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Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios of overweight children and adolescents

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SUMMARY

OBJECTIVE: This study aimed to compare neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio of overweight children and adolescents with the eutrophic ratios and to verify whether these ratios are associated with age, inflammation, Z-score of body mass index, and waist-to-height ratio.

METHODS: This is a cross-sectional study involving 64 overweight and 106 eutrophic children and adolescents. Data on weight, height, and waist circumference (body mass index and waist-to-height ratio), blood count (neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio), and high-sensitivity C-reactive protein were collected.

RESULTS: The mean age of participants was 8.4±3.2 years. The ratios did not differ between the overweight and non-overweight groups. The platelet-to-lymphocyte ratio has shown a direct and independent association with body mass index (p=0.031) and waist-to-height ratio (p=0.018), a fact not observed for neutrophil-to-lymphocyte ratio. The ultrasensitive C-reactive protein level was higher in the obesity group (p=0.003). Both ratios had a direct and independent association with age.

CONCLUSION: The ratios did not differ between the overweight and non-overweight groups. There was a direct and independent association of platelet-to-lymphocyte ratio with overweight, not observed in neutrophil-to-lymphocyte ratio. The ratios have significantly increased according to the age of the participants.

KEYWORDS: Pediatric obesity. Inflammation. Neutrophils. Lymphocyte count. Platelet count.

INTRODUCTION

Childhood obesity has reached epidemic proportions and is currently a serious public health issue. Its global prevalence has increased 10-fold in the past four decades[1]. In Brazil, the prevalence of overweight in the general population has increased from 43 to 60% between 2002 and 2019, currently reaching 30% of children between 5 and 9 years of age and 19.4% of adolescents[2]. It is known that overweight children are more likely to become obese adults[3].

The pathophysiology of excessive weight gain is complex with interactions between genetic and environmental factors[4]. Excessive adiposity causes a low-grade chronic systemic inflammation, responsible for several comorbidities associated with it[5].

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) obtained from blood count are recognized as simple ways to assess inflammation and prognosis of several diseases as infections, mental disorders, and neoplasic diseases[6-11]. Although it is easily accessible and low-cost markers, there are few studies that assess NLR and PLR in children and adolescents, especially in our field. In the overweight pediatric age group, in which a low-grade inflammatory state predominates, such markers can be important as predictive factors for the development of complications such as insulin resistance and cardiovascular events.

The aims of this study were to compare NLR and PLR of overweight children and adolescents with the eutrophic ratios and to verify the association of these ratios with age, inflammation, Z-score of body mass index (BMIz), and waist-to-height ratio (WHtR).

METHODS

This is a cross-sectional, controlled study, involving 64 overweight children and adolescents, and 106 eutrophic and healthy individuals grouped by age and gender as a comparison group. The study was conducted at the Cidade dos Meninos Maria

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Imaculada Institution, which serves underprivileged children in the city of Santo André, Brazil.

Inclusion criteria were as follows: children/adolescents enrolled at the institution in 2019, aged over 4 years. Exclusion criteria were as follows: family members and children who did not consent to participate in the study, people with short stature or thinness, children aged 4–5 years classified as at risk of overweight, children with chronic diseases except asthma and allergic rhinitis, children who made use, within 30 days prior to blood collection, of systemic corticosteroids or non-steroidal anti-inflammatory drugs, and children who were ill within 30 days prior to collection.

Participants and their family members signed a free and informed consent form and an assent form, with detailed explanations on the research protocols.

A questionnaire was applied to the people responsible for the individuals, covering information about preexisting diseases, medications in use, and current health conditions.

The application of the questionnaire, physical examination, anthropometric measurements, and blood collection were performed in appropriate spaces in the institution.

Regarding anthropometric measurements, weight (kg), height (m), and waist circumference (cm) were measured. Waist circumference was obtained at the midpoint between the 10th rib and the iliac crest[12]. Subsequently, BMIz and WHtR were calculated. WHtR was classified as altered when the value was ≥0.5[13]. For the BMIz classification, the cutoff points recommended by the World Health Organization (WHO) were adopted[14].

The school had 541 enrolled students, of which 173 were excluded for being under 4 years of age and 23 for not consenting to participate. A questionnaire was applied and a physical examination was performed in 345 participants, of which 57 were excluded due to changes in the physical examination and eight due to the questionnaire. Of 280 considered eligible for the study, 60 did not consent to blood collection and 50 were not invited to be paired with the participants. At the end, 170 children and adolescents participated in all stages of the study.

Blood samples were obtained via vacuum venipuncture. The complete blood count was evaluated by automated flow cytometry and the ultrasensitive C-reactive protein (us-CRP) was analyzed by turbidimetric method. Laboratory tests were performed at the Clinical Analysis Laboratory of the Centro Universitário FMABC. NLR was obtained by dividing the number of neutrophils and the number of lymphocytes. PLR was obtained by dividing the platelet count and the number of lymphocytes.

Data were entered into an Excel spreadsheet (Microsoft) and analyzed using the Stata (r) Software (StataCorp, LC) version 11.0. Qualitative variables were presented as absolute and percentage numbers. Parametric data were expressed as mean±-standard deviation, with p-value calculated using Student's t-test. Non-parametric data expressed as median (minimum–maximum), with p-value calculated by the Mann-Whitney test. To compare the classifications of variables between eutrophic and overweight children, we used the χ^2 test. For correlation analysis, the Spearman's test was applied. For regression analysis, multivariate linear regression was performed. The significance level adopted was 5%.

The study was approved by the Research Ethics Committee of the Centro Universitário FMABC under opinion number: 3,058,583, CAAE: 02670518.7.0000.0082.

RESULTS

A total of 170 children and adolescents were evaluated. The general characteristics of the study participants are shown in Table 1. The mean age was 8.4±3.2 years, 71.2% were prepubescent, and there was a slight predominance of males (52.4%).

Regarding nutritional status, 106 (62.4%) were eutrophic and 64 (37.6%) were overweight (overweight, obesity, and severe obesity). As for WHtR, 64 (37.6%) had values considered to be increased (Table 1). WHtR was high in 21.7% of eutrophics and 64.1% of the overweight group (p<0.001).

Table 2 shows that there was no difference in the count of leukocytes, neutrophils, lymphocytes, platelets, red cell distribution width (RDW) (anisocytosis index), NLR, and PLR when comparing the medians of eutrophic, overweight, and obese individuals. The median of us-CRP was higher in the obesity group (p=0.003).

Spearman's correlation was performed between age, BMIz, and WHtR with laboratory variables. There was a direct and significant correlation between age and mean platelet volume

Table 1. General characteristics of the study population.

Variable		N	%
Sex	Male	89	52.4
Age, years	4–5	32	18.8
	5–10	78	45.9
	≥10	60	35.3
Pubertal development	Prepubescent	121	71.2
Nutritional diagnosis	Eutrophy	106	62,4
	Overweight	39	22.9
	Obesity	19	11.2
	Severe obesity	6	3.5
Waist-to-height ratio	≥0.5	64	37.6

(MPV) (r=0.2077; p<0.001), NLR (r=0.3903; p<0.001), and PLR (r=0.2713; p<0.001) and an inverse correlation with leukocyte count (r=-0.2039; p=0.007), lymphocytes (r=-0.4672; p<0.001), and platelets (r=-0.3445, p<0.001). BMI and WHtR showed significant and direct correlation with us-CRP (r=0.1619; p<0.001 and r=0.2518; p<0.001, respectively). WHtR was directly associated with platelet count (r=0.1508; p<0.001) and lymphocyte count (r=0.2328; p=0.002).

Spearman's correlation between us-CRP, NLR, and PLR with laboratory variables was also applied. There was a direct and significant correlation between us-CRP and RDW (p<0.001), which did not happen for NLR and PLR.

Multivariate linear regression analysis was performed, considering NLR and PLR as dependent variables (Table 3). NLR was directly and independently associated with age (p<0.001), while PLR was directly and independently associated with age (p<0.001), BMIz (p=0.031), and WHtR (p=0.018).

DISCUSSION

This study showed that NLR and PLR did not differ between overweight and non-overweight children and adolescents. Both ratios have increased according to the age of the participants. There was a direct and independent association of PLR with BMI and WHtR, the fact not observed for NLR.

A study performed in Turkey with 187 children and adolescents aged 6–15 years (130 obese and 57 eutrophic) have shown that NLR and CRP concentrations were significantly higher in the obese group compared to healthy controls. PLR did not differ between the groups. Some hypotheses can be suggested to explain the difference in relation to our findings: the study group from Turkey did not include overweight individuals, only obese; in addition, the mean age (12.84±2.04 years) was higher than that of our study (8.4±3.2 years)[15].

The ratios were also assessed in adults. A cross-sectional and controlled study with 90 participants from Turkey (45 severely

Table 2. Comparison of laboratory variables between groups of obesity (n=25), overweight (n=39), and eutrophic (n=106) children and adolescents.

Variable	Eutrophia (n=106)	Overweight (n=39)	Obesity (n=25)	p
Leukocytes (k/mm^3)	6.95 (2.9–14.6)	6.4 (3.3–10.8)	7.4 (3–23.4)	0.23
Neutrophils (k/mm^3)	2.5 (0.32–8.71)	2.47 (0.46–4.78)	3.51 (0.2–15.64)	0.30
Lymphocytes (k/mm^3)	2.81 (1.02–15.64)	2.79 (1.28–6.06)	2.79 (1.62–7.1)	0.80
Platelets (k/mm^3)	297 (70–517)	284 (219–459)	304 (209–487)	0.92
RDW (%)	13.2 (11,9–15,6)	13.1 (11.8–14.9)	13.3 (12–14.6)	0.50
NLR	0.82 (0.11–3.99)	0.89 (0.12–0.61)	1.09 (0.06–0.66)	0.30
PLR	102.07 (35.35–249.02)	113.2 (46–236.5)	106.8 (38–224)	0.68
us-CRP (mg/L)	0.3 (0.1–13.5)	0.5 (0.1–10)	0.9 (0.1–11)	0.003

Non-parametric data are expressed as median (minimum–maximum). RDW: anisocytosis index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio, us-CRP: ultrasensitive C-reactive protein.

Table 3. Linear regression of variables associated with neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio (n=170).

Variable	Coefficient	Standard error	p	Confidence interval
NLR-dependent variable				
Age	0.005	0.001	0.000	0.003 to 0.008
BMIz	0.087	0.049	0.083	-0.011 to 0.185
WHtR	-1.591	1.119	0.186	-3.954 to 0.771
us-CRP	0.035	0.020	0.084	-0.004 to 0.767
PLR-dependent variable				
Age	0.324	0.089	0.000	0.147 to 0.501
BMIz	7.636	3.519	0.031	0.688 to 14.585
WHtR	-201.356	84.341	0.018	-367.8 to -34.82
us-CRP	1.113	1.456	0.446	-1.762 to 3.990

Independent variables: age, BMIz, WHtR, and us-CRP. NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; BMIz: Z-score of body mass index; WHtR: waist-to-height ratio; us-CRP: ultrasensitive C-reactive protein.

obese and 45 eutrophic) with mean ages of 33±7 and 33±5 years, respectively, showed a statistically significant difference between groups for PLR (p=0.033) and RDW (p<0.001). Severely obese individuals with overweight/obesity have showed PLR values significantly higher comparing to euthropic[16]. However, three studies conducted with adults (n=1,054) have found no association between BMI and PLR[17-19]. A Korean study evaluated the medical records of 15,654 individuals (median age 46 years, age range 14–90 years) observed that leukocyte, neutrophil, and lymphocyte counts, even within their normal range, are closely related to the presence of metabolic syndrome components after adjustment for age, sex, smoking, alcohol consumption, education, and income. The study did not assess NLR and PLR. Low-grade inflammation associated with metabolic syndrome may be the cause of the increased leukocyte count[20].

Regarding NLR, three studies (n=2,090) did not observe an association between BMI and ratio[17,18,21]. A study with 231 participants (mean 57.1±16.3 years) observed lower NLR (p=0.04) in obese compared to eutrophic individuals. According to the Spearman's test, there was a significant and negative correlation, although weak, between BMI and NLR (r=-0.145; p=0.029). The mean lymphocyte count was higher in the group of overweight and obese individuals (p=0.011), influencing lower NLR values in overweight[19].

A retrospective study conducted in Taiwan with 34,013 participants (10,475, 30.8% with metabolic syndrome) have demonstrated that increased NLR is a significant risk factor for metabolic syndrome (p<0.001), demonstrating that this ratio can help identify individuals at risk for this syndrome[22].

One study evaluated 60 adolescents aged 11–16 years (obese group: 30; control group: 30) in 2021 and found no significant difference between the groups regarding leukocyte, neutrophil, lymphocyte, platelet, NLR, and PLR counts (p>0.05)[23].

In this study, only PLR showed an association with BMI and WHtR in children and adolescents. The association with WHtR, which reflects visceral adiposity and is related to insulin resistance, and the fact that PLR is simply obtained from the blood count, suggests the importance of this assessment and the investigation of its relationship with associated morbidities in children and adolescents, in future studies.

The highest median values of us-CRP in overweight individuals point to the low-grade chronic inflammation present in this group. Other studies also describe the association between overweight and inflammation detected by us-CRP[18,21,24]. The presence of inflammation in overweight individuals is admittedly a risk factor for comorbidities. A study with 1,376 children and adolescents from Greek schools (mean age of 11.19±0.66 years) showed that CRP levels can early identify metabolic syndrome[25].

A strong point of the study was the careful selection of the sample, excluding children and adolescents with acute or chronic diseases that present with inflammation from the collection. The main limitations of the study were the assessment of a single institution on the outskirts of the city of Santo André/SP, not allowing to state that the data can be extrapolated to the general population, and also the cross-sectional design, not allowing the assessment of cause-effect.

CONCLUSIONS

Neutrophil-to-lymphocyte ratio (NLR) and PLR did not differ between the groups of overweight and non-overweight children and adolescents. PLR was independently associated with BMI and WHtR, a fact not observed for NLR. The ratios increased significantly and independently with the age of the participants.

ETHICAL ASPECTS

All authors declare that there is no professional or financial conflict of interest. This study was approved by the Research Ethics Committee of the FMABC University Center (dated December 5, 2018, CAAE: 02670518.7.0000.0082, opinion number: 3.058.583). Families received information, risks, and benefits from the study. Literate children received a TALE and their guardians a TCLE.

AUTHORS' CONTRIBUTIONS

LGY: Data curation, Investigation, Writing – original draft. **JCPF**: Data curation, Investigation, Project administration, Visualization, Writing – original draft. **FISS**: Conceptualization, Formal Analysis, Software, Validation, Writing – review & editing. **ROSS:** Conceptualization, Methodology, Resources, Supervision, Writing – review & editing.

REFERENCES

1. World Health Organization. Obesity and overweight. 2021. [cited on Nov 2021]. Available from: http://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight

2. Instituto Brasileiro de Geografia e Estatísticas. Pesquisa Nacional de Saúde, IBGE 2019. Atenção Primária à Saúde e Informações Antropométricas. Rio de Janeiro: Instituto Brasileiro de Geografia e Estatísticas; 2020.

3. Horesh A, Tsur AM, Bardugo A, Twig G. Adolescent and childhood obesity and excess morbidity and mortality in young adulthood-a systematic review. Curr Obes Rep. 2021;10(3):301-10. https://doi.org/10.1007/s13679-021-00439-9
4. Thomas-Eapen N. Childhood obesity. Prim Care. 2021;48(3):505-15. https://doi.org/10.1016/j.pop.2021.04.002
5. Hamjane N, Benyahya F, Nourouti NG, Mechita MB, Barakat A. Cardiovascular diseases and metabolic abnormalities associated with obesity: what is the role of inflammatory responses? A systematic review. Microvasc Res. 2020;131:104023. https://doi.org/10.1016/j.mvr.2020.104023
6. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, et al. Hematological findings and complications of COVID-19. Am J Hematol. 2020;95(7):834-47. https://doi.org/10.1002/ajh.25829
7. Russell CD, Parajuli A, Gale HJ, Bulteel NS, Schuetz P, de Jager CPC, et al. The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: a systematic review and meta-analysis. J Infect. 2019;78(5):339-48. https://doi.org/10.1016/j.jinf.2019.02.006
8. Mazza MG, Lucchi S, Tringali AGM, Rossetti A, Botti ER, Clerici M. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: a meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2018;84(Pt A):229-36. https://doi.org/10.1016/j.pnpbp.2018.03.012
9. Mazza MG, Lucchi S, Rossetti A, Clerici M. Neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio and platelet-lymphocyte ratio in non-affective psychosis: a meta-analysis and systematic review. World J Biol Psychiatry. 2020;21(5):326-38. https://doi.org/10.1080/15622975.2019.1583371
10. Zhang N, Jiang J, Tang S, Sun G. Predictive value of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in non-small cell lung cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Int Immunopharmacol. 2020;85:106677. https://doi.org/10.1016/j.intimp.2020.106677
11. Kumarasamy C, Tiwary V, Sunil K, Suresh D, Shetty S, Muthukaliannan GK, et al. Prognostic utility of platelet-lymphocyte ratio, neutrophil-lymphocyte ratio and monocyte-lymphocyte ratio in head and neck cancers: a detailed PRISMA compliant systematic review and meta-analysis. Cancers (Basel). 2021;13(16):4166. https://doi.org/10.3390/cancers13164166
12. Sant'Anna MdS, Tinoco AL, Rosado LE, Sant'Ana LF, Mello AdC, Brito IS, et al. Body fat assessment by bioelectrical impedance and its correlation with different anatomical sites used in the measurement of waist circumference in children. J Pediatr (Rio J). 2009;85(1):61-6. https://doi.org/10.2223/JPED.1871
13. Shrestha R, Upadhyay SK, Khatri B, Bhattarai JR, Kayastha M, Upadhyay MP. BMI, waist to height ratio and waist circumference as a screening tool for hypertension in hospital outpatients: a cross-sectional, non-inferiority study. BMJ Open. 2021;11(11):e050096. https://doi.org/10.1136/bmjopen-2021-050096
14. World Health Organization. The WHO child growth standards. Genebra: WHO; 2020. Available from: https://www.who.int/growthref/en/
15. Aydin M, Yilmaz A, Donma MM, Tulubas F, Demirkol M, Erdogan M, et al. Neutrophil/lymphocyte ratio in obese adolescents. North Clin Istanb. 2015;2(2):87-91. https://doi.org/10.14744/nci.2015.25238
16. Erdal E, İnanir M. Platelet-to-lymphocyte ratio (PLR) and Plateletcrit (PCT) in young patients with morbid obesity. Rev Assoc Med Bras (1992). 2019;65(9):1182-7. https://doi.org/10.1590/1806-9282.65.9.1182
17. Furuncuoğlu Y, Tulgar S, Dogan AN, Cakar S, Tulgar YK, Cakiroglu B. How obesity affects the neutrophil/lymphocyte and platelet/lymphocyte ratio, systemic immune-inflammatory index and platelet indices: a retrospective study. Eur Rev Med Pharmacol Sci. 2016;20(7):1300-6. PMID: 27097950
18. Yu JY, Choi WJ, Lee HS, Lee JW. Relationship between inflammatory markers and visceral obesity in obese and overweight Korean adults: an observational study. Medicine (Baltimore). 2019;98(9):e14740. https://doi.org/10.1097/MD.0000000000014740
19. Koca TT. Does obesity cause chronic inflammation? The association between complete blood parameters with body mass index and fasting glucose. Pak J Med Sci. 2017;33(1):65-9. https://doi.org/10.12669/pjms.331.11532
20. Kim DJ, Noh JH, Lee BW, Choi YH, Chung JH, Min YK, et al. The associations of total and differential white blood cell counts with obesity, hypertension, dyslipidemia and glucose intolerance in a Korean population. J Korean Med Sci. 2008;23(2):193-8. https://doi.org/10.3346/jkms.2008.23.2.193
21. Bahadır A, Baltacı D, Türker Y, Türker Y, Iliev D, Öztürk S, et al. Is the neutrophil-to-lymphocyte ratio indicative of inflammatory state in patients with obesity and metabolic syndrome? Anatol J Cardiol. 2015;15(10):816-22. https://doi.org/10.5152/akd.2014.5787
22. Liu CC, Ko HJ, Liu WS, Hung CL, Hu KC, Yu LY, et al. Neutrophil-to-lymphocyte ratio as a predictive marker of metabolic syndrome. Medicine (Baltimore). 2019;98(43):e17537. https://doi.org/10.1097/MD.0000000000017537
23. Türkkan E, Dağ NÇ, Arabacı Ç, Dikker O, Dağ H. Evaluation of inflammatory hematological ratios (NLR, PLR, MLR and Monocyte/HDL-Cholesterol Ratio) in obese adolescents. Iberoam J Med. 2022;4(1):11-7. https://doi.org/10.53986/ibjm.2022.0002
24. Swärd P, Rosengren BE, Jehpsson L, Karlsson MK. Association between circulating furin levels, obesity and pro-inflammatory markers in children. Acta Paediatr. 2021;110(6):1863-8. https://doi.org/10.1111/apa.15774
25. Vassilopoulou E, Giannopoulou E, Theodosiou A, Karaglani E, Manios Y, Moschonis G. Adipokines and C-reactive protein as indicators of MetS presence in obese Greek children: the healthy growth study. Toxicol Rep. 2021;8:1645-50. https://doi.org/10.1016/j.toxrep.2021.08.004