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Keywords: *cutaneous manifestations; family health; health services; primary health care.*

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Dermatologic Manifestations in Patients with Metabolic Syndrome in Brazil

Lívia Cavalcante de Araújo [α], Rayssa Claudia Oliveira Duarte [σ], Rafael Vilela Borges [ρ], Maykon Jhuly Martins de Paiva [ω], Sávia Denise Silva Carlotto Herrera[¥] & Marcos Gontijo da Silva[§]

Abstract- Metabolic syndrome (MS), a cluster of cardiovascular risk factors associated with increased mortality, exhibits systemic manifestations in various organs, including the skin. This study aimed to investigate the prevalence of dermatological manifestations in patients with MS attending primary healthcare units staffed by Family Health residents in Gurupi, Tocantins, Brazil. This descriptive, cross-sectional epidemiological study enrolled 93 men and women aged between the ages 25 and 60 y across four Basic Health Units and used a questionnaire administered during medical consultations. In total, 69.89% of samples exhibited dermatological manifestations. Morbid obesity was the leading factor linked to MS and skin alterations, with 100% of these patients presenting with some form of dermatosis, the most identified cutaneous manifestations by prevalence were erythematous lesions, papules and plaques, vesicles and blisters, scaling, and changes in pigmentation. The high prevalence of dermatological manifestations in patients with MS with pseudoacanthosis nigricans being the most frequent, can alert healthcare professionals to suspect MS and prevent long-term complications.

Keywords: cutaneous manifestations; family health; health services; primary health care.

I. Introduction

Metabolic syndrome (MS) presents a considerable challenge in primary care because of its complex nature and negative impact on health. This chronic, non-communicable disease (NCD) clusters metabolic disorders, including dyslipidemia, glucose intolerance, and insulin resistance (IR) [1, 2], doubles the risk of death and quintuples the risk of developing type 2 diabetes mellitus (T2DM) [3]. According to the International Diabetes Federation (IDF), approximately one-quarter of adults suffer from MS globally and face two and three times the risk of death and stroke, respectively, compared with the general population [4, 5].

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Studies in South America revealed a wide range of MS prevalence, from 12.3% to 44.6%, which is influenced by the chosen diagnostic criteria. In Brazil, the reported prevalence is 29.6% [6], for adults, even soaring to 40% in those over 60 years of age [7]. However, some studies, relying on self-reported numerical criteria, estimate a lower prevalence of 9%. This discrepancy is likely due to underestimation, highlighting the importance of standardized assessments for accurate diagnosis and a comprehensive understanding of MS prevalence and its components [8, 9].

A prevalence study in the northeastern region revealed that 50.7% of adults with T2DM also have MS. This dual burden, characterized by the accumulation of cardiometabolic changes, inflicts extensive economic and social losses [2, 10]. In addition, genetic predisposition, IR, abdominal obesity, physical inactivity, unhealthy diet, chronic inflammation, and hormonal imbalances could all contribute to the MS development [6]. The latest health report released by the World Health Organization in 2018 highlights the rising prevalence of chronic NCDs, such as MS and emphasizes the need for continued research on their risk factors to inform effective control measures [11].

MS involves a cluster of metabolic alterations including arterial hypertension, abdominal obesity, dyslipidemia, and impaired glucose metabolism. Although several studies have estimated MS prevalence using the Adult Treatment Panel III criteria (NCEP, 2001), it is recommended to adopt a standardized set of criteria for improved comparisons and study effectiveness [12].

According to the IDF criteria for diagnosing MS, an individual must have a high waist circumference and at least two of the following: triglycerides (TG) ≥150 mg/dL, high-density lipoprotein cholesterol <40 mg/dL (men) or <50 mg/dL (women), blood pressure ≥130/85 mmHg or use of antihypertensive drugs; and fasting glucose ≥100 mg/dL or a previous diagnosis of T2DM [4,13].

As obesity is a component of MS, individuals with obesity often have elevated levels of glucose, insulin, IR, or inflammatory markers [14]. Chronic inflammation and increased adipose tissue lead to an increase in inflammatory signals, which trigger IR, boost glucose, TG, and low-density lipoprotein, while

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hyperinsulinemia promotes renal sodium reabsorption and stimulates the sympathetic nervous system, leading to endothelial cell dysfunction and inhibition of nitric oxide, a vasodilator [15, 16].

The link between the skin and IR is intriguing, as certain hormones, such as alpha-melanocyte-stimulating hormone, participate not only in melanin production, but also in insulin signaling, impacting food regulation [17, 18]. Therefore, the mechanisms affecting insulin sensitivity also influence skin equilibrium [14, 19, 20].

Hyperinsulinemia, often triggered by insulin receptor insensitivity, stimulates keratinocyte and fibroblast growth by activating insulin growth factor-1 receptors. This growth can manifest in various skin conditions. Chronically high levels of pro-inflammatory molecules, on the other hand, can induce IR, leading to microvascular dysfunction. This includes the accumulation of harmful advanced glycation end products, impaired epithelial homeostasis, and reduced blood flow and nutrient supply to the skin [14, 21, 22].

This microcirculatory alteration is an established mechanism in diseases such as obesity, T2DM, arterial hypertension, and MS [23–25]. Furthermore, even in the prediabetic or normoglycemic stages, metabolic dysfunction preceding hyperglycemia can cause damage due to increased insulin resistance, oxidative stress, and activation of inflammatory pathways [24, 26]. Therefore, cutaneous manifestations, common with metabolic alterations, can potentially serve as an early warning sign for MS or indicate its severity [14, 19, 21]. This two-way street arises from shared biomarkers, such as hyperinsulinemia, oxidative stress, and inflammatory markers, including interleukin-6. Studies have confirmed the elevated levels of these markers in various cutaneous pathologies and MS, highlighting their strong association.

Strong associations have been established between MS and conditions, such as acanthosis nigricans, acne, and psoriasis. Acrochordons, androgenetic alopecia, hidradenitis suppurativa, recurrent aphthous stomatitis, and hirsutism also show potential links with MS, whereas other conditions, such as diagonal earlobe crease, Garrot's nodules, rosacea, lichen planus, vasculitis, scleroderma, and keratosis pilaris, have demonstrated moderate connections [14, 16, 27–30].

Although reports have indicated a correlation between MS and dermatological alterations, the underlying mechanisms remain poorly understood. This lack of a complete understanding underscores the need for further exploration of this connection. Primary healthcare plays a fundamental role in the Brazilian healthcare system, encompassing a broad segment of the population, and directly impacting health promotion. However, the lack of targeted investigations into this specific reality can compromise the quality of the medical care provided, as interventions may not adequately reflect local needs and characteristics. Thus, it is imperative to address this gap through studies addressing relevant health issues in Brazilian primary healthcare to provide a solid foundation for more effective and locally adapted clinical practices [16, 31].

Therefore, our study aimed to assess the prevalence of dermatological manifestations associated with MS in patients attending primary healthcare units in Gurupi, Tocantins, where Family Health residents work. By meticulously examining the profile of this population, we aimed to achieve several key objectives: track the frequency of both MS and its associated dermatological manifestations, inform the development of proactive methodologies, empower healthcare professionals through targeted engagement and training, and facilitate the efficient resolution of the challenges posed by this intriguing interplay between metabolic dysfunction and skin health.

II. Materials and Methods

The study was conducted from August to November 2021 as a descriptive cross-sectional epidemiological investigation. We selected Gurupi, located in the southern Tocantins, as the study setting. Gurupi, with an estimated population of 86,647, according to the Brazilian Institute of Geography and Statistics, is the state's third-largest city and serves as a regional hub for the south.

Four basic health units (*Unidades Básicas de Saúde* [UBS]) participating in the University of Gurupi's Medical Residency Program for Family and Community Health were selected. These units, strategically chosen for their large service area, strong professional communication network, and potential for future community-wide interventions, were: Hélio Naves Cansado (Vila Íris), João Manoel dos Santos, Ulisses Moreira Milhomem (Pedroso), Miguel Peres de Carvalho (Vila Nova).

After obtaining authorization from the Municipal Health Department and approval from the Research Ethics Committee of University of Gurupi (opinion number: 4.880.322), informed consent was obtained. All volunteer participants who completed the questionnaire during their medical consultations signed an informed consent form (ICF). The study population included adults (> 18 y) of both sexes, pregnant women, and older adults residing within the selected UBS catchment areas who signed the ICF. The investigated public corresponds to 39% men and 61% women. Patients under 18 years old, those declining informed consent, and individuals not residing within the UBS areas were excluded. Our sample comprised all UBS patients seen by resident physicians who either had a preexisting MS diagnosis or received MS confirmation through questionnaire administration.

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Owing to the COVID-19 pandemic and restrictions on elective consultations, the number of patients examined in the four selected units was lower than anticipated during the study period (August to November 2021). Approximately 5,920 services were provided during these 4 months. Given the estimated 30% prevalence of MS in the Brazilian population (NCEP, 2001), this would yield a potential study population of 1,776 individuals. Based on a predetermined sample size calculation with a 5% margin of error and a 95% confidence interval (https://calculareconverter.com.br/calculo-amostral/), 316 participants were recruited. However, the final sample size of 93 represented only 29.43% of the planned target, owing to the impact of the pandemic.

Following the administration of the questionnaire, data were entered into an Excel 2016 (Microsoft Corporation, Redmond, WA, USA) spreadsheet. Demographic and clinical characteristics are described in the tables and figures. The chi-square test was used to assess the association between skin diseases and demographic and clinical characteristics, whereas the odds ratio (OR) was used to analyze the risk of acquiring one or more dermatoses. A two-tailed p-value was used in this study and $p \leq 0.05$ was considered statistically significant.

III. Results

The study sample differed from the initial expectations owing to the COVID-19 pandemic. Family Health Strategy teams were directed to prioritize care for suspected COVID-19 cases, thereby significantly reducing the number of consultations available. Consequently, we enrolled 93 patients with MS, representing 29.43% of the anticipated sample size.

Among the participants, 65 (69.89%) exhibited some form of skin alteration. The sample was predominantly female (70.97%), with 52.69% aged between 40 and 60 years. Moreover, a high prevalence of comorbidities was observed (50.54% had diabetes, 73.12% had hypertension, and 84.95% had a waist circumference exceeding 88 cm in women and 102 cm in men). Furthermore, 91.83% of participants were overweight or with obesity (Table 1).

Correlating demographic and clinical factors with the presence of any dermatological alterations revealed an association between morbid obesity (body mass index [BMI] > 40) and skin conditions (Table 1).

Among the identified skin alterations, pseudoacanthosis nigricans was the most common, affecting 33 patients (50.77%). Androgenetic alopecia was observed in 23 patients (33.8%), followed by acrochordons in 19 (29.23%) (Figure 1).

Among the 65 patients who presented with dermatological manifestations, 60% (n = 39) exhibited coinfection with multiple skin conditions. Notably, 25 patients (26.88%) had two distinct dermatoses, while eight (8.60%) and six (6.45%) had three and four, respectively (Figure 2).

Further analysis revealed a correlation between the BMI and number of skin conditions per patient. Obese individuals showed a higher propensity for multiple dermatoses, culminating in a 32.8-fold increased risk of four or more skin manifestations in morbidly obese patients (Table 2). To explore the associations between BMI and the number of skin conditions per patient more comprehensively, we performed a multivariate analysis using logistic regression models. This approach allowed us to independently assess the impact of BMI, while controlling for potential confounders. We considered demographic variables, such as age and sex, in addition to other relevant clinical factors.

IV. Discussion

Our study population predominantly consisted of women (66%), of which 68% had systemic arterial hypertension. Age, sex, diabetes, and hypertension did not emerge as significant risk factors for skin alterations among patients with MS. This finding diverges from certain studies suggesting that certain dermatoses exhibit age-specific preferences and correlations with MS [32].

Among our diabetic population, 68.09% had skin alterations and 31.91% did not. This suggests no significant relationship between diabetes and dermatological manifestations, in contrast to a study conducted at a University Hospital in Ribeirão Preto, where a high incidence (81%) of skin lesions in diabetic patients was observed [33]. Other studies also reported a higher frequency of dermatological lesions in patients with diabetes, particularly those with decompensation [32].

Our data revealed a strong association between the BMI and dermatological alterations. Our findings regarding the robust association between BMI and dermatological alterations align with and complement the existing literature. Recent systematic reviews and meta-analyses have investigated the link between MS and skin diseases, providing valuable insights into the intricate relationship between metabolic factors and dermatological conditions.

Sodagar et al. [34] conducted a comprehensive systematic review and meta-analysis that emphasized the association between MS and prevalent skin diseases. These findings contribute to a growing body of evidence supporting the link between metabolic factors and dermatological alterations.

A prospective cross-sectional study by Aryanian et al. [35] delved into the high incidence of MS components in patients with lichen planus, shedding light on the specific dermatological manifestations

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associated with metabolic disturbances. Furthermore, an investigation of the global prevalence of MS in patients with psoriasis over the past two decades offers insights into the evolving landscape of these associations [36].

A systematic review and meta-analysis by Ying et al. [37], specifically focusing on the risk of MS in patients with lichen planus, further enriched our understanding of the complex interplay between dermatological and metabolic health. By acknowledging and citing these studies, we aimed to contextualize our findings within the broader literature, reinforcing the significance of the observed association between BMI and dermatological alterations.

None of the MS patients with a BMI <18.5 experienced skin conditions, while the percentages with dermatoses progressively increased across higher BMI categories: 42.86% (18.5–24.9), 72% (25–29.9), 67.57% (30–34.9), and 71.43% (35–39.9). All patients with a BMI >40 had dermatological alterations, suggesting the strong influence of obesity. This association was statistically significant, with morbidly obese patients (BMI >40) demonstrating a 32.8-fold higher risk of having four or more dermatoses than the other groups.

Obesity emerged as a key determinant of the dermatological manifestations in this study. None of the healthy participants exhibited any skin alterations. Among those with ideal weight, less than half developed dermatological alterations. The prevalence of skin changes increased steadily with increasing BMI categories: >50% in both overweight and grade 1–2 obese individuals and 100% in patients with grade 3 obesity.

The three most frequent skin conditions, presented in descending order, were pseudo-acanthosis nigricans (50.77%), androgenetic alopecia (33.8%), and acrochordons (29.23%). Furthermore, 60% of the individuals showed co-occurrence of multiple skin manifestations.

While the multifaceted functions of the skin and their potential correlation with dermatological alterations in MS are well documented, the underlying mechanisms remain incompletely understood and require further investigation [16, 31]. This underscores the importance of healthcare professionals remaining vigilant for dermatological manifestations as potential indicators of MS, thereby contributing to the prevention of future cardiovascular and dermatological complications [32, 38].

This study had certain limitations. First, the sample size was relatively small, which may have affected the generalizability of the findings to a broader population. The cross-sectional nature of the study design implies inherent limitations, including the inability to establish causality and susceptibility to bias owing to the lack of longitudinal follow-up. Furthermore, it is important to recognize the potential selection bias. Finally, owing to the specific nature of our cohort, generalizing the results to different demographic and geographic contexts is limited. These limitations should be considered when interpreting the findings of this study.

Although existing research suggests a link between skin changes and MS, robust data and comprehensive studies examining this relationship are limited. Filling this knowledge gap by conducting in-depth research will contribute significantly to a more comprehensive understanding of the overall profile and societal impact of this connection.

In conclusion, our study revealed a high prevalence of dermatological manifestations, particularly pseudo-acanthosis nigricans, in individuals with MS. Additionally, we observed a higher incidence of MS in women, individuals with systemic arterial hypertension, and individuals with morbid obesity. Morbid obesity has emerged as a strong risk factor for skin alterations. These findings highlight the importance of healthcare professionals being attentive to dermatological presentations as potential indicators of MS. Early identification and proactive management of MS can help prevent or mitigate long-term complications, including those affecting the cardiovascular and skin systems. Beyond the aforementioned areas, future investigations could benefit from exploring new frontiers at the interface between MS and dermatology. Understanding the molecular mechanisms underlying the skin alterations associated with MS may pave the way for more targeted therapies and specific prevention strategies. Innovative approaches, such as studies on the skin microbiome in individuals with MS, may reveal the connections between metabolic health and skin microbiota composition. Furthermore, considering the emerging role of artificial intelligence in medicine, the application of advanced machine learning techniques can provide more refined insights into dermatological patterns associated with MS. By pursuing these directions, future research can not only expand our knowledge, but also catalyze practical advancements in the clinical approach to MS and its dermatological implications.

V. Statements and Declarations

a) Competing Interests and Funding

The authors state no conflict of interest. This study was supported by the Universidade de Gurupi. The funder had no role in the study design; in the collection, analysis or interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

b) Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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c) *Consent to Participate*

Informed consent was obtained from all individual participants included in the study.

d) *Ethics Approval*

Authorization was provided by the Municipal Health Department. The Research Ethics Committee of University of Gurupi (opinion number: 4.880.322) approved this research.

Author Contributions

Conceptualization: Lívia Cavalcante de Araújo. *Methodology:* Rayssa Claudia Oliveira Duarte. *Data curation:* Rafael Vilela Borges. Writing-Original draft preparation, Visualization, *Investigation:* Maykon Jhuly Martins de Paiva. Supervision, *Validation:* Sávia Denise Silva Carlotto Herrera. *Writing- Reviewing and Editing:* Marcos Gontijo da Silva.

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Tables

Table 1: Demographic and clinical characteristics of the study group with metabolic syndrome-related to dermatological alterations in patients treated at the Basic Health Units of Gurupi-TO, Brazil (2022)

		n. Total	% Total	Dermatological alteration (Yes)		Dermatological alteration (No)		χ^2	*p-value*
				n.	%	n.	%		
Age range in years	>40	17	18.28%	15	88.24%	2	11.76%	3.33	0.07
	40–60	49	52.69%	34	69.39%	15	30.61%	0.01	0.91
	>60	18	19.35%	11	61.11%	7	38.89%	0.82	0.37
Sex	Male	27	29.03%	22	78.57%	6	21.43%	1.12	0.29
	Female	66	70.97%	44	67.69%	21	32.31%		
Diabetes	Yes	47	50.54%	32	68.09%	15	31.91%	0.15	0.70
	No	46	49.46%	33	71.74%	13	28.26%		
Hypertension	Yes	68	73.12%	45	66.18%	23	33.82%	1.66	0.20
	No	25	26.88%	20	80.00%	5	20.00%		
BMI	<18.5	1	1.08%	0	0.00%	1	100%	2.35	0.12
	18.5–24.9	7	7.53%	3	42.86%	4	57.14%	2.63	0.10
	25–29.9	25	26.88%	18	72.00%	7	28.00%	0.07	0.79
	30–34.9	37	40.22%	25	67.57%	12	32.43%	0.28	0.59
	35–39.9	14	15.05%	10	71.43%	4	28.57%	0.02	0.90
	>40	9	9.68%	9	100.0%	0	0.00%	4.29	0.04
Waist circumference (cm). ♀: >88 cm, ♂: >102 cm	Yes	79	84.95%	58	73.42%	21	26.58%	3.10	0.08
	No	14	15.05%	7	50.00%	7	50.00%		

BMI: Body Mass Index; %: percentage; >: Higher than; <: Lower than; n: Number; χ^2: Chi-squared; p: Level of significance; ♀: Female; ♂: Male

Table 2: Correlation between the number of dermatoses and BMI in the study group with metabolic syndrome

No. of Dermatoses	BMI	n.	%	OR	CI	χ^2	*p*
One	<18.5	0	0	-	-	0.35	0.553
	18.5–24.9	3	12.05%	0.45	0.23–9.23	0.89	0.900
	25–29.9	9	37.50%	1.99	0.73–5.39	1.85	0.173
	30–34.9	6	25.00%	0.40	0.14–1.12	3.12	0.077
	35–39.9	3	12.50%	0.75	0.19–2.97	0.16	0.685
	>40	3	12.50%	1.50	0.34–6.53	0.29	0.587
Two	>18.5	0	0	-	-	0.79	0.987
	18.5–24.9	0	0	-	-	2.78	0.096
	25–29.9	5	20.00%	0.60	0.20–1.82	0.82	0.364
	30–34.9	**16**	**64.00%**	**3.89**	1.48–10.23	**8.07**	**0.004**
	35–39.9	2	8.00%	0.41	0.08–1.96	1.33	0.249
	>40	2	8.00%	0.76	0.14–3.92	0.11	0.740
Three	>18.5	0	0	-	-	0.37	0.542
	18.5–24.9	0	0	-	-	0.71	0.399
	25–29.9	3	37.50%	0.70	0.23–1.82	0.86	0.964
	30–34.9	1	12.50%	0.19	0.02–1.62	2.79	0.094
	35–39.9	**4**	**50.00%**	**7.50**	1.61–34.81	**8.35**	**0.0038**
	>40	0	0	-	-	0.93	0.333

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Four	>18.5	0	0	-	-	0.07	0.792
	18.5–24.9	0	0	-	-	0.52	0.470
	25–29.9	0	0	-	-	2.36	0.125
	30–34.9	2	33.33%	0.73	0.13–4.20	0.13	0.722
	35–39.9	0	0	-	-	1.14	0.286
	>40	**4**	**66.67%**	**32.80**	4.79–224.31	**23.83**	**0.000001**

BMI: Body Mass Index; %: percentage; >: Higher than; <: Lower than; n: Number; χ^2: Chi-squared; p: Level of significance; OR: Odds ratio; CI: Confidence interval

Figure Legends

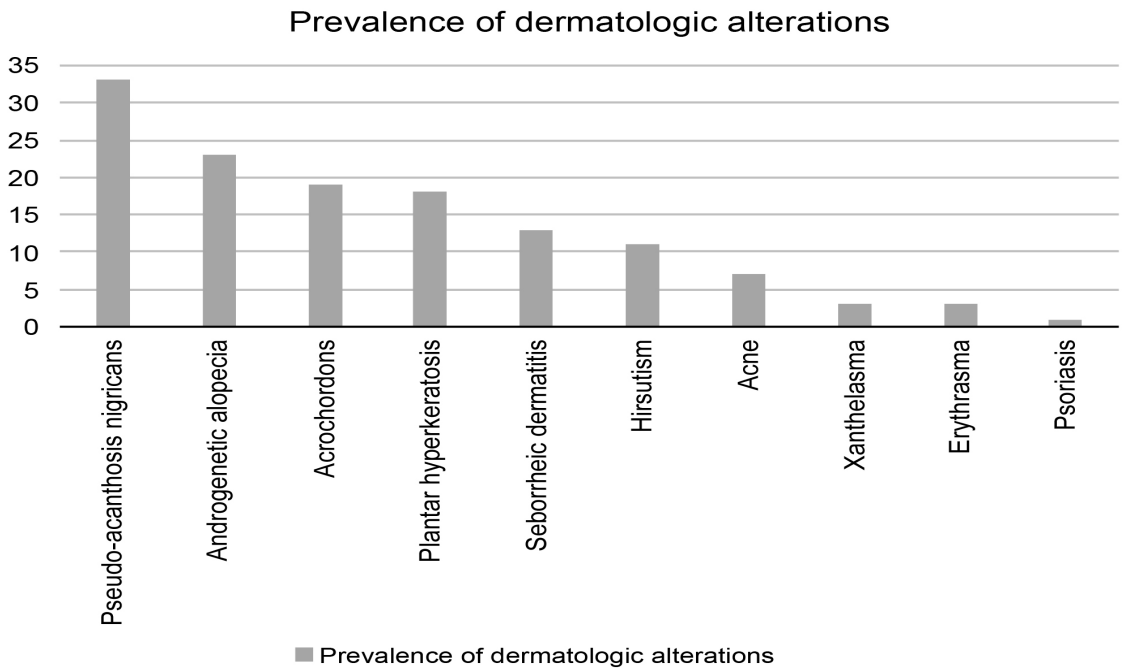

Figure 1: Prevalence of dermatological alterations in the study group with metabolic syndrome in patients treated at the Basic Health Units of Gurupi-TO, Brazil (2022)

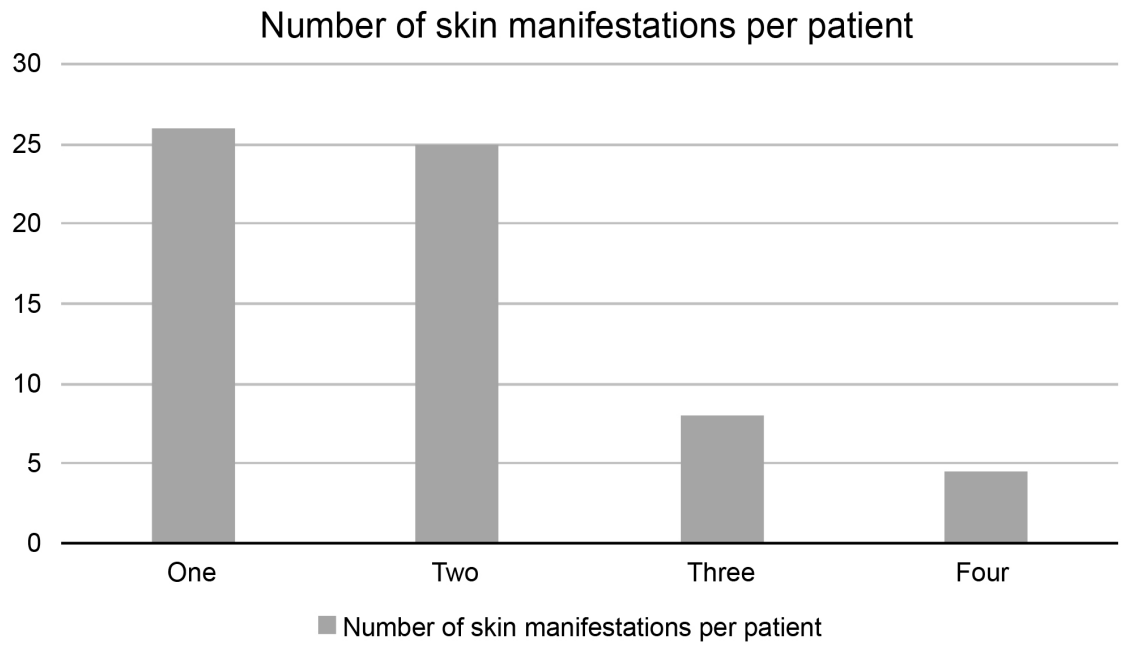

Figure 2: Number of skin manifestations per patient in the MS Study Group in patients treated at the Basic Health Units of Gurupi-TO, Brazil (2022)

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