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Differences in health-related quality of life in patients with mild and severe chronic venous insufficiency: A systematic review and meta-analysis

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Objective: Chronic venous insufficiency (CVI) has a broad spectrum of clinical expression, ranging from mild to severe cases, which negatively impacts the health-related quality of life (HRQoL). However, the comparison in HRQoL between mild and severe CVI has not yet been systematically discussed, which could assist in the adoption of preventive strategies
Methods: A systematic review and meta-analysis was conducted (protocol register https://osf.io/mr4aj/) following a search of the MEDLINE, CINAHL, Web of Science, LILACS, and Scopus databases, using the terms related to CVI and HRQoL. Observational studies that assessed the HRQoL in individuals with CVI in different degrees of severity were included, without date restriction
Results: We retrieved 4750 titles and abstracts and 9 were included in this review. The HRQoL was worse in patients with severe CVI compared to mild patients at Short-form of Health Survey (SF-36) (mean difference 11.02, 95% CI from 8.62 to 13.43; $p<0.001$), Chronic Venous Insufficiency Quality Of Life Questionnaire (CIVIQ-14) (mean difference 13.07; 95% CI from 11.33 to 14.82; $p<0.001$) and Aberdeen Varicose Veins Questionnaire (mean difference 7.7; 95% CI: -12.82 to -2.58; $p=0.003$), especially in the physical domains. There was no difference in the HRQoL between severe and mild patients at CIVIQ-20 ($p=0.09$)
Conclusion: The HRQoL was worse in the physical domains in patients with severe CVI when compared to mild patients. However, the heterogeneity of the results was high and the data should be interpreted with caution.

Introduction

Chronic venous insufficiency (CVI) is characterized by venous hypertension that may be associated with venous valves incompetence associated with calf pump dysfunction[1,2]. The disease generates great costs for the public health system[3], especially the most severe cases, with venous leg ulcers[4]. Furthermore, the CVI has high prevalence rates, estimated at 25% of the general population[1]. In the clinical course, patients may evolve with venous dilation, edema, pain, atrophie blanche and ulcerations, in more advanced stages[5].

The severity of CVI is usually evaluated by the Clinical class, Etiology, Anatomy, and Pathophysiology (CEAP) classification[6]. The classification encompasses from asymptomatic patients to recurrent or active venous leg ulcers, the most severe clinical form of the disease[7]. These clinical manifestations have progressive evolution, with a tendency to develop ulcerations[8], severe pain[9], itch on the legs[10], in addition to being frequently associated with comor-

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bidities, especially when it affects the older population[11]. All clinical manifestations can lead to social restrictions and daily activities, which can worse their health-related quality of life (HRQoL). A recent systematic review of qualitative studies[13] demonstrated the impact of CVI, specifically in patients with varicose veins, on anxiety, and concern about the negative reaction of others to the appearance of their legs. The authors also demonstrate some reports of patients regarding social restriction, many of them failing to participate in leisure or exercise activities.

The assessment of HRQoL in patients with CVI is complex since the disease has a broad spectrum of clinical expression and many factors can worsen the HRQoL, ranging from aesthetic aspects to the functional limitations due to venous ulcers. The HRQoL, together with the CEAP classification, has been used as a valuable tool to improve decision-making, such as referral to specialized centers[12,13]. However, studies that assessed HRQoL in CVI showed different results. Ortega[14], for example, found better HRQoL results in more severe cases when compared to less severe in some HRQoL domains, while De Jesus[15] found a significant difference between mild and severe stages of the disease. In addition, a recent review suggests that the HRQoL may not reflect the severity of the disease, due to different perceptions of symptoms[16]. Therefore, the difference in the HRQoL of patients with CVI should be discussed, especially the comparison between mild and severe patients. The identification of the possible difference, as well as the most affected domains of HRQoL, can assist in the risk stratification as well as in the adoption of effective therapeutic management. Despite the importance of HRQoL in patients with CVI, it remains unclear whether there is a difference between mild and severe patients, and the present study was addressed to systematically discuss the differences in the HRQoL of these patients.

Materials and methods

Study design

This systematic review aimed to compare the HRQoL between mild and severe CVI. The study was edited following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)[17] and the Cochrane recommendations[18]. The protocol has been prospectively registered on the Open science framework (https://osf.io/mr4aj/, DOI 10.17605/OSF.IO/MR4AJ).

Search strategy and study selection

Search strategies have been conducted on Medical Literature Analysis and Retrieval System Online (MEDLINE), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Science Web, Latin American & Caribbean Health Sciences Literature (LILACS), and Scopus databases. There were no language or date restrictions, until December 2020. Search terms were related to "Venous insufficiency", "Quality of life", "Chronic venous disease", and "Varicose veins". In addition, a hand search was conducted to identify systematic reviews for potentially relevant full texts. After searches, retrieved references were exported to an Endnote® file, and duplicates were removed. Two independent reviewers (WTS and MRA) checked for possible full texts by titles and abstracts. Studies that met our eligibility criteria were included in the review and when there were discrepancies between reviewers, they were resolved by a third reviewer (HSC).

Eligibility criteria

This review included published observational studies, such as cross-sections, cohort, or control case studies, which assessed HRQoL in individuals with CVI of both sexes and any age. Eligibility criteria included studies a) that evaluated patients with CVI; b) that assessed the HRQoL and c) that compared the HRQoL in patients with mild and severe CVI. Exclusion criteria were articles in duplicate and those that did not match the objective of this review. There were no restrictions on the year of publication until June 2020.

Due to the different clinical and pathophysiological findings between CEAP classes zero to 3 and 4 to 6[19], patients were stratified into mild and severe. The HRQoL scores of patients in the CEAP class from zero to 3 were grouped using the Cochrane calculator and defined as patients with mild CVI. The results of patients in CEAP classes 4 to 6 were also grouped and these patients were defined as patients with severe CVI.

Quality of papers

Two independent reviewers (WTS and MRA) assessed the methodological quality of included studies using AXIS (for cross-sectional studies). The AXIS was used to verify the methodological quality and risk of bias. It consists of 20 items, that are related to the quality of reporting, study design, and possible biases[20].

Outcome and data analysis

The primary outcome was the difference in HRQoL scores between patients with mild and severe CVI. All questionnaires that assessed HRQoL were included and this variable was expressed in score. The extracted data were sample characteristics, clinical classification, HRQoL results, and methodological quality.

The software Review Manager 5.4 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used to conduct meta-analyses for the outcome measures, i.e., HRQoL score, reported as the mean difference with 95% confidence interval (CI). Heterogeneity was defined as low, moderate, or high according to I^2 values (25, 50, or 75%, respectively). A forest plot was used to display the results of the meta-analysis. Data analysis was performed using the fixed-effects model when the results showed low heterogeneity ($I^2 \leq 25\%$) and the random-effects model when the results showed moderate or high heterogeneity (I2 >25%).

Results

The electronic search strategy identified 4750 titles and abstracts, of which 150 were duplicates and were excluded. The remaining 1600 were screened, and 97 references were selected as potentially included studies. Of these articles, 9 met our inclusion criteria. Figure 1 outlines the flow of papers through the review.

Characteristics of the studies

The mean methodological quality score was 13.78/20, ranging from 11 to 16 Four questionnaires were used in the included studies, both generic [Short-form Health Survey (SF-36)] and specific for CVI [Chronic Venous Disease Quality of Life Questionnaire (CIVIQ-20, CIVIQ-14) and Aberdeen Varicose Veins Questionnaire (AVVQ)].

The SF-36 is a generic questionnaire that encompasses eight domains: physical functioning, role physical, bodily pain, general health, social functioning, role emotional, vitality, and mental health. The total score ranges from 0 (the most affected) to 100 (without commitment)[21]. The physical component is composed of physical functioning, role physical, bodily pain, general health, and vitality domains. The mental component is composed of social

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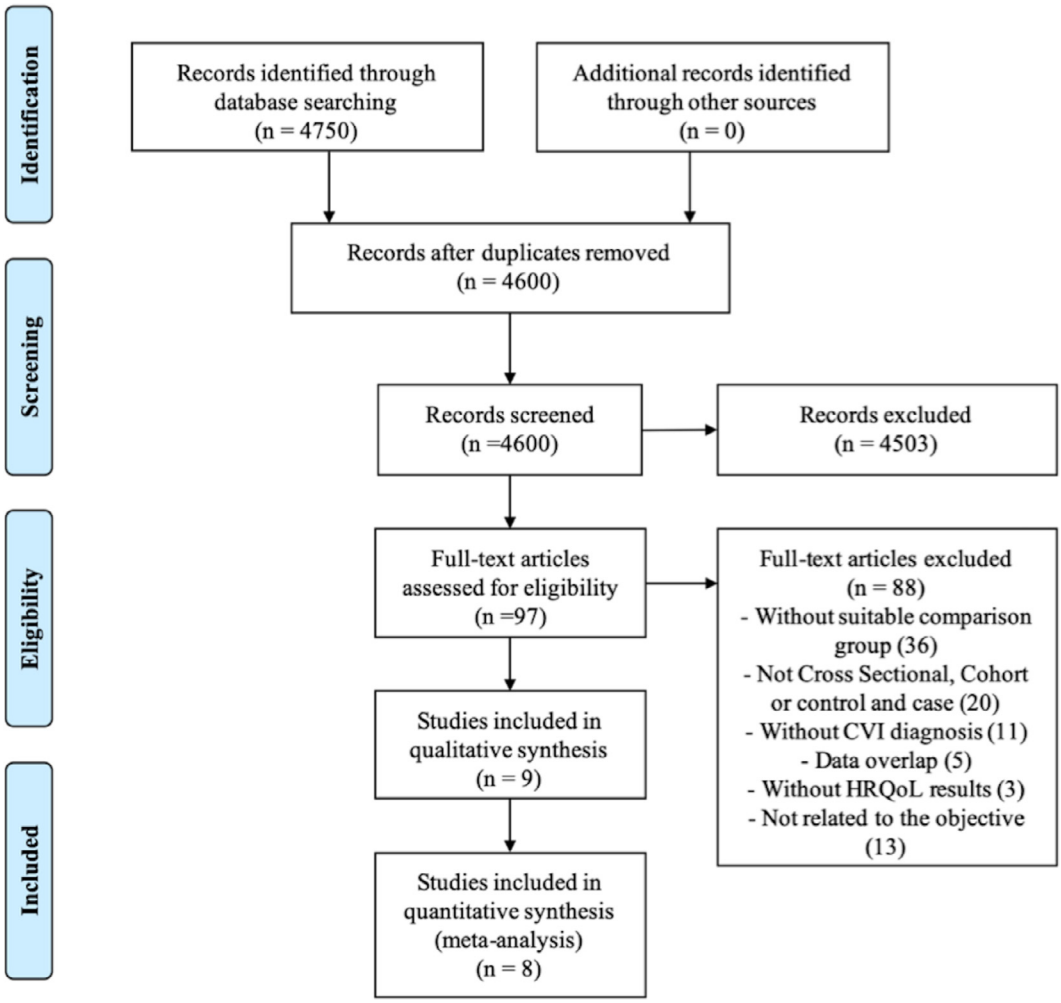

Fig. 1. Flow of studies through the review.

functioning, role emotional, mental health, general health, and vitality.

The Aberdeen Varicose Veins Questionnaire (AVVQ), developed for patients with varicose veins[22], is a specific questionnaire for CVI that includes physical, socio functional, and psychological dimensions. The score ranges from 0 to 100, with higher scores indicating better HRQoL[22]

CIVIQ-20 was created in 1996 by Launois and colleagues[23] and is composed of 20 items and four dimensions, (pain, physical, psychological and social dimensions). The result ranges from zero (better HRQoL) to 100 (worse HRQoL)[23]. The CIVIQ-14, the short version of CIVIQ-20, was created in a multicenter study involving 18 countries conducted by Launois (2012) in an attempt to obtain a more stable questionnaire than CIVIQ-20. It is also a specific questionnaire and consists of 14 items in three dimensions (pain, physical and psychological). The score ranges from 0 (better HRQoL) to 100 (worst HRQoL)[24]. However, to facilitate understanding, the score was reversed (100 - score found = inverted score), thus obtaining a result directly proportional to the HRQoL[25].

HRQoL by SF-36

Four studies that evaluated the HRQoL by the SF-36 were included[26–29], and the mean score for quality was 14/20, ranging from 12 to 15. The mean scores of the SF-36 domains between patients with mild and severe CVI are shown in Table 1.

The forest plot (Figure 2) showed that, in patients with mild CVI (n=2511), the HRQoL was significantly better (mean difference 11.02; 95% CI from 8.62 to 13.43; $p<0.001$) when compared to severe CVI (n=454). In mild CVI, the HRQoL was also significantly better ($p<0.05$) in the domains physical functioning (mean difference 17.93; 95% CI from 7.41 to 28.44), role physical (mean difference 19.68; 95% CI from 7.81 to 31.55), bodily pain (mean difference 11.31; 95% CI from 2.24 to 20.37), general health (mean difference 12.22; 95% CI from 1.87 to 22.56) and vitality (mean difference 10.91; 95% CI from 2.63 to 19.19) when compared to severe CVI. There were no differences in the social functioning, role emotional, and mental health domains. The heterogeneity of the results was high in all analyzes ($I^2>$ 60%). In the analysis of all 8 subgroups together, the HRQoL at SF-36 was 11.02 (95% CI 8.62 to 13.43) points lower in patients with severe CVI when compared to mild ones ($p<0.001$).

HRQoL by CIVIQ-20

Two studies assessed the HRQoL by CIVIQ-20[14,30]. The score for quality was 15/20, ranging from 14 to 16. The mean scores of the CIVIQ-20 between patients with mild and severe CVI are shown in

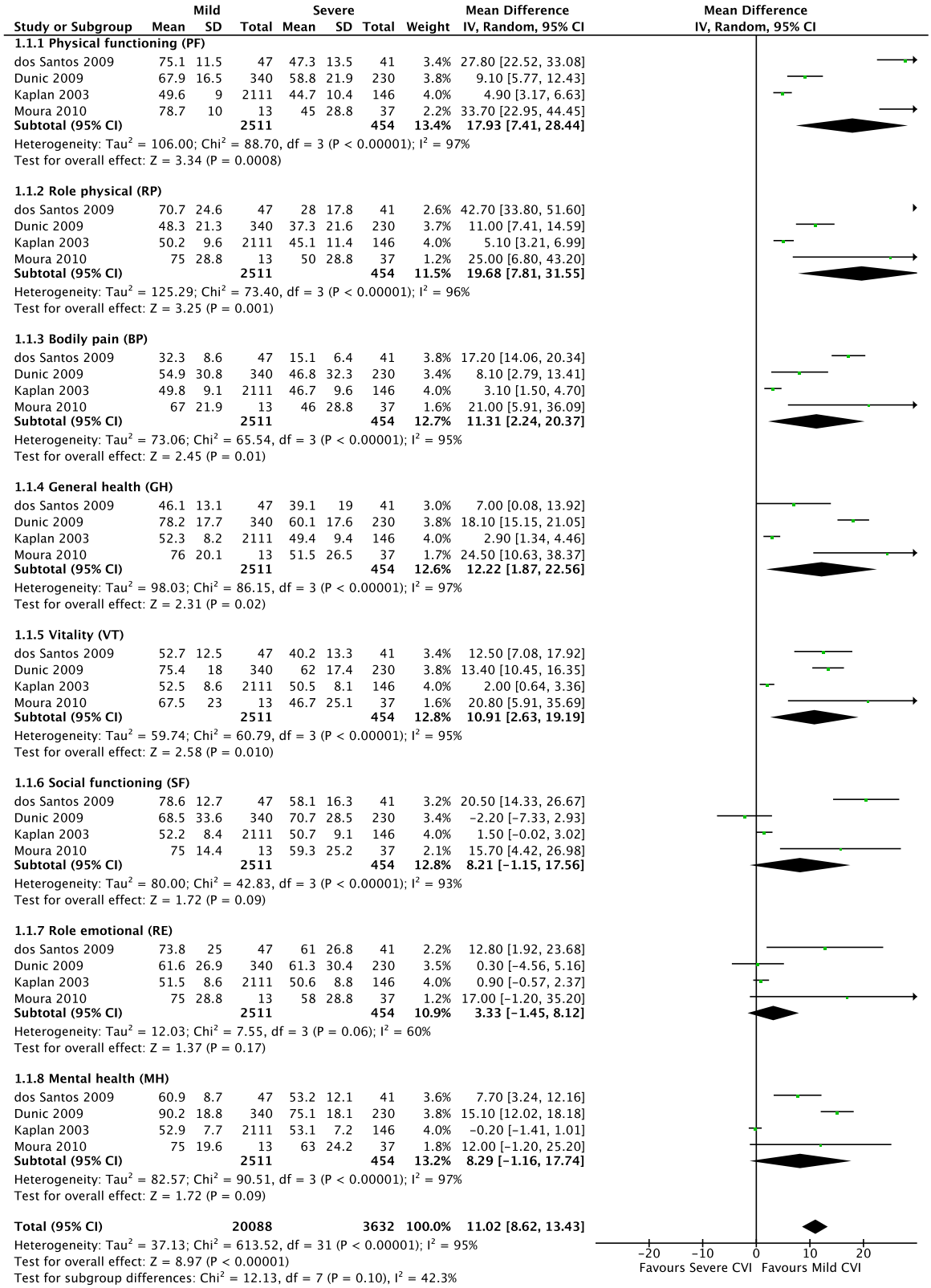

Fig. 2. Mean difference in HRQoL between patients with mild disease and severe CVI. SD: standard deviation; 95% CI: 95% confidence interval.

Table 1
Results of HRQoL by SF-36.

Study	Population		Score of SF-36	Score for quality							
		Clinical classification	PF	RP	BP	GH	VT	SF	RE	MH	
Dos Santos et al. (2009)	n=88; 30 to 70 years, 87.5% females	Mild n=47	75.1 (11.5)	70.7 (24.6)	32.3 (8.6)	46.1 (13.1)	52.7 (12.5)	78.6 (12.7)	73.8 (25.0)	60.9 (8.7)	15/20
		Severe n=41	47.3 (13.5)	28.0 (17.8)	15.1 (6.4)	39.1 (19.0)	40.2 (13.3)	58.1 (16.3)	61.0 (26.8)	53.2 (12.1)	
Dunić et al. (2009)	n=570; 61±13.7 years; 80% females	Mild n=340	67.9 (16.5)	48.3 (21.3)	54.9 (30.8)	78.2 (17.7)	75.4 (18.0)	68.5 (33.6)	61.6 (26.9)	90.2 (18.8)	15/20
		Severe n=230	58.8 (21.9)	37.3 (21.6)	46.8 (32.3)	60.1 (17.6)	62.0 (17.4)	70.7 (28.5)	61.3 (30.4)	75.1 (18.1)	
Kaplan et al. (2003)	n=2404; 65.7% females	Mild n=2111	49.6 (9.0)	50.2 (9.6)	49.8 (9.1)	52.3 (8.2)	52.5 (8.6)	52.2 (8.4)	51.5 (8.6)	52.9 (7.7)	12/20
		Severe n=146	44.7 (10.4)	45.1 (11.4)	46.7 (9.6)	49.4 (9.4)	50.5 (8.1)	50.7 (9.1)	50.6 (8.8)	53.1 (7.2)	
Moura et al. (2010)	n=50; 52.4 years; 74% females	Mild n= 13	78.7 (10)	75 (28.8)	67 (21.9)	76 (20.1)	67.5 (23)	75 (14.4)	75 (28.8)	75 (19.6)	14/20
		Severe n= 37	45 (26.6)	50 (28.8)	46 (28.8)	51.5 (26.5)	46.7 (25.1)	59.3 (25.2)	58 (28.8)	63 (24.2)	

Data presented as mean (standard-deviation). Abbreviations: Abbreviations: PF =Physical Functioning; RP =Role Physical; BP= Bodily Pain; GH = General Health; SF= Social Functioning; RE= Role-Emotional; VT= Vitality; MH= Mental Health

Table 2
Results of HRQoL by CIVQ-20.

Study	Population	Clinical classification	Score of CIVIQ-20 Total Score	Score for quality
Branisteanu et al. (2019)	n= 1893; 79.08% females	Mild n=1635	72.6 (17.3)	14/20
		Severe n=258	50.2 (19.0)	
Ortega-Santana et al. (2014)	n=468; 44.3±11.2 years; 71.2% females	Mild n=420	46.9 (23.6)	16/20
		Severe n=48	41.4 (22.5)	

Data presented as mean (standard-deviation).

Table 3
Results of HRQoL by CIVQ-14.

Study	Population		Score of CIVIQ-14				Score for quality
		Clinical classification	Pain	Physical	Psychological	Total Score	
Radak et al. (2013)	n= 2260; 57.4±12.9 years; 72.5% females	Mild n=1860	59.3 (16.9)	60.7 (22.9)	78.0 (9.6)	67.8 (17.1)	14/20
		Severe n=400	50.6 (17.0)	45.6 (23.0)	64.3 (20.0)	54.7 (17.3)	
Sinožić et al. (2017)	n=428; 54±21.3 years;78% females.	Mild n=367	68.5 (20.9)	74.5 (19.7)	80.0 (15.3)	77.9 (15.9)	11/20
		Severe n=61	52.0 (26.5)	62.7 (21.6)	77.0 (14.4)	65.0 (18.4)	

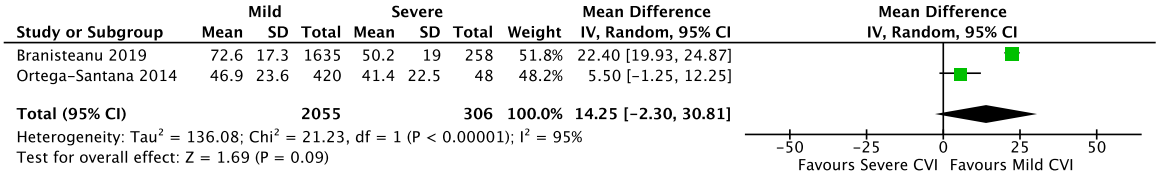

Fig. 3. Mean difference in HRQoL between patients with mild disease and severe CVI by CIVIQ-20. SD: standard deviation; 95% CI: 95% confidence interval.

Table 2. The forest-plot (Figure 3) showed no significant difference (p = 0.09) in HRQoL between patients with mild CVI (n = 2055) and severe (n = 306), with mean difference 14.25 (95% CI from -2.30 to 30.81).The heterogeneity of the results was high (I^2 = 95%).

HRQoL by CIVIQ-14

Two studies that evaluated the HRQoL by CIVIQ-14 were included[31,32]. The mean score for quality was 12.5/20 and values were demonstrated in Table 3. The forest plot (Figure 4) showed that, in patients with mild CVI (n=2227), the HRQoL was significantly better (p<0.001) in the domains physical (mean difference 14.59; 95% CI from 12.31 to 16.87) and pain (mean difference 11.84; 95% CI from 4.34 to 19.34), as well as in total score (mean difference 13.07; 95% CI from 11.33 to 14.82) when compared to severe CVI (n=461). There was no difference (p=0.11) in the psychological domain between groups with mild and severe CVI. The heterogeneity of the results was low in the total score and physical domain (I^2 <25%) and high in the pain and psychological domains (I^2> 75%).

HRQoL by AVVQ

Only one study (n=107, 50.1±14.7 years, 87.9% females)[15], with a mean score for quality of 13/20, used the AVVQ to assess the HRQoL. The mean total score in mild CVI was significantly higher (p=0.003) when compared to severe CVI (35.8±16.3 versus 28.1±10.6), with a mean difference of 7.7 (95% CI: -12.82 to -2.58).

Discussion

To the best of our knowledge, this was the first review that systematically discusses the differences in the HRQoL of patients with

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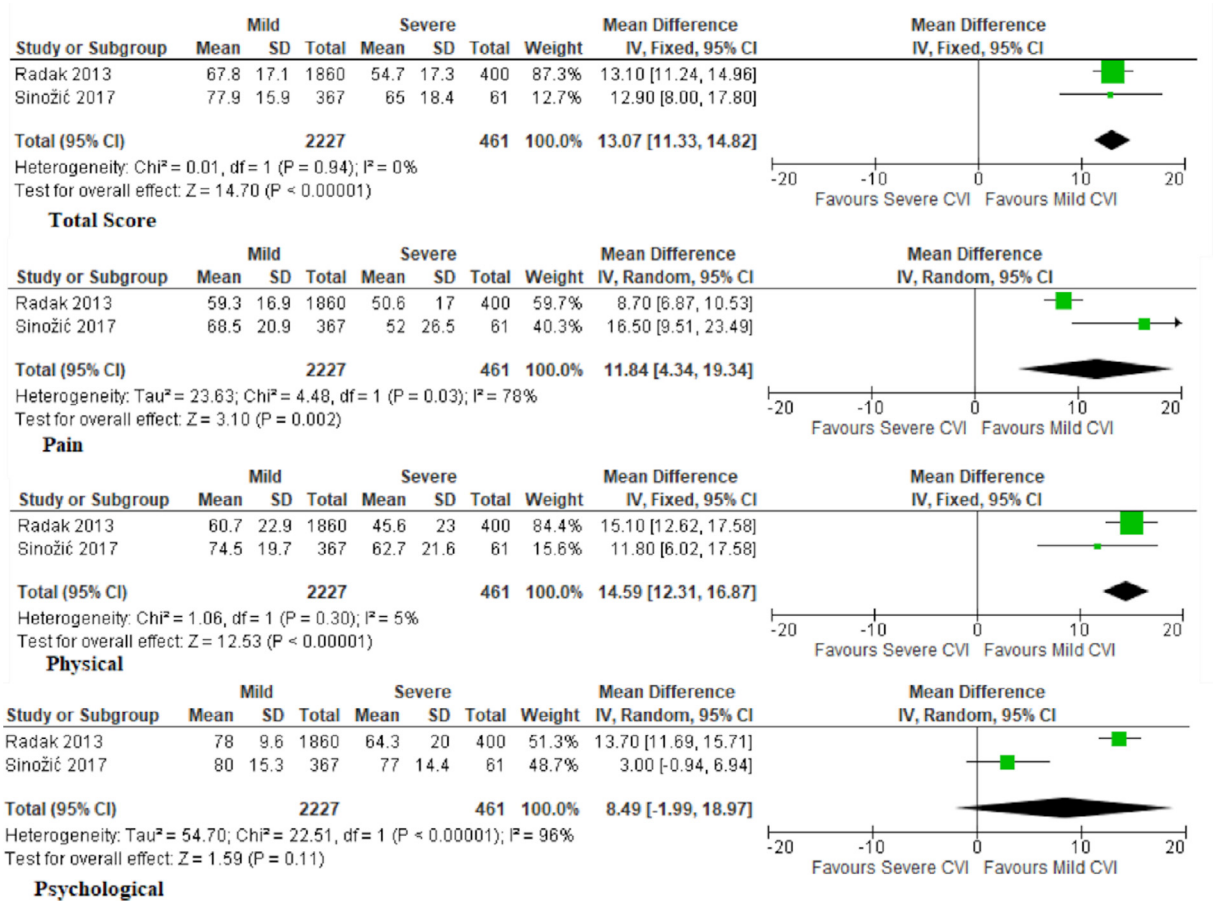

Fig. 4. Mean difference in HRQoL between patients with mild disease and severe CVI by CIVIQ-14. SD: standard deviation; 95% CI: 95% confidence interval.

mild and severe CVI. The main findings of the present study were that: 1) the HRQoL assessed by the SF-36 was worse in patients with severe compared to mild CVI, especially in physical domains, 2) the HRQoL was worse in severe compared to mild CVI in CIVIQ-14 and AVVQ and 3) there was no difference between mild and severe CVI when HRQoL was assessed by CIVIQ-20. Thus, early intervention based on physical exercise and compression stockings is desirable and should be directed to patients with CVI even in the early stages of the disease. Although the possible impairment of the mental component in the more advanced stages of the disease is well discussed, the aesthetic constraint leading to a lack of interest in participating in leisure activities that expose compromised veins[33]. However, the results of the present study demonstrated that physical impairment is the one that most affects the HRQoL of severe patients.

At SF-36, the only generic questionnaire used in the included studies, patients with mild CVI have a score of 11.02 points higher than severe patients. All domains of the physical component of SF-36, i. e., physical functioning, role physical, bodily pain, general health, and vitality, were reduced in patients with severe CVI compared to mild patients. The physical and functional abnormalities are commonly found in patients in more advanced stages of CVI. Previous studies have shown that muscle strength of plantar[34] and dorsiflexors[34,35] was reduced in CVI patients when compared to healthy individuals. A reduction in ankle range of motion was also verified with disease progression[36], mainly due to swelling. Together, edema, reduced muscle strength, and limited ankle range of motion can lead to functional impairment. Physical abnormalities related to gait and balance have also been previously demonstrated[37]. Finally, the pain domain, also related to the physical component, was significantly lower in the group with severe CVI. Pain is identified as one of the most frequent complications in the advanced stages of CVI and, unlike the initial stages, it can be constant and not induced only by orthostatism[38]. In addition, pain can lead to physical inactivity and, subsequently, reduce the effectiveness of the calf pump function and increase the severity of the disease. Therefore, the present study demonstrated the potential impact of severe CVI on the physical aspects of HRQoL when compared to mild patients. However, the heterogeneity of the results was high and they should be interpreted with caution.

On the other hand, mental aspects do not seem to be different between patients with mild and severe CVI at SF-36. Previous studies have already reported the presence of social isolation and depression in patients with CVI[33,39], but two points must be taken into account. Firstly, the heterogeneity of the results was high. Secondly, the SF-36, a generic questionnaire, does not include the specific characteristics of the disease in the HRQoL, such as the shame of exposing the affected regions[40]. This limitation has already been described in other conditions, such as chronic kidney disease[41]. Thus, the impact of CVI on mental aspects of HRQoL remains uncertain, since our findings are not conclusive.

The specific questionnaires for CVI, the CIVIQ-20, CIVIQ-14, and AVVQ were also included in the present study. The only questionnaire that did not find differences in the HRQoL of patients with mild and severe disease was the CIVIQ-20. The results showed a trend towards better HRQoL in patients with mild CVI ($p = 0.09$) at CIVIQ-20, but that difference was not significant. Two hypotheses

can partially explain these results. Firstly, the meta-analysis was composed of only two studies and with high heterogeneity. Secondly, the two included studies found controversial results. While one study[30] showed worsening HRQoL with disease progression, the study Ortega-Santana et al.[14] found similar values between patients with mild and severe CVI. According to the authors, these values can be justified by the progressive adaptation and acceptance of patients in more severe forms of the disease. However, further studies are needed to verify the hypothesis. In contrast, in the CIVIQ-14, the HRQoL of patients with severe CVI was significantly worse when compared to mild ones, with very low heterogeneity. Additionally, there was a significant difference in the physical function and pain domains, with no difference in the psychological function domain. These results are similar to those found in SF-36, demonstrating a reduction in physical aspects and pain compared to psychological and mental aspects.

Regarding AVVQ questionnaire, the HRQoL is also worse in critically ill patients when compared to patients with mild CVI. However, only one study that used such a questionnaire was included. Although all questionnaires have presented, at least, a trend of worse HRQoL in patients with severe CVI, we also emphasize the challenge of finding a questionnaire to HRQoL that addresses the broad spectrum of clinical expression of the disease. A review[42] has shown that, of the available CVI-specific questionnaires, none was suited to assess the whole spectrum of venous disease.

These results demonstrate the impact of the CVI progression on HRQoL, mainly in the physical aspect. In the clinical setting, we highlighted the importance of early physical intervention in patients in the mild stages of the disease. Despite the aesthetic complaint, many patients may experience a reduction in lower limbs strength[35], ankle range of motion[43], and balance[37]. Therefore, the treatment should be directed to the physical components to avoid worsening HRQoL and complications related to the disease. As perspectives, once the impact of CVI on the physical aspects of patients was demonstrated in the present review, we highlight the need for clinical trials to verify the impact of physical therapy on the HRQoL of these patients. Furthermore, due to the different results found in some questionnaires, we also reinforce the need for studies that investigate the psychometric properties of HRQoL questionnaires, to guide the choice of an adequate and potentially useful instrument in patients with CVI.

The present study has strengths and limitations. Among the limitations, potential biases regarding electronic search and methodological quality of the included studies should be discussed. The mean score for methodological quality ranged from 11 to 16, out of a total of 20. The main reasons for lower scores were: 1) not discussing the limitations of the study; 2) not reporting or presenting a conflict of interest 3) not justifying the sample size; 4) lack of information on the strategy, frequency, and characterization of the cases of non-responders. In the present review, there was high heterogeneity among the included studies. However, the results should be considered, since this is a common bias in studies involving the HRQoL of patients with CVI, especially due to the broad spectrum of clinical expression of the disease, as discussed by previous studies[40,42]. As a strength, the present study systematically discussed, for the first time, the impact of CVI progression on the HRQoL.

Conclusion

This systematic review showed that the HRQoL tends to decrease according to the progression of CVI, mainly in physical aspects. However, the results were heterogeneous and there is a need to discuss the applicability of the available questionnaires.

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References

1. Rabe E, Berboth G, Pannier F. Epidemiology of chronic venous diseases. *Wien Med Wochenschr*. 2016;166:260–263.
2. Santler B, Goerge T. Chronic venous insufficiency - a review of pathophysiology, diagnosis, and treatment. *J Dtsch Dermatol Ges*. 2017;15:538–556.
3. Carlton R, Mallick R, Campbell C, Raju A, O'Donnell T, Eaddy M. Evaluating the expected costs and budget impact of interventional therapies for the treatment of chronic venous disease. *Am Health Drug Benefits*. 2015;8:366.
4. Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons N. Burden of venous leg ulcers in the United States. *J Med Econ*. 2014;17:347–356.
5. Eberhardt RT, Raffetto JD. Chronic venous insufficiency. *Circulation*. 2014;130:333–346.
6. Lurie F, Passman M, Meisner M, Dalsing M, Masuda E, Welch H, et al. The 2020 update of the CEAP classification system and reporting standards. *J Vasc Surg Venous Lymphat Disord*. 2020;8:342–352.
7. Kelechi TJ, Johnson JJ, Yates S. Chronic venous disease and venous leg ulcers: An evidence-based update. *J Vasc Nurs*. 2015;33:36–46.
8. Lee AJ, Robertson LA, Boghossian SM, Allan PL, Ruckley CV, Fowkes FG, et al. Progression of varicose veins and chronic venous insufficiency in the general population in the Edinburgh Vein Study. *J Vasc Surg Venous Lymphat Disord*. 2015;3:18–26.
9. Radak DJ, Tanaskovic SZ, Vlajinac HD, Marinkovic JM, Maksimovic MZ. Relationship Between Pain and CEAP C Categories of Chronic Venous Disease. *Angiology*. 2016;67:670–675.
10. Paul JC, Pieper B, Templin TN. Itch: association with chronic venous disease, pain, and quality of life. *J Wound Ostomy Continence Nurs*. 2011;38:46–54.
11. Fokou M, Moifo B, Fongang E, Teyang A, Muna W. Characteristics of patients and patterns of chronic venous disease of the lower limbs in a referral hospital in Cameroon. *J Vasc Surg Venous Lymphat Disord*. 2018;6:90–95.
12. National Clinical Guideline Centre (UK). Varicose Veins in the Legs: The Diagnosis and Management of Varicose Veins. London: National Institute for Health and Care Excellence (UK); 2013.
13. Lane T, Sritharan K, Herbert J, Franklin I, Davies A. Management of chronic venous disease by primary care. *Phlebology*. 2013;28:299–304.
14. Ortega-Santana F, Limiñana J, Ruano F, Ortega-Centol A, Palomino-Martín A, Jiménez F. The influence of the CIVIQ dimensions on quality of life of patients with primary superficial venous incompetence. *Eur J Vasc Endovasc Surg*. 2014;48:452–458.
15. FdJ Leal, Couto RC, Pitta GBB. Validação no Brasil de questionário de qualidade de vida na doença venosa crônica (Questionário Aberdeen para veias varicosas no Brasil/AVVQ-Brasil). *J Vasc Bras*. 2015;14:241–247.
16. Onida S, Davies AH. Varicose veins: diagnosis and management. *Nurs Times*. 2013;109:16–17.
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
18. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*. 2019;10 Ed000142.
19. Labropoulos N. How Does Chronic Venous Disease Progress from the First Symptoms to the Advanced Stages? A Review. *Adv Ther*. 2019;36:13–19.
20. Downes MJ, Brennan ML, Williams HC, Dean RS. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). *BMJ Open*. 2016;6.
21. Ware J, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. *sf-36v2 health survey: Administration guide for clinical trial Investigators*. Lincoln, RI: QualityMetric Incorporated; 2008:1–34.
22. Garratt A, Ruta D, Abdalla M, Russell I. Responsiveness of the SF-36 and a condition-specific measure of health for patients with varicose veins. *Qual Life Res*. 1996;5:223–234.
23. Launois R, Reboul-Marty J, Henry B. Construction and validation of a quality of life questionnaire in chronic lower limb venous insufficiency (CIVIQ). *Qual Life Res*. 1996;5:539–554.
24. Launois R, Le Moine J, Lozano F, Mansilha A. Construction and international validation of CIVIQ-14 (a short form of CIVIQ-20), a new questionnaire with a stable factorial structure. *Qual Life Res*. 2012;21:1051–1058.
25. Launois R. CIVIQ users' guide. https://www.civiq-20.com (accessed 10 March 2021). 2021
26. RFFNd Santos, Porfírio GJM, Pitta GBB. A diferença na qualidade de vida de pacientes com doença venosa crônica leve e grave. *J Vasc Bras*. 2009;8:143–147.
27. Dunić I, Medenica L, Bobić B. Djurković-Djaković O. Patients' reported quality of life in chronic venous disease in an outpatient service in Belgrade, Serbia. *Eur J Dermatol*. 2009;19:616–620.

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28. Kaplan RM, Criqui MH, Denenberg JO, Bergan J, Fronek A. Quality of life in patients with chronic venous disease: San Diego population study. *J Vasc Surg*. 2003;37:1047–1053.
29. Moura R, Goncalves GS, Navarro TP, Britto RR, Dias RC. Relationship between quality of life and the CEAP clinical classification in chronic venous disease. *Braz J Phys Ther*. 2010;14:99.
30. Branisteanu D-E, Feodor T, Baila S, Mitea I-A, Vittos O. Impact of chronic venous disease on quality of life: Results of vein alarm study. *Exp Ther Med*. 2019;17:1091–1096.
31. Radak DJ, Vlajinac HD, Marinković JM, Maksimović M, Maksimović ZV. Quality of life in chronic venous disease patients measured by short Chronic Venous Disease Quality of Life Questionnaire (CIVIQ-14) in Serbia. *J Vasc Surg*. 2013;58:1006–1013.
32. Sinožić T, Baždarić K, Šverko D, Ružić A, Katić M. Validation of the Croatian version of CIVIQ quality of life questionnaire in patients with chronic venous disorders. *Croat Med J*. 2017;58:292–299.
33. Lumley E, Phillips P, Aber A, Buckley-Woods H, Jones GL, Michaels JA. Experiences of living with varicose veins: a systematic review of qualitative research. *J Clin Nurs*. 2019;28:1085–1099.
34. Cetin C, Serbest MO, Ercan S, Yavuz T, Erdogan A. An evaluation of the lower extremity muscle strength of patients with chronic venous insufficiency. *Phlebology*. 2016;31:203–208.
35. Ercan S, Cetin C, Yavuz T, Demir HM, Atalay YB. Evaluation of the Isokinetic Calf Muscle Strength and the Range of Motion of Joint in C3 Chronic Venous Insufficiency. *Vasc Specialist Int*. 2019;35:95–100.
36. Bertochi T, Gomes RZ, Martins M. Ankle joint mobility as a predictor of treatment prognosis in patients with chronic venous insufficiency with venous ulcers. *J Vasc Bras*. 2019;18.
37. van Uden CJ, van der Vleuten CJ, Kooloos JG, Haenen J, Wollersheim H. Gait and calf muscle endurance in patients with chronic venous insufficiency. *Clin Rehabil*. 2005;19:339–344.
38. Barron GS, Jacob SE, Kirsner RS. Dermatologic complications of chronic venous disease: medical management and beyond. *Ann Vasc Surg*. 2007;21:652–662.
39. ACdSA Aguiar, D Sadigursky, Martins LA, TMdO Menezes, ALdS Santos, LAd Reis. Social repercussions experienced by elderly with venous ulcer. *Rev Gaucha Enferm*. 2016:37.
40. Zenati N, Bosson J, Blaise S, Carpentier P. Évaluation de la qualité de vie liée à l'insuffisance veineuse chronique (IVC). Revue systématique de la littérature. *J Med Vasc*. 2017;42:290–300.
41. Erez G, Selman L, Murtagh FE. Measuring health-related quality of life in patients with conservatively managed stage 5 chronic kidney disease: limitations of the Medical Outcomes Study Short Form 36: SF-36. *Qual Life Res*. 2016;25:2799–2809.
42. Catarinella FS, Nieman FH, Wittens CH. An overview of the most commonly used venous quality of life and clinical outcome measurements. *J Vasc Surg Venous Lymphat Disord*. 2015;3:333–340.
43. de Moura RM, Gomes Hde A, da Silva SL, Britto RR, Dias RC. Analysis of the physical and functional parameters of older adults with chronic venous disease. *Arch Gerontol Geriatr*. 2012;55:696–701.

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