Title: Complete Blood Count Parameters as Prognostic Factor of Stroke: A Systematic Review

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Abstract

Purpose: Stroke is known as a common cause of disability all over the world. Stroke prognosis estimation has always been a topic of interest. In this study, it was tried to investigate the prognostic value of laboratory findings of complete blood count in a systematic review.

Methods: In this systematic review, literature from Medline via (PubMed, Ovid) Embase, Scopus, The Cochrane Library, and ProQuest between 1988 and 2020 were included. A combination of Mesh and free terms were included in the search strategy; “Stroke", "Red Cell Distribution Width", "Blood Cell Count", "Mean corpuscular hemoglobin", "Mean Corpuscular Volume" and with the abbreviation, in all fields. Data synthesis was achieved using content analysis.

Findings: Elevated red blood cell distribution width was associated with stroke, cardiovascular events, and all-cause deaths among patients with prior stroke. Mean platelet volume has not any prognostic significance in ischemic stroke. There was a poor association between mean corpuscular volume (MCV) and stroke prognosis. Globulin and hemoglobin level predicted short-term mortality following acute ischemic stroke.

Conclusion: Complete blood count as a routine and efficient test performed in health care centers can be used to estimate the prognosis of stroke.

Keywords: Stroke, Erythrocyte Indices, Blood Cell Count, Prognosis
Introduction

Stroke is known as the second common cause of mortality and the third most common cause of morbidity all over the world (1, 2). In 2013, about 10 million individuals had a stroke (3). Through the years the incidence of stroke has decreased in developed countries and increased in developing countries (4). Besides death, stroke has always been known as one of the most debilitating health conditions known to affect patients physically, mentally, and emotionally (5-7). Because of this concern, patients always ask about the prognosis and possibility of symptoms of withdrawal after strokes, also physicians have always tried to minimize the consequences of stroke. Rehabilitating and trying to return the patients' functional status to the functional state before the stroke has been always one of the main policies in treating patients with stroke. So prognosis assessment has been always of significant importance (8).

Many factors have been proposed to be involved in the prognosis of stroke. Stroke subtype, patient age, the severity of the stroke, and infarct location are factors influencing the prognosis of stroke (9-11). Some laboratory findings have been proposed as prognostic factors. Also, laboratory findings have been a part of prognosis estimation in many studies; e.g. red cell distribution width (RDW) is used to predict the functional outcomes and severity of the cerebrovascular events (12), although not all studies confirm this fact (13, 14). Also it has been proposed that mean platelet volume (MPV) may indicate the prognosis of ischemic stroke (15). Similar controversial prognostic factors among laboratory findings have been defined for stroke.

Considering the importance of prognosis estimation and controversial factors proposed in the literature, this study was tried to investigate the prognostic value of laboratory findings of complete blood count in a systematic review to minimize controversies.

Materials and Methods

Search Strategy

In the current study, the literature from PubMed, Medline, Ovid, Embase, Scopus, The Cochrane Library, Google Scholar, and ProQuest were systemically reviewed between 1988 and 2020. The search strategy included multiple free and Mesh terms "Stroke", "Red Cell Distribution Width", "Mean corpuscular hemoglobin", "Mean Corpuscular Volume" with the abbreviation, in all fields.

Inclusion and exclusion criteria
The publication types of articles and reviews were included and letters, errata, brief commentaries, meetings abstract, editorials, and papers that Subtopics were excluded from the study. Patients with other types of brain injuries and transient ischemic attacks were excluded in this systematic review.

**Selection of Studies**

One review author screened titles and abstracts obtained from database searches. Two of the authors independently reviewed the full-text articles for relevant abstracts against inclusion criteria. Finally, disagreements were resolved in inclusion by discussion. The full-texts of selected studies were assessed by two investigators for quality assessment using with JBI (Joanna Briggs Institute) checklists.

**Data extraction and Statistical Analysis**

The extraction of the data from the included studies was performed by one of the authors while another author checked the results. In case of disagreements were resolved by consensus. Data required for the objective of the review was obtained from the full-text of each article and included the trial name, year of publication, number of randomized participants, intervention tested, and Type of study, Sample size, Mean age, Results.

For the data synthesis studies were grouped according to the Prognostic impact of laboratory parameters of complete blood count, RDW, MPV, MCV, hemoglobin, other laboratory factors. Data synthesis was achieved using content analysis. A simple description of data was obtained using content analysis (16) and as a method to describe systematically and objectively, and quantify phenomena (17).

**Results**

**Literature search:**

A total of 1219 articles were retrieved in our initial search of databases. Of these, 67 were identified for possible inclusion and these articles were reviewed in detail. After meticulously reading the full texts, 39 excluded for the following reasons: 28 were not about laboratory factors for stroke prognosis and were irrelevant to the subject, 7 were letters, case-reports, or conferences abstract, and, 4 reported the factors in children but not adults. As a result, 27 eligible studies were included in this systematic review (Figure 1). Included articles were subjected to a critical evaluation. If the disagreements between the two reviewers happened, this disagreement was resolved through discussion or consulting with a third reviewer.
**Study characteristics:**

Characteristics of 27 included studies are shown in table 1. All studies were published after 2008. A total of 71504 patients were included in these studies. Designs of studies were as follow 7 prospective cohorts, 8 retrospective cohorts, and 5 cross-sectional and 7 case controls. The mean age in all of the included studies was more than 54 years except for two with the mean age of 38 and 43. In total, 15 laboratory factors of RDW, MPV, MCV, Hemoglobin, Globulin, Neutrophil/lymphocyte ratio (NLR), folate, Red blood cell (RBC), CHADS2, ESR, WBC, Polymorph, mononuclear cells, total protein level, and other CBC parameters were reported and surveyed in the studies.
Records identified through database searching (n=1219)

Duplicate studies (n=696)

Records screened (n=523)

Records excluded because of non-relevant (n=456)

Full-text articles assessed for eligibility (n=67)

40 Full-text articles excluded, with reasons
28 were not about laboratory factors for stroke
2 were letters
5 reported the factors in children but not adults
5 were conference Abstracts

Studies included in systematic review (n=27)

Ovid: 170
PubMed: 160
Embase: 273
Scopus: 300
ProQuest: 161
Web of science: 155

Figure 1. Search and selection process of systematic review.
Prognostic effect of laboratory factors:

1. RDW
13 studies were reporting RDW factor in stroke prognosis. Of these, one reported that RDW can predict the long term outcomes in patients with acute cerebral infarction (12). High RDW correlated with increased risk of carotid atherosclerosis which is associated with future risk of stroke (18). Also, independent of formal atherosclerotic risk factors and anemia RDW was associated with stroke occurrence in a general population, (19) and enhances the predictive performance for stroke in patients with atrial fibrillation (20). It was stated that RDW more than 14% were known to increase the risk of stroke by 2.5 fold and considered as a predictor of stroke independently of inflammation and anemia (21). Also, high RDW was associated with cerebrovascular events (22, 23) and strongly contributed to both cardiovascular and all-cause deaths in patients with prior stroke (22). Another study showed that the diagnostic performance of RDW to differentiate patients with stroke was decent (24). Based on propensity score analysis, RDW is a hematological parameter predicting stroke among patients with heart failure (25). RDW also predicted the functional outcomes and severity of the stroke when patients had symptoms less than 24 hours (26). The RDW level has an important reference value for identifying the prognosis in elderly patients with cerebral infarction (27) and severe hemiplegia (28). On the other hand, some studies presented a different result, in which RDW did not predict functional outcome or severity in patients with acute ischemic stroke (13). The one last study reported that none of the CBC parameters such as RDW have no prognostic significance in ischemic stroke (29).

2. MPV
Four studies surveyed the prognostic impact of MPV in stroke, one of which showed that MPV may be an important indicator of prognosis in ischemic stroke (15). However the remaining showed that MPV has not any prognostic significance in ischemic stroke (29-31), although it may be important in the early diagnostic approach (29).

3. MCV
The prognostic effect of MCV was mentioned in two studies. One showed a poor prognosis of high MCV (32), and the other showed that MCV was an independent predictor of ischemic stroke short-term mortality (33).
4. **Hemoglobin**

Two studies dealt with hemoglobin effect on stroke prognosis. There was a relationship between hemoglobin and unilateral spatial neglect test in a way that the higher the hemoglobin level, the better the unilateral spatial neglect test performance (34). Also hemoglobin and globulin level could predict short-term mortality after acute cerebrovascular events (35).

5. **Other laboratory factors**

Other laboratory factors including NLR, folate, RBC, ESR, WBC, Polymorph, CHADS2, Leukocyte, neutrophil, lymphocyte, monocyte, mononuclear cells, total protein level, and platelet counts were assessed in the remaining studies. CHADS2 score could predict ischemic stroke in chronic heart failure patients without atrial fibrillation irrespective of the RDW level (36). Low folate levels were significantly related to poor prognosis (32). Higher NLR as an emerging biomarker of inflammation is predictive of thromboembolic stroke among patients with non-valvular (37). RBC, Leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts have not any prognostic significance in ischemic stroke (15, 29, 33). However, neutrophil and leukocyte counts also may be able to predict the prognosis of transient ischemic attacks (15). Another study showed a significant association between reduced platelet count and high risk of acute ischemic stroke, as with elevated levels of mononuclear cells (31). Based on the results of another study, total protein, WBC, neutrophil, lymphocyte, and ESR levels may be considered as a predictive factor for the severity of stroke (35).

**Discussion:**

Our study provides a systematic review of studies investigating parameters of complete blood count tests and stroke. The complete blood count is a routine and cheap laboratory test performed in health care centers. So possible prognostic value of complete blood count parameters can be used as a cost-efficient for prognosis estimation.

In a literature review by Lappegard about RDW and risk of arterial cardiovascular disease, it was concluded that many large prospective studies and some low scale retrospective studies have proposed relationships between RDW stroke. Also, studies describing the contrary are few. RDW is related to myocardial infarction, atherosclerosis, and stroke, and can potentially be used as a novel biomarker for risk stratification and prevention of disease (38).

In a study by Tonelli about the relation between RDW and cardiovascular event rate in people with coronary disease it was concluded that a graded independent relation between the risk of vascular
events and mortality among people with a history of myocardial infarction and higher levels of RDW exists (39). In another study, Kaya et al. investigating the relationship between RDW and stroke in patients with stable chronic heart failure it was suggested that RDW might be playing a prominent role for stroke in patients with heart failure (25). In a study by Vijayashree about the relevance of RDW determination in stroke, it was shown that higher RDW values are discovered in stroke patients compared to the control group; RDW more than 13.0 is predictive of increased stroke risk, but the RDW value does not show a linear correlation with the severity of stroke (40). Also in our study, most of the articles studied indicated that RDW can be used as a prognostic factor for stroke occurrence risk, severity, and stroke long-term consequences. RDW was associated with incident stroke in a general population, independent of other well-known risk factors, also elevated RDW was found to be associated with increased stroke occurrence and strongly predicted both cardiovascular in patients with known stroke.

In a study by O'Maley about MPV in stroke patients it was concluded that an and a reduction in platelet count and increased MPV are features of acute and nonacute phases of stroke (41). In another study, Bath et al. concluded that MPV is predicting the risk of stroke among patients with a history of transient ischemic attack or stroke independently, so the measurement of MPV may reveal some prognostic information for physicians about patients with a history of cerebrovascular disease (42). In a study by Greisenegger et al. about high MPV association with an adverse outcome in patients with acute ischemic cerebrovascular events, it was concluded that an increased MPV is a predictor of an adverse outcome for acute ischemic strokes independently not considering some other clinical factors (43). In the present study, most of the included articles did not have a precise suggestion about the prognostic value of MPV; only two studies proposed a probable prognostic value for MPV (15, 29).

As far as MCV is affected in many medical conditions (44-47), it is difficult to estimate the prognostic value of MCV in stroke patients; but in the present study, just two studies presented some information about the prognostic value of MCV, which both of them showed worse prognosis associated with high MCV.

High hemoglobin concentration may represent a risk factor for ischemic stroke and a risk factor for atherosclerosis (48, 49), but information about the association of hemoglobin with outcome after acute stroke is controversial. In a study by Sacco et al., it was concluded that increased
hematocrit might reflect as an independent predicting factor of mortality among female patients with ischemic stroke but not in male (50), among patients with an acute ischemic stroke increased hematocrit was significantly associated with greater infarct size and reduced reperfusion index (51). Also, a pilot study about the association between the discharge destination and baseline hematocrit at the time of the ischemic stroke showed that normal hemoglobin was associated with a better discharge outcome but was not related to mortality rate (52). In the present study, higher hemoglobin levels were associated with better outcomes of stroke. RDW seems cannot predict mortality or morbidity (53), and on the other hand, the study of Feng GH indicates that RDW is a strong predictor for mortality and risk of ischaemic stroke (54). More studies are required to evaluate and validate this but in stroke patients, most of the time, we can predict the variate of stroke by patients presentation in the emergency department (55). The knowledge of medical students is not enough for evaluation and managing stroke patients (56) and on the other hand, knowledge of people are not enough too (57), then it is better to prepare some kind of information depends on our audience about the sign and symptoms of stroke patients and relation of this sign and symptoms to the location of stroke (58).

In conclusion, complete blood count as a routine and efficient test performed in health care centers can be used to estimate the prognosis of stroke. Although not all the parameters of complete blood count are not of prognostic value if this test be interpreted precisely it might come in handy to perform necessary steps to enhance the prognosis of stroke and prevent debilitating consequences of stroke. Finally, based on the blood count the physicians cannot estimate the outcome of the patients and management setting, thus, searching for any marker is necessary.

Author’s Contribution

Concept: S.S.V; Study design: A.A, S.S.V; Systematic search: N.V; Critical reviews: S.M; Data extraction: H.A, S.M.; Writing: N.V., S.S.V, and H.A.
References:


Table 1. Characteristics of included studies in systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Type of study</th>
<th>Sample size</th>
<th>Mean age</th>
<th>Tests used</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim (12)</td>
<td>2012</td>
<td>Retrospective</td>
<td>847</td>
<td>65.88</td>
<td>RDW</td>
<td>A biomarker for the prediction of long-term outcomes in patients with acute cerebral infarction</td>
</tr>
<tr>
<td>Furer (18)</td>
<td>2015</td>
<td>Prospective</td>
<td>126</td>
<td>66</td>
<td>RDW</td>
<td>High RDW in related to increased risk for preclinical and clinical carotid atherosclerosis.</td>
</tr>
<tr>
<td>Ani (22)</td>
<td>2009</td>
<td>Retrospective</td>
<td>480</td>
<td>64 % of sample size aged ≥ 65</td>
<td>RDW</td>
<td>13.7% vs.13.2% (mean RDW in stroke patients vs. non stroke patients: P&lt;0.001)</td>
</tr>
<tr>
<td>Demir (24)</td>
<td>2013</td>
<td>Cross sectional</td>
<td>236</td>
<td>37.6</td>
<td>RDW</td>
<td>Good diagnostic power of RDW</td>
</tr>
<tr>
<td>Kaya (25)</td>
<td>2015</td>
<td>Prospective</td>
<td>133</td>
<td>65.9</td>
<td>RDW</td>
<td>16.9 ± 1.14 vs. 14.6 ± 1.4 (mean ± SD in stroke patients vs. non stroke patients: p&lt;0.001)</td>
</tr>
<tr>
<td>Kara (26)</td>
<td>2015</td>
<td>Prospective</td>
<td>138</td>
<td>69 % of sample size aged &gt;65</td>
<td>RDW</td>
<td>In stroke patients who have symptoms &lt;24 hours, the RDW may be useful in predicting the severity and functional outcomes of the stroke.</td>
</tr>
<tr>
<td>Lappegård (53)</td>
<td>2015</td>
<td>Prospective</td>
<td>1152</td>
<td>-</td>
<td>RDW</td>
<td>RDW is associated with incident stroke in a general population, independent of anaemia and traditional atherosclerotic risk factors</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Study Design</td>
<td>N</td>
<td>RDW</td>
<td>Summary</td>
<td></td>
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</tr>
<tr>
<td>Fei (28)</td>
<td>2015</td>
<td>Case-control</td>
<td>209</td>
<td>-</td>
<td>The RDW level has an important reference value for identifying the prognosis in elderly patients with cerebral infarction and severe hemiplegia.</td>
<td></td>
</tr>
<tr>
<td>Soderholm (23)</td>
<td>2015</td>
<td>Prospective cohort</td>
<td>26879</td>
<td>58</td>
<td>RDW in the highest quartile was associated with increased incidence of total stroke and cerebral infarction.</td>
<td></td>
</tr>
<tr>
<td>Siegler (27)</td>
<td>2016</td>
<td>Retrospective cohort</td>
<td>179</td>
<td>54</td>
<td>RDW elevation is associated with cerebral infarction and poor outcome after aneurismal subarachnoid hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Ntaios (13)</td>
<td>2011</td>
<td>Retrospective cohort</td>
<td>1504</td>
<td>72</td>
<td>RDW does not predict severity or functional outcome in patients with acute ischemic stroke.</td>
<td></td>
</tr>
<tr>
<td>Saliba (20)</td>
<td>2014</td>
<td>Retrospective cohort</td>
<td>38024</td>
<td>74.5</td>
<td>RDW is directly associated with the risk of stroke regardless of anemia status, and improves the predictive accuracy for stroke in patients with atrial fibrillation.</td>
<td></td>
</tr>
<tr>
<td>Vaya (21)</td>
<td>2014</td>
<td>Case control</td>
<td>349</td>
<td>43.5</td>
<td>RDW &gt;14% increases the risk of CS by 2.5 fold and constitutes a predictor of CS independently of anemia and inflammation.</td>
<td></td>
</tr>
<tr>
<td>Icme (29)</td>
<td>2014</td>
<td>Retrospective cohort</td>
<td>104</td>
<td>66.5</td>
<td>MPV, leukocyte, neutrophil, lymphocyte, monocyte, PLT, RDW and PDW MPV may be important in early diagnostic approach, but neither MPV nor the other CBC parameters have any prognostic significance in ischemic stroke.</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Type</td>
<td>n</td>
<td>Mean Age</td>
<td>Measures</td>
<td>Findings</td>
</tr>
<tr>
<td>------------</td>
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</tr>
</tbody>
</table>
| Güldiken   | 2008 | Case control | 102   | 69       | MPV                         | *No significant change in MPV was seen in acute ischemic stroke  
*High leukocyte and neutrophil levels are markers for the large vessel disease subtype and severity of ischemic stroke  
*Neutrophil count is found to be a risk factor for the stroke severity                                                                                                                                                                                                                                                                  |
<p>| Icme       | 2014 | Retrospective cohort | 275   | 67.5     | MPV, Leukocyte, neutrophil, lymphocyte, monocyte, and PLT | MPV may be an important indicator of prognosis in ischemic stroke, whereas leukocyte and neutrophil counts may be important prognostic indicators of transient ischemic attack. There were no significant differences in the complete blood count parameters that we studied for the hemorrhagic stroke group                                                                 |
| Luvizutto   | 2014 | Cross sectional | 40    | 66       | Hemoglobin                  | Low hemoglobin levels may indicate a worse performance in USN cancellation and bissection tests in acute phase of stroke.                                                                                                                                                                                                                 |
| Ertas      | 2012 | Cross sectional | 126   | 70       | NLR                         | 5.6±3.4 vs. 3.1±2.1 (mean ± SD of stroke (+) vs. stroke (-) in Atrial fibrillation (+) patients)                                                                                                                                                                                                                                        |
| Aksoy      | 2012 | Retrospective cohort | 272   | 65       | MCV, Folate                  | High MCV and low folate levels were significantly related with poor prognosis                                                                                                                                                                                                                                                             |
| Hatamian   | 2014 | Cross sectional | 98    | 71       | RBC, MCV                    | The RBC count and MCV are independent predictors of ischemic stroke short-term mortality                                                                                                                                                                                                                                             |
| Kondo      | 2016 | Prospective cohort | 118   | -        | CHADS2                      | CHADS2 score could predict ischemic stroke in CHF patients without AF irrespective of the RDW level                                                                                                                                                                                                                                   |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study Design</th>
<th>N</th>
<th>RDW</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang (31)</td>
<td>2015</td>
<td>Case control</td>
<td>100</td>
<td>57</td>
<td>Mononuclear cells, PLT, PDW, MPV, and PCT. There was an association of elevated levels of mononuclear cells and reduced platelet count with higher AIS risk.</td>
</tr>
<tr>
<td>Nayak (35)</td>
<td>2011</td>
<td>Prospective cohort</td>
<td>13</td>
<td>61</td>
<td>Hb, Globulin, ESR, WBC, polymorph, lymphocyte, and total protein levels. Hb, Globulin are used as a predictive biomarker for short-term mortality after AIS. ESR, WBC, polymorph, lymphocyte, and total protein levels as predictors of severity of AIS.</td>
</tr>
<tr>
<td>Sarhan (58)</td>
<td>2019</td>
<td>Case control</td>
<td>300</td>
<td>66.76</td>
<td>RDW</td>
</tr>
<tr>
<td>Paramita (60)</td>
<td>2018</td>
<td>Cross sectional</td>
<td>490</td>
<td>59.57</td>
<td>RDW</td>
</tr>
<tr>
<td>Pinhoa (61)</td>
<td>2018</td>
<td>Cohort</td>
<td>602</td>
<td>74.19</td>
<td>RDW</td>
</tr>
<tr>
<td>Turcato (62)</td>
<td>2017</td>
<td>Retrospective observational</td>
<td>316</td>
<td>73.27</td>
<td>RDW</td>
</tr>
</tbody>
</table>

RDW: Red blood cell distribution width, MPV: Mean platelet volume, MCV: Mean corpuscular volume, PLT: Platelet count, NLR: Neutrophil/lymphocyte ratio, RBC: Red blood cell, ESR: Erythrocyte sedimentation rate