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REVIEW ARTICLE

Assessment of cardiovascular risk factors in patients with idiopathic inflammatory myopathies: a systematic review

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Abstract

We performed a systematic review of cardiovascular risk factors in idiopathic inflammatory myopathies (IIMs) and their cardiovascular outcomes, including acute coronary syndrome and stroke. A qualitative systematic review was conducted from January 1956 to December 2022 according to the PRISMA protocol using three electronic databases: PubMed, Web of Science, and Scopus. The studies were analyzed based on the following eligibility criteria: at least one combination of the terms described in the search strategy appeared in the title, written in English, Portuguese, or Spanish, and addressed risk factors for cardiovascular diseases in IIMs. Brief reports, reviews, papers addressing juvenile IIMs, congress proceedings, monographs, and dissertations were excluded. Twenty articles were included. According to the literature, most patients with IIMs are middle-aged North American or Asian women, with dyslipidemia and hypertension. The prevalence of the cardiovascular risk factors was generally low in IIMs, but with a high incidence of acute myocardial infarction. Further theoretical and prospective studies are needed to define the actual impact of each variable (e.g., hypertension, diabetes, smoking, alcoholism, obesity, and dyslipidemia) on the cardiovascular risk of patients with IIMs.

Keywords Cardiovascular risk · Dermatomyositis · Idiopathic inflammatory myositis · Myositis · Polymyositis

Introduction

Systemic autoimmune myopathies or idiopathic inflammatory myopathies (IIMs) are chronic autoimmune diseases characterized by wide multiorgan involvement in the skin, articular, cardiovascular, respiratory, and gastrointestinal systems. The most common diseases in this group are dermatomyositis (DM), polymyositis (PM), anti-synthetase syndrome (ASSD), inclusion body myositis (IBM), and immune-mediated necrotizing myopathies (IMNM) [1–3].

Cardiovascular risk in patients with systemic autoimmune diseases is higher than that in the general population [4, 5]. However, the literature on the metabolic pathways responsible for this characterization is still scarce, especially with respect to diseases, such as IIMs [6–10], unlike other diffuse connective tissue diseases, such as systemic lupus erythematosus and rheumatoid arthritis [11].

This reality is of concern, as the literature indicates a high incidence of cardiovascular involvement in IIMs, ranging from 9 to 72% [8]. A recent British cohort showed mortality rates among patients with PM and DM to be three times higher than those in the control group [6]. Population-based studies in Taiwan [9], Scandinavia [12], and Sweden [13] showed mortality rates 1.5—7.7 times higher than those in the control group, with cardiovascular causes being one of the three main causes. Risk factors such as hypertension, diabetes mellitus, dyslipidemia, and smoking appear to be more prevalent in this population [7, 13, 14].

Therefore, this study aimed to conduct a systematic review of the incidence of cardiovascular risk factors in IIMs and their cardiovascular outcomes, such as acute coronary syndrome and stroke. We hypothesized that the inflammatory process associated with the predilection of the immune response against the muscles, which is intrinsic to IIMs, might lead to a higher cardiovascular risk in this group.

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Method

Literature review We performed a qualitative systematic literature review according to the PRISMA protocol (http://www.prisma-statement.org/) using three electronic databases in the following order: PubMed, Web of Science, and Scopus. The electronic searches used variants of the following research MeSH (Medical Subject Headings) terms with a syntax adjusted to each database: "Metabolic syndrome"; "dyslipidemia"; "Obesity"; "systemic arterial hypertension"; "Hypertension; "diabetes mellitus"; "Tobacco Use"; "Alcoholism"; "Sedentary Behavior"; "Heart Disease Risk Factors"; "Myocardial infarction"; "Stroke" with each of the following MeSH terms referring to autoimmune inflammatory myopathies: "myositis"; "systemic autoimmune myopathies"; "idiopathic inflammatory myopathies"; "Dermatomyositis"; "Polymyositis"; "anti-synthetase syndrome"; "anti-synthetase syndrome"; "immune mediated necrotizing myopathies"; "necrotizing myopathies"; "inclusion body myositis"; "amyopathic dermatomyositis"; "hypomyopathic dermatomyositis"; "clinically amyopathic dermatomyositis".

The study question was developed using PICO acronyms. "P" refers to patients with IIMs; "I" is the risk factor for cardiovascular diseases according to the American Heart Association [15]; "C" is the group compared with the normal population, and "O" is the outcome regarding prognosis.

Data collection Data collection was performed at two timepoints: September 20, 2022, and January 10, 2023. A literature search was conducted between January 1956 and December 2022. Manuscripts were selected primarily through the analysis of their titles and abstracts. Two researchers collected data individually to ensure the trustworthiness of the findings, and divergences were addressed by a third senior researcher. Each sample article was read thoroughly and the information was inserted into a spreadsheet (Table 1), including the author, publication year, study type, country, age (median in years), sex, subtype of IIM, main findings (alcohol consumption, tobacco use, abdominal circumference, body mass index, hypertension, diabetes mellitus, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride (TG), fasting blood glucose, acute coronary syndrome, brain stroke), and quality of the studies.

For each of these variables, we calculated the number of patients with alterations found, as well as the percentages compared to the total number of patients.

To analyze the quality of each study (Table 1), and based on the convenience of the present study, tools were used, including the Study Quality Assessment Tool (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools), of the National Heart, Lung, and Blood Institute. The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used for the cohort and observational studies. These tools classify studies as "Good," "Fair", or "Poor", based on the presence or absence of relevant methodological elements for each type of study.

Eligibility criteria Papers were analyzed based on the following eligibility criteria: at least one combination of the terms described in the search strategy appeared in the title, written in English, Portuguese, or Spanish, and addressed cardiovascular risk in IIMs. Reviews, monographs, dissertations, brief reports, congress proceedings, and studies on juvenile DM were excluded.

Manuscripts listed in more than one database were counted only once. Cardiovascular risk in articles about IIMs was excluded if they addressed other neuromuscular diseases.

Ethical issue Considering that this is a systematic literature review, Resolution 510/16 of the Brazilian National Health Council (CNS, acronym in Portuguese) dismisses the approval by a Human Research Ethics Committee. This review was registered on the PROSPERO platform under number CRD42022381508.

Results

Of the 3,501 articles found, 251 were repeated and 20 met the eligibility criteria (Fig. 1). In the analyzed sample, at least ten were cross-sectional [4–8, 14, 16–18]; seven were cohorts [7, 11, 13, 19–22], and the others were case-controls [23–25]. Regarding location, most articles were from patients in Europe (35%), North America (25%), and Asia (25%), and a minority were from South America (15%) (Table 1).

For heuristic reasons, we divided the results as follows: "cardiovascular risk factors in IIMs" and "acute coronary syndrome and stroke in patients with IIMs."

As shown in Table 1, out of the 18,974 patients in the analyzed sample, 14,292 patients had DM (75.3%), 1,722 patients had PM (9.0%), and 50 patients had ASSD (0.26%). Females were the most common, with 13,796 (96.5%) patients between their fifth and seventh decades of life. The country with the largest sample was the US with 5,145 patients [16, 18, 21], followed by Taiwan with 2,913 patients [20, 23, 24].

Regarding the risk factors for cardiovascular events, the participants had hypertension (1,742 cases, 9.2%), diabetes mellitus (835 cases, 4.4%), smoking (925 cases, 4.8%), and alcoholism (577 cases, 3.0%).

Table 1 Risk factor for cardiovascular diseases in patients with idiopathic inflammatory myopathies and qualitative assessment

Quality assessment	Authors (year) Study design, Country	No. of patients	Mean age (years)	Female (n%)	Alcohol consumption	Smoking	Abdominal circumference	Body mass index (kg/m^2)	Hypertension	Diabetes mellitus	LDL, HDL TG (mg/dL)	Glucose (mg/dL)	Acute coronary syndrome	Stroke
Good	Orescka et al. (2022) Cross-sectional, Czechia [5]	16 DM 7 PM 8 ASSD 7 IMNM	39	32 (82)	3	0	NA	25.9 (23.2–31.1)	18	6	NA	NA	NA	NA
Good	Zhou et al. (2022) Cross-sectional, China [8]	12 DM	46	6 (50)	NA	3	NA	21.9 (20.1–25.3)	2	2	NA	NA	6	NA
Good	D'Silva et al. (2021) Cohort, United Kingdom [7]	410 DM 407 PM	58	516 (61.3)	567	518	NA	27 (26–28)	260	67	NA	NA	93	17
Good	Párraga-Pietro et al. (2021) Cross-sectional, United Kingdom [4]	603 IIMs	58	386 (64)	NA	154	NA	NA	253	132	NA	NA	82	NA
Fair	Bae et al. (2020) Cross-sectional, US [18]	23 DM 2 PM, 2 IBM	53	14 (60.8)	0	4	NA	NA	10	06	114–117 55–62 157–186	NA	7	2
Good	Moshtaghi-Svensson et al. (2019) Cross-sectional, Sweden [14]	219 DM 444 other IIMs	61	369 (56)	NA	NA	NA	NA	98	35	NA	NA	25	34
Good	Leclair et al. (2019) Cohort, Sweden [13]	218 DM 437 other IIMs	60	367 (56)	NA	NA	NA	NA	88	28	NA	NA	20	15
Good	Weng et al. (2019) Cohort, Taiwan [23]	640 DM 505 PM	51	826 (72.1)	NA	NA	NA	NA	264	125	NA	NA	294	NA
Fair	Araujo et al. (2018) Cross-sectional, Brazil [19]	42 ASSD	41	33 (78)	NA	9	90 (80–102)	24.8 (23.4–29.4)	11	5	121 (92–144) 51 (37–65) 136 (80–221)	85 (76–99)	2	0
Good	Schiffenbauer et al. (2018) Cross-sectional, US [16]	267 PM 198 other IIMs	46	330 (71)	NA	180	NA	NA	NA	NA	NA	NA	NA	NA
Good	Guerra et al. (2017) Case–control, Italy [26]	28 IIMs	66	22 (78.6)	NA	2	NA	26.4 ± 4.2	12	2	NA	NA	NA	NA
Fair	Silva et al. (2016) Cross sectional, Brazil [10]	35 DM	33.3	35 (100)	0	0	26	24.2 ± 3.5	3	1	175.2 ± 36.8 103.2 ± 32.1 48 (42–63)	81 (76–89)	0	0
Good	Rai et al. (2016) Case–control, Canada [25]	424 PM 350 DM	58	477 (61.6)	NA	NA	NA	NA	NA	90	NA	NA	60	20

Table 1 (continued)

Quality assessment	Authors (year) Study design, Country	No. of patients	Mean age (years)	Female (n%)	Alcohol consumption	Smoking	Abdominal circumference	Body mass index (kg/m^2)	Hypertension	Diabetes mellitus	LDL, HDL TG (mg/dL)	Glucose (mg/dL)	Acute coronary syndrome	Stroke
Good	Diederichsen et al. (2015) Cross-sectional, Denmark [17]	52 PM 24 DM	60	49 (64)	NA	40	NA	30	54	10	NA	NA	NA	NA
Good	Lin et al. (2015) Cohort, Taiwan [22]	2,029 DM/PM	49	1,376 (67.8)	NA	NA	NA	NA	256	121	NA	NA	NA	43
Fair	Wang et al. (2014) Case–Control, China [24]	60 PM	42.9	44 (73.3)	5	6	NA	NA	NA	NA	72.9 ± 30.94 42.3 ± 0.69 16.74 ± 0.27 34.01 ± 0.8	NA	NA	NA
Fair	De Moraes et al. (2013) Cross-sectional, Brazil [6]	84 DM	41.5	67 (79.8)	2	9	97.5 (88–106)	27.5 (24–32.2)	15	NA	181 (160–232) 88 (108–135.5) 49 (40–61.5)	84 (77–98)	2	4
Good	Lai et al. (2013) Cohort, Taiwan [20]	1,488 DM	57	1.001 (67.3)	NA	NA	NA	NA	320	171	NA	NA	260	46
Good	Linos et al. (2013) Cohort, US [21]	10,156 DM	58	7,413 (72.3)	NA	NA	NA	NA	NA	NA	NA	NA	1,624	NA
Good	Tisseverasinghe et al. (2009) Cohort, Canada [11]	607 DM	64.2	433 (70)	NA	NA	NA	NA	53	19	NA	NA	34	NA
Total patients: 18,974		14,292 DM 1,722 PM 50 ASSD 881 Others IIMs non-specific in studies		13,796	577	925		20.1–31.1 (26.1)	1,644	800	72–232 42–135 48–186	81–98	2,484	147

Data showed as median (mean ± standard deviation)

ASSD anti-synthetase syndrome, *DM* dermatomyositis, *IIMs* idiopathic inflammatory myopathies, *IBM* inclusion body myositis, *TG* triglyceride, *NA* not available, *PM* polymyositis

Abdominal circumference (number of patients with > 80 cm)

The mean abdominal circumference was ≥ 90 cm, and the body mass index was 26.1 kg/m^2. In the laboratory, fasting blood glucose values showed an average of 89.5 mg/dL, and mean values of LDL-cholesterol, HDL-cholesterol, and triglycerides were 152 mg/dL, 88.5 mg/dL, and 117 mg/dL, respectively. Finally, it is important to emphasize that 13.2% (2,484 cases) and 0.9% (147 cases) of the patients had acute myocardial infarction and stroke, respectively. However, 880 patients did not have a defined clinical, serological, or imaging phenotypic profile for any IIMs.

As for the use of glucocorticoids and other immunosuppressive therapies such as methotrexate, azathioprine, and human immunoglobulin, it was present in eight studies with a prevalence between 40%—60% [4, 5, 8, 10, 11, 17–19, 25, 26]. However, when comparing the control groups with IIMs in terms of cardiovascular risk, only one study [5] showed a positive relationship between exposure and outcome.

Discussion

Cardiovascular risk factors in IIMs

According to the literature, most patients with IIMs are middle-aged North American or Asian women whose main cardiovascular risk factors are hypertension [6, 11, 19], diabetes mellitus [4, 20, 22, 23], smoking [4, 6–8, 16–19, 23, 26], and alcohol use [5–7, 24]. Among the risk factors mentioned, hypertension associated with dyslipidemia was the greatest predictor of acute myocardial infarction in different cohorts [6, 11, 19].

As for the analysis of the prevalence of comorbidities and unhealthy lifestyle habits, studies carried out by the World Health Organization (WHO) report that diabetes mellitus in the general population ranges from 5.6%—13.1%, arterial hypertension is 12.1%—28.1%, 18.8% are smokers, and 31.7% consume alcoholic beverages [28]. Except for arterial hypertension, whose prevalence in our study was the variation range of the general population (9.2%), the other comorbidities had a lower prevalence among IIMs: diabetes mellitus (835 cases, 4.4%), smoking (925 cases, 4.8%), and alcoholism (577 cases, 3.0%). This fact can be attributed to the possibility that patients with IIMs, due to having severe chronic diseases, tend to take better care of themselves and have regular medical follow-ups. The low prevalence of these comorbidities may be due to multiple factors, such as under reporting, selection bias, and lower mean age of patients with IIMs in comparison to the healthy population. However, despite this low prevalence of cardiovascular events, a high incidence of acute myocardial infarction was observed.

However, an important limitations of the literature should be mentioned: only four articles mapped alcohol use in patients with IIMs [5–7, 24], with a total of 577 individuals. It is important to emphasize that the amount of alcohol consumed was not measured and specific questionnaires to assess recreational use *versus* alcohol abuse were not used.

Considering anthropometric and laboratory alterations, the average abdominal circumference was ≥ 90 cm [6, 7, 19] and the serum levels of LDL-cholesterol varied between 72—232 mg/dL [6, 7, 18, 19], both above the levels recommended by the American Heart Association [29]. Variations are probably due to ethnic and cultural differences in the samples. Asian patient groups [8] have a healthier diet/lifestyle than European [26], Latin American [6, 10, 19], and mainly North American groups [7, 24]. Regarding dyslipidemia versus statin use in patients with IIMs in this review, a study by Bae et al. [18] did not demonstrate important muscle changes in patients with IIMs using statins. However, it is worth mentioning the small sample size, absence of risk autoantibodies for more aggressive IIMs, and the retrospective nature of the study.

It is interesting to note that fasting blood glucose was only described in two papers [10, 19], one of which included a patient with diabetes, and the other was not characterized. Thus, the mean blood glucose values may be underestimated or overestimated, and should be interpreted with caution.

Glucocorticoids were present in 50%—60% of patients with IIMs in the analyzed studies [4, 8, 10, 11, 17–19, 25, 26]. There was no statistically significant difference between the impact of glucocorticoid use (cumulative dose, prednisone > 20 mg/day or pulse therapy) on cardiovascular risk [4, 8, 10, 11, 17–19, 25, 26] or prevention of cardiac remodeling [25, 26]. However, these data were not consistent, and a study [5] demonstrated that the cumulative dose of glucocorticoids had an impact on the cardiovascular risk of patients with IIMs.

However, it is difficulty of stratifying these data due to the small samples analyzed, since it is a rare disease. In addition, it is worth noting that some of the control groups in some studies used glucocorticoids for other comorbidities, which may have influenced the statistical analyses.

Acute coronary syndrome and stroke in a patient with IIMs

The cardiovascular disease hazard ratio of patients with IIMs varies from 1.6 to 2.4 times in different cohorts [4, 6, 13, 21–23, 25] compared to the control groups, being more prominent in the first years of the disease and among patients with DM/PM. Araújo et al. demonstrated an increase in metabolic syndrome in women with ASSD [18]. As for the incidence of stroke (ischemic and hemorrhagic), it seems that patients with IIMs have a 1.1-time higher incidence and are younger than the general population [14].

In patients with IIMs some pathophysiological factors may cause to increase cardiovascular risk: (i) systemic inflammatory process with increased adipocytokine [6] and

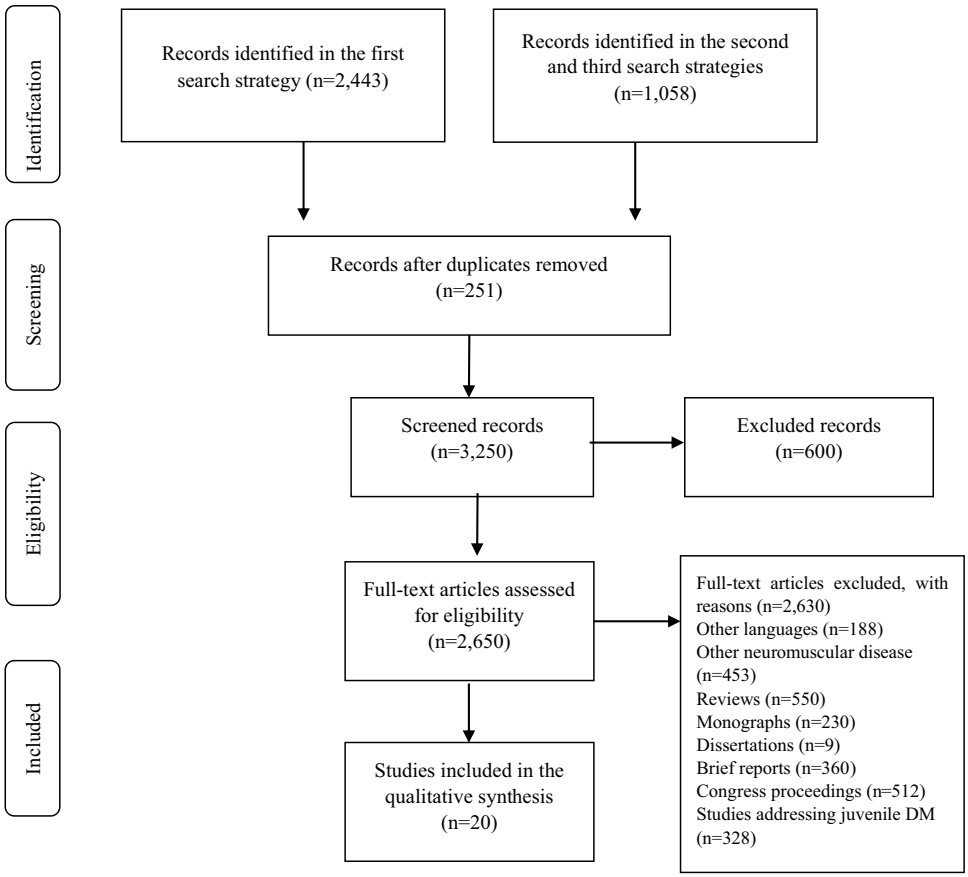

Fig. 1 PRISMA flowchart

predominant interferon-α gene signature [4]; (ii) higher incidence of insulin resistance [19]; (iii) direct myotoxicity to the heart by myositis, including correlation with specific autoantibodies, such as anti-melanoma differentiation-associated gene 5 (anti-MDA5) [8], and with the impact of medications in the treatment, such as high-dose glucocorticoids, which act by promoting dysglycemia, changes in serum lipid levels, and blood pressure peaks [10–13]. Thus, a valid hypothesis is that the cardiovascular risk of patients with IIMs is a multifactorial result of inflammatory changes, treatment consequences, inadequate lifestyle, and associated comorbidities. Thus, these risk factors may explain the high prevalence of acute myocardial infarction, and cerebrovascular diseases in patients with IIMs compared to the general population.

Some papers even state that the incidence of heart disease is higher than that of stroke [4, 14]. We hypothesize that, especially in the first years of the disease, there is direct aggression to the cardiomyocytes, promoting injury and potentializing damage to the heart, which may not occur in the central nervous system.

It should be noted that although cardiovascular disease has been proven to be an important factor for death in patients with IIMs [7, 8, 17, 26], the mapping of its real impact is still quite limited, with the absence of effective markers for early screening [7].

Among cardiac abnormalities in IIMs, the literature mentions: (i) a higher incidence of subclinical diastolic dysfunction [26], and (ii) left ventricular diastolic dysfunction and increased myocardial uptake on Tc^{99} scintigraphy, denoting myocarditis [17].

Regarding the phenotypic profile that is most affected by cardiovascular disease, a Chinese cohort demonstrated that in IIMs with anti-MDA-5 autoantibodies, cardiovascular disease is also an important mortality factor [8], whereas an Italian study found a higher incidence of cardiovascular disease in PM [4].

When analyzing the cardiovascular risk factors between DM and PM (Table 2), we observed that patients with DM had a higher prevalence of almost all factors, except for body mass index. However, the values were quite close to each other, indicating that this may be a collection bias. Furthermore, it is important to note that only four studies [7, 18, 23, 25] provided data that could be compared between IIMs, lacking data for ASSD, IBM or IMNM.

Finally, we highlight the following limitations of the present study: (i) absence of control groups in most studies; (ii) small sample size [10, 17, 18]; (iii) the retrospective nature of some articles [4, 6–8, 14, 18, 22, 23]; (iv) the non-phenotypic characterization (clinical, laboratory, serological, or imaging) of a large part of IIMs [16, 22, 26], and

Table 2 Comparison of cardiovascular risk factors among patients with idiopathic inflammatory myopathies

Risk factors	D'Silva et al. (2021) [7]			Bae et al. (2020) [18]			Rai et al. (2016) [25]			Weng et al. (2009) [23]		
	410 DM	407 PM	*P*	33 DM	8 PM	*P*	350 DM	424 PM	*P*	640 DM	505 PM	*P*
Decade of life	Sixth	Sixth	0.488	Sixth	Seventh	0.593	Sixth	Sixth	0.010	Sixth	Sixth	0.681
Female, *n* (%)	269 (65.6)	247 (60.6)		13 (39.3)	2 (25.0)		252 (72.0)	226 (53.3)		454 (70.9)	372 (73.6)	
Diabetes mellitus, *n* (%)	32 (7.8)	35 (8.5)	0.703	3 (9.0)	2 (25.0)	0.294	57 (16.2)	33 (7.7)	0.001	68 (10.6)	57 (11.2)	0.749
Arterial hypertension, *n* (%)	127 (30.9)	133 (3.1)	0.707	3 (9.0)	2 (25.0)	0.294	0	0	-	140 (21.8)	124 (24.5)	0.399
Dyslipidemia, *n* (%)	41 (10.0)	50 (12.2)	0.353	9 (27.2)	2 (25.0)	0.921	55 (15.7)	30 (7.0)	0.020	96 (15.0)	88 (17.4)	0.346
Smoking, *n* (%)	173 (42.1)	167 (41.0)	0.829	4 (12.1)	0	-	0	0	-	NA	NA	-
Alcohol consumption, *n* (%)	245 (59.7)	292 (71.7)	0.101	NA	NA	-	0	0	-	NA	NA	-
Median body mass index (kg/m^2)	27 (6.5)	28 (6.8)	0.875	NA	NA	-	0	0	-	NA	NA	-
Stroke, *n* (%)	8 (1.9)	9 (2.2)	0.799	3 (9.0)	0	-	NA	NA	-	NA	NA	-
Acute myocardial infarction, *n* (%)	38 (9.2)	55 (13.5)	0.089	4 (12.1)	0	-	37 (10.5)	23 (5.4)	0.014	NA	NA	-

DM dermatomyositis, *NA* not available, *PM* polymyositis

(v) non-characterization in the literature of the duration of comorbidities such as arterial hypertension, diabetes mellitus, or tobacco load, which alters the burden of the disease and may predispose to consequences such as infarction or stroke. However, some of these limitations are from the literature, such as the absence of randomized clinical trials and the rarity of IIMs.

Final considerations

According to data in the literature, and considering the limitations of the present review, it seems that the prevalence of the cardiovascular risk factors was generally low in IIMs, but with a high incidence of acute myocardial infarction. Thus, prospective studies are needed to compare populations stratified by continent (for example, Western versus Eastern population, male versus female) and risk factors to better understand the impact of each risk factor on the cardiovascular health of patients with IIMs.

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Declarations

Conflict of interest The authors declare they do not have a conflict of interest.

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