Red Blood Cell Distribution Width (RDW) Mortality & Morbidity Implications

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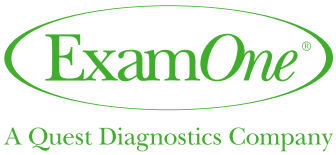

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Preface

Reinsurers and insurance laboratories periodically undertake both mortality and protective value studies on laboratory tests used or proposed for use in life insurance underwriting.

In order to gain a broader understanding of the insurability implications of these tests and others used clinically (and therefore frequently seen in medical records procured for underwriting purposes), we also need in-depth reviews of the medical literature. These reviews help us establish the potential significance of the tests in a risk assessment context.

This paper reviews the world literature as of February 2014 on red blood cell distribution width (RDW), a routine component of the complete blood count (CBC). As you will read, the mortality and morbidity implications of RDW are diverse and substantial.

We invited all reinsurers and laboratories in the US to support us by making a modest cosponsorship contribution to offset a portion of our labor costs and other expenses.

All three labs and eight of the eleven reinsurers stepped up to cosponsor this project. It is reassuring that they recognize the importance of this type of research.

The corporate logos of these proactive firms are shown on the cover page of this paper. We hope you will take opportunities to thank their representatives for helping make this paper possible.

Lastly, all opinions expressed in this paper are solely my own, and do not necessarily reflect the views or practices of the cosponsors.

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March 17, 2014

"Today, the accumulating mass of RDW literature supports the conclusion that RDW is a valid and major predictor of health outcomes."

Benjamin D. Horne, PhD, MPH, FACC
Intermountain Heart Institute
Salt Lake City, Utah
Cardiology
122(2012):213[editorial]

Background on RDW

"The red blood cell (RBC) distribution width (RDW) is a measurement of the size variation as well as an index of the heterogeneity of erythrocytes (i.e., anisocytosis)…"

Martina Montagnana, MD, et al
University of Verona, Italy
Clinical Chemistry and Laboratory Medicine
50(2012):635

- RDW is one of the red blood cell indices, along with mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC).
- It is now routinely included in CBCs done worldwide.
- RDW test results will be cited in a substantial portion of medical history records secured by underwriters.
- Because most clinicians are not aware of the implications of RDW outside of its association with anemia, attending physicians will likely ignore elevated RDW readings unless they are working up the patient due to unexplained anemia.
- Therefore most elevated RDW readings will be ignored in a clinical environment.

RDW Determination and Reporting of Results

RDW can be calculated in two ways. The predominant method is called RDW-CV. It determines RDW based on MCV and reports it as a percentage (RDW %).

The other is RDW-SD, which measures RDW directly and reports values in femtoliters (fL). While this method is said to be superior, it has not yet been widely embraced, at least in the US. [Constantino]

From both clinical and underwriting perspectives, only elevated and, on occasion, high normal RDW have health-related significance. We found just one study where below normal RDW was said to be significant. That study will be cited further on.

Given all of the evidence at hand, below normal RDW test results should be ignored by underwriters. [Montagnana]

RDW normal ranges vary considerably between laboratories. [Poludasu]

- The reference (normal) range on a Coulter autoanalyzer is 12.09%-15.19%.
- In 2 prominent laboratory reference manuals, reference ranges are set at 11.6%-14.6% and 11.0%-14.5%, respectively. [Vaspayee, Pagana]
- We contacted the International Council for Standardization in Hematology and they advised there are no plans to set RDW standards in this regard.
- Therefore, we will continue to see RDW normal ranges fluctuate between 11.0% and 15.0%; perhaps higher.
- Underwriters should base their RDW assessments on the reference range cited in the CBC report they are reviewing.

The preponderance of evidence cited in this review is consistent with the conclusion that all RDW elevations, in both anemic and non-anemic persons, confer increased mortality and morbidity risk.

RDW Stability in Blood Specimens

RDW % (RDW-SD) is driven by MCV. Because MCV is unstable in blood samples, RDW % would be expected to have the same drawback. [de Baca]

Laboratory experts have reported that RDW is unstable at room temperature and that significant changes occur between 6 and 24 hours after specimen collection. [Cornbleet, Hill, Park]

We asked the 3 US insurance laboratories for their opinions on the potential for getting reliable RDW % determinations on paramedically collected blood samples.

- One lab stored 8 samples and tested them as long as 7 days after collection. They reported an average coefficient of variation of 2.27% and stated, *"RDW seems stable under these conditions."*
- Another lab told us that RDW is too unstable to be measured when specimen analysis is delayed. They did not cite specific data.
- The third lab did not respond to our request.

Unfortunately, we do not have enough information as yet to sort this matter on the basis of specimens actually collected for underwriting purposes. Given the findings reported by one lab on a small sample, it may be worth investigating this question further in our industry.

For now, evidence from clinical laboratory sources suggests that we will not get credible RDW % readings in our testing milieu.

It remains to be determined whether we would get valid RDW determinations by using the RDW-SD method (which is not influenced by MCV).

Mechanisms Associated with Elevated RDW

"Red blood cells may represent a 'real-time' biomarker of an underlying abnormal pathophysiologic state."

Sandip K. Zalawadiya, MD, et al
Detroit Medical Center
American Journal of Cardiology.
109(2012):1664

"Given that RDW rises with age and strongly predicts mortality, it is conceivable that anisocytosis might reflect impairment of multiple physiologic systems related to the aging process or caused by inflammation and age-associated diseases."

Kushang V. Patel, PhD, MPH, et al
National Institute of Aging
Archives of Internal Medicine
169(2009):515

In addition to anisocytosis, a wide range of suspected mechanisms linked to elevated RDW have been reported in the literature. Some have a high degree of supportive evidence, while others are more speculative at this time. Please see Table One on the following page.

Inflammation and RDW

In terms of factors impacting RDW, the most robust evidence to date implicates inflammation.

In a group of 3,845 outpatients, median age 60, investigators reported this correlation between RDW quartiles and two major inflammatory markers: high sensitivity C-reactive protein (hs-CRP) and erythrocyte sedimentation rate (ESR).

RDW Quartile	% hs-CRP > 3 mg/L	% ESR > 40 mm/hr
1	28%	8%
2	35%	10%
3	48%	23%
4	63%	40%

Table One
Mechanisms Associated with Elevated RDW

- Inflammation
- Cigarette smoking
- Nutritional deficiencies
- Obesity
- Oxidative stress
- Physical inactivity/sedentary lifestyle
- Increased circulating immature red blood cells
- Impaired iron metabolism
- Increased blood viscosity and other thrombotic mechanisms
- Suppressed bone marrow function
- Hemolysis (enhanced red blood cell destruction)
- Abnormal hemoglobin variants
- Neurohormonal and endocrine system activation
- Diminished capacity for systemic repair, recovery and defense
- Tissue hypoxia/hypoxemia
- Physiologic impairments associated with aging
- Chronic hyperglycemia
- Shorter telomere length

Agarwal, Allen, Al-Najjar, Azab, Cavusoglu, Chrobak, Constantino, Fukuta, Geletzke, Goldstein, Gonzalo-Calvo, Hammarsten, Hunziker-1, Lippi-1, Martinez-Velilla, Ozcu-1, Patel-2, Patel-3, Savov, Semba, Sokucu, Veeranna-1, Wolters

They concluded that RDW has a strong association with inflammation, independent of the effects of hemoglobin, ferritin and MCV. [Lippi-1]

Eight additional studies document significant links between RDW and various inflammatory markers, including CRP, ESR, tumor necrosis factor-alpha, high normal/elevated white blood cell counts and fibrinogen, in both the general population and disease-specific contexts. [Celik-2, Horne, Lappe, Malandrino, Ozcan-1, Patel-1, Wang-1, Zalawadiya-3]

Cigarette Smoking

In 15,852 community-dwelling subjects, Perlstein et al revealed this association between percentages of active smokers, mean number of pack years (PY) of consumption and RDW quintiles:

RDW Quintile	% Active Smokers	Mean Pack Years
1	18.5%	8.9
2	24.6%	9.9
3	30.7%	10.8
4	36.5%	12.4
5	37.9%	13.4

Two additional general population studies also report significantly higher percentages of current smokers with high normal/elevated RDW, in 15,460 and 1,654 subjects, respectively. [Wang-1, Zalawadiya-1]

There are also 5 investigations, ranging from 1,469 to 13,039 persons, where smoking is marginally, but not significantly, more common at higher RDW levels. [Lappe, Malandrino, Osadnik, Tonelli, Ye]

It appears that current smokers are more disposed to higher RDW readings than current abstainers, and that there is some association between aggregate cigarette exposure – as credibly measured with pack years – and RDW levels.

Obesity

In 15,460 community-dwelling individuals, 16% in the 1st RDW quintile were obese (BMI ≥ 30), as compared to 28.5% in the top quintile. [Zalawadiya-3] Another study showed a similar breakdown across RDW quintiles (16.5% in 1st quintile vs. 32.3% in 5th quintile). [Perlstein]

Alcohol Use

When comparing heavy drinkers and control subjects,

Seppa and Sillanaukee found RDW was higher in alcohol dependent subjects (alcoholics) to a highly significant extent.

Wickramasinghe also reported a link between RDW and being alcohol dependent.

Nutritional Deficiencies/Serum Albumin

When RDW quartiles were matched to the percentage of community subjects meeting study criteria for nutritional factor deficiencies, 33.2% in the 4th RDW quartile met these criteria, as compared with 14.6%, 17.2% and 21.9% in the first 3 quartiles, respectively. [Zalawadiya-3]

Four studies reveal a consistent and significant inverse relationship between RDW and serum albumin. [Chen, Lappe, Malandrino, Patel-1]

Physical Activity

In one large assessment, subjects in the 1st RDW quintile were twice as likely to meet criteria for being "more active." [Perlstein]

Another study found RDW levels were inverse to the extent of reported physical activity. [Emans]

Telomere Length

Telomeres are specialized structures that stabilize the ends of chromosomes. Telomere length has been referred to as a "biologic clock," and many studies have now demonstrated that relatively shorter telomeres are a marker for disease and early mortality risk in a wide range of contexts. [Bodnar]

In the Dallas Heart Study encompassing 3,157 subjects ages 18 to 85, short telomere length was associated with elevated RDW to a highly significant extent (said to be equivalent to that seen in cigarette smokers). [Kozlitina]

RDW and Laboratory Tests

High RDW is an independent predictor of elevated homocysteine levels, and homocysteine is a proven marker for increased CV risk. [Vaya-1, Zalawadiya-2]

RDW and brain natriuretic peptides (BNP, NT-proBNP) are statistically independent of one another and can be used together in risk prediction. [Fukuta]

There is no significant correlation between RDW and ALT, AST or alkaline phosphatase. [Hammarsten] We could not find any data concerning the relationship between RDW and GGT or carbohydrate deficient transferrin (CDT).

RDW is associated with at least 18 different mechanisms known to be related to increased risks of one or more diseases. It also correlates with smoking, obesity and nutritional deficiencies.

These findings strongly support the evidence for a powerful correlation between elevated RDW and increased mortality, which will be addressed in this paper.

RDW & Anemia

"Although the RDW is one of the most studied and frequently used CBC parameters, it is not well understood."

Benie Constantino, ART, MLT, SH
CML Healthcare Inc.
Mississauga, Ontario
LabMed
44(2013):e2

"RDW appears to be most useful in patients who are not overtly anemic, where it represents an early abnormality not yet evident on other routine tests."

Shyam Poludasu, MD, et al
State University of New York Downstate Medical Center
Thrombosis and Hemostasis
102(2009):581

In clinical practice, RDW is used in combination with MCV to troubleshoot the cause of an underlying anemia. [Montagnana]

RDW is elevated in a variety of anemic states, many of which have prominent insurability implications: [Bessman, Gupta, Meio, Tefferi]

- Aplastic anemia
- Vitamin B-12 and folate deficiency (with or without overt anemia)
- Hemolytic anemia
- Anemia accompanying hypothyroidism
- Refractory anemia in myelodysplastic syndrome
- Rx-induced anemia
- Sideroblastic anemia
- Iron deficiency (with or without overt anemia)

RDW is most useful in distinguishing megaloblastic anemia in patients without elevated MCV (macrocytosis). [Chan]

The #1 cited use for RDW is in the differential diagnosis of microcytic anemia, principally between iron deficiency and beta thalassemia.

Ironically, its effectiveness in this capacity has now been shown to be relatively poor… whereas its *"importance as a general marker has been maintained."* [Beyan, Buch, Buttarello, Ntaios, Urrechaga]

Clinical use of RDW is currently limited to the differential diagnosis of anemia and nutritional deficiencies disposing to anemia.

Because current laboratory guidelines do not reference its implications in other contexts, most of what we will now share with you is apt to be "off the radar" of attending physicians.

RDW & Circulatory Disease

This is the domain where RDW has been most extensively investigated.

CV disease also happens to be the leading cause of death.

> *"…reliable data emerged from several epidemiological investigations disclosed a new and otherwise unpredictable scenario in the clinical usefulness of this measure, supporting the hypothesis that RDW might be a useful parameter for gathering meaningful clinical information, either diagnostic or prognostic, on a variety of cardiovascular and thrombotic disorders."*
>
> Montagnana
> Op. Cit.

History of Cardiovascular Disease (CVD)

In a study of 15,652 community subjects, the prevalence of baseline cardiovascular disease increased progressively across quintiles of RDW and was independently predictive of preexisting CVD. [Perlstein]

RDW Quartile	% Known Disease
1	4.1%
2	4.6%
3	5.9%
4	7.7%
5	9.9%

Among 8,499 individuals in the US NHANES study, similar findings were cited in 4 CVD contexts, with the highest prevalence in the 4th RDW quartile: [Afonso]

RDW Quartile	% Known Disease			
	CAD	Prior MI	Prior Stroke	Angina
1	3.3%	3.4%	2.4%	2.7%
2	4.4%	4.3%	3.4%	3.1%
3	4.4%	4.1%	4.0%	4.5%
4	6.3%	7.7%	5.6%	4.7%

In 8,175 general population subjects, the percentage having a history of prior MI in the top 2 RDW quartiles was twice as high as in the 1st and 2nd quartiles, and 50% greater than in the 3rd quartile. [Patel-1]

In 619 patients with ST-segment elevation myocardial infarction (STEMI), those with an RDW > 14% were

4 times more likely to have a history of heart failure and 2.5-fold more apt to have sustained a prior MI, as compared to subjects with an RDW of 13% or lower. [Azab]

And in 13,039 patients with known peripheral arterial disease (PAD), those in the 4th RDW quartile were 3-fold and 1.7-fold more likely to have heart failure at baseline, as compared to patients in the 1st and 3rd quartiles, respectively. [Ye]

Elevated RDW is an independent marker for substantially increased odds of a CV event history.

Angiography

In 193 non-anemic patients undergoing coronary angiography because of a history of stable angina, mean baseline RDW was 14.4 in those with angiographically significant disease, as compared to 12.5 when the study was negative.

The authors cited 13.25% as the best RDW cutoff for risk of obstructive CAD with a PPV (positive predictive value) of 89% and a NPV (negative predictive value) of 71%. [Isik-1]

In 677 Chinese patients having angiography because of angina or a positive treadmill stress test, RDW was an independent predictor of significant CAD, using a cutoff of 12.85%. [Ma]

In 917 patients with suspected CAD, Akilli et al performed both dobutamine stress echocardiography and angiography. Mean RDW increased significantly with the number of ischemic segments on the echo study and had a 94.2% PPV for obstructive CAD when RDW was 13.5% or higher.

In a Turkish investigation of 233 ACS (acute coronary syndrome) patients, RDW was an independent predictor of inadequate/absent collateral circulation, and it outperformed troponin in this context. [Duran]

Barcin and coworkers showed that RDW correlated with impaired exercise capacity on treadmill stress testing, in both CAD patients and healthy individuals. RDW was significantly linked to failure to achieve more than 7 METS, and we know that low MET output is an established marker for excess mortality.

Elevated RDW is associated with angiographic obstructive coronary disease, as well as other adverse cardiac test findings.

Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG)

In CAD and post-ACS patients undergoing PCI, RDW is an independent predictor of a number of unfavorable findings:

- When 14% or higher, the odds ratio for poor perfusion (no re-flow phenomenon) was 2.9. At this RDW threshold, the odds ratio for intermediate duration mortality was 5.9. [Isik-2]
- Another study reported an odds ratio of 2.2 for poor perfusion post-PCI when RDW was > 14.8%. [Karabulut]
- In STEMI patients having a PCI, elevated RDW predicted for an increased thrombus burden. [Tanbooga]
- RDW was an independent marker for major post-PCI bleeding. [Fatemi-2]

RDW is also significantly associated with post-PCI mortality:

In 1,689 PCI cases, 4th vs. 1st quartile RDW was a multivariate-adjusted marker for 12-month mortality. After 4 years post-PCI, RDW > 15.6% vs. < 13.3% had a mortality hazard ratio of 5.2 after adjustment for other risk factors, including hemoglobin. [Poludasu]

Eighteen months post-PCI adjusted CV mortality hazard ratios for elevated RDW (> 14.8%) were 1.8 overall and 2.7 in patients free of anemia. [Uyarel]

In 763 anterior MI patients undergoing PCI, RDW > 14.8% increased the risk of in-hospital death 3.7-fold. [Ilhan]

In patients undergoing CABG, RDW was a potent

marker for adverse findings and consequences:

- » It was an independent predictor of developing saphenous vein graft disease. [Akyel, Dogan]
- » An RDW of 13.45% or higher was associated with a significantly increased risk of new onset atrial fibrillation. [Ertas]
- » In 8,615 consecutive subjects undergoing isolated CABG and followed for 5.8 years, RDW was an independent predictor of both in-hospital and long-term survival. [Warwick-1]

RDW is a marker for a wide range of unfavorable outcomes in coronary interventions, including increased inpatient, intermediate-term and long-term mortality following PCI.

CV Events and CV Mortality (excluding post-ACS)

Lappe et al looked at mortality in 1,489 patients with known CAD, mean age 65.

Twelve-month all-cause mortality in the 5th vs. 1st RDW quintile had a hazard ratio of 7.9. After 5 years, all-cause mortality in the 4th and 5th RDW quintiles was 1.7-fold greater than in the first 3 quintiles.

These Duke University Medical Center cardiologists said, "Elevated RDW was associated with a strong graded risk of mortality."

In an Israeli investigation of 3,222 CAD patients undergoing coronary angiography, the 3-year risk of mortality and new cardiac events was over twice as great when RDW was elevated and increased 12% for each 1% increase in RDW. [Arbel-1]

In the Cholesterol and Recurrent Events Study involving 4,111 subjects with prior MI, Tonelli et al "…found a graded independent relation between higher levels of RDW and the risk of heart failure, cardiovascular events and all-cause death" as follows:

RDW Quartile	HR for 60-Month Outcomes		
	All-Cause Death	New MI	Onset HF
1	1.0	1.0	1.0
2	1.3	1.1	1.1
3	1.4	1.2	1.2
4	1.8	1.4	1.8

These results are highly significant after adjustment for 23 risk factors, including left ventricular ejection fraction (LVEF), waist-hip ratio, MCV, hemoglobin, etc.

In 2,550 stable angina patients followed for 30 months, 4th quartile RDW (≥ 14.1%) had a dramatic impact on mortality: [Osadnik]

RDW Quartile	% Dead at 30 Months
1	4.3%
2	6.8%
3	7.3%
4	17.1%

Four more studies reported similar findings. In one of these, the authors stated that RDW is a "…stronger marker for CHD death than hs-CRP." [Cavusoglu, Newby, Ren, Veeranna-2]

In addition, 2 studies examined the impact of anemia on RDW in the context of new CV events and mortality.

After following 7,556 persons, average age 42, for a decade, RDW correlated with the Framingham Risk Score and CV events in both anemic and non-anemic subjects: [Zalawadiya-1]

RDW Percentile	HR for CV Events After 10 Years Framingham Risk Score	
No Anemia	**< 10% vs. 10-20%**	**< 10% vs. > 20%**
≤ 75th	1.00	1.00
> 75th	1.77	2.45
Anemia	**< 10% vs. 10-20%**	**< 10% vs. > 20%**
≤ 75th	0.76	0.39
> 75th	3.32	4.83

These data show that RDW in the 75th or higher percentile of readings is a potent CV risk marker in two Framingham Risk Score contexts and that anemic subjects with high RDW are more substantially impacted.

In a 16-year Taiwanese study, a similar pattern of findings – distinguished by the presence vs. absence of anemia – showed increased CV mortality and new events based on the 75th RDW percentile. [Chen]

Post-ACS Mortality

In a 4-year Staten Island (New York) follow-up of 619 patients with non-ST-segment elevation MI (NSTEMI), mortality doubled between the 1st and 2nd RDW tertiles and then doubled again between the 2nd vs. 3rd tertiles (7.3%, 14.1% and 30%, respectively).

The relative impact of RDW was the same in subjects with low, normal and high MCV. The authors advocated use of admission RDW in NSTEMI risk stratification. [Azab]

In a Turkish study, RDW > 14% was associated with 19% 3-year post-ACS mortality, as compared to 5.6% when RDW was ≤ 14%. [Gul]

In 1,709 post-MI patients followed 27 months, mortality was 1.8-fold greater in the 3rd quintile and 2.8 times higher in the 5th quintile, as compared to the 1st quintile. Results were similar in those with or without anemia. [Dabbah]

Similar results were reported in 4 additional studies over intervals of 1 to 12 months post-ACI. [Lee-1, Nabais, Polat, Wang-1]

Two investigations showed that elevated RDW predicted for ACS events in emergency department patients. [Lippi-2, Uysal]

Other studies revealed:

- 2-fold greater risk of MI complications when RDW was > 14.5 [Xu]
- 3 times greater risk of bleeding events in STEMI patients if RDW was > 15.7% [Goncalves]
- 35% greater probability of post-ACS readmission when RDW was > 16.3% [Ephrem]

RDW is a potent marker for CV events and mortality in persons with known/suspected coronary disease, as well as those with prior ACS events.

Heart Failure

In the Malmo Diet and Cancer Study involving 26,784 subjects ages 45-73 free of baseline CV history and followed for 15 years, the 4th vs. 1st RDW quartile hazard ratio for heart failure hospitalization was 1.6 after adjustment for NT-proBNP. RDW and NT-proBNP were independent of one another. [Borne]

In another study, RDW added to the predictive power of NT-proBNP for finding echocardiographic parameters consistent with heart failure. [Oh-1]

After following 17,555 healthy middle-aged individuals for 11 years in the EPIC-Norfolk Study, Emans et al reported a 40% increased likelihood of heart failure in the 4th vs. 1st quartile, after full adjustment.

In patients referred for echocardiography due to suspected heart failure, RDW was significantly linked to LVEF < 40%, dilated ventricles, high pulmonary artery pressure and low stroke volume. Odds of a heart failure diagnosis doubled in the 4th vs. 1st quartile. [Holmstrom]

Other Heart Failure Considerations

- 4 studies show RDW is significantly inverse to LVEF. [Lappe, Poludasu, Tonelli, Wang-1]
- RDW > 13.6% was an independent predictor of echocardiographic criteria for diastolic heart failure. [Celik-1]
- RDW was a significant marker for new CV events in patients with heart failure and preserved LV function in 2 studies, at thresholds of > 14.5% and 15%, respectively. [Akiyama, He]
- High RDW is associated with the need for cardiac resynchronization therapy, as well as increased odds of failed outcomes. [Celikyurt, Rickard]
- It also correlates with impaired exercise capacity, low heart rate variability and increased risk of stroke in heart failure. [Kaya, Ozcan-2, van Craenenbroeck]

Nine studies report significantly increased mortality in heart failure patients. [Allen, Al-Najjar, Aung-2, Felker, Pascual-Figal, Nishizaki, Nunez, Shengbo, van Kimmenade]

We will not review these studies because nearly all such cases are deemed uninsurable for life and morbidity risk products.

Other Cardiac and Circulatory Disease Contexts

RDW has a number of associations with atrial fibrillation (AF):

- 30% increased AF risk (4th vs. 1st quartile) in 27,124 community-dwelling middle-aged and older Swedes followed for 13.6 years [Adamsson Eryd]
- Independently predictive of AF in middle-aged Turkish subjects [Baltay]
- Independent marker for non-valvular AF (OR 4.18) [Gungor]
- Progressively greater AF prevalence across quartiles of RDW in 2,550 patients with stable CAD (17.4% in 4th quartile and 11.3% in 3rd, as compared to 6.4% in 1st quartile) [Osadnik]
- Same increased risk for thromboembolic events in AF patients as that associated with low LVEF [Kurt]

RDW is also independently linked to excess mortality and other adverse outcomes in transcatheter aortic valve implantation (TAVI). [Aung-1, Connell, Magri]

RDW increases the likelihood of coronary syndrome X (chest pain with normal coronary arteries) as the cause of chest pain in patients not thought to be experiencing an ACS event. [Qing]

RDW ≥ 13.9% is an independent marker for multiple adverse findings, including increased mortality in Eisenmenger syndrome. [Yang-2]

Top quartile RDW increases the risk of all-cause death in survivors of out-of-hospital cardiac arrest. [Kim-1]

RDW is an independent marker for increased mortality in pulmonary hypertension. [Hampole, Rhodes]

RDW is a "strongly and independently" predictive marker for increased carotid intima-media thickness and coronary plaque based on ultrasonography. [Wen]

In one study, RDW was independently predictive of all-cause post-cerebral infarction mortality, with the risk rising 33% per 1% increase in RDW. [Kim-2] In another investigation, RDW in the top quartile had hazard ratios of 2.0 and 2.4 for all-cause and CV mortality, respectively. [Ani]

In 6,950 subjects in the US NHANES study, RDW correlated in a highly significant manner with ankle-brachial index (ABI) readings consistent with a diagnosis of lower extremity peripheral arterial disease (PAD). [Zalawadiya-3]

RDW Quartile	% ABI 0.9
1	4.2%
2	6.1%
3	10.3%
4	13.9%

These investigators described RDW as a "strong and independent marker" for 10-year risk of new onset PAD in another paper on the same study. [Zalawadiya-2]

In a Mayo Clinic study, 4th quartile RDW was associated with both low (≤ 0.9) and elevated (≥1.4) ABI. Elevated ABI results from artery compression and is highly predictive of future symptomatic PAD. [Ye]

Elevated RDW has a strong association with adverse findings and outcomes in a wide range of cardiac and circulatory contexts, and should be regarded as an independent risk marker in these settings.

RDW, Diabetes & Hypertension

RDW is independently associated with an increased risk of type 2 diabetes (T2DM). [Patel-1, Perlstein, Tonelli]

In a new study, Engstrom et al found that the 14-year risk of T2DM in 26,709 baseline nondiabetics was actually inverse to RDW, with a 48% greater risk in the 1st vs. 4th quartile. This is the only study we found in the entire literature review where low RDW was significant.

Until we have more data, the preponderance of evidence favors high RDW was a T2DM risk predictor.

Malandrino et al followed 3,497 diabetics and demonstrated a significant association between high RDW and the risk of major diabetic complications:

RDW Quartile	Hazard Ratios for Complications			
	MI	HF	Any Vascular	Nephropathy
1	1.0	1.0	1.0	1.0
2	1.7	2.4	1.3	1.3
3	2.5	2.4	1.6	1.2
4	2.5	4.4	2.1	2.3

They stated that "…the magnitude of the increased risk associated with high RDW levels is comparable to other established markers such as CRP and HbA1-c."

In a Japanese investigation, RDW ≥ 14% increased the risk of mortality 2.6-fold in diabetics followed for 4 years after an elective PCI for stable coronary disease. [Tsuboi]

High RDW is also predictive of elevated HbA1-c readings in both diabetics and nondiabetics. [Ramesh, Veeranna-1]

In prediabetics, as well as individuals predisposed to type 2 DM based on a positive family history, elevated RDW increases the probability of a future diabetes diagnosis. RDW also appears to be a marker for major diabetic complications and higher mortality.

Four studies show an increased risk of hypertension across subsets of RDW in both the general population and MI patients. [Perlstein, Tonelli, Wang-1, Zalawadiya-3]

Kilicasian et al have now demonstrated that RDW is a significant and independent marker for 4 different geometric patterns of LVH in middle-aged patients with untreated essential hypertension. They used a cut-off of > 14.5% to identify those with the highest probability of concentric hypertrophy and the other 3 recognized patterns.

If systolic blood pressure does not decrease nocturnally by at least 10%, this is referred to as "non-dipper" hypertension, and it is associated with adverse CV outcomes.

Two studies confirm that RDW of 14%+ is an independent marker for non-dipper hypertension. [Gunebakmaz, Ozcan-1]

RDW & Chronic Renal Disease

Chronic inflammation promotes abnormal mesangial cell proliferation and increased renal permeability. Because RDW is clearly a marker for inflammation,

nephrologists postulate that it should be associated with manifestations of chronic kidney disease. [Afonso]

In a study involving 8,585 outpatients, chronic kidney disease was "strongly and independently predicted by RDW," with or without anemia. [Lippi-3]

RDW Quartile	% eGFR < 60
1	5%
2	7%
3	11%
4	19%

Solak and coworkers reported that RDW > 13.5% was linked to:

- Reduced eGFR
- Reduced flow-mediate dilation (FMD), a marker for subclinical atherosclerosis
- Elevated carotid intima-media thickness
- Elevated CRP

Three investigations found that RDW was strongly associated with chronic kidney disease based on eGFR in community-dwelling subjects, as well as patients with known CAD or PAD. [Osadnik, Perlstein, Ye]

There is also a relationship between RDW and the odds ratio for developing microalbuminuria (MA). After full risk factor adjustment –including hemoglobin, MCV, B-12 and folate levels, iron and hs-CRP – the risk of MA increased across RDW quartiles: [Afonso]

RDW Quartile	Odds Ratio for Microalbuminuria
1	1.0
2	1.2
3	1.7
4	2.5

In kidney transplant recipients, RDW greater than the median was a univariate marker for 2.7-fold increased all-cause mortality. The multivariate adjusted risk was still significant at 1.3. [Musci]

RDW adds value as a marker for increased risk of chronic kidney disease.

RDW & Liver Disease

Underwriters often encounter cases of more common liver diseases such as nonalcoholic fatty liver disease (NAFLD) and chronic hepatitis B.

Any readily accessible and well-substantiated marker for progression of fibrosis and for developing life-threatening complications such as cirrhosis would be quite valuable in our risk assessments.

Cao and associates demonstrated an association between high RDW and fibrosis progression that they attribute to its link to ongoing inflammation.

Three studies document the impact of RDW in NAFLD.

- In a case-control study, RDW was an independent predictor of NAFLD and was recommended as a resource in NAFLD assessment algorithms. [Yang-1]
- After evaluating 24,547 Korean patients previously diagnosed with NAFLD, RDW ≥ 13.2% was a significant predictor of advanced fibrosis. The odds ratio for advanced fibrosis was 1.8, comparing subjects in the 1st vs. 4th RDW quartile. [Kim-4]
- Cengiz et al showed that RDW > 13.6% was a marker for nonalcoholic steatohepatitis (NASH) in NAFLD patients. The risk of advanced fibrosis was highest when RDW was 15.9% or higher.

Lou et al reported in a case-control study that "RDW values are significantly increased in patients with hepatitis B and associated with the severity."

	Mean RDW
Controls	13.0%
Acute HBV	14.4%
All chronic HBV	16.4%
Severe chronic HBV	18.3%

MELD Score is an algorithm for predicting chronic liver disease outcomes. In this study, there was a significant relationship between RDW and the odds ratio for a high MELD Score (odds ratio 2.5).

Cao et al found that RDW was independently associated with cirrhosis in HBV. Mean RDW was 13.4% in patients free of cirrhosis vs. 16.2% with cirrhosis on liver biopsy.

Maruyama and coworkers studied the association between RDW and alcoholic liver disease (ALD). RDW was significantly higher in subjects with known alcohol-incited pathology (17.1%), as compared to those with non-alcoholic related mechanisms (13.9%).

RDW was also a significant indicator of advanced (Child-Pugh 2/3) cirrhosis, and RDW decreased with alcohol abstinence.

Evidence to date suggests that high RDW could be used with AST:ALT ratio, platelet count and other variables to identify chronic liver disease cases with a heightened risk of advanced fibrosis and progression to cirrhosis.

RDW & Lung Disease

In a group of 8,175 subjects age 45 and older, the prevalence of chronic lung disease at baseline increased progressively across RDW quintiles. At a cutoff of > 14.1%, the prevalence was 19%, as compared to 12% in the 1st quintile. [Patel-1]

Among patients with PAD, the percentage with comorbid COPD increased across RDW quartiles from 13.6% in the 1st to 19.2% in the 4th. [Ye]

Grant and associates evaluated 1,616 subjects (ages 35 to 79) who were free of respiratory disease. Over the course of their study, they found a direct relationship between RDW and number of pack years of cigarette smoking, and an inverse association between both FVC and FEV-1 and RDW, which persisted after adjusting for smoking.

After performing pulmonary function tests on a cohort of automobile welders, Subhashee et al reported a statistically significant inverse relationship between RDW and FVC/FEV-1 ratio.

In idiopathic pulmonary fibrosis, median survival was 43 months when RDW was 15% or less, as compared to just 16 months at higher RDW levels. [Nathan]

Three investigations of the impact of RDW in patients with known COPD have been published to date:

- In 270 stable patients, RDW > 15% was independently predictive of right ventricular dysfunction and pulmonary hypertension, as well as mortality. [Seyhan]
- Sincer et al showed that mean RDW was higher (16.1%) in COPD patients vs. controls (13.6%), and RDW > 17.7% conferred an odds ratio of 2.1 for echocardiographic evidence of RV failure.
- The neutrophil-to-lymphocyte ratio (NLR) is an established predictor of COPD exacerbations. RDW was found to closely correlate with NLR in both stable and exacerbated COPD cases. [Gunay]

RDW shows promise as a marker for advanced disease and unfavorable outcomes in applicants with known/suspected COPD.

RDW & GI Disorders

RDW cannot distinguish between ulcerative colitis and Crohn disease. [Yesil]

However, 5 studies report that high RDW is associated with active inflammatory bowel disease in both anemic and non-anemic cases. [Cakal, Huang, Oustamanolakis, Song, Yesil]

RDW also plays a role in assessing celiac disease:

- In one study, RDW was elevated in 76% at diagnosis and decreased after 12 months if the patient remained on a gluten-free diet, with seroconversion of endomysial antibodies and

normalization of serum iron, B-12 and folate levels. [Mitchell]

- A second investigation confirmed the association between maintaining a gluten-free diet and progressive decline in RDW over 12 months. [Sategna Guidetti]
- When RDW was >17.25%, it was a predictor of intestinal atrophy (IA), and these researchers advocated using RDW as a surrogate marker for biopsy-proven IA. [Harmanci]

RDW & Cancer

We found 7 studies regarding RDW and cancer.

In 322 patients with unexplained cytopenias, RDW was a multivariate indicator of myelodysplastic syndrome (odds ratio 3.5) and was second only to patient age as a marker for MDS. [Buckstein]

We know that:

- The prevalence of MDS is increasing.
- It is often asymptomatic for years.
- We have few clues to assess MDS risk.

RDW may be a valuable resource in this context.

Seretis et al showed that RDW is significantly associated with larger primary breast cancers, as well as the number of positive lymph nodes.

Bell and coworkers found that elevated RDW was independently predictive of right colon tumors in 225 colon cancer patients.

Two studies demonstrated that RDW is a significant prognostic marker in lung cancer. [Koma, Warwick-2]

In patients with hairy cell leukemia, RDW > 18.8% was indicative of active disease, and it decreased with successful treatment. [Chrobak]

Beyazil et al investigated 194 patients with obstructive jaundice.

If RDW was > 14.8%, 68% had underlying cancer, as compared to just 27% at lower RDW levels. This association was highly significant after adjusting for other predictors.

It will be interesting to see if future studies better define the cancer-related implications of RDW. These early studies suggest it could have prognostic implications in potentially insurable cases.

RDW in Other Disorders

Sleep Apnea

In 137 subjects undergoing polysomnography, RDW was significantly higher in those diagnosed with obstructive sleep apnea (OSA), and RDW > 13.5% was independently predictive of comorbid CV disease (odds ratio 1.5). [Ozcu-1]

In a similar cohort, RDW > 15% was a marker for a high apnea-hypopnea index, significantly associated with severe OSA and inverse to oxygen saturation levels during sleep. [Sokucu]

DVT/Pulmonary Embolism

In the Malmo Diet and Cancer Study, the hazard ratio for developing deep vein thrombosis (DVT) was 1.7-fold greater in the 3rd and 4th RDW quartiles vs. the 1st quartile, and 2.5-fold higher in the top 5% of RDW readings. The authors concluded that RDW was an independent 14-year predictor of DVT risk. [Zoller]

In 702 patients with a pulmonary embolism (PE), the odds of dying increased sharply across RDW quartiles, and the recommended cutoff for a high risk of inpatient death was 15%. [Ozcu-3]

Zorlu et al reported similar findings in PE inpatients.

In 431 patients undergoing lower limb venous studies, RDW was the only independent predictor of DVT; it was also a marker for proximal vs. distal lesions. [Cay]

Systemic Lupus Erythematosus (SLE)

In 105 cases, high RDW was associated with increased levels of fibrinogen and CRP in non-anemic SLE patients. [Vaya-2]

Another study found that RDW correlated positively with CRP, ESR and extent of SLE activity. Treatment with glucocorticoids lowered RDW. [Hu]

Depression

May et al looked at 49,257 patients undergoing angiography for suspected CAD. After 5 years, there was a significant association between RDW and interim onset of clinically significant depression:

RDW Quartile	HR for Developing Depression
1	1.00
2	1.22
3	1.40
4	1.50
5	1.81

This association persisted when patients with a prior depression history were excluded.

Functional Dependence

In 120 nursing home patients, 3 markers were significant predictors of impaired physical function: RDW, interleukin-6 and soluble tumor necrosis receptor-1. [de Gonzalo-Calvo]

Dementia

Weuve et al evaluated 2,556 community-dwelling elders in the Chicago Health and Aging Project. The risk of developing dementia increased cross RDW quartiles. Likelihood of a dementia diagnosis was 42% greater in the 4th vs. 1st quartile and increased 6% for every 1% increase in RDW.

RDW was also significant in the following contexts:

- Predicting for cerebral sinus thrombosis in patients presenting with suspicious headache. [Demir]
- RDW > 14.7 correlated with a 77% increase in inpatient mortality in acute pancreatitis. [Senol]
- In emergency department patients with acute dyspnea of undetermined etiology, RDW > 14.3% increased 30-day mortality 2.3-fold and 1.3-fold in subjects with RDW of 12.9%-14.3% as compared to < 12.9%. [Hong]
- RDW was an independent predictor of the presence and severity of preeclampsia. [Keskin Kurt]
- RDW > 19% was a marker for thrombotic thrombocytopenic purpura. [Nagajothi]
- RDW was a significant predictor of high stage sarcoidosis, as well as a marker for disease progression. [Ozcu-2]

These studies provide early evidence that RDW is an important consideration in diagnosis, disease severity and/or prognosis across a wide range of impairments.

Future studies should enhance our understanding of the implications of elevated RDW in these and other contexts.

RDW in Surgery & Hospitalization

Among 898 subjects undergoing elective non-cardiac surgery, 30-day post-surgical outcomes were substantially worse in those with RDW in the 4th vs. 1st quartile: [Basha]

	Adjusted 30-Day Odds Ratios
Death	3.6
Acute Coronary Event	4.2
Arrhythmia	1.9
Heart Failure Hospitalization	4.1
Sudden Cardiac Death	4.2

These odds ratios were reported after adjustment for major risk factors, including those specifically related

to the surgical procedure.

In 9,538 hospitalized trauma patients in Salt Lake City, Utah, the likelihood of death within the ensuing 12 months correlated with RDW in a highly significant manner: [Majercik]

RDW Quintile	% Deceased at 12 Months	
	Men	Women
1	0.5%	0.5%
2	0.4%	2.1%
3	0.8%	3.0%
4	1.7%	4.2%
5	8.3%	8.8%

In a Boston-based follow-p of 74,784 consecutive discharged inpatients (no IUC cases), there was an upsloping mortality curve across RDW deciles. [Hunziker-1]

- » Mortality went up 1.24-fold per 1% increase in RDW.
- » Mean RDW was 14.6% in survivors vs. 16.5% in those who died.
- » Mortality was 0.2% in the lowest RDW decile vs. 4.4% in the highest 10% of readings, resulting in a multivariate odds ratio of 6.6.

Three additional studies showed significantly increased mortality in the same context. [Gonzalo-Calvo, Martinez-Velilla, Perez-Martin]

Two investigations report a close association between high RDW and 30-day and 90-day post-hospitalization mortality in patients with community-acquired pneumonia (CAP). [Braun-1, Lee-2]

In a brand new study, 3815 patients admitted for CAP, mean age 69, were followed for 90 days after discharge. RDW was linked to a 3-fold increase in 90-day mortality and after adjustment for all other markers including BUN, it remained significant (OR 1.50). [Braun-2]

Three other studies reveal a marked increase in death risk after ICU discharge based on high RDW levels at admission. [Hunziker-2, Oh-2, Wang-2]

Four teams of researchers reported increased mortality in sepsis patients with high RDW. [Jo, Kim-3, Ku, Sadaka]

In MI patients free of anemia at admission who subsequently developed anemia, RDW > 15% was an independent predictor of anemia arising during hospitalization, which in turn correlated with higher mortality. [Salisbury]

RDW could be a helpful marker in assessing otherwise insurable cases involving hospitalization and non-cardiac surgery.

RDW & All-Cause Mortality

"Red blood cell distribution width is likely a marker for chronic processes leading ultimately to a fatal outcome in inpatients and the general population."

Sabrina Hunzicker, MD, MPH, et al
Beth Israel Deaconess Medical Center, Boston
American Journal of Medicine
125(2012):283

The primary benchmark by which the value of an underwriting resource is ultimately measured is its impact on all-cause mortality.

We found 6 individual investigations and a 6-study metaanalysis that examined the all-cause mortality linked to elevated RDW in various populations and contexts. We will cite each of them briefly.

After following 225,006 members, ages 40 and older, of a large Israeli HMO (health maintenance organization) for 6 years, the following data were cited: [Arbel-2]

Hazard Ratio for All-Cause Mortality	
	RDW ≥17% vs. ≤13%
Men	3.26
Women	4.57

This is after full adjustment for risk factors. The hazard ratios were basically the same for anemic and non-

anemic patients.

In 119,530 emergency, inpatient and outpatient patients, mean age 55 and adjusted for age, gender, other CBC findings, etc., RDW had a significant link to all-cause mortality: [Muhlestein]

RDW Quintile	HR for All-Cause Mortality
1	1.00
2	1.12
3	1.33
4	1.64
5	2.66

Among 36,226 elderly patients followed in New York City outpatient clinics, RDW > 16.6% conferred a 1.9-fold increased mortality risk in anemic subjects and a much higher risk (3.7-fold) in those who were not anemic at baseline.

In non-anemic patients with macrocytosis (MCV > 100), the RDW hazard ratio was 7.8, compared to cases with anemia and MCV ≤ 100. [Lam]

In the 5-year JUPITER Study of 17,197 patients free of CV disease, Horne and coworkers used a multicomponent CBC score to assess all-cause mortality. The #1 predictor was RDW.

When RDW was in the 3rd tertile (15.3%+ in males and 14.9%+ in females), mortality was 46% greater as compared to the 1st tertile. [Horne]

Perlstein et al followed 14,310 community-based subjects, ages 20-80, for almost 9 years, and reported these highly-significant hazard ratios for mortality by RDW quintile:

RDW Quintile	Mortality Hazard Ratios			
	All-Cause	CV Disease	Cancer	Lung Disease
1	1.00	1.00	1.00	1.00
2	1.13	1.40	0.84	1.94
3	1.07	1.11	1.22	2.74
4	1.31	1.47	1.31	1.42
5	2.00	2.34	1.88	5.89

RDW was not a significant predictor of mortality due to external causes.

In a metaanalysis of 6 studies involving 11,309 elderly subjects, the hazard ratio for mortality increased 1.14 per 1% increment in RDW after full adjustment, including age, gender, medical history, conventional risk factors, eGFR, CBC and serum albumin. [Patel-2]

The death rate per 1000 person years was 37.5 when RDW was < 12.5, as compared to 109 at an RDW of 16 or higher, and the rate increased progressively at 7 levels of RDW between these extremes.

In the words of the authors: "…RDW is a newly-recognized and powerful predictor of mortality in community-dwelling older adults with and without major age-associated diseases."

Lastly, Garbharran and associates looked at mortality in 698 consecutive UK patients admitted with a hip fracture. Mean age was 78.

RDW Quartile	% Decreased in 12 months
1	12%
2	15%
3	29%
4	36%

These findings were independent of age, gender and other hip fracture risk factors.

It is clear that elevated RDW is a potent marker for excess mortality in adults, especially at older ages.

RDW & Underwriting

We have reviewed 202 studies and reports bearing on the association between elevated RDW and both mortality and morbidity risk.

Based upon what we now know about RDW, 12 summary observations are appropriate to put all of this in perspective:

1. RDW is reported in nearly all CBCs, and reference ranges will likely vary between laboratories.
2. The weight of current evidence suggests that RDW cannot be credibly reported using paramedically collected blood specimens. Nevertheless, industry laboratories should undertake further investigation of this question.
3. RDW is both a significant and independent risk marker in many contexts. For the most part, it is not redundant to other risk factors we use in underwriting.
4. The preponderance of the evidence cited here is consistent with the view that all elevated RDW readings confer excess mortality and morbidity risk.
5. Robust associations with cardiovascular disease (especially coronary artery disease) mortality and all-cause mortality in a general population setting provide the strongest evidence for the value of RDW in risk appraisal.
6. Evidence of its implications continues to accumulate, and more studies are now being done in North America and Europe.
7. Elevated RDW would appear to be incompatible with preferred risk status, especially considering that top quartile and quintile RDW readings are largely within the normal reference range.
8. It is likely that most clinical physicians know little or nothing about RDW other than in the context of the differential diagnosis of anemia.
9. RDW is "free" in the sense that there is no added out-of-pocket cost once we have secured medical records.
10. To make use of RDW, underwriters must take time to ferret out readings in medical records. Therefore, the decision to make use of RDW comes down to an insurer's priorities. Will they enhance the risk selection evidence at hand by encouraging underwriters to routinely check out RDW when reviewing medical records – or – will their preoccupation with productivity override this opportunity?
11. Firms doing outsourced APS summaries would be well served to report RDW elevations.
12. All underwriting manuals must have RDW underwriting guidelines.

Because 11 proactive firms stepped up to support us in this research, we now know what there is to know about RDW as a potential underwriting resource.

We will continue to track RDW in the medical literature and report on relevant new studies in our free monthly e-newsletter *Hot Notes*. Over 5,000 underwriters and other individuals in 52 countries read *Hot Notes*.

If you do not yet subscribe to *Hot Notes*, you may do so via this link: **hankgeorgeinc.com/HotNotes**.

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