

Supplementary Table 1. Clinical characteristics and comorbid medical disorders for patients with VV categorized by the disease severity.

Characteristic	Grade 1, n=2467	Grade 2, n=668	Grade 3, n=1509	P-value
n (%)				
Age (years)				< 0.0001
≥ 65	1756 (71.18)	428 (64.07)	529 (35.06)	
< 65	711 (28.82)	240 (35.93)	980 (64.94)	
Age (mean±SD)	55.57 ± 14.76	57.20 ± 17.45	56.50 ± 17.31	
Gender				0.0332
Male	773 (31.33)	277 (41.47)	746 (49.44)	
Female	1694 (68.67)	391 (58.53)	763 (50.56)	
Hypertension				0.0721
No	2020 (81.88)	539 (80.69)	1191 (78.93)	
Yes	447 (18.12)	129 (19.31)	318 (21.07)	
Diabetes				< 0.0001
No	2296 (93.07)	617 (92.37)	1334 (88.40)	
Yes	171 (6.93)	51 (7.63)	175 (11.60)	
Hyperlipidemia				0.8288
No	2342 (94.93)	633 (94.76)	1468 (95.29)	
Yes	125 (5.07)	35 (5.24)	71 (4.71)	
Coronary artery disease				0.6442
No	2379 (96.43)	648 (97.01)	1462 (96.89)	
Yes	88 (3.57)	20 (2.99)	47 (3.11)	

P-value was calculated based on the two sample t test and Pearson's chi-square test.

Supplement Table 2. Baseline characteristics and comorbid medical disorders for the control cohort and patients with varicose vein (VV).

Characteristic	Varicose vein Grade1	Varicose vein Grade1 control	Standardized difference	Varicose vein Grade2	Varicose vein Grade2 control	Standardized difference	Varicose vein Grade3	Varicose vein Grade3 control	Standardized difference
n (%)	n = 2467	n = 9497		n = 668	n = 2541		n = 1509	n = 5722	
Age (years)			0.02882			0.01557			0.01539
≥ 65	1756 (71.18)	6870 (72.48)		428 (64.07)	1647 (64.82)		529 (35.06)	1964 (34.32)	
< 65	711 (28.82)	2609 (27.52)		240 (35.93)	894 (35.18)		980 (64.94)	3758 (65.68)	
Age (mean±SD)	55.57 ± 14.76	55.14 ± 14.69	0.02891	57.20 ± 17.45	56.91 ± 17.52	0.01664	56.50 ± 17.31	56.09 ± 17.38	0.02336
Gender			0.00891			0.01014			0.00726
Male	773 (31.33)	2931 (30.92)		277 (41.47)	1041 (40.97)		746 (49.44)	2808 (49.07)	
Female	1694 (68.67)	6548 (69.08)		391 (58.53)	1500 (59.03)		763 (50.56)	2914 (50.93)	
Hypertension			0.03885			0.04022			0.05681
No	2020 (81.88)	7901 (83.35)		539 (80.69)	2090 (82.25)		1191 (78.93)	4646 (81.20)	
Yes	447 (18.12)	1578 (16.65)		129 (19.31)	451 (17.75)		318 (21.07)	1076 (18.80)	
Diabetes			0.04942			0.06897			0.06569
No	2296 (93.07)	8936 (94.27)		617 (92.37)	2391 (94.10)		1334 (88.40)	5174 (90.42)	
Yes	171 (6.93)	543 (5.73)		51 (7.63)	150 (5.90)		175 (11.60)	548 (9.58)	
Hyperlipidemia			0.08073			0.09142			0.08733
No	2342 (94.93)	9153 (96.56)		633 (94.76)	2455 (96.62)		1468 (95.29)	5549 (96.98)	
Yes	125 (5.07)	326 (3.44)		35 (5.24)	86 (3.38)		71 (4.71)	173 (3.02)	
Coronary artery disease			0.07654			0.07737			0.08244
No	2379 (96.43)	9263 (97.72)		648 (97.01)	2495 (98.19)		1462 (96.89)	5617 (98.16)	
Yes	88 (3.57)	216 (2.28)		20 (2.99)	46 (1.81)		47 (3.11)	105 (1.84)	

Supplement Table 3. ICD-9 codes versus chart review diagnosis among outpatients with VV

Code	No.	Clinical diagnosis	No.
454.9 Asymptomatic varicose veins	1188	VV	1188
		Others	0
454.1 With inflammation	775	VV	775
		Others	0
454.0 Varicose veins of lower extremities With ulcer	152	VV	152
		Others	0
454.2 With ulcer and inflammation	87	VV	87
		Others	0

Supplement Table 4. ICD-9 codes-derived severity grading versus Clinical–
Etiological–Anatomical–Pathophysiological (CEAP) stages of inpatients with VV

Code	No.	CEAP stage	No.
454.9 Asymptomatic varicose veins	193	C0-2	183
		C3-4	6
		C5-6	4
454.1 With inflammation	56	C0-2	0
		C3-4	56
		C5-6	0
454.0 Varicose veins of lower extremities With ulcer	86	C0-2	6
		C3-4	0
		C5-6	80
454.2 With ulcer and inflammation	12		

	CEAP 0-2	Not CEAP	
Test +	183	10	183/193 (94.8)
Test -	6	136	136/142 (95.7)
	183/189 (96.8)	136/146 (93.1)	

Statistic	Estimate	95% CI
Sensitivity	96.83%	93.22% to 98.83%
Specificity	93.15 %	87.76% to 96.67%
Positive Predictive Value	94.82%	90.95% to 97.08%
Negative Predictive Value	95.77 %	91.15% to 98.03%

	CEAP 3-4	Not CEAP	
Test +	56	0	56/56 (100)
Test -	6	273	273/279 (97.8)
	56/62 (90.3)	273/273 (100)	

Statistic	Estimate	95% CI
Sensitivity	90.32%	80.12% to 96.37%
Specificity	100.00 %	98.66% to 100.00%
Positive Predictive Value	100.00%	
Negative Predictive Value	97.85 %	95.51% to 98.98%

	CEAP 5-6	Not CEAP	
Test +	80	6	80/86 (93)
Test -	4	245	245/249 (98.4)
	80/84 (95.2)	245/251 (97.6)	

Statistic	Estimate	95% CI
Sensitivity	95.24%	88.25% to 98.69%
Specificity	97.61 %	94.87% to 99.12%
Positive Predictive Value	93.02%	85.79% to 96.71%
Negative Predictive Value	98.39 %	95.92% to 99.38%

Supplement Table 5. Sensitivity analysis of hazard ratio in patients with VV compared with the matched control cohort

	VV	Control
History of pregnancy (ICD-9-CM : V22, V23.2, 761.5), N(%)	169 (3.64)	598 (3.37)
Adjusted HR (95% CI); p-value²		
all-cause mortality as endpoint	1.37 (1.19, 1.57); < 0.0001	Reference
MACE as endpoint	2.06 (1.89, 2.23); < 0.0001	Reference
For Grade 3 and matched controls		
all-cause mortality as endpoint	1.84 (1.48, 2.28); < 0.0001	Reference
MACE as endpoint	2.46 (2.14, 2.82); < 0.0001	Reference
Myocardial infarction, stroke, coronary angioplasty or CABG, N(%)	19 (0.41)	457 (2.58)
Adjusted HR (95% CI); p-value³		
all-cause mortality as endpoint	1.36 (1.18, 1.57); < 0.0001	Reference
MACE as endpoint	1.95 (1.8, 2.12); < 0.0001	Reference
For Grade 3 and matched controls		
all-cause mortality as endpoint	1.84 (1.49, 2.28) ; < 0.0001	Reference
MACE as endpoint	2.32 (2.02, 2.66); < 0.0001	Reference

HR = Hazard Ratio; CI = Confidence Interval

2 Adjusted for history of pregnancy, age, gender, hypertension, diabetes, hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease, cancer, atrial fibrillation, heart failure, ischemic heart disease, chronic renal insufficiency

3 HR is calculated for population without history of Myocardial infarction, stroke, coronary angioplasty or CABG and the value is adjusted for age, gender, hypertension, diabetes, hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease, cancer, atrial fibrillation, heart failure, ischemic heart disease, chronic renal insufficiency