

1 Change in Neutrophil-to-Lymphocyte Ratio after acute and chronic exercise: A Systematic
2 Review and Meta-Analysis

3 **Running head: NLR change in exercise: A meta-analysis**

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19 **Abstract**

20 **Background:**

21 Chronic inflammation contributes to many common diseases, and exercise is a widely accessible
22 tool to modulate it. This meta-analysis evaluates the neutrophil-to-lymphocyte ratio (NLR), a
23 simple inflammatory marker, to better understand and optimize the anti-inflammatory effects of
24 exercise. The present meta-analysis aims to systematically evaluate existing evidence on NLR
25 changes induced by acute and chronic exercise.

26 **Methods:**

27 This study was registered in PROSPERO (CRD420251042422). Studies were selected based on
28 PICO criteria: Population (P) – human participants regardless of age or health; Intervention (I) –
29 acute or chronic exercise; Comparison (C) – NLR levels before exercise; Outcome (O) – Within-
30 subject change in NLR measured before and after exercise. We searched PubMed, EMBASE,
31 Scopus, Web of Science, and the Cochrane Library extensively. Pooled results were expressed as
32 mean difference (MD) with 95% confidence intervals (CI) using STATA version 19.0.

33 **Results:**

34 Twenty-six studies with a total of 1203 participants were included. NLR levels showed no
35 significant change immediately after acute exercise (MD = 0.03; 95% CI: -0.24 to 0.30; $p =$
36 0.82; $k = 12$, $I^2 = 93.6\%$) but increased significantly one-to-three hours post-exercise (MD =
37 1.23; 95% CI: 0.46 to 1.99; $p = 0.002$; $k = 5$, $I^2 = 93.3\%$). Chronic exercise was associated with a
38 significant overall decrease in NLR (MD = -0.30; 95% CI: -0.56 to -0.04; $p = 0.02$; $k = 15$, $I^2 =$
39 98.4%). Studies with older participants reported greater reductions in NLR following chronic
40 exercise. Sensitivity analysis confirmed that no single study had a disproportionate influence on
41 the pooled estimates, and publication bias tests did not suggest bias.

42 **Conclusion:**

43 Acute exercise induces a transient increase in NLR between one-to-three-hours post-exercise,
44 while chronic exercise leads to sustained reductions, reinforcing the value of exercise as a non-
45 pharmacologic strategy to reduce systemic inflammation, as reflected by this inflammatory
46 marker.

47

48

49 **New & Noteworthy**

50 Neutrophil-to-lymphocyte ratio (NLR) was unchanged immediately after acute exercise but
51 increased significantly by one to three hours later, reflecting a transient inflammatory response.

52 Chronic exercise leads to a significant reduction in NLR, indicating long-term anti-inflammatory
53 benefits.

54 Studies with older participants reported greater reductions in NLR following chronic exercise.

55 **Keywords**

56 Meta-analysis; Neutrophil to lymphocyte ratio; Exercise; Inflammation

57

58 **Introduction**

59 Exercise has a major impact on the immune system, with effects that differ depending on
60 intensity, duration, and frequency (1). Certain forms of acute exercise can elicit a transient
61 inflammatory response, depending on the exercise modality, intensity, and individual
62 characteristics. For example, recent meta-analysis found that exercise performed under both
63 hypoxic and normoxic conditions led to an increase in IL-6 levels, while TNF- α elevation was
64 observed only during hypoxic exercise (2). However, chronic training has been shown to provide
65 anti-inflammatory advantages through many pathways, thereby holding considerable promise for
66 the prevention and treatment of conditions associated with chronic inflammation (3-7). For
67 example, a recent meta-analysis reported that, regardless of the type of training, exercise reduced
68 circulating levels of several inflammatory and metabolic markers—including adiponectin, C-
69 reactive protein (CRP), interleukins (IL-6, IL-18, IL-20), leptin, and tumor necrosis factor- α
70 (TNF- α)—in individuals who were overweight or with obesity (4). Another meta-analysis
71 suggested that in patients with type 2 diabetes, exercise reduces the level of inflammatory
72 cytokines, including CRP, TNF- α , and IL-6 (5). Also, Sheldon et al. examined exercise-induced
73 inflammatory and metabolic adaptations in older adults and found that aerobic training produced
74 the greatest anti-inflammatory benefits, followed by resistance training(7).

75 These divergent responses between acute and chronic exercise highlight a complex pattern of
76 immune modulation that may be effectively captured using integrated indicators like neutrophil
77 to lymphocyte ratio (NLR)(8). Neutrophils, as part of the innate immune response, are among the
78 first responders to exercise-induced stress or muscle damage, releasing enzymes and reactive
79 species that promote inflammation (9). Lymphocytes, in contrast, mediate adaptive immunity and
80 contribute to immune surveillance and recovery(10). The dynamic and often opposing behavior
81 of these two cell types during and after exercise underpins the utility of the NLR, measured

82 within the blood circulation, as a simple and integrative marker reflecting the balance between
83 pro-inflammatory activation and immune regulation.

84 NLR is a widely accessible, simple, and sensitive biomarker of inflammation (11) and has been
85 used and studied in a variety of disorders, including cancer, urinary tract infection, COVID-19
86 infection, stroke, and myocardial infarction (12-17). In contrast to commonly studied cytokines
87 that require specialized laboratory techniques, NLR is easily calculated from standard
88 hematological parameters, offering a cost-effective and widely accessible measure of systemic
89 inflammatory status that may enhance translational applicability. Despite the presence of
90 numerous original studies examining NLR modulation following acute or long-term exercise, no
91 meta-analysis or systematic review has been conducted on this subject to date.

92 To address this gap, the present meta-analysis aims to systematically evaluate the existing
93 evidence on the variations in NLR levels induced by acute and chronic exercise. By
94 consolidating these findings, this study seeks to elucidate the role of NLR in exercise, offering
95 insights into its potential as a predictive marker for recovery and advancing our understanding of
96 the interplay between exercise, inflammation, and recovery processes. By elucidating the
97 inflammatory profile associated with exercise, this work may provide a foundation for
98 optimizing exercise prescriptions for people needing anti-inflammatory interventions.

99 **2. Method**

100 The protocol of the study was registered in PROSPERO (ID: CRD420251042422), and the
101 completed PRISMA checklist is provided as **Supplementary tables S1 and S2**.

102

103 **2.1. Search Strategy**

104 We systematically searched PubMed, Embase, Web of Science, Cochrane, and Scopus for
105 articles published before September 2, 2025. The search strategy was: ("exercise"[MeSH Terms]
106 OR "exercise"[Title/Abstract] OR "Sport"[Title/Abstract] OR (("Physical"[All Fields] OR "high-
107 intensity interval"[Title/Abstract] OR "weightlifting"[Title/Abstract] OR "Moderate-Intensity
108 continuous"[Title/Abstract] OR "strength"[Title/Abstract] OR "aerobic"[Title/Abstract] OR
109 "resistance"[Title/Abstract])) AND ("training"[Title/Abstract] OR "Program"[Title/Abstract]))
110 AND ("Neutrophil to lymphocyte ratio"[All Fields] OR "NLR"[All Fields]). No limitations

111 regarding date or language were imposed. Reference lists of eligible studies were also screened.
112 **Supplementary table S3** contains the complete search strategies for each database.

113 **2.2. Study selection**

114 Every article found through systematic searches of electronic databases was converted to the
115 EndNote bibliographic and reference manager software. All duplicates were omitted. Two
116 authors then independently reviewed the abstracts and titles, and potential studies were assessed
117 for eligibility using predetermined criteria. Any disagreements were settled via discussion by the
118 third author.

119 **2.3. Eligibility Criteria**

120 The PICO framework was used to define the inclusion criteria.:

- 121 - Population (P): Human participants of any age or health status, regardless of baseline physical
122 activity level;
- 123 - Intervention (I): Acute or chronic exercise programs, with NLR assessed in peripheral human
124 blood samples;
- 125 - Comparison (C): NLR levels of peripheral human blood measured before exercise compared to
126 levels after exercise;
- 127 - Outcome (O): Within-subject change in NLR measured before and after exercise.

128
129 Exclusion criteria were as follows:

- 130 1. Non-peer-reviewed studies (e.g., conference abstracts), patents, or non-comparative studies
131 (e.g., case series, case reports);
- 132 2. Non-quantitative studies (e.g., book chapters, commentaries, reviews, editorials);
- 133 3. Animal model studies;
- 134 4. Studies focusing on specific tissues (e.g., cerebrospinal fluid) rather than peripheral blood.

135 **2.4. Data Extraction**

136 For each included study, we extracted: first author, year, country, sample size, mean age, sex (%
137 male), BMI, exercise type and duration (acute or chronic), health status (healthy vs. patient),
138 exercise intensity, and NLR data pre- and post-exercise.

139 **2.5. Risk of Bias Assessment**

140 We assessed methodological quality using the National Institutes of Health (NIH) Quality

141 Assessment Tool for Before-After (Pre-Post) Studies Without Control Group, which includes 12
142 items on design, outcome reliability, adherence, and statistics(18). Each item was rated “Yes,”
143 “No,” “Cannot determine,” or “Not reported.” Two reviewers independently evaluated all studies
144 and reconciled inconsistencies through discussion.

145

146 **2.6. Statistical Analysis**

147 The statistical analysis was carried out using STATA version 19.0 (Stata Corporation, College
148 Station, TX, USA). In studies where only graphical findings were presented rather than
149 numerical data, we digitized the graphs and retrieved the data using WebPlotDigitizer Software.
150 The reliability of WebPlotDigitizer has been previously validated (19). We imputed $r = 0.7$. The
151 correlation coefficient (r) accounts for the within-subject relationship between pre- and post-
152 intervention values(20-22). Overall mean difference (MD) in NLR values, along with the
153 corresponding 95% confidence intervals (CIs), was reported. When the median and interquartile
154 range were reported, we converted them to mean \pm standard deviation (SD) using the method by
155 Wan et al. (23). In addition, standard error (SE) was converted to SD using $SD = SE \times \sqrt{n}$
156 To further assess statistical heterogeneity among the studies, the Cochran Q test (χ^2) and the I^2
157 test were utilized (24). A random-effect model was then employed, with subgroup analysis based
158 on participants' health status, exercise intensity, and quality of evidence, and meta-regression
159 based on age, percentage of males, sample size, BMI, and exercise duration used to determine
160 the source of heterogeneity. To categorize exercise severity for subgroup analysis, we used the
161 authors' own classification of exercise intensity. When studies did not report exercise intensity,
162 we used the following definitions to determine exercise intensity(25):

163 1. High-intensity or severe exercise was defined as: (i) $\geq 77\%$ of maximum heart rate (HR_{max}),
164 (ii) $\geq 64\%$ of VO_{2max}, (iii) Rating of Perceived Exertion (RPE) ≥ 14 , or (iv) $\geq 70\%$ of 1-repetition
165 maximum (1RM) for resistance training.

166 2. Moderate-intensity exercise was defined as: (i) 64-76% of HR_{max}, 46-63% of VO_{2max}, or 50-
167 69% of 1RM, 9ii) or RPE between 11–13.

168 Sensitivity analysis was conducted by a leave-one-out meta-analysis to illustrate the impact of
169 each individual study on the overall estimate by sequentially excluding one study from the meta-

170 analysis. In addition, GRADE (Grading of Recommendations Assessment, Development and
171 Evaluation) method was used to assess the certainty of evidence(26). The funnel plot, Egger's
172 test, and Begg's test were all used to investigate publication bias. A two-tailed $p < 0.05$ indicated
173 statistical significance.

174 **3. Result**

175 **3.1. Study Selection and Characteristics**

176 The PRISMA flow diagram in **Figure 1** shows the selection process for studies included in this
177 meta-analysis. Initially, 1885 records were identified. After removing duplicates, studies were
178 screened in two steps: first by title/abstract, then by full-text review. Through this process, our
179 meta-analysis includes 26 studies with 1203 participants in total. Among these, 12 studies
180 assessed NLR changes immediately after acute exercise (27-38), with five of those also
181 evaluating NLR changes one to three hours post-exercise (29, 30, 34-36). Fifteen studies focused
182 on NLR changes after chronic exercise (29, 39-52). Among the acute exercise studies,
183 10 involved healthy participants (28, 30-38), and eight were rated as having high methodological
184 quality (27, 29-34, 38). In chronic exercise group, 10 studies included participants with chronic
185 disorders (29, 40, 42-44, 47-49, 51, 52), and 11 demonstrated high methodological quality (29,
186 39-45, 48, 51, 52). Additional details on the acute and chronic exercise studies are provided in
187 **Tables 1 and 2**, respectively. In addition, **supplementary table S4** shows the quality assessment
188 results of each included study using NIH tool.

189 **3.2. Meta-analysis of the differences in NLR level before and immediately after acute** 190 **exercise**

191 Immediately after acute exercise, there was no significant change in NLR levels (MD = 0.03;
192 95% CI: -0.24 to 0.30; $p = 0.82$, **Figure 2**). Based on GRADE method, the certainty of evidence
193 was downgraded to very low (**Supplementary table S5**). Substantial heterogeneity was present
194 across studies ($I^2 = 93.6\%$, p for heterogeneity < 0.001), and a random-effects model was used.

195 For exercise intensity, studies assessing moderate exercise reported no effect on NLR (MD
196 =0.10; 95% CI: -0.26 to 0.45; $p = 0.59$), while those evaluating vigorous exercise also showed
197 no significant change (MD = -0.02; 95% CI: -0.35 to 0.32; $p = 0.92$). The between-group
198 difference was not statistically significant ($p = 0.65$, **Figure S1**).

199 For participant health status, studies involving healthy individuals or athletes showed no effect
200 (MD = 0.02; 95% CI: -0.26 to 0.29; $p = 0.91$), and those including patients with chronic
201 disorders also reported no significant change (MD = 0.10; 95% CI: -0.34 to 0.55; $p = 0.65$). The
202 between-group difference was not significant ($p = 0.75$, **Figure S2**).

203 For NIH quality assessment, studies rated as good (MD = -0.00; 95% CI: -0.38 to 0.38; $p =$
204 0.99) and those rated as fair (MD = 0.10; 95% CI: -0.24 to 0.45; $p = 0.56$) both showed null
205 effects. The between-group difference was not statistically significant ($p = 0.69$, **Figure S3**).
206 Overall, these factors did not explain the observed heterogeneity.

207 Meta-regression analyses revealed that none of the examined covariates—sample size
208 (coefficient = 0.0023; $p = 0.71$), age (coefficient = -0.0041; $p = 0.75$), BMI (coefficient = -0.072;
209 $p = 0.43$), or male percentage (coefficient = -0.0054; $p = 0.38$)—were significantly associated
210 with the effect size. All models showed substantial residual heterogeneity (I^2 ranging from 79.7%
211 to 94.1%), indicating that these variables did not explain the between-study variability. The
212 adjusted R^2 values were near zero (ranging from -11.8% to 2.8%), suggesting no meaningful
213 reduction in heterogeneity. These findings indicate that sample size, age, BMI, and sex
214 distribution are unlikely to be major sources of heterogeneity in the effect of acute exercise on
215 NLR.

216 **3.3. Meta-analysis of the differences in NLR level before and one-to-three hours after acute** 217 **exercise**

218 The meta-analysis of five studies assessing NLR levels one-to-three hours after acute exercise
219 demonstrated a statistically significant increase in NLR (MD = 1.23; 95% CI: 0.46 to 1.99; $p =$
220 0.002, **Figure 3**). Based on GRADE method, the certainty of evidence was downgraded to very
221 low (**Supplementary table S5**). Substantial heterogeneity was present across studies ($I^2 =$
222 93.3%, p for heterogeneity < 0.001), and a random-effects model was applied.

223 For exercise intensity, moderate exercise was associated with a significant increase in NLR (MD
224 = 1.10; 95% CI: 0.14 to 2.05; $p = 0.02$), whereas vigorous exercise showed a non-significant
225 trend toward an increase (MD = 1.45; 95% CI: -0.11 to 3.01; $p = 0.06$). The between-group
226 difference was not statistically significant ($p = 0.71$, **Figure S4**).

227 For participant health status, studies involving healthy individuals or athletes demonstrated a
228 significant increase in NLR (MD = 1.18; 95% CI: 0.22 to 2.15; $p = 0.01$), while those including
229 patients with chronic disorders did not (MD = 1.43; 95% CI: -0.38 to 3.24; $p = 0.12$). The
230 between-group difference was not significant ($p = 0.81$, **Figure S5**).

231 For NIH quality assessment, studies rated as Good showed a significant increase in NLR (MD =
232 1.29; 95% CI: 0.40 to 2.17; $p = 0.005$), whereas studies rated as Fair did not (MD = 1.13; 95%
233 CI: -0.85 to 3.11; $p = 0.26$). The between-group difference was not statistically significant ($p =$
234 0.89 , **Figure S6**).

235 Meta-regression analyses revealed that none of the examined covariates—sample size
236 (coefficient = 0.009; $p = 0.87$), age (coefficient = 0.026; $p = 0.54$), BMI (coefficient = -0.419; p
237 = 0.35), or male percentage (coefficient = -0.015; $p = 0.35$)—were significantly associated with
238 the effect size. All models showed substantial residual heterogeneity (I^2 ranging from 89.5% to
239 94.6%), indicating that these variables did not explain the between-study variability. The
240 adjusted R^2 values were close to zero (ranging from -28.6% to 14.5%), suggesting no
241 meaningful reduction in heterogeneity. These findings indicate that sample size, age, BMI, and
242 sex distribution are unlikely to be major sources of heterogeneity in the effect of acute exercise
243 on NLR.

244 **3.4. Meta-analysis of changes in NLR following chronic exercise**

245 The meta-analysis of 15 studies evaluating changes in NLR levels before and after chronic
246 exercise showed a significant overall reduction in NLR (MD = -0.30; 95% CI: -0.56 to -0.04; p
247 = 0.02, **Figure 4**). Based on GRADE method, the certainty of evidence was downgraded to low
248 (**Supplementary table S5**). Substantial heterogeneity was observed across studies ($I^2 = 98.4%$, p
249 for heterogeneity < 0.001), and a random-effects model was used.

250 When stratified by exercise intensity, moderate exercise was associated with a non-significant
251 reduction in NLR (MD = -0.32; 95% CI: -0.73 to 0.09; $p = 0.12$), and severe exercise also
252 showed a non-significant reduction (MD = -0.28; 95% CI: -0.62 to 0.06; $p = 0.10$). The
253 between-group difference was not significant ($p = 0.87$, **Figure S7**).

254 For participants' health status, healthy individuals showed no significant change in NLR (MD =
255 -0.03; 95% CI: -0.34 to 0.28; $p = 0.83$), whereas people with comorbidities demonstrated a

256 significant reduction (MD = -0.47; 95% CI: -0.80 to -0.13; $p = 0.006$). The between-group
257 difference was not statistically significant ($p = 0.06$, **Figure S8**).

258 In terms of NIH quality assessment, studies rated as good showed a significant reduction in NLR
259 (MD = -0.44; 95% CI: -0.75 to -0.12; $p = 0.007$), whereas those rated as fair did not (MD =
260 0.01; 95% CI: -0.16 to 0.17; $p = 0.93$). The difference between subgroups was statistically
261 significant ($p = 0.01$, **Figure S9**). These findings suggest that chronic exercise is generally
262 associated with reductions in NLR, with stronger evidence observed in studies rated as higher
263 quality.

264 Meta-regression analyses were conducted to explore potential sources of heterogeneity in the
265 change in NLR following chronic exercise. Age was significantly associated with the effect size
266 (coefficient = -0.017; 95% CI: -0.034 to -0.0004; $p = 0.04$), suggesting that studies with older
267 participants tended to report greater reductions in NLR. In contrast, sample size (coefficient = -
268 0.001; 95% CI: -0.005 to 0.002; $p = 0.35$), BMI (coefficient = -0.087; 95% CI: -0.209 to 0.035;
269 $p = 0.14$), male percentage (coefficient = 0.0015; 95% CI: -0.006 to 0.009; $p = 0.68$), and
270 exercise duration (coefficient = 0.027; 95% CI: -0.031 to 0.086; $p = 0.33$) were not significantly
271 associated with effect size. Residual heterogeneity remained very high in all models (I^2 ranging
272 from 95.17% to 98.49%), indicating that these covariates did not adequately explain the
273 between-study variability.

274 3.5. Leave-one-out sensitivity analysis

275 As shown in **figure 5**, the leave-one-out sensitivity analysis revealed that no single study had a
276 disproportionate influence on the overall effect size for changes in NLR following both acute and
277 chronic exercise. These results suggest that the overall findings are stable and not driven by any
278 single study.

279 3.6. Publication bias

280 **Figure 6** presents funnel plots assessing potential publication bias among studies evaluating
281 changes in NLR in response to exercise. For studies examining NLR immediately after acute
282 exercise (**Figure 6A**), the funnel plot appeared largely symmetrical, and neither Egger's test ($p =$
283 0.41) nor Begg's test ($p = 0.58$) suggested evidence of publication bias. Similarly, for studies
284 evaluating NLR one-to-three hours after acute exercise (**Figure 6B**), the funnel plot also

285 appeared symmetrical, and neither Egger's test ($p = 0.07$) nor Begg's test ($p = 0.25$) indicated
286 evidence of publication bias. Taking together, these results suggest that publication bias is
287 unlikely to have substantially influenced the observed findings. Similarly, for studies evaluating
288 changes in NLR after chronic exercise (**Figure 6C**), the funnel plot appeared symmetrical.
289 Neither Egger's test ($p = 0.78$) nor Begg's test ($p = 0.20$) provided evidence of publication bias.
290 Together with the results for acute exercise, these findings suggest that the observed effects are
291 unlikely to be driven by small-study effects or selective publication.

292

293 **4. Discussion**

294 This meta-analysis explored the effect of exercise on NLR, a readily accessible marker of
295 systemic inflammation and immune response. The results of our study highlight that NLR can
296 function as a useful lens through which to understand how exercise influences inflammatory
297 pathways, complementing evidence from cytokine studies and other immune markers. By
298 reflecting the dynamic balance between neutrophils and lymphocytes, NLR provides a simple
299 way to track how acute and chronic exercise modulates systemic inflammation.

300 *4.1. NLR change immediately after acute exercise*

301 No significant difference was observed in NLR levels immediately following acute exercise.
302 This likely reflects the short time frame required for measurable systemic changes to occur after
303 exercise. While immune processes such as neutrophil mobilization and cytokine release are
304 initiated soon after physical activity, these responses may not yet be detectable in circulating
305 blood counts in the immediate post-exercise window. Thus, the lack of change in NLR right after
306 exercise may be due to the delay between the onset of immune activation and its measurable
307 expression in peripheral blood.

308 *4.1.1. Heterogeneity of results immediately after acute exercise*

309 Considerable heterogeneity was observed in NLR responses immediately after acute exercise.
310 We explored whether this variability could be explained by factors such as participants' health
311 status, exercise intensity, study quality, age, sex distribution, sample size, or BMI, but none of
312 these factors consistently accounted for the differences between studies. It is possible that

313 unmeasured influences contributed to this heterogeneity, including other individual-level factors
314 such as sleep quality, recent diet, hydration status, exercise training experience and starting
315 fitness.

316 *4.2. NLR change one-to-three hours after acute exercise*

317 The second meta-analysis, including studies measuring NLR after one-to-three
318 hours following acute exercise, demonstrated a statistically significant increase. This is
319 consistent with a transient stress-induced immune response, increased neutrophils (53, 54), and
320 relative lymphocytic suppression (55). In fact, the increased NLR reflects a physiological
321 response to exercise-induced muscle stress and tissue repair processes, which require the
322 engagement of innate immune components. These results emphasize the significance of sampling
323 time when assessing post-exercise inflammatory markers. It has long been recognized that
324 skeletal muscle inflammation is triggered by acute exercise. For example, in a study by Jiménez-
325 Jiménez et al., eleven participants, ages 66 to 75, performed two eccentric exercise sessions
326 separated by eight weeks of training. In peripheral blood mononuclear cells from older
327 individuals, they found that acute eccentric exercise increases the expression of several genes
328 associated with inflammation and the activation of nuclear factor Kappa B (NF- κ B) immediately
329 after and at 3 h after cessation of a bout of eccentric-damaging protocol (56).

330 *4.2.2. Heterogeneity of results one-to-three hours after acute exercise*

331 Subgroup analyses examined whether exercise intensity, participant health status, or study
332 quality could explain the variability in the results. Although NLR increased significantly in some
333 subgroups, such as in healthy participants, exercise with moderate intensity, or studies rated as
334 good quality, other subgroups showed similar trends without reaching significance. However, the
335 differences between these subgroups were not statistically meaningful, indicating that the
336 apparent variation was not due to real group differences. In line with this, meta-regression based
337 on age, sample size, sex distribution, and BMI also did not identify any significant sources of
338 heterogeneity. The observed heterogeneity may stem from unaccounted individual-level factors,
339 such as differences in the time frame of NLR measurement, sleep quality, recent dietary intake,
340 hydration status, or baseline inflammatory condition.

341 *4.3. Chronic exercise*

342 In contrast to acute exercise, there was a significant overall decrease in NLR linked to chronic
343 exercise. This supports the well-established anti-inflammatory benefits of long-term physical
344 activity (57). Our findings that NLR decreases after long-term exercise are consistent with
345 mechanistic studies demonstrating that regular training attenuates inflammatory signaling. For
346 example, Jiménez-Jiménez et al. reported that although acute eccentric exercise enhanced NF- κ B
347 activation, and the expression of genes associated with inflammation in elderly individuals; these
348 effects were significantly blunted following eight weeks of eccentric training. This supports the
349 interpretation that chronic exercise reduces baseline inflammatory activity and enhances the
350 body's ability to regulate immune responses(56).

351 *4.3.2. Heterogeneity of results after chronic exercise*

352 The observed variability in NLR responses to chronic exercise appears to be largely explained by
353 differences in study quality and participant age, which emerged as major sources of
354 heterogeneity across studies.

355 The subgroup analysis based on NIH quality ratings revealed that methodological rigor
356 substantially influenced the observed effect of chronic exercise on NLR. Studies rated as good
357 demonstrated a clear reduction in NLR, whereas those rated as fair showed no change. The
358 statistically significant difference between these subgroups indicates that higher-quality designs
359 tend to capture the anti-inflammatory effect of long-term exercise more consistently. This may
360 reflect more standardized protocols and better control of confounding variables in well-
361 conducted studies. Conversely, fair-quality studies—often with smaller sample sizes or
362 incomplete reporting—may underestimate or obscure true biological changes due to greater
363 measurement variability.

364 In addition, meta-regression identified age as a significant moderator. The negative coefficient
365 suggests that studies with older participants reported greater reductions in NLR following
366 chronic exercise. This pattern aligns with physiological expectations: older adults typically
367 exhibit higher baseline systemic inflammation(58) and thus may experience a more pronounced
368 normalization of immune balance with sustained exercise. Regular physical activity likely
369 mitigates age-related immune-senescence and chronic low-grade inflammation
370 (“inflammaging”), leading to larger measurable decreases in NLR in this subgroup(59).

371 The primary limitation of our meta-analysis is the high heterogeneity observed among the
372 included studies. While the main sources of variability were identified in the chronic exercise
373 analysis, particularly related to study quality and participant age, they could not fully explain the
374 acute exercise results. To address this issue, we used a random-effects model to provide more
375 robust and generalized estimates; however, some residual heterogeneity may still influence the
376 pooled outcomes. In addition, the certainty of evidence was low for chronic exercise and very
377 low for acute exercise according to the GRADE approach, primarily reflecting heterogeneity in
378 study design, participant characteristics, and outcome assessment. These findings indicate that
379 current evidence is limited and should be interpreted with caution.

380 In conclusion, our results emphasize the dynamic and time-dependent nature of immune
381 responses to exercise. While acute exercise induces a transient increase in inflammatory markers
382 after a delay, chronic exercise contributes to sustained reductions, supporting exercise as a
383 practical approach to inflammation control.

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388 analysis, Sh.Kh.; data extraction, screening of articles, and quality assessment, Sh.Kh., S.M., and
389 F.F.; writing—original draft preparation, Sh.Kh., S.M., and F.F.; writing—review and editing,
390 R.K.S.; supervision, R.K.S.; All authors have read and agreed to the published version of the
391 manuscript.

392

393 **Abbreviations**

394 IL: Interleukin

395 NLR: neutrophil to lymphocyte ratio

396 SE: standard error

397 SD: Standard deviation

- 398 MD: Mean difference
- 399 CI: 95% confidence interval
- 400 RCT: Randomized Controlled Trial
- 401 BMI: Body Mass Index
- 402 TNF- α : Tumor necrosis factor-alpha
- 403 PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses
- 404 MET: Metabolic equivalent of task
- 405 NIH: National Institutes of Health
- 406 CRP: C-reactive protein
- 407 nuclear factor Kappa B (NF- κ B)
- 408 GRADE: Grading of Recommendations Assessment, Development and Evaluation

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411 **Supplementary Material:** <https://doi.org/10.6084/m9.figshare.31079284>

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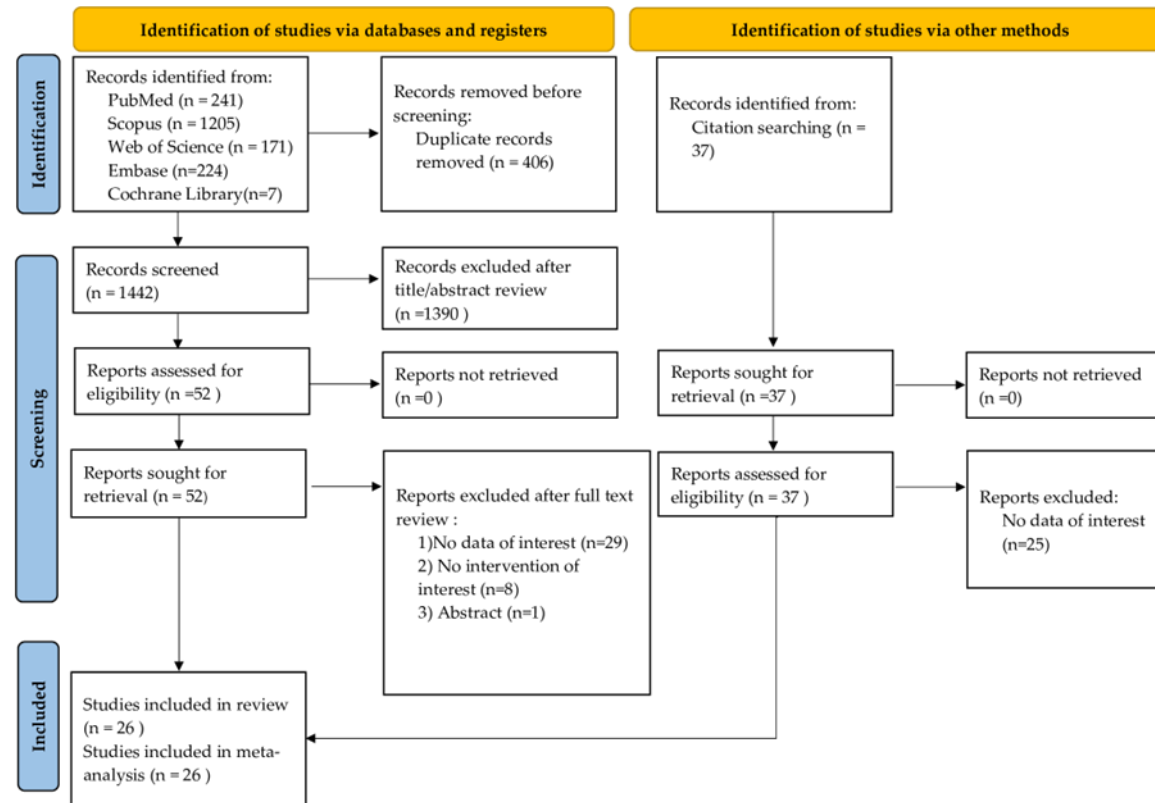
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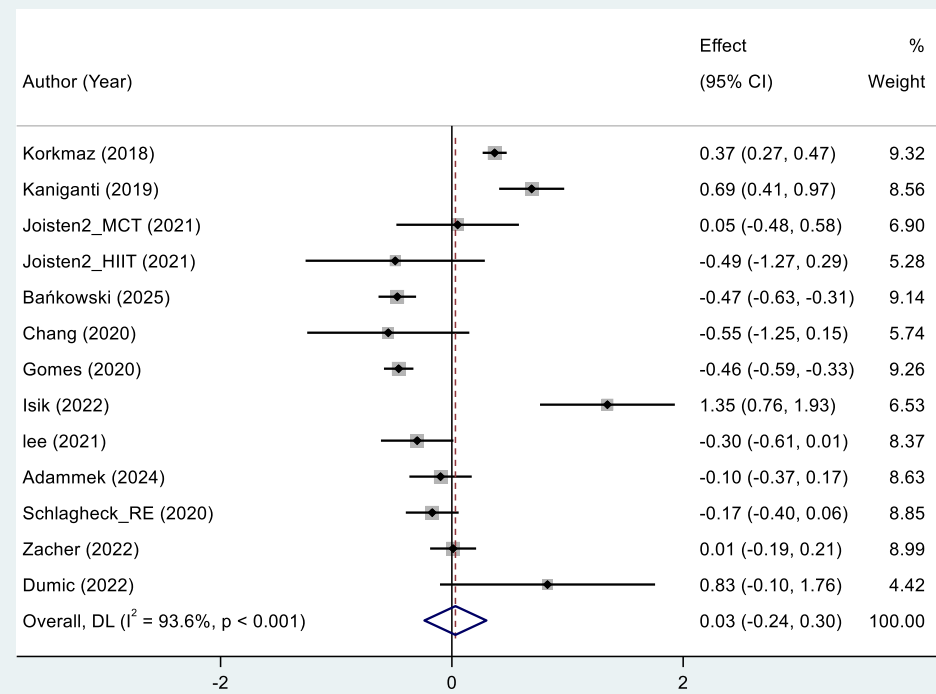
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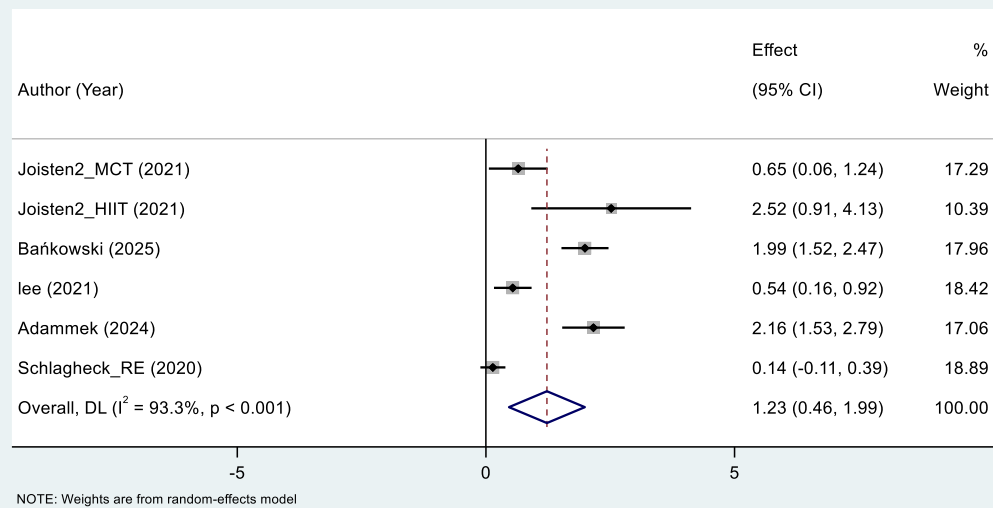
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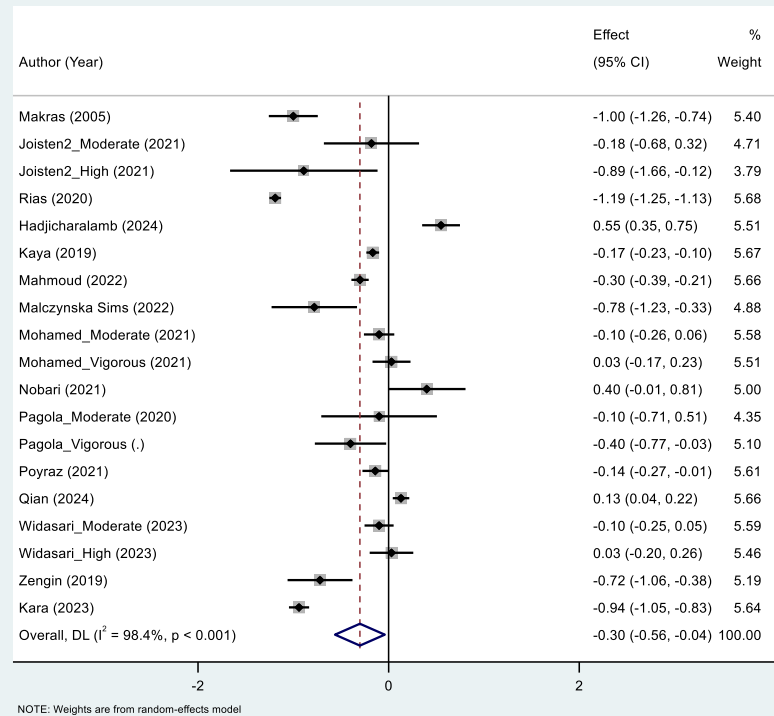
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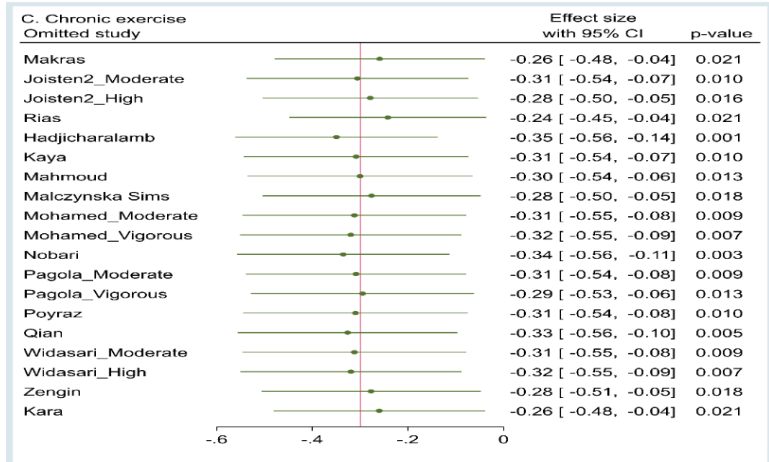
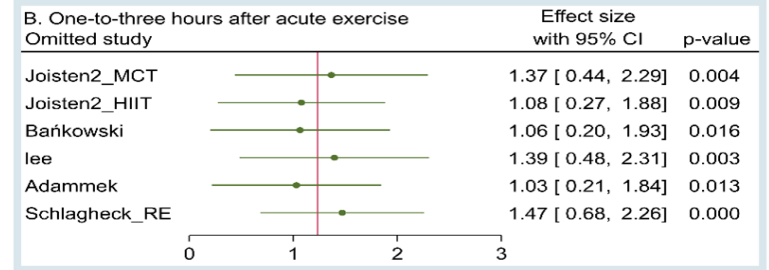
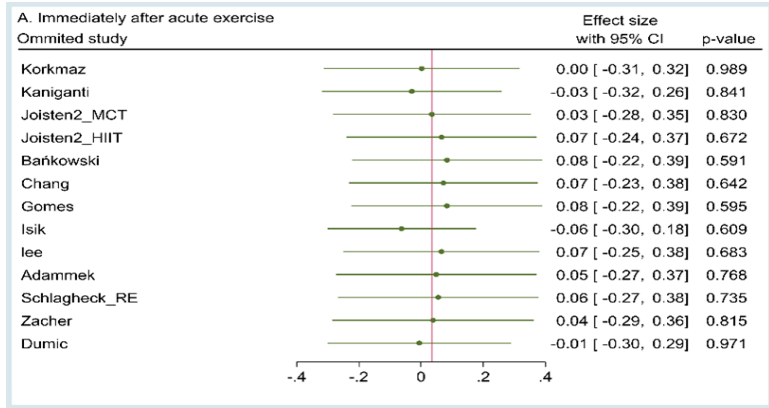


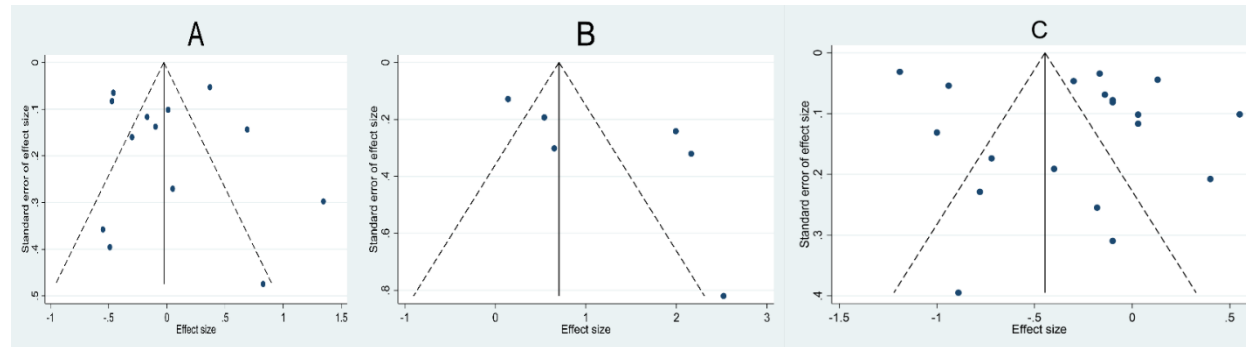


NOTE: Weights are from random-effects model









Studies in acute exercise analysis

Participants	Mean age	BMI	Exercise type	Gender (Male %)	Sample Size	NLR level			Exercise protocol
						Pre-exercise	Immediately after exercise	One to three hours after exercise	
with y ms	57	-	Treadmill exercise testing	78%	113	2.04 ± 0.63	2.41 ± 0.78	-	Bruce protocol
l- ined fters	19	-	Weightlifting training sessions (snatch, clean and jerk, and back squats)	38.46%	13	1.46 ± 0.64	2.15 ± 0.69	-	High-intensity weightlifting training sessions (75% relative intensity)
with e s	49.7	25.4	24 minutes Single bout of Moderate-Intensity continuous training on a bicycle ergometer	45.45%	33	3.18 ± 2.00	3.23 ± 2.01	After 3 hours: 3.83 ± 2.38	Moderate-intensity continuous training at 65% of their maximum heart rate
	50.9	25.3	5 × 1.5-minute intervals, Single bout of High-intensity interval	31.42%	35	3.80 ± 3.27	3.31 ± 2.15	After 3 hours: 6.32 ± 6.54	High-Intensity interval training at 95%–100% of their maximum heart rate

			training on a bicycle ergometer						
r aged	38.33	23.85	Treadmill running test	100%	30	1.73 ± 0.61	1.26 ± 0.55	After 1 hour: 3.73 ± 1.68	A graded maximal treadmill running test with increasing speed/tilt until exhaustion
I d-letes	21.35	21.55	Repeated vertical jumping exercises	100%	20	1.5 ± 2.16	0.95 ± 1.09	-	High intensity jumping exercises at a frequency of 0.7 Hertz (12 repetitions of 10 jumps; total of 120 jumps)
ional y al oners	31	25.7	Single High-intensity functional training session, gymnastics, also known as the 'Cindy' workout	52.17%	23	1.26 ± 0.43	0.80 ± 0.25	-	Training consisted of completing as many rounds of 5 pull-ups, 10 push-ups, and 15 air squats as feasible within a 20-minute timeline
, elite do	20.5	21.12	90 minutes of unit training tailored to taekwondo, which includes a 50-minute high-intensity interval training component	50%	24	2.15 ± 1.11	3.50 ± 2.0	-	The range of training intensity was 80–90%

ed lthy	25.1	23.66	30 minutes of treadmill-based fixed-intensity trial	100%	16	2.06 ± 0.78	1.76 ± 0.86	After 1.5 hours: 2.60 ± 1.08	60% VO2max exercise challenge
	25.5	22.9	40-minute aerobic exercise on a bicycle Ergometer	50%	12	1.64±0.60	1.54±0.63	After 1 hour: 3.80±1.44	A moderate intensity of 60% VO2 peak was chosen
	24.6	25.4	Acute resistance exercise for 50 minutes	100%	24	1.99 ± 0.76	1.82 ± 0.71	After 1 hour: 2.13 ± 0.85	Exercise machine at 70% one repetition maximum
l c	16.1	20.3	Hallman-Venrath protocol on a standardized bicycle ergometer	44%	25	1.42 ± 0.56	1.43 ± 0.70	-	Maximal exercise test
ional	39.25	26.13	Recreational SCUBA dive at 20–30 meters depth, lasting 30 minutes each, in cold seawater conditions	100%	14	1.87 ± 0.70	2.70 ± 2.19	-	A dive was conducted to a maximum depth of 20 meters for a duration of 30 minutes, involving a steady descent to the maximum depth

										and a gradual rise to the surface without a decompression stop.
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Body Mass Index; NIH, National Institutes of Health

Studies in chronic exercise analysis

Participants	Sample size	Mean age (years)	BMI	Gender (Male%)	Exercise intervention/evaluation	NLR pre-exercise	NLR post-exercise	Exercise protocol
Young males in military camp	48	21.3	23.2	100%	4 weeks 5x/week moderate intermittent mixed endurance exercise and resistance exercise	3.3 ± 1.25	2.3 ± 0.69	Gymnastic and climbing backpacks
Patients with Multiple Sclerosis	33	49.7	25.4	45.45%	Moderate-intensity continuous training on a bicycle ergometer, 3 times per week for 3 weeks.	3.18 ± 2.00	3.00 ± 1.72	Moderate-intensity training at heart rate.
	35	50.9	25.3	31.42%	Training with high-intensity intervals on a bicycle ergometer, 3 times weekly for 3 weeks.	3.80 ± 3.27	2.91 ± 2.27	High-Intensity 95%–100% heart rate.
Patients with type 2 diabetes mellitus	20	54.70	-	35%	Regular walking for a duration of at least 30 minutes, five times/week for 8 weeks.	2.55 ± 0.18	1.36 ± 0.18	Walk around roads for a minutes/week

ned nt soccer	36	16.4	22.3	100%	8-week soccer-specific training 6 days/week, 8 friendly matches, and 48 training sessions. The sessions lasted between 60 and 90 minutes.	1.15 ± 0.35	1.70 ± 0.80	Soccer-spe training
nt patients of ac ation unit	211	56.28	-	46%	30 sessions of the tailored cardiac rehabilitation program in 10 weeks. Cycle ergometer training, strengthening exercises (after 2 weeks), and tailored adjustments every 10 sessions (based on Borg scale and progress).	1.70 ± 0.67	1.53 ± 0.60	Aerobic ex structured t muscle gro lower extre of the max repetitions
y, ht, non- sal women	19	Between 28 and 43	29.6 9	0%	linear or nonlinear periodized resistance training, 3 weekly training sessions for 12 weeks.	2.21 ± 0.27	1.91 ± 0.25	Resistance 60–90% of
ho have gnosed with n's disease	15	64.24	26.5 5	60%	12 weeks of High-Intensity Interval Training using a stationary cycloergometer. Three 1-hour training sessions were completed three times per week, for a total of 36 training sessions lasting 60 minutes.	2.58 ± 1.16	1.8 ± 0.5	High-Inten 60–80% of maximum
	30	Between 18 - 35		-	40-minute aerobic program using cycle ergometer	1.78 ± 0.6	1.68 ± 0.3	Aerobic pr week (on d

and healthy with a past of COVID-19			less than 35		protocols, 6 weeks, 3 sessions/week.			moderate in peak heart
	30				Resistance training for the lower body using free weights (e.g., weightlifting, sand bags), 6 weeks, 3 sessions/week.	1.7 ± 0.78	1.73 ± 0.54	The resista initiated pr sessions, w set of exerc three sets a 70% of one
onal youth ayers	15	15.5	21.7	100%	Players participated in 4 training sessions and one match per week for 14 weeks.	1.5 ± 0.6	1.9 ± 1.1	All particip standardize on the intro heart rate d been report maximum
m breast urvivors who iously cancer- atigue at	10	51	27.3	0%	Unsupervised Aerobic training, instructed to complete ≥150 min/week moderate-vigorous physical activity, and less supervised resistance exercises for 16 weeks.	2.3 ± 0.6	2.2 ± 1.3	Moderate e training: ≥ moderate-v activity + F
	9	47	25.8		Supervised high-intensity aerobic (treadmill running, aerobic games, cycle-ergometer pedaling, or elliptical ergometer exercise) and Resistance exercises for 16 weeks.	2.0 ± 0.8	1.6 ± 0.6	High-inten very hard i resistance t

er sive patients.	58	56	26.3 0	44.8%	16-week supervised cardiac rehabilitation program (aerobic exercise on a cycle ergometer). Each session is 60 minutes, twice a week for the first 4 weeks, then three times a week for the next 12 weeks.	2.21 ± 0.69	2.07 ± 0.66	Moderate-i exercise pr maintained rating of 11 Scale.
with type 2 diabetes mellitus	22	-	24.7 6	-	Two weeks of pre-adaptation training followed by eight weeks of slow-velocity eccentric-only resistance training, conducted three times per week every other day for a duration of ten weeks.	1.38 ± 0.28	1.51 ± 0.25	Borg RPE between 11
healthcare with a history of moderate COVID-19 infection	19	40.11	27.5 8	21.9%	Moderate intensity: Continuous aerobic exercise lasting 30 minutes every day, prescribed as treadmill walking for 6 weeks.	1.93 ± 0.47	1.83 ± 0.38	Three mile starting pac 69% of ma
	11	33.09	25.2 6	81.8%	30 minutes a day of interval high-intensity aerobic exercise, prescribed as running or jogging on a treadmill for 6 weeks.	1.74 ± 0.54	1.77 ± 0.41	Initiate wit to attain 70 heart rate.
with STEMI patients, who	68	58.23	-	79.4%	8 weeks of cycling ergometry at least 1 month after primary PCI, for an average of 4 sessions	3.11 ± 1.95	2.39 ± 1.03	70-85% of

nt primary					weekly, each lasting 30 minutes.			
ronary ease ng exercise- rdiac ation	200	56.2	28.3	78%	Aerobic exercise on a cycle ergometer + muscle training before sessions for 5 days each week, totaling 6 weeks. Each session lasted 30 minutes.	2.64 ± 1.04	1.70 ± 0.55	Progressive 85% of ma reserve afte The RPE fo was 13–15

ex; NLR, Neutrophil to Lymphocyte Ratio; MET, Metabolic Equivalent of Task; STEMI, ST-segment elevation myocardial infarction

h

Acute exercise increased and chronic exercise decreased Neutrophil-to-Lymphocyte Ratio

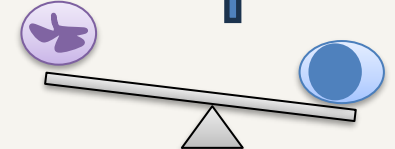
METHODS

OUTCOME

No change in NLR



↑ NLR



↓ NLR



Change in NLR was reported

CONCLUSION

While acute exercise induces a transient increase in NLR after a delay, chronic exercise contributes to sustained reduction, reinforcing its role as a non-pharmacologic strategy for inflammation control.

PROSPERO Code : CRD420251042422

Twenty-six studies involving a total of 1203 participants were included