HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.65632
Haydarpasa Numune Med J 2025;65(4):402–406


hnhtipdergisi.com

SYSTEMATIC META-ANALYSIS

# Red Blood Cell Distribution Width in Migraine: A Systematic Review and Meta-Analysis

Giuseppe Lippi[1], Camilla Mattiuzzi[2]

[1]Department of Clinical Biochemistry, University of Verona, Verona, Italy
[2]Medical Director, Rovereto Hospital, Provincial Agency for Social and Health Services (APSS), Trento, Italy

## Abstract

**Introduction:** Migraine is a prevalent and disabling neurological disorder with a complex and partially understood pathophysiology. Red blood cell distribution width (RDW), a routine hematological parameter, has emerged as a potential biomarker of systemic inflammation, which may be relevant in migraine.

**Methods:** We conducted a systematic review and meta-analysis of studies reporting RDW values in individuals with and without migraine. Electronic databases (PubMed, Scopus, Web of Science) and Google Scholar were searched through June 23, 2025. Inclusion criteria comprised case-control studies comparing RDW in migraineurs and healthy controls.

**Results:** Five case-control studies comprising 1,240 participants (709 with migraine and 531 without) met the inclusion criteria. RDW values were higher in migraine patients in four of the five studies. The overall pooled weighted mean difference (WMD) in RDW was 0.24 (95% CI: –0.15 to 0.62; $I^2$=97%). After excluding one outlier study, the WMD increased to 0.47 (95% CI: 0.18 to 0.76).

**Discussion and Conclusion:** Our findings suggest a trend toward elevated RDW in individuals with migraine. While promising, the results are limited by high heterogeneity and methodological inconsistencies across studies, underscoring the need for further standardized research.

**Keywords:** Migraine; RDW; red blood cell distribution width.

Migraine is a highly prevalent and disabling neurological disorder, affecting approximately 12–15% of the global population, with a marked female predominance and a peak incidence during the most productive years of life [1,2]. It also ranks among the leading causes of disability-adjusted life years (DALYs) worldwide [2], imposing substantial individual and societal burdens due to its recurrent, often severe attacks and the associated disability caused by a wide range of debilitating symptoms, including nausea (up to vomiting), dizziness or vertigo, photophobia, phonophobia, osmophobia, allodynia, and post-migraine fatigue [1].

The complex and multifactorial pathophysiology of migraine remains incompletely understood; however, it is thought to involve genetic predisposition, neurovascular dysfunction, cortical spreading depression, and inflammation [3]. In this context, the identification of accessible and reliable laboratory biomarkers that reflect underlying pathophysiological mechanisms, aid in risk assessment, support diagnosis, and enable monitoring of disease progression is of considerable clinical importance.

Red blood cell distribution width (RDW), a routinely reported parameter in the complete blood count (CBC),

**Correspondence:** Giuseppe Lippi, M.D. Department of Clinical Biochemistry, University of Verona, Verona, Italy
**Phone:** +39 045 812 43 08 **E-mail:** giuseppe.lippi@univr.it
**Submitted Date:** 23.06.2025 **Revised Date:** 27.08.2025 **Accepted Date:** 08.09.2025
Haydarpaşa Numune Medical Journal

reflects variability in the size of circulating erythrocytes [4]. Traditionally used in the differential diagnosis of anemia, RDW has more recently emerged as a potential biomarker of various pathological conditions characterized by systemic inflammation, oxidative stress, and endothelial dysfunction—key pathways that may also be implicated in the pathogenesis of migraine [5]. Accordingly, this systematic review and meta-analysis aimed to summarize the available evidence on RDW in patients with and without migraine and to evaluate whether this parameter may serve as a potential biomarker in this clinical setting.

## Materials and Methods

We conducted a comprehensive electronic search in Medline (via PubMed), Scopus, and Web of Science using the keywords "red blood cell distribution width" OR "RDW" AND "migraine," applied to all searchable fields. Because anemia status was not consistently reported across studies, it was not feasible to apply anemia as an exclusion criterion in this meta-analysis. The search was performed without restrictions on date (up to June 23, 2025) or language. The protocol adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. An additional search was performed in Google Scholar using the same predefined keywords to capture studies not indexed in the primary databases, limited to the first 1000 items.

Titles, abstracts, keywords, and full texts of all retrieved records were systematically screened. Studies were included if they reported RDW values in individuals with (cases) and without (controls) a diagnosis of migraine based on the criteria of the International Headache Society [6]. The reference lists of the included studies were also manually screened using forward and backward citation tracking to identify additional potentially relevant studies.

### Statistical Analysis

A pooled analysis was conducted to calculate the weighted mean difference (WMD) and corresponding 95% confidence intervals (95% CI) for RDW values between migraine and non-migraine subjects. A random-effects model was used to account for heterogeneity due to variations in study populations, hematological analyzers used to measure RDW, and measurement units. Heterogeneity was assessed using the $\chi^2$ test and the $I^2$ statistic with the inverse variance heterogeneity (IVhet) model. All analyses were performed using MetaXL software, Version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia). This study was conducted in accordance with the principles of the Declaration of Helsinki and relevant local legislation. Ethical approval was not required, as the study was a meta-analysis and therefore exempt from local institutional review board requirements.

## Results

A total of 22 articles were initially identified through searches of the three primary scientific databases (Fig. 1). Of these, 19 were excluded after title, abstract, or full-text screening for the following reasons: 14 did not specifically include patients with migraine, 3 did not report RDW values, and 2 were review articles. An additional two eligible studies were identified through manual searching in Google Scholar. Consequently, five studies comprising a total of 1,240 participants (709 with migraine and 531 without) met the inclusion criteria and were included in the pooled analysis, as summarized in Table 1 [7–11]. All included studies had a case-control design. Three studies reported the laboratory instruments used to measure RDW and specified the measurement unit as percentage (%), with each using a different hematological analyzer. In contrast, two studies did not report the type of analyzer

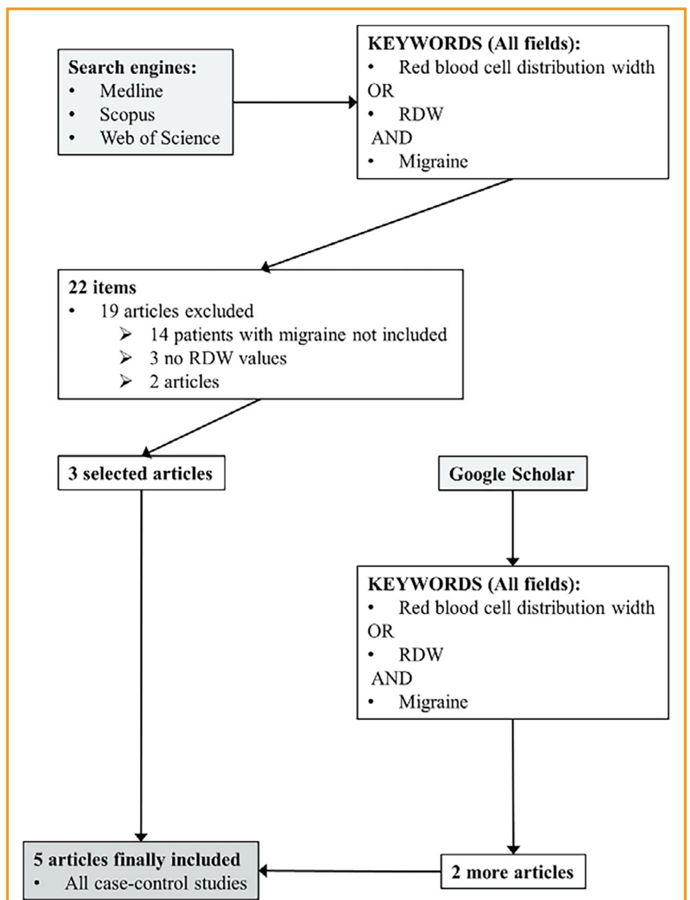


**Figure 1.** Flow-chart detailing search criteria, eligibility, exclusion/inclusion, and final outcome of our search.

RDW: Red blood cell distribution width.

**Table 1.** Summary of the studies included in the pooled analysis

| Authors | Study design | Sample size (patients) | Instrumentation | Measure unit | Values (cases vs. controls) |
|---|---|---|---|---|---|
| Celikbilek et al. [7], | Case-control | 200 (100 with migraine) | Coulter LH 750 (Beckman Coulter) | Percent (%) | 13.8±0.5 vs. 13.1±0.3 |
| Acar et al. [8], | Case-control | 165 (100 with migraine) | Pentra DF Nexus (Hariba Medical) | Percent (%) | 14.6±1.7 vs. 14.4±1.6 |
| Gül et al. [9], | Case-control | 167 (100 with migraine) | Non-available | Percent (%) | 13.8±1.3 vs. 13.2±1.0 |
| Meamar et al. [10], | Case-control | 200 (100 with migraine) | Sysmex K1000 (Sysmex Corp) | Non-available | 13.4±0.2 vs. 13.1±0.1 |
| Kömürcü et al. [11], | Case-control | 508 (309 with migraine) | Non-available | Non-available | 13.3±0.8 vs. 13.9 ±1.1 |

used or the measurement unit. Although the measurement unit of RDW was not explicitly stated in two studies, it can reasonably be inferred that the values were expressed as percentages based on the reported data. The overall risk of bias was low across all included studies (Fig. 2). The funnel plot of the studies included in the meta-analysis is shown in Figure 3 and demonstrates marked asymmetry, suggesting the presence of potential publication bias or small-study effects, with studies of smaller sample size appearing to be unevenly distributed and clustering predominantly on one side of the pooled effect estimate. This asymmetry indicates that negative or non-significant results may be underrepresented in the available literature.

The results of the random-effects meta-analysis are presented in Figure 4. In all but one study, RDW values were higher in patients with migraine than in control subjects. The overall pooled weighted mean difference (WMD) in RDW between migraine and non-migraine groups was 0.24 (95%CI: –0.15 to 0.62), with substantial heterogeneity (Cochrane's Q: 150.9; $I^2$=97%). After logit transformation, the WMD was 0.37 (95%CI: 0.27–0.35). Following exclusion of the single study by Kömürcü et al. [11], which reported

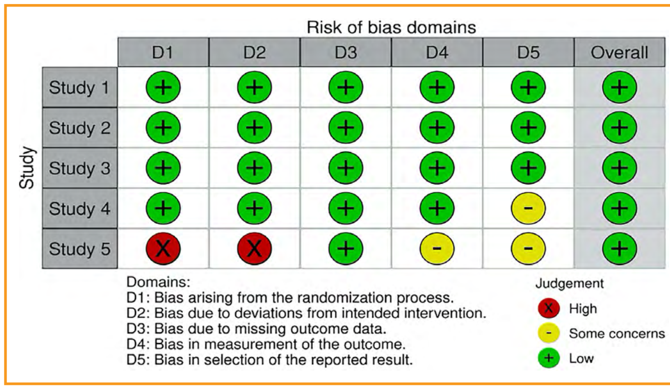


**Figure 2.** Risk of bias evaluated according to Risk of bias tools – ROBVIS.

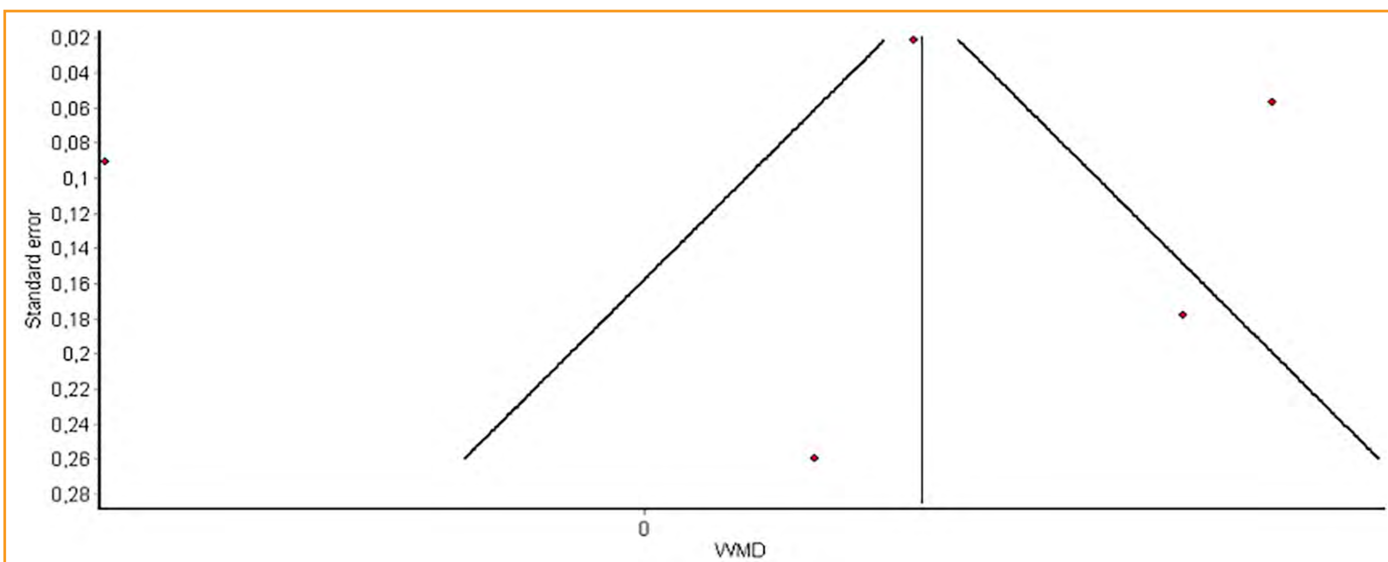


**Figure 3.** Funnel plot of studies included in the meta-analysis.

WMD: Weighted mean difference.

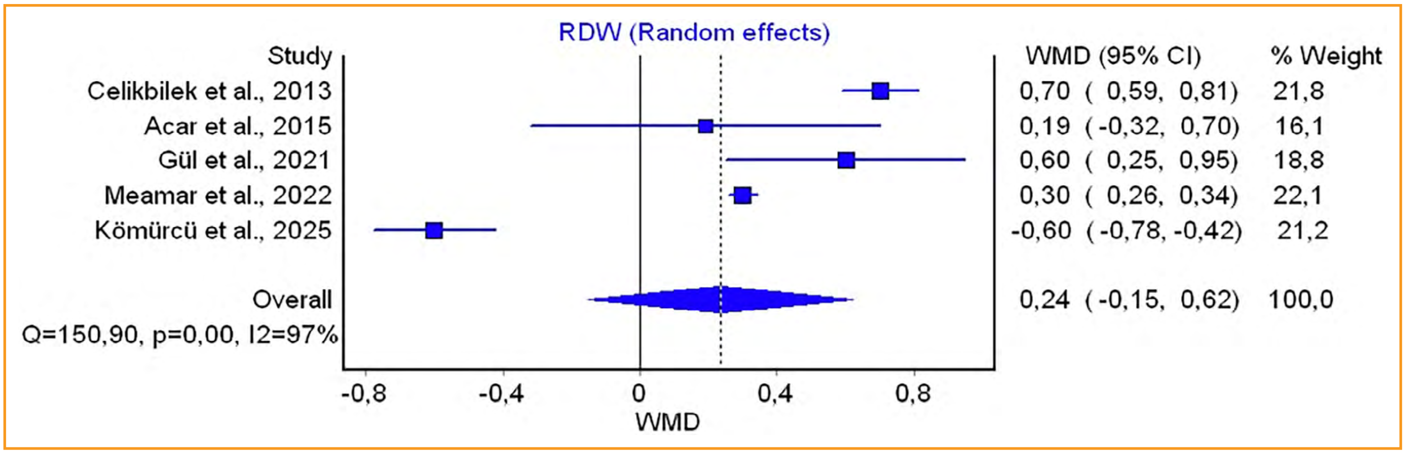


**Figure 4.** Weighted mean difference and 95% confidence interval (95% CI) of red blood cell distribution width (RDW) values in patients with or without migraine.

WMD: Weighted mean difference.

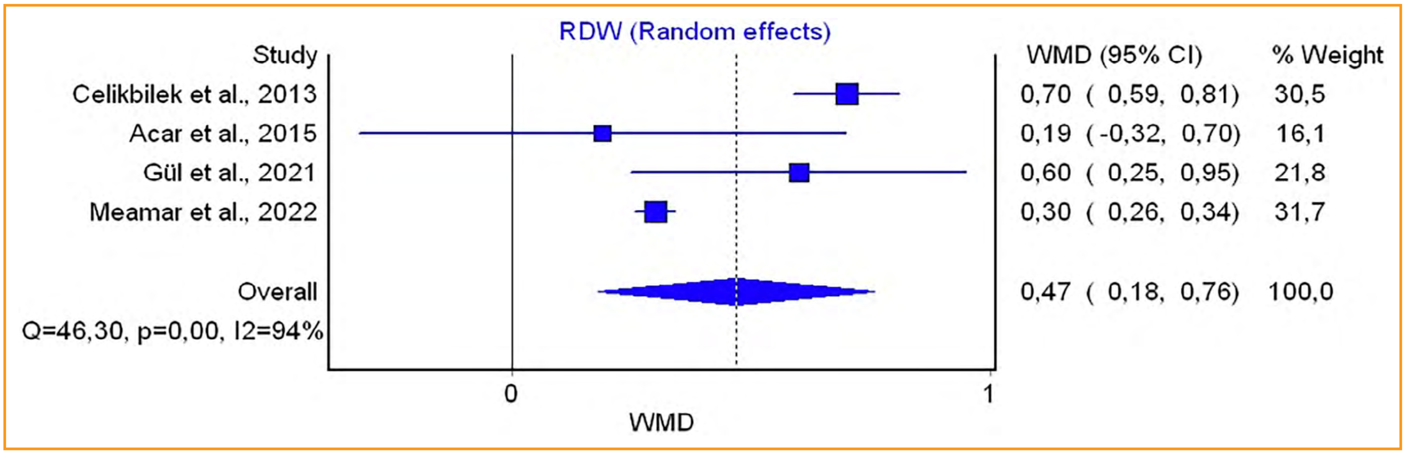


**Figure 5.** Weighted mean difference and 95% confidence interval (95% CI) of red blood cell distribution width (RDW) values in patients with or without migraine after excluding the study of Kömürcü et al. [11].

WMD: Weighted mean difference.

lower RDW values in migraine patients, the pooled WMD became statistically significant and positive (WMD=0.47; 95%CI: 0.18 to 0.76), although heterogeneity remained high (Cochrane's Q: 49.3; $I^2$=94%) (Fig. 5). After logit transformation, the WMD was 0.35 (95%CI: 0.31–0.39).

## Discussion

RDW has gained increasing attention in recent years as a potential biomarker for a range of pathological conditions, many of which are characterized by persistent inflammation, oxidative stress, and endothelial dysfunction [4]. In general, an elevated RDW reflects increased heterogeneity in erythrocyte volume, which may ultimately influence cerebrovascular tone, nociceptive signaling, and immune responses [5]. Although RDW lacks specificity for any particular pathology, it is inexpensive, widely available, and relatively reproducible [12], making it a potentially attractive laboratory parameter in the context of migraine, provided that its diagnostic or prognostic utility is confirmed.

The aim of the present meta-analysis was to investigate the potential association between RDW and migraine by synthesizing data from the available scientific literature. Our pooled analysis indicates a trend toward higher RDW values in individuals with migraine compared with healthy controls. Specifically, four of the five included studies reported significantly elevated RDW levels among migraine patients, with individual WMDs consistently in the positive direction and with the overall trend becoming significant after logit transformation [7–10]. However, the study by Kömürcü et al. [11] markedly deviated from this pattern, reporting lower RDW values in migraine patients. Inclusion of this study substantially attenuated the overall pooled effect, rendering it statistically non-significant and increasing heterogeneity ($I^2$=97%) (Fig. 1). In a sensitivity analysis excluding the study by Kömürcü et al. [11], the pooled WMD increased and achieved statistical significance, (Fig. 5) although heterogeneity remained high ($I^2$=94%).

The study by Kömürcü et al. [11] may differ methodologically, most notably in its exclusive inclusion of migraine patients without aura, a subgroup that may represent a distinct clinical phenotype. Interestingly, while Celikbilek et al. [7] reported identical RDW values in patients with and without aura (13.7 vs. 13.7; p=0.732), Meamar et al. [10] observed a non-significant trend toward higher RDW values in the aura group (15.1 vs. 13.4). Potential sources of heterogeneity include differences in population demographics, migraine subtypes (e.g., with or without aura), disease duration, and comorbid conditions. An additional and important contributor to heterogeneity is variability in devices and laboratory protocols used for RDW measurement, which may yield systematically different results across studies. This methodological inconsistency, combined with clinical variability, likely explains the very high level of heterogeneity observed in the analysis ($I^2$>94%). Moreover, the limited number of eligible studies and the relatively small cumulative sample size reduce statistical power and restrict the robustness and generalizability of the findings. A comprehensive meta-regression analysis was not feasible due to insufficient reporting of key clinical and laboratory variables across the included studies. Taken together, these factors underscore the need for future studies employing standardized measurement techniques, larger sample sizes, and more homogeneous patient populations to validate and extend the present results.

## Conclusion

Future research should address these limitations by employing larger, prospective cohorts, accounting for relevant confounding variables, and adopting standardized RDW assessment methods. Additionally, it would be informative to explore whether RDW correlates with migraine severity, frequency, duration, or therapeutic response, which could further clarify its clinical utility.

**Ethics Committee Approval:** Ethical approval was not required, as the study was a meta-analysis and therefore exempt from local institutional review board requirements.

**Use of AI for Writing Assistance:** Not declared.

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions:** Concept – G.L., C.M.; Design – G.L., C.M.; Data collection and/or processing – G.L.; Analysis and/or interpretation – G.L.; Literature search – G.L., C.M.; Writing – G.L.; Critical review – C.M.

**Conflict of Interest:** The authors declare that there is no conflict of interest.

**Financial Disclosure:** Not declared.

## References

1. Safiri S, Pourfathi H, Eagan A, Mansournia MA, Khodayari MT, Sullman MJM, et al. Global, regional, and national burden of migraine in 204 countries and territories, 1990 to 2019. Pain 2022;163:e293–309. [CrossRef]
2. Mattiuzzi C, Lippi G. Updates on migraine epidemiology. Eur J Neurol 2020;27:e13. [CrossRef]
3. Charles A. The pathophysiology of migraine: implications for clinical management. Lancet Neurol 2018;17:174–82. [CrossRef]
4. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: A simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci 2015;52:86–105. [CrossRef]
5. Lippi G, Cervellin G, Mattiuzzi C. Migraine and erythrocyte biology: a review. Int J Lab Hematol 2014;36:591–7. [CrossRef]
6. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629–808. [CrossRef]
7. Celikbilek A, Zararsiz G, Atalay T, Tanik N. Red cell distribution width in migraine. Int J Lab Hematol 2013;35:620–8. [CrossRef]
8. Acar E, Beydilli H, Karagöz Ü, Yıldırım B, Kırlı İ, Kılınç RM, et al. Neutrophil-lymphocyte ratio can distinguish migraine patients from other patients with nonspecific headache in the emergency department. Acta Med Mediterranea 2015;31:829–34.
9. Gül BZ, Gözübatık Çelik RG, Selçuk B, Aksoy S, Gül M, Soysal A. New indicator of inflammation in migraine: red blood cell distribution. Haydarpasa Numune Med J 2021;61:166–71.
10. Meamar R, Janghroban S, Ansari B, Saeedi A, Atefi A, Tavakoli F. Evaluation of red cell distribution width alterations with severity of migraine. Canon J Med 2022;3:15–8.
11. Kömürcü HF, Erkalaycı C, Gozke E. Hemogram and inflammatory indices in pain-free periods in migraine patients without aura. Neurol Res 2025;47:44–50. [CrossRef]
12. Lippi G, Pavesi F, Bardi M, Pipitone S. Lack of harmonization of red blood cell distribution width (RDW). Evaluation of four hematological analyzers. Clin Biochem 2014;47:1100–3. [CrossRef]