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Associations between hematological biomarkers and muscle health in women with sickle cell disease.

Asociaciones entre biomarcadores hematológicos y la salud muscular en mujeres con enfermedad de células falciformes

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Abstract

OBJECTIVE: To investigate the association between hematological/metabolic biomarkers and handgrip strength, appendicular muscle mass, and relative muscle power in women with sickle cell disease.
MATERIALS AND METHODS: A cross-sectional study was conducted with women with sickle cell disease from a reference center. Handgrip strength was assessed via dynamometry, appendicular skeletal muscle mass by bioimpedance, and relative muscle power via the 30-second chair stand test. Fasting blood samples measured C-reactive protein, cystatin C, albumin, and rheumatoid factor.
RESULTS: There were included 46 women with a median age of 36 years. ROC curve showed good discrimination for mean corpuscular volume (area under the curve [AUC] 0.78) and mean corpuscular hemoglobin (AUC 0.79); C-reactive protein had an AUC of 0.69. Mean corpuscular volume and mean corpuscular hemoglobin were significantly associated with lower muscle mass after confounder adjustment. Age was associated with reduced muscle power (OR 1.14-1.16; 95% CI: 1.02-1.37), but not with C-reactive protein.
CONCLUSION: Mean corpuscular volume and mean corpuscular hemoglobin are promising biomarkers for assessing muscle health in women with sickle cell disease. These findings emphasize the critical need to integrate objective functional tests (grip strength, muscle power assessments) into routine clinical practice for this population.
KEYWORDS: Sickle cell disease; Biomarkers, C-reactive protein; Mean corpuscular volume; Mean corpuscular hemoglobin, Woman.

Resumen

OBJETIVO: Investigar la asociación entre biomarcadores hematológicos-metabólicos y la fuerza de prensión manual, masa muscular apendicular y potencia muscular relativa en mujeres con enfermedad de células falciformes.
MATERIALES Y MÉTODOS: Estudio transversal que incluyó mujeres con enfermedad de células falciformes (mediana edad: 36 años) de un centro de referencia. Se evaluó la fuerza de prensión (dinamometría), la masa muscular apendicular (bioimpedancia) y la potencia muscular relativa (prueba de sentarse-levantarse en 30 segundos). Se midieron la proteína C reactiva (PCR), la cistatina C, la albúmina y el factor reumatoide en sangre.
RESULTADOS: Se incluyeron 46 pacientes con mediana de edad de 36 años. La curva ROC mostró buena discriminación para el volumen corpuscular medio (área bajo la curva [AUC] 0.78) y la hemoglobina corpuscular media (AUC 0,79). La proteína C reactiva tuvo un AUC de 0.69. El volumen corpuscular medio y la hemoglobina corpuscular media se asociaron significativamente con menor masa muscular tras ajustar.

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La edad se asoció con menor potencia muscular, pero no con la proteína C reactiva.
CONCLUSIONES: El volumen corpuscular medio y la hemoglobina corpuscular media son biomarcadores prometedores para evaluar la salud muscular en mujeres con enfermedad de células falciformes. Estos hallazgos subrayan la necesidad de integrar pruebas funcionales objetivas (fuerza de prensión, potencia muscular) en la práctica clínica rutinaria en esta población.
PALABRAS CLAVE: Enfermedad de células falciformes; biomarcadores; proteína C reactiva; volumen corpuscular medio; hemoglobina corpuscular media; mujer.

INTRODUCTION

Sickle cell disease is one of the most prevalent genetic conditions worldwide, particularly among populations of African descent. Characterized by the presence of sickle-shaped red blood cells, sickle cell disease results in severe complications such as pain crises, hemolytic anemia, recurrent infections, and organ damage, significantly affecting the quality of life of individuals with the disease.[1] In Brazil, sickle cell disease represents a significant public health challenge due to its high prevalence and socio-economic impact.[2]

Muscle mass loss and reduced strength are common in individuals with sickle cell disease, exacerbating the disease's complications and increasing functional dependency. Several studies emphasize the serious impact of muscle dysfunction on health, associating it with all-cause mortality in older adults.[3-6]

Despite the relevance of muscle strength assessments, body composition, and biomarkers in individuals with sickle cell disease, specific evidence regarding the Brazilian population remains scarce. International studies highlight the importance of these assessments, but in Brazil, research is still limited. A few studies[7-10] address these aspects, but their scope is narrow, limiting the understanding of functional capacity in patients with sickle cell disease.

Previous studies have shown that individuals with sickle cell disease have reduced muscle strength compared to healthy controls. Ogunsile et al. (2018) observed that handgrip strength in patients with sickle cell disease was significantly lower than in controls, even after adjusting for confounders.[11] Ohara et al. (2014) reported that respiratory muscle strength and handgrip strength were below predicted values in individuals with sickle cell disease.[12] More recent studies also point to muscle dysfunction related to gross motor performance, suggesting the need for physiotherapy interventions.[13] Furthermore, the literature indicates that elevated interleukin levels are associated with poorer physical performance in children and young adults with sickle cell disease, highlighting the impact of the inflammatory state on functional capacity.[14]

Biomarkers are objectively measurable and widely used to assess normal and pathological biological processes or responses to therapeutic interventions.[15] Identifying biomarkers associated with muscle function is essential for early diagnosis, personalized treatment, and developing prevention and rehabilitation strategies. The literature suggests that muscle dysfunction may be associated with plasma biomarkers such as rheumatoid factor, C-reactive protein, cystatin C, and albumin.[16]

In the context of sickle cell disease, hematological biomarkers are essential for monitoring organ

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quality and functionality, directly impacting muscle oxygenation and metabolism. Metabolic biomarkers, such as C-reactive protein and rheumatoid factor, have been associated with systemic inflammatory status.[17,18,19] Albumin, linked to increased mortality, reflects disease severity,[20] impaired liver function,[21] and nutritional status,[22] while cystatin C is associated with renal function.[23,24] These biomarkers, reflecting different aspects of health, contribute through distinct pathways to skeletal muscle degradation, with consequences such as loss of strength and muscle power.

This cross-sectional study aimed to evaluate the association between handgrip strength, appendicular skeletal muscle mass index, and relative muscle power with hematological and metabolic biomarkers in women with sickle cell disease treated at a reference center in Feira de Santana, Bahia.

This investigation may provide new perspectives for clinical monitoring and targeted therapeutic interventions, promoting the integration of functional tests into clinical practice and contributing to a more personalized approach to the care of individuals with sickle cell disease.

MATERIALS AND METHODS

A cross-sectional study was conducted with women with sickle cell disease in Feira de Santana, Brazil. The ethics committee approved the study (ID: CAAE: 56729322.6.0000.0053), and it complies with the principles of the Declaration of Helsinki.

Participants

Participants were eligible if they were 18 years or older and had a diagnosis of any type of sickle cell disease. Individuals were excluded if they were not independent in all their functions, had cognitive impairments, could not answer the questionnaire due to other health issues, or were unable to complete the full battery of tests, which led to the exclusion of some male and female participants.

Study procedures

All women and men attending the reference center were invited to participate in the study. Eligible participants signed a consent form and subsequently underwent a battery of tests from January to March 2024. Initially, researchers collected sociodemographic, anthropometric, and other variables of interest, including handgrip strength tests and the 30-second chair stand test, and participants were referred for blood examinations.

Handgrip strength

Handgrip strength was assessed using a hydraulic hand dynamometer (Baseline® Hydraulic Hand Dynamometer). The specific cutoff for low grip strength was set at < 16 kg for women.[25] Participants performed three attempts, and the average handgrip strength of the dominant hand was calculated.

Appendicular muscle mass

Appendicular skeletal muscle mass was estimated using bioelectrical impedance analysis with the InBody H20N scale. This device was calibrated prior to measurements. Before the assessment, the following criteria were verified: participants were not allowed to engage in physical exercise beforehand; a fasting period of 2-3 hours were required, including abstaining from alcohol and excessive water intake, and the bladder had to be emptied; all metal objects were removed.

The InBody H20N scale provides readings of body composition, including body skeletal muscle mass (BSMM) in kg and other parameters, to estimate appendicular skeletal muscle mass.

Human cadaver studies have shown that trunk muscle accounts for 25% of BSMM,[26] thus appendicular skeletal muscle mass was estimated by dividing BSMM by 1.25.

Appendicular muscle mass index

The appendicular muscle mass index (AMMI) was calculated as appendicular skeletal muscle mass divided by height squared. Appendicular skeletal muscle mass was determined by dividing body skeletal muscle mass by 1.25, and women were classified as having low appendicular muscle mass index (AMMI, defined as appendicular skeletal muscle mass /height^2) when AMMI was < 6 (kg/m^2).

Relative muscle power

Muscle power (W) refers to the ability to produce force as quickly as possible. To calculate the muscle power generated during the chair stand test, the following formula was derived from Alcazar et al.:[27,28]

$$\text{Muscle power (W)} = \frac{\text{NR x BW x HC x 9.81}}{30}$$

NR: Number of repetitions in the chair stand test.
BW: Body weight of participants (kg).
HC: Height of the chair (m).
9.81 is the constant for acceleration due to gravity (m/s^2).

30 is the time in seconds for the chair stand test. Relative muscle power evaluates the ability of women to generate force quickly relative to their body weight, expressed as watts per kilogram (W/kg). For the purposes of comparisons, the 25th percentile of the distribution was used, with values below P_{25} considered low power.

Blood sample collection

Blood samples were collected in a tube without anticoagulant in the morning from fasting participants. The procedure followed is recommended by the Brazilian Society of Clinical Pathology/ Laboratory Medicine (SBPC/ML) and is described by Xavier et al.[29]

Biomarkers

The biomarkers used included complete blood count and lipid profile. Albumin was determined by the colorimetric method, while C-reactive protein, cystatin C, and rheumatoid factor were analyzed in serum using the immunoturbidimetric method, following standard procedures.

Statistical analysis

Statistical analysis of the data was conducted using R software. Categorical variables were described in terms of absolute and relative frequencies, while quantitative variables were expressed as mean ± standard deviation. Differences between groups were examined using the Mann-Whitney test for non-parametric continuous variables and the chi-square test for categorical variables.

To investigate associations between relative muscle power, appendicular skeletal muscle mass index (ASMMI), and biomarkers, logistic regression models were applied, adjusted for potential confounding factors such as age. Odds ratios (OR) and their 95% confidence intervals (CI95%) were estimated using the glm function from the "stats" package in R, with a significance level of 5% ($p < 0.05$). ROC curves were analyzed to evaluate the discriminative capacity of biomarkers concerning the functional parameters of women with sickle cell disease.

RESULTS

The study sample consisted of 46 women. However, data for complete laboratory tests were collected from 43 participants. All women who

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participated in the study self-identified as either Black or Brown.

The participants in the study had a median age of 36 years, ranging from 25 to 42 years. The majority reported experiencing physical weakness (83%), did not engage in physical activity at least three times per week (83%), and all were using medications. Additionally, 68% required emergency medical care in the past year, and none were smokers.

The median individual income was $235, with a first quartile (Q1) of $89 and a third quartile (Q3) of $235. Regarding physical characteristics, the median weight was 61 kg, muscle mass was 21.8 kg, and body fat percentage was 34%. The body mass index (BMI) had a median of 23.6 kg/m^2. The median of the average hand grip strength from three attempts for the dominant hand was 23.3 kg, the Appendicular skeletal muscle mass was 17.44 kg, the appendicular skeletal muscle mass index was 6.68 kg/m^2, and relative muscle power was 1.47 W/kg. The results of the descriptive characteristics are presented in **Table 1**.

The results of the analysis of categorized variables related to hand grip strength, the appendicular skeletal muscle mass index, and relative muscle power are presented in **Table 2**.

No significant differences were found between the groups with low hand grip strength (< 16 kg) and normal strength in any of the biomarkers. Unlike hand grip strength, the appendicular skeletal muscle mass index showed significant differences between groups with low index (< 6 kg/m^2) and normal index. The group with low muscle mass was significantly younger ($p < 0.018$). The values are presented in **Table 2**.

According to the appendicular skeletal muscle mass index, there were significant differences for erythrocytes ($p < 0.044$), MCV ($p < 0.036$), MCH ($p < 0.03$), triglycerides ($p < 0.032$), and rheumatoid factor ($p < 0.003$). For other variables, such as MCH concentration, leukocytes, and cholesterol, no significant differences were observed. **Table 2**

The analysis of relative muscle power revealed that age was significantly higher in the group below the 25th percentile (P25) ($p < 0.008$). There were also differences in C-reactive protein ($p < 0.044$) and rheumatoid factor ($p < 0.023$). However, no differences were found for variables such as erythrocytes, MCV, MCH, and albumin.

In the group with low appendicular muscle mass index, the MCV was 104 ± 14 fL, exceeding the reference range of 83.0 to 101.0 fL. The MCH was also elevated, with an average of 35.7 ± 4.8 pg, surpassing the reference value of 27.0 to 32.0 pg.

Regarding C-reactive protein (CRP), a mean value above the threshold of 0.50 mg/dL was identified. Additionally, when compared to cardiovascular risk criteria, the average CRP level in the group with relative muscle power above the 25th percentile (P_{25}) also exceeded the limit of 0.30 mg/dL.

Our multivariable analysis, adjusted for confounders including age, treatment, number of crises, and diagnosis, revealed significant associations between muscle health parameters and various biomarkers (**Table 3**). Specifically, for appendicular skeletal muscle mass index (ASMMI), our findings indicate that for every 1 kg/m^2 reduction in ASMMI, there was a 13% increase in the odds of having elevated MCV levels (OR: 1.13 [95% CI: 1.03-1.28], $p = 0.025$ in Model 3). Similarly, a decrease in ASMMI was associated with a 42% increase in the odds of presenting elevated MCH levels (OR: 1.42 [95% CI: 1.10-2.08], $p = 0.024$ in Model 3). These associations remained significant across different adjustment models, highlighting a consistent relationship between these hematological parameters and muscle mass.

Table 1. Descriptive characteristics of participants (n = 46[1])

Variables	n[2]	n
Age (years)	44	36 (25-42)
Treatment	46	
Folic acid (FA)		30
Hydroxyurea + folic acid (H + FA)		16
Diagnosis	46	
Sickle cell disease with crisis (HbSS)		31
Sickle cell disease without crisis (HbSC)		14
Thalassemia (Hb β+/β+)		1
Do you often feel physical weakness?	41	
Yes		34
Do you engage in physical activity?	41	
No		34
Do you smoke?	41	
No		41
Do you take medications?	41	
Yes		41
In the past year, have you required emergency medical care for health issues?	41	
Yes		28
Pain crisis in the last year (number)	41	3 (2-5)
Individual income (dollars per month)	41	235 (89-235)
Anthropometric measurements		
Weight (kg)	43	61 (52-71)
Muscle mass (kg)	43	21.8 (19.8-24)
Body fat (%)	43	34 (31-38)
BMI (kg/m²)	43	23.6 (19.8-26.6)
Median of hand grip strength (kg)	43	23.3 (20-28.3)
Appendicular skeletal muscle mass (kg)	43	17.44 (15.84-19.16)
Appendicular muscle mass index (kg/m²)	43	6.68 (6.08-7.07)
Relative muscle power (W/kg)	43	1.47 (1.32-1.62)

[1] n (%) sample; median (interquartile range). [2] n complete data.

For relative muscle power (**Table 4**), women with low relative muscle power had approximately 4 times higher odds of presenting elevated C-reactive protein (CRP) levels. While the p-value for the association in Model 3 was 0.3 (OR: 4.31 [95% CI: 0.30 to 91.8]), the consistent odds ratios across different models (ranging from 4.31 to 4.65) suggest a potential, however not statistically significant in all models, association between inflammation and reduced muscle power. Moreover, age consistently emerged as a significant factor associated with reduced relative muscle power. Across all models, an increase in age was associated with higher odds of reduced

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Table 2. Biomarkers according to hand grip strength, muscle mass index, and muscle power

Variables	Handgrip strength (kg)			Appendicular skeletal muscle mass index (kg/m²)			Relative muscle power (w/kg)		
	Low strength n = 3	Normal n = 40	p-value[2]	Low mass n = 9	Normal n = 34	p-value[2]	Below P25 n = 9	Above P25 n = 34	p-value[2]
Age (years)	34 ± 12	36 ± 11	>0.9	28 ± 12	37 ± 10	***0.018***	44 ± 8	33 ± 10	**0.008**
Erythrocytes (10^6/µL)	2.33 ± 0.03	3.12 ± 0.95	0.4	2.51 ± 0.75	3.19 ± 0.95	***0.044***	2.77 ± 0.90	3.16 ± 0.95	0.6
MCV (fL)	106 ± 7	93 ± 15	0.3	104 ± 14	92 ± 14	***0.036***	97 ± 12	93 ± 16	0.8
MCH (pg)	35.5 ± 2.4	31.3 ± 5.5	0.3	35.7 ± 4.8	30.7 ± 5.2	***0.03***	32.1 ± 4.5	31.4 ± 5.7	0.8
MCH concentration (g/dL)	33.60 ± 0.14	33.47 ± 1.16	> 0.9	34.22 ± 0.77	33.33 ± 1.14	0.065	33.24 ± 1.42	33.55 ± 1.05	0.8
RDW (%)	15.85 ± 1.06	17.53 ± 3.26	0.6	17.60 ± 3.08	17.41 ± 3.26	0.6	18.45 ± 3.68	17.15 ± 3.05	0.5
Leukocytes (/µL)	8360 ± 1669	7262 ± 2322	0.5	6538 ± 1947	7480 ± 2346	0.4	8039 ± 2792	7118 ± 2136	0.4
Neutrophils (/µL)	4041 ± 870	4108 ± 1774	> 0.9	3262 ± 1500	4278 ± 1743	0.2	4359 ± 2323	4040 ± 1593	0.9
Eosinophils (/µL)	318 ± 23	237 ± 262	0.3	361 ± 467	217 ± 193	0.8	223 ± 163	247 ± 278	0.6
Lymphocytes (/µL)	2965 ± 233	2196 ± 746	0.1	2374 ± 636	2211 ± 774	0.7	2382 ± 477	2197 ± 810	0.3
Monocytes (/µL)	984 ± 538	504 ± 187	0.13	491 ± 92	539 ± 251	0.5	584 ± 378	516 ± 177	0.8
Platelets (/µL)	470,500 ± 24,749	333,471 ± 153,824	0.11	366,333 ± 170,597	336,033 ± 151,636	0.7	362,250 ± 188,614	335,036 ± 144,438	0.7
MPV (fL)	11.70 ± 0.71	10.95 ± 1.05	0.2	11.50 ± 1.51	10.89 ± 0.92	0.3	10.58 ± 0.59	11.11 ± 1.11	0.2
Total cholesterol (mg/dL)	143 ± 13	143 ± 44	0.7	126 ± 38	146 ± 44	0.3	141 ± 40	143 ± 45	> 0.9
HDL cholesterol (mg/dL)	53 ± 17	41 ± 11	0.2	52 ± 23	40 ± 7	0.3	39 ± 8	43 ± 13	0.6
LDL cholesterol (mg/dL)	72 ± 23	81 ± 38	> 0.9	58 ± 23	85 ± 39	0.059	81 ± 36	81 ± 39	> 0.9
Triglycerides (mg/dL)	85 ± 55	113 ± 46	0.5	76 ± 35	118 ± 45	**0.032**	115 ± 40	110 ± 48	0.6
Albumin (g/dL)	4.45 ± 0.49	4.57 ± 0.35	0.7	4.57 ± 0.27	4.57 ± 0.37	0.9	4.45 ± 0.62	4.60 ± 0.23	> 0.9
C-reactive protein (mg/dL)	0.79 ± 0.95	0.73 ± 1.38	> 0.9	0.38 ± 0.32	0.80 ± 1.47	0.2	1.75 ± 2.68	0.44 ± 0.32	**0.044**
Cystatin C (mg/L)	0.74 ± 0.25	0.80 ± 0.28	0.9	0.71 ± 0.12	0.81 ± 0.30	0.5	0.96 ± 0.48	0.74 ± 0.15	0.093
Rheumatoid factor (UI/mL)	4.60 ± 0.00	5.78 ± 6.67	0.6	6.97 ± 2.29	5.46 ± 7.03	**0.003**	3.64 ± 0.39	6.31 ± 7.26	0.023

[1] Mean ± SD. [2] Wilcoxon rank sum test; Wilcoxon rank sum exact test.

Table 3. Association between appendicular skeletal muscle mass index, and biomarkers: odds ratios adjusted for age, treatment, number of crise and diagnosis

	Appendicular skeletal muscle mass index (kg/m²)					
	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	p-value
Model 1						
MCV (fL)	1.12	1.02-1.29	**0.045**	-	-	-
MCH (pg)	-	-	-	1.38	1.07, 2.01	**0.033**
Age	0.91	0.81-1.00	0.084	0.91	0.81- 1.01	0.092
Treatment						
FA	-	-		-	-	
H + FA	0.46	0.03-5.06	0.5	0.41	0.03-4.70	0.5
Model 2						
MCV (fL)	1.11	1.02-1.24	**0.031**	-	-	-
MCH (pg)	-	-	-	1.34	1.08-1.85	**0.025**
Age	0.91	0.81-1.00	0.063	0.91	0.80-1.00	0.068
Crisis number	0.90	0.63-1.11	0.5	0.89	0.61-1.11	0.5
Model 3						
MCV (fL)	1.13	1.03-1.28	**0.025**	-	-	-
MCH (pg)	-	-	-	1.42	1.10- 2.08	**0.024**
Age	0.89	0.79-0.99	0.040	0.89	0.78- 0.98	**0.043**
Diagnosis						
HbSS	-	-		-	-	
HbSC	8.97	0.58-243	0.13	11.9	0.62-535	0.13

[1] OR: odds ratio; CI: confidence interval.
HbSS: homozygous sickle cell anemia (the person inherited the sickle cell gene from both parents). HbSC: compound heterozygous sickle cell disease (the person inherited one sickle cell gene and another abnormal hemoglobin gene).
HbSS was considered the reference category in the regression models.

relative muscle power. Specifically, in Model 3, for every one-year increase in age, there was a 16% increase in the odds of having reduced relative muscle power (OR: 1.16 [95% CI: 1.04 to 1.37], p = 0.032).

Figure 1 illustrates the discriminative capacity of the analyzed biomarkers by presenting their AUC values. MCH demonstrated good discrimination with an AUC of 0.79, slightly outperforming MCV which had an AUC of 0.78. C-reactive protein (CRP) showed a reasonable discriminative capacity with an AUC of 0.69, though it was lower than that of both MCV and MCH. Overall, MCH exhibited slightly better performance in distinguishing outcomes compared to both MCV and CRP.

For MCH in relation to the appendicular skeletal muscle mass index, our analysis identified two possible cut-off points, both achieving an accuracy of 78%. The higher cut-off point of 36.75 pg yielded a sensitivity of 0.90 and a specificity of 0.67. The lower cut-off point of 34.20 pg exhibited a specificity of 0.83 and a sensitivity of 0.73. Both identified cut-off points were above the established reference range for MCH (27.0 to 32.0 pg). In the context of C-reactive protein (CRP) and relative muscle power, two potential cut-off points were identified, both resulting in

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Table 4. Association between relative muscle power, and biomarkers: odds ratios adjusted for age, treatment, number of crise and diagnosis

	Relative muscle power (w/kg)		
	OR[1]	95% CI[1]	p-value
Model 1			
C-reactive protein	4.52	0.31-101	0.3
Age	1.14	1.02-1.37	0.055
Treatment			
FA	-	-	
H + FA	1.56	0.15-16.3	0.7
Model 2			
C-reactive protein	4.65	0.30-112	0.3
Age	1.16	1.04-1.37	**0.032**
Number of crise	0.99	0.79-1.16	> 0.9
Model 3			
C-reactive protein	4.31	0.30-91.8	0.3
Age	1.16	1.04-1.37	**0.032**
Diagnosis			
HbSS	-	-	
HbSC	0.57	0.02-6.33	0.7

[1] OR: odds ratio; CI: confidence interval.
HbSS: homozygous sickle cell anemia (the person inherited the sickle cell gene from both parents). HbSC: compound heterozygous sickle cell disease (the person inherited one sickle cell gene and another abnormal hemoglobin gene). HbSS was considered the reference category in the regression models.

an overall accuracy of 69.6%. The higher cut-off for CRP, 0.82 mg/dL, presented a sensitivity of 89% and a specificity of 50%. In contrast, the lower cut-off of 0.28 mg/dL showed a sensitivity of 39% and a specificity of 100%. Both CRP cut-off points exceeded the standard reference range for cardiovascular disease risk assessment.

DISCUSSION

The aim of this study was to explore possible associations between biomarkers derived from blood tests, lipid profiles, proteins, and inflammatory biomarkers with grip strength, appendicular skeletal muscle mass, and relative muscle power in a sample of women with sickle cell disease. Our results did not show significant differences in biomarkers concerning grip strength categories, possibly due to the cut-off points used. However, after adjusting for age and confounders, we found statistically significant associations between appendicular skeletal muscle mass index and the hematological parameters MCV and MCH.

Elevated MCV and MCH were observed in the group with low appendicular skeletal muscle mass index. Elevated MCV may indicate macrocytic anemia, often associated with deficiencies in vitamins B12 and B9 (folic acid) or bone marrow disorders.[30,31] In macrocytic anemia, red blood cells are larger than normal, hindering oxygen transport and causing symptoms such as fatigue and weakness, which compromise physical capacity and muscle mass preservation. On the other hand, nutritional deficiencies are known to elevate MCV and MCH and directly affect muscle health, as micronutrients (B9 and B12) are essential for energy production and muscle regeneration.[32] Elevated MCH can impair muscle health by affecting energy production and tissue repair.[33] Although elevated MCH reflects a greater amount of hemoglobin per red blood cell, these red blood cells, despite containing more hemoglobin, are less efficient at transporting oxygen. This contributes to reduced functional and muscular capacity.[34]

Scientific evidence regarding the relationship between MCH, MCV, and appendicular skeletal muscle mass index in individuals with sickle cell disease is limited. Mostashari et al. (2023) observed lower oxygen saturation in skeletal muscle in sickle cell disease patients compared to healthy controls, suggesting that chronic hemolytic anemia compromises muscle oxygenation, as lower hemoglobin levels are associated with reduced tissue oxygenation. The sickle shape of red blood cells exacerbates this condition by obstructing blood vessels and

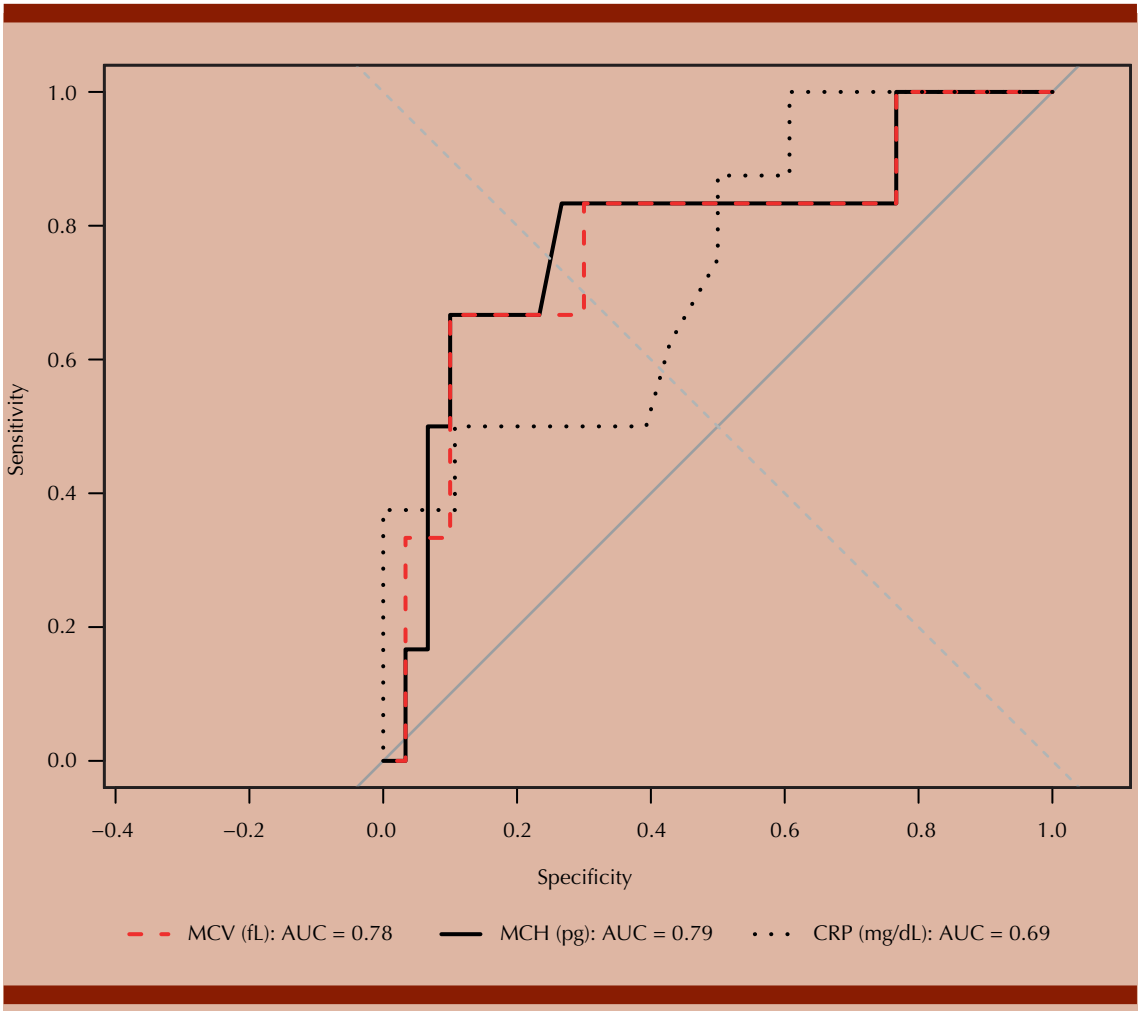

Figura 1. Performance of biomarkers in classification: Comparative AUC.

impairing muscle oxygenation.[35] Other studies indicate that markers of anemia and hemolysis are related to cerebrovascular complications, which can negatively impact muscle mass and function.[36] Furthermore, in sickle cell disease, the anemia status of patients correlates inversely with muscle strength and endurance.[37] Studies in children with sickle cell disease suggest that hemoglobin levels and nutritional status directly affect muscle mass,[38,39] and inflammation and hemolysis impair functional capacity.[14] Silva et al. (2023) found that in children with sickle cell disease, exercise capacity correlated negatively with hemolysis (reticulocytes) and inflammation (interleukin 6) biomarkers.[14]

C-reactive protein (CRP), a widely recognized inflammatory marker, was associated with relative muscle power in our study, with its values consistently observed at high levels. Elevated CRP levels may indicate a chronic inflammatory state, which can contribute to decreased muscle strength in women with sickle cell disease. Previous studies show that CRP levels are significantly higher in sickle cell disease patients compared to healthy controls,[19] and inflamma-

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tion can negatively impact muscle function and overall physical performance.[40,41,42] Chronic inflammation can lead to muscle catabolism, where muscle tissue is degraded to provide energy, resulting in muscle mass loss.[43] Moreover, inflammation can cause fatigue and weakness, making it difficult to engage in physical exercise, which is essential for muscle mass preservation. Insulin resistance and decreased protein synthesis, associated with chronic inflammation, also contribute to muscle loss.[44]

While our findings suggest associations between muscle mass loss and hematological biomarkers like MCV and MCH, these associations should be interpreted with caution. The influence of sickle cell disease genotype and treatment on hematological parameters is critical.[45] Hydroxyurea, for instance, is known to increase MCV and MCH values,[46] which could confound the observed associations with muscle mass. Our study did not include detailed about transfusion history, limiting the ability to disentangle these effects.[47] Future studies should incorporate transfusion history to clarify whether MCV and MCH are direct biomarkers of sarcopenia or reflect treatment-related hematological changes.

The exclusive inclusion of female participants in our study restricts the generalizability of the findings, as sex differences in muscle physiology and sickle cell disease severity could influence both biomarker profiles and muscle outcomes. While we measured CRP as a marker of systemic inflammation, other inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and vascular cell adhesion molecule-1 (VCAM-1) have been shown to be elevated in sickle cell disease and associated with muscle damage.[48] Additionally, growth differentiation factor 15 (GDF-15), a marker of erythroid stress, correlates with muscle loss and decreased strength in sickle cell disease patients.[49,50,51] Recent research also implicates mitochondrial dysfunction and molecular regulators of muscle growth in sickle cell disease-related muscle impairment. Elevated circulating mitochondrial DNA (mtDNA) is associated with reduced aerobic capacity and muscle strength,[52,53] while increased levels of myostatin, a negative regulator of muscle mass, correlate with fatigue and muscle atrophy.[54,55,56] The lack of these additional biomarkers in our study represents a limitation and suggests that a broader inflammatory and molecular profile is needed to better understand the mechanisms underlying functional parameters in sickle cell disease.

The variability among sickle cell disease genotypes adds complexity to the interpretation of biomarker associations. Setayesh et al. (2024) reported that, despite the relatively milder hemolytic and inflammatory profiles observed in patients with the HbSC genotype, muscle dysfunction can still occur, potentially driven by microvascular disturbances and metabolic alterations.[57] Sathi (2020) further highlighted that the erythrocyte dehydration characteristic of HbSC disease may impair muscle perfusion, contributing to metabolic imbalances and functional deficits.[58] Lonardo et al. (2024) found that altered lipid profiles, particularly low HDL cholesterol, are associated with reduced muscle mass independently of inflammation,[59] reinforcing the multifactorial nature of low functional parameters in sickle cell disease. Furthermore, studies such as those by Hao et al. (2024), Wang et al. (2024), and Liu et al. (2024) demonstrate that disruptions in lipid metabolism, including imbalances in ceramides and sterols, can exacerbate muscle atrophy and functional decline.[60,61,62]

Emerging studies on extracellular vesicles and microRNAs offer mechanistic insights into muscle pathology in sickle cell disease. It is known that erythrocyte-derived exosomes containing miR-144-3p can influence metabolic pathways, potentially affecting muscle protein synthesis and contributing to muscle wasting.[63]

Metabolomic profiling has identified specific metabolic signatures associated with sarcopenia in older Chinese, including decreased creatine and carnitine levels, which may impair energy metabolism and muscle function.[64] These findings highlight the complex interplay between erythrocyte-derived factors and muscle health in sickle cell disease, emphasizing the need for further investigation into genotype-specific mechanisms.

The biomarkers analyzed in this study demonstrated good discriminatory capacity, with MCH showing a slightly higher AUC. The two identified cut-off points for MCH and appendicular skeletal muscle mass index (36.75 pg and 34.20 pg) offer distinct trade-offs between sensitivity and specificity, while maintaining the same overall accuracy. The higher cut-off (36.75 pg) is highly effective at identifying individuals with low appendicular skeletal muscle mass index, making it useful for broad screening where minimizing false negatives is critical. However, its lower specificity means it might incorrectly classify some healthy individuals. Conversely, the lower cut-off (34.20 pg) is excellent at correctly identifying individuals with normal appendicular skeletal muscle mass index, which is valuable when confirming the absence of muscle loss. Given that both cut-off points are above the normal MCH reference range, our findings suggest that MCH values greater than 32.0 pg could serve as a practical clinical indicator of low appendicular skeletal muscle mass index in women with sickle cell disease, warranting further investigation.

CRP exhibited a reasonable distinction capability but was inferior to hematological biomarkers, two CRP cut-off points (0.82 mg/dL and 0.28 mg/dL) for relative muscle power also present different clinical utilities. The higher cut-off (0.82 mg/dL) with its high sensitivity is well-suited for detecting active inflammatory processes likely contributing to reduced relative muscle power, making it valuable for early detection of potential muscle power issues. However, its lower specificity implies it might not precisely differentiate all cases. The lower cut-off (0.28 mg/dL), with its perfect specificity, is highly reliable for ruling out relative muscle power reduction when CRP is below this level. Its low sensitivity, however, means many true cases of reduced relative muscle power might be missed. Importantly, both CRP cut-off points are elevated beyond typical healthy ranges and fall within risk categories for cardiovascular disease. Clinically, CRP levels exceeding 0.28 mg/dL could signal a potential link between chronic inflammation and diminished relative muscle power in women with sickle cell disease, highlighting the need for comprehensive assessment.

MCH and MCV proved to be more effective in assessing functional muscle health. The mean values of the analyzed hematological and inflammatory parameters revealed significant associations with muscle mass. The consulted literature suggests that anemia and inflammation may negatively impact functional parameters due to elevated levels of these biomarkers. Incorporating grip strength and muscle power tests into clinical practice may provide additional functional assessments of muscle health in individuals with the disease, anticipating weakness and muscle mass loss. However, further research is needed to clarify this relationship.

The inclusion of objective strength tests in clinical practice for patients with sickle cell disease represents a significant advancement in their care. Regular muscle strength assessments allow for the early detection of sarcopenia, enabling preventive and therapeutic interventions before muscle loss becomes more severe. Identifying high-risk patients facilitates the implementation of more effective strategies, such as personalized exercise programs and appropriate nutritional follow-up. Sarcopenia prevention should begin in childhood, with the promotion

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of regular physical activity and access to quality healthcare.[65] The lack of access to specialized healthcare services and the absence of adapted physical activity programs can worsen sarcopenia in these patients. Moreover, individuals who have lived with the disease for a longer period tend to experience greater muscle loss, indicating that chronic exposure to sickle cell disease, combined with unfavorable socioeconomic conditions, may exacerbate muscle loss, in addition to the biological factors inherent to the disease.

This study fills a critical gap in scientific knowledge about biomarkers in women with sickle cell disease and represents the largest case series on this topic globally. While the cross-sectional design limits causality, it provides strong evidence linking hematological and metabolic biomarkers to muscular health, offering new clinical insights. Although limitations like the absence of detailed nutritional assessments and broader inflammatory markers exist, the findings emphasize the need for further research. The results have significant social impact, highlighting the urgency for tailored interventions to improve quality of life and care for this underserved population.

Limitations

This study has some limitations. The small sample size and inclusion of only female participants limit the statistical power and generalizability. Especially in the palmar grip strength group, the low-strength subgroup was small, with only 3 cases. Additionally, the limited panel of inflammatory and molecular biomarkers assessed precludes a comprehensive understanding of the pathophysiology of muscle loss in sickle cell disease.

CONCLUSION

Our findings confirm the associations between muscle loss with hematological parameters such as MCV and MCH. However, these biomarkers should not yet be considered definitive indicators of muscle loss without accounting for nutritional factor and treatment histories (as transfusions). Future studies with larger, more diverse cohorts and expanded biomarker panels, including inflammatory cytokines, mitochondrial markers, and molecular regulators of muscle mass, are needed to elucidate the complex mechanisms driving muscle impairment in sickle cell disease, before to establish these as definitive indicators. These findings underscore the critical need to integrate objective functional tests, such as grip strength and muscle power assessments, into routine clinical practice for this population.

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