Association between serum copper concentrations and body composition in children with spinal muscular atrophy: a cross-sectional study

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Running title: Serum copper and body composition in SMA children

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ABSTRACT

Background and Objectives: The role of serum copper in modulating body composition in patients with spinal muscular atrophy (SMA) remains uncertain. This study aimed to illustrate the correlation between serum copper concentrations and body composition in children with SMA. **Methods and Study Design:** This study was conducted at a pediatric medical center in China from July 2019 to August 2022. The study encompassed anthropometric measurements, serum analysis for copper, magnesium, zinc, and iron, as well as comprehensive body composition assessments. Multivariate analysis was utilized to assess the connection between serum copper concentrations and metrics of body composition. **Results:** This cross-sectional analysis encompassed 87 patients [median (IQR) age: 7 years (5–10), 58.0% female] diagnosed with SMA who were undergoing comprehensive multidisciplinary management. The results revealed a positive association between the serum copper concentration and both fat mass percentage (β = 0.50, 95% confidence interval (CI): 0.07 to 0.92, $p = 0.025$) and fat-muscle ratio (β = 0.02, 95% CI: 0.01 to 0.03, $p = 0.009$). Conversely, a negative correlation was detected between the concentrations of serum copper and muscle mass percentage (β = -0.70, 95% CI: -1.11 to -0.29, $p = 0.001$). **Conclusions:** These findings suggest a correlation between copper concentrations and body composition in SMA, which offers valuable insights for addressing metabolic dysregulation in patients with SMA.

Key Words: anthropometric variables, body composition, pediatric patients, serum copper, spinal muscular atrophy

INTRODUCTION

Spinal muscular atrophy (SMA), which is characterized by degenerating motor neurons, often results in skeletal muscle atrophy and, if left untreated, potential premature death.[1] Pediatric-onset SMA has been subdivided into three main types (types 1 to 3). This classification is based on the age of onset and maximum motor function achieved in untreated patients. Type 1: no sitting or rolling, Type 2: sits, no walking, and Type 3: walks (limited).[1] Over the past few decades, multidisciplinary supportive care guidelines for SMA have been established as the standards of care.[2,3] Recently, treatment strategies targeted at elevating functional survival motor neuron (SMN) protein concentrations have demonstrated both safety and clinically significant improvements in achieving motor milestones.[4] However, whether these SMN-inducing therapies effectively address body composition abnormalities commonly observed in patients with SMA, such as reduced muscle mass and increased fat mass, remains unclear.[5]

The simultaneous presence of sarcopenia and obesity in individuals indicates an increased risk of negative health consequences, including insulin resistance, dyslipidemia, and hypertension, which are precursors of type 2 diabetes mellitus and cardiovascular diseases.[6]

Physical activity and nutritional interventions have been documented as effective strategies for managing obesity and sarcopenia.[7] However, improving body composition through exercise in individuals with SMA is challenging. Studies have confirmed the role of micronutrients in obesity and sarcopenia, although the specific mechanisms remain unclear.[8-10] Copper, an essential trace element, serves as a crucial catalytic co-factor in enzymatic reactions, playing a vital role in cellular metabolism.[11] It participates in mitochondrial function, inflammatory responses, antioxidative functions, and fat metabolism.[12] However, excessive copper concentrations may lead to oxidative damage and inflammatory reactions, potentially contributing to the development of obesity.10 High concentrations of copper have been linked to reactive oxygen species (ROS) caused by oxidative stress, which can activate proteolytic systems, causing muscle protein breakdown and subsequent muscle loss. Moreover, ROS may impair mitochondrial function and biogenesis, thereby contributing to muscle degradation.[13-14] In addition, zinc, magnesium, and iron are all vital trace elements that have been implicated in oxidative stress processes and potentially have prominent roles in the development of sarcopenia, a condition characterized by muscle loss, as well as the accumulation of excessive fat mass.[15-17]

Multiple studies consistently demonstrate a correlation between the concentrations of serum copper and body composition in the general population.[18-21] However, whether the serum copper concentrations are related to body composition in patients with SMA remains confusing.

This study aimed to investigate a possible correlation between the concentration of serum copper and body composition assessed by dual-energy X-ray absorptiometry (DXA).

MATERIALS AND METHODS

Participants and study design

This cross-sectional study enrolled individuals diagnosed with spinal muscular atrophy (SMA) at our hospital between July 2019 and August 2022. The criteria for inclusion were as follows: (1) genomic characterization of 5qSMA, (2) age under 18 years, and (3) provision of informed consent. Individuals meeting the following criteria were excluded: (1) the presence of a concomitant illness or a recent history of acute illness, (2) previous spinal fusion surgery or the existence of metallic surgical implants, (3) receipt of disease-modifying treatment, and

(4) absence of dual-energy X-ray test results. The research protocol was approved by the Ethics Committee of Children's Hospital, Zhejiang University School of Medicine (2019-IRB-171). Written informed consent was obtained from the participants' parent/legal guardians/next of kin to participate in the study. Figure 1 illustrates the process for selecting patients.

Measurement of variables

Anthropometric measurements were consistently taken by a proficient dietitian who followed established conventional criteria and recognized measurement protocols. In cases where the patient was unable to stand, height measurement was substituted with arm span. Blood samples were collected and centrifuged to separate the serum, which was subsequently analyzed using the MB5 multi-channel atomic absorption spectrophotometer (Beijing Persee General Instrument Company Limited, Beijing, China) to determine the copper, iron, magnesium, and zinc concentrations. Blood samples were obtained after a fasting period for lipid profiling. Serum concentrations of triglycerides and cholesterol were accurately measured using a Beckman Coulter automated biochemical analyzer. Disease classification was determined based on the highest level of athletic capacity attained. Data on the frequency, content, and intensity of rehabilitation therapy in pediatric patients were also recorded. Patients undergoing rehabilitation therapy a minimum of three times weekly, with each session lasting at least 1 hour, were categorized into the rehabilitation group, while those who did not meet these criteria were classified into the non-rehabilitation group.

Study outcomes (dependent variables)

Following a 12-h fasting period, the body composition parameters of each participant, encompassing fat mass, fat-free mass, and bone mass, were evaluated through whole-body DXA scans (Hologic Horizon W model, Hologic Inc., Danbury, CT, USA). Muscle mass (MM) was calculated by subtracting the bone mass from the fat-free mass. Fat mass percentage (FM%) and muscle mass percentage (MM%) were ascertained by dividing each respective mass by the total body weight. The Fat-to-Muscle Ratio (FMR) was also derived as a quotient of fat mass to muscle mass.[22]

Statistical analysis

Continuous data are depicted using mean (standard deviation) in cases of normal (Gaussian) distribution or using medians along with interquartile ranges (IQR) for data exhibiting skewness. Categorical variables were expressed in terms of frequencies and proportions. For continuous data, analysis of variance in serum copper tertiles was conducted with the Kruskal–Wallis H test for skewed data and the one-way ANOVA for data with a normal distribution. For categorical variables, the chi-square test was implemented.

FM%, MM%, and FMR were included as the outcome variables, and other variables were included as potential confounders, in generalized linear models (GLMs) to assess the associations. Furthermore, multivariate linear regression models were performed to evaluate the associations. Covariates were chosen according to their relevance to the outcomes of interest or if they led to modifications in the effect estimates exceeding 10%. After considering the clinical significance, we adjusted for age, sex, type, height, total cholesterol (TC), zinc, iron, and magnesium. Serum copper concentrations were also categorized into categorical variables based on tertiles, and the p value for the trend was calculated to confirm the results. Results are presented as beta coefficients (β) with accompanying 95% confidence intervals (CIs).

Sensitivity analyses were conducted to confirm the findings' accuracy and reliability. To investigate the possible influence of unmeasured confounders on the association between serum copper concentrations and body composition, E-values were computed. These values determine the smallest effect size an unaccounted confounder would need to nullify the observed relationship between the two variables.

Statistical significance was established at a two-tailed p value of <0.05. The R software package (http://www.R-project.org, The R Foundation) and Empowerstats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA) were utilized for all statistical computations.

RESULTS

Baseline characteristics

In total, 150 patients were initially selected for screening. After excluding ineligible candidates, 87 patients were subsequently included in the analysis for this study. Table 1 provides a comprehensive overview of the participants' baseline characteristics categorized based on serum copper tertiles. The median age of the participants was 7 years, with an interquartile range (IQR) of 5–10 years and a slight male predominance (57.5%).

The data revealed notable variations in certain baseline characteristics across serum copper tertiles. Specifically, age and height displayed significant differences, with the first tertile having a median age of 9 years (p = 0.027) and the tallest average height compared to the other tertiles (*p* = 0.015). In contrast, the analysis revealed no notable differences in the distribution of sex and SMA types among the tertiles, with *p* values of 0.472 and 0.238, respectively. Regarding biochemical assessments, significant variation was observed in zinc concentrations across tertiles (*p* = 0.009), whereas triglyceride, cholesterol, and iron concentrations were consistent. Significant differences were also observed in the fat mass percentage and fat-to-muscle ratio among the tertiles (*p* = 0.010 and *p* = 0.026, respectively).

Association between variables and body composition parameters

Table 2 summarizes the associations between various characteristics and body composition parameters (MM%, FM%, and FMR) in children with SMA. Notably, serum copper concentrations and MM% were found to have a significant negative association (β = -0.49, 95% CI: -0.89 to -0.08, *p* = 0.020), indicating that higher serum copper concentrations correspond to a lower MM%. Additionally, height and weight were identified as influential factors that showed significant associations with body composition parameters, with weight being particularly prominent. In contrast, other evaluated variables such as age, sex, and some biochemical parameters (zinc, iron, and magnesium) did not show significant associations with the assessed body composition measurements in the studied cohort.

Independent relationship between serum copper concentrations and body composition parameters

Table 3 presents the results of a comprehensive multivariate linear regression analysis investigating the association between the concentrations of serum copper and crucial body composition metrics (FM%, MM%, and FMR) in individuals with SMA.

In the unadjusted model, serum copper exhibited a significant negative association with MM% (β = -0.49, 95% CI: -0.89 to -0.08, *p* = 0.021), a relationship that persisted even after adjustment for confounding variables, for instance, age, sex, cholesterol, iron, magnesium, type, height, and zinc in Model 2. The fully adjusted model revealed that an increase of one unit in serum copper was associated with an increase in FM% (β = 0.50, 95% CI: 0.07 to 0.92, *p* = 0.025) and a rise in FMR (β = 0.02, 95% CI: 0.01 to 0.03, *p* = 0.009).

A stratified analysis, categorizing serum copper into tertiles, further elucidated the relationship dynamics. Notably, participants within the higher serum copper tertiles exhibited a notable reduction in MM%, coupled with an elevation in FM% and FMR, compared to their counterparts with serum copper concentrations below 17.73 µmol/L in Model 2 (fully adjusted) ($p < 0.01$ for trend), although the trends were not consistent in Crude and Model 1 for FM% and FMR.

DISCUSSION

In our cross-sectional research conducted in China, which included 87 individuals diagnosed with SMA, univariate and multivariate linear regression analyses were utilized to explore the relationship between serum copper concentrations and body composition. In both the unadjusted and slightly adjusted models, a notable correlation was identified between serum copper concentrations and MM%, while no substantial link was observed between serum copper concentrations and either FM% or FMR. However, in the comprehensively adjusted model, a negative association was seen between serum copper concentration and MM%, in contrast to a positive association with both FM% and FMR. This pattern persisted when serum copper concentration was analyzed as a categorical variable.

Our study aligns with previous research, underscoring a pronounced correlation between elevated serum copper concentrations and obesity prevalence in pediatric populations. Analyses from the 2011–2014 and 2011–2016 National Health and Nutrition Examination Surveys have shown a substantive positive association between serum copper concentrations and obesity indices in individuals aged 6–19 years.[19, 23] Notably, these investigations predominantly utilized the body mass index (BMI) and waist circumference as metrics for obesity characterization, notwithstanding their limitations in distinguishing adipose tissue from muscle mass. A previous study by Wu et al. revealed significant correlations between elevated serum copper concentrations and an increased body fat percentage in an adult cohort, broadening our understanding.[21] Similarly, Liang et al. revealed intricate correlations, demonstrating that elevated plasma copper concentrations are associated with increased fat deposition and an altered ratio of fat to lean mass in the pediatric cohort, evaluated using DXA.[18] Our investigation aligns with the findings reported by Lee et al., who observed elevated hair copper concentrations in individuals with reduced muscle mass, showing consistency with our study despite using blood samples for copper quantification.[20] In contrast, Ngu et al. employed bioelectrical impedance analysis in their study and discovered a positive correlation between the concentrations of serum copper and body fat mass, along with an inverse relationship with skeletal muscle mass in adults with characteristics of metabolic syndrome.[24] Our study delves into these relationships within the specific population of individuals with SMA, diverging from a broader population focus. Our research, consistent with existing studies, sheds light on body composition characteristics in individuals suffering from SMA, marked by higher fat mass and reduced fat-free mass compared to healthy individuals.[25,26] Central to our findings is the confirmation of a significant association between serum copper concentrations and body composition dynamics, specifically tailored to the unique physiology of patients with SMA.

Although treatments such as disease-modifying therapies have demonstrated notable clinical impacts, particularly in terms of muscle mass and strength, they do not constitute a complete cure, and their effects are not consistently substantial.[27,28] Our findings suggest a novel approach for treating individuals with SMA, indicating that a reduction in serum copper concentrations could potentially contribute to a reduction in fat mass and a rise in muscle mass, providing specific benefits in addressing metabolic dysregulation in SMA. To validate and expand upon these initial findings, further investigations and clinical trials are imperative, with the ultimate goal of translating them into effective treatment strategies for the SMA population.

A meta-analysis performed by Banach et al. firmly established the association between decreased serum zinc and magnesium concentrations and increased fat mass, whereas the relationship between serum iron concentrations and fat mass remains inconclusive and warrants further investigation.[15] Additionally, another meta-analysis by Van Dronkelaar et al., which focused on the older adult population failed to demonstrate a significant correlation between serum zinc, magnesium, and iron concentrations and muscle mass.[29] Constrained by a limited sample size, our study has insufficient statistical power to comprehensively analyze the correlations among body composition, and zinc, magnesium, and copper concentrations. Notably, our study population comprises children with SMA which differs significantly from the predominantly adult and older adult cohorts investigated in the aforementioned meta-analyses.

To the best of our knowledge, the present study is one of the few investigations examining the relationship between serum copper concentrations and body composition in patients with SMA. This observational study is inherently susceptible to various confounding factors. However, we implemented rigorous statistical adjustment methods to minimize potential confounders. Furthermore, to confirm the reliability of the findings, additional analyses were conducted by categorizing serum copper into tertiles and examining the trends. These measures strengthen the validity of our conclusions.

Our study had several inherent limitations. First, the cross-sectional design employed prevented us from establishing causal relationships based on our findings. Given the rarity of the disease, our sample size was limited. However, with such a small sample size, we found a correlation between serum copper and muscle mass and fat mass in the SMA population, and the calculated statistical power of this test was 0.73 for MM%, 0.72 for FM%, and 0.70 for FMR. Furthermore, as our study focused exclusively on patients with SMA, the results cannot be extrapolated to the non-SMA population. Additionally, our participants were predominantly over five years old, which may have limited the direct applicability of our findings to those under the age of five years. Lastly, our study did not include inter- and intra-coefficient analysis of serum trace elements. Despite potential measurement errors, our findings demonstrated a relationship between serum copper and body composition. Had the measurements been more precise, the effect size might have been stronger, with narrower confidence intervals, although any errors present likely biased the results towards the null hypothesis.

In this investigation involving individuals with SMA, serum copper demonstrated an inverse relationship with MM% and a positive relationship with FM% and FMR. Our research further adds to valuable practical evidence that contributes to the ongoing discussion on the role of lower serum copper concentrations in enhancing body composition.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors have no conflicts of interest to declare.

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Table 1. Baseline characteristics of children with spinal muscle atrophy according to the tertiles of serum copper†

Variable	Tertile 1‡	Tertile 2‡	Tertile 3‡	*p* value
N	26	32	29	
Age, years	9.00 (5.25–12.00)	6.00 (4.00–8.00)	7.00 (6.00–10.00)	0.027
Sex (n, %)				0.472
Male (%)	15 (57.7%)	16 (50.0%)	19 (65.5%)	
Female (%)	11 (42.3%)	16 (50.0%)	10 (34.5%)	
Type§				0.238
1 (%)	2 (7.69%)	4 (12.5%)	0 (0.00%)	
2 (%)	12 (46.2%)	19 (59.4%)	16 (55.2%)	
3 (%)	12 (46.2%)	9 (28.1%)	13 (44.8%)	
Rehabilitation				0.329
No (%)	12 (48.0%)	16 (50.0%)	9 (32.1%)	
Yes (%)	13 (52.0%)	16 (50.0%)	19 (67.9%)	
Height (cm)	131.1 (19.5)	117.0 (17.4)	126.3 (18.1)	0.015
Weight (kg)	28.4 (13.9)	23.7 (11.1)	26.9 (11.9)	0.341
TG (mmol/L)	0.88 (0.37)	0.76 (0.30)	0.96 (0.47)	0.138
TC (mmol/L)	4.30 (0.77)	4.39 (0.96)	4.29 (1.16)	0.912
Zinc (μ mol/L)	84.9 (12.1)	78.7 (8.52)	87.7 (13.4)	0.009
Iron (mmol/L)	8.88 (0.97)	8.45 (0.77)	8.70 (0.92)	0.178
Magnesium (mmol/L)	1.59 (0.15)	1.63 (0.14)	1.69 (0.16)	0.048
Muscle mass percentage (%)	55.2 (10.6)	51.0 (10.4)	49.2 (6.56)	0.060
Fat mass percentage (%)	40.0 (9.55)	46.7 (9.61)	45.9 (6.98)	0.010
Fat-muscle-ratio	0.77 (0.29)	0.98 (0.36)	0.96 (0.25)	0.026

TG, triglycerides; TC, cholesterol

†Values are presented as n/N (%), median (IQR), or mean (standard deviation).

‡Serum copper level (μmol/L): Tertile 1, 16.6 (15.6–17.1); Tertile 2, 19.2 (18.5–20.3); Tertile 3, 25.1 (23.2–28.5).

§Type 1: No sitting or Rolling, Type 2: Sits, no walking, Type 3: Walks (limited).

Table 2. Association between variables and body composition

Variables	Statistics†	Muscle mass percentage (%)‡	Fat mass percentage (%)‡	Fat-muscle-ratio‡
Age	7.00 (5.00–10.0)	-0.08 (-0.56, 0.40) 0.749	0.14 (-0.33, 0.60) 0.563	0.00 (-0.01, 0.02) 0.600
Sex (n,%)				
Male (%)	50 (57.5%)	0	0	0
Female (%)	37 (42.5%)	-1.91 (-6.00, 2.17) 0.362	0.98 (-2.96, 4.91) 0.627	0.05 (-0.09, 0.18) 0.484
Type				
1	6 (6.90%)	0	0	0
2	47 (54.0%)	-1.78 (-9.85, 6.29) 0.667	-1.19 (-8.90, 6.51) 0.762	0.03 (-0.23, 0.30) 0.818
3	34 (39.1%)	2.12 (-6.12, 10.35) 0.616	-5.14 (-13.0, 2.72) 0.203	-0.12 (-0.39, 0.15) 0.380
Rehabilitation				
No	37 (43.5%)	0	0	0
Yes	48 (56.5%)	-0.31 (-4.43, 3.81) 0.883	-0.42 (-4.45, 3.61) 0.839	0.00 (-0.13, 0.14) 0.961
Height (cm)	124.4 ± 19.0	-0.10 (-0.20, 0.01) 0.070	0.07 (-0.03, 0.18) 0.159	0.00 (-0.00, 0.01) 0.067
Weight (kg)	26.2 ± 12.3	-0.32 (-0.47, -0.17) <0.0001	0.29 (0.15, 0.44) 0.0002	0.01 (0.01, 0.02) <0.0001
TG (mmol/L)	0.86 ± 0.39	-4.85 (-9.93, 0.23) 0.065	3.15 (-1.78, 8.08) 0.214	0.13 (-0.04, 0.30) 0.131
TC (mmol/L)	4.33 ± 0.97	-1.17 (-3.26, 0.92) 0.276	0.94 (-1.07, 2.94) 0.364	0.03 (-0.04, 0.10) 0.453
Zinc (μmol/L)	83.6 ± 11.9	0.02 (-0.15, 0.19) 0.846	-0.03 (-0.19, 0.13) 0.721	-0.00 (-0.01, 0.00) 0.733
Iron (μmol/L)	8.66 ± 0.89	0.55 (-1.73, 2.84) 0.635	-0.24 (-2.44, 1.95) 0.828	-0.01 (-0.08, 0.07) 0.816
Magnesium (μmol/L)	1.64 ± 0.15	-9.75 (-23.01, 3.50) 0.153	11.6 (-1.05, 24.22) 0.076	0.33 (-0.11, 0.76) 0.150
Copper (μmol/L)	20.8 ± 4.87	-0.49 (-0.89, -0.08) 0.020	0.40 (0.00, 0.79) 0.051	0.01 (-0.00, 0.03) 0.057

TG, triglycerides; TC, cholesterol

†Data are presented as n, n (%), mean ± SD, or median (IQR).

‡Data are represented as β (95% CI) and p value.

Table 3. Multivariable linear regression analysis about serum copper and body composition†

Exposure	Crude‡	Model 1§	Model 2¶
Muscle mass percentage (%)			
Copper	-0.49 (-0.89, -0.08) 0.020	-0.50 (-0.91, -0.09) 0.019	-0.70 (-1.11, -0.29) 0.001
Copper tertile			
Low	0	0	0
Middle	-4.17 (-9.04, 0.71) 0.098	-4.24 (-9.27, 0.78) 0.102	-4.70 (-9.49, 0.09) 0.058
High	-5.96 (-10.91, -1.01) 0.021	-6.11 (-11.10, -1.13) 0.019	-8.75 (-13.90, -3.61) 0.001
p for trend	0.021	0.018	0.001
Fat mass percentage (%)			
Copper	0.40 (0.00, 0.79) 0.051	0.40 (0.00, 0.80) 0.051	0.50 (0.07, 0.92) 0.025
Copper tertile			
Low	0	0	0
Middle	6.75 (2.17, 11.33) 0.005	7.23 (2.52, 11.95) 0.004	6.85 (2.08, 11.62) 0.006
High	5.97 (1.32, 10.62) 0.014	6.01 (1.33, 10.69) 0.014	7.45 (2.32, 12.58) 0.006
p for trend	0.018	0.017	0.006
Fat-muscle-ratio			
Copper	0.01 (-0.00, 0.03) 0.057	0.01 (-0.00, 0.03) 0.056	0.02 (0.01, 0.03) 0.009
Copper tertile			
Low	0	0	0
Middle	0.20 (0.05, 0.36) 0.014	0.22 (0.05, 0.38) 0.011	0.24 (0.08, 0.40) 0.005
High	0.19 (0.03, 0.35) 0.024	0.19 (0.03, 0.36) 0.023	0.28 (0.11, 0.45) 0.002
p for trend	0.029	0.027	0.003

†Data are presented as the β coefficient (95% CI) p value. The lowest tertile was the reference for serum. Outcome variables: Muscle mass percentage, fat mass percentage, and fat-muscle ratio. Exposure variable: Serum copper and copper tertile.
‡Crude: not adjusted.
§Model 1: adjusted for age and sex.
¶Model 2: adjusted for age, sex, cholesterol, iron, magnesium, type, height, and zinc concentrations
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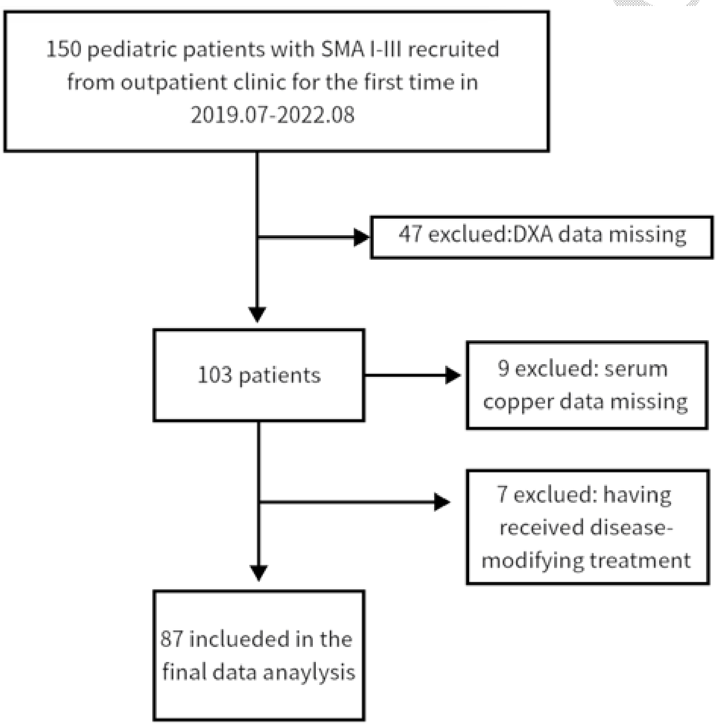

Figure 1. Flow diagram of patient selection during the study