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Global, multilingual, physician-invited, patient-completed digital registry enabling pre-consultation engagement and supporting more efficient care pathways in venous disease

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Lower limb venous diseases are prevalent chronic conditions that require standardized, efficient, and patient-centered clinical assessment across diverse healthcare settings. Despite increasing digitalization of healthcare, scalable multilingual digital infrastructures capable of supporting standardized pre-consultation data collection and physician-validated real-world evidence generation remain limited. We conducted a global, cross-sectional observational study, using an innovative physician-invited/patient-completed digital registry, designed to enable pre-clinical engagement. The registry was conceived as a modular, multilingual digital infrastructure, allowing individuals to include clinical data prior to any physician encounter who will then validate the already acquired information, while also completing the healthcare professional part· We assessed geographic reach, usability, engagement in data completion, and cross-sectional associations between demographic, clinical factors and disease stage, defined as CEAP clinical class and Venous Clinical Severity Score (VCSS). 6457 patients from 59 countries from Africa, Asia, Europe, North and South America enrolled in the registry before their first specialist consultation. Completion of all the required data was achieved by 1355 patients from 12 countries. Among participating physicians, the platform usability was rated as easy in 94.2% of responses, while its overall usefulness was rated as high or very high in 76.6% of responses. Privacy concerns were expressed in 17% of cases. Cross-sectional analyses identified risk factor profiles associated with CEAP class ≥ 4 and VCSS ≥ 8·5. These stage-associated profiles differed from those previously reported, reflecting the need for a detailed integration of appropriately collected real-world data in venous disease investigations. A global, multilingual, physician-invited/patient-completed digital registry may facilitate earlier patient engagement and has the potential to support more efficient care pathway, moreover across linguistic contexts, with more timely data capture. This registry provides a scalable digital infrastructure for standardized patient- and physician-validated data collection across multiple countries, with potential applicability to multidisciplinary clinical practice and research. Such infrastructure may facilitate earlier and broader diagnostic insights, including for conditions beyond the initial reason for care seeking, and provide a robust foundation for machine learning, reducing reliance on synthetic datasets and supporting scalable, equitable digital health innovation across medical specialties.

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The global reach is a feature characterizing both digitalization and lower limb venous disease: yet, while the pathology is obviously a negative element, the digitalization offers a positive health opportunity. Chronic venous disease (CVD) affects over 50% of the adult population of the industrialized countries and it can lead to conditions impacting the quality of life, if not the life itself[1–3]. Yet standardized real-world data collection remains limited by heterogeneous clinical documentation, language barriers, and the time available for structured history taking during routine consultations. These challenges hinder comparisons across healthcare systems and reduce the quality of multinational real-world evidence. The scientific data highlight the impact of genetics and environment on CVD. Yet, no large-scale publications delivering appropriate real-world data are available also in this field[4]. The available papers are offering the analysis of a specific population rather than a worldwide global perspective[5]. Another aspect making CVD an appropriate clinical model is its co-existence with other medical conditions, highlighting the importance of comprehensive standardized clinical assessment across different medical territories: a clear risk of developing other pathologies has been identified in these patients[6]. In the context of CVD, comprehensive standardized data collection is essential to capture symptoms that may suggest involvement of different venous territories. For example, the inclusion of pelvic symptoms may help identify patients who could benefit from further evaluation for pelvic venous disorders, a frequently under-recognized condition in women requiring dedicated clinical assessment and appropriate imaging rather than simple visual inspection[7]. Existing digital solutions for CVD remain clinician-initiated, centre-specific or limited to post-diagnostic phases of care. As a result, they fail to address a critical gap in the data collection: time-efficiency. Accurate and comprehensive patient history is central to the diagnosis. However, in routine clinical practice, history taking is frequently constrained by limited consultation time. As a result, patient histories can be incomplete. Language barriers further compound these challenges[8]. In multinational studies, heterogeneity in history-taking practices and translation quality further challenges data harmonization across sites[9–11]. From a scientific perspective, time and language barriers contribute to systematic bias in data collection[12]. Patient-reported symptoms, social and life-determinants of health are often underrepresented, reducing the precision of the practiced medicine, while incrementing the odds of confounding factors that could alter both the diagnostic and scientific research conclusions. In CVD, a typical example comes from the practice of aquatic sports. The immersion of the body into a hydrostatic pressure environment can represent a great benefit for the venous and lymphatic circulation, leading to a potential bias if the study population is enjoying this habit[13]. While it is not possible to capture every potential confounding factor, a standardized digital registry should systematically collect as many clinically relevant variables as feasible, thereby improving phenotypic characterization and reducing the risk of unmeasured confounding in future observational analyses. In this study, we evaluate a global, multilingual, open-access, physician-invited/patient-completed and doctor completed digital registry for venous disease, named "v-registry". It represents a novel approach by enabling patients to complete standardized medical history before the clinical encounter, thereby shifting history acquisition upstream and with the potential to improve consultation efficiency, while maintaining physician validation. The platform supports standardized pre-consultation phenotyping and it has been conceived as a modular, transferable infrastructure that may facilitate future multidisciplinary applications, precision medicine research, and machine-learning development based on physician-validated real-world data. The present study evaluates the feasibility and international implementation of this digital infrastructure while investigating cross-sectional associations between patient characteristics and disease presentation according to the CEAP classification and the Venous Clinical Severity Score (VCSS).

Methods

We conducted a global, cross-sectional observational study using v-registry. The registry is accessible for free worldwide and it is available in 13 languages. The registry is designed as a modular platform enabling structured data capture prior to physician encounter. The platform allows patients to enter demographic information, symptoms, medical history, lifestyle factors, and disease-specific measures relevant to venous conditions. Automatically the digital platform calculates the body mass index (BMI)[14], the thrombotic risk (Caprini Score) and the Venous Clinical Severity Score (VCSS)[15,16]. The patient-reported medical history included the presence or absence of predefined comorbidities, namely arthrosis, cancer, diabetes mellitus, heart disease, hemorrhoidal disease, arterial hypertension, chronic lung disease, pelvic pain, thyroid disorders, and an "other" option for acute or chronic conditions specified by the patient. The registry recorded self-reported physician-diagnosed thrombophilic disorders through a predefined dropdown menu, including prothrombin G20210A mutation, protein C deficiency, protein S deficiency, antithrombin deficiency, hyperhomocysteinemia, and other specified thrombophilic disorders. The treating physician invites the patient by e-mail to access the secure v-registry platform and complete the standardized pre-consultation questionnaire before the scheduled clinical visit. Participating physicians were instructed to invite all consecutive eligible patients scheduled for consultation during the study period. The platform uses a dual-server architecture in order to separate personally identifiable information from anonymized research data, thereby enhancing data security and privacy. Patients independently

complete the patient-reported section of the registry before the consultation. During the subsequent clinical encounter, the physician reviews and validates the patient-entered information, completes the clinician-specific variables, and finalizes the dataset. In this study, participation was open to physicians worldwide with at least five years of clinical practice in phlebology. Recruitment was conducted through an international e-mail campaign distributed to the global contact network of the v-WIN Foundation (43,862 contacts), inviting eligible physicians to participate in the registry. Physicians who volunteered and confirmed their eligibility were granted access to the platform and incorporated the registry into their routine clinical practice. Overall, 171 physicians elected to participate and contributed physician-validated data to the registry and to the usability survey. Only records containing complete patient-reported and physician-validated information were included in the primary statistical analyses of this investigation. Following completion of the patient-reported questionnaire and during the subsequent in-person consultation, in the study the treating physician systematically reviewed all patient-entered information together with the patient. Any discrepancies or inaccuracies were corrected, after which the physician completed the clinician-specific section of the registry, including physical examination findings, duplex ultrasound results, and the CEAP classification[17]. Only physician-validated datasets were considered eligible for the primary analyses. Patients were eligible if they were scheduled for a vein specialist visit. Doctors were eligible if they practiced phlebology for at least 5 years. There were no geographic restrictions for both patients and doctors. The primary analyses were conducted using a complete-case approach. Only participants with complete patient-reported information and physician-validated clinical data were included in the statistical analyses. Records with incomplete questionnaires or incomplete physician validation were excluded from the primary analyses. Primary study outcomes were the implementation and performance of the digital registry, including physician engagement, platform usability, perceived usefulness, privacy perception, and successful physician validation of patient-reported data. Secondary analyses described the characteristics of the international cohort and explored cross-sectional associations between patient characteristics and clinical disease presentation, as assessed by the CEAP clinical classification and the Venous Clinical Severity Score (VCSS). The v-registry was specifically developed for this project. To our knowledge, this manuscript provides the first peer-reviewed description of the platform, its architecture, and its implementation in international clinical practice.

Statistical analysis

Statistical analyses were conducted to characterize participants according to CEAP ≥ 4 and VCSS ≥ 8·5. Categorical variables are presented as counts and percentages, whereas continuous variables are summarized as medians with interquartile ranges. Univariable comparisons were performed using chi-square or Wilcoxon tests, as appropriate. Both univariable and multivariable logistic regression models were fitted for CEAP ≥ 4 and VCSS ≥ 8·5, with results reported as odds ratios (OR) and 95% confidence intervals (CI).Variable selection was guided by data inspection and clinical judgment. All analyses were carried out using R version 3·4·2. Ethnicity was included as a categorical variable. The reference category was determined by the factor coding used in the regression model. As with any categorical predictor, the choice of reference category does not influence model fit or statistical significance but only the interpretation of the estimated odds ratios. BMI was modelled as a continuous variable on its original scale (i.e., not mean-centered). Consequently, in models including a BMI-by-sex interaction, the main effect of sex should not be interpreted independently of BMI.

Ethics and governance

The study was conducted in accordance with the Declaration of Helsinki. Digital informed consent was obtained from all participants. Ethical committee approval was obtained (IRB: 5/2025/Oss/UniFe).

V-Registry technical notes on digital health data privacy and intercontinental protection

The project was designed by adopting a legal-strategic approach grounded in the principle of privacy by design, understood not as the mere implementation of security measures, but as an architectural and decision-making criterion integrated from the very conception of the system. Legal input accompanied technological development, guiding organizational and IT choices in light of the GDPR principles, the Guidelines of the Italian Data Protection Authority on the processing of health data, and European best practices on anonymization and pseudonymization. The strategy was primarily based on the substantive application of the principle of data minimization (Article 5 GDPR), translating it into a structural separation between identifying data and health data. Personal identification databases and clinical databases were designed as distinct and segregated environments, linked exclusively through a pseudonymous code automatically generated by the system. This choice does not represent a mere technical measure, but rather an ex-ante legal decision aimed at reducing the risk of re-identification and limiting the exposure of health data, a category of data subject to enhanced protection under Article 9 GDPR. Pseudonymization was therefore used as a tool for accountability and risk management, consistently with Article 25 GDPR. Access to the correlation table linking codes to identities was further restricted according to strict necessity and separation-of-duties criteria, thereby reinforcing the principles of integrity and confidentiality. This is complemented by the systematic adoption of data encryption both at rest and in transit, as a technical measure aligned with Article 32 GDPR and proportionate to the nature and sensitivity of the information processed. The approach did not end with the initial system configuration. The project provides for the periodic execution of data protection impact assessments (DPIAs), updated with each technological or functional evolution of the platform. The DPIA was conceived as a dynamic risk-governance tool, aimed at continuously verifying the proportionality of the processing, the adequacy of the measures adopted, and the ongoing effectiveness of safeguards for data subjects. A further qualifying element is the clear delineation of the legal bases for processing. The system was structured so as to clearly distinguish clinical purposes, based on the lawfulness conditions applicable to the processing of health data by healthcare professionals, from any additional processing activities. The segregation between identifying data and health

data, together with the possible use of anonymized data for research purposes, makes it possible to circumscribe the scope of consent, reducing complexity and risks of unlawfulness. Finally, considering the international scope of the registry, the legal analysis included a comparative assessment of the different national legal systems involved, with particular attention to cross-border data transfers and compatibility with local regulations on the protection of health data. The objective was to ensure a model compliant not only with the GDPR, but also with applicable national laws, through appropriate technical and contractual solutions capable of supporting the project's worldwide operation. Taken as a whole, the initiative represents an example of integration between law and technology, in which compliance does not intervene ex post, but rather structures the system itself, transforming data protection from a regulatory constraint into a design driver.

Results

Between October 2024 and October 2025, 6457 patients from 59 countries, from Africa, Asia, Europe, North and South America, were registered in the v-registry following physician invitation. Among these, patients completed the pre-consultation questionnaire to varying degrees. After physician validation during the clinical visit, 1355 participants from 12 countries had complete patient and physician-reported datasets and were therefore included in the primary statistical analyses. Participants with incomplete datasets were excluded from the complete-case analyses (Fig. 1).

The included cases were from 12 countries, indicating a total compliance to the full completion of the data collection by 21% of all the patients who filled in at least some data and by 20·3% of all the countries that accessed v-registry. The national breakdown of the countries who filled in the registry entirely is reported in Fig. 2.

From this campaign, 171 eligible physicians from the above reported 12 countries enrolled and all contributed data to the registry. filled in the usability, privacy concern and usefulness surveys. The digital platform usability was considered easy by 94·2% and not easy by 5·8% of the healthcare professionals (Fig. 3A). Despite the explanation of a strict privacy protection according to the different countries' legislation, 17% of doctors still expressed concerns regarding the safety of digital health data management (Fig. 3B). In terms of usefulness of the proposed digital platform, 47·4% scored it as extremely useful, 29·2% as useful 6·4% as not useful, 17% declared to not have developed an opinion yet, while nobody considered it mildly useful or pointless (Fig. 3C).

In 1355 participants, CEAP ≥ 4 was significantly associated with older age and higher BMI. Each additional year of age from a baseline of 47 years increased the risk by 6% (OR 1·06, 95% CI 1·04–1·07, $p < 0·001$), while each 1-point increase in BMI from 27·3 kg/m² increased the risk by 7% (OR ··07, 95% CI 1·04–1·10, $p < 0·001$). Higher Caprini scores above 4 (OR 1·22 per point, 95% CI 1·14–1·30, $p < 0·001$) and VCSS above 4 (OR 1·21 per point, 95% CI 1·16–1·27, $p < 0·001$) were also associated with greater risk. The presence of comorbidities increased the likelihood of CEAP ≥ 4 (OR 1·90, 95% CI 1·37–2·64, $p < 0·001$), as did a history of superficial venous thrombosis (OR 3·17, 95% CI 1·35–6·88, $p = 0·010$) and Asian ethnicity compared with African ethnicity (OR 15·3, 95% CI 2·83–135, $p = 0·001$). Participants with temporary or no compression had lower risk (OR 0·21, 95% CI 0·11–0·38, $p < 0·001$), while those receiving care in public settings were at higher risk than those in private settings (OR 1·58, 95% CI 1·09–2·26, $p = 0·015$) (Table 1). In multivariable analysis, higher BMI (OR 1·11, 95% CI 1·08–1·14), older age (OR 1·07 per year, 1·05–1·08), and prolonged standing or sitting (OR 1·65, 1·15–2·38) were independently associated with CEAP ≥ 4 (Table 2). In 1355 participants, VCSS ≥ 8·5 was significantly associated with higher BMI, with a 6% increase in risk per BMI point above 27·3 kg/m² (OR 1·06, 95% CI 1·03–1·09, $p < 0·001$), a history of superficial venous thrombosis (OR 2·74, 95% CI 1·24–5·78, $p = 0·014$), and Asian ethnicity compared with African ethnicity (OR 12·8, 95% CI 2·42–112, $p = 0·002$), noting that the wide confidence interval reflects the small number of Asian participants. Protective factors included absence of family history (OR 0·60, 95% CI 0·43–0·84, $p = 0·002$), compression at 23–32 mmHg (OR 0·34, 95% CI 0·14–0·72, $p = 0·004$), and temporary or no compression use (OR 0·36, 95% CI 0·23–0·54, $p < 0·001$). Clinically, higher Caprini scores above 4 (OR 1·22 per point, 95% CI 1·14–1·29, $p < 0·001$) and CEAP ≥ 4 (OR 13·5, 95% CI 9·43–19·5, $p < 0·001$) were also associated with VCSS ≥ 8·5 (Table 3).

In the multivariable model for VCSS ≥ 8·5, BMI was positively associated with risk (OR 1·01, 95% CI 1·00–1·02), with a significant interaction between BMI and male sex (OR for interaction 1·09, 1·07–1·11), indicating that the effect of BMI on VCSS is stronger in males. Male sex alone was associated with lower baseline odds (OR 0·09, 0·06–0·15), but this effect is modified by BMI (Table 4). Figure 4 highlights the factors influencing more severe venous disease. Red bubbles indicate predictors that increase the risk of higher CEAP or VCSS scores, while blue indicates protective effects. Larger bubbles reflect stronger associations. Clinically, higher BMI and older age increase both clinical appeareance (CEAP ≥ 4) and severity (VCSS ≥ 8·5) scores, suggesting these are universal risk factors. Extended periods of sitting or standing and receiving care in a public setting are linked only to more advanced CEAP, whereas male gender and the interaction between BMI and gender are specifically associated with higher clinical severity (VCSS).

Some factors (for example, BMI) consistently influence both CEAP and VCSS severity, whereas others, like comorbidities, appear to affect CEAP only, confirming the different meaning of the different CEAP and VCSS scores (Table 5). Sensitivity analysis has been performed in a mixed-effect model accounting for nesting of responses within countries. The results are consistent with those reported in the multi-variables models outcomes as specified above. The Fig. 5 shows a moderate positive association between CEAP class (1–6) and VCSS (0–30).

VCSS values tend to increase progressively with higher CEAP categories, as highlighted by the upward-sloping regression line. The estimated Pearson correlation ($R = 0·57$, $p < 2·2 \times 10^{-16}$) indicates a statistically significant and moderately strong relationship. However, there is substantial variability within each CEAP level, with VCSS scores widely dispersed, especially in intermediate classes (2–4). This suggests that while disease clinical appearance (CEAP) is associated with higher clinical scores (VCSS), CEAP alone does not fully explain the heterogeneity in VCSS. At higher CEAP levels (CEAP 5–6), VCSS values are generally higher, but still show overlap with lower classes, reinforcing the idea that the relationship is trend-driven rather than deterministic.

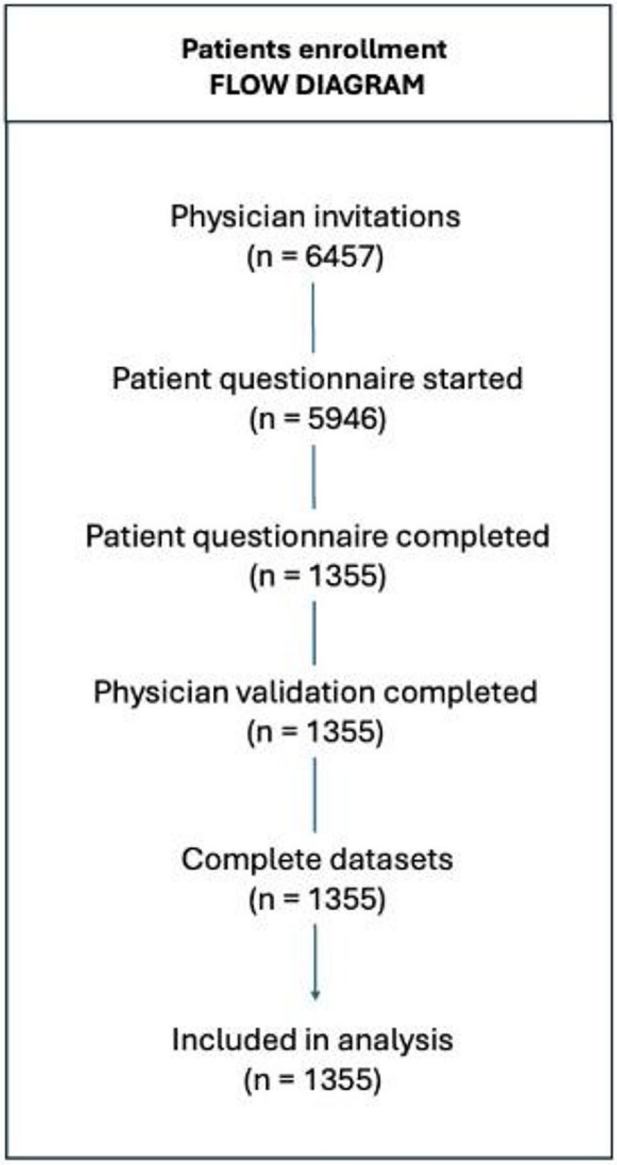

Fig. 1. Patients inclusion flow diagram: the study included the patients who fulfilled all the registry and who were then validated by the physician who visited them.

Discussion

This study demonstrates the feasibility of implementing a multilingual, physician-validated digital registry capable of standardized real-world data collection across diverse international healthcare settings. The modular design of the platform may facilitate future adaptation to multidisciplinary clinical practice and research. The standardized international dataset generated through the v-registry may facilitate future benchmarking of clinical practice across healthcare systems and support comparative effectiveness and health services research. However, the present study did not evaluate appropriateness of care, affordability, or clinical governance.(Fig. 6)[18].

The coverage of all South, Central and North America, together with Africa, Europe and Asia offers the first bird's eye view on CVD burden by means of a fully standardized multi-lingual data collection. The standardized physician-validated dataset generated through the registry provides new insights into factors associated with chronic venous disease presentation, including the complementary roles of the CEAP classification and the Venous Clinical Severity Score (VCSS), while highlighting potential confounding variables that should be considered in future clinical and epidemiological investigations. The observation that CEAP and VCSS showed different associations with patient characteristics is consistent with previous evidence indicating that CEAP is primarily a classification system rather than a measure of disease severity. Accordingly, it should not be interpreted as a surrogate for histopathological severity or used interchangeably with VCSS[19]. The threshold of 4 for CEAP was chosen as clinically considered a "no return" point after venous-hypertension induced iron

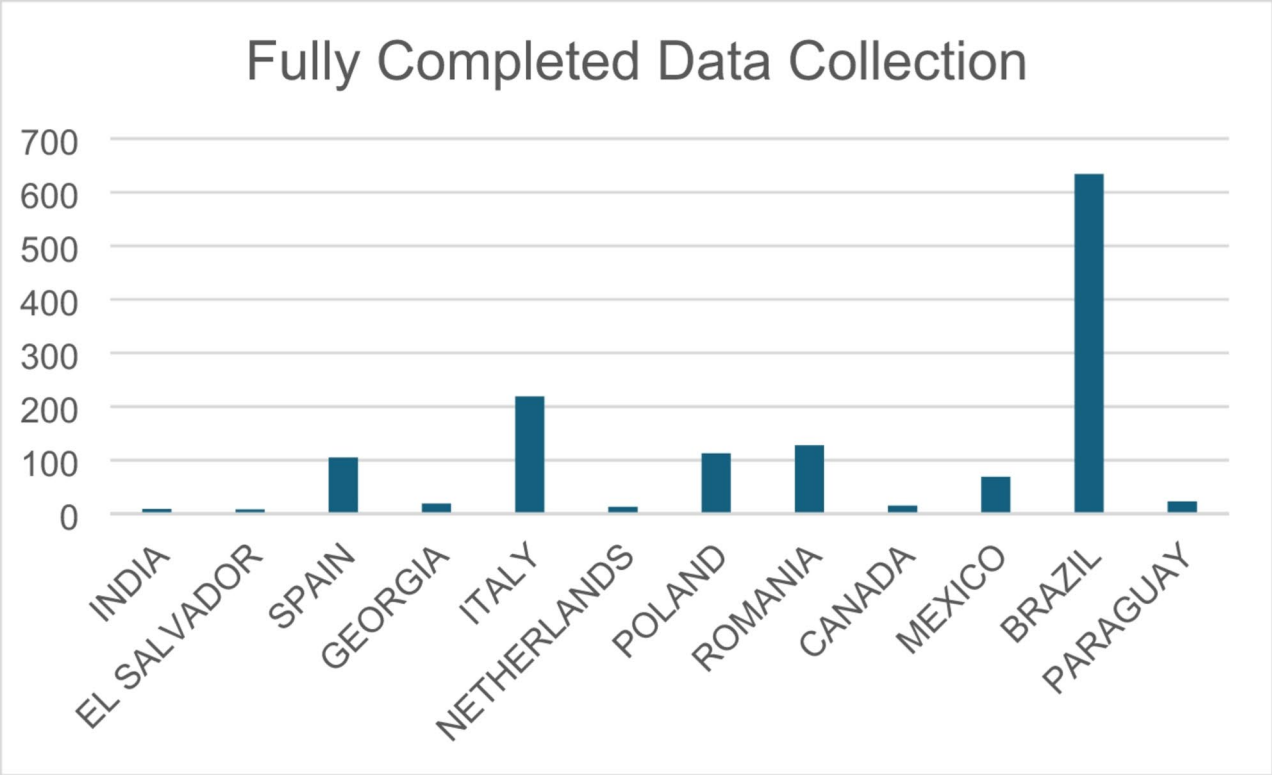

Fig. 2. Breakdown of the nations included in the analysis following their full completion of all the data required in v-registry.

deposition in the subcutaneous tissue. The value of 8·5 for VCSS was set for consistency with previous literature on the topic, demonstrating the related association with venous edema[20]. The herein proposed digital health data collection model allowed to highlight groundbreaking factors in CVD burden. Gender equality in CVD is among the most interesting findings of this investigation: while usually considered a disease more frequent in women, the digital health platform used in a real-world global setting showcased no significant male/female differences, except whenever BMI increases, actually exposing more the male than the female gender. The outcome highlights the need of further investigation on the topic, also in light of the heterogeneity currently present in the scientific literature, with even contradicting findings reporting a higher male rather than female prevalence[21]. The correlation between VCSS and CEAP was already reported as mild-moderate and mainly limited to the highest scores[22]. Yet, the literature on the topic is heterogeneous considering there is also evidence of a moderate-strong correlation in another study conducted on Spanish patients[23]. Up to our knowledge, the herein obtained data regarding VCSS and CEAP represent the first worldwide real-world scenario analysis, made possible thanks to the integration of a digital platform. Although CEAP and VCSS are frequently reported together, they should not be considered interchangeable. CEAP is a disease classification system primarily describing clinical presentation and anatomical characteristics, whereas VCSS quantifies the current clinical severity of venous disease. Consequently, the present analyses evaluate the degree of association between these complementary constructs rather than implying that one predicts or causes the other. The inclusion of the Caprini score was intended to provide a standardized assessment of each patient's thrombotic risk profile. Although originally developed for venous thromboembolism risk stratification, the present findings suggest that this composite score may also be useful when exploring the relationship between thrombotic predisposition and chronic venous disease phenotypes. Future studies should further investigate this association. This is in line also with the herein found previous superficial venous thrombosis impact on both CEAP and VCSS scores. Interestingly, age confirmed the correlation with CEAP as per the abundant literature on the topic, yet it showed no association with VCSS, providing another first insight in the complexity of the CVD burden factors contribution[24]. BMI assessment confirmed its pivotal role in CVD burden, as per the previous publications reporting its impact on both CEAP[25] and VCSS scores[26]. Yet, a recent publication highlighted how BMI was not correlated to VCSS in a Turkish population assessment[27]. This finding highlights the need of a digital platform able to collect real-world data in a global context, while filtering for the different variables in order to remove possible confounding factors and to identify the real specific weight of the different contributors to the disease. An exploratory association between ethnicity and disease classification was observed. However, these estimates should be interpreted with considerable caution because some ethnic subgroups were represented by a small number of participants, resulting in wide confidence intervals. Therefore, these findings should be regarded as hypothesis-generating rather than conclusive and warrant confirmation in larger, geographically balanced

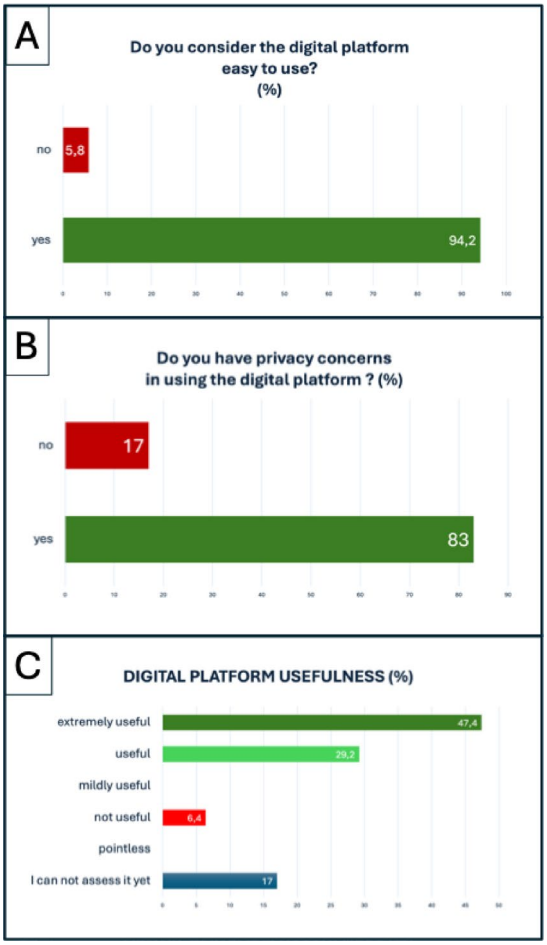

Fig. 3. Usability, privacy concerns and usefulness of the v-registry digital platform according to the healthcare professional users. **(A)** is reporting a yes/no answer to how easy to be used the platform is. **(B)** is related to the yes/no answer to eventual concerns in privacy management despite the platform guarantee anonymity and independent servers and legally approved data collection methodology. **(C)** shows the level of usefulness of the digital platform according to the healthcare professional users.

international cohorts. However, a clear distinction should be made between ethnic groups living within the same geographical region, as in the San Diego study, and ethnic groups evaluated across different countries and therefore exposed to distinct environmental, socioeconomic, healthcare, and lifestyle contexts[5]. Also in this scenario, the digital health platform solution demonstrates the potentials of enhancing the reliability of the related data and consequent personalized medicine. Another fundamental aspect in healthcare is the setting where it happens, yet CVD management scientific literature is missing this topic. Up to our knowledge, this is the first investigation demonstrating a difference between the two realities, pointing out how public setting received higher CEAP classes, while no difference was reported for VCSS. These findings suggest that clinical presentation according to the CEAP classification and symptom severity as assessed by the VCSS may not always progress in parallel, further supporting the complementary roles of these two assessment instruments. The only available paper on the topic was limited to the Italian population and reported no difference in CEAP and VCSS for the public vs. private context[28]. The registry also provides a robust foundation for future machine learning applications. By generating real-world data at scale, it may reduce reliance on synthetic datasets and support clinically grounded, transparent, and equitable algorithm development[29,30]. Among the limitations, the cross-sectional design limits causal inference. The present analyses considered comorbidities as a composite variable representing the presence of one or more predefined chronic conditions. Although this approach provides an overall estimate of comorbidity burden and avoids model overparameterization, individual comorbidities may differ in their association with chronic venous disease. Future analyses based on larger datasets will allow evaluation of the contribution of specific comorbid conditions separately. Participation required digital access and literacy, which may introduce selection bias.

Moreover, the present study did not evaluate workflow efficiency outcomes such as consultation duration, diagnostic delay, treatment delay, physician workload, or patient satisfaction. Consequently, any potential effect of the registry on healthcare efficiency remains hypothetical and should be assessed in dedicated prospective implementation studies. Selection bias should also be considered. Because only participants with complete patient-reported and physician-validated datasets were included in the primary analyses, the study relied on a

Variable	Overall (*N* = 1355)	CEAP < 4 (*N* = 1187)	CEAP ≥ 4 (*N* = 168)	OR (95% CI)	*p*-value
Characteristics					
Age (years)	49 [40–59]	47 [39–57]	59 [49–69]	1·06 (1·04–1·07)	< 0·001
BMI	27·6 [24·7–30·8]	27·3 [24·4–30·5]	29·2 [26·6–32·9]	1·07 (1·04–1·10)	< 0·001
Water intake (L/day)	2·0 [1·5–2·0]	2·0 [1·5–2·0]	2·0 [1·5–2·0]	0·80 (0·59–1·07)	0·135
Cigarettes/day	0 [0–0]	0 [0–0]	0 [0–0]	0·98 (0·86–1·12)	0·784
Sports sessions/week	0 [0–2]	0 [0–2]	0 [0–3]	1·03 (0·94–1·12)	0·551
Hours per sports session	0 [0–1]	0 [0–1]	0 [0–1]	1·07 (0·88–1·30)	0·503
Sex – female	1189 (88·6%)	1035 (88·1%)	154 (92·2%)	Ref	—
Sex – male	153 (11·4%)	140 (11·9%)	13 (7·8%)	0·63 (0·33–1·10)	0·109
Ethnicity – African	36 (2·7%)	30 (2·5%)	6 (3·6%)	Ref	—
Ethnicity – Asian	9 (0·7%)	2 (0·2%)	7 (4·2%)	15·3 (2·83–135)	0·001
Ethnicity – Caucasian	1200 (88·6%)	1057 (89·0%)	143 (85·1%)	0·66 (0·29–1·81)	0·393
Ethnicity – Hispanic	110 (8·1%)	98 (8·3%)	12 (7·1%)	0·61 (0·21–1·91)	0·377
Prolonged sitting/standing job – no	731 (53·9%)	648 (54·6%)	83 (49·4%)	Ref	—
Prolonged sitting/standing job – yes	624 (46·1%)	539 (45·4%)	85 (50·6%)	1·23 (0·89–1·70)	0·209
Family history – no	970 (71·6%)	857 (72·3%)	113 (67·3%)	Ref	—
Family history – yes	384 (28·4%)	329 (27·7%)	55 (32·7%)	1·27 (0·89–1·79)	0·183
Comorbidities – no	865 (63·9%)	781 (65·8%)	84 (50·3%)	Ref	—
Comorbidities – yes	489 (36·1%)	406 (34·2%)	83 (49·7%)	1·90 (1·37–2·64)	< 0·001
Thrombophilic disorders – no	1337 (98·7%)	1172 (98·7%)	165 (98·2%)	Ref	—
Thrombophilic disorders – yes	18 (1·3%)	15 (1·3%)	3 (1·8%)	1·48 (0·33–4·59)	0·565
Superficial venous thrombosis – no	1325 (97·8%)	1166 (98·2%)	159 (94·6%)	Ref	—
Superficial venous thrombosis – yes	30 (2·2%)	21 (1·8%)	9 (5·4%)	3·17 (1·35–6·88)	0·010
Previous deep venous thrombosis – no	1294 (95·5%)	1129 (95·1%)	165 (98·2%)	Ref	—
Previous deep venous thrombosis – yes	61 (4·5%)	58 (4·9%)	3 (1·8%)	0·37 (0·09–1·02)	0·056
Alcohol – no	1054 (77·8%)	914 (77·0%)	140 (83·3%)	Ref	—
Alcohol – yes	301 (22·2%)	273 (23·0%)	28 (16·7%)	0·67 (0·43–1·02)	0·061
Smoking – no	1335 (98·5%)	1170 (98·6%)	165 (98·2%)	Ref	—
Smoking – yes	20 (1·5%)	17 (1·4%)	3 (1·8%)	1·30 (0·29–3·97)	0·689
Compression prescribed – 15–21 mmHg	242 (18·4%)	203 (17·7%)	39 (23·4%)	Ref	—
Compression prescribed – 20–30 mmHg	955 (72·5%)	843 (73·3%)	112 (67·1%)	0·69 (0·47–1·04)	0·073
Compression prescribed – 23–32 mmHg	115 (8·7%)	101 (8·8%)	14 (8·4%)	0·73 (0·36–1·38)	0·334
Compression prescribed – none	5 (0·4%)	3 (0·3%)	2 (1·2%)	3·52 (0·40–23·9)	0·227
Compression duration – lifetime	1019 (77·2%)	862 (74·8%)	157 (93·5%)	Ref	—
Compression duration – no/temporary	301 (22·8%)	290 (25·2%)	11 (6·6%)	0·21 (0·11–0·38)	< 0·001
Care setting – private	1037 (77·0%)	924 (78·1%)	113 (69·3%)	Ref	—
Care setting – public	309 (23·0%)	259 (21·9%)	50 (30·7%)	1·58 (1·09–2·26)	0·015
Scores					
CEAP score	2·0 [2·0–3·0]	2·0 [2·0–2·0]	4·0 [4·0–6·0]	NE*	0·996
Caprini score	4·0 [3·0–5·0]	4·0 [3·0–5·0]	5·0 [4·0–7·0]	1·22 (1·14–1·30)	< 0·001
VCSS (0–30)	4·0 [3·0–7·0]	4·0 [3·0–6·0]	9·0 [7·0–14·0]	1·21 (1·16–1·27)	< 0·001
VCSS ≥ 8·5	243 (17·9%)	136 (11·5%)	107 (63·7%)	13·5 (9·43–19·5)	< 0·001

Table 1. Participant characteristics and clinical scores according to CEAP classification. Data are presented as median [IQR] or n (%). Odds ratios (OR) with 95% confidence intervals (CI) and p-values indicate the association of each variable with CEAP ≥ 4 compared with CEAP < 4. Significant associations ($p < 0·05$) are highlighted.* Not estimable.

complete-case approach. Individuals who completed the entire workflow may differ from those with incomplete registrations with respect to motivation, digital literacy, disease severity, socioeconomic characteristics, or healthcare engagement. Since baseline information was not systematically available for incomplete registrations, these differences could not be formally assessed. Consequently, the reported associations should be interpreted with caution and may not be fully representative of the overall population accessing the registry. Moreover, although the registry enrolled patients from 59 countries, complete datasets included in the present analyses originated from a smaller subset of participating countries, potentially limiting the global representativeness of the findings. Differences in healthcare organization, digital infrastructure, patient engagement, and implementation of the registry across countries may have contributed to this distribution, although these factors were not specifically investigated in the present study. Future studies should evaluate these implementation-

Predictor	Odds Ratio	95% CI	*p*-value
BMI	1·11	1·08–1·14	< 0·001
Gender (male vs. female)	0·74	0·38–1·33	0·333
Age (per 1-year increase)	1·07	1·05–1·08	< 0·001
Job ≥ 4 h continuous sitting/standing (yes vs. no)	1·65	1·15–2·38	0·007
Care setting (public vs. private)	1·63	1·11–2·39	0·012

Table 2. Multivariable logistic regression of factors associated with CEAP ≥ 4. Odds ratios (OR) with 95% confidence intervals (CI) and p-values indicate the independent association of each predictor with higher CEAP classification. Effective sample size: $N = 1{,}342$.

Variable	Overall ($N = 1355$)	VCSS < 8·5 ($N = 1112$)	VCSS ≥ 8·5 ($N = 243$)	OR (95% CI)	*p*-value
Characteristics					
Age (years)	49 [40–59]	49 [41–58]	46 [39–62]	1·00 (0·99–1·01)	0·491
BMI	27·6 [24·7–30·8]	27·3 [24·4–30·4]	29·4 [26·2–32·8]	1·06 (1·03–1·09)	< 0·001
Water intake (L/day)	2·0 [1·5–2·0]	2·0 [1·5–2·0]	2·0 [1·5–2·0]	0·86 (0·66–1·10)	0·227
Cigarettes/day	0 [0–0]	0 [0–0]	0 [0–0]	0·98 (0·88–1·10)	0·776
Sports sessions/week	0 [0–2]	0 [0–2]	0 [0–3]	1·06 (0·99–1·15)	0·108
Hours per sports session	0 [0–1]	0 [0–1]	0 [0–1·5]	1·25 (1·06–1·48)	0·007
Sex – female	1189 (88·6%)	974 (88·5%)	215 (88·8%)	Ref	—
Sex – male	153 (11·4%)	126 (11·5%)	27 (11·2%)	0·97 (0·62–1·49)	0·910
Ethnicity – African	36 (2·7%)	29 (2·6%)	7 (2·9%)	Ref	—
Ethnicity – Asian	9 (0·7%)	2 (0·2%)	7 (2·9%)	12·8 (2·42–112)	0·002
Ethnicity – Caucasian	1200 (88·6%)	984 (88·5%)	216 (88·9%)	0·89 (0·41–2·27)	0·798
Ethnicity – Hispanic	110 (8·1%)	97 (8·7%)	13 (5·3%)	0·55 (0·20–1·62)	0·268
Prolonged sitting/standing job – no	731 (53·9%)	593 (53·3%)	138 (56·8%)	Ref	—
Prolonged sitting/standing job – yes	624 (46·1%)	519 (46·7%)	105 (43·2%)	0·87 (0·66–1·15)	0·328
Family history – no	970 (71·6%)	777 (69·9%)	193 (79·4%)	Ref	—
Family history – yes	384 (28·4%)	334 (30·1%)	50 (20·6%)	0·60 (0·43–0·84)	0·002
Comorbidities – no	865 (63·9%)	718 (64·6%)	147 (60·5%)	Ref	—
Comorbidities – yes	489 (36·1%)	393 (35·4%)	96 (39·5%)	1·19 (0·90–1·59)	0·226
Thrombophilic disorders – no	1337 (98·7%)	1096 (98·6%)	241 (99·2%)	Ref	—
Thrombophilic disorders – yes	18 (1·3%)	16 (1·4%)	2 (0·8%)	0·61 (0·09–2·17)	0·486
Superficial venous thrombosis – no	1325 (97·8%)	1093 (98·3%)	232 (95·5%)	Ref	—
Superficial venous thrombosis – yes	30 (2·2%)	19 (1·7%)	11 (4·5%)	2·74 (1·24–5·78)	0·014
Previous deep venous thrombosis – no	1294 (95·5%)	1063 (95·6%)	231 (95·1%)	Ref	—
Previous deep venous thrombosis – yes	61 (4·5%)	49 (4·4%)	12 (4·9%)	1·14 (0·57–2·11)	0·701
Alcohol – no	1054 (77·8%)	851 (76·5%)	203 (83·5%)	Ref	—
Alcohol – yes	301 (22·2%)	261 (23·5%)	40 (16·5%)	0·64 (0·44–0·92)	0·015
Smoking – no	1335 (98·5%)	1096 (98·6%)	239 (98·4%)	Ref	—
Smoking – yes	20 (1·5%)	16 (1·4%)	4 (1·6%)	1·18 (0·33–3·28)	0·776
Compression prescribed – 15–21 mmHg	242 (18·4%)	198 (18·4%)	44 (18·2%)	Ref	—
Compression prescribed – 20–30 mmHg	955 (72·5%)	766 (71·3%)	189 (78·1%)	1·11 (0·78–1·61)	0·579
Compression prescribed – 23–32 mmHg	115 (8·7%)	107 (9·9%)	8 (3·3%)	0·34 (0·14–0·72)	0·004
Compression prescribed – none	5 (0·4%)	4 (0·4%)	1 (0·4%)	1·24 (0·04–9·20)	0·863
Compression duration – lifetime	1019 (77·2%)	806 (74·6%)	213 (89·1%)	Ref	—
Compression duration – no/temporary	301 (22·8%)	275 (25·4%)	26 (10·9%)	0·36 (0·23–0·54)	< 0·001
Care setting – private	1037 (77·0%)	849 (76·6%)	188 (79·0%)	Ref	—
Care setting – public	309 (23·0%)	259 (23·4%)	50 (21·0%)	0·87 (0·62–1·22)	0·435
Scores					
CEAP ≥ 4	168 (12·4%)	61 (5·5%)	107 (44·0%)	13·5 (9·43–19·5)	< 0·001
Caprini score	4·0 [3·0–5·0]	4·0 [3·0–5·0]	5·0 [4·0–6·0]	1·22 (1·14–1·29)	< 0·001
VCSS (0–30)	4·0 [3·0–7·0]	4·0 [3·0–5·0]	10·0 [9·0–13·0]	—	0·988

Table 3. Participant characteristics, clinical history, and scores according to VCSS categories. Data are presented as median [IQR] or n (%). Odds ratios (OR) with 95% confidence intervals (CI) and p-values indicate the association of each variable with VCSS ≥ 8·5 compared with VCSS < 8·5.

Predictors	Estimates	95% CI	*p*-value
BMI	1·01	1·00–1·02	0·002
Gender [male]	0·09	0·06–0·15	< 0·001
Age (per 5-year increase)	1·02	1·00–1·03	0·030
Job ≥ 4 h continuous sitting/standing [yes]	0·99	0·92–1·06	0·760
Care setting [public vs. private]	0·97	0·89–1·05	0·434
BMI × gender [male]	1·09	1·07–1·11	< 0·001

Table 4. Multivariable model for VCSS ≥ 8·5. Odds ratios (OR) and 95% confidence intervals (CI) indicate the independent association of each predictor with VCSS ≥ 8·5. Effective sample size: $N = 1{,}342$.

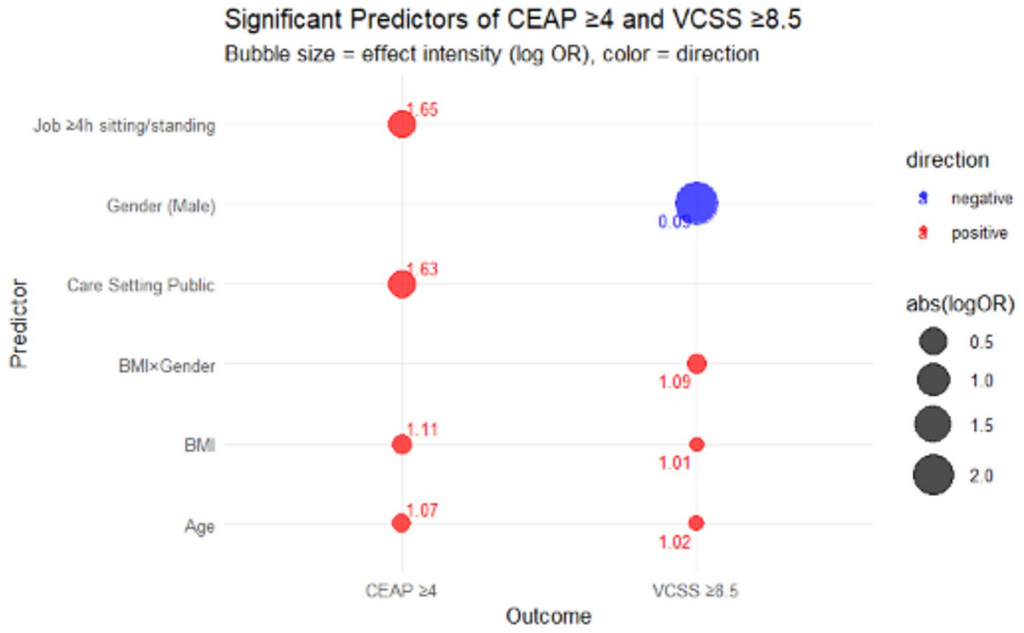

Fig. 4. Multivariable Significant predictors of advanced venous disease. Bubble size represents the strength of the association (log odds ratio), while color indicates the direction of effect (red = higher risk, blue = protective).

	CEAP ≥ 4	VCSS ≥ 8·5	Interpretation
BMI	✓	✓	**Shared risk factor**
Age	✓	✓	Shared risk factor
Comorbidities	✓	✖	Clinical appearance burden
Job ≥ 4 h continuous sitting/standing [yes]	✓	✖	Clinical appearance only
SVT	✓	✓	Thrombo-inflammatory pathway
Ethnicity	✓	✓	Uncertain (imprecision)

Table 5. Concordance and divergence of factors associated with anatomical (CEAP ≥ 4) and clinical (VCSS ≥ 8·5) severity in chronic venous disease. Checkmarks indicate factors significantly associated with each outcome. Shared predictors (e·g·, BMI, superficial venous thrombosis, ethnicity) suggest common underlying pathways, whereas discordant factors (e·g·, age and comorbidities) indicate differential contributions to CEAP versus VCSS disease aspects; estimates for ethnicity should be interpreted with caution due to imprecision.

related factors in greater detail. Approximately one-fifth of registered patients completed all required physician-validated data fields and were included in the primary analyses. Only participants with complete mandatory patient-reported items and physician-validated clinical data were eligible for the primary analyses. Optional variables (e.g. gender declaration and selected demographic questions) could remain unanswered ("prefer not to answer", undeclared gender, or other non-mandatory items). Consequently, analyses involving these variables were performed using the available observations for each model, and the effective sample size is reported in the corresponding tables. Although this demonstrates the feasibility of implementing an international

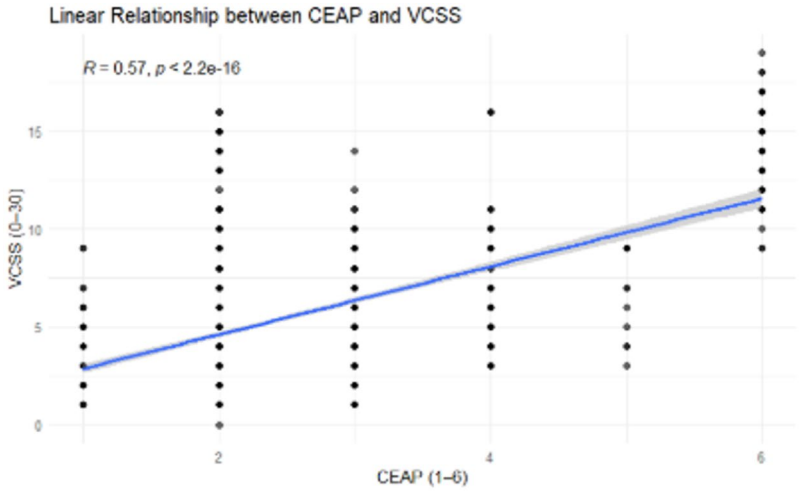

Fig. 5. Linear regression between CEAP clinical class and Venous Clinical Severity Score. Scatter plot of VCSS (0–30) across CEAP classes (1–6) with a fitted linear regression line and 95% confidence interval, illustrating the trend and dispersion of clinical severity across disease stages.

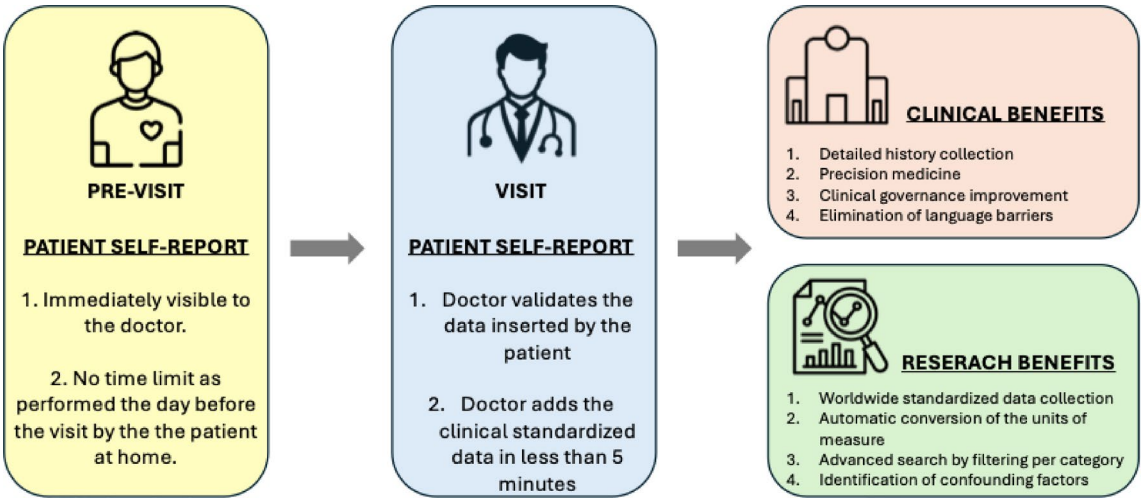

Fig. 6. V-Registry digital platform solution. Conceptual representation of potential future applications of standardized international real-world data generated by the v-registry. These applications were not directly evaluated in the present study.

multilingual digital registry, the reasons underlying incomplete participation remain unknown because the current platform does not capture implementation metrics such as e-mail opening rates, partial questionnaire completion, technical difficulties, digital literacy, or patient-specific reasons for discontinuation. Consequently, selection bias cannot be excluded, and the analyzed cohort may differ from patients who did not complete the registration process. Future iterations of the platform will incorporate these metrics to better characterize patient engagement and optimize registry implementation. Approximately one-fifth of registered patients completed all required physician-validated data fields and were included in the primary analyses. Although this demonstrates the feasibility of implementing an international multilingual digital registry, the reasons underlying incomplete participation remain unknown because the current platform does not capture implementation metrics such as e-mail opening rates, partial questionnaire completion, technical difficulties, digital literacy, or patient-specific reasons for discontinuation. Consequently, selection bias cannot be excluded, and the analyzed cohort may differ from patients who did not complete the registration process. Future iterations of the platform will incorporate these metrics to better characterize patient engagement and optimize registry implementation. The upgraded version of the registry will incorporate mandatory collection of a minimal baseline dataset prior to questionnaire completion to permit characterization of non-completers and evaluation of potential selection bias. Although all patient-reported information was reviewed and validated by the treating physician before inclusion in the final dataset, the degree of agreement between the initial patient-entered information and the physician-validated

records was not formally quantified. Future studies should evaluate the accuracy of patient-reported clinical histories for individual variables, including previous thrombotic events and comorbidities.

Conclusion

A global, physician-invited/patient-completed, multilingual digital registry enables pre-clinical engagement, potential time-optimised care pathways, and novel severity phenotyping in venous disease. As a generalizable digital health model, it offers a scalable foundation for multidisciplinary collaboration, precision medicine, and machine learning applications based on real-world data across clinical specialties. Up to our knowledge, this is digital tool is unique in its legally connecting the patient with the healthcare professional even before the first visit happens, in its being available in 13 languages all around the world and in its offering a standardized format of data collection that can optimize the generation of real world data from all around the world, including information both on the type of patient and related physician, therefore representing an effective tool for reliable machine learning. Future studies should prospectively compare conventional consultations with the physician-invited, patient-completed workflow to quantify its impact on consultation duration, completeness of clinical history, diagnostic accuracy, physician workload, patient satisfaction, and healthcare costs.

Data availability

Data access policies and conditions will be made available upon reasonable request in accordance with privacy, ethical and governance frameworks. Aggregate de-identified participant data will be available, together with the statistical analysis plan and the informed consent forms. The data will be available with publication by writing to gnssrg@unife.it. A signed data access agreement will be required.

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Author contributions

Conceptualisation: SG, YWC, DA. Data curation: SG, YWC, CA, NC, SCM, KC, CE, EG, DA, EM. Methodology: DA. Project administration: SG, YWC. Software: SG, YWC. Supervision: SG, DA. Validation: SG, DA. Visualisation: SG, YWC, DA. Writing (original draft): SG, MP, DA. Review and editing: SG, YWC, CA, GBS, NC, SCM, KC, SD, CE, EG, RJ, ZL, AL, EAL, EM, MM, GP, MP, LR, AR, RR, SR, IS, DA. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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