.0 [84.8, 125.6]	100.0 [62.6, 100.0]	0.036
PV	100.0 [77.6, 125.6]	100.0 [72.3, 103.8]	0.320
GSV	172.2 [100.0, 766.7]	100.0 [100.0, 177.8]	0.007
FFV (mL)			
EIV	101.7 [93.9, 122.8]	100.0 [61.2, 100.0]	0.001
FV	100.0 [84.6, 122.8]	100.0 [62.6, 100.0]	0.019
PV	100.0 [77.6, 123.7]	100.0 [72.3, 103.8]	0.237
GSV	230.3 [100.0, 620.0]	100.0 [100.0, 177.8]	<0.001
BFV (mL)			
EIV	0.0 [0.0, 75.3]	0.0 [0.0, 100.0]	0.195
FV	0.0 [0.0, 0.0]	0.0 [0.0, 100.0]	0.029
PV	0.0 [0.0, 0.0]	0.0 [0.0, 100.0]	0.045
GSV	0.0 [0.0, 57.1]	100.0 [0.0, 100.0]	0.002
RF (%)			
EIV	0.0 [0.0, 75.1]	0.0 [0.0, 100.0]	0.044
FV	0.0 [0.0, 0.0]	0.0 [0.0, 100.0]	0.014
PV	0.0 [0.0, 0.0]	0.0 [0.0, 100.0]	0.043
GSV	0.0 [0.0, 84.1]	100.0 [0.0, 100.0]	0.001
ASV (mL)			
EIV	101.7 [95.8, 123.7]	100.0 [61.2, 100.0]	<0.001
FV	100.0 [82.5, 122.8]	100.0 [62.6, 100.0]	0.012
PV	100.0 [81.8, 123.7]	100.0 [71.1, 103.8]	0.207
GSV	166.7 [100.0, 520.0]	100.0 [100.0, 160.0]	0.001
MF (mL)			
EIV	101.5 [92.3, 122.9]	100.0 [54.1, 100.0]	0.001
FV	100.0 [85.2, 127.4]	100.0 [62.5, 100.0]	0.029
PV	100.0 [74.6, 124.1]	100.0 [71.6, 104.1]	0.396
GSV	175.0 [100.0, 800.0]	100.0 [100.0, 200.0]	0.017
VTI (cm)			
EIV	100.3 [85.8, 122.5]	100.0 [72.3, 100.0]	0.013
FV	100.0 [81.1, 128.0]	100.0 [80.9, 100.0]	0.233
PV	100.0 [69.6, 119.8]	100.0 [76.9, 114.6]	0.938
GSV	132.9 [91.3, 424.5]	100.0 [100.0, 175.9]	0.129

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Reflux (n=65)	Obstruction (n=77)	P value
MV (cm)			
EIV	100.2 [85.8, 123.8]	100.0 [72.4, 100.0]	0.013
FV	100.0 [80.9, 127.9]	100.0 [81.0, 102.7]	0.278
PV	100.0 [69.7, 120.0]	100.0 [74.3, 114.6]	0.921
GSV	133.1 [91.3, 425.0]	100.0 [100.0, 178.1]	0.137

Data were presented as median [25th percentile, 75th percentile]. PC-MRI, phase-contrast magnetic resonance imaging; SV, stroke volume; EIV, external iliac vein; FV, femoral vein; PV, popliteal vein; GSV, great saphenous vein; FFV, forward flow volume; BFV, backward flow volume; RF, regurgitant fraction; ASV, absolute stroke volume; MF, mean flux; VTI, velocity time integral; MV, mean velocity.

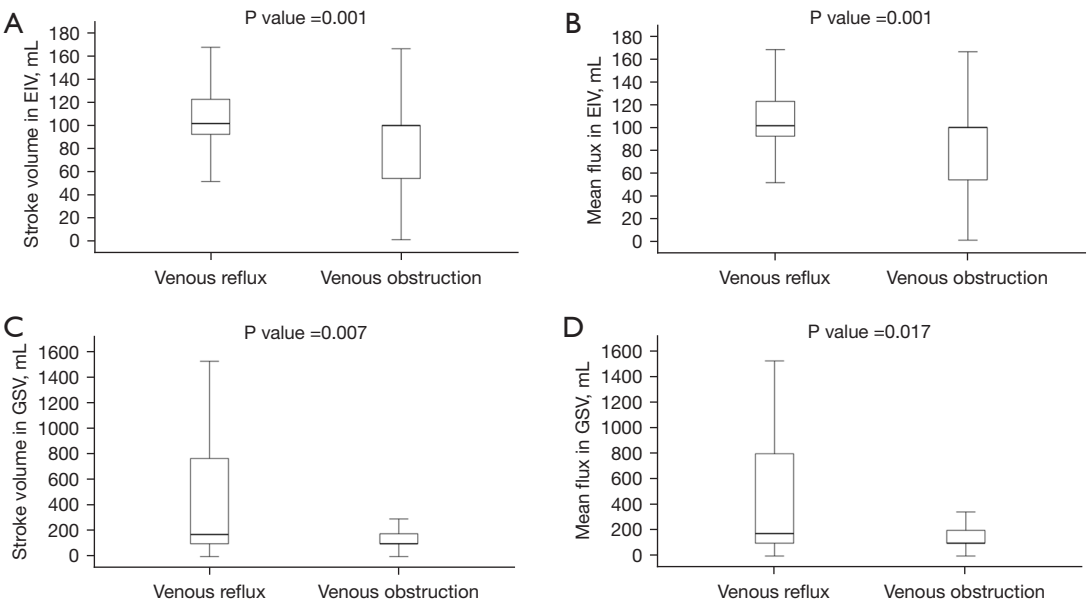

Figure 5 Box and whisker plots showing the ratios (morbid limb to normal limb) data in the patients with single-leg venous disease: (A) stroke volume in EIV segment; (B) mean flux in EIV segment; (C) stroke volume in GSV segment; (D) mean flux in GSV segment. EIV, external iliac vein; GSV, great saphenous vein.

insufficiency.

2D PC-MRI analysis also showed a remarkable ability to differentiate from venous reflux to venous occlusive leg disease (SV, FFV, ASV, MF, VTI, and MV in the IVC, EIV, FV, and GSV segments, respectively, P≤0.001; AUC =62–68.8%, P≤0.001). The ratios data of morbid limb to normal limb in the same patients were evaluated to minimize individual bias. The results revealed significant differences between the reflux and obstruction in patients with single-leg venous disease (SV, FFV, ASV, and MF in the EIV, FV, and GSV segments, respectively; P<0.05). Further analysis revealed the ability to use ratio data (morbid limb to normal limb) for discriminating venous reflux from venous obstruction (SV, FFV, ASV, and MF in the EIV, FV, and GSV segments, respectively; AUC =60.2–68.7%, P<0.05). This diagnostic capability is critical for preoperative evaluation. The superficial systems could be improved by blocking the necrotic superficial vein. While the deep system caused by venous obstruction could be improved by opening the blood vessels or medical treatments. A conventional diagnostic tool, such as ultrasonography, is challenging to diagnose complicated venous diseases,

Table 4 Ability to use 2D PC-MRI data (ratio of morbid limb to normal limb) for discriminating venous reflux from venous obstruction in patients with single-leg venous disease

Variables	AUC (95% CI) (%)	P value	Cut-off
SV (mL)			
EIV	66.7 (57.8, 75.5)	0.001	>73.20
FV	60.2 (50.9, 69.5)	0.037	>100.00
GSV	63.0 (53.7, 72.4)	0.008	>146.67
FFV (mL)			
EIV	66.7 (57.9, 75.6)	0.001	>100.25
FV	61.4 (52.1, 70.6)	0.020	>100.00
GSV	68.7 (59.8, 77.6)	<0.001	>128.89
BFV (mL)			
FV	58.3 (48.9, 67.7)	0.088	–
PV	57.7 (48.3, 67.1)	0.116	–
GSV	63.5 (54.2, 72.7)	0.006	≤87.50
RF (%)			
EIV	58.3 (48.9, 67.7)	0.087	–
FV	59.4 (50.1, 68.7)	0.053	–
PV	58.2 (48.8, 67.6)	0.092	–
GSV	65.6 (56.6, 74.7)	0.001	≤87.93
ASV (mL)			
EIV	67.4 (58.7, 76.2)	<0.001	>100.25
FV	62.2 (53.0, 71.4)	0.013	>100.00
GSV	66.4 (57.4, 75.5)	0.001	>116.13
MF (mL)			
EIV	66.5 (57.6, 75.4)	0.001	>100.00
FV	60.6 (51.3, 69.9)	0.030	>104.35
GSV	61.5 (52.0, 70.9)	0.019	>160.00
VTI (cm)			
EIV	62.0 (52.7, 71.3)	0.014	>100.00
MV			–
EIV	62.1 (52.8, 71.4)	0.013	>100.00

2D, two-dimensional; PC-MRI, phase-contrast magnetic resonance imaging; ; AUC, area under the curve; CI, confidence interval; SV, stroke volume; EIV, external iliac vein; FV, femoral vein; GSV, great saphenous vein; FFV, forward flow volume; BFV, backward flow volume; PV, popliteal vein; ASV, absolute stroke volume; RF, regurgitant fraction; MF, mean flux; VTI, velocity time integral; MV, mean velocity.

especially the iliac veins, and patients with obesity or edema. This study proposes a non-invasive method to objectively assess hemodynamics and subjective morphological diagnosis, which is crucial for versatile venous interventions.

Ultrasounds are more inexpensive and more available than other methods. There are many studies and diagnostic

criteria that have proved the clinical utility of ultrasound in the diagnosis of LEVD. It is reported that the sensitivity, specificity, accuracy, and kappa index of ultrasound-detected chronic iliac vein obstruction were 92.4%, 80.0%, 86.7%, and 0.730 (high agreement), respectively (17). In contrast, MRI is costly and the quantitative PC-MRI technology is not easily performed. In this study, 3D TSE-STIR MRV-detected cases of venous obstruction with a sensitivity of 88.5%, a specificity of 88.62%, an accuracy of 88.67%, and a kappa index of 0.765. The results showed that 3D TSE-STIR MRV exhibited excellent diagnostic accuracy as did an ultrasound. However, we considered that MRI technology could not replace ultrasound in the clinical. Patients with the suspected LEVD should still undergo ultrasonography first. Then arrange an MRI examination if needs in the clinical. We have reported how to arrange ultrasonography for lower extremity venous pathology and how to proceed with the treatment of NC-MRA (7). Another advantage of quantitative PC-MRI technology is that it is able to fill in the gap that some patients with venous diseases (such as obesity) could not detect pelvic blood flow by ultrasonography. In our previous study, May-Thurner syndrome was suspected in many patients with compression of the left common iliac vein detected on 3D TSE-STIR MRV (13). Clinicians could decide whether the further intervention was needed based on the difference in blood flow of pelvic and leg veins. Another study found that 73.8% of ultrasonography-negative patients could be diagnosed as positive by 3D TSE-STIR MRV. Of these, 15.3% of patients underwent additional vascular surgery based on positive 3D TSE-STIR MRV findings (5). The clinical utility of quantitative PC-MRI in LEVDs is rare, but our findings suggest that it should be applicable.

Unlike DUS, which can provide anatomical and hemodynamic assessments, 3D MRV only provides anatomical assessment. Thus, this study conducted quantitative 2D PC-MRI to complement the lack of hemodynamic analysis in the NC-MRA protocol. There are several technical issues of 2D PC-MRI to be discussed. First, the details of applying 2D PC-MRI analysis for peripheral vessel analysis need to be discussed. When performing 2D PC-MRI scanning on axial planes, the generated plane images contained phase-shifting information for each pixel. By drawing the ROI covering the vascular lumen, the hemodynamic variables will present the average phase-shifting information of voxels within the draw region. When assessing lower extremity venous structure using 2D PC-MRI, SV reflects the net flow volume that passes through the drawn contour during one heartbeat. BFV reflects the volume of flow that passes through the drawn contour during one heartbeat in the backward.

Our study has limitations. First, the application of 2D PC-MRI for peripheral vessel analysis is not widely comprehended. The application of various hemodynamic variables in LEVD has still been unknown and needs to be explored in the clinical utility. Thus, this study uses DUS as the standard reference for grouping and compares the difference of 2D PC-MRI measurements to explore the meaning of the variables. Second, this research was a nonrandomized design. Significant differences in variables (age, gender, comorbidities) between groups (venous reflux, venous obstruction, and healthy controls) were noticed. Third, the controls are young in age, much female gender, and a small sample size could not allow power calculation. In addition, DUS was not performed in this group, so asymptomatic reflux could not be ruled out. A large sample size, long follow-up interval on clinical correlation, and a randomized study design may be required to provide solid therapeutic suggestions. Fourth, systemic hemodynamics differ in body positions such as supine, sitting, or standing (18). And it has been reported that blood flow detected by doppler ultrasound changes with the body positions. When standing, the blood flow rate of the portal vein is significantly lower than when in the supine position; when the head was raised, the mean cerebral blood flow velocity of the middle cerebral artery was enhanced (19,20). In this study, due to the limitations of the MRI examination, the patients were placed in a supine position and equipped with an ECG monitor and a respiratory monitor for MRI scanning.

In summary, this study showed that non-contrast MRI protocol, including gated 3D TSE-STIR MRV for anatomic diagnosis and quantitative 2D PC-MRI for hemodynamic analysis, was reliable and helpful in evaluating LEVD. The gated 3D TSE-STIR sequence displayed excellent performance for the diagnostic tests and substantial interrater agreement to standard ultrasonography. 2D PC-MRI analysis revealed broadly different among the patients with venous reflux, venous obstruction, and healthy controls. 2D PC-MRI analysis also showed remarkable ability to differentiate from venous reflux to venous occlusive leg disease.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-1194/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1194/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The Institutional Review Board of Chang Gung Memorial Hospital approved this study (institutional review board Nos. 201802137B0, 201901058B0, 202100938B0 and 202102344B0). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consents were obtained from all participants.

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Supplementary

Table S1 Diagnostic values of magnetic resonance venography for venous obstruction compared to duplex ultrasonography

3D TSE-STIR MRV	Value
Sensitivity (%)	88.5
Specificity (%)	88.62
Positive predictive value (%)	84.04
Negative predictive value (%)	91.93
Accuracy (%)	88.67
Cohen's kappa coefficient (κ)*	0.765

*, duplex ultrasonography was used as the diagnostic reference standard. The degree of agreement between 3D TSE-STIR MRV and duplex ultrasonography for the presence of venous obstruction was assessed by Cohen's kappa value (κ). 3D TSE-STIR MRV, three-dimensional turbo spin-echo short tau inversion recovery magnetic resonance venography.

https://dx.doi.org/10.21037/qims-22-1194

Table S2 Ability to use 2D PC-MRI data for discriminating different diagnoses among diseased legs

Variables	Reflux versus normal			Obstruction versus normal			Obstruction versus reflux		
	AUC (95% CI) (%)	P value	Cut-off	AUC (95% CI) (%)	P value	Cut-off	AUC (95% CI) (%)	P value	Cut-off
SV (mL)									
IVC	72.6 (64.6, 80.5)	<0.001	>10.36	81.8 (74.9, 88.6)	<0.001	>9.34	62.0 (55.3, 68.8)	0.001	>7.92
EIV	50.2 (41.7, 58.8)	0.967	–	72.9 (65.0, 80.8)	<0.001	>2.11	67.2 (60.6, 73.7)	<0.001	>2.11
FV	50.1 (40.1, 60.1)	0.986	–	68.0 (59.1, 76.9)	0.002	>0.83	64.7 (58.0, 71.5)	<0.001	>0.85
PV	55.6 (46.9, 64.2)	0.333	–	58.2 (49.1, 67.4)	0.167	–	59.3 (52.4, 66.2)	0.008	>0.23
GSV	50.1 (40.9, 59.2)	0.990	–	74.4 (66.3, 82.5)	<0.001	>0.005	68.5 (62.1, 74.9)	<0.001	>0.23
FFV (mL)									
IVC	73.1 (64.9, 81.2)	<0.001	>10.36	82.1 (75.4, 88.9)	<0.001	>9.34	62.1 (55.3, 68.9)	0.001	>7.92
EIV	51.2 (42.6, 59.9)	0.832	–	72.9 (64.9, 80.8)	<0.001	>2.11	67.2 (60.6, 73.7)	<0.001	>1.5
FV	50.1 (40.2, 60.0)	0.982	–	68.5 (59.7, 77.3)	0.002	>0.83	65.0 (58.3, 71.7)	<0.001	>0.85
PV	55.2 (46.6, 63.9)	0.361	–	58.5 (49.4, 67.6)	0.154	–	59.4 (52.5, 66.3)	0.008	>0.19
GSV	50.1 (41.0, 59.3)	0.982	–	74.5 (66.6, 82.4)	<0.001	>0.06	68.4 (62.0, 74.8)	<0.001	>0.2
BFV (mL)									
IVC	51.5 (39.1, 63.9)	0.792	–	56.8 (42.9, 70.7)	0.256	–	56.8 (50.0, 63.6)	0.054	–
EIV	58.3 (46.1, 70.5)	0.149	–	52.2 (39.6, 64.9)	0.708	–	57.3 (50.5, 64.2)	0.037	≤0
FV	57.4 (45.2, 69.6)	0.198	–	52.5 (39.9, 65.1)	0.673	–	56.0 (49.1, 63.0)	0.086	–
PV	52.7 (41.3, 64.2)	0.634	–	57.6 (45.9, 69.3)	0.203	–	55.0 (48.1, 61.9)	0.153	–
GSV	51.0 (39.1, 62.9)	0.859	–	58.7 (45.8, 71.5)	0.146	–	58.6 (51.9, 65.4)	0.014	≤0
RF (%)									
IVC	51.5 (39.1, 63.9)	0.792	–	56.9 (43.0, 70.7)	0.248	–	56.7 (50.0, 63.5)	0.055	–
EIV	57.7 (45.3, 70.1)	0.180	–	52.1 (39.7, 64.5)	0.723	–	55.1 (48.2, 62.0)	0.151	–
FV	59.8 (47.5, 72.1)	0.086	–	54.7 (42.0, 67.4)	0.429	–	56.3 (49.4, 63.2)	0.075	–
PV	57.0 (45.1, 68.9)	0.224	–	52.8 (40.3, 65.4)	0.632	–	55.5 (48.7, 62.4)	0.116	–
GSV	55.2 (43.0, 67.4)	0.365	–	50.8 (37.3, 64.3)	0.894	–	58.0 (51.2, 64.7)	0.023	≤0
ASV (mL)									
IVC	73.8 (65.5, 82.1)	<0.001	>10.36	82.4 (75.6, 89.1)	<0.001	>9.34	62.2 (55.5, 69.0)	0.001	>7.92
EIV	52.1 (43.3, 60.9)	0.708	–	72.6 (64.6, 80.7)	<0.001	>2.11	66.4 (59.8, 73.0)	<0.001	>1.5
FV	51.1 (41.2, 61.1)	0.843	–	68.9 (60.2, 77.7)	0.001	>0.81	64.7 (58.0, 71.4)	<0.001	>0.85
PV	55.1 (46.4, 63.8)	0.376	–	58.6 (49.5, 67.7)	0.150	–	59.4 (52.4, 66.3)	0.008	>0.19
GSV	50.1 (40.9, 59.2)	0.992	–	74.7 (66.7, 82.6)	<0.001	>0.13	68.8 (62.4, 75.2)	<0.001	>0.12
MF (mL)									
IVC	71.3 (63.4, 79.1)	<0.001	>11.99	81.5 (74.6, 88.4)	<0.001	>12.16	61.8 (55.1, 68.6)	0.001	>6.45
EIV	52.5 (44.2, 60.9)	0.662	–	68.6 (60.4, 76.8)	0.002	>1.97	65.8 (59.1, 72.5)	<0.001	>2.23
FV	53.4 (43.9, 62.9)	0.552	–	64.4 (55.2, 73.6)	0.015	>0.9	63.7 (57.0, 70.4)	<0.001	>0.98
PV	58.1 (49.8, 66.3)	0.160	–	54.7 (45.6, 63.8)	0.433	–	58.7 (51.8, 65.6)	0.013	>0.34
GSV	51.8 (43.0, 60.7)	0.748	–	72.4 (64.2, 80.6)	<0.001	>0.02	67.9 (61.4, 74.3)	<0.001	>0.23
VTI (cm)									
IVC	65.0 (56.3, 73.8)	0.009	>6.85	80.2 (73.0, 87.3)	<0.001	>7	64.2 (57.7, 70.8)	<0.001	>3.54
EIV	71.7 (64.8, 78.6)	<0.001	≤4.64	54.0 (45.2, 62.8)	0.502	–	66.6 (60.0, 73.1)	<0.001	>2.15
FV	51.6 (39.5, 63.7)	0.781	–	65.6 (55.2, 76.0)	0.009	>1.16	63.2 (56.4, 69.9)	<0.001	>1.99
PV	57.6 (48.6, 66.5)	0.187	–	51.7 (42.3, 61.1)	0.777	–	52.5 (45.4, 59.7)	0.470	–
GSV	52.1 (42.1, 62.1)	0.718	–	68.4 (59.2, 77.6)	0.002	>0.03	63.8 (57.1, 70.5)	<0.001	>0.54
MV (cm)									
IVC	64.5 (56.0, 73.1)	0.011	–	79.1 (71.8, 86.4)	<0.001	>5.06	63.7 (57.1, 70.3)	<0.001	>4.03
EIV	72.0 (65.0, 79.0)	<0.001	≤5.75	52.1 (43.2, 60.9)	0.730	–	64.0 (57.3, 70.8)	<0.001	>3.35
FV	51.7 (39.9, 63.5)	0.765	–	61.2 (50.6, 71.7)	0.061	–	61.9 (55.1, 68.7)	0.001	>2.21
PV	60.1 (51.4, 68.8)	0.078	–	54.5 (45.3, 63.8)	0.448	–	52.0 (44.8, 59.2)	0.572	–
GSV	50.3 (40.6, 60.0)	0.957	–	66.5 (57.4, 75.7)	0.005	>0.04	63.0 (56.2, 69.8)	<0.001	>0.46

2D, two-dimensional; PC-MRI, phase-contrast magnetic resonance imaging; AUC, area under the curve; CI, confidence interval; SV, stroke volume; IVC, inferior vena cava; EIV, external iliac vein; FV, femoral vein; PV, popliteal vein; GSV, great saphenous vein; FFV, forward flow volume; BFV, backward flow volume; ASV, absolute stroke volume; RF, regurgitant fraction; MF, mean flux; VTI, velocity time integral; MV, mean velocity.

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