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The early detection of anaemia and aetiology prediction through the modelling of red cell distribution width (RDW) in cross-sectional community patient data

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Abstract

Background: Red cell distribution width (RDW) is a marker of iron-deficient anaemia that can also assist differentiation of other anaemias. RDW also has been suggested as an effective marker for earlier anaemia detection. The RDW-anaemia relationship was investigated in cross-sectional community patient data, and the capacity of RDW to predict the diagnostic value of second tier anaemia markers assessed.

Methods: Routine and second tier assay data were provided by the laboratory Sullivan Nicolaides Pathology. The cohort was divided into male and female groups stratified by age, and correlation analyses assessed associations of RDW to haemoglobin and ferritin. Analysis of covariance (ANCOVA) was performed for both routine and second tier markers to investigate their significance for RDW prediction.

Results: RDW had statistically significant negative correlation with haemoglobin for both sexes and age ranges ($p<0.01$). The RDW relationship with serum ferritin was non-linear, representing two populations. ANCOVA showed categorical ferritin as a significant RDW predictor for younger females, with vitamin B12 a significant RDW predictor for older men. Haemoglobin, mean corpuscular haemoglobin (MCH) and second tier iron markers (e.g., transferrin) were significant RDW predictors for both sexes and ages investigated. An individual longitudinal female case study showed RDW as very sensitive to haemoglobin decrease, with ferritin not as responsive.

Conclusions: RDW had a significant negative association with haemoglobin in cross-sectional community patient data. ANCOVA showed ferritin as a significant RDW predictor for younger females only. This study confirms the utility of RDW as a marker for early anaemia detection, and useful to accelerated diagnoses of anaemia aetiology.

Keywords: aetiology; anaemia; ANCOVA; ferritin; red cell distribution width (RDW).

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Introduction

Red cell distribution width (RDW) is the standard deviation or coefficient of variation percent (CV%) of the red blood cell (RBC) volume that is determined by an automated haematology analyser, calculated from the mean corpuscular volume (MCV). Erythrocytes are typically 6–8 μm in diameter, and for some anaemias there are significant variations in cell size. Higher RDW values indicate greater variation in red cell size (anisocytosis) [1], which is caused by problems with the production or destruction of the erythrocytes. RDW is used with other full blood count/complete blood count (FBC/CBC) indices to diagnose anaemia, and if indicated, additional specialised second

tier tests of iron metabolism and storage (e.g., ferritin), and nutritional markers (e.g., vitamin B12), will be requested to classify the cause of the anaemia and guide subsequent treatment. The RDW is elevated in macrocytic anaemias and nearly all cases of iron deficiency anaemia (IDA), and has been found as valuable for differentiating thalassaemia from iron deficiency [2].

However, an elevation in the RDW is not characteristic of all anaemias, for example, the anaemia of chronic disease, hereditary spherocytosis, acute blood loss, aplastic anaemia, and certain hereditary haemoglobinopathies present with a normal RDW [3]. RDW has been also associated with the estimation of mortality due to cancer, heart or respiratory disease, as well as "all cause" mortality, for intensive care and other patients [4–6], as well as liver and renal conditions [1, 7], suggesting a wider diagnostic utility beyond anaemia.

A clinical update by Dugdale [8] reported an inverse relationship of RDW (CV%) with haemoglobin concentration that developed over several months, and noted that increases in RDW preceded clinically significant haemoglobin decreases by several weeks, hence proposing that RDW be considered as a valuable routine marker for the early detection of iron-deficient anaemia (IDA). In addition, it was suggested that while ferritin and folate are "gold-standard" tests for anaemia, these second tier tests are "complex and expensive", while RDW can be easily calculated from routine haematology profiles at no additional cost. Motivated by this observation, the aims of this study were to validate the RDW/Haemoglobin relationship in a large cohort of community patients, and secondly investigate whether RDW had significant associations with second tier anaemia tests in males and females of reproductive and post – reproductive age ranges. As a practical laboratory diagnosis consideration, the potential for RDW to provide a specific anaemia diagnosis without resort to expensive and time consuming second tier tests, was of additional interest.

Materials and methods

Data

Cross-sectional pathology data from female and male community patients were provided by the diagnostics laboratory, Sullivan Nicolaides Pathology (Brisbane, Australia) and represented individuals investigated for anaemia over August – September 2012. Routine full blood count (FBC/CBC) profiles and second tier laboratory tests associated with the investigation of anaemia were included; specifically serum ferritin, serum iron, vitamin B12, red cell folate (RCF), transferrin and saturation. Laboratory reference ranges for routine and second tier anaemia markers are listed in Table 1. Results for routine markers were collected on the Sysmex XE2100 platform (Roche Diagnostics, Sydney), while ferritin, serum iron were measured on the Roche Modular (Roche Diagnostics, Sydney Australia).

Table 1: Reference intervals for all routine erythrocyte indices and second tier tests conducted for anaemia investigations included in the analyses of RDW variation by ANCOVA.

Red cell markers (explanatory variables)	Laboratory reference range	
	Male	Female
Routine red cell markers		
Haemoglobin (Hb)	125–175 g/L[a]	110–165 g/L[a]
Haematocrit (Hct)	0.38–0.54[a]	0.34–0.47[a]
Mean corpuscular volume (MCV)	80–100 fL	80–100 fL
Mean corpuscular haemoglobin (MCH)	27.5–34 pg	27.5–34 pg
Mean corpuscular haemoglobin concentration (MCHC)	310–360 g/L	310–360 g/L
Red cell count (RCC)	$4.2–6.5\times10^{12}$/L[a]	$3.7–5.6\times10^{12}$/L[a]
Special, second tier tests for anaemia investigation		
Ferritin	25–220 ng/mL	25–10 ng/mL
Serum Iron	5–30 µmol/L	5–30 µmol/L
Saturation	20–55%	20–55%
Transferrin	445–472 µmol/L	445–472 µmol/L
Red cell folate (RCF)	>150 nmol/L	>150 nmol/L
Serum Folate	>7.0 nmol/L	>7.0 nmol/L
Vitamin B12 (VitB12)	>150 pmol/L	>150 pmol/L
Red cell distribution width (RDW) (Response variable)		11–16% (CV%) 30–50 fL (SD)

[a]Reference interval applies to an age range of 14–>100 years for males and females.

From the total cases provided (n=8760), data were selected in the age range of 15–50 years and then separated into female (n=1770) and male (n=686) cases. From this, data were further sorted into cases that comprised both routine and second tier blood test data required for investigation of anaemia in individual female (n=744) and male (n=215) cases. An identical process was performed for female and male cases of 55 years of age and older (total number of cases investigated were: females: n=1892; males: n=1076).

Human Ethics approval for this project was granted by Committees from both Bond University and The Australian National University.

Statistical analysis

Pearson's correlation was performed for the analysis of RDW and haemoglobin relationships. Correlation analysis of the RDW vs. serum ferritin relationship was conducted by the non-parametric Spearman's correlation method, given the non-linear relationship between these two variables.

All investigations of RDW variation were conducted by analysis of covariance (ANCOVA) with ferritin assigned as a fixed binary factor; female ferritin category thresholds were set at less or greater than 40 ng/mL, and male thresholds at less or greater than 100 ng/mL, informed by scatter plots that showed a "broken stick", "hockey stick" or piecewise linear relationship between RDW and linear serum ferritin, which was particularly pronounced for young females.

Separate ANCOVA were performed for routine erythrocyte indices and second tier anaemia markers. Haemoglobin, linear serum ferritin and binary ferritin category were included as predictor variables for all analyses. Prior to ANCOVA, colinearity among predictor variables was assessed by Pearson's correlation (two-tails) and variation inflation factor (VIF), with highly colinear predictor variables (VIF>10) removed from the model before analysis (MCV was not included as a predictor variable for any analysis). All correlations and ANCOVA were performed using SPSS version 21.

Results

RDW relationship to haemoglobin and ferritin

Pearson's correlation analysis of RDW in relation to haemoglobin (Hb) was conducted for females and males of both age ranges examined. Supporting the previous observation by Dugdale [8], Hb had a significant negative association ($p<0.01$) with RDW for each sex and age range examined (Figure 1A–D). The majority of individuals within each community population examined fell inside the reference ranges for both RDW and haemoglobin, as seen as a tight cluster for each scatterplot. The plots also detected occasional individual cases that had normal haemoglobin but elevated RDW, or low haemoglobin and RDW within the reference range, suggesting other disorders besides iron-deficient anaemia [9, 10]. The strength of correlation (r) ranged between −0.38 to −0.43 for both female groups and older males, with younger (15–50 years) males weaker than −0.30.

As the "gold-standard" for the diagnosis of iron deficient anaemia (IDA), serum ferritin was considered carefully as a predictor of RDW variation. For females and males of >55 years, and females between 15 and 50 years, significant ($p<0.001$) negative correlations ($r=-0.14$–0.29) were found for RDW and ferritin. A weaker, but significant negative correlation was also found for 15–50 years males ($r=-0.15$; $p=0.031$). Plots of RDW and ferritin (Figure 2A–2D) showed non-linear relationships, particularly for both female cohorts, and suggested two distinct subpopulations of ferritin response in relation to RDW measurement, defined by a greater range of RDW responses for ferritin concentrations less than 40 ng/mL. For subsequent ANCOVA, binary ferritin category was introduced into the RDW models to control for the two distinct populations. The impact of ferritin for the RDW models presented is summarised in Tables 2 and 3.

Determination of RDW variation predictors by ANCOVA models examining routine red cell indices and second tier tests for anaemia diagnosis

ANCOVA modelling showed strong associations between RDW and Hb, red cell count and MCHC for both sexes and age ranges, with age also strongly associated with RDW for females of both age ranges and males greater than 55 years of age (Tables 2 and 3). Model adjusted R^2 values ranged between 0.311–0.403 for female and male RDW models of routine red cell markers and ferritin, but were weaker for models of ferritin, haemoglobin and second tier anaemia markers, ranging from R^2 0.058 to 0.258. Caution must be exercised particularly when interpreting second tier models for men ranging in age from 15 to 50 years ($R^2=0.058$) and women greater than 55 years of age ($R^2=0.100$).

The gold-standard special test for iron-deficient anaemia, serum ferritin, was examined in ANCOVA models as both a linear and categorical predictor variable due to its curved distribution pattern in relation to RDW (Figure 2). Ferritin was a significant predictor of RDW only for females in the 15–50 year age group, and only as a categorical predictor variable. Neither linear nor categorical ferritin showed a significant relationship with RDW for women older than 55 years, or males of either age range

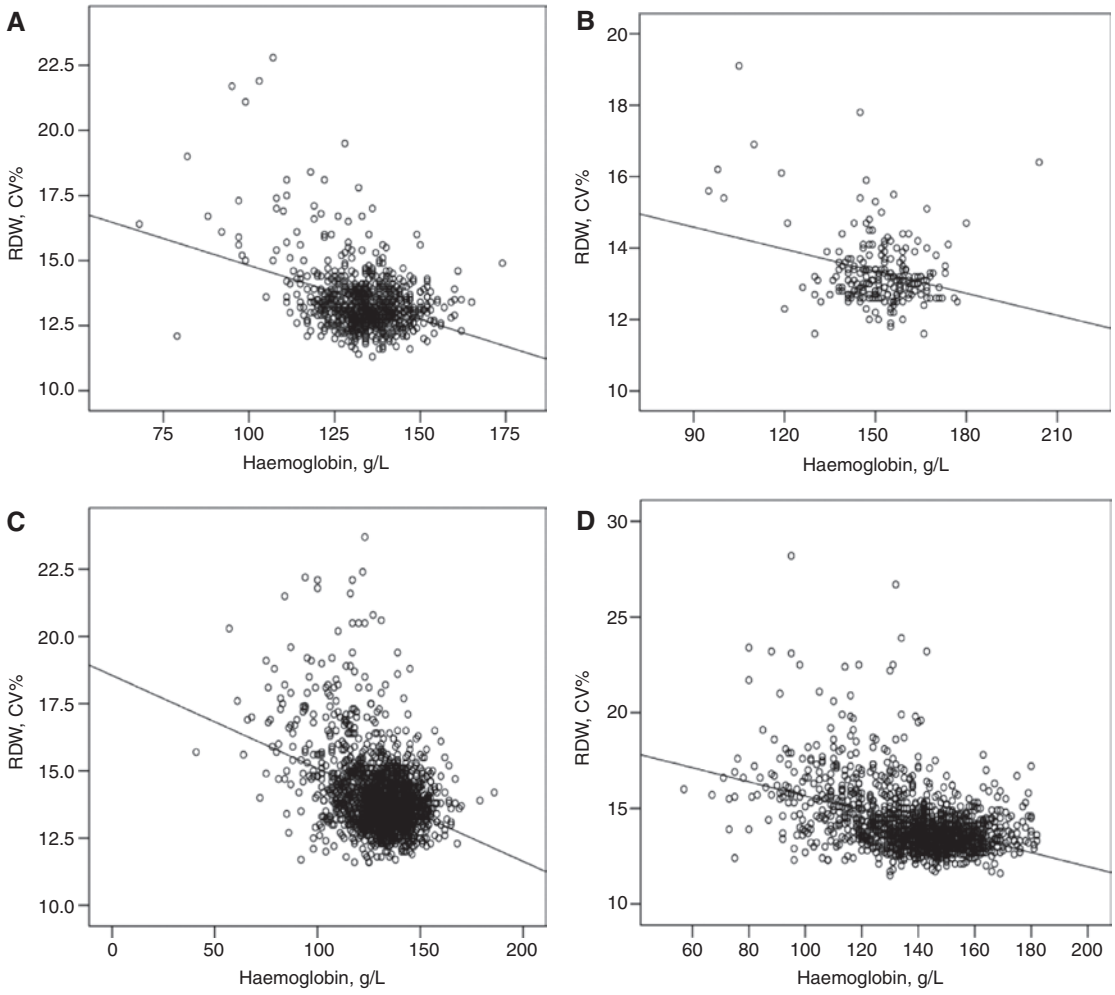

Figure 1: Red cell distribution width (RDW) relationship with haemoglobin measurement for a sample of (A) 15–50-year-old female (r=−0.38: p<0.01: n=744), (B) 15–50-year-old male (r=−0.28: p<0.01: n=215), (C) 55 years and older female (r=−0.39: p<0.01: n=1892), and (D) 55 years and older male (r=−0.43: p<0.01: 1076) community patients presenting for a laboratory investigation of anaemia. Collected from individual patients over August–September 2012 (Queensland, Australia).

(Tables 2 and 3). The results suggest therefore, that ferritin should be considered as a leading primary diagnostic test for women of reproductive age, and not for men and post-menopausal women.

Additional second tier measures of iron status (serum iron, saturation, transferrin) were also considered for ANCOVA models. Transferrin and serum iron measurements were significant RDW predictors for both male cohorts and women from 15 to 50 years of age, but not older women. Vitamin B12 and red cell folate (RCF) were also included in ANCOVA models, and confirming the primacy of RDW as a marker for iron-deficient anaemia, in general were not significant RDW predictors. However, vitamin B12 was found as a very significant (p=0.001) RDW predictor for men aged 55 years and older, possibly extending the diagnostic capacity of RDW beyond iron deficiency for older men.

A longitudinal case study of RDW, haemoglobin, MCV and ferritin interaction

Figure 3 shows the temporal comparison of RDW, Hb, ferritin and MCV over approximately 34 months (December 2009 to September 2012) for an individual female community patient (42 years old). In agreement with the previous observation [8, 9], RDW increased above 15% with a subsequent accelerating decrease of routine Hb measurements, as RDW continued to increase. The kinetics of MCV followed an almost identical pattern to haemoglobin for this patient. Ferritin was a slow responder compared to the kinetics of RDW, Hb and MCV. From an initial serum level of 73 ng/mL (24th February 2010), ferritin dropped to a range of 5–8 ng/mL for 17 months, recovering to 20 ng/mL by early 2012, but not to within the reference interval in spite of Hb, MCV and RDW recovering to within reference interval

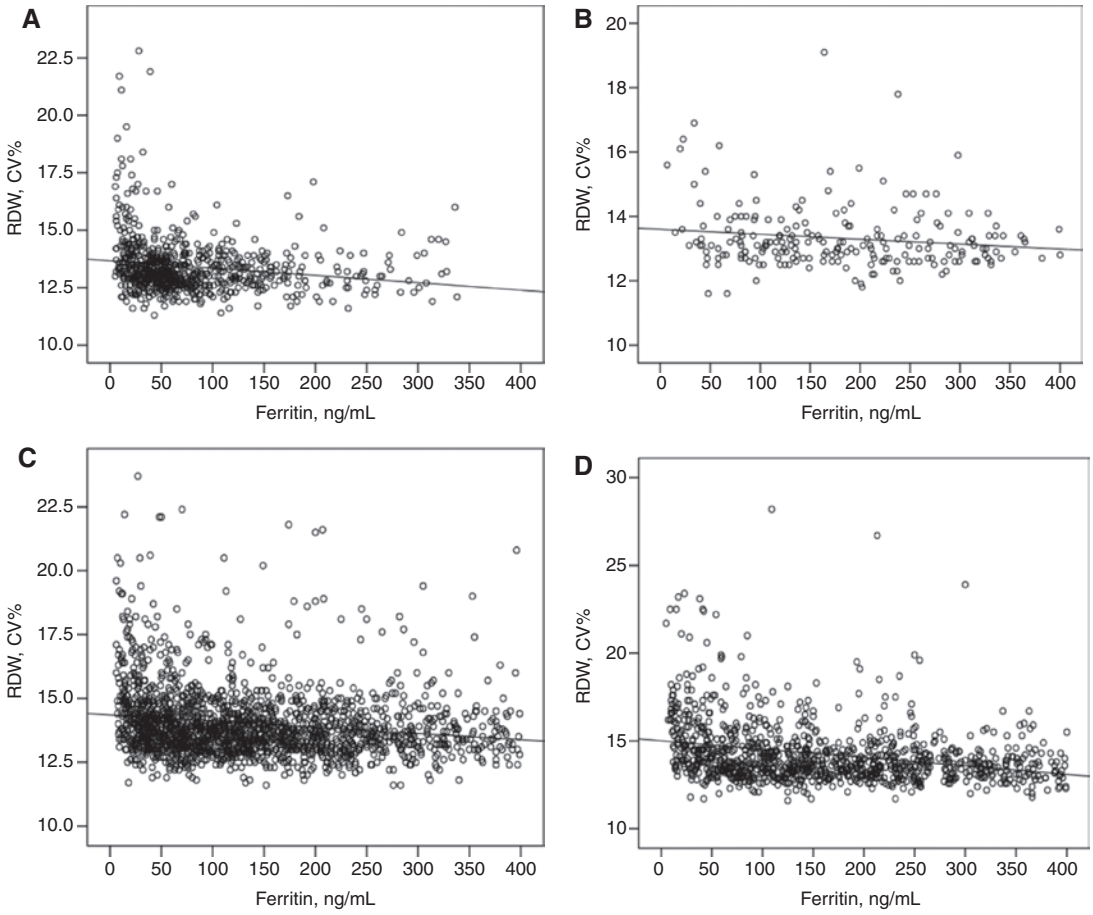

Figure 2: Red cell distribution width (RDW) relationship with serum ferritin measurement for a sample of (A) 15–50-year-old female (r=−0.17: p<0.001: n=744), (B) 15–50-year-old male (r=−0.15: p=0.031: n=215), (C) 55 years and older female (r=−0.14: p<0.001: n=1892), and (D) 55 years and older male (r=−0.28: p<0.001: n=1076) community patients presenting for a laboratory investigation of anaemia. Collected from individual patients over August–September 2012 (Queensland, Australia).

concentrations (Table 1). When RDW reached its peak of 32.6%, haemoglobin and MCV concentrations were recovering towards healthy, non-anaemic values. The next round of tests, conducted 8 months after the RDW peak, reported all red cell indices and RDW within their specific reference intervals, with corresponding serum ferritin measured at 20 ng/mL. Presumably therapy was attempted for this patient that may explain aspects of the observed red cell and iron marker kinetics, but clinical notes were not available to comment with certainty.

Discussion

The analyses presented confirmed Dugdale's previously reported relationship between increasing RDW and decreasing Hb [8], but in cross-sectional data representing hundreds of community patients. This was further explored and confirmed by a longitudinal case study (Figure 3) that demonstrated the inverse relationship between RDW and Hb over time, as well as the associated long-term perturbations of MCV and serum ferritin for the same female community patient. The long term, longitudinal kinetics of RDW with other routine and second tier markers were performed on several female community patients, with various response patterns identified; the further analysis of these RDW kinetics will be the subject of a separate future investigation.

The capacity of routine RDW measurements to predict the importance of second tier anaemia markers (e.g., ferritin, vitamin B12), and hence likely anaemia aetiology, was the subject of ANCOVA. The observation that RDW had a broken stick distribution in relation to serum ferritin necessitated the choice of ANCOVA, rather than linear regression, since ferritin could be introduced as a categorical variable in an analysis that included several continuous predictor (explanatory) variables [11], and thus controlled for the impact of the non-linear RDW-ferritin

Table 2: ANCOVA modelling of red cell distribution width (RDW – CV%) variation for females aged between 15 and 50 years or 55 years of age and older using (a) age, mean corpuscular haemoglobin concentration (MCHC), red cell count (RCC), or (b) second tier laboratory assays for anaemia investigation as explanatory variables. All models (a–b) included haemoglobin, linear ferritin values and binary ferritin categories (0, 1)[a] as explanatory variables. Mean corpuscular volume (MCV) was not included in any investigation since it was used to calculate RDW.

(a) Explanatory variables	Females: 15–50 years of age (Model adjusted R^2=0.403)			Females: ≥55 years of age (Model adjusted R^2=0.311)		
	F	p-Value	Partial η^2	F	p-Value	Partial η^2
Haemoglobin	112.27	<0.001	0.132	119.31	<0.001	0.060
Ferritin (linear)	0.47	0.495	0.001	0.15	0.702	<0.001
Ferritin (category)	7.99	0.005	0.011	1.13	0.289	0.001
Age	49.14	<0.001	0.063	18.56	<0.001	0.01
MCHC	29.52	<0.001	0.039	162.80	<0.001	0.08
RCC	106.00	<0.001	0.126	65.60	<0.001	0.034
(b) Explanatory variables	**Females: 15–50 years of age (Model adjusted R^2=0.220)**			**Females: ≥55 years of age (Model adjusted R^2=0.10)**		
	F	p-Value	Partial η^2	F	p-Value	Partial η^2
Haemoglobin	56.94	<0.001	0.072	17.26	<0.001	0.025
Ferritin (linear)	0.424	0.515	0.001	0.23	0.635	<0.001
Ferritin (category)	8.30	0.004	0.011	0.41	0.523	0.001
Serum iron	37.563	<0.001	0.049	28.59	<0.001	0.041
Transferrin	18.43	<0.001	0.024	1.62	0.203	0.002
Red cell folate	0.005	0.942	<0.001	1.53	0.217	0.002
Vitamin B12	0.238	0.626	<0.001	3.16	0.076	0.005

[a]Ferritin categories: 15–50 years of age (Category 0=5–40 ng/mL) (n=240): (Category 1=41–350 ng/mL) (n=504). ≥55 years of age (Category 0=6–40 ng/mL) (n=301): (Category 1=41–399 ng/mL) (n=1505).

Table 3: ANCOVA modelling of red cell distribution width (RDW) variation for males aged between 15 and 50 years or 55 years of age and older using (a) age, mean corpuscular haemoglobin concentration (MCHC), red cell count (RCC), or (b) second tier laboratory assays for anaemia investigation as explanatory variables. All models (a–b) included haemoglobin, linear ferritin values and binary ferritin categories (0, 1)[a] as explanatory variables. Mean corpuscular volume (MCV) was not included in any investigation since it was used to calculate RDW.

(a) Explanatory variables	Males: 15–50 years of age (Model adjusted R^2=0.363)			Males: ≥55 years of age (Model adjusted R^2=0.394)		
	F	p-Value	Partial η^2	F	p-Value	Partial η^2
Haemoglobin	14.62	<0.001	0.066	120.67	<0.001	0.101
Ferritin (linear)	0.270	0.604	0.001	1.78	0.182	0.002
Ferritin (category)	0.170	0.680	0.001	0.614	0.433	0.001
Age	1.92	0.168	0.009	14.62	<0.001	0.013
MCHC	35.33	<0.001	0.145	50.59	<0.001	0.045
RCC	23.56	<0.001	0.102	89.31	<0.001	0.077
(b) Explanatory variables	**Males: 15–50 years of age (Model adjusted R^2=0.058)**			**Males: ≥55 years of age (Model adjusted R^2=0.258)**		
	F	p-Value	Partial η^2	F	p-Value	Partial η^2
Haemoglobin	0.32	0.571	0.002	27.84	< 0.001	0.079
Ferritin (linear)	0.17	0.685	0.001	0.92	0.338	0.003
Ferritin (category)	0.34	0.561	0.002	0.45	0.504	0.001
Serum iron	6.23	0.013	0.031	11.81	0.001	0.035
Transferrin	7.16	0.008	0.036	8.59	0.004	0.026
Red cell folate	0.22	0.639	0.001	0.09	0.768	< 0.001
Vitamin B12	2.65	0.106	0.014	12.15	0.001	0.036

[a]Ferritin categories: 15–50 years of age (Category 0=7–99 ng/mL) (n=55): (Category 1=100–400 ng/mL) (n=159). ≥55 years of age (Category 0=5–99 ng/mL) (n=379): (Category 1=100–400 ng/mL) (n=695).

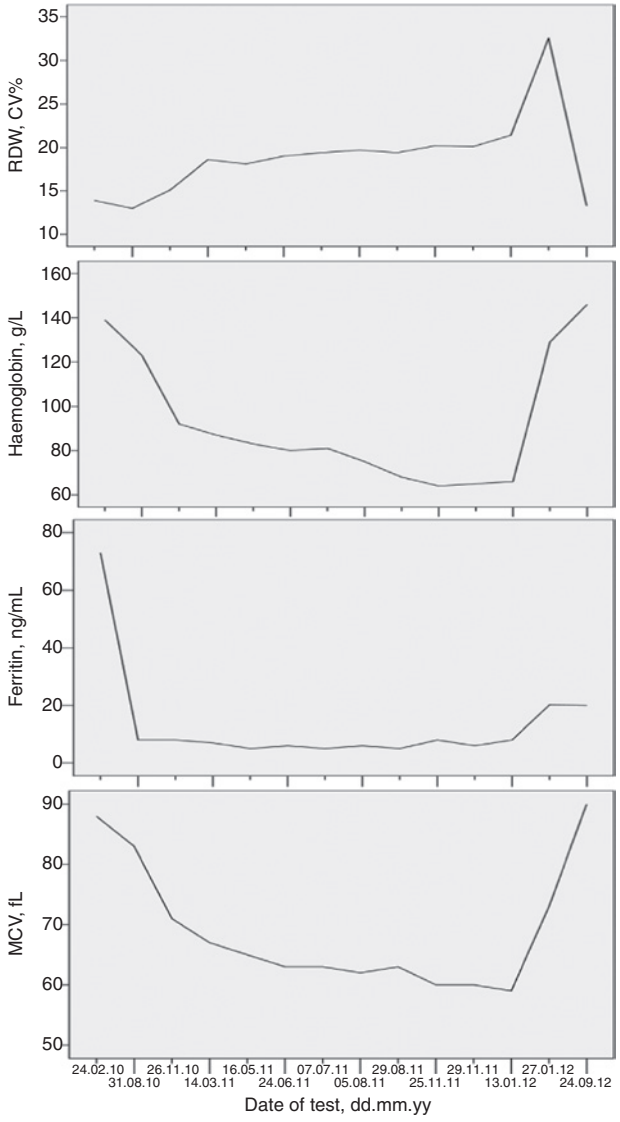

Figure 3: The longitudinal comparison of RDW, haemoglobin, ferritin and MCV variation over 34 months (from December 2009 to September 2012) for an individual female community patient (42 years old). Each time point represented had all four markers measured on the same day. No clinical notes were available to assist interpretation of the data, for example, if an anaemia therapy was commenced during the period presented.

relationship. As a predictor of RDW, ferritin was only statistically significant for younger (15–50 years) women, and confirming the choice of ANCOVA, was only significant as a categorical, not linear, predictor variable. Serum ferritin was not a significant RDW predictor for older women (>55 years), nor men of either age range investigated. Serum iron and transferrin were consistent RDW predictors among the second tier tests (but transferrin was not significant for >55 years women). The strong correlation between these iron sufficiency markers and RDW is well known [12], however the low correlation with transferrin in the older group has not been reported previously. In general, RCF and vitamin B12 were not significant predictors of RDW variation, however, vitamin B12 was found as a significant RDW predictor for men of 55 years of age or older; a previous study has supported RDW sensitivity to detecting B12 deficiency [13]. This male sex and age connection of RDW with vitamin B12 warrants further investigation as it may reflect wider health concerns for older men, for example nutritional status and associated behaviours.

Beyond anaemia diagnosis, there is compelling evidence that RDW is also valuable for other health conditions, with a particularly strong interest in RDW and cardiac disease, and longer-term implications for subsequent morbidity and mortality. RDW has been reported to be a prognostic marker in chronic heart failure [14] with an increased morbidity and mortality of an adjusted hazard ratio of 1.17 per 1 SD above normal [15]. Of additional interest to cardiac health and morbidity/mortality was the useful role of RDW when monitoring patients post ST elevation infarction [16], and for outcomes post cardiac catheterisation [17], as well as a range of other cardiac assessments, including acute myocardial infarction in young patients [18–21]. There has been evidence that the RDW may predict mortality in newly hospitalised patients, critically ill patients and in older community patients [4, 22–25], with RDW also a marker of diabetes in the elderly through a HbA1c association [26]. Increased RDW also may be a useful marker for the assessment of liver function, with associations noted for both non-alcoholic steatohepatitis and fibrosis [27], and HBV induced liver cirrhosis [28]. Underpinning RDW associations with the diverse array of disease is a likely link to increased inflammation [3, 29] and disrupted erythropoiesis. RDW has been suggested as a marker of oxidative stress or physiological reserve [25], which suggests that under acute cellular stress and resultant tissue hypoxia, there would be increased production and release of mature erythrocytes into the peripheral blood stream. The release of large immature red cells with poor oxygen binding capacity would lead to increasing RDW that implies a suboptimal response to oxidative stress, and a poor clinical outcome. Investigating the role of inflammation in coronary heart disease, studies have combined RDW with C-reactive protein (CRP) to enhance mortality prediction [30, 31].

As previously observed [8], RDW has a significant negative correlation with haemoglobin that provides for the early detection of iron-deficient anaemia (IDA) well in advance of clinically significant decreases in longitudinal Hb measurements, but often is not presented routinely on

laboratory reports. In further exploring the utility of RDW for early detection of anaemia, ANCOVA models were conducted on cross-sectional community patient data to assess whether RDW also could give early indications of anaemia aetiology, and perhaps reduce the need to perform additional second tier tests. As the gold-standard second tier test for IDA, serum ferritin was included in all ANCOVA with separate models conducted for routine and second tier test covariates, in data stratified by age and sex. Interestingly ferritin was not universally significant, with some variations in RDW predictor patterns found for different age and sex. RDW can be elevated in the absence of iron, folate or B12 deficiency, blood loss or haemoglobinopathies [11]. In evaluating RDW as an early marker for anaemia and its cause, several other health conditions that alter RDW need to be considered as well, which could be eliminated by access to clinical notes and other laboratory results (e.g., troponin); this study did not have access to clinical notes to screen for cardiac or other comorbidities that influence RDW. From the results presented here, RDW variation for younger women (15–50 years) was largely explained by iron-deficiency, whereas the significance of RDW in the older cohorts may be more closely associated with immune/inflammatory function connected with physiological stress, and disordered haematopoiesis.

In a broader conceptual sense, this study demonstrated the value of looking at routine laboratory results as a total marker network, rather than only specific tests that are traditionally considered to be directly diagnostic for a disease. Subtle changes in laboratory result patterns, including changes within a reference interval, may reveal insights into pathological processes dictated by relationships with other disease markers in data networks investigated. Results from this and similar studies, once validated will augment laboratory diagnosis, as well as possibly modify the need for second tier testing with some health conditions.

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