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RESEARCH ARTICLE

Socio-demographic Characteristics of Patients Diagnosed with Advanced Chronic Venous Insufficiency (C4-C6) Correlated with Clinical and Para-clinical Findings

Imre Eniko Reka*, Imre M

University of Medicine and Pharmacy of Tirgu Mures, Romania

Chronic venous insufficiency's frequency reaches almost 25% in European countries. The aim of this present study was to assess the correlation between sociodemographic characteristics as well as clinical findings and para-clinical findings of aCVI patients. A total number of 2636 patients diagnosed with CVI were evaluated for over an 8 year time period (2006-2013). In case of 795 of them, diagnosis of aCVI (C4-C6) has been established. The following variables have been evaluated: demographic data, etiology, risk factors, chronic diseases as risk factors, signs and symptoms, laboratory findings and even the therapeutic approach.All the assessed data has been evaluated using descriptive statistics, t-Student test, and chi square test. Also the relative risk (RR) and Odds ratio (OR) has been calculated. The mean age of aCVI patients was significantly higher (p=0.001) than the age of patients with stage C1-3 CVI. A positive correlation (p<0.0001) between combined venous disorders and clinical stage of CVI has been found. Deep vein thrombosis proved to be correlated (p=0.02) with evolution of CVI to venous ulcer (stage C6). Worsening of advanced venous insufficiency was also correlated with presence of peripheral arterial diseases, and/or metabolic diseases (p<0.0001, and p=0.02). Based on our results, the typical profile of a patient with aCVI has been outlined. Using this profile, the general practitioner and even the internal medicine specialist can recognize in advance patients with an elevated risk of developing aCVI, and accordingly can choose a more appropriate therapeutic approach.

Keywords: advanced chronic venous insufficiency, socio-demographic characteristics, C4-C6 class venous disorder, venous patient profile

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Introduction

Chronic venous insufficiency is a common, however important clinical and social problem. According to the latest assessments, its frequency reaches almost 25% in European countries [1-3]. Advanced chronic venous insufficiency (aCVI) has however a lower, but increasing incidence over the last years (around 6.8% in 2012) [4,5]. Several studies have been performed in the last ten years, assessing the etiology and epidemics of chronic venous disease and its advanced form, including venous ulcer. Patients form Italy, Spain, Poland and even Romania were evaluated over this time period [6-9]. Despite all of the resulting comprehensive information, chronic venous insufficiency and its most advanced form (venous ulcer) often remains undiagnosed, being overlooked and underestimated by both patients and physicians [4,5].

Chronic venous insufficiency has a very broad spectrum of clinical manifestations, due to a very diversified etiology [1,2,7]. Previously it was believed that venous leg ulcers develop exclusively as a consequence of post-thrombotic insufficiency of the deep venous system of lower extremities. Development of new diagnostic modalities such as Eco Doppler Duplex Scan, demonstrated that this disabling disease could be caused by the insufficiency of the superficial as well as deep venous system [10-12]. In order to standardize the reporting and treatment of the diverse manifestations of chronic venous insufficiency, a comprehensive classification system (CEAP) has been developed to allow uniform diagnosis [10,13]. The quality of life in patients with CVI decreases over time. When reaching advanced stages the patient starts to represent not only a diagnostic and therapeutic challenge, but also a social and economic issue. Early recognition of this disease and accurate foresight of its evolution over time can prevent development of advanced, invalidating stages or venous ulcer. Foreseeing the evolution of CVI has to be based not only on the evolution of the disease, but on the CVI patient profile also. The present paper proposes assessment of the correlation between socio-demographic characteristics as well as clinical findings and para-clinical findings of aCVI patients, and creation of a patient profile, based on which the general practitioner or specialist can foresee the elevated risk of developing aCVI and venous ulcer.

Methods

From January 2006 to December 2013 all data of a total number of 2636 patients previously diagnosed with CVI has been retrospectively evaluated. Files of the patients were gathered from 11 different general practices, one

* Correspondence to: Eniko Reka Imre
E-mail: imreeniko@imetics.ro

outpatient clinic, one hospital, and one university hospital. Based on CEAP classification, patients were grouped in two different groups: clinical stage C1-3 CVI, and advanced C4-6 CVI patients (aCVI) [14].

Out of the total 2636 patients, 1841 were found to have C1-3 stage, and 795 patients aCVI. The following variables were evaluated: demographic data (age, gender, demographic origin); etiology (venous disorders: varicose veins, primary deep vein insufficiency, venous thrombosis (including post-thrombotic syndrome); risk factors: heredity, prolonged orthostatism, trauma, obesity; chronic diseases as risk factors: type 2 diabetes mellitus, hypertension, congestive heart failure, renal insufficiency; signs and symptoms: pain, venous claudication, edema, pigmentation, healed venous ulcer, active venous ulcer; laboratory findings: erythrocyte sedimentation rate (ESR), number of thrombocytes, lipid profile, coagulation profile, inflammatory markers; and even the therapeutic approach. Based on the recorded signs, symptoms and other clinical findings the Venous Clinical Severity Score has been calculated [15].

Age, gender and demographic origin (urban or rural) were used as grouping variables, for the assessment of correlation and risk.

Time trend of clinical stage of CVI as well as time trend of gender, age, origin and venous severity score of aCVI patients was also assessed.

The relevant sample size was calculated based on the total number of population of Romania in 2011 (19.599.506 citizens), with a margin of error of 2%, and a confidence level of 95%. Based on these data the relevant sample size proved to be of 2401 patients. Thus the total number of 2636 patients, provided an adequate power, and a corresponding confidence interval (CI).

All the assessed data has been evaluated using descriptive statistics, F-test, t-Student test, and chi square test. For relevant data, the relative risk (RR), Odds ratio (OR), and absolute risk reduction (AAR) has been calculated together with the corresponding 95% CI.

Results

Demographics

Out of the total number of 2636 patients previously diagnosed with CVI, 1511 (57.32%) were females, and 1125 (42.68%) were males. The mean age was 61.61±13.27 years (95% CI 61.11; 62.12). There has been a highly significant difference between the mean age of the two genders (p<0.0001). The mean age of women was 60.73±13.37 years, while men had a mean age of 62.78±13.05 years. Based on the demographic origin, 49.84% of CVI patients were originating from a rural area, while 50.15% of them were living in cities. Distribution of genders showed no correlation with the demographic origin of patients (p=0.765).

Advanced chronic venous insufficiency (aCVI; stage C4-6) was found in 795 patients (30.15% of the total 2636 CVI patients) (Figure 1). The mean age of these aCVI patients was 62.86±12.71 years (95% CI 61.97; 63.75) with a corresponding distribution of genders of 47.30% males and 52.70% females.

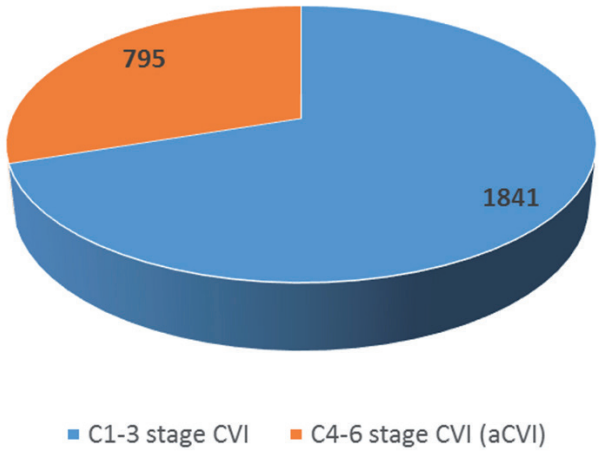

Fig. 1. Distribution of Chronic venous insufficiency patients based on clinical severity

Correlating the clinical severity of chronic venous disease, with gender of patients, we observed that female gender positively correlates with CVI severity (p=0.0016), presenting a relative risk of aCVI of 1.21 (95%CI: 1.07; 1.35).

Compared to the C1-3 class CVI patients, the mean age of patients with aCVI was significantly higher (p=0.001). There was no significant difference between the mean age of men and women in the aCVI group (p=0.86), however we found a significant difference between the mean age of rural and urban aCVI patients. Accordingly the mean age of rural patients (63.88±12.97 years) was significantly higher (p=0.014) than the mean age of patients living in urban areas (61.67±12.32 years). The demographic distribution of aCVI patients was: 427 (53.72%) originating from rural areas, and 368 (46.28%) from urban areas (Figure 2).

The rural origin of the patients proved to be positively correlated to the clinical stage of CVI (p=0.01), however the relative risk of developing aCVI, determined for these rural origin patients was only 1.11 (95%CI: 1.02; 1.20).

Etiology –venous disorders

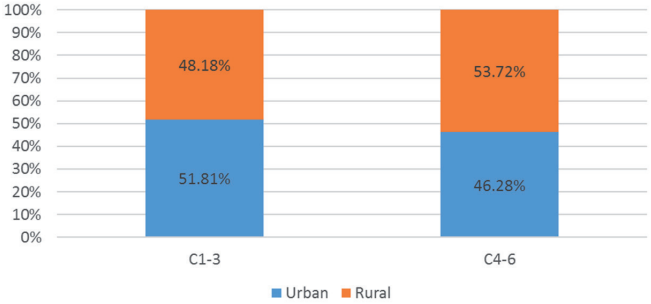

Fig. 2. Frequency of CVI patients based on demographic areas

Out of the 2636 patient diagnosed with CVI, 2216 (93.77%) of them were found with only one venous diagnosis: varicose veins, deep vein thrombosis (including the corresponding post thrombotic syndrome), or primary chronic insufficiency of deep veins. In the rest of 420 patients (15.93%), the diagnosis was actually a combination of the above mentioned venous diseases. Accordingly varicosity of the lower limb veins was present in 46.35% of CVI patients, deep vein thrombosis in 51.21% of CVI patients, while chronic venous insufficiency of the deep veins in only 13.62% of CVI patients.

In the aCVI group, 615 out of 795 (77.35%) patients were found with only one type of venous disorder, while 22.64% of them were found to have more than one type of venous diseases. Simultaneously the chi-square test demonstrated that there is a highly significant positive correlation ($p<0.0001$) between the combined etiology (presence of two or more different types of venous disorders) and the clinical stage of CVI. Accordingly multiple venous disorders correlated significantly with C4-6 stages of CVI. More than that, evaluating the frequency of different etiologies of patients diagnosed with aCVI, a significant positive correlation ($p=0.002$) has been demonstrated between deep vein thrombosis, and C6 stage of aCVI (venous ulcer). Accordingly, patients with history of deep vein thrombosis, already having aCVI, presents a relative risk of 1.49 (95%CI: 1.20, 1.87) of developing venous ulcer as natural evolution of the disease.

Etiology - risk factors

Hereditary, prolonged orthostatism, trauma of the limb and obesity as the four most important risk factors of venous diseases have been evaluated. Hereditary was found as present in 90.55% of the total number of evaluated patients, while prolonged orthostatism was found in 7.51%, traumatism of the lower limb in 3.83%, and obesity in 34.18% of the total number of CVI patients. Distribution and frequency of these risk factors are presented in Table I. Correlations of these risk factors with different clinical stages of CVI were also evaluated. Hereditary venous disorders were negatively correlating ($p=0.005$) with C4-6 stage CVI. Simultaneously traumatism of the lower limb and obesity were also negatively correlated with C4-6 stage CVI ($p=0.019$, and $p=0.0001$ respectively). Prolonged orthostatism however presented no significant correlation with the clinical stages of CVI ($p=0.44$). Despite of these negative correlations, the relative risk of developing aCVI was notable for traumatism of the lower limb and for obesity. Accordingly the RR assessed was: hereditary: 1.04 (95%CI: 1.01; 1.06), prolonged orthostatism: 0.89 (95%CI: 0.66; 1.20) traumatism of the lower limb: 1.58 (95%CI: 1.07; 2.33), obesity: 1.24 (95%CI: 1.12; 1.39).

Table I. Distribution and frequency of Chronic Venous Insufficiency risk factors

	C1-3	C4-6	Total CVI
Hereditary	62.52%	28.03%	90.55%
Orthostatism	5.42%	2.09%	7.51%
Trauma	2.28%	1.56%	3.83%
Obesity	22.23%	11.95%	34.18%

Etiology – other diseases as risk factors

Presence of other diseases as risk factors was evaluated for all CVI and for aCVI patients also. The occurrence of other systemic diseases, or affections with impact on the CVI, are presented in Table II. According to the chi-square test, presence of peripheral arterial disease (PAOD) and presence of metabolic disorders positively correlates with the severity of CVI ($p<0.0001$ and $p=0.02$ respectively) (Figure 3). Based on the above data, the calculated relative risk of developing aCVI in patients with chronic venous insufficiency combined with PAOD proved to be 3.10 (95%CI: 2.54;3.80), while in case of concomitant metabolic disorders RR = 1.35 (95%CI: 1.20; 1.52).

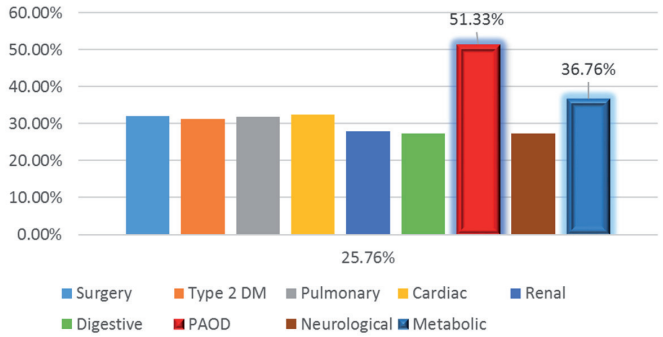

Fig. 3. Frequency of other chronic diseases as risk factors of aCVI

Signs and symptoms

All the signs and symptoms registered during the patient's clinical examination have been evaluated and correlated with the demographic characteristics (age, gender, demographic origin) of CVI patients. Moreover the Venous Severity Score has been calculated for each patient.

While correlating the signs and symptoms with the clinical stage of CVI, we observed a highly significant positive

Table II. Occurrence of other systemic diseases as risk factors

	Traumatism	Surgery	Type 2 DM	Pulmonary	Cardiac	Renal	Digestive	PAOD	Neurological	Metabolic
C1-3	98	165	252	301	1282	314	761	237	162	499
C4-6	34	78	115	141	616	122	287	250	61	290
TOTAL	132	243	367	442	1898	436	1048	487	223	789

correlation between relevant clinical symptoms and aCVI. Accordingly, the correlation coefficient determined by the chi-square test (p), the calculated relative risks and the odds ratio were: for venous pain: p<0.0001; RR: 1.06(95%CI: 1.04;1.07; OR: 5.98 (95%CI: 3.02; 11.84), for venous claudication: p<0.0001; RR: 1.39(95%CI: 1.32;1.47); OR: 2.85 (95%CI: 2.35; 3.45), for the edema of the lower limb: p<0.0001; RR: 1.23(95%CI: 1.20;1.27); OR: 8.11 (95%CI: 5.40; 12.17; and for the pigmentation of the skin p<0.0001; RR: 13.62(95%CI: 11.48;16.15); OR: 168.17 (95%CI: 122.15; 231.53).

Simultaneously we have correlated the clinical findings with the gender of the patients. No significant correlation have been found using the chi-square test, however determining the Odds ratio, we observed that females show a high risk of edema and pain RR: 1.01(95%CI: 0.98;1.04) OR: 1.31(95%CI: 0.60; 2.87) and RR: 1.01(95%CI: 0.99;1.02), OR: 2.25 (95% CI: 0.56; 9.06) respectively, while males have a higher risk of venous ulcer RR: 1.58(95%CI: 1.31;1.89), OR: 1.99 (95% CI: 1.50; 2.63). As for the demographic origin of patients, we have found a highly significant positive correlation of presence of venous ulcer in patients coming from rural areas (p=0.0008) with a relative risk of 1.58 (95%CI: 1.31;1.91). More than that, risk stratification has showed an increased risk of patients from rural area to develop the following invaliding venous symptoms: pain 2.34 (95%CI: 0.58; 9.43), edema 1.61(95%CI: 0.73; 3.54), pigmentation 2.29 (95%CI: 1.32; 3.97) and venous ulcer 2.07 (95%CI: 1.54; 2.78).

Venous clinical Severity Score

Although the CEAP system is an excellent scheme for standardized classification of chronic venous disease, it is a relatively static system. The C (clinical) class of disease does represent a spectrum of disease severity, but it does not allow a practical assessment of change in response to treatment or adverse events. The Venous Clinical Severity Score (VCSS) consists of nine clinical descriptors, each graded on a scale of 0 to 3 representing the spectrum of absent, mild, moderate, and severe features. The nine descriptors are pain, varicose veins, edema, pigmentation, induration, inflammation, number of active ulcers, duration of active ulceration, and size of the largest current ulcer.(16) Our results showed that male gender is positively correlated with higher VCSS values (p=0.037) and RR= 1.15(95%CI: 1.01;1.30). Concomitantly we observed a significant positive correlation between the rural origin of the patients and higher VCSS values (above 5 points) (p<0.0001) with a RR=1.37(95%CI: 1.20;1.57). Frequency of venous clinical severity score is presented in Table III.

Paraclinical findings

The erythrocyte sedimentation rate (ESR), the number of thrombocytes, lipid profile, coagulation profile, and inflammatory markers were all determined. We have found significant differences only in case of erythrocyte sedimentation rate (ESR) and the number of thrombocytes, which proved to be different in females and males with aCVI (p= 0,011 and p=0.0005 respectively), however more statistical analysis has to be performed, to determine the clinical relevance of these results.

Time-trends

We examined the time trend of all CVI, of aCVI and the percentage of aCVI from CVI. Our result were not concordant with those found in corresponding literature. (2,7,8) We have found an increasing trend of CVI and a decreasing trend of aCVI. Moreover the percentage of patients with aCVI from CVI presented a significant decrease over time, with an R2 =0.9493. (Figure 4.) Evaluation of the trend of demographic origin and gender of patients with aCVI, revealed a divergent tendency of urban rural origin, and a convergent tendency of genders. Accordingly the number of patients coming from rural areas showed a nearly constant trend (R2=0.083), while the number of aCVI patients living in cities decreased (R2=0.268). Simultaneously gender of aCVI patients tended to remain constant, while the total number of aCVI patients decreased

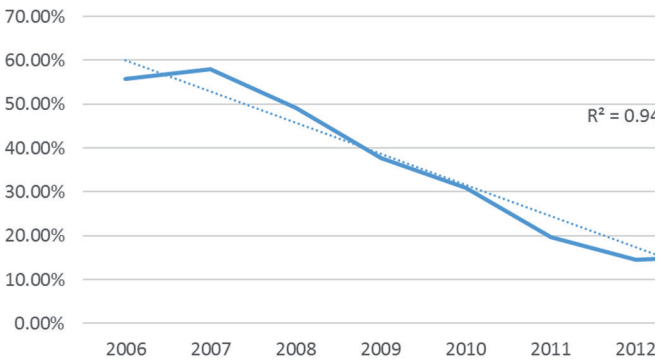

Fig. 4. Percentage of aCVI from CVI patients over time

Table III. Distribution and frequency of venous clinical severity score by gender and demographic origin of patients

	VCSS=0	VCSS=1	VCSS=2	VCSS=3	VCSS=4	VCSS=5	VCSS=6	VCSS=7	VCSS=8	VCSS=9	VCSS=10	VCSS=11	VCSS=12	VCSS=13	VCSS=14	VCSS=15	VCSS=16
Male	6	84	111	187	310	161	101	26	18	29	37	24	12	11	2	2	4
Female	0	126	235	350	333	187	100	44	6	21	20	43	18	11	10	0	2
Urban	6	97	189	233	379	178	112	29	11	14	18	37	3	10	4	0	2
Rural	0	113	157	309	264	170	89	41	13	36	39	30	27	12	8	2	4

over the years. Accordingly the trend of frequency of male aCVI patients was R2=0.125 while the trend of aCVI female patients was R2=0.182.

Discussion

Chronic venous insufficiency and its aggravated form (the advanced chronic venous insufficiency) is a common disease, however it has a very important impact not only on the health, but also on the social status of the patient. Early diagnosis, and a proper therapeutic approach can be in benefit not only of the patient, but also of the family, of the general practitioner, of the specialist, and in wider view on the entire healthcare system.

The importance of this study consists in creating a profile of the CVI and aCVI patient, based on the demographics, diagnostics, and clinical examination, symptomatology, and laboratory findings. Based on the created profile, the risk stratification and the time trends evaluated in our study, the general practitioner and/or the specialist can choose a more effective way to follow and treat these patients.

The mean age of CVI patients was 61.61±13.27 years, however male patients turned to be more significantly older than females ($p<0.0001$). The mean age of aCVI patients 62.86±12.71 years .was significantly higher ($p=0.001$) than the age of patients with less severe CVI (stage C1-3), but there is no difference between the mean age of male and female aCVI patients ($p=0.86$). The mean age of aCVI patients originating from rural areas was significantly higher ($p=0.014$), and there was a significant correlation between rural origin and CVI clinical stage ($p=0.01$). Chronic venous insufficiency is known to be a consequence of several venous and non-venous disorders. Accordingly, we evaluated the underlying affections, and we have correlated them with age, gender, demographic origin of patients and clinical severity of CVI. The chi square test revealed a highly significant ($p<0.0001$) positive correlation between combined venous disorders and clinical stage of CVI. Our result showed also, that deep vein thrombosis as etiologic factor, significantly correlates ($p=0.02$) with evolution of CVI to venous ulcer (stage C6), bringing into account a relative risk of RR=1.49.

Other risk factors as family history of venous diseases, traumatism of the lower limb, or obesity negatively correlates with aCVI, and positively with C1-3 stage CVI. In case of these risk factors the relative risk of developing C1-3 stage CVI is more significant than developing stage C4-6 venous insufficiency.

Evaluation of other chronic diseases as risk factors, showed a highly significant positive correlation of development of advanced venous insufficiency in patients suffering also from peripheral arterial diseases, and/or metabolic diseases ($p<0.0001$, and $p=0.02$ respectively). The relative risk of CVI patients to develop advanced form of this disease and even venous ulcer turned to be RR=3.10 in case of concomitant PAOD, and RR=1.35 in case of other metabolic disorders.

Signs and symptoms are important in determining the appropriate therapeutic approach and prognosis of CVI patients. Presence or absence of these risk factors provides a risk stratification which can be individualized for every patient. Accordingly our results showed that males have an increased risk for developing venous ulcer (RR=1.58; OR=1.99), while females have an increased risk of edema and venous pain (RR=1.01; OR=1.31, and RR=1.01; OR=2.25). Males are more exposed to trauma of the leg, they are neglecting hygiene, and they don't address easily to their family physician, thus presenting an increased risk of venous ulcer, while females tend to be overweighed and also to be more sedentary, which explains the higher rate of edema and venous pain. The risk of venous ulcer is associated also with rural origin of the patient (RR=2.07). Moreover these villager patients have a higher risk of severe pain, edema or pigmentation (RR=2.34; RR=1.61; and RR=2.29). These differences between patients from rural/urban area, can be originated in the difference in lifestyle between these geographic areas. Patients living in the rural area are more exposed to minor/major trauma of lower limb, lack of hygiene, and orthostatic position. More than that, they usually find it much more difficult to access the healthcare system, and also tend to overlook the mild symptoms of CVI.

Based on the signs, symptoms and other clinical findings the Venous Clinical Severity Score was calculated. Our results showed that male gender is positively correlated with higher VCSS values ($p=0.037$), with RR=1.15. Simultaneously we observed a significant positive correlation between the rural origin of the patients and higher VCSS values ($p<0.0001$) with a RR=1.37.

Time trends of frequency and distribution of CVI and aCVI patients was also evaluated. Accordingly we found an increasing trend of CVI and a decreasing trend of aCVI. We observed also an increasing trend of patients coming from villages, and an according trend of patients living in villages.

Based on the above presented results two different CVI patient profiles have been outlined. The CVI patient in general as well as patient with stage C1-3 CVI, can be defined as a supraponderal or even obese 61 year old female, living in the urban area with familial history of venous insufficiency, suffering from varicose veins, and presenting symptoms like edema, and pain of the lower limb, with a VCSS of less than 3 points. Simultaneously, the patient with advanced venous insufficiency is likely a 64 year old men, living in a small village, with history of deep venous thrombosis combined with other venous dysfunctions or risk factors, diagnosed also with peripheral arterial disease and other metabolic disorders, presenting edema, pain and pigmentation of the lower limb's skin, with an elevated risk of venous ulcer, and a VCSS over 5 points.

Conclusions

Based on the presented correlations and on the calculated relative risk, our study outlined two different profiles of

patients with CVI and advanced CVI (aCVI). These results indicate that identification of with these two profiles, could be a useful tool for the general practitioner and also for the specialists not only in the diagnostic process, but even in the process of choosing the therapeutic approach, or estimating the potential prognostic of patients with CVI.

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