SAGE Open Medicine

SAGE Open Medicine
Volume 10: 1–13

DOI: 10.1177/20503121221118992
journals.sagepub.com/home/smo
SAGE

Global impact and contributing factors in varicose vein disease development

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Abstract

Varicose veins are convoluted, expanded, and stretched subcutaneous veins of the lower leg and are the most frequently reported medical condition. This condition has a higher prevalence in Western and developed countries. Inadequacy of the valves results in reflux of blood in the veins of the lower leg. The present study aims to describe the epidemiology and contributing factors (risk factors and pathological factors) in the development of varicose veins disease. PubMed/Medline, Science Direct, Google Scholar, SciFinder, Scopus, and Web of Science databases were explored to include potential research and review articles. Finally, 65 articles were considered appropriate to include in the study. Pain, swelling, heaviness, and tingling of the lower limbs are the most common sign and symptoms caused by varicose veins while in some individuals it is asymptomatic. The Prevalence of varicose veins varies geographically. Currently, it is reported that globally about 2%–73% of the population is affected by varicose veins while the prevalence rate in Pakistan is 16%–20%. Different risk factors associated with the advancement of varicose veins are age, gender, occupation, pregnancy, family history, smoking, BMI and obesity, exercise, genetic factor, and current lifestyle. In varicose veins, some contributory elements may also play an important role in the disease development, incorporating constant venous wall aggravation, hereditary variation, and persistent venous hypertension. This condition has now turned into a curable issue that was previously viewed broadly as less important for treatment, determining the individual's satisfaction. Moreover, the mechanisms behind the risk factors involve diet, physical work, and hormonal contribution. These are more likely to be explored.

Keywords

Varicose veins, epidemiology, risk factors, pathology

Date received: 8 February 2022; accepted: 21 July 2022

Introduction

Varicose veins (VVs) are the most frequently reported medical condition that causes significant morbidity and long-lasting costs for the patient.[1–4] Therefore, it requires great attention. VVs are convoluted, expanded, and stretched subcutaneous veins of the lower leg and are an easily observable clinical condition. Inadequacy of the valves results in reflux of blood in the veins of the lower leg which is a typical symptom of VVs.[5] With higher prevalence in Western and developed countries, this disease varies geographically. In the United States, VVs disease extends to chronic venous insufficiency (CVI), which is a significant morbidity, and if VVs are left untreated, it may lead to serious complications. For example, edema, thrombophlebitis, external hemorrhage, lipodermatosclerosis, dermatitis, skin pigmentation or discoloration, induration, and ulceration.[6–9]

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In 1994, American Venous Forum (AVF) proposed Clinical-Etiology-Anatomy-Pathophysiology (CEAP) which is an exceptionally valuable mechanism for specialists to diagnose the underlying pathology/disease and suitable treatment in its early stage. VVs disease belongs to class 2 among the six classes of CEAP characterization.[10] Recently, an update on CEAP classification described revisions and incorporated new subclasses in C2r (recurrent VVs) and C4c (Corona phlebectatica)[11] (Table 1). In lower extremities, superficial and deep veins engage distinct compartments that are divided by fascia, covering the leg muscles. In these compartments, the superficial compartment is a low-pressure chamber, and the deep compartment is a high-pressure chamber because of the functioning of calf muscles and their ability to pump the venous blood toward the heart. In a normal situation, when calf muscle contracts, the valves of the perforating veins get close to maintain the high pressure of the deep veins from being transmitted to the superficial veins. The relaxation of the calf muscles results in temporarily lowering the pressure in the deep veins than the pressure in the superficial venous system.[2] Disruption of any vein of lower leg like perforator veins, small or great saphenous veins may lead to VVs.[12]

Nowadays, VVs have turned into a curative health issue with various symptoms as well as serious complications that were viewed broadly as less important for treatment and also influenced the individual quality of life.[13] Various studies have highlighted the relationship of VVs with the numerous risk factors which include particularly increasing age, family history, occupation-based predominantly related to prolong standing, obesity, pregnancy,[4] smoking, alcoholism, hormonal substitution treatment (HST), constipation, diabetes, hypertension, and physical damage to lower legs.[2,14] It has also been reported that VVs can also occur even in those adults who have no risk factors, indicating that some intrinsic genetic factors may contribute to develop VVs. However, the genetic involvement of VVs is also not extensively explored. Some contributory factors to the development of VVs include constant venous wall aggravation, hereditary variation, and persistent venous hypertension.[15] Primarily, we aimed to highlight the global epidemiology of the VVs. Secondarily, we described various contributing factors (risk factors and pathological factors) more comprehensively that play an important role in the development and progression of VVs disease. In the present study, we have comprehensively discussed various aspects of the VVs disease that give some direction for later studies to further investigate the contributory factors and underlying mechanisms of the VVs disease extensively.

Methodology

An efficient literature survey of the PubMed/Medline, Science Direct, Google Scholar, SciFinder, Scopus, and Web of Science databases were explored. Suitable keywords were utilized to collect the primary data, including "intermittent VVs," "neovascularization," "epidemiology," "prevalence," "incidence of VVs," "etiology," "clinical manifestations/features," "signs and symptoms," "hereditary association," "risk factors," "pathogenesis," "diagnosis," "effect on quality of life," and "global burden of VVs." To write this review, the research articles till 2022 were surveyed for consideration. Initially, 180 research items were obtained for the collection of the literature related to the VVs followed by the finalization of the screening process. After eliminating the duplicates, further articles were excluded based on preprint and abstract screening. Subsequently, the articles were evaluated based on full-text, congenital ailments, and animal studies. Original research articles, review/mini-review articles, and case reports were included as data collection and articles written in English were considered only in this study. Ultimately, 65 articles were taken into consideration to write this review as shown in the flow chart diagram (Figure 1).

Table 1. CEAP classification of chronic venous diseases.

CEAP classification	
C0	Non-visible or palpable signs of venous disease
C1	Telangiectasias or reticular veins
C2	Varicose veins
C2r	Recurrent varicose veins
C3	Edema
C4	Changes in skin and subcutaneous tissue secondary to chronic venous disease
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or atrophie blanche
C4c	Corona phlebectatica
C5	Healed venous ulcer
C6	Active venous ulcer
C6r	Recurrent active venous ulcer

CEAP: Clinical-Etiology-Anatomy-Pathophysiology.

Results

Epidemiology

VVs disease is one of the most commonly observed medical condition influencing teenagers, adults, and elders around the globe. Developing countries have a lower prevalence rate than developed countries.[2,12] It is assessed that 33% of the general population aged between 18 and 64 years are influenced by VVs. Further rise in prevalence results in a great degree of costs in the treatment of VVs.[16] In Western nations, VVs are found in 10%–15% of males and 20%–25% of females.[2] The San Diego population-based investigation evaluated a higher prevalence of VVs in Hispanics (26%) and lesser in Asians (18%) but found commonly in non-Hispanic Whites.[17] An epidemiologic study led in the United States uncovered that the 40–80 year age group including 11 million men and 22 million women had VVs.[18]

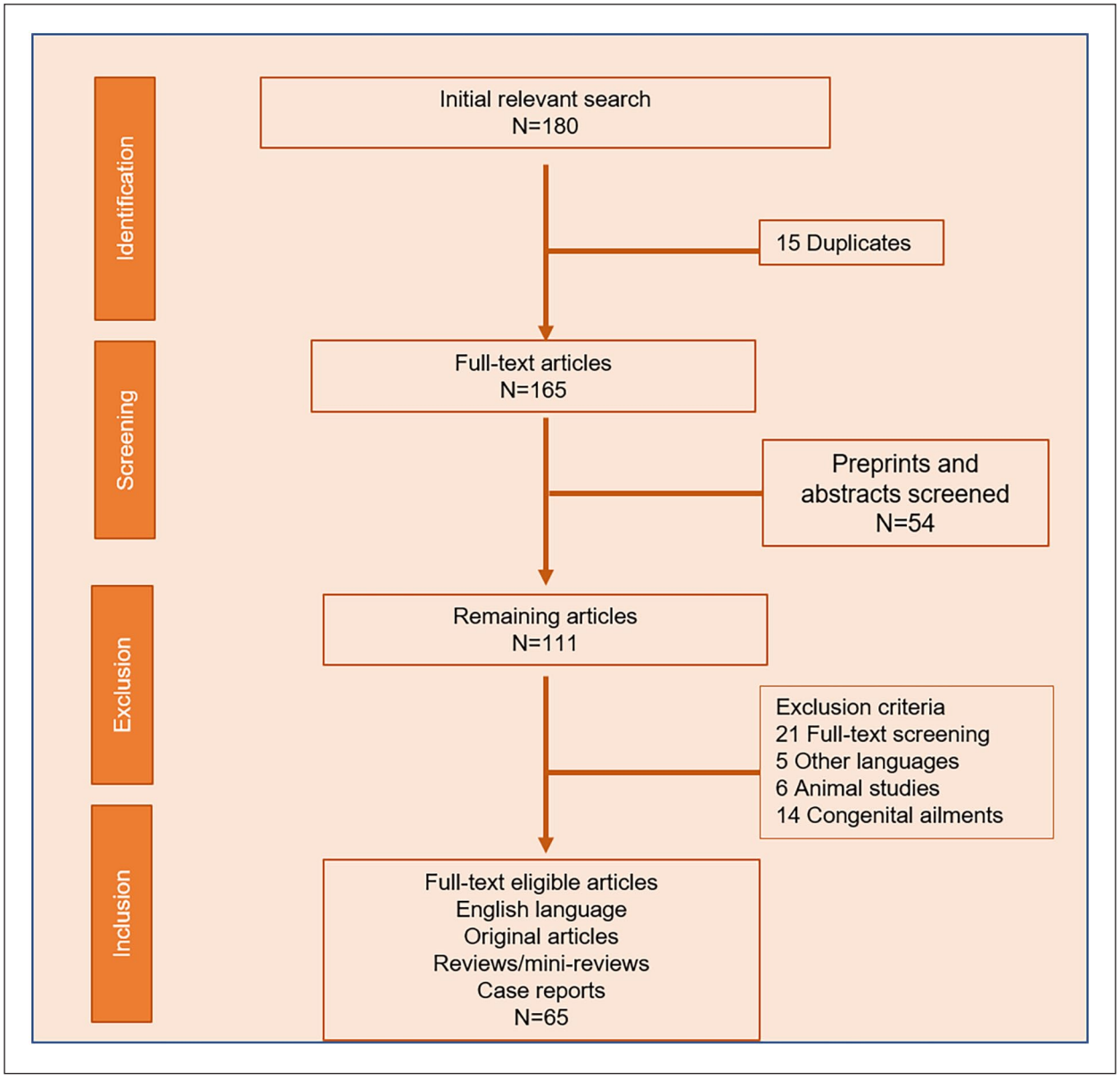

Figure 1. Flow chart diagram.

Various surveys were conducted in Asia, among them; an examination in Japan revealed a 45% of prevalence rate of VVs which was mild to severe.[19] In China, Shanghai, an research conducted on 30,712 patients having an age of more than 15 years that were working in different enterprises, demonstrated a prevalence rate of 8.39% of VVs[20] whereas in Tehran, Iran, a study reported a 36% prevalence rate of VVs in the same age groups.[21] Another study in southern Taiwan described a 24.2% of prevalence rate of VVs in the lower legs.[14] In the United Kingdom, it is assessed that 33% of the population has VVs of the lower legs. The general sign and symptoms encountered by patients are pain, swelling, heaviness, and tingling sensation while few remain asymptomatic.[8] Clark et al.[22] in South Wales reported VVs a prevalence rate of 57% in females and 63% in males with 71% prevalence rates in the people whose age range from 60 to 97 years, whereas Oklu et al.[15] recorded a prevalence rate of VVs nearly 2.6% in females and 2% in males. In South Korea, a population-based investigation examined 2165 subjects; among them 1203 were female and 962 were male subjects. Bahk et al.[23] revealed a 31.3% of prevalence rate of VVs. In Amol, Iran, a cross-sectional examination of 225 members revealed that 73.1% of the members developed VVs of the lower leg,[3] and in Saudi Arabia, a study proposed a 62.0% of VV prevalence rate.[24] In Pakistan, a multicenter cross-sectional and observational investigation was conducted on 3000 subjects. They reported an overall prevalence of CVD was 39%, and

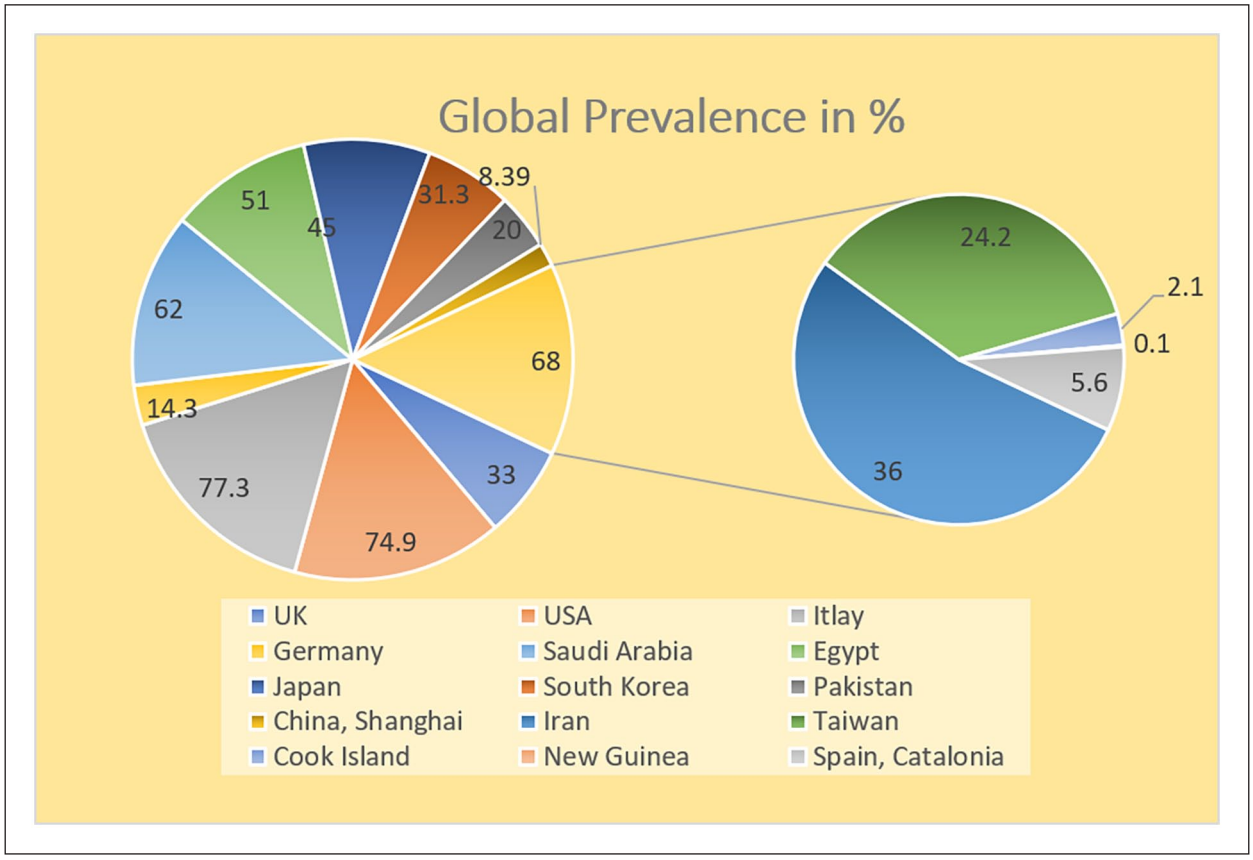

Figure 2. Global prevalence for chronic venous diseases.

among them, they observed a 16% prevalence rate of VV.[25] Another study indicated about 20% of the prevalence rate in Pakistan. A study conducted in Cairo, Egypt, concluded more than 51% of VVs incidence rates among the targeted population.[26] In Germany, Rabe et al.[27] reported a 14.3% prevalence rate of VVs. Previous investigations documented a minimal prevalence rate of VVs in New Guinea at 0.1% and the Cook Islands,[28] while the highest prevalence rates were 77.3% in Italy,[29] and 74.9% in the United States.[30] A recent study, conducted in Spain, Catalonia, explored a large-scale (5.8 million) population, and reported more than 5.6% of prevalence and incidence of 4.62 people/year of VVs. These figures are lower in comparison to the previously reported studies because of large-scale population inclusion as they investigated more than 80% of individuals living in Catalonia[31] (Figure 2, Table 2).

Risk factors

Various risk factors have been linked to VVs disease development and worsening which include age, particularly increasing age; gender; pregnancy as well as parity; family history; occupation-based, predominately prolonged standing; body mass index (BMI) and obesity; and genetic involvement (Table 3).

Age. Age is viewed as a key factor in the development and progression of various diseases including VVs. Numerous reports showed that prevalence of VVs increased with age because of debilitation of the lower leg muscles and lessening in the flexibility of venous valves.[9] Recently, a large-scale study conducted on 5.8 million people also suggested age is the biggest risk factor in the development of VVs that become double above the age of 65 years.[31] In Budapest, Hungary, a population-based study revealed the definite impact of age on the events of VVs disease development and reported that the prevalence rate of VVs rises with the increment in the age and observed the highest prevalence of 82.1% at the 71–80 years of age or more.[33] Another report also documented a 41% of prevalence rate of VVs from 51 to 60 years of age. However, developing countries have a lower prevalence rate than highly developed countries.[2,12] Taken together, these reports indicated age as the major factor in the development of VVs disease.

Gender. Various studies suggested the relationship of VVs with gender and found a higher prevalence in women than men while few reports demonstrated no distinction. Evans et al. reported that men have more risk of developing VVs whereas Carpentier stated that women have a high risk.[38,57] Recently, a report illustrated the prevalence of VVs that

Table 2. Epidemiology of varicose veins in different countries.

Country	Publication year	Reference
Japan	1990	Hirai et al.[19]
China	1990	Sun[20]
Iran	1996	Nassiri et al.[21]
San Diego, USA	2003	Criqui et al.[17]
Germany	2003	Rabe et al.[27]
Italy	2005	Chiesa et al.[29]
Finland	2009	Ahti et al.[32]
United Kingdom	2010 and 2013	Clark et al.[22] and Marsden et al.[8]
South Korea	2012	Bahk et al.[23]
Budapest, Hungary	2012	Bihari et al.[33]
Pakistan	2013 and 2014	Khan et al.[25] and Latif et al.[34]
Taiwan	2014	Chen and Guo[14]
Saudi Arabia	2014 and 2020	Al Shammeri et al.[24] and Dalboh et al.[35]
Egypt	2020	Aly et al.[26]
Spain	2021	Homs-Romero et al.[31]
Cooks Island and New guinea	1999	Clement[28]

varies internationally from 2% to 56% in males and 1% to 73% in females,[2,12] whereas another population-based investigation revealed distinctive prevalence in youngsters, from 7%–40% in males and 14%–51% in females.[3] Moreover, Tampere[36] and multi-ethnic[17] studies additionally revealed female sex as a risk factor for VVs.[23] In a cross-sectional investigation, Bahk et al.[23] exhibited a higher prevalence rate of VVs among women than men and announced a 21.8% and 9.5% of prevalence rate of VVs in women and men, respectively. An examination led in the city of Rijeka, in addition, detailed that females are more prone to VVs.[63] The Bonn vein study conducted among 3072 people showed that 1350 men and 1722 women have VVs between 18 and 79 years.[37] On the contrary, a small-scale study conducted in Mangalore, India, indicated men with high cases of VVs.[13] A population-based investigation revealed the prevalence of 10%–30% in males and 25.1%–55% in females, mostly in the Western world.[7] Various key factors that may contribute to the disease development and progression have yet to be identified and require further studies. It remains controversial who has more risk of developing VVs; however, most of the research showed that the female gender are more prone toward VVs as compared to men.

Family history. Family history includes different medical conditions including hypertension, metabolic ailments, coronary heart diseases, and so forth. VVs additionally have solid relationships with family history. A few studies have demonstrated familial inclusion for VVs. Hirai et al.[19] showed that 42% of Japanese had a positive family history of VVs and 14% without any family history had VVs. Carpentier[38] showed that first-degree relatives were the main key factor in developing VVs among both genders.

Krysa et al. reported that patients having a positive family history of venous disorders had been revealed previously in mid-1855 that VVs may occur in such individuals.[62] Brinsuk et al. included 24 monozygotic and 22 dizygotic twins. He looked at venous system functioning among them and disclosed the solid impact of family history on the VVs.[40] In a case-control study, Cornu-Thenard et al. reexamine the familial factors in people having a positive history of VV disease. They found that 90% of youngsters had VVs when both guardians had VVs. When one parent was affected, there had been 25% possibility for men and 62% possibility for women of occurring VVs ailment.[64] A Chinese report revealed a positive relation of family history with a 70%–92% possibility of developing VVs[65] while a Finnish report found 1.6-fold increase in the possibility of developing VVs.[32] All these studies suggested positive relation of VVs disease with the family history and one study suggested that among families, women have a high risk of developing VVs.

Occupation. Among various occupations, the occupation that requires prolonged standing including teachers,[35] clerks, dealers, laborers, road cleaners, receptionists, security guards, and nursing staff, has been shown as a key factor for the high prevalence rate of the VVs. Bahk et al.[23] reported that the occupation with long standing hours in both males and females resulted in a higher prevalence of VVs regardless of age. Few other studies also found the relationship between prolonged standing with the VVs disease.[23,33,66] Bihari et al.[33] reported 65% of people working in such occupations with VVs and 54% of incidence among the people connected with inactive work.

Nursing is also believed to be a high-risk profession in terms of the VVs disease development because of its long-standing position during work.[42,43] A cross-sectional investigation was conducted in Amol, Iran, which documented similar findings and illustrated a 73% of prevalence rate among the medical attendants.[3] Ziegler et al.[41] also showed a

Table 3. Risk factors contributing to varicose vein disease development.

Risk factor	Reference	Publication year
Age	Beebe-Dimmer et al.[2]	2005
	Naoum et al.[9]	2007
	Bihari et al.[33]	2012
	DePopas and Brown[12]	2018
	Homs-Romero et al.[31]	2021
Gender	Laurikka et al.[36]	2002
	Criqui et al.[17]	2003
	Bahk et al.[23]	2012
	Chen and Guo[14] and Das et al.[7]	2014
	Sharif Nia et al.[3]	2015
	Rabe at al.[37]	2016
Family history	Hirai et al.[19]	1990
	Carpentier[38] and Cornu-Thenard et al.[39]	2000 and 1994
	Brinsuk et al.[40]	2004
	Ahti et al.[32]	2009
Occupation	Zeigler et al.[41]	2003
	Nasiri-Foourg et al.[42]	2005
	Bahk et al.[23] and Bihari et al.[33]	2012
	Sharif Nia et al.[3]	2015
	Khan et al.[25]	2013
	Dalboh et al.[35]	2020
	Ali et al.[43]	2022
Pregnancy and parity	Stansby[44] and Rabhi et al.[45]	2000
	Skøtt and Carter[46]	2002
	Golledge and Quigley[47]	2003
	Beebe-Dimmer et al.[2]	2005
	Bamigboye and Smyth[48]	2007
	Zahariev et al.[49]	2009
	Oats and Abraham[50]	2010
	Bihari et al.[33]	2012
	Hall et al.[51]	2016
	DeCarlo et al.[52]	2022
BMI and obesity	Criqui et al.[17]	2003
	Beebe-Dimmer et al.[2]	2005
	Kohno et al.[53]	2014
	DePopas and Brown[12]	2018
Exercise	Klonizakis et al.[54]	2009
	Sharif Nia et al.[3]	2015
	Mok et al.[55]	2021
Hereditary	Sverdlova et al.[56]	1998
	Evans et al.[57] and Le Flem et al.[58]	1999
	Le Flem et al.[59]	2001
	Brice et al.[60]	2002
	Mellor et al.[61]	2007
	Krysa et al.[62]	2012

BMI: body mass index.

34% of prevalence rate of VVs among the hospital staff. Accumulative evidence suggested that occupation with long standing hours has a critical relationship in the development as well as the progression of the VVs disease.

Pregnancy and parity. Various investigations demonstrated that pregnancy is the significant factor in increasing the incidence of VVs in the females, as nulliparous women have the least prevalence of VVs in contrast to multiparous.[2,52] During pregnancy, VVs are more visible particularly at early stages because of over secretion of progesterone.[49] Various physiological modifications happen during pregnancy which incorporates weight increase, rise in blood volume, vasodilatation, fetal development, and abdominal pressure. These

physiological changes in the body give foundation to the development of the VVs and lead to the incompetency of venous valves, resulting in the backflow of the blood.[46] The possible reasons for developing VVs may include pregnancy-induced hypertension, a rise in the pelvic pressure as well as hormonal changes that most often settled after the birth.[47]

During pregnancy, anatomical and physiological changes in the body are needed for the development and birth of the baby[50] and the frequency of VVs in pregnant women is expected up to 40%.[44,45,48] A cross-sectional study that was conducted among 1835 pregnant women demonstrated that 172 females (9.4%) experienced VVs.[51] Bihari et al.[33] in an epidemiological study showed that among 350 female participants, nulliparous women were observed with 40.3%, primiparous with 66.1%, biparous with 71.9% of VVs, and the women who had three deliveries or more than that had 75.0% of VVs. Thus, these data suggest that pregnancy and parity is one of the potential risk factors of VVs as the incidence increase with the increase in multi-parity.

BMI and obesity. Females in the upper quartile of BMI have a greater possibility of developing VVs and there is no relation found between the BMI and VVs in males.[12,17] Past investigations showed BMI relationship between the advances of VVs among the women. A previous report showed that the elevated women's BMI is associated with the VVs while among men, this relationship has not been significant because of gender inconstancy.[2]

An investigation was directed in Japan that demonstrated the relationship between being overweight with the development of the VVs. Weight applies a relative increment in the intravenous pressure that may result in reflux of blood in the lower legs.[53] These studies suggest that females with higher BMI are at higher risk of developing VVs, and being overweight might also be a contributory factor in VVs disease occurrence and worsening.

Exercise. Sharif Nia et al.[3] have seen a relationship between the consistent exercise and VVs severity. Klonizakis et al. investigated the effect of acute exercise on the microvascular endothelial function (MEF) in VVs diseased patients following surgery. They found that acute exercise improved the MEF following surgery as compared to the standing position in the patients who have VVs disease. Although exercise strengthens micro-vessel inner wall functioning, they found no indication that a long workout time can enhance the VVs risk.[54] A recent report also evaluated the impact of physical functioning and proposed that lowering of physical function is associated with a higher risk of VVs.[55] Thus, these findings suggest that exercise is a potential risk factor in VVs development and may have a protective role to decrease the VVs risk.

Hereditary inclusion. VVs are turning out to be a common medical condition and it keeps running in families.[57] If there should be an occurrence of VVs, forkhead box protein C2 (*FOXC2*) was the first gene outlined which led to mutation and was strongly linked with venous valve failure in superficial and deep veins of the lower legs.[62] Brice et al. revealed that the mutation in the *FOXC2* gene causes an uncommon hereditary disorder called lymphoedema distichiasis, and VVs are a very common feature of this condition. They expected that this gene may be engaged with VVs progression in normal people. They investigated 2060 female twin pairs and presumed that the *FOXC2* gene inclines individuals to VVs.[60] Another examination demonstrated that each individual having *FOXC2* change had confirmed venous reflux when analyzed with duplex ultrasound scanning after contrasted with controls.[61] *FOXC2* mutation is also known to influence both superficial and deep vein valves.[62] An endothelial cell surface glycoprotein receptor named thrombomodulin (TM) has additionally been discovered to be involved in the VVs advancement.[59] Previously, the *TM* gene was detected in people having venous thrombosis (VT),[58] and a study reported the association of VT with the VVs and said that the patients with VT also had VVs disease.[62] The *C677T* methylenetetrahydrofolate reductase (*MTHFR*) functional polymorphism has additionally been connected with the development of arterial diseases, now its relationship with the development of VVs has also been demonstrated.[62] Moreover, Sverdlova et al. studied 98 subjects with VVs and 297 control subjects connected with *C677T MTHFR* functional polymorphism and its relationship with the VVs. They had reported a higher prevalence rate of VVs disease.[56]

Contributory elements in pathogenesis

Normally, blood streams from superficial veins to deep veins and from the lower legs to the heart in a venous valve pathway. Insufficiency in the bloodstream induces reverse flow which turns into a pooling of the blood in the veins and hence causes venous hypertension. Dilatation and contortion of the veins happen because of venous hypertension. This venous hypertension applies more hydrostatic pressure on the calves which disrupts the blood pumping mechanism because of the perforating veins. This venous inadequacy later on results in VVs.[67] Various researches showed that the reflux of blood causes weakness and persistent dilatation of the venous walls that give rise to valve inadequacy. Various studies reported that a decrease in elastin content and disturbing synthesis of collagen debilitates the vein wall. Furthermore, constant irritation and arrival of the cytokines may be the contributing components. Physical injury and harm to the valve cusps are additionally among one of the reasons for valve inadequacy.[2,56,68–75] It stays dubious whether valve inadequacy causes a change in the venous wall or is a consequence of raised hydrostatic pressure that may affect both venous and valvular competency (Figure 3). Collagen content manages the elasticity of the venous wall, and elastic filaments present in the extracellular matrix (ECM) direct the flexibility

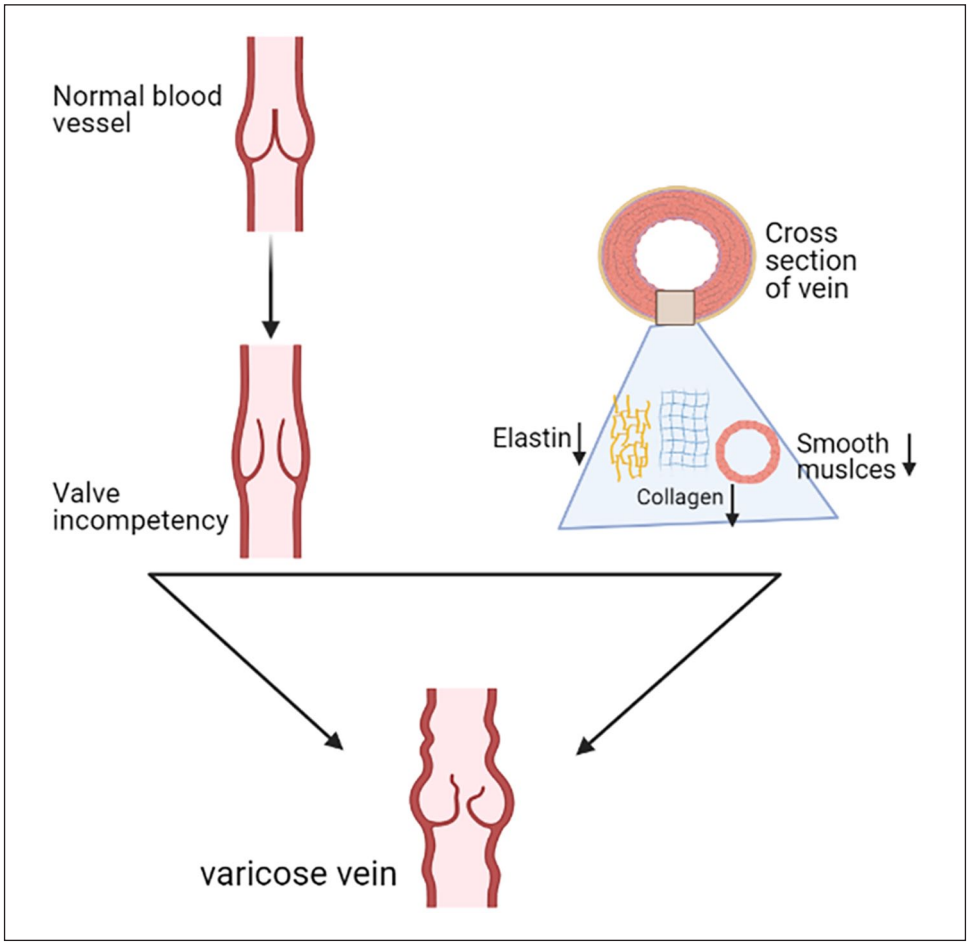

Figure 3. Contributing factors in VVs disease development: Valve incompetency can lead to pooling of blood in the veins of the lower limbs which causes continuous dilatation of the veins. Deficiency in structural contents of the veins including smooth muscles, collagen, and elastin also appeared to be involved in VVs disease development.

of the venous wall. This change in cellular component and ECM results in alteration in the venous wall and loss of tone.[9] Furthermore, the venous wall is comprised of endothelial coating of ECM composed of smooth muscle cells (SMC), proteoglycans, collagen, and elastin. Stability among the production and degradation of any of these proteins and ECM supported the incompetency of vessel valves.[9] However, Venturi et al.[76] reported a solid relationship between the decrease in elastin content and venous wall dilatation. Reduction in elastin and its precursors causes fragmentation and disruption of the existing elastin fibers. Whether the decrease in the SMC, loss of SMC relationship with elastin filaments, or improved elastase activity involved in VVs development is a matter of further research. At first, there is an increment in the numbers of the elastin filaments at the early stages of the VVs, then reduces, and fragmentation occurs that ultimately led to the progression of the disease. Reduction in elastin increments with the age could be a factor behind the VVs disease advancement (Figure 3). In an examination, a correlation was found in the ECM components in adult patients (26–35 years) and the older patients (36–45 years). Moreover, women were more influenced.[77] Fewer stores of collagen III and fibronectin were seen in the SMC and fibroblasts among the patients with VVs and normal levels of collagen V than in typical patients. It was seen that the rise in the level of collagen I synthesis is because of the rise in the general collagen generation.[78] Decrease in elasticity is because of lower collagen III levels. This rise in the levels of collagen I cause partition and diversion of SMC in the tunica media. Changes in the collagen I/III content are possibly a contributing factor in causing weakness and a decrease in the adaptability of the venous wall and may cause VVs. Disturbed stability of endothelial cell activation results in rise in SMC deposition, and demolition of EMC results in rise to changes that affect venous dilatation, extension, strength, and adjustment of the venous wall.[9,79]

Clinical manifestations

The prevalence rate of VVs is rising rapidly[13] and can transform into emotional disability, skin changes leading to the cosmetic as well as major health issue, and

Table 4. Clinical manifestations of varicose vein from various studies.

Reference	Clinical manifestations	Publication year
McGuckin et al.[80]	Skin changes	2002
Saarinen et al.[83]	Ulceration, tingling, edema	2005
Murli and Navin[82]	Spasms, heaviness of the lower appendage, cellulitis, superficial thrombophlebitis, and bleeding	2008
Robertson et al.[85]	Edema, skin inflammation (reticular veins)	2009
Hamdan[81]	Pain, tiredness, swelling and restlessness, needle-like sensation, burning sensation, tenderness, and leg spasms	2012
Khan et al.[25]	Pain and heaviness of lower leg, night spasms, swelling, burning and tingling sensations	2013
Sharif Nia et al.[3]	Lipodermatosclerosis	2015
Joseph et al.[13]	Skin inflammation, heaviness of lower appendages, ulceration, tingling, pain, edema, cellulitis, lipodermatosclerosis, bleeding	2016
Manetti at el.[86]	Bleeding	2021

inconvenience, and can influence personal satisfaction.[80] In the United States, medicinal costs of VVs may accomplish $1 billion annually, and progression of VVs leads to ulcerations. Symptoms may include pain, heaviness of lower legs, tiredness, swelling and restlessness, needle-like sensation, burning sensation, tenderness, and spasms. These symptoms regularly turn out to be more terrible with every passing day.[81]

Joseph et al.[13] reported ulceration as the most common complication of the VVs while different studies reported pain in 56% of the cases and a few investigations also revealed 37% and 80% of people with pain.[34,82–84] Edema of lower legs was found in 42%–66% of the case and another study reported 20% of the cases of VVs with edema.[13,82,83,85] An investigation in Malaysia also reported some clinical manifestations like spasms 53%, heaviness of the lower legs 54%, cellulitis 13%, superficial thrombophlebitis 34%, and bleeding 9% of the cases, separately.[13,82] Joseph et al.[13] and Murli and Navin[82] found tingling in 20% of the cases whereas an investigation in Finland revealed 26% of the cases with tingling. In the United Kingdom, a study reported reticular veins in more than 18% of VVs cases which is the normal indication of skin inflammation.[85]

Previously, a report illustrated skin inflammation in 20% while Joseph et al. revealed 27% of cases with skin inflammation in VVs patients. A UK study revealed lipodermatosclerosis in 3% of the cases[13]; on the other hand, Sharif Nia et al.[3] reported 3.31% of transformation into lipodermatosclerosis after developing VVs. An investigation done in Pakistan revealed 3% of patients with bleeding and 6% with VVs disease.[34] Another cross-sectional investigation conducted in Pakistan recorded pain in lower legs 59%, heaviness of lower leg 43%, night spasms 34%, swelling 29%, sticks and needles sensation 20%, burning sensation 19%, and tingling 15% of clinical manifestations of the VVs.[25]

A recent study highlighted a case report of bleeding VVs along with the previous literature as a life-threatening condition that results in skin ulceration which leads to hemorrhagic shock because of blood loss and causes death. After reviewing the literature, the author reported 36 cases of hemorrhage that result because of VVs rupture. Among them, 11% of cases were traumatic while the remaining 89% were spontaneous[86] (Table 4). These numbers can be increased in near future and require further intention.

Discussion

VVs disease is the most common vascular condition of the current era. In this study, we aimed to highlight the worldwide prevalence of the VVs and various contributing factors (risk factors and pathological factors) that importantly lead to the development and advancement of VVs disease. We identified 180 research items for the collection of the literature related to the VVs and screening of the duplicate research, preprints, and abstract evaluation. Furthermore, full-text articles were screened to exclude articles on congenital diseases, and animal studies. Original research, review/mini-review articles, and case reports written in English were included to collect the data. Finally, 65 articles were chosen to conduct the study.

According to geographical regions, globally, the prevalence of VVs varies greatly. Our study outcomes and previous reports suggested that Western and developed countries are more affected by the VVs as compared to the developing countries.[2,12] Surprisingly, the minimum prevalence was observed in New Guinea followed by Cook Islands[28] whereas the highest prevalence rate was found in Italy[29] and the United States.[30]

Currently, age, gender, family history, occupation, genetic involvement, obesity, exercise, smoking, parity, BMI, and current lifestyles are the major risk factors that can contribute to develop and worse the VVs disease. The study outcomes revealed aging as the key risk factor in VVs disease development and incidence[2,12,33] According to a recent report, it becomes doubled over 65 years of age.[31] Several reports suggested that the female gender along with pregnancy and parity,

and BMI in the upper quartile have more risk of developing VVs[2,12,33,44–46,48,51] and men have less, whereas a report opposed to it showing that men have a high risk of developing VVs.[57] Numerous reports also demonstrated positive relation of family history with the VVs disease development whereas some of the patients with no family history of varicosity have also developed VVs.[87] The occupations that acquire prolonged standing posture during work including teachers, clerks, dealers laborers, road cleaners, receptionists, security guards, and health care professionals are more prone to develop VVs.[23,33,39–41] In addition, being overweight and not exercising apply a relative increment in the risk of getting VVs and that can be encountered by having mild to moderate exercise.[53,54] VVs are an exceptionally basic clinical manifestation and it keeps running in families suggesting their hereditary inclusion.[57] *FOXC2*, *TM*, and *C677T MTHFR* genes were previously said to be linked with the development of VVs.[59,61,62] As the prevalence of VVs varies geographically, their symptoms and severity also vary. Pain is among the most common symptoms observed by the various reports, and bleeding of the VVs is recently highlighted as life-threatening symptom leading to death. Our study outcomes revealed various other symptoms which include skin ulceration, spasms, heaviness of the lower legs, swelling, tingling, lipodermatosclerosis, cellulitis, reticular veins, and thrombophlebitis.

Our study highlighted some important contributory factors that may play a key role in the pathogenicity of VVs. (1) The reflux of blood caused by weak vessel walls and persistent dilatation of the venous walls can give rise to valve inadequacy, (2) decrease in elastin content and (3) disruption in the synthesis of collagen debilitates the vein wall. (4) Constant irritation, arrival of the cytokines, and (5) physical trauma to the valve cusps because of thrombosis are also among the reasons for valve disability.[2,56,68–75] (6) Disturbed stability of endothelial cell activation can lead to rise in SMC, deposition, and demolition of EMC, and these changes affect venous dilatation, stretching, strengthening, and modification of the venous wall.[9,79] It has also been reported that awareness and knowledge regarding the VVs disease and its contributory factors can play a role in the intervention of the VVs ailment.[88]

Our research has few study limitations. First, the primary focus of the study was only VVs among the six classes of CEAP classification that later become more complicated, severe, and painful if undiagnosed or neglected, and affects an individual's life quality. Second, we focused on the epidemiology, risk factors, contributing factors in the pathogenesis of VVs, and clinical manifestations around the world excluding the methods/techniques for diagnosis and interventions that will be our next study target. In addition, there was no definite sample size/power analysis performed for this study. However, all the facts and findings suggest that extensive investigations are required to prevent the disease and its course.

Conclusion

Continued rise in the incidence of VVs disease is turning out to be a global curative issue and a matter of great degree concern for the treatment of VVs that can further transform into emotional disability, skin changes, inconvenience, and can influence personal satisfaction. VVs disease usually affects the peoples of the middle ages both men and women and particularly involves the individuals associated with the prolonged standing occupation. Unfortunately, despite newer evaluation methods and techniques in diagnosis and surgery, the complete cure for this medical condition is a matter of great concern. Currently, more studies are required to clarify the relationships among the various risk factors including family history, smoking, parity, and BMI that can contribute to worsen the VVs condition. Moreover, molecular targets involved in VVs disease development needed to be identified. Regular awareness and educational programs shall be organized to facilitate the people in lifestyle changes to reduce the effect of risk factors contributing to the worsening of the VVs disease.

Acknowledgements

The authors express their deepest gratitude to the dean and principal of the Faculty of Medicine and Allied Health Sciences, The Islamia University of Bahawalpur, for their kind support.

Author contributions

MRA designed the present study and wrote the article. AH and SJ assisted in literature searches related to the present study. MSS also helped in article drafting and editing. HMA and KA critically reviewed the article. JUR and SK helped in the substantial revision of the article. ASH, SRR, and AS provided their help in critical English revision. All the authors approved the final version of the revised article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Not applicable because we did not use any animal or human subjects in the present study.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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