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Original Article / *Özgün Makale*

Latent class analysis for exploring distribution patterns of primary superficial venous insufficiency

Primer yüzeyel venöz yetmezliğin dağılım paternlerinin belirlenmesinde gizli sınıf analizi

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ABSTRACT

Background: This study aims to identify specific segmental distribution patterns of lower extremity chronic venous disease based on latent class analysis of Doppler mapping results.

Methods: A total of 1,871 lower extremities of 1,218 treatment-naïve patients (536 males, 682 females; mean age 45.4 years; range, 21 to 87 years) with chronic venous disease referred for Doppler examination between September 2009 and August 2018 were included. Refluxing superficial venous segments of the lower extremities were mapped and recorded in database in 10 distinct anatomic locations as follows: saphenofemoral junction and proximal greater saphenous vein, mid and distal thigh greater saphenous vein, anterior and posterior accessory saphenous veins, proximal and distal calf greater saphenous vein, saphenopopliteal junction and proximal lesser saphenous vein, distal lesser saphenous vein, and intersaphenous veins including Giacomini's vein. Repeated examinations were excluded. The latent class analysis was applied to identify any possible anatomic distribution patterns of chronic venous disease.

Results: Bayesian information criteria revealed three latent class models fit for refluxing segment distribution as follows: 58.2% (n=1,089) were above-the-knee greater saphenous vein segments including saphenofemoral junction (pattern 1); 29.3% (n=548) were below-the-knee greater saphenous vein segments (pattern 2); and 12.5% (n=234) were lesser saphenous vein segments and intersaphenous veins including Giacomini's vein (pattern 3). There was no age- or sex-specific differences in the chronic venous disease distribution patterns.

Conclusion: The latent class analysis, by identifying previously unseen subgroups within the sampled population, provides a new approach to classification of reflux patterns in chronic venous disease. Identification of latent classes may provide understanding of different pathophysiological bases of venous reflux and more optimal planning for interventions.

Keywords: Chronic venous disease, latent class analysis, venous insufficiency, venous reflux.

ÖZ

Amaç: Bu çalışmada Doppler haritalama sonuçlarına göre gizli sınıf analizine dayanarak, alt ekstremitenin kronik venöz hastalığının spesifik segmental dağılım paternleri belirlendi.

Çalışma planı: Çalışmaya Eylül 2009 - Ağustos 2018 tarihleri arasında Doppler incelemesi için yönlendirilen daha önce tedavi edilmemiş, kronik venöz hastalığı olan 1,218 hastanın (536 erkek, 682 kadın; ort. yaş 45.4 yıl; dağılım, 21-87 yıl) toplam 1,871 alt ekstremitesi alındı. Alt ekstremitenin geri akışlı yüzeyel ven segmentleri 10 farklı anatomik lokasyonda haritalandı ve veri tabanına kaydedildi: safenofemoral kavşak ve proksimal büyük safen ven, orta ve distal kalça büyük safen ven, ön ve arka aksesuar safen venler, proksimal ve distal kalf büyük safen ven, safenopopliteal kavşak ve proksimal büyük safen ven, distal küçük safen ven ve Giacomini veni dahil olmak üzere intersafen venler. Tekrarlı incelemeler hariç tutuldu. Kronik venöz hastalığının muhtemel anatomik dağılım paternlerini belirlemek için gizli sınıf analizi uygulandı.

Bulgular: Bayes bilgi kriterleri, geri akışlı segment dağılımına uyan üç gizli sınıf modeli ortaya çıkardı: %58.2'si (n=1089) safenofemoral kavşak dahil diz üstü büyük safen ven segmentleri (patern 1); %29.3'ü (n=548) diz altı büyük safen ven segmentleri (patern 2) ve %12.5'i (n=234) küçük safen ven segmentleri ve Giacomini veni dahil olmak üzere intersafen venler (patern 3). Kronik venöz hastalık dağılım paternleri arasında yaş veya cinsiyete özgü farklılıklar izlenmedi.

Sonuç: Gizli sınıf analizi, çalışılan popülasyon içerisinde daha önce görülmemiş alt grupları belirleyerek, kronik venöz hastalığın geri akış paternlerinin sınıflandırılmasında yeni bir yaklaşım sunmaktadır. Gizli sınıfların belirlenmesi, venöz geri akışın farkı patofizyolojik temellerinin anlaşılmasını ve girişimler için daha uygun planlama yapılmasını sağlayabilir.

Anahtar sözcükler: Kronik venöz hastalık, gizli sınıf analizi, venöz yetmezlik, venöz reflü.

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Chronic venous disease (CVD) is a spectrum of functional and morphological abnormalities of peripheral veins which manifest by long term signs or symptoms necessitating further assessment and treatment. Chronic venous disease is an important cause of patient distress and, with a prevalence as high as 60%, presents a significant burden on healthcare resources. Underlying pathophysiology of CVD still remains ambiguous.[1] Primary venous insufficiency shows a segmental distribution. Doppler ultrasonography enables mapping of afflicted segments for planning of ideal and patient-tailored treatment. Suboptimal mapping may result in over- or undertreatment of patients.[2] However, our understanding of the patterns of segmental involvement in primary superficial venous insufficiency, despite numerous prior studies, is still incomplete and frequently debated.[3-7] This is where latent class analysis (LCA), a powerful and flexible statistical tool of growing popularity, can be of great utility. The LCA finds and describes otherwise hidden and unknown subpopulations and provide key insights for etiology discovery and patient-oriented treatment, when one-size models are inadequate. The LCA organizes a seemingly heterogeneous patient population into latent homogenous groups depending on the type of indicator variables they adopt.[8-10]

In the present study, we aimed to identify latent classes of CVD with specific distribution patterns, which may hint at similar etiology or progression characteristics, from within a large group of patients with primary insufficiency of lower limb superficial veins, utilizing the LCA based on whether a given venous segment is refluxing in a particular patient.

PATIENTS AND METHODS

This study included a total of 1,871 lower extremities of 1,218 treatment-naïve patients (536 males, 682 females; mean age 45.4 years; range, 21 to 87 years) with CVD referred to our outpatient vascular interventions clinic for Doppler examination and endovascular or surgical treatment between September 2009 and August 2018. All patients were medical or surgical treatment-naïve adults presenting with symptoms of lower extremity venous insufficiency. Exclusion criteria were as follows: having a history of major trauma including orthopedic interventions or any endovascular or surgical venous interventions, documented deep or superficial venous thrombosis, and the presence of additional reflux in deep venous system or perforating veins. Repeated examinations were also excluded. A written informed consent was obtained from each patient. The study protocol was approved by the Marmara University School of Medicine Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Imaging and data collection

Doppler mapping of CVD distribution was performed by a single radiologist experienced in venous imaging. An ultrasonography unit (Logiq S8, General Electrics, Fairfield, CT, USA) with a 12 to 16 MHz linear transducer was used. As the standard practice, the whole thigh and leg regions were mapped, while the patients were standing upright; a wide field of view (FOV) and a frame rate of 30 frames/sec was employed. Venous insufficiency was defined as the presence of flow reversal lasting more than 0.5 sec during provocation maneuvers (Figure 1). Refluxing segments were recorded in database as 10 distinct anatomic locations in accordance with modern phlebology nomenclature (Table 1).[11] Concomitant variables were the age and sex of the patient. Distribution of age and sex within subclasses of CVD were evaluated using variance analysis.

LCA software

The LCA was applied to reveal any possible anatomic distribution patterns of venous insufficiency. It was performed using open source and public domain statistics programs R Studio (v1.1.463, R Foundation for Statistical Computing, Boston, MA, USA) software

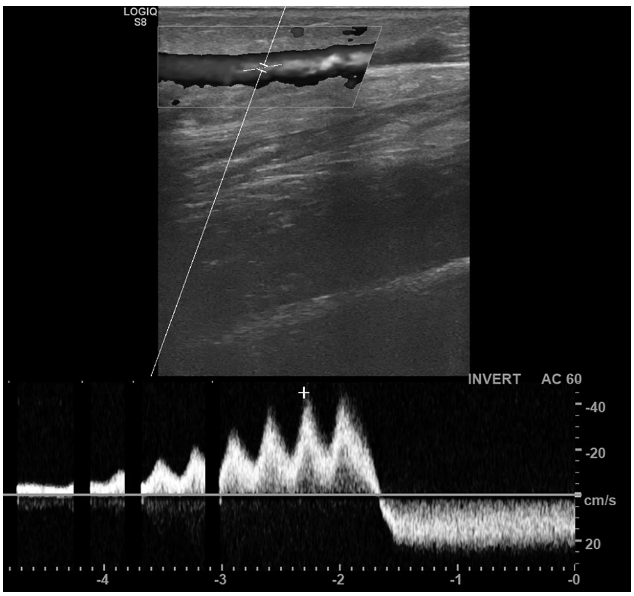

Figure 1. Real-time Doppler ultrasonography of a below-the-knee segment of great saphenous vein demonstrating venous insufficiency as flow reversal lasting >0.5 sec during provocation maneuvers.

Table 1. Designation of 10 refluxing superficial venous segments in Doppler mapping

1	SFJ and proximal third of thigh GSV
2	Middle third segment of thigh GSV
3	Distal third segment of thigh GSV
4	Anterior accessory saphenous vein
5	Posterior accessory saphenous vein
6	Proximal half segment of calf GSV
7	Distal half segment of GSV
8	SPJ and proximal half of LSV
9	Distal half of LSV
10	Intersaphenous veins including Giacomini's

SFJ: Saphenofemoral junction; GSV: Greater saphenous vein; SPJ: Saphenopopliteal junction; LSV: Lesser saphenous vein.

with poLCA (Polytomous Variable Latent Class Analysis, v1.4.1, Civiqs, Oakland, CA, USA) statistical package.

Input data, criterion variables, and LCA parameters

The input data of LCA are joint distribution of signs and symptoms and physiological markers, also called criterion variables, which in our example are whether a particular segment is affected determined by venous mapping. With 10 dichotomous criterion variables, the input data are the relative proportions of occurrence of each of 2^{10} =1,024 distinct combinations of items. Parameters to be estimated were as follows: prevalence of each latent class (unconditional probabilities; i.e., prevalence of each reflux distribution pattern emerging from analysis) and distribution of criterion variables within each latent class (conditional probabilities, independent of each other within each group, i.e., distribution of whether a particular segment is refluxing or not in each pattern emerging from analysis). These parameters were, then, combined mathematically into a likelihood function, and the set which maximized the likelihood function determined the membership of each individual in one of the latent classes.[8,10]

Model selection for latent classes

A challenge of LCA is that before we estimated our LCA model we had to choose how many groups we needed to have. The aim was to identify a plausible classification structure for CVD distribution patterns with the smallest number of classes so that the model was still adequate for the data, but also parsimonious. In this study, the number of latent classes, i.e., distinct patterns of segmental involvement, was defined according to the Bayesian information criterion (BIC) which compares multiple models - e.g., one with two groups, another with three groups, another with four groups - against each other.[12-14]

RESULTS

A total of 1,871 lower extremities had Doppler evidence of CVD. The BIC revealed a three-latent class model fit for refluxing segment distribution. We began LCA model selection with a one-class model which included all 10 criterion variables from dataset; then, we built, hierarchically, a series of models with an increasing number of classes: The two-class model had poor fit based on a consensus of the goodness-of-fit and BIC and the four-class model had a higher BIC value, indicating a less goodness-of-fit than the three-class-model (Table 2).

Refluxing segment distribution was observed in these three latent classes (Figure 2). The most common pattern (58.2%; n=1,089) included above-the-knee GSV segments including the saphenofemoral junction (SFJ) and anterior/posterior accessory saphenous veins. The second most common pattern of CVD (29.3%; n=548) included below-the-knee GSV segments. The least common pattern (12.5%; n=234) had clustering of CVD of LSV segments and intersaphenous veins including Giacomini's vein (Figure 3). There was no age- or sex-related differences within the CVD segmental distribution patterns (Table 3).

Table 2. Bayesian information criteria indicating a three-latent class model fit

LCA model	Number of parameters	Degrees of freedom	L^2 p-value	BIC
1 class	10	1013	<0.0001	3814
2 classes	21	1002	< 0.01	919
3 classes	32	991	0.32	**-227**
4 classes	43	980	0.47	-168

BIC: Bayesian information criteria; LCA: Latent class analysis; L^2: Likelihood chi-squared.

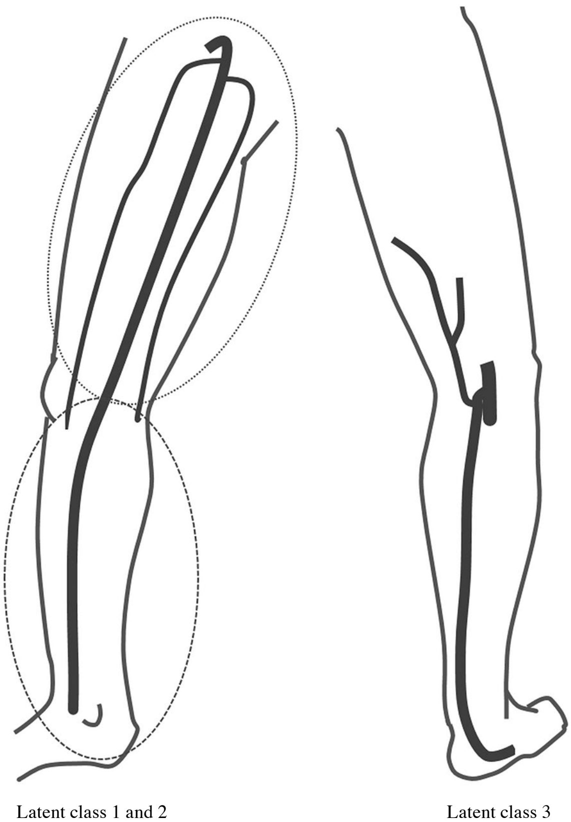

Figure 2. Schematic representations of superficial venous reflux distribution patterns 1, 2, and 3.

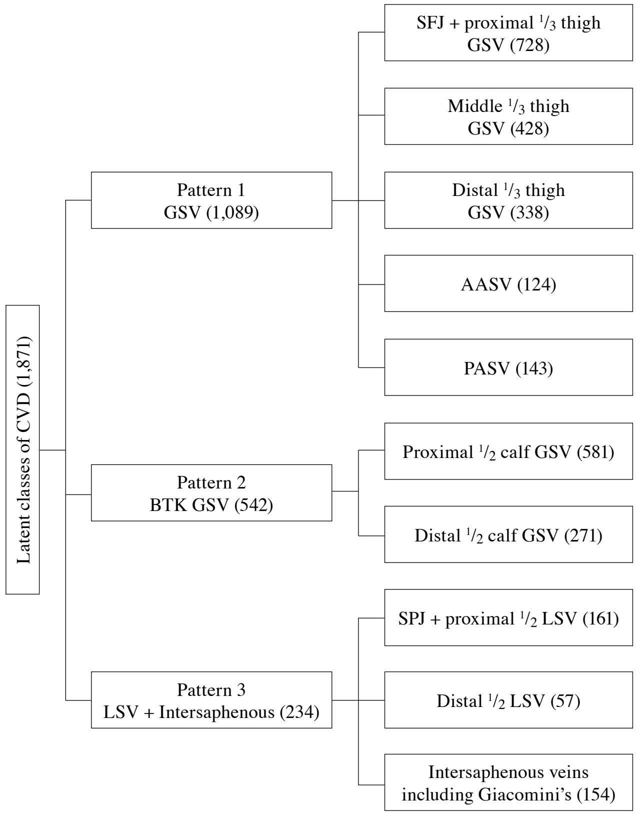

Figure 3. Latent class analysis of segmental distribution of chronic venous disease revealed three latent patterns of reflux. Number of patients are stated in parentheses.

SFJ: Saphenofemoral junction; GSV: Greater saphenous vein; AASV: Anterior accessory saphenous vein; PASV: Posterior accessory saphenous vein; SPJ: Saphenopopliteal junction; LSV: Lesser saphenous vein; BTK: Below the knee; CVD: Chronic venous disease.

DISCUSSION

In the present study, LCA was applied to the refluxing venous segment maps of a large clinical sample and revealed three previously overlooked distribution patterns of CVD in lower extremity superficial veins. One of the major advantages of LCA, in contrast to the distance-based traditional cluster analysis techniques, is that it is model-based which provides more formal criteria for choosing the final model while using the LCA.[10] The segmental nature of CVD in GSV has been previously presented with a classification attempt into five subgroups as proximal, distal, segmental, multi-segmental, and diffuse, providing a means for assessment of progression of CVD by comparing the prevalence over time; however, it was not based on specific anatomic descriptors.[7] Using the LCA, on the other hand, we were able to provide a structural framework to classify CVD patients into more anatomically homogenous subgroups which, in turn, served as basis for pattern recognition.

Of three subclasses, the most common pattern (58.2%) was above-the-knee GSV segments including SFJ (n=728) and accessory saphenous veins. This is consistent with a previous large-scale, cross-sectional study which reported 53% involvement of the SFJ in 2,019 limbs.[15] The least common pattern of reflux (12.5%) comprised insufficient LSV segments and intersaphenous veins including Giacomini's vein. This prevalence is similar to that stated in a published series reporting 11.6% involvement in 2,036 limbs.[2] Of particular importance is that LCA revealed that intersaphenous venous insufficiency had a tendency

Table 3. Variance of age and sex distribution among latent classes

LCA subgroup	Female: Male ratio (%)	Age (mean±SD)
Pattern 1	632:457 (58:42)	43.8±14.1
Pattern 2	290:258 (53:47)	48.1±10.6
Pattern 3	126:108 (54:46)	46.4±16.2

LCA: Latent class analysis; SD: Standard deviation.

to cluster with CVD of LSV, but not with that of GSV. This finding is consistent with a previous study, although not proved, indicating a similar pattern by estimating odds ratio for presence of Giacomini's vein reflux in cases with LSV insufficiency to be nearly twice as that of cases with refluxing GSV (odds ratio of 12 and 6.6, respectively).[16] The second most common pattern (29.3%) consisted of below-the-knee GSV segments. This is seemingly different from previous studies which report reflux of below-the-knee GSV as high as 68%.[4] In our study population, the number of limbs with refluxing calf segments of GSV is, indeed, 852 (45.5% of all limbs). This is due to the fact that LCA estimates latent class models for analysis of multivariate categorical data and manifest variables may contain any number of polytomous outcomes. Hence, the number of patients with positive results for each one of 10 categorical variables, i.e., total number of individuals with reflux of a given venous segment, is greater than the number of members of the latent class, encompassing the particular venous segment. In other words, a patient allocated to patterns 1 or 3 may also have below-the-knee GSV involvement, since LCA is a likelihood estimation, but not, per se, a tally count.[10]

There are two seemingly conflicting models on progression of CVD over time. Retrograde progression theory is centered on case series with proximal segmental involvement, such as SFJ and proximal thigh GSV reflux, becoming more diffuse in a descending fashion. Antegrade progression, on the other hand, is based on observation of predominantly distal to proximal, and also segmental to more diffuse, evolution of CVD in cohorts.[5] The LCA of our study population classified patients into two separate homogenous subgroups with below-the-knee and above-the-knee involvement and this may imply that both ascending and descending progressions are distinct and plausible processes.

In the current study, the patterns of involvement in CVD did not reveal significant sex-based differences. This is consistent with the current literature stating that CVD is not particularly a female disease.[17] Another finding is that patients assigned into three subclasses did not have statistically significant age differences. In the current literature, it has been reported that CVD shows progression with a rate of 4.3% per year.[3] It is also possible to assess changes in latent classes over time by utilizing an extension of LCA called latent transition analysis.[18] This exploratory LCA study, on the other hand, is unable to construct such progression patterns, since it is solely based on single cross-sectional observations, but not on cohorts.

The lower limb superficial venous system commonly exhibits variations due to segmental or complete aplasia, hypoplasia, and duplications of saphenous veins. Anterior and posterior accessory veins, circumflex veins, hypertrophic venous tributaries, and intersaphenous and cranial extensions of saphenous veins contribute to adequate venous drainage in variant anatomy. Identification of such variations is necessary for correct diagnosis and treatment; however, the effect of having a variant anatomy (compared to having a "normal" one, which may be much less frequent than expected) on pathophysiology of venous reflux has not been well established, yet.[19-21] Due to the design of this particular study, i.e., selection of criterion variables, we cannot predict the exact effect of venous variations on the pathophysiology or distribution of venous insufficiency.

Nonetheless, the LCA findings are to be construed in the context of certain limitations. First, as in any multivariate classification algorithm, the LCA assumes that manifest variables - i.e., refluxing venous segments - have no association after controlling for latent variables. This assumption of local independence may not be always true due to the nature of variables entered into the analysis. Second, the LCA solution is critically dependent on input dataset - i.e., maps of refluxing segments of each patient. Thus, patterns obtained with LCA may contrast with our results, when employed in a different population. Since patterns of involvement and relevant prevalence are from a specific study population, any inferences obtained from this particular analysis may have limited generalizability of the results. In addition, with a study population originating from an outpatient vascular interventions clinic, it is likely that sample composition was influenced by potential sampling biases. Finally, LCA, by its very definition, classifies patients, but not refluxing segments, into unseen subgroups. This precludes proving the existence of an underlying class system and imposing that these classes upon input data may obscure a simpler spectrum of involvement.[10,12,18,22,23]

In conclusion, the latent class analysis, by identifying previously unseen subgroups within the sampled population, provides a new approach to classification of reflux patterns in chronic venous disease. Identification of latent classes may provide understanding of different pathophysiological basis of venous reflux and more optimal planning for interventions.

Declaration of conflicting interests

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