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REVIEW

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Neutrophils as indicators of obesity-associated inflammation: A systematic review and meta-analysis

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Summary

Introduction: The aim of this study is to evaluate and compare the suitability of routine blood neutrophil values as indicators of obesity-associated inflammation.

Methods: In this systematic review and meta-analysis, we assess absolute neutrophil counts (ANCs) and neutrophil-to-lymphocyte ratio (NLR) values in subjects with and without obesity and analyze the weight of both parameters on the disease. Additionally, correlation studies between ANC and NLR with BMI, a parameter internationally accepted to define obesity are performed.

Results: Quantitative data from 12 (ANC) and 11 (NLR) studies were included, with a total of 4475 participants. The meta-analysis shows that while both parameters are increased in the obesity group, ANC values present higher differences with the control and less heterogeneity among studies. Additionally, unlike NLR, ANC demonstrates a positive and significant correlation with BMI.

Conclusion: Overall, this meta-analysis demonstrates that ANC is a more reliable and stable parameter than NLR for the assessment of obesity-related inflammation, which offers clinicians a novel tool to assist in preventing complications related to obesity.

KEYWORDS
inflammation, neutrophil, neutrophil-to-lymphocyte ratio, obesity

Abbreviations: ANC, Absolute neutrophil count; NLR, Neutrophil-to-lymphocyte ratio; BMI, Body mass index; AT, Adipose tissue; TNFα, Tumor necrosis factor alpha; IL8, Interleukin 8; IL6, Interleukin 6; IL1β, Interleukin 1 beta; CCL-2, (C–C motif) ligand 2; MMP9, Matrix metalloproteinase-9; MPO, Myeloperoxidase; T2D, Type 2 diabetes; fMLP, N-Formyl-Met-Leu-Phe; NE, Neutrophil Elastase.

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1 | INTRODUCTION

The number of people affected by obesity is projected to reach one billion by 2030, after tripling in the last three decades.[1] Obesity and its comorbidities (type 2 diabetes mellitus, dyslipidemia, and hypertension) significantly increase the risk of cardiovascular disease,[2] musculoskeletal disorders,[2] impaired mental health,[3] and certain types of cancer.[4] Obesity is considered a low-grade inflammatory disease led by the expansion of adipose tissue (AT), with a far-reaching impact on other metabolic tissues. The white AT is composed of adipocytes and different immune cells, including macrophages, dendritic cells, B and T lymphocytes, and neutrophils.[5] In subjects with obesity, the AT produces high levels of pro-inflammatory cytokines like TNFα, IL6, IL8, and IL1β[6–9] (Figure 1A). Leukocytosis, involving neutrophilia, is common in obesity. While the mechanisms underlying neutrophilia in obesity are widely unexplored, monocyte release from the bone marrow and recruitment into the AT are better understood. Animal models suggest that bone marrow adipocytes may prime monocytes to invade AT,[10] contributing to the pool of tissue macrophages, and identify molecular instruments that regulate hematopoietic activation in obesity, such as the TLR4, TRIF and MyD88 pathways[11] (Figure 1B). Although the exact cause of obesity-related leukocytosis is not fully understood, certain molecules like TNFα, leptin, and adiponectin contribute to the hematopoietic environment.[12–14]

Neutrophils are the most abundant blood cells and the first inflammatory effectors recruited to sites of inflammation. As such, an increase in neutrophil numbers is considered a clear marker of inflammation, not only in acute episodes, but also in chronic diseases.[15,16] Studies on animal models show that also in obesity neutrophils are the first immune cells infiltrating the tissue.[17] As opposed to other immune cells, neutrophils do not populate AT in homeostasis. Lean AT contains immunosuppressive CD4+ regulatory T cells (Tregs),[18] anti-inflammatory M2-like macrophages,[19,20] and type 2 innate lymphoid (ILC2).[21] However, under obesity conditions, there is a severe

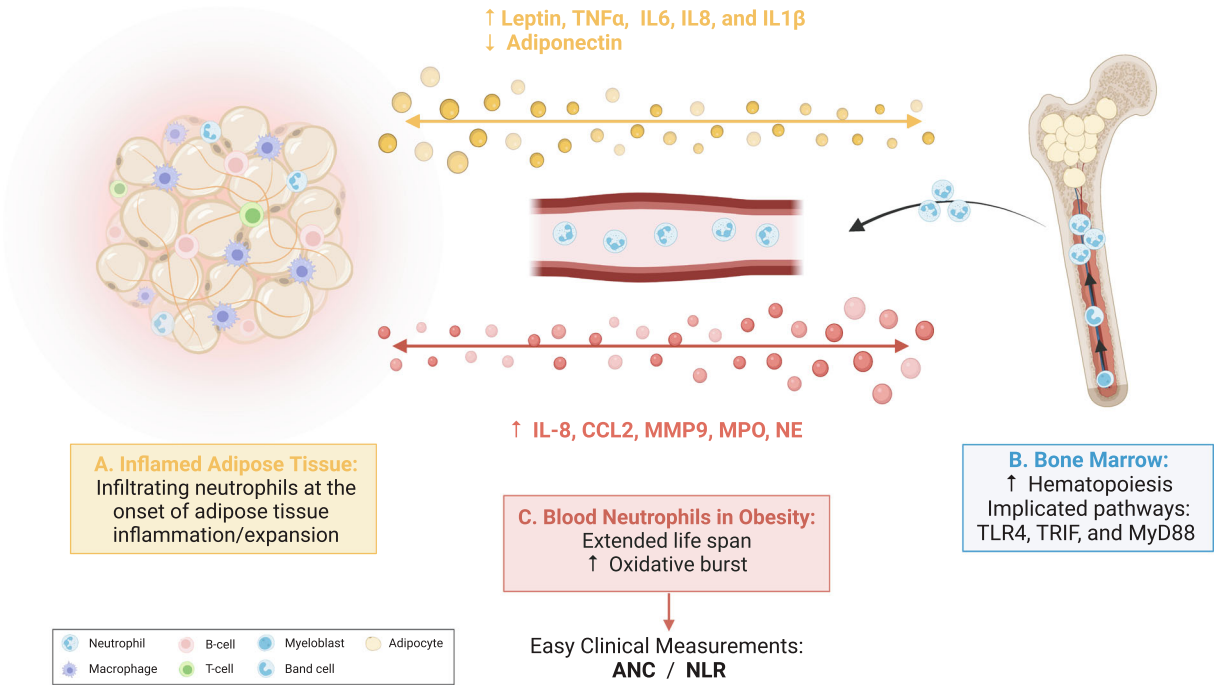

FIGURE 1 Mechanisms involved in obesity-related inflammation and neutrophilia. (A) Neutrophils infiltrate into inflamed adipose tissue and support the recruitment of other immune cells. Inflamed adipose tissue releases leptin, TNFα, IL6, IL8, and IL1β and decreases the secretion of adiponectin. (B) Bone marrow myelopoiesis is enhanced by signals released by the adipose tissue and bone marrow adipocytes, activating pathways involved in the production and liberation of neutrophils to the bloodstream like TLF4, TRIF and MyD88. (C) The increase of activated circulating neutrophils results in incremented pro-inflammatory molecules like IL8, CCL2, MMP9, MPO, and NE in blood. Routinely used parameters like absolute neutrophil count (ANC) and neutrophil-to-lymphocyte-ratio (NLR) to measure blood neutrophils may serve as indicators of obesity-related inflammation. Created with BioRender.com.

growth of pro-inflammatory CD4+ type 1 T helper (Th1) cells,[22] cytotoxic CD8+ T cells,[23] and M1-like macrophages.[20] Also, neutrophils that gather in the AT of obesity patients present a particular transcriptional profile, which is different from circulating neutrophils.[24] Based on the available reports, it is unclear whether neutrophils have a transient or a rather stable presence in the tissue.[17,25] However, it seems clear that their accumulation in the AT vasculature leads to the overstimulation of the endothelium, worsening the inflammatory state.[26,27]

Elevated circulating levels of neutrophils aggravate the state of obesity patients.[28–33] Furthermore, blood neutrophils from subjects with obesity are particularly pro-inflammatory, as they release significantly higher levels of pro-inflammatory mediators such as interleukin 8 (IL8), chemokine motif ligand 2 (CCL2), matrix metalloproteinase 9 (MMP9), and myeloperoxidase (MPO),[27,34] and exhibit greater capacity to produce superoxides at basal conditions and in response to fMLP and zymosan.[35] Several key enzymes of neutrophils play pivotal roles in obesity and its complications, contributing to their progression. While MPO is linked to insulin resistance and inflammation in overweight individuals,[36] neutrophil elastase (NE) degrades the molecular adapter that transmits signals from the insulin receptor to intracellular pathways, known as the insulin receptor substrate 1.[25] Consequently, mice deficient in NE exhibit reduced inflammation in AT.[25,37] This growing evidence underscores the critical role of neutrophils in obesity-associated inflammation (Figure 1C).

Adipocytes release active molecules like leptin and adiponectin, which affect neutrophil function and granulopoiesis (Figure 1A–C). Leptin, on the one hand, has been demonstrated to increase hematopoiesis.[12,13] In neutrophils, it acts like a survival signal by suppressing apoptotic pathways, which may contribute to extend their time in circulation.[38] In addition, leptin receptor binding activates neutrophils, stimulating enhanced migration and oxidative burst capacity[39] (Figure 1B). On the other hand, the presence of adiponectin (non-obesity conditions) results in limitations of neutrophil functions, by reduced production of CXCL8 phagocytic capacity.[34,40] Adipocytes are also present in cavities of the bone marrow. In healthy individuals, they exhibit a beige phenotype (a blend of brown and white), shifting towards a white phenotype in the presence of metabolic diseases.[41] Bone marrow adipocytes secrete adipokines and cytokines known to play a role in the regulation of hematopoiesis.[13,42,43] However, discerning bone marrow adipocyte effect from the systemic adiposity is complex. Likewise, some of the cytokines of the bone marrow are also produced in the AT.[44,45] Consequently, a reciprocal exchange of signals occurs between the visceral AT and bone marrow, influencing the levels of circulating neutrophils (Figure 1).

Given the role of neutrophils in inflammation, measuring their count in the bloodstream is a valuable method for assessing the level of inflammation. Blood cell count is one of the most commonly performed routine laboratory tests due to its low cost and availability; therefore, the absolute neutrophil count (ANC) has become a hallmark in describing the grade of inflammation. Neutrophil-to-lymphocyte ratio (NLR) has recently emerged as an alternative inflammatory marker. NLR is now widely accepted as an indicator of systemic inflammation, as it is thought to indicate the balance between innate (neutrophil) and adaptive (lymphocyte) immune reactions. The relationship between this parameter and several chronic inflammatory diseases such as systemic lupus erythematosus, rheumatoid arthritis and atherosclerosis has been investigated.[46–48] However, only a few studies have evaluated the relationship between NLR and obesity, leading to inconsistent findings.[49–51] Despite their wide use as inflammatory parameters, whether ANC and NLR can serve as reliable indicators of obesity-associated inflammation remains to be clarified.

In this systematic review and meta-analysis, we compile the ANC and NLR data published to date in subjects with and without obesity and analyze the weight of both parameters on the disease and their correlation with BMI. This study aims to establish a standardized assessment of the effectiveness of two routine laboratory parameters, ANC and NLR, in identifying obesity-related inflammation.

2 | MATERIAL AND METHODS

2.1 | Registration

This systematic review and meta-analysis follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.[52] The study protocol was registered with PROSPERO (International Prospective Register of Systematic Reviews) with registration number CRD42022368528.

2.2 | Literature search and inclusion criteria

Eligible studies were identified by searching in electronic bibliography databases (PubMed, Embase, Cochrane Library) and other sources (Internet browsers). The search was last executed on October 16, 2023. The search terms for ANC: (obesity AND "neutrophil count"), and for NLR: (obesity) AND (("neutrophil to lymphocyte ratio") OR ("neutrophil-to-lymphocyte-ratio") OR ("NLR")) were used. Only studies in humans were included. Experimental methods, protocols, reviews or systematic reviews, abstracts, and conference proceedings were excluded from this search. At least two emails with logical intervals (about 3 weeks) were sent to the corresponding author of the manuscripts in cases of missing data or lack of access to full texts.

Body mass index (BMI) was used to stratify participants as patients with obesity (BMI ≥ 30 kg/m^2) or controls (18.5 kg/m^2 ≥ BMI < 30 kg/m^2). Inclusion criteria were as follows: (1) human studies measuring blood levels of neutrophils in adult non-pregnant patients with obesity and controls, (2) articles written in English or Spanish, (3) obesity defined as BMI ≥ 30 kg/m^2, (4) studies reporting at least 10 cases in obesity and/or control group. Studies with participants with reported comorbidities were excluded. Apart from the records identified during the database search, NLR was calculated from publications in the list of ANC searches that included data on lymphocyte counts.

2.3 | Article selection and data extraction

Three researchers were involved in the selection process. Data were extracted independently from included studies by two authors (G.G-C and A.O-G.). After removing duplicates, all retrieved articles underwent an initial title and abstract screening, followed by full-text screening for eligible abstracts. Disagreements were resolved by discussion between the two authors and consultation was made with a third author (M.M.). The literature search records were managed using the Mendeley software. The following information was extracted from each study: first author, year, country, sample size, BMI, age and sex percentage of the participants, and outcome measurements (ANC and NLR data). The characteristics of the eligible studies for meta-analysis are summarized in Table 1.

2.4 | Quality assessment

The quality assessment of the included studies was evaluated independently from the included studies by two authors (A. R-M, G. G-C). Disagreements were resolved by discussion between the two authors, and consultation was made with a third author (A. O-G). Study quality was appraised using the Critical Appraisal Skills Programme (CASP) checklists[63] in all the included studies of the present systematic review and meta-analysis. The results of the assessment are shown in the Table S1.

2.5 | Data analysis

Two different meta-analyses were conducted to examine the global effect size based on the values of ANC or NLR. Firstly, the effect size for each study was calculated using the log of fold change (obesity vs control), and the standard error was calculated as combined standard deviations. Subsequently, the meta-analyses of continuous outcomes were carried out using the "metagen" function from the "meta" package in the R language (version 4.1.3). Heterogeneity was assessed using the I^2 index, which considers 25% or less as low heterogeneity, between 25 and 50% as moderate, and over 75% as high heterogeneity. Publication bias was examined through Egger's test and funnel plot analysis. Correlation R^2 was performed using Spearman correlation and visualized with ggplot2. To help understand the practical importance of the effect found, we calculated the Hedge's g parameter and translated this effect size into Cohen's U3 index.

3 | RESULTS

3.1 | Literature selection

The database and manual search resulted in 1387 publications on ANC, of which 217 were removed before screening as duplicates. Out of the 1170 records screened, 866 were excluded for general reasons (animal studies, publications other than articles, topics not related or written in a different language). After removing reports with missing unprovided data (18) and publications out of the inclusion criteria (274), 12 studies were included in the analysis. The detailed process is illustrated in the PRISMA flow diagram of Figure 2. Publication bias was assessed for both searches following Egger model.[64] Figure S1 illustrates the funnel plot for the meta-analysis of ANC. The results of Egger's regression test indicate a symmetrical distribution of the points in the funnel plot ($t = 0.38$, $df = 9$, p value $= 0.71$), which implies that there is no significant publication bias ($t = -0.90$, $df = 9$, p value $= 0.39$).

The literature search on NLR led to 1269 records, with 270 duplicates removed before the screening. Eight hundred seventeen records were excluded for general reasons and 5 for missing unprovided data. After assessment for eligibility, 166 publications were omitted, resulting in 11 studies being included in the analysis (Figure 3). Likewise, the Egger test for funnel plot of NLR (Figure S1B) indicates the absence of publication bias in the meta-analysis ($t = -0.90$, $df = 9$, p value $= 0.39$).

3.2 | Study characteristics

Table 1 shows the characteristics and data of the 12 studies included in the analysis of ANC. These studies were performed in 10 different countries distributed throughout 3 continents (25% Asia, 25% America and 50% Europe). The participants were classified according to their BMI as control (< 30 kg/m^2) or obesity group (≥ 30 kg/m^2). Obesity and control groups were matched for age and sex in 58.3% of the studies, while 8.3% and 25% were matched only for age or sex, respectively. Regarding the analysis of NLR, Table 2 displays the summary of entries utilized for the study and their features, located in 8 countries on 3 different continents (54.5% Asia, 9.1% America, and 36.4% Europe). The percentage of studies matched for age and sex in the selection of articles for the analysis was 72.7%, while 9.1% and 18.2% were matched only of age or sex, respectively. The quality assessment of the articles included in both studies can be found in the Table S1.

3.3 | Meta-analysis

3.3.1 | ANC and BMI in obesity

Figure 4 depicts the forest plot for the meta-analysis of the association between ANC and obesity, comparing a group of 1224 subjects with obesity with 813 healthy subjects. The meta-analysis shows that the group of patients with obesity presents elevated numbers of circulating neutrophils (absolute counts) compared to the control group, suggesting a higher level of inflammation. Cohen's U3 for ANC is calculated at 25%, indicating that 25% of the obesity group is above the mean of the control group. Three studies have a higher contribution and influence on overall heterogeneity and results,[28,57,60] Rashad et al.[60] being the most prominent (Figure S2A). Nevertheless, the analysis reveals low heterogeneity among the studies ($I^2 = 25\%$, $\tau^2 = 0.0059$, $p = 0.20$). In agreement with the good homogeneity of

TABLE 1 Summary and characteristics of the studies included in the meta-analysis of ANC and obesity.

Author (year)	Country	Sample size (*n*)		ANC (10^3 cells/μL)		Age (years)		BMI (kg/m^2)		% male		Participant selection
		Obesity group	Control	Obesity group	Control	Obesity group	Control	Obesity group	Control	Obesity group	Control	
Asrih et al. (2022)[29]	Switzerland	16	16	3.7 ± 0.9	3.6 ± 1.3	54.5 ± 9.0	60.0 ± 8.0	36.9 ± 3.2	23.1 ± 1.5	50	50	Age and sex matched
Bahadır et al. (2015)[28]	Turkey	821	446	4.5 ± 1.5	4.0 ± 1.3	37.6 ± 10.4	35.9 ± 10.2	37.0 ± 2.1	26.1 ± 1.7	n.p.	n.p.	Age and sex matched
Borato et al. (2016)[53]	Brazil	35	27	2.9 ± 0.3	3.0 ± 0.2	37.4 ± 5.7	46.45 ± 4.9	21.2 ± 0.7	34.1 ± 1.3	17	26	Age and sex matched
Blanks et al. (2020)[54]	USA	11	10	4.3 ± 0.5	2.7 ± 0.3	32.5 ± 4.3	28.1 ± 2.4	32.0 ± 3.6	23.1 ± 1.1	27.3	70	Age matched
Christou et al. (2020)[55]	Greece	25	25	3.8 ± 1.1	3.5 ± 1.1	38.0 ± 9.0	41.0 ± 10.0	38.0 ± 6.5	22.1 ± 1.9	44	40	Age and sex matched
Costa et al. (2023)[56]	Brazil	19	10	3.6 ± 1.2	2.1 ± 0.9	28.6 ± 7.1	27.6 ± 6.2	34.1 ± 3.8	22.5 ± 1.4	42.1	40	Not matched
Mortensen et al. (2009)[57]	Denmark	41	62	3.5 ± 0.2	2.91 ± 0.1	48.1 ± 1.6	56.0 ± 1.3	36.7 ± 0.5	25.7 ± 0.4	68.3	67.7	Age. sex and BMI matched
Osorio-Conles et al. (2017)[58]	Spain	47	33	4.4 ± 0.4	3.5 ± 1.2	49.4 ± 10.0	52.1 ± 10.6	40.6 ± 5.0	26.6 ± 2.4	100	100	Age and sex matched
Raghavan et al. (2016)[59]	India	76	88	5.3 ± 1.5	4.0 ± 1.3	45.9 ± 11.0	45.5 ± 12.0	34.3 ± 3.5	24.2 ± 2.2	0	0	Sex matched
Rashad et al. (2013)[60]	Egypt	40	53	4.6 ± 0.3	3.1 ± 0.2	28.4 ± 7.0	27.1 ± 4.3	34.7 ± 1.0	25.4 ± 1.2	0	0	Sex matched
Rigamonti et al. (2013)[61]	Italy	15	15	4.4 ± 0.4	3.20 ± 0.3	36.5 ± 1.9	32.1 ± 2.7	45.4 ± 1.3	24.1 ± 0.8	100	100	Age and sex matched
Solá et al. (2009)[62]	Spain	31	67	4.3 ± 1.4	3.5 ± 1.2	34.0 ± 11.0	32.0 ± 9.0	46.0 ± 6.0	22.4 ± 2.3	22.6	33	Age and sex matched

Abbreviations: ANC, absolute neutrophil count; BMI, body mass index; n.p., not provided.

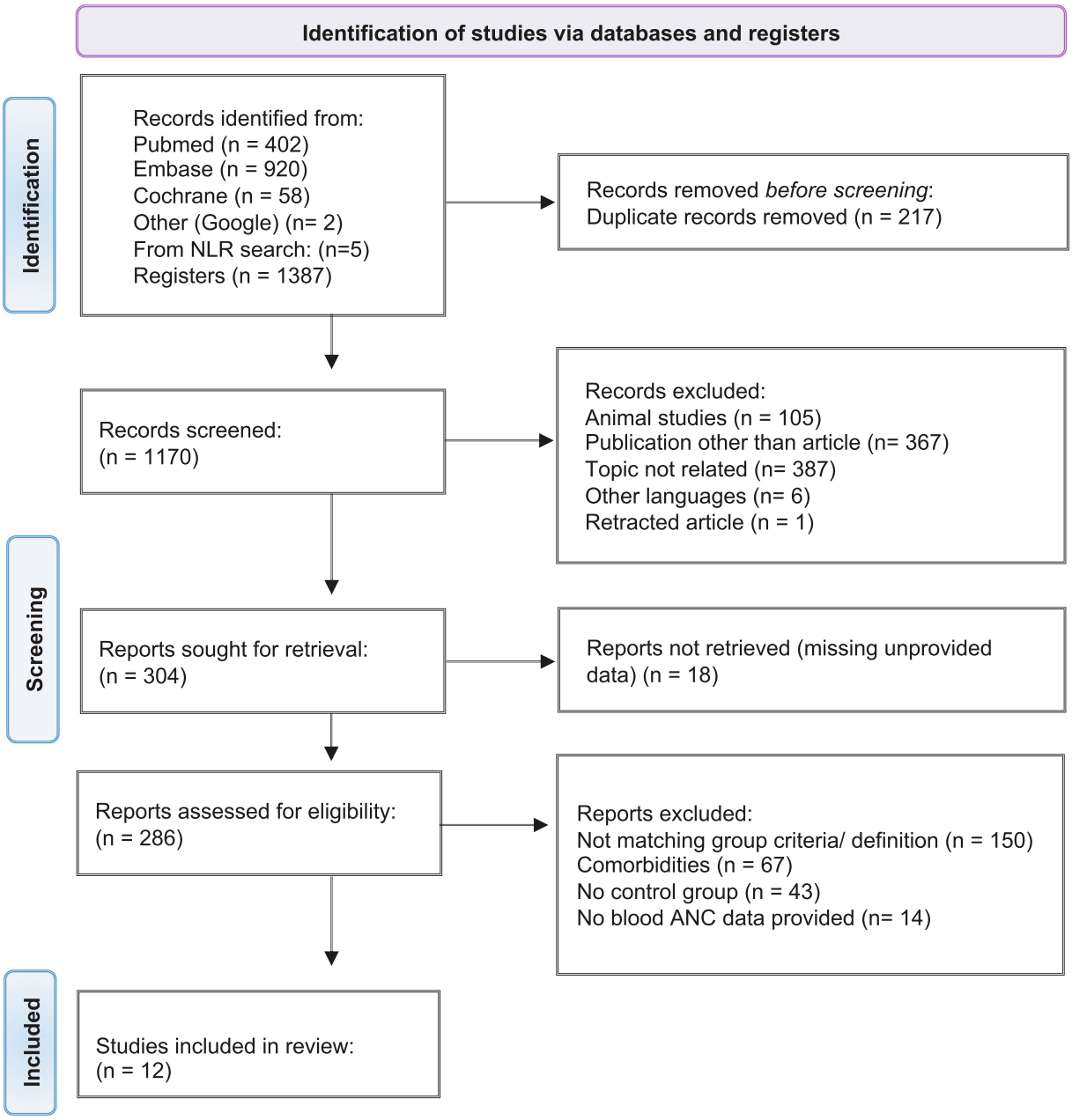

FIGURE 2 Flow diagram of the selection process of the studies in the meta-analysis of ANC.

the studies, there is a limited difference between the overall treatment effect obtained after common and random effect models, which are 0.24 [0.20; 0.29] and 0.25 [0.17; 0.33], respectively (Figure 4).

3.3.2 | NLR and BMI in obesity

The meta-analysis of NLR also shows that the obesity group (1478 subjects) presents higher values than the control group (960 subjects). In this case, the calculated Cohen's U3 is 17%, and the heterogeneity among studies, as opposed to ANC, is considered high ($I^2 = 68\%$, $t^2 = 0.0410$, $p < 0.01$). Accordingly, the overall effect obtained by common or random effects models differ considerably; 0.22 [0.17;0.27] versus 0.16 [−0.00;0.32], respectively (Figure 5). The studies El−Eshmawy et al.[65] and Yilmaz et al.[69] have the highest influence on the overall result and contribution to overall heterogeneity. However, 3 other surveys[28,66,68] demonstrate moderate influence and contribution (Figure S2B).

3.3.3 | NLR in healthy and control individuals

The meta-analysis of NLR also shows that the obesity group (1478 subjects) presents higher values than the control group (960 subjects). In this case, the calculated Cohen's U3 is of 17% and studies demonstrate higher heterogeneity than the analysis of ANC ($I^2 = 68\%$,

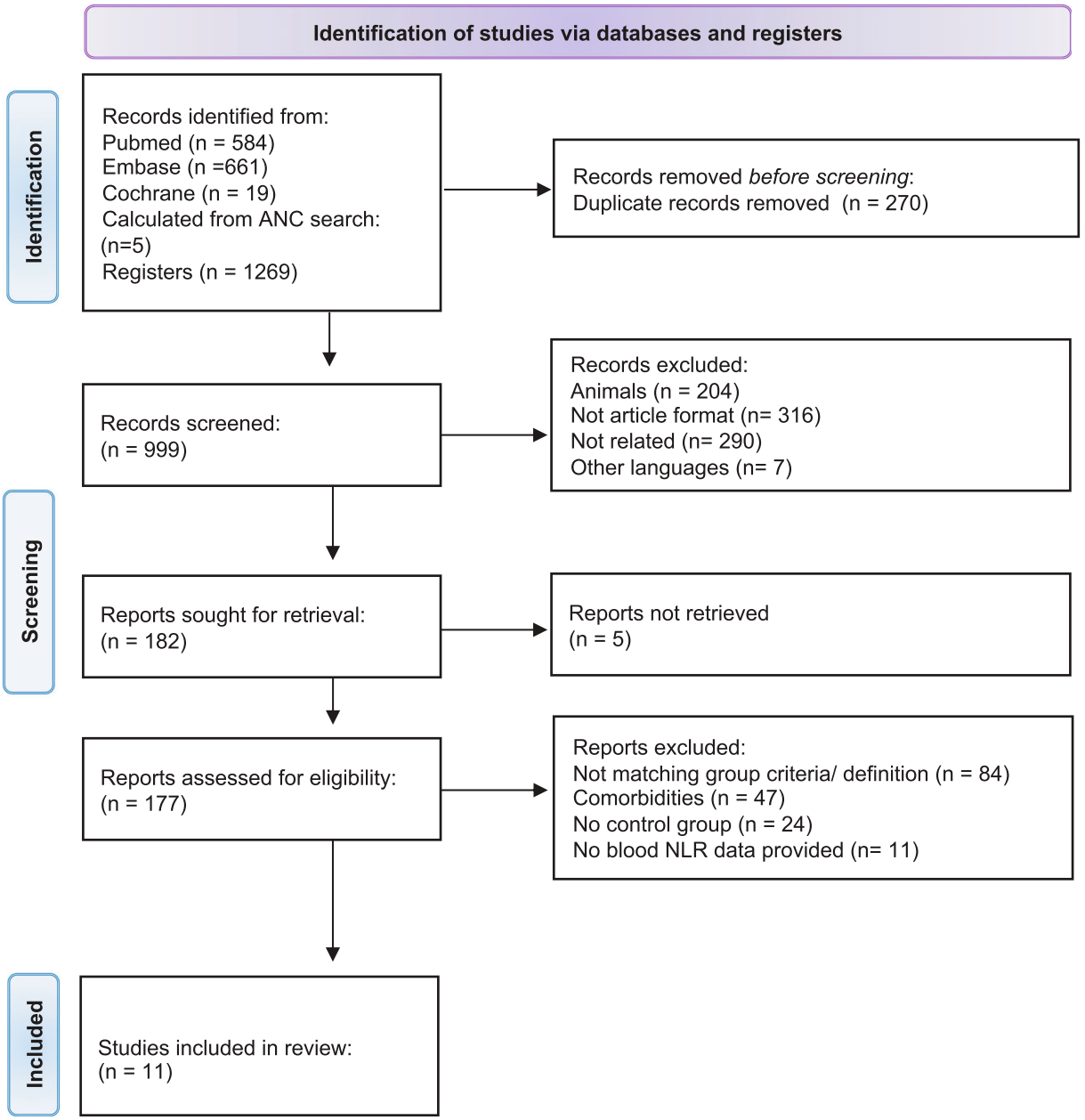

FIGURE 3 Flow diagram of the selection process of the studies in the meta-analysis of NLR.

$t^2 = 0.0410$, $p < 0.01$). Accordingly, the overall effect obtained by common or random effects models differ considerably: 0.22 [0.17;0.27] versus 0.16 [−0.00;0.32], respectively (Figure 5). The studies El−Eshmawy et al.[65] and Yilmaz et al.[69] have the highest influence on the overall result and contribution to overall heterogeneity (Figure S2B). However, 3 other surveys[28,66,68] demonstrate moderate influence and contribution.

3.4 | Correlation between neutrophil values and obesity

To determine whether a higher BMI results in more circulating neutrophils, we conducted correlation analyses with ANC and NLR. The mean values of BMI and ANC of the 12 studies were analyzed for correlation to elucidate whether higher BMI values correspond to higher ANC. A clear correlation was found between BMI and ANC, with a Spearman's coefficient of 0.610 and a p value of 0.002 (Figure 6A). Interestingly, the correlation was visibly stronger on the morbid obesity BMI range, anticipating that the inflammation status denoted by a rise of ANC is particularly associated with morbid obesity profiles. Likewise, the correlation between BMI and NLR derived from the 11 studies of this section of the meta-analysis was investigated. Surprisingly, BMI and NLR values showed a very vague, non-significant positive correlation (Spearman's coefficient of 0.240) with a p value of 0.28 (Figure 6B). These results suggest that the correlation between BMI and neutrophil levels disappears when corrected by the lymphocyte values.

TABLE 2 Summary and characteristics of the studies included in the meta-analysis of NLR and obesity.

Author (year)	Country	Sample size (*n*)		NLR		Age (years)		BMI (kg/m^2)		% Male		Participant selection
		Obesity group	Control	Obesity group	Control	Obesity group	Control	Obesity group	Control	Obesity group	Control	
Asrih et al. (2022)[29]	Switzerland	16	16	2.1 ± 0.6	1.9 ± 1.0	54.5 ± 9.0	60.0 ± 8.0	36.9 ± 3.2	23.1 ± 1.5	50	50	Sex matched
Bahadır et al. (2015)[28]	Turkey	821	446	2.1 ± 1.0	1.8. ± 0.8	37.6 ± 10.4	35.9 ± 10.2	36.9 ± 2.1	26.1 ± 1.7	n.p.	n.p.	Age matched
Christou et al. (2020)[55]	Greece	25	25	1.8 ± 1.3	1.6 ± 1.1	38.0 ± 9.0	41.0 ± 10.0	38.1 ± 6.5	22.1 ± 1.9	44	40	Age and sex matched
Costa et al. (2023)[56]	Brazil	19	10	1.3 ± 1.5	1.2 ± 0.9	28.6 ± 7.1	27.6 ± 6.2	34.1 ± 3.8	22.5 ± 1.4	42.1	40	Age and sex matched
El-Eshmawy et al. (2022)[65]	Egypt	50	50	1.3 ± 0.1	1.0 ± 0.1	36.5 ± 12.1	33.9 ± 11.5	42.2 ± 6.6	22.5 ±2.2	50	50	Age and sex matched
Naser et al. (2023)[66]	Turkey	70	174	1.9 ± 0.8	1.8 ± 0.7	48.1 ± 12.1	43.1 ± 11.7	34.0 ± 3.6	25.3 ± 2.8	40	48.9	Sex matched
Raghavan et al. (2016)[59]	India	76	88	2.2 ± 0.7	1.8 ± 0.6	45.9 ± 1.0	43.5 ± 12.0	34.3 ± 3.5	24.2 ± 2.2	0	0	Sex matched
Rigamonti et al. (2013)[61]	Italy	15	15	1.5 ± 2.6	1.4 ± 10.0	36.5 ± 1.9	32.1 ± 2.7	45.4 ± 1.3	24.1 ± 0.8	100	100	Age and sex matched
Torres et al. (2018)[67]	Poland	40	40	2.3 ± 1.0	2.8 ± 0.8	63.5 ± 7.9	61.2 ± 9.3	34.5 ± 3.5	22.7 ± 1.8	55	57.5	Age and sex matched
Yıldırım et al. (2022)[68]	Turkey	40	40	0.5 ± 1.0	0.6 ± 0.1	49.9 ± 8.3	48.8 ± 8.6	35.0 ± 3.7	26.8 ± 1.7	50	50	Age and sex matched
Yilmaz et al. (2015)[69]	Turkey	205	95	3.4 ± 0.9	1.8 ± 1.0	45.2 ± 11.3	45.8 ± 10.9	44.5 ± 5.2	21.3 ± 3.7	6.8	10.6	Age and sex matched

Abbreviations: BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; n.p., not provided.

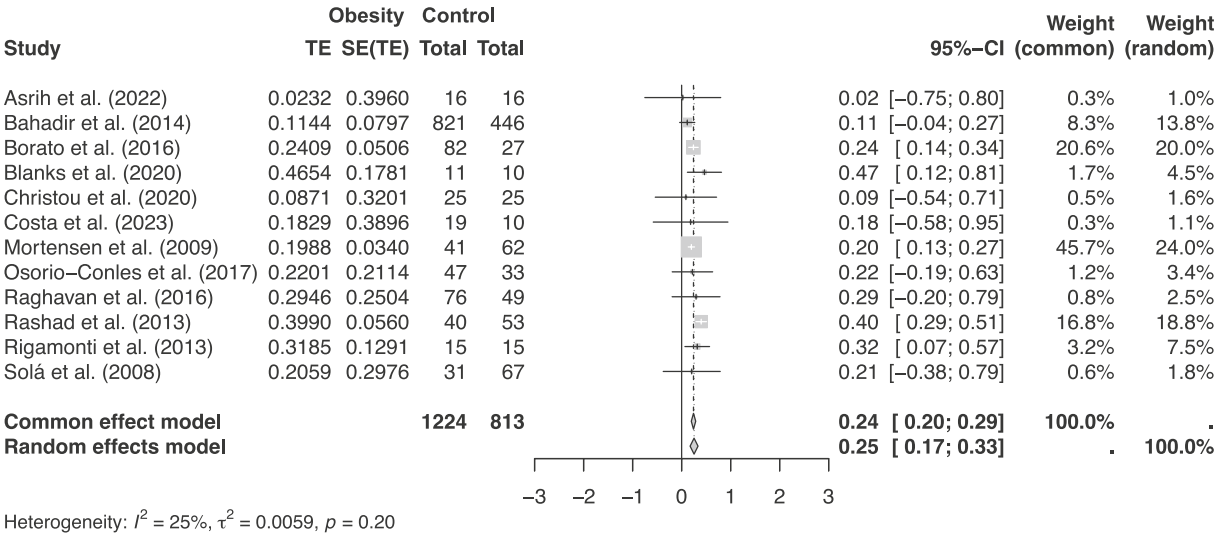

FIGURE 4 Forest plot of ANC in obesity.

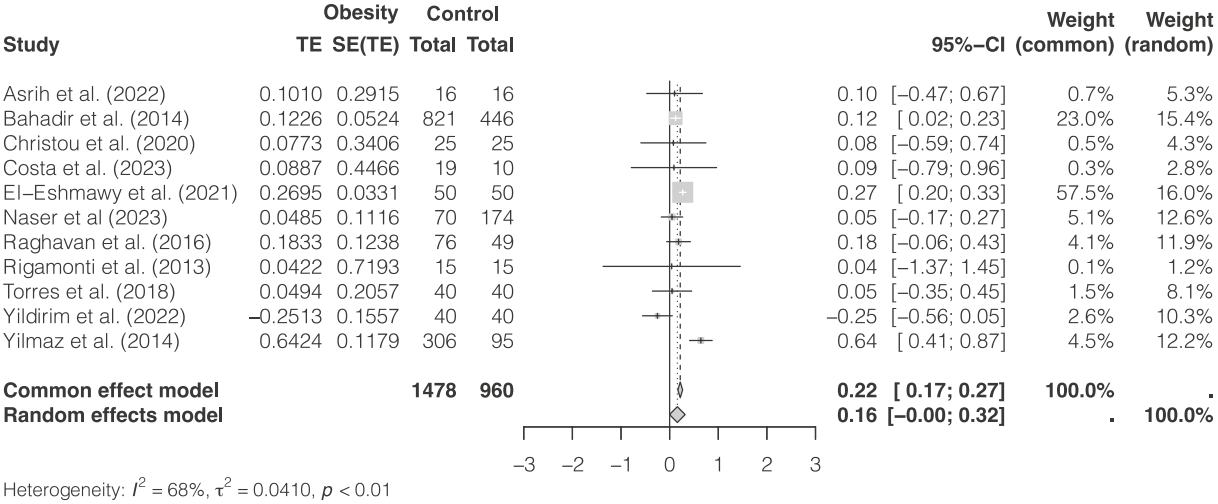

FIGURE 5 Forest plot of NLR in obesity.

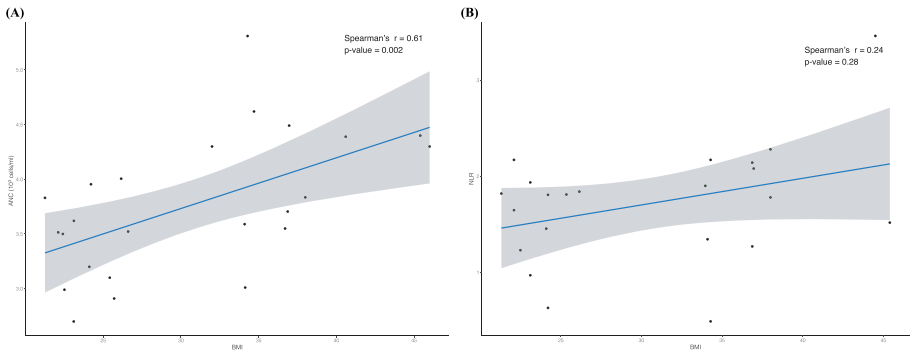

FIGURE 6 Spearman's rank correlation of ANC (A) and NLR (B) with BMI.

4 | LIMITATIONS OF THE STUDY

The results of our study should be interpreted in light of certain limitations. The current international classification of obesity is based on BMI. Here, we have focused on obesity determined by BMI due to the lack of consensus in other anthropometric parameters. Nonetheless, it is important to recognize that this parameter does not always accurately reflect an individual's obesity status, especially in populations engaged in endurance physical activity, as it does not consider fat/muscle body composition and circumference. Moreover,

standardizing the types of adiposities could provide a more accurate parameter for assessing obesity in comparative studies. In this meta-analysis, the overweight population was not studied separately from the control group, as it was conducted with a specific focus on obesity. Interestingly, both correlation analyses (ANC and NLR with BM) exhibit a gap of data on the overweight BMI range (> 25 kg/m^2). Further investigations are needed to decode the suitability of neutrophil levels in overweight subjects as predictive markers of a pro-inflammatory state. The differences in AT depots between women and men are well established. Despite of the efforts to perform sex matched studies, more research is needed to explore the differences in obesity between sexes. In this regard, this disparity is not addressed in our study. Additionally, it is important to note that comorbidities were not included in the analysis, as studies reporting comorbidities in their participants were excluded.

Another limitation arises from the fact that, although the pro-inflammatory activity of neutrophils in obesity has been previously documented, specific neutrophil activity markers, such as NE and MPO, were not analyzed in this study. Therefore, caution should be exercised when drawing conclusions about the inflammatory activity of neutrophils.

5 | DISCUSSION

Obesity is a major health issue that affects people worldwide and is linked to chronic inflammation. Inflammation is a key factor in the development of obesity-related complications such as cardiovascular diseases, metabolic syndrome, insulin resistance, and diabetes mellitus.[70] Given that inflammation often triggers many of the health complications that arise from obesity, and that circulating neutrophil levels serve as an important clinical indicator of the body's inflammatory state, we decided to explore whether these neutrophil values can be used in clinical practice to predict obesity-associated inflammation. To date, a few studies have investigated this issue. However, a more comprehensive analysis across different cohorts is necessary to draw meaningful conclusions. Therefore, we have analyzed studies that published data on individuals with and without obesity (without additional comorbidities) in relation to routine neutrophil clinical parameters, which comprise ANC and NLR, and examined the appropriateness of both clinical markers.

Our present systematic review and meta-analysis represents the first extensive investigation into whether circulating neutrophil levels differ between subjects with and without obesity. It contains 17 individual studies that included a total of 1582 patients with obesity and 1251 subjects without obesity. This comprehensive analysis incorporates cohorts from three different continents, namely Asia, Europe and America. The inclusion of diverse ethnicities in the study ensures that the results are representative of a wide range of populations. Furthermore, 6 of the 11 records analyzed for NLR are also listed in the analysis of ANC. This gives further consistency to the study, since it implies that more than 70% of the participants in the obesity group and 60% in the control group are the same in both ANC and NLR analyses.

The meta-analyses of these studies showed that both ANC and NLR were significantly increased in patients with obesity and this effect was more clearly observed with ANC than with NLR. Hence, obesity could be a potential contributing factor to unexplained persistent neutrophilia, which has been observed in some obesity patients.[30] ANC shows superiority over NLR in terms of robustness and homogeneity, making it a more predictable and reliable marker to estimate the inflammatory condition in obesity. We delved further into the relationship between blood neutrophil values and obesity and studied the correlation between ANC and NLR with BMI, as a worldwide standardized criterion for obesity. While NLR exhibited poor results, ANC presented a clear positive correlation. A possible explanation is that NLR normalizes the level of neutrophils to the total of lymphocytes, which comprises a pool of cells with often antagonizing functions. For instance, T helper cells $CD3^+CD4^+$ (Th1) produce interferon (IFN-γ) and contribute to the pro-inflammatory state.[71] On the other hand, $CD3^+CD4^+FOXP3^+$ (Tregs) can modulate the activity of other T cells and, more importantly, inhibit monocyte immigration and direct them towards an anti-inflammatory polarization state.[72]

Neutrophils have been traditionally considered as a homogeneous highly differentiated cell population with limited diversity. However, it is now clear that neutrophils are a heterogeneous population, varying depending on the conditions.[73] Yet, it remains to be determined whether these populations are distinct subsets resulting from differentiation or are a consequence of the activation by cytokines present during ongoing disease or inflammatory processes.

Chronic and acute inflammation renders changes in neutrophil subsets, ranging from immunosuppressive to disease-specific neutrophils.[74] Similarly, neutrophils in AT display an activated state, which is however, distinct from other states of neutrophil activation.[24] Nevertheless, their ability to recruit or activate other immune cells appears to be consistent with observations in other inflamed tissues. An increased neutrophil presence in AT is observed during early stages of obesity as opposed to the late stages.[25] Neutrophils secrete TNFα and MCP1, which exacerbates inflammation and induces recruitment of monocytes into the AT.[75] Consequently, the presence of neutrophils in AT in obesity is followed by an increase in pro-inflammatory cells (CD4+ Th1 cells and M1 macrophages) and a decrease in anti-inflammatory cells (Tregs and M2 macrophages).[24] Of note, the deletion of neutrophil elastase in a murine HFD-induced obesity model leads to decreased tissue inflammation, accompanied by improved glucose tolerance and increased insulin sensitivity.[25] They are also increased in obesity-associated cardio-metabolic diseases, such as metabolic syndrome and type 2 diabetes.[76] Furthermore, a clear association has been established between neutrophil counts, but no other leukocytes, and cardiovascular outcomes.[77] Thus, neutrophils may be the first immune cells to initiate the inflammatory cascade in obesity, inducing a shift in phenotype and recruitment of pro-inflammatory cells, similar to what is observed in other chronic diseases.

Despite their well-known pro-inflammatory profile, neutrophils can exhibit anti-inflammatory functions in specific scenarios. For instance, neutrophil depletion during the early stages of cancer has been found to be detrimental, whereas in later stages it appears

beneficial, suggesting a protective role.[78,79] Furthermore, neutrophils have shown to have a key function in the resolution phase of the inflammation.[80] Nevertheless, based on available reports, it seems unlikely that neutrophils play an anti-inflammatory role in obesity. Accumulating evidence highlights the importance of neutrophil phenotypic and functional heterogeneity not only in inflammation, but also in homeostasis.[73] Specific neutrophil phenotypes in homeostasis of tissues like lungs, spleen or skin suggest a role for this cell in maintaining steady states.[81–83] However, the understanding of neutrophil homeostatic subpopulations remains scarce and falls significantly short compared to the more extensive knowledge available for other immune cells, such as macrophages. As opposed to T cells and macrophages, neutrophils are not usually found in high numbers in the lean AT.[24] Hence, their role in tissue maintenance appears to be limited.

We propose that a communication pathway is established during the onset of inflammation in obesity, connecting AT and bone marrow through the bloodstream (Figure 1). In this context, neutrophils are likely pivotal in initiating the recruitment sequence of other inflammatory cells, similar to what occurs in other inflammatory episodes.[84–86] Heightened neutrophil counts in obesity may result from pro-inflammatory and hematopoietic signals originating from AT. Given the observed increase in ANC values in individuals with obesity and the identified linear correlation with BMI, it could be hypothesized that ANC could serve as a prognostic indicator for identifying overweight individuals at risk of developing obesity, disclosing the low-grade inflammation that precedes obesity. As the systemic dysregulation associated with obesity is partially responsible for obesity-related complications such as cardiovascular events and T2D, monitoring circulating neutrophil levels, measured as ANC, could aid in preventing future health complications. However, it is important to note that the neutrophil pro-inflammatory state and activity have not been analyzed in this study. Given the heterogeneity of neutrophils, future research efforts should focus on exploring these aspects.

6 | CONCLUSIONS

Our findings confirm that absolute neutrophil count (ANC) and neutrophil-to-lymphocyte ratio (NLR) are elevated in patients with obesity. Considering the greater difference from the control group and the stronger correlation with BMI, we conclude that ANC is a better candidate to predict the pro-inflammatory state in obesity. Therefore, we recommend the use ANC over NLR as a standard hematological biomarker to assist clinicians in the early prognosis and monitorization inflammation risk in obesity.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest are declared by the authors.

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SUPPORTING INFORMATION

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