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Severe varicose veins and the risk of mortality: a nationwide population-based cohort study

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ABSTRACT

Objective Varicose veins (VVs) are common and although considered benign may cause morbidity. However, the association between VV severity and cardiovascular and mortality risks remains unknown. The aim of this study was to investigate the factors associated with overall mortality in patients with VV.

Methods A total of 4644 patients with newly diagnosed VV between 1999 and 2013 were identified from Taiwan's National Health Insurance Database. VV severity was classified from grade 1 to 3 according to the presentation of ulcers or inflammation. Moreover, 9497, 2541 and 5722 age-matched, sex-matched and chronic cardiovascular risk factor-matched controls, as assessed based on propensity score, were separately selected for three grading VV groups. Enrolled patients were analysed using conditional Cox proportional hazards regression analysis to estimate risk of mortality and major adverse cardiovascular events (MACEs) in the VV and control groups.

Results Most patients with VV were free from systemic disease. However, compared with matched controls, patients with VV showed a 1.37 times increased risk of mortality (95% CI 1.19 to 1.57; p<0.0001). Compared with matched controls, older (age ≧65 years) (adjusted HR: 1.38; 95% CI 1.17 to 1.62; p=0.0001) and male patients with VV (adjusted HR 1.41; 95% CI 1.18 to 1.68; p=0.0001) showed increased risk of mortality. Furthermore, compared with controls, patients with VV showed 2.05 times greater risk of MACE. Compared with matched controls, population at grade 3 increased 1.83 times risk of mortality and 2.04 to 38.42 times risk of heart failure, acute coronary syndrome, ischaemic stroke and venous thromboembolism.

Conclusions This nationwide cohort study demonstrated that patients with VV are at a risk of cardiovascular events and mortality. Our findings suggest that presence of VV warrants close attention in terms of prognosis and treatment.

Strengths and limitations of this study

- The strengths of this study are its population-based design with a large sample size including study and control cohorts.
- All insurance claims were reviewed by medical reimbursement specialists.
- However, some risk factors of varicose vein including smoking habits, lack of movement, overweight and glycated haemoglobin levels were not available in this database.
- Our novel findings indicated that patients at severe grades of varicose vein had higher risks of mortality and major adverse cardiovascular events.
- The presence of varicose vein should catch more awareness of potential coexisting risks of mortality and cardiovascular events.

INTRODUCTION

Varicose veins (VVs) can be considered a common disease with prevalence ranging from 2% to 56% in the adult population.[1] Following clinical examination, VV diagnosis is primarily based on the presence of enlarged and twisted veins in the lower extremities.[1 2] Among people with VV, 1%–4% of individuals show higher severity grades (Clinical–Etiological–Anatomical–Pathophysiological (CEAP) classification, 5–6).[1 2] Although VVs lead to leg swelling, venous eczema and ulceration in some cases, they are regarded as a benign disease.[3 4] Moreover, the association between the severity of VV and risk of future adverse events remains unknown. In fact, the majority of the previous studies have focused on the importance of superficial venous thrombosis or deep vein thrombosis (DVT).[5] In a 30-year cohort study, mortality risk among patients with DVT and pulmonary embolism (PE) was markedly higher than that in age-matched and sex-matched patients, particularly within the first 30 days.[6] Similarly, another population-based case–control study demonstrated that having VV was a risk factor for venous thromboembolism, although the association of VV severity with survival and cardiovascular events remains unknown.[7] In addition, although age, family history and female sex are the known risk factors for VV, the effects of underlying diseases or sex on outcomes of VV remain unclear.[1] We hypothesised that presence of VV can be used as a

marker for cardiovascular risk. Therefore, the aim of this study was to investigate the association of VV with survival and cardiovascular outcomes.

METHODS

Data source

Taiwan launched a single-payer National Health Insurance (NHI) programme on 1 March 1995. This database contains details of almost every Taiwanese resident (coverage rate >98% in 2009), making it one of the world's largest and most complete population-based sources. The data used in this study were retrieved from the Longitudinal Health Insurance Database 2000 (LHID2000)—a subset of the NHI database containing all claims data from 1996 to 2013, covering 1 million beneficiaries randomly selected in 2000. At that time, there were no significant differences in age, sex and healthcare costs between patients with VV and matched controls. LHID2000 provided encrypted patient identification numbers; sex; date of birth; admission and discharge dates; International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes of diagnoses and procedures; prescription details; registry data in the Catastrophic Illness Patient Database; and costs covered and paid for by NHI. Details of the National Health Insurance Research Database (NHIRD) are described in previous studies.[8 9] Moreover, the accuracy of major disease diagnoses in the NHIRD, including stroke and acute coronary syndrome (ACS), has been validated.[9]

Patient and public involvement

No patient involved.

Study design

This nationwide population-based, retrospective cohort study was conducted to investigate the association between VV and subsequent mortality. Patients with at least three claims for outpatient VV diagnosis in 1 year or with one claim for inpatient VV diagnosis (ICD-9-CM codes 454, 454.0, 454.1, 454.2, 454.8 and 454.9) were considered as VV cases. Patients with a first-time diagnosis of VV from January 1999 to December 2012 were included in the cohort. Codes for VV were considered reliable for diagnosis based on clinical symptoms. The date of the first-time VV diagnosis was considered the index date in this study. To ensure accurate VV diagnosis, and to avoid potentially confounding effects, patients with DVT (ICD-9-CM codes 453.40, 459.1, 671.4, 671.3, 451.83, 459.3, 453.4, and 451.11) or PE (ICD-9-CM codes 415.1, 415.11, 673, 673.2, and 673.8) in an ambulatory setting before the index date were excluded. In addition, VV severity was categorised as grade 1 uncomplicated (ICD-9-CM code 454.9), grade 2 with ulcer (ICD-9-CM code 454.0) or inflammation (ICD-9-CM code 454.1) and grade 3 with both ulcer and inflammation (ICD-9-CM code 454.2).

Three control cohorts (n1=9497, n2=2541 and n3=5722; four control subjects for every enrolled patient with VV), not diagnosed with VV from 1996 to 2013, were selected for three VV grade groups separately. To eliminate potential selection bias, the controls were matched using propensity score (PS) method at a 4:1 ratio for baseline characteristics of age, sex and chronic cardiovascular risk factors, including hypertension (ICD-9-CM codes 401–405, A260, A269, 4372), diabetes (ICD-9-CM codes 250, A181, A189, A229, A239, 3572, and 3620), hyperlipidaemia (ICD-9-CM code 272),and coronary artery disease (CAD; ICD-9-CM codes 410–414). The PS for identified VV cases and controls were estimated using the fitting logistic regression model. Based on greedy algorithm matching, eight control subjects (the nearest neighbour matching of VV) were selected as matched controls.[10] If a case failed to be assigned to the four matched controls, it was dropped from the set of matches. In addition, since the primary VV treatment was covered by insurance, it prevented VV from overdiagnosis. The matched controls were assigned the same index date as that of the corresponding VV patient.

Outcomes

The primary outcome was mortality, and the secondary outcome was major adverse cardiovascular events (MACEs), including acute (ACS, ICD-9-CM codes 410, 410.7, 411.1, 411.81 and 414.8), congestive heart failure (CHF, ICD-9-CM codes 428, 428.0, 428.1, 428.2 and 428.9), ischaemic stroke (ICD-9-CM code 436), DVT and PE. Mortality was identified using the 'in-hospital death' or 'discharge under critical condition' codes at discharge. Enrolment in the NHI programme is mandatory for all people in Taiwan, and registration must be withdrawn within 30 days after death. Patients with the above-mentioned mortality-related codes and those withdrawn from the NHI programme within 30 days after discharge from the last hospitalisation were presumed to have died. All subjects were followed up from the index date to death (lost to follow-up) or until 31 December 2013, whichever was earlier.

Validation of the accuracy of VV diagnosis and CEAP grading

To validate the accuracy of the VV diagnosis, we reviewed the charts of all patients (inpatients and outpatients) using ICD-9-CM diagnosis codes for VV who visited Chi-Mei Medical Center (Tainan, Taiwan) from 2010 to 2015. Our aim was to determine the accuracy and consistency of code usage. A vascular specialist reviewed patient discharge and clinical records. In addition to examining the accuracy of VV diagnosis, the reviewer compared CEAP stages with our ICD-9-CM-derived grades in inpatients. Subsequently, we further investigated the sensitivity, specificity and predictive value of the ICD codes for clinical diagnosis, as well as the applicability of our VV grading system. In particular, as ICD-9-CM coding and VV descriptions are associated with insurance payment, the accuracy of VV diagnosis and the reliability of VV severity grading increased. The consistency between CEAP and grading stages were evaluated by kappa score, whose

value between 0.8 and 1.0 was considered as an almost perfect agreement.

Statistical analyses

Continuous and categorical baseline characteristics between the case and control groups were separately compared by standardised mean difference (SMD), an assessment approach for evaluating the balance between variables after PS matching. SMD greater than 0.1 is considered to denote a meaningful imbalance in variables.

Conditional Cox proportional hazards regression analysis was used to estimate the risk of mortality and MACE in the VV and control groups. Adjusted HRs were estimated by adjusting for chronic obstructive pulmonary disease (ICD-9-CM codes 490–496), cancer (ICD-9-CM codes 140–208), atrial fibrillation (ICD-9-CM codes 427.31), heart failure (ICD-9-CM codes 428), ischaemic heart disease (ICD-9-CM codes 410–414), chronic renal insufficiency (ICD-9-CM codes 403, 404, 582, 585–588). Moreover, the investigation was extended to stratified subgroup analysis. HRs between the VV and control groups were separately estimated in subgroups of population aged <65 years or ≥65 years; males or females; and subgroups with or without a diagnosis of hypertension, diabetes, hyperlipidaemia or CAD. The Kaplan-Meier method was used to separately estimate the 3-year 6-year and 9-year survival rates in the control and VV groups. Kaplan-Meier curves of mortality and MACE were plotted for controls and patients with three grades of VV severity. Differences in survival curves between the control and VV groups were examined using the log-rank test.

With respect to mortality, CHF, ACS, ischaemic stroke and DVT +PE endpoints, the risks for VV with three separate severity grades were further estimated by comparison against each matched controls.

Finally, sensitivity analyses were conducted to determine the influence from subjects with pregnancy history (ICD-9-CM codes V22, V23.2, 761.5), peripheral artery disease (PAD, ICD-9-CM codes 440.0, 440.2, 440.3, 440.8, 440.9, 443, 444.0, 444.22, 444.8, 447.8 and 447.9) medical history and patients treated with operations (ICD-9-CM procedure code 3859, 3889 and NHIRD order code 69013, 69014, 69015, 69016, 69017, 69019, 69020, 69021) including ligation and stripping procedures after VV diagnosis.

A two-tailed p<0.05 was considered statistically significant. All analyses were performed using the SAS software, V.9.4 (SAS) and Stata software V.15.0 (StataCorp)

RESULTS

Characteristics of the study population

A total of 4644 patients with newly diagnosed VV were identified during January 1999 to December 2012. Among them, 2467, 668 and 1509 VVs were separately classified into 1, 2 and 3 severity grade. For each VV group, age-matched, sex-matched and chronic disease-matched patients without VV were separately included for comparison. The covariates between VV and matched groups are well balanced after PS matching. All patients were tracked from the index dates until achieving the primary outcomes or the end of the study. The mean age of patients with VV was 55.70±16.03 years, the majority of the patients were female (61.33%), and most of them did not present with chronic diseases such as hypertension, diabetes, hyperlipidaemia and CAD (table 1). Significantly different distribution of age, sex and diabetes among three severity VV groups were displayed (p<0.05) (online supplementary table 1). Interestingly, more female patients (68.67%) were diagnosed with a lower severity (grade 1). Also, the baseline characteristics and comorbid medical disorders for three grading VV groups and three separately matched controls were listed in online supplementary table 2.

Long-term mortality risk

Compared with matched controls, the outcomes of patients with VV were worse. The estimated survival at 3, 6 and 9 years were 97.6%, 95.6%, and 93.5%, respectively, in patients with VV compared with 98.5%, 97.1%, and 95.6%, respectively, in controls (figure 1A). A log-rank test revealed a significant difference in survival curves of patients with VV and controls (p<0.0001). The survival curves of controls and patients with different severities of VV are presented in figure 1B. Lower survival rates over time were observed in patients with highest VV severity (grades 3) but not in those with grade 1–2. Significant difference between survival curves between VV grading 3 and corresponding controls were revealed by log rank test (p<0.0001). However, no significant differences were found between survival curves of patients with VV severity grades (1-2) and corresponding controls (grade 1: p=0.3191; grade 2: p=0.3599).

Overall, HR of all-cause mortality adjusted for chronic obstructive pulmonary disease, cancer, atrial fibrillation, heart failure, ischaemic heart disease, chronic renal insufficiency in patients with VV was 1.34 times higher (adjusted HR 1.37; 95% CI 1.19 to 1.57; p<0.0001) than that in controls (table 2). Stratified analysis revealed 1.38 and 1.41 times increased risks of mortality in older (age ≥65 years; adjusted HR 1.38; 95% CI 1.17 to 1.62; p=0.0001) and male patients with VV (adjusted HR 1.41; 95% CI 1.18 to 1.68; p=0.0001). Notably, despite no significant effect of VV on the survival of patients with hypertension, hyperlipidaemia or CAD was observed, patients with both VV and diabetes presented 1.50 times higher risk of mortality compared with those without VV (adjusted HR 1.50; 95% CI 1.05 to 2.15; p=0.0254). Furthermore, VV at grade 3 show 1.83 (95% CI 1.48, 2.27; p<0.0001) greater risk of mortality adjusted for chronic obstructive pulmonary disease, cancer, atrial fibrillation, heart failure, ischaemic heart disease, chronic renal insufficiency.

Table 1 Baseline characteristics and comorbid medical disorders for the control cohort and patients with varicose vein

Characteristic, n (%)	Varicose vein, n=4644	Matched controls, n=17 742	Standardised difference
Age (years)			0.02275
<65	3164 (68.13)	12 275 (69.19)	
≧65	1480 (31.87)	5467 (30.81)	
Age (mean±SD)	55.70±16.03	56.10±16.04	0.02514
Gender			0.00944
Male	1796 (38.67)	6780 (38.21)	
Female	2848 (61.33)	10 962 (61.79)	
Hypertension			0.04519
No	3750 (80.75)	14 637 (82.50)	
Yes	894 (19.25)	3105 (17.50)	
Diabetes			0.05807
No	4247 (91.45)	16 501 (93.01)	
Yes	397 (8.55)	1241 (6.99)	
Hyperlipidaemia			0.08429
No	4413 (95.03)	17 157 (96.70)	
Yes	231 (4.97)	585 (3.30)	
Coronary artery disease			0.07832
No	4489 (96.66)	17 375 (97.93)	
Yes	155 (3.34)	367 (2.07)	

P value was calculated based on the two sample t-test and Pearson's X^2 test.

Long-term MACE risk

MACE risk significantly increased in patients with VV (HR 2.05; 95% CI 1.89 to 2.23; p<0.0001), particularly in relatively younger (age,<65 years; adjusted HR 2.17; 95% CI 1.92 to 2.46; p<0.0001) or male (adjusted HR 2.32; 95% CI 2.06 to 2.62; p<0.0001) patients (table 3). In addition, patients with VV showing cardiovascular risk factors, including hypertension, diabetes, hyperlipidaemia and CAD, were at a higher risk of MACE than were matched controls. In patients with VV, 3-year, 6-year and 9-year MACE-free rates were 91.17%, 84.99% and 79.27% (figure 2A). These rates dramatically declined further with disease severity (figure 2B). In terms of individual cardiovascular outcomes, patients with grade 3 VV were at a greater risk of CHF (adjusted HR 2.05; 95% CI 1.71 to 2.46; p<0.0001), ACS (adjusted HR: 2.04;

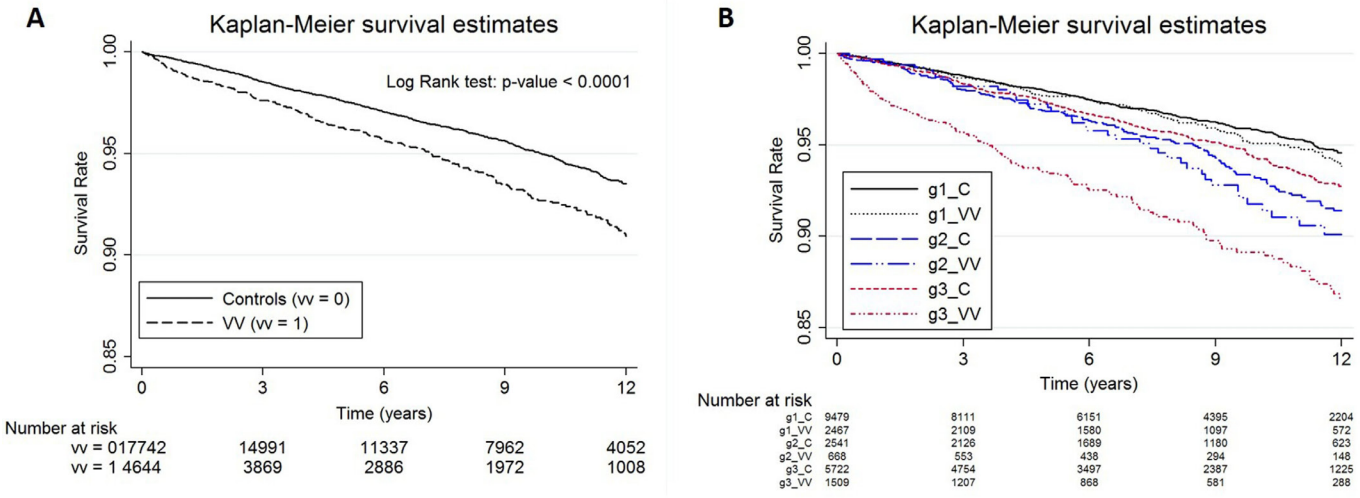

Figure 1 (A) Kaplan-Meier estimates of 12-year survival between patients with varicose veins (VV) and the matched control cohort. (B) Kaplan-Meier estimates of 12-year survival between patients with VV categorised by the disease severities and the matched control cohort.

Table 2 Crude and adjusted HRs of all-cause mortality in patients with VV compared with the matched control cohort during the follow-up period

Cohort all (n=22 386)	Crude HR (95% CI)	P value	Adjusted HR (95% CI)†	P value
Overall analysis				
VV	1.43 (1.25 to 1.64)	<0.0001*	1.37 (1.19 to 1.57)	<0.0001*
Controls	1(reference)		1(reference)	
Stratified analysis				
Age (years)				
<65 (years)				
VV	1.49 (1.144 to 1.93)	0.0030*	1.2 (0.92 to 1.57)	0.1803
Controls	1(reference)		1(reference)	
≧65 (years)				
VV	1.41 (1.2 to 1.66)	<0.0001*	1.38 (1.17 to 1.62)	0.0001†
Controls	1(reference)		1(reference)	
Gender				
Male				
VV	1.46 (1.23 to 1.74)	<0.0001*	1.41 (1.181 to 1.68)	0.0001†
Controls	1(reference)		1(reference)	
Female				
VV	1.38 (1.1 to 1.74)	0.0058*	1.31 (1.04 to 1.65)	0.0227†
Controls	1(reference)		1(reference)	
Hypertension				
VV	1.14 (0.87 to 1.49)	0.3476	1.16 (0.88 to 1.52)	0.2957
Controls	1(reference)		1(reference)	
Diabetes				
VV	1.5 (1.06 to 2.14)	0.0226*	1.5 (1.05 to 2.15)	0.0254†
Controls	1(reference)		1(reference)	
Hyperlipidaemia				
VV	0.99 (0.39 to 2.54)	0.9865	1.01 (0.39 to 2.61)	0.9914
Controls	1(reference)		1(reference)	
Coronary artery disease				
VV	1.14 (0.64 to 2.03)	0.6565	1.05 (0.58 to 1.92)	0.8716
Controls	1(reference)		1(reference)	

*P<0.05.
†Adjusted for chronic obstructive pulmonary disease, cancer, atrial fibrillation, heart failure, ischaemic heart disease, chronic renal insufficiency.
VV, varicose veins.

95% CI: 1.58 to 2.63; p<0.0001) and ischaemic stroke (adjusted HR 2.06; 95% CI 1.58 to 2.69; p<0.0001) than were controls (table 4). In particular, with the highest VV severity there was an increasing risk of venous thrombotic events, including DVT and PE (grade 3: adjusted HR 38.4; 95% CI 16.4 to 90.1; p<0.0001) (table 4).

Validation of the accuracy of VV diagnosis and ICD-9-CM-derived VV grading

During 2010–2015, a total of 2202 outpatients and 347 inpatients were reported to have VV in Chi-Mei Medical Center. Among the outpatients, 1188 were coded as uncomplicated VV (ICD-9-CM code 454.9), 775 were coded as VV with inflammation (ICD-9-CM code 454.1), 152 were coded as VV with ulcers (ICD-9-CM code 454.0) and 87 were coded as VV with ulcer and inflammation (ICD-9-CM code 454.2) (online supplementary table 3). Notably, none were coded incorrectly. Compared with CEAP stage, as determined based on chart reviews, only a few inpatients were incorrectly or unclearly diagnosed using ICD-9-CM-derived VV codes (online supplementary table 4). For example, among patients with higher VV grades (CEAP stage 5–6), the positive and negative

Table 3 Crude and adjusted HRs of MACE in patients with VV compared with the matched control cohort during the follow-up period

Cohort all (n=22 386)	Crude HR (95% CI)	P value	Adjusted HR (95% CI)†	P value
Overall analysis				
VV	2.08 (1.91 to 2.25)	<0.0001*	2.05 (1.89 to 2.23)	<0.0001*
Controls	1(reference)		1(reference)	
Stratified analysis				
Age (years)				
<65 (years)				
VV	2.21 (1.95 to 2.5)	<0.0001*	2.17 (1.92 to 2.46)	<0.0001*
Controls	1(reference)		1(reference)	
≧65 (years)				
VV	1.98 (1.78 to 2.21)	<0.0001*	1.96 (1.76 to 2.18)	<0.0001*
Controls	1(reference)		1(reference)	
Gender				
Male				
VV	2.35 (2.09 to 2.65)	<0.0001*	2.32 (2.06 to 2.62)	<0.0001*
Controls	1(reference)		1(reference)	
Female				
VV	1.87 (1.67 to 2.09)	<0.0001*	1.85 (1.66 to 2.07)	<0.0001*
Controls	1(reference)		1(reference)	
Hypertension				
VV	1.65 (1.42 to 1.92)	<0.0001*	1.62 (1.39 to 1.89)	<0.0001*
Controls	1(reference)		1(reference)	
Diabetes				
VV	1.4 (1.11 to 1.76)	0.0042*	1.37 (1.08 to 1.72)	0.0081
Controls	1(reference)		1(reference)	
Hyperlipidaemia				
VV	1.5 (1.03 to 2.17)	0.0353*	1.56 (1.07 to 2.29)	0.0224
Controls	1(reference)		1(reference)	
Coronary artery disease				
VV	1.93 (1.38 to 2.7)	0.0001*	1.99 (1.41 to 2.82)	0.0001*
Controls	1(reference)		1(reference)	

*P<0.05.
†Adjusted for chronic obstructive pulmonary disease, cancer, atrial fibrillation, heart failure, ischaemic heart disease, chronic renal insufficiency.
.MACE, major adverse cardiovascular event; VV, varicose veins.

predictive values with ICD-9-CM-derived codes were 93% and 98.4%, respectively. Specifically, the sensitivity and specificity of ICD-9-CM-derived grading were up to 95.2% and 97.6%, respectively. The calculated kappa score between CEAP stages and grading severity is 0.92 (95% CI 0.88 to 0.96).

Sensitivity analyses

VV and controls with pregnancy history were identified and examination the influence in sensitivity analysis (online supplementary table 5). After additionally adjustment for history of pregnancy, the results remain showing great impacts on mortality and MACE (adjusted HR for death (1.37 (95% CI 1.19 to 1.57), p<0.0001; adjusted HR for MACE 2.01 (95% CI 1.89 to 2.23), p<0.0001).

After excluding 472 subjects with Myocardial infarction, stroke, coronary angioplasty or CABG, remaining VV and corresponding controls were included for sensitivity analysis. Comparing with corresponding matched controls, those conservatively treated VV patients were found 1.36 times risks of mortality (adjusted HR 1.36 (95% CI 1.18 to 1.57), p<0.0001) and 1.95 times risks

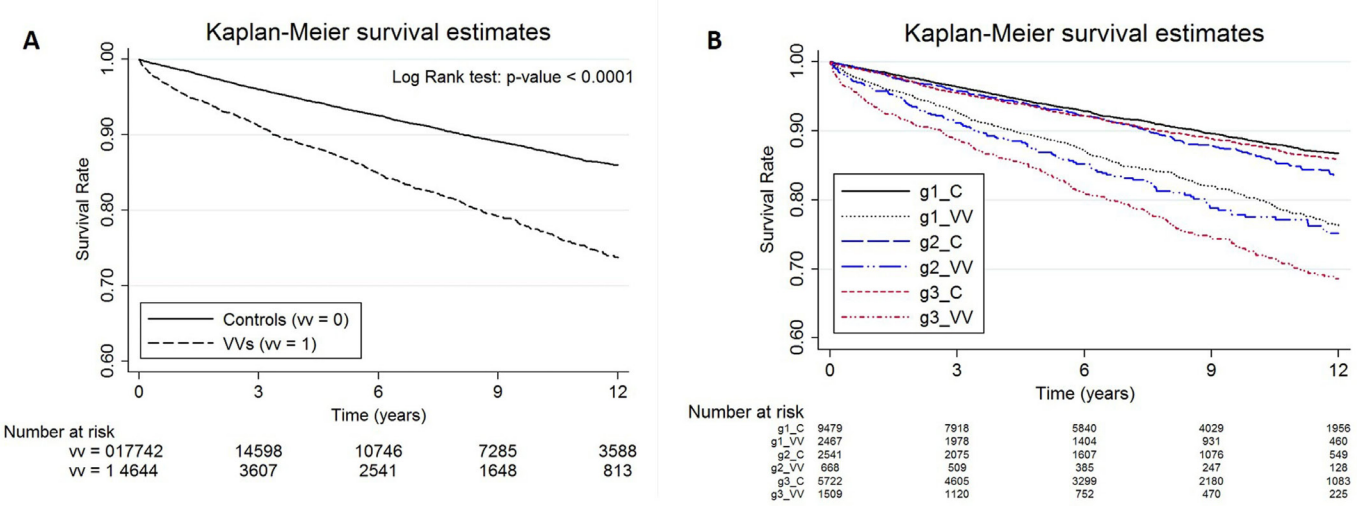

Figure 2 (A) Kaplan-Meier estimates of 12-year free from MACE between patients with varicose veins (VV) and the matched control cohort. (B) Kaplan-Meier estimates of 12-year free from MACE between patients with VV categorised by the disease severities and the matched control cohort. MACE, major adverse cardiovascular event.

of MACE (adjusted HR 1.95 (95% CI 1.80 to 2.12), p<0.0001).

DISCUSSION

The primary findings of this study were that (1) patients with VV were at increasing risks of mortality and cardiovascular events, especially those with VV at grade 3 compared with matched controls; (2) having VV had a significant impact on the survival of male patients. To the best of our knowledge, this nationwide population-based study is the first to comprehensively describe the association of VV with patients' cardiovascular outcomes.

Although VV are common, their potential threat to health has not been well investigated previously.[1 2] Valve

Table 4 The adjusted HRs of mortality and MACE in patients with VV compared with the matched control cohort during the follow-up period

	Grade 1 control	Grade 1	Grade 2 control	Grade 2	Grade 3 control	Grade 3
No of mortality, N (%)	343 (3.62)	99 (4.01)	147 (5.79)	44 (6.59)	266 (4.65)	136 (9.01)
Adjusted HR for mortality (95% CI)†	Referent	1.08 (0.86 to 1.36)	Referent	1.13 (0.8 to 1.6)	Referent	1.83 (1.48 to 2.27)*
No of CHF, N (%)	552 (5.82)	238 (9.65)	181 (7.12)	80 (11.98)	358 (6.26)	190 (12.59)
Adjusted HR for CHF (95% CI)†	Referent	1.68 (1.44 to 1.96)*	Referent	1.79 (1.37 to 2.34)†	Referent	2.05 (1.71 to 2.46)*
No of ACS, N (%)	291 (3.07)	125 (5.07)	72 (2.83)	24 (3.59)	174 (3.04)	95 (6.30)
Adjusted HR for ACS (95% CI)†	Referent	1.7 (1.37 to 2.11)*	Referent	1.25 (0.78 to 1.99)	Referent	2.04 (1.58 to 2.63)*
No of ischaemic stroke, N (%)	236 (2.49)	99 (4.01)	90 (3.54)	31 (4.64)	162 (2.83)	89 (5.90)
Adjusted HR for ischaemic stroke (95% CI)†	Referent	1.59 (1.25 to 2.01)*	Referent	1.4 (0.92 to 2.12)	Referent	2.06 (1.58 to 2.69)*
No of DVT+PE, N (%)	14 (0.15)	56 (2.27)	7 (0.28)	13 (1.95)	6 (0.10)	63 (4.17)
Adjusted HR for DVT+PE (95% CI)†	Referent	14.9 (8.26 to 26.86)*	Referent	6.27 (2.46 to 15.96)*	Referent	38.42 (16.38 to 90.13)*

*P<0.05.
†Adjusted for chronic obstructive pulmonary disease, cancer, atrial fibrillation, heart failure, ischaemic heart disease, chronic renal insufficiency.
ACS, acute coronary syndrome; CHF, congestive heart failure; DVT, deep vein thrombosis; MACE, major adverse cardiovascular event; PE, pulmonary embolism; VV, varicose veins.

dysfunction-mediated activation of leukocytes, release of enzymes and remodelling of the vascular wall lead to venous valve destruction and incompetence.[11] VV may cause inflammation, oedema, ulcers,[11] endothelial dysfunction[12] and subsequent DVT.[5] In addition, overexpression of inducible nitric oxide synthase and transforming growth factor-β1 has been documented in patients with VV.[13] In this study, the risk of all-cause mortality and MACE was higher in patients with VV than it was in matched controls, indicating that VV-induced systemic inflammation may be associated with cardiovascular events regardless of the development of venous thromboembolic events. Notably, the lower survival rates were observed in patients with highest VV severity but not in those with grade 1–2. This also reflects that the chronic inflammation induced by a higher grade of VV may be associated with increasing mortality and MACEs. However, only a few studies have compared development of VV with arterial disease and reported inconsistent findings.[2 14] A previous study in Finland has reported a twofold higher incidence of new arterial disease in individuals with VV than in those without it, although the incidence of new hypertension was similar.[14 15] Thus, VV and arterial disease may have a common aetiology, but VV were not related to hypertension. Furthermore, Chang *et al* have reported the association of VV with the incidence of venous thromboembolism and PAD.[16] Reportedly, myocardial infarction and heart failure increase the risk of thromboembolism.[17] In contrast, patients with thromboembolic events were at a higher risk of subsequent myocardial infarction and stroke.[18] However, whether this association is causal or represents common risk factors warrants further research. Notably, compared with controls, patients with VV were at a higher risk of mortality independent of age and sex. Specifically, the significant impact of VV was observed in male patients. In previous research, older age and female sex were found to be the most relevant risk factors for VV.[1] VV incidence increases with increasing age. However, Heit *et al* have reported that younger patients with VV were at a significantly increased risk of subsequent DVT, whereas the risk was attenuated with increasing age.[7] Similarly, Lohr *et al* also reported that although female presented with a higher prevalence of lower grade VV (CEAP 2–3) compared with male (50.5% vs 30.1%), there were more higher grade VVs with trophic skin changes (CEAP 4–6) found in male than in female (5.4% vs 2.8%).[19] Also, DVT was more common in males compared with females (11.3% vs 7.8%).[19] Earlier onset of VV in the younger population implies a higher risk of concomitant arterial diseases or systemic inflammations. As described previously, female sex, pregnancy, and predominately being in the sitting posture are risk factors for VV.[20] However, despite the valid correlation between use of oestrogen supplements and DVT, whether sex hormones contribute to the development of VV remains unclear.

There were several strengths of this study. First, we included an unselected, large, nationwide cohort of patients with VV. By including the data of 4644 patients over a 12-year period, this study provided adequate statistical power for the analysis of long-term outcomes for VV. Second, we compared the VV cohort with a matched, VV-free cohort, which helped distinguish the characteristics of the VV population in terms of survival and outcomes. Third, among patients with VV, the effects of sex on mortality and MACE were emphasised because VV may have been ignored in these specific populations. Forth, we included patients presenting with VV of various severity grades, which allowed for a comprehensive investigation of overall effects of severity. Finally, a recently published article evaluated and supported the accuracy of several major outcomes, including MI, hypertension, diabetes, stroke, CHF and VV, in NHIRD.[21]

However, this study had several limitations. According to previous meta-analysis and research, smoking habits, quality of life, lack of movement, pregnancy history, overweight and glycated haemoglobin levels are considered VV risk factors, with some of these being related to increased mortality risk. Although NHIRD provides a complete clinical medical history over decades for 1 million people, currently the NHIRD lacks information regarding people's lifestyle and clinical laboratory test results. Therefore, the selected confounders in this study were limited to age, sex and four chronic cardiovascular risk factors. The small corresponding area under the receiver operating characteristic curve indicated that the relevant confounders were not appropriately identified. To explore the effects of VV on mortality and MACE with minimum confounding bias, a future study including more comprehensive VV-related risk factors is imperative. Second, the miscoding of VV severity may have led to the exclusion of cases. This might explain why 47% of the included patients are with advanced venous disease (grade 2 or 3), different from the general distribution of disease severity. Nevertheless, to overcome the inherent limitations, we verified the accuracy of VV diagnosis using chart review by a specialist. Overall, both the validation methods indicated a satisfactory accuracy of VV coding in the NHI database. Third, owing to difficulties in completing CEAP staging according to ICD-9, we established our own grading system. However, even though this novel ICD-9-CM-derived grading system clearly differentiated patients with various severities, it remained different from the generally applied CEAP staging system and disease progression could hardly be represented. Similarly, to validate the reliability of the ICD-9-CM-derived grading system, we reviewed medical records of inpatients with VV and observed satisfactory sensitivity and specificity. Forth, while ligation and stripping surgeries may affect the outcomes, through excluding patients receiving surgical treatment for VV we performed sensitivity test. It also revealed significant increases of risks of mortality and MACE in patients with VV compared with risks in the matched controls. Likewise, after excluding the potential influences of PAD, we also found great impacts of mortality and MACE in the population with VV. Finally,

increased mortality with higher ICD-9-CM-derived grades indicated that our grading system specifically reflected the severity of VV but the cause of mortality was not available in this database.

CONCLUSIONS

VVs are a common condition typically believed to be benign; however, our results suggest that they warrant close attention. Compared with matched controls, patients with VV were at increasing risks of mortality and cardiovascular events, especially those with VV at grade 3. Therefore, these findings should alert clinicians regarding the importance of detecting VV at an early stage.

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