NLR and RDW as Potential Biomarkers of Frailty: A Scoping Review Postprint

Authors: GOU Dengqun, ZHANG Lu, XU Yuanli, JIANG Mingjiao, WU Hemei, TAO Ming

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Abstract

Background: Frailty, as an aging-related condition, has emerged as a critical health concern in aging populations in recent years. The neutrophil-to-lymphocyte ratio (NLR) and red blood cell distribution width (RDW) are readily accessible novel inflammatory markers in clinical practice. Understanding the association between their alterations and frailty may facilitate the identification and monitoring of frailty onset and progression, thereby providing references for future frailty-related research. However, existing studies are scarce and exhibit considerable heterogeneity, rendering them unsuitable for traditional meta-analysis; consequently, this study utilizes a scoping review approach. Objective: To conduct a scoping review of studies investigating NLR and RDW as potential biomarkers of frailty, thereby providing references for elucidating frailty pathogenesis and developing or refining frailty assessment tools. Methods: Eight databases were systematically searched: PubMed, Embase, Cochrane Library, Web of Science, CNKI, Wanfang, VIP, and SinoMed, from inception to March 1, 2022. Study quality was evaluated using the Newcastle-Ottawa Scale and the Agency for Healthcare Research and Quality (AHRQ) cross-sectional study assessment criteria. Two investigators independently screened literature and extracted data. Results: Fourteen studies were included. The majority demonstrated that NLR and RDW are positively associated with frailty risk and severity, represent independent risk factors for frailty development, and can predict frailty progression. Conclusion: As potential frailty biomarkers, NLR and RDW provide supplementary evidence regarding frailty pathogenesis and offer a novel theoretical foundation for future development or refinement of frailty assessment instruments. However, further research is required to determine their optimal predictive values for frailty across different age and sex groups.

Full Text

NLR and RDW as Potential Biomarkers of Frailty: A Scoping Review

Authors: Gou Dengqun[1], Zhang Lu[1], Xu Yuanli[1], Jiang Mingjiao[2], Wu Hemei[1], Tao Ming[1]*

[1]Nursing Department, Affiliated Hospital of Zunyi Medical University, Zunyi, 563000, Guizhou, China
[2]Nursing Department, The Third Affiliated Hospital of Zunyi Medical University, Zunyi, 563000, Guizhou, China

*Corresponding author: Tao Ming, Professor, Master' s Supervisor; E-mail: 2284142542@qq.com

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Abstract

Background: Frailty, as an aging-related condition, has emerged as a critical health concern in aging populations. Neutrophil-to-Lymphocyte Ratio (NLR) and Red Blood Cell Distribution Width (RDW) represent novel inflammatory markers that are readily obtainable in clinical practice. Understanding their association with frailty could help identify and monitor frailty development, providing valuable insights for future research. However, existing studies are limited and highly heterogeneous, making traditional meta-analysis inappropriate. Therefore, this study employed a scoping review methodology.

Objective: To synthesize research on NLR and RDW as potential biomarkers of frailty, providing a reference for clarifying frailty pathogenesis and developing or improving frailty assessment tools.

Methods: We searched eight databases—PubMed, Embase, Cochrane Library, Web of Science, CNKI, Wanfang, VIP, and SinoMed—from inception to March 1, 2022. Literature quality was assessed using the Newcastle-Ottawa Scale and the Agency for Healthcare Research and Quality cross-sectional study evaluation criteria. Two researchers independently screened literature and extracted data.

Results: Fourteen articles were included. Most studies demonstrated that NLR and RDW were positively correlated with frailty risk and severity, representing independent risk factors for frailty and capable of predicting frailty progression.

Conclusion: As potential biomarkers of frailty, NLR and RDW provide additional evidence for frailty pathogenesis and offer a new theoretical foundation for developing or improving frailty assessment tools. However, optimal predictive cutoff values for different age and gender groups require further investigation.

Keywords: Frailty; Neutrophil-to-Lymphocyte Ratio; Red Blood Cell Distribution Width; Biomarkers; Scoping Review

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Frailty is a non-specific state characterized by decreased physiological reserve, reduced stress resistance, increased vulnerability, and heightened disease susceptibility in older adults [1]. Among individuals over 50, frailty prevalence reaches approximately 12% [2], leading to numerous adverse outcomes including disability [3], multimorbidity [4], and mortality [5], making it a major public health concern. While frailty pathogenesis remains unclear, chronic inflammation is widely recognized as a key underlying mechanism. Neutrophil-to-Lymphocyte Ratio (NLR) is a novel inflammatory marker encompassing two leukocyte subtypes that reflects the balance between neutrophils and lymphocytes [6]. Red Blood Cell Distribution Width (RDW) is a parameter reflecting erythrocyte heterogeneity in blood [7]. As easily detectable, highly reproducible, and low-cost inflammatory markers, NLR and RDW have been shown in multiple studies [8-10] to correlate with frailty, though their underlying mechanisms require systematic investigation. Furthermore, research indicates that incorporating biomarkers into frailty assessment tools can enhance predictive capacity [11], underscoring the importance of studying frailty biomarkers. Therefore, following Daudt et al.'s enhanced scoping review framework [12], this study systematically analyzed literature on NLR and RDW as potential frailty biomarkers to provide insights into frailty pathogenesis and inform the development or refinement of frailty assessment tools.

1.1 Search Strategy

We searched eight databases: PubMed, Embase, Cochrane Library, Web of Science, CNKI, Wanfang, VIP, and SinoMed, from inception to March 1, 2022. For English databases (PubMed example), we used combined free-text and MeSH terms: ("red blood cell distribution width" [Title/Abstract] OR "RDW" [Title/Abstract] OR "neutrophil-to-lymphocyte ratio" [Title/Abstract] OR "NLR" [Title/Abstract]) AND ("Frailty" [MeSH Terms] OR "Frailty" [Title/Abstract] OR "frail* "[Title/Abstract]). For Chinese databases (CNKI example), the search strategy was: (SU= '红细胞分布宽度' + 'RDW' + '中性粒细胞/淋巴细胞比值' + '中性粒细胞与淋巴细胞比值' + 'NLR') AND (SU= '衰弱'). We also manually searched reference lists of relevant articles.

1.2 Inclusion and Exclusion Criteria

Inclusion criteria: (1) Articles examining the relationship between NLR or RDW and frailty; (2) Original research; (3) Chinese or English language publications. **Exclusion criteria:** (1) Irrelevant topics; (2) Animal studies; (3) Low-quality literature; (4) Duplicate publications, conference abstracts, or unavailable full text.

1.3 Literature Screening

Retrieved citations were imported into NoteExpress V3.5 for deduplication. Two trained researchers independently conducted initial screening by title and abstract, followed by full-text screening based on inclusion/exclusion criteria. Disagreements were resolved through discussion with a third researcher.

1.4 Literature Quality Assessment

Cohort and case-control studies were evaluated using the Newcastle-Ottawa Scale (NOS) [13], which comprises three domains (study group selection, comparability, and exposure) with a maximum score of 9 (0-3 = low quality, 4-6 = moderate, 7-9 = high). Cross-sectional studies were assessed using the Agency for Healthcare Research and Quality (AHRQ) criteria [14], containing 11 items totaling 11 points (0-3 = low, 4-7 = moderate, 8-11 = high quality) [15]. Two researchers independently performed quality assessment, with disputes resolved through consensus or third-party adjudication.

1.5 Data Extraction and Analysis

Two researchers independently extracted data, with disagreements resolved through discussion with a third researcher. Extracted data included: (1) Basic article information (author, publication year, country/region); (2) Sample characteristics, study design, assessment tools, and study results.

2.1 Literature Screening Results

The initial search yielded 172 articles. After removing duplicates, screening titles/abstracts, and reviewing full texts, 14 articles were ultimately included. The screening process is illustrated in [Figure 1: see original paper].

2.2 Characteristics and Quality Assessment of Included Studies

The 14 included studies were published between 2002-2022 from China (n=7), United States (n=5), Turkey (n=1), and Romania (n=1), comprising 9 cross-sectional studies, 1 cohort study, and 4 case-control studies. Methodological quality assessments are presented in Tables 1 and 2.

Table 1: Study Characteristics and Relationship Between NLR and Frailty

Study	Country	Population	Study Design	Frailty Assessment	NLR Grouping	NLR-Frailty Relationship	Age (years) Mean±SD	Sex (% female)
Zhang H et al. [16]	China	Community elderly	2-year follow-up	FP quartiles: Q1$ 1.26, 1.26<Q2 1.71, 1.71<Q3 2.35, Q3 >2.35|(1) Cross-sectional: No correlation between NLR and frailty risk. (2) Longitudinal: Positive correlation, Q4 vs Q1: 4.21×$ higher frailty progression risk	78.03$±4.46$|53.13||Wang et al.[12]|Turkey|Elderly|Case-control|FP|43.06/50.44|Gilmore N et al.[17]|USA|Breast cancer patients|Case-control|FP quartiles: Q1(0.17-1.43), Q2(1.44-2.13), Q3(2.14-3.31), Q4(3.32-16.49)|NLR is a risk factor; each unit increase associated with 7.554×$ higher frailty risk	5.16|$ range 32-... 72.3±7.1 ... Non-significant correlation ... chemotherapy ... positive correlation ... Xu W et al. [20]|China|Elderly ... frailty ... chemotherapy frailty|53.4±10.6(range 22-90)|100||Giri S et al.[18]|USA|Multiple myeloma patients|Case-control|Q1(0.17-1.43), Q2(1.44-2.13), Q3(2.14-3.31), Q4(3.32-16.49)|Q4 vs Q1: 2.1×$ higher frailty risk	72.3±... (range 32-90)|61.29/45.45 ...	
Bodolea C et al. [21]	Romania	CVD patients ($ 60)|Case-control|—|Positive correlation but non-significant in multivariate analysis|65.07±12.9(range 23-90)|56.4||Hou P et al.[9]|China|CHD patients(60)|Cross-sectional|FP quartiles: Q1(1.8), Q2(1.9-2.6), Q3(2.7-3.6), Q4(> 3.6)|Positive correlation with frailty score; Q3 vs Q1: 2.528×; Q4 vs Q1: 2.894×$ higher risk	71 (IQR 65-77)	44.6				

Study	Country	Population	Study Design	Frailty Assessment	NLR Grouping	NLR-Frailty Relationship	Age (years) Mean±SD	Sex (% female)
Nishijima TF et al. [22]	USA	Cancer patients ($ 65)	64 (range 65-92); Cross-sectional	79.7	CFI tertiles: T1(< 2.5), T2(2.5–4.2), T3(> 4.2)	Positive correlation; T3 vs T1: 3.81×$ higher frailty risk		

Note: R=age range; IQR=interquartile range; FP=Frailty Phenotype; TFI=Tilburg Frailty Indicator; FI=Frailty Index; EFS=Edmonton Frailty Scale; CFI=Carolina Frailty Index; Q1=first quartile; T1=first tertile; –=not reported.

Table 2: Study Characteristics and Relationship Between RDW and Frailty

Study	Country	Population	Study Design	Frailty Assessment	RDW Grouping	RDW-Frailty Relationship	Age (years) Mean±SD	Sex (% female)
Li Q et al. [23]	China	Inpatients ($ 60)	Cross-sectional	FP	Q1 reference: Normal <15.7%, High $ 15.7×$ higher risk	Q1(12.5×$ higher risk	78.2$±5.0	58.8±4.9
Li C et al. [8]	China	Community elderly ($ $65)	Cross-sectional	SOF index	Normal <15.7%, High $ 15.7×$ higher risk	No correlation with frailty	73.5$±6.8	71.5

Note: R=age range; IQR=interquartile range; FP=Frailty Phenotype; SOF=Study of Osteoporotic Fractures; Q1=first quartile; −=not reported.

2.3.1 Frailty Assessment Tools

Among the 14 included studies, the Frailty Phenotype was most frequently used (7 studies) [9, 16, 21, 23-26]. Other tools included the Tilburg Frailty Indicator [10], modified Frailty Phenotype [17], modified Frailty Index [18], Edmonton

Frailty Scale [19], 38-item Frailty Index [20], 36-item Frailty Index (Carolina Frailty Index) [22], and modified Study of Osteoporotic Fractures index [8].

2.3.2 Relationship Between NLR and Frailty

Nine studies [9, 10, 16-22] examined NLR and frailty. Seven studies [9, 10, 16-18, 20, 22] found positive correlations between NLR and frailty risk/severity, identifying NLR as an independent risk factor and predictor of frailty progression. However, one prospective longitudinal study of community-dwelling older adults [16] showed that while baseline NLR predicted frailty deterioration at 2 years, it was not associated with baseline frailty status. Bilgin et al.' s study of type 2 diabetes patients [19] also found no correlation between NLR and frailty. Bodolea et al.' s research on older cardiovascular disease (CVD) patients [21] reported a positive correlation that became non-significant in multivariate analysis (see Table 1).

2.3.3 Relationship Between RDW and Frailty

Seven studies [8, 9, 21, 23-26] analyzed RDW-frailty associations. Five studies [8, 9, 23-25] demonstrated positive correlations between RDW and frailty risk/severity, with RDW as an independent risk factor and predictor of progression. Li et al. [23] found sex differences, with women showing higher frailty risk than men at equivalent RDW levels. However, two studies [21, 26] found no correlation between RDW and frailty in community-dwelling older adults, and while RDW correlated positively with frailty risk in older CVD patients, multivariate analyses showed no significant differences (see Table 2).

3.1 Analysis of Result Heterogeneity

Leng et al. [26] retrospectively analyzed only 30 community-dwelling older adults when examining RDW-frailty relationships. Similarly, Bilgin et al.'s case-control study [19] included only 108 participants. Bodolea et al. [21] lacked data on antiplatelet medication use in their older CVD patient cohort. These limitations —small sample sizes, retrospective designs, and failure to adjust for confounders —likely introduced bias into their findings.

3.2 Potential Mechanisms of NLR as a Frailty Biomarker

The precise mechanisms linking NLR to frailty remain unclear, but analytical [10, 18] and descriptive [9, 16, 17, 20, 22] studies have provided insights. Multi-system dysregulation represents a key connection, primarily manifested through chronic inflammation mediated by age-related immune system changes. With aging, the innate immune system (comprising neutrophils, monocytes/macrophages) produces increased free radicals and pro-inflammatory cytokines under persistent antigen stimulation, while the adaptive immune system (lymphocytes) exhibits declined cellular and humoral immunity due to phenotypic and functional changes in T and B cells [27, 28]. These

alterations create a chronic inflammatory state characterized by increased pro-inflammatory and decreased anti-inflammatory cytokines [27]. Mounting evidence identifies chronic inflammation as a critical frailty mechanism [29-32]. Pro-inflammatory cytokines such as IL-1α, IL-6, and TNF-α can inhibit IGF-1-mediated anabolism; IGF-1 plays crucial roles in muscle regeneration, maintenance, and protein synthesis, and its reduction leads to impaired muscle strength and decreased protein synthesis, ultimately causing frailty [33-35]. NLR reflects the balance between innate and adaptive immunity—neutrophilia indicates pro-inflammatory pathway activation, while lymphopenia reflects suppressed cellular/humoral immunity [36, 37]. Thus, NLR may indirectly reflect how inflammation-mediated immune changes influence frailty development.

3.3 Potential Mechanisms of RDW as a Frailty Biomarker

Current evidence suggests inflammation [8, 9, 21, 23-25] and oxidative stress [8, 21] link RDW to frailty. Pro-inflammatory cytokines (TNF-α, IL-1, IL-6) affect erythrocyte membrane morphology, maturation, and lifespan, increasing circulating red cell volume heterogeneity. Mechanistically: First, TNF-α activates sphingomyelinase, degrading sphingomyelin in the erythrocyte membrane and altering membrane structure and cytoskeleton, thereby affecting function, lifespan, and cell volume [38-40]. Second, IL-1 and TNF-α inhibit erythropoietin synthesis/activity [41] and downregulate erythropoietin receptor expression [42], releasing larger, immature reticulocytes into circulation and altering RDW [42, 43]. Third, Fe^{2+} release into circulation via ferroportin-1 (FPN1) is essential for hemoglobin synthesis. Hepcidin binds FPN1, causing iron internalization and inhibiting iron release from tissue macrophages. During inflammation, IL-6 upregulates hepcidin expression via the IL-6R-JAK2-STAT3 pathway, blocking Fe^{2+} entry into circulation, reducing hemoglobin synthesis, and increasing smaller immature erythrocytes that elevate RDW [39, 45]. These pro-inflammatory cytokines' roles in frailty pathogenesis have been established [33-35]. Oxidative stress—characterized by impaired balance between oxidants and antioxidant defenses [41]—increases intracellular calcium, promotes proteasome activation, accelerates muscle catabolism, reduces muscle function, and triggers inflammatory responses that cause frailty [46]. Bodolea et al. [21] and Salvagno et al. [41] demonstrated that oxidative stress significantly impacts erythrocyte homeostasis and survival, potentially altering RDW by increasing red cell turnover. Therefore, inflammation and oxidative stress likely represent shared pathophysiological pathways linking RDW to frailty, with RDW reflecting frailty development.

3.4 Current Research Limitations

This review identified several gaps: (1) **Study design:** Most were small cross-sectional or retrospective studies; only five [16-18, 20, 25] were large prospective studies, all secondary analyses of existing datasets. Additionally, most analyzed single time-point associations without capturing temporal relationships.

(2) **Data analysis:** Studies failed to stratify by age and sex despite known physiological differences affecting RDW, NLR, and frailty prevalence. Furthermore, no research has identified optimal cutoff values for NLR and RDW in frailty prediction.

4 Conclusion

Across diverse populations, NLR and RDW correlate positively with frailty risk and severity, representing independent risk factors and predictors of frailty progression. These findings provide additional evidence for inflammation as a frailty mechanism and offer insights into the potential roles of NLR and RDW in frailty pathogenesis. They also provide a scientific basis for incorporating these biomarkers into future frailty assessment tools. However, optimal predictive values for different age and sex groups require further investigation.

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Note: Figure translations are in progress. See original paper for figures.