Clinical Utility of Red Cell Distribution Width in the investigation of Non-Hematological Disorders, in a Tertiary Care Teaching Hospital, Addis Ababa, Ethiopia: A Case Control Study.

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Abstract: Background: Red cell distribution width (RDW) is a measurement of the degree of anisocytosis, or the degree of red cell size variability present in a blood sample. RDW has been reported as a significant diagnostic as well as prognostic laboratory marker for many non-hematological disorders. The objective of this study was to describe the clinical utility of RDW in the investigation of non hematological disorders at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

Methods: A Case-control and questionnaire based study was conducted at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. A convenient sampling technique was employed and a total sample size of 150 (100 cases and 50 apparently healthy controls) and 100 clinicians were included from May to August, 2015. Cases were adult patients diagnosed with heart, liver and kidney diseases. RDW was determined using Sysmex XT-2000*i* Automated Hematology Analyzer. Frequency, mean, paired t test and chi square were calculated P values less than 0.05 were considered statistically significant.

Result: Half of the clinicians had the knowledge that elevated RDW could be an indication of non hematological diseases. However, 68% (68/100) of them rated that they rarely or never use RDW in the investigation or follow up of patients having non hematological diseases. The clinical laboratory method course for medicine students was rated as inadequate by the majority of them. Paired t test revealed mean difference of 2.53± 4.3 existed between the cases and control groups with a confidence interval of 1.31-3.76 ($p<0.001$). The association between the three diseases and elevated RDW was found to be statistically significant ($P<0.05$) with 95% confidence interval (0.000-0.030).

Conclusion: RDW's clinical utility by clinicians at TASH in the investigation or follow up of patients with non hematological diseases was insufficient indicating that awareness should be created. Half of the clinicians had the knowledge that elevated RDW could be an indication of non hematological diseases yet failed to utilize it. Reason behind it is yet to be identified but the habit of utilizing RDW in the investigation of diseases other than anemia should be encouraged.

Key words: RDW, clinical utility, non-hematological disease, Ethiopia.

Background

Red cell distribution width (RDW) is an automated measurement of red cell size variability in the peripheral blood(1). The parameter is measured as a component of the red cell indices in the total/complete blood count (CBC). The normal range of RDW is between 11.5%and 14.5%. RDW is mostly utilized in the differential diagnosis of anemia (2, 3). However, many researchers have reported that RDW is related with elevated morbidity rate in many diseases as well as all-

cause mortality. Even so, it is used rarely compared with other hematological parameters. It has been reported that RDW is a widely ignored red cell indices despite its relevance in various hematological as well as non hematological diseases (1, 4).

More studies are indicating that RDW is a significant lab marker for the diagnosis and prognosis of patients with hepatitis B, severe sepsis, inflammation, type 2 diabetes mellitus, acute kidney injury, acute coronary syndrome, active Crohn's disease, intestinal tuberculosis, community-acquired pneumonia and acute pancreatitis. The above mentioned researches and others showed that red cell distribution width was significantly increased especially in the mortality of the patients (5-13). But this study was only focused on heart, liver and kidney diseases. A number of patients suffering from either chronic or acute heart, liver or kidney diseases visit Tikur Anbessa Specialized hospital in order to be diagnosed and treated. Establishing the association between RDW and the three diseases will be vital in improving the health care service in Tikur Anbessa Specialized Hospital, consequently in Ethiopia.

This study aimed of this research was to identify if RDW is clinically utilized in the investigation of non hematological disorders by clinicians at Tikur Anbessa Specialized Hospital using a self-administered pre-tested questionnaire. Previously conducted study in Ethiopia found RDW to be the least utilized parameter compared to the other red cell indices in the diagnosis as well as in patient management. TASH being the highest level referral and the largest teaching hospital of the country, introducing the utility of this simple lab marker which has multiple clinical applications with no additional cost, not only improves patient management in this hospital but ultimately do the same in the other health facilities.

Materials and Methods

A case-control, questionnaire and laboratory based study was conducted from May till August 2015 at Tikur Anbessa Specialized Hospital which is affiliated with Addis Ababa University. Convenient sampling technique was employed during this study. Cases were chosen as adult patients with heart, kidney and liver diseases who were already diagnosed and being treated at Tikur Anbessa Specialized Hospital. Patients already exhibiting signs of anemia were excluded from this study. Apparently healthy participants with no history of heart, kidney and liver diseases and who were not currently taking any medication were taken as controls. 5 ml of blood

were collected from the case and control groups and complete blood count (CBC) was analyzed for both groups using SYSMEX XT-2000i automated hematology analyzer. RDW results were recorded from the results obtained from the complete blood cell count analysis.

Questionnaires were also distributed to volunteering specialists, residents, interns and general practitioners currently working in the internal medicine and pediatrics department in order to assess the clinical utility of RDW in the investigation and follow up of patients with heart, kidney and liver diseases. Frequency of using RDW either in the investigation or follow up of patients with non hematological diseases were asked through the questionnaires. Other questions such as if they had the knowledge that elevated RDW was linked with non hematological diseases, what were the other clinical conditions RDW was normally utilized by the clinicians at TASH and if clinical laboratory methods courses were adequate in introducing the clinical usefulness of RDW. Descriptive statistics like frequency, mean, median and range was employed. Pearson chi square was calculated to establish association between elevated RDW and heart, kidney and liver diseases. Paired t test was also calculated to determine the mean difference between the case and control groups.

The study was approved after it was reviewed by the research and ethical review committee of the department of medical laboratory science and department of internal medicine, School of Medicine at Tikur Anbessa Specialized Hospital College of Health Sciences, Addis Ababa, Ethiopia. Clinicians and patients were included after providing their consent. No additional blood samples were collected for the purpose of this study as patients for whom CBC was requested as part of their routine work up were included. For apparently healthy controls, the aim of this study was explained and 5 ml EDTA blood was collected based on their consent. Data confidentiality was maintained by password protecting electronic files and by locking hard copies throughout the study.

Results

Clinical utility of RDW in the investigation and follow up of heart, kidney, liver and other non hematological diseases

Out of the 35 pediatricians at TASH, 2, 3& 9 of them use RDW always, frequently or sometimes respectively. The rest 21/35 (60%) rated that they rarely or never use the parameter in the investigation of non hematological diseases. Out of the 55 internists who participated in

the study, 40 (72.7%)of the internists rated that they rarely or never use RDW, however, only 1 reported the frequent use of the parameter. The other 13(23.6%) rated that they sometimes use RDW. All of the 10 general practitioners and Interns rated that they sometimes or never use this parameter. From the total percentage, 68% of the doctors rated that they rarely or never use RDW in the investigation or follow up of the patients (Figure 1)

Clinician's knowledge about utility of RDW in the investigation of cardiac, kidney and liver diseases

Knowledge that elevated RDW can aid in the investigation of heart, kidney and liver patients was assessed among clinicians. Overall, 51% of the clinicians responded “Yes” while the remaining 49% responded “No”. When data is disaggregated by specialty, 19/35 (54.3%) of the pediatricians, 24/55 (43.6%) of internists and 6/10 (60%)of the GPs and interns answered “No” while 31/55 (56.4%) and 16/35 (45.7%) of the internists and pediatricians, respectively, answered “Yes”.

Feedback of clinicians on clinical conditions RDW is usually utilized

When clinicians were requested about clinical conditions in which RDW is usually utilized, anemia was the clinical conditions in which RDW was commonly utilized as reported by 52% of the clinicians, that is in 31/55 of internists and 20/35 of pediatricians. RDW was also utilized for the other non- hematological diseases as reported by 15% of the clinicians. However, 30% of the doctors had no response and 4% of them answered that they never use it.

Adequacy of clinical laboratory methods (CLM) course in medicine

Half (50%) of Clinicians feedback indicated that in the clinical laboratory methods course the introduction of RDW as a clinical significant parameter in the investigation and follow up of heart, kidney, liver and other non hematological diseases, was fair to poor, While 18% of the clinicians rated that it was excellent or very good. The remaining 32% rated good.

Association between RDW use and year of experience

Pearson chi-square was utilized in order to establish association between specialist's year of experience and RDW use at TASH it was found that the association was not statistically significant ($p>0.05$).

RDW values in the case and control groups

Distribution of RDW value for the case(heart, kidney and liver) and control (apparently healthy people) group.

The mean and range of RDW were calculated for both groups. Paired t test of RDW was also calculated. The Mean ±SD RDW value for cases was 15.2±3.37(Range= 12.1-31.1) which was significantly higher than the control groups. The corresponding RDW values for the control group were 13.3±0.79 (Range=11.9-15.8).Paired t test revealed a P value with 95% confidence interval of (CI= 1.31-3.75, P<0.001) (Figure 2).

Association between elevated RDW value and the disease type (cardiac, kidney& liver)

Elevated RDW value (>14.5) was observed in 40% of the cases and only 8% of the apparently healthy controls had elevated RDW values. Pearson chi-square test was employed to determine the association between the disease types and elevated RDW results and the association was found to be statistically significant (P<0.05) with 95% confidence interval (0.000-0.030). Out of the 40 heart patients, 20 (50%) of them had elevated RDW(RDW>14.5). From the total number of 32 kidney and 28 liver patients, 6 and 14 (50%) of them had elevated RDW respectively (RDW>14.5) (Table 1).

Association between Age, Sex and Elevated RDW in the case group (heart, kidney and liver patients) at TASH from May- August 2015.

Median for age in the case and control group was calculated to be 38 (Range=18-79) and 35 (Range= 22-70) respectively. Percentage of male and female patients in the case group were 53% and 47% respectively. In the control group, 46% were male and 54% were female. The association of age and elevated RDW in the case group was not found to statistically significant (P=0.967). Similarly, the association between sex and elevated RDW was not statistically significant (P=0.1).

Discussion

The study aimed at assessing the knowledge and clinical utility of RDW in the investigation of non hematological disorders at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. By using a self administered questionnaire. It had established that the clinical utilization of RDW in the investigation and follow up of heart, kidney and liver diseases was insufficient. Another

research's findings supported the present study stating that RDW was the least frequently utilized parameter (4). In contrary, a study conducted in 2009 reported that clinicians utilize RDW in the investigation as well as follow up of cardiac patients, establishing that RDW is an important parameter which can aid as predictive parameter for the outcome of a disease and support clinician's decision in choosing treatment for the patients (1). Moreover, study conducted in 2015 by Xu also contradicts with our study reporting that clinicians are widely using RDW in the investigation inflammation and liver fibrosis caused by hepatitis B infection (14). In china, there was a research done by Huang *et al* which reported that clinicians utilized RDW as a predictive index of mortality rate for acute kidney patients which contradicted the findings of our study (11).

Knowledge that elevated RDW is an indicator of non hematological diseases is an ongoing research which is investigating not only the association between elevated RDW and heart, kidney, liver diseases but also other diseases including different malignancies. Clinicians who participated in our study stated that half of them had the knowledge yet failed to apply it. Half of the clinicians who participated in the study rated the introduction of RDW in clinical laboratory methods course for medicine students as fair to poor. A study conducted in Ethiopia by Birhaneselassie *et al* supported these results urging that there should be better curriculum which incorporates updated studies regarding the association of elevated RDW with the diseases other than the hematological ones (15).

RDW is commonly used to manage patients with anemia. More than half of the clinicians at TASH reported that RDW was only clinically utilized for the diagnosis and investigation of different kinds of anemia including IDA. Only less than a quarter of the clinicians reported that they use it in the investigation of non hematological diseases. Along with many text books and studies including a study conducted in 2015 by Liu *et al* agrees with our findings stating that RDW is widely utilized for the management of patients with anemia (16). Our study aimed to create awareness among clinicians that RDW is clinically significant in the investigation of not only anemia but also non hematological diseases.

Association between clinician's year of experience and RDW use was considered in the present study but the result was not statistically significant. Our result contradicts with a survey conducted in America by Sandhaus *et al* which found a statistically significant association between year of experience and RDW use ($P<0.05$). Clinicians who worked for less than 10 years used RDW a lot more than clinicians who worked for more than 10 years (4). This finding

entail that RDW's clinical significance in the investigation of non hematological diseases is relatively new idea and still being exhaustively researched. Researchers and educators at TASH should be updating students concerning current findings.

This study, to the best of our knowledge, is the first of its kind in Ethiopia which tried to identify clinical utility of RDW by obtaining feedback from clinicians and tried to establish the clinical significance of RDW by conducting a case control study. There is a statistically significant mean difference between the RDW value in the case (15.2±3.36%, $p<0.001$) and in the control group (13.39±0.79). This shows that patients with heart, liver or kidney diseases had elevated RDW as oppose to apparently healthy people suggesting the need for introducing the parameter in the clinical management of such patients.

Normally, patients with chronic diseases such as heart, liver or kidney diseases are bound to develop anemia of chronic diseases as a result they will have increased RDW. Anemic patients were excluded from our study for such reasons and in attempt to prove that RDW can be an early independent marker in the investigation of these non hematological diseases. A case control study by Lou *et al*, found that there was a statistically significant mean difference between the case (chronic liver patients) (16.376±2.43%, $P<0.001$) and apparently healthy people (13.03±1.33%) which corresponded with our findings (15). Another study conducted by Oh *et al* found that patients with kidney diseases had a mean of 15.7±2.3 with a range of 11.7-28.0 which is in line with our study (9).

Association of elevated RDW and heart, kidney and liver diseases was found to be statistically significant with 95% confidence interval (CI: 0.000-0.030, $p=0.01$). Out of the 40 heart patients, half (50%) had elevated RDW (RDW> 14.5). A systematic analysis of cohort studies by Huang *et al* also documented similar findings with our study , in which patients with Heart failure had 1% RDW increase especially those with fatal outcomes (95% CI: 1.06–1.14, $P=0.01$) (17). Patient outcome was not studied in our study. However, it is important to have a better understanding of the association between elevated RDW and non hematological diseases.

Explanation why or how patients with heart diseases had elevated RDW without onset of anemia is that the elevation of RDW may describe an underlying inflammatory state which might lead to impaired erythrocyte maturation. In addition, inflammatory cytokines released due to heart

disease may impact normal bone marrow function and iron metabolism (18). The scientific explanation behind elevated RDW in non hematological diseases was not investigated in our study. There was also a statistically significant association between elevated RDW and kidney patients (95% CI: 0.000-0.30, P=0.01). Out of the 32 kidney patients, 19% had elevated RDW (> 14.5). In another study conducted by Oh *et al*, they found that out of the total number of kidney patients enrolled in the study 67.5% of them had elevated RDW (≥14.6). The study went on to disclose that there was a statistically significant association between elevated RDW and fatality due to kidney diseases (RDW value= 16.0± 2.5, P< 0.01) (9). In our study, there was no follow up or investigation of clinical outcomes of patients with kidney diseases.

Regarding liver patients, it was found that out of the total number who participated in this study, half of them had elevated RDW level (> 14.5) with an established the association using Pearson chi square test (95% CI: 0.000-0.030, P<0.001). In consistence with this, Cengiz *et al* also found that elevated RDW (> 14.5) had a statistically significant association with liver diseases especially patients with severe fibrosis (95% CI: 1.129-2.711, P<0.01) (19). Similar findings were reported by Lou *et al* who found a statistically significant association with elevated RDW and chronic liver disease (P<0.001). The study further concluded that patients with higher RDW levels were at higher risk of fatal outcomes. Again patients follow up or clinical outcomes of patients with liver diseases were not performed during the course of our study (5).

The scientific cause behind elevation of RDW levels in liver or kidney patients has not been investigated in our study. Along with RDW levels, investigation of other non hematological parameters could have helped with the identification of the source behind increased RDW level in those patients. This is a potential limitation of our study.

Conclusion

RDW's clinical utility at TASH in the investigation or follow up of patients with non hematological diseases by clinicians was insufficient indicating that awareness should be created. Half of the clinicians had the knowledge that elevated RDW could be an indication of non hematological diseases yet failed to utilize it. Reason behind it is yet to be identified but the habit of utilizing RDW in the investigation of diseases other than anemia should be urged and

encouraged. The adequacy of CLM course in medicine was rated fair to poor by most clinicians, proving that the course needs to be dynamic by incorporating different study findings which will support the education to be all rounded and updated. There was no statistical significant association between year of experience and RDW use which shows that RDW is a newly researched parameter in the investigation of non hematological diseases and the awareness has not been yet created in Ethiopia. There was a statistically significant mean difference between the case and control group. This establishes RDW can assist in the investigation of non hematological diseases. There was a statistically significant association between elevated RDW and non hematological diseases confirming that patients suffering from heart, kidney or liver diseases had elevated RDW independent of anemia establishing that RDW is a clinically significant marker which should be used more often.

List of Abbreviations

AAU	Addis Ababa University
AKI	Acute Kidney Injury

CBC	Complete blood count
CI	Confidence interval
CLM	Clinical Laboratory Methods
RDW	Red cell distribution width
SOP	Standard Operating Procedure
TASH	Tikur Anbessa Specialized Hospital

Competing interests

The author(s) declare that they have no competing interests.

Authors Contribution

MwT developed the research design, manuscript, conducted the data collection from patients, and performed statistical analysis and interpretation of data. AT contributed in the conception, design of the study and approved final version to be published. AG and MT provided expert outlook in this study and approve final version to be published..

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Figures and Tables

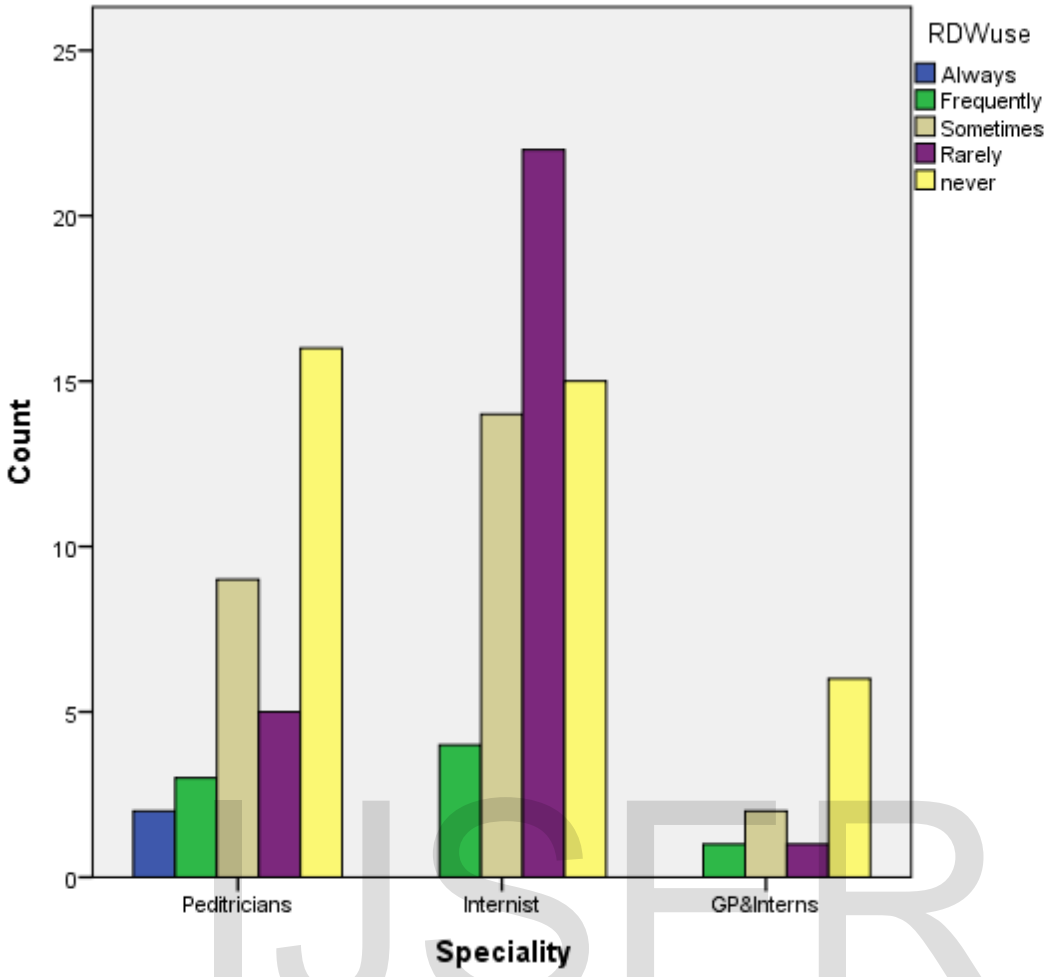

Fig 1. Clinical utility of RDW in the investigation of non hematological diseases by clinicians at TASH from May- August, 2015.

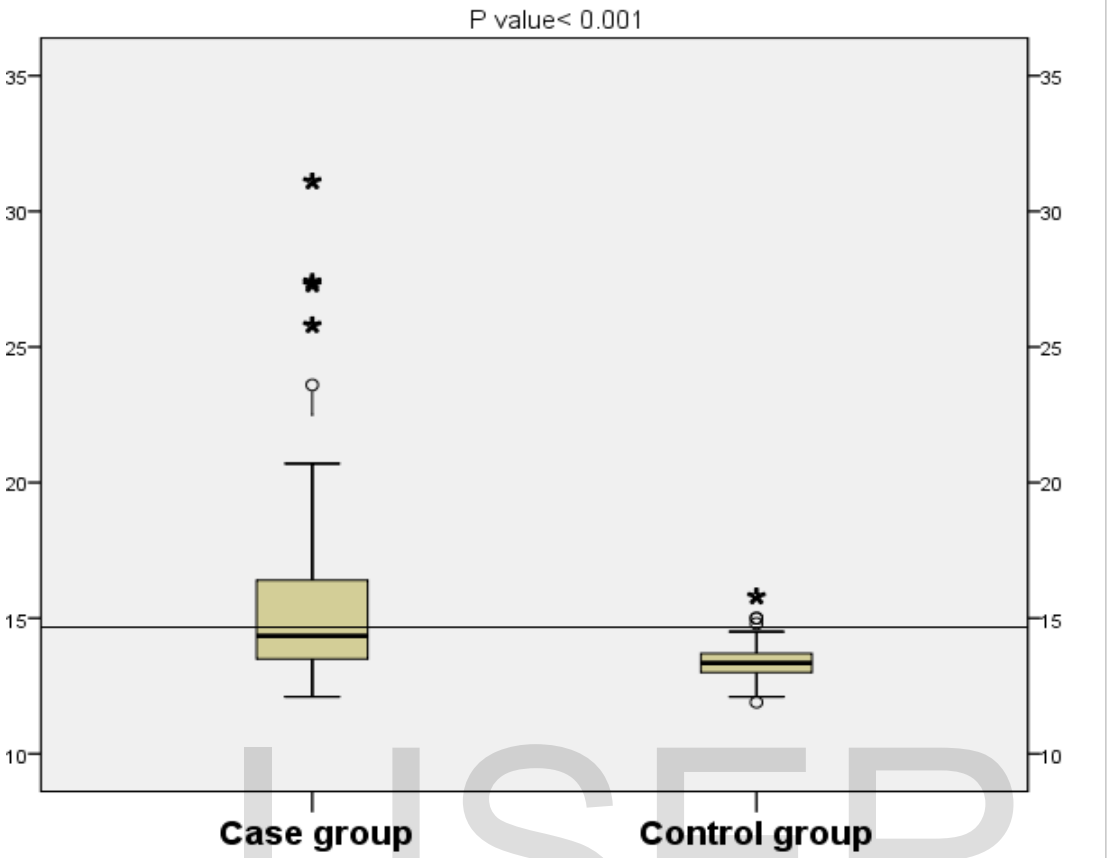

Figure 2. Whiskers and box plot of distribution of RDW value for the case (cardiac, kidney and liver patients) and control group (apparently healthy) at TASH from May-August, 2015.

Table 1: Association between elevated RDW and disease types(hear, kidney & liver) at TASH from May- August, 2015.

Disease type	RDW result			P value
	Normal(RDW=11.5-14.5)	Elevated (RDW> 14.5)	Total	
Heart	20	20	40	
Kidney	26	6	32	
Liver	14	14	28	
Total	60	40	100	
		Confidence interval (95%)		0.01
	Value	Lower bound	Upper bound	
Pearson Chi square	8.854	0.000	0.030	