Incidence and significance of an elevated red blood cell distribution width among hospitalised HIV-infected adult patients

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Short title: RDW in hospitalised HIV infected adults

Key words: red blood cell distribution width, anisocytosis, inflammation, malignancy, outcome, HIV infection

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Word count: Abstract = 200

Text = 1022

Abstract

We audited the records of unselected hospitalized HIV-positive adults admitted to a University-affiliated inner London hospital to identify the frequency of elevated red blood cell distribution width (RDW), and potential associations with specific diagnoses, and with outcome. Of 259 patients audited, 188 (73%) were men. Patients' median age was 47 years (interquartile range: IQR =41-54). An elevated RDW was seen in 50 patients (19%); 200 (77%) had an elevated CRP, and 77 (30%) had a low haemoglobin. Only five patients had an elevated RDW without an elevated CRP and/or low haemoglobin. An elevated RDW was associated with a wide range of infectious, inflammatory and malignant conditions similar to observed associations reported in the general non-HIV infected adult population. Additionally an elevated RDW occurred both in patients with well-controlled HIV infection and in receipt of antiretroviral therapy, as well as in those with newly-diagnosed and poorly-controlled infection. Five (10%) of 50 patients with an elevated RDW needed ICU admission and two (4%) died. Two (0.95%) of 209 patients with a normal RDW needed ICU admission and four (1.9%) died. The findings of this audit are limited by the relatively small number of patients and the single site nature of the audit.

Introduction

The red blood cell distribution width (RDW) is a measure of the heterogeneity in erythrocyte size and is routinely performed as part of a full blood count.[1] An increase in RDW, called anisocytosis, reflects an increased variation in red blood cell (RBC) size resulting from the presence of small or large RBCs, or both. Anisocytosis can result from nutritional deficiency, including vitamin B_{12} and folate deficiency (large RBC), iron deficiency (small RBC), and in malignancy or chronic inflammation, resulting in anaemia of chronic disease. There is increasing interest in the role of RDW as a biomarker for inflammatory states[2] and as a prognostic tool. Studies indicate an elevated RDW is an independent predictor of adverse outcomes among patients with cardiac failure,[3] infective endocarditis,[4] cerebrovascular disease,[5] all cause renal disease,[6], acute exacerbations of chronic obstructive pulmonary disease,[7] empyema,[8] and haematological malignancy.[9] Additionally, an elevated RDW is a predictor of mortality in older patients,[10] post-operative patients,[11] and critically ill patients in the intensive care unit (ICU).[12] By contrast, the significance of an elevated RDW in HIV-positive adults is less well understood. An association between elevated RDW and poor outcome from pneumonia,[13] and increased risk of cardiovascular disease[14] is described in HIV-positive individuals. We audited the records of hospitalized HIV-positive adults to identify the frequency of elevated RDW, and associations with specific diagnoses, and outcome.

Methods

A retrospective audit of electronic records of consecutive unselected HIV-positive adult patients hospitalised between 01 March 2015 and 30 April 2017 at the Royal Free London, a provider of HIV care for 3700 HIV-positive adults. Data collected included patient demographics (age, gender), CD4 count, HIV viral load, if in receipt of antiretroviral therapy (ART), admission blood RDW (elevated, >16%), haemoglobin (low, <110 g/L), CRP (elevated, ≥5 mg/L), need for ICU admission, outcome: survival, or death (during hospitalization, or within 3 months of discharge from hospital) and final diagnosis. A comparison of those with elevated and normal RDW who were either admitted to ICU or who died was done using a

two-tailed Fisher exact test (GraphPad Prism Version 6.0h for Mac OS X: GraphPad Software, L Jolla, California, USA).

Results

Of 259 patients, 188 (73%) were men. Patients' median age was 47 years (interquartile range: IQR =41-54). Two hundred (70%) were taking ART and 141 had an undetectable viral load (<40 copies/ml); median CD4 count was 409 cells/mm^3 (IQR =197-641). Fifty-nine were not taking ART; median CD4 count was 80 cells/mm^3 (IQR =28-280).

An elevated RDW was seen in 50 patients (19%), 200 (77%) had an elevated CRP, and 77 (30%) had a low haemoglobin. The relationship between these abnormalities is shown in Figure 1. In 45 of 50 patients with an elevated RDW it occurred either with a raised CRP (14), a low haemoglobin (4), or both (27). Five patients had an elevated RDW without an elevated CRP or low haemoglobin. An elevated RDW was observed in 15/71 (21.1%) of women and 35/188 (18.6%) of men. Table 1 shows diagnoses in the 50 patients with an elevated RDW, with and without a raised CRP, low haemoglobin, or both. A wide variety of bacterial, viral and fungal infections, non-infectious inflammatory conditions and malignancy were observed, as well as an elevated RDW being seen in patients with poorly-controlled HIV infection and those not in receipt of ART, who did not have infectious, inflammatory, or malignancy co-pathology. Diagnoses among 209 patients with a normal RDW were similar, including infectious, inflammatory and malignant conditions.

Five (10%) of the 50 patients with elevated RDW required ICU admission and two (4%) died in hospital. By contrast two of 209 (0.95%) with a normal RDW needed ICU admission and four (1.9%) died (two in hospital, two within three months of hospital discharge): p =0.004 and p =0.337, respectively: two-tailed Fisher exact test.

Discussion

This audit identified that almost 20% of unselected HIV-positive adults admitted to a University-affiliated specialist hospital had an elevated RDW. An elevated RDW was

associated with a wide range of infectious, inflammatory and malignant conditions, similar to observed associations reported in the general non-HIV infected adult population.[3-9] Among unselected adults hospitalised with general medical conditions an elevated RDW was identified in 31.7% (186 of 586), and in the majority was associated with infectious, or inflammatory conditions.[15]

Most patients with an elevated RDW also had a low haemoglobin and or an elevated CRP, but an elevated RDW in isolation occurred in a small number of patients with a variety of conditions. Patients with elevated RDW included those with well-controlled and poorly-controlled HIV infection, and others with newly-diagnosed infection and who were not in receipt of ART. In a recent analysis of the Hawaii Ageing with HIV-Cardiovascular Study of ART-treated adults, an elevated RDW, and systemic inflammatory biomarkers including fibrinogen, D-dimer and CRP were associated with CD8+ T-cell populations related to immune activation and exhaustion (but not senescence).[16] This suggests that even among ART-treated patients HIV induces a persistent inflammatory state and that elevated RDW is a marker of immune dysregulation as well as being a marker of anaemia and/or intercurrent infection, inflammatory conditions, and malignancy.

There was an association between an elevated RDW and a patient's need for ICU admission, but not with mortality. This latter observation contrasts with previous studies showing an association between elevated RDW and mortality,[3-12] but this audit is limited by the relatively small number of patients and by its single site nature. Another limitation is that there is potential selection bias, as Royal Free London Hospital has on-site tertiary specialist liver and renal services: overall 18% of patients with an elevated RDW had renal or liver disease.

In conclusion, an elevated RDW was detected in almost 20% of hospitalised HIV-positive adults but there was no association with specific infectious, inflammatory, or malignant conditions. Patients with an elevated admission RDW included those with both controlled and uncontrolled HIV infection. In most the elevated RDW was associated with a low haemoglobin and or an elevated CRP. Patients with an elevated RDW were more likely to be

admitted to the ICU, but were no more likely to die, when compared to those with a normal RDW.

Declaration of conflicting interests

The authors(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Figure 1. Relationship between elevated RDW, elevated CRP and low haemoglobin among 259 hospitalized HIV-infected adults.

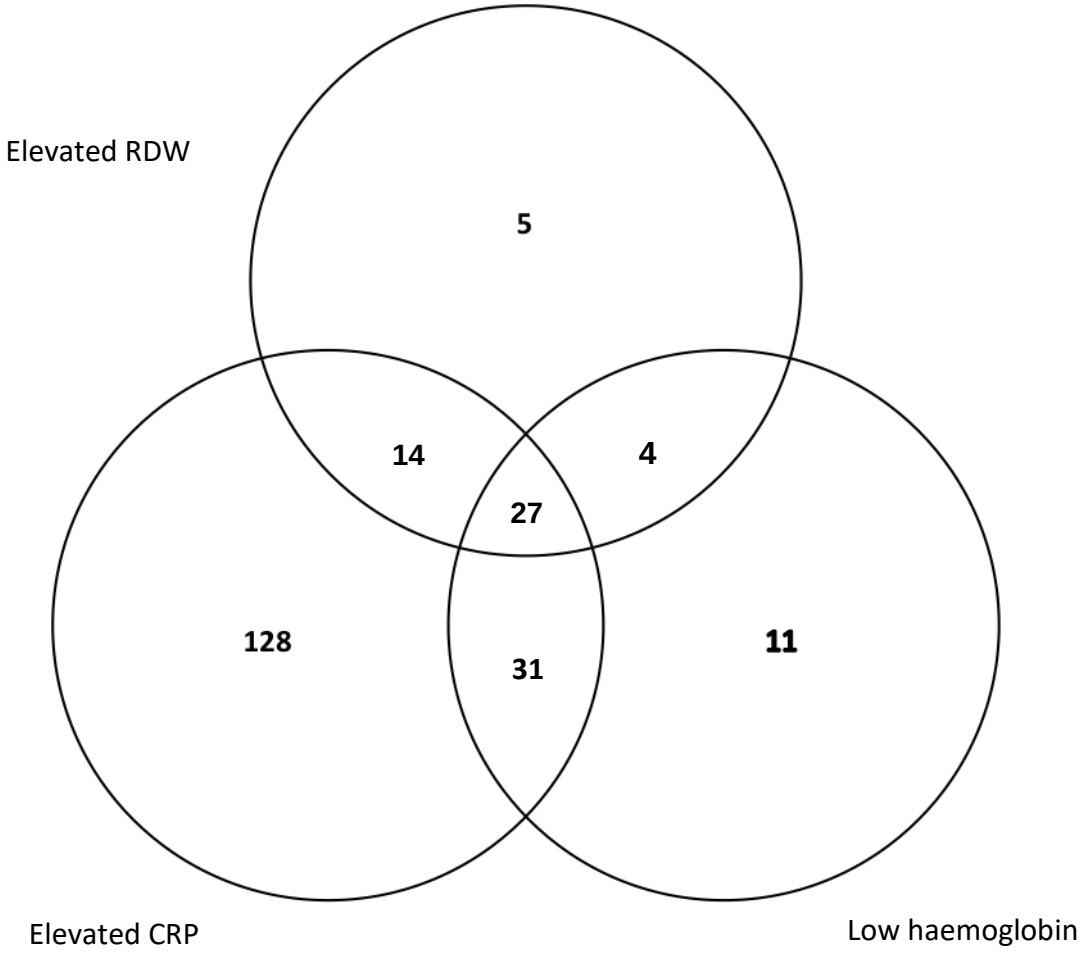

Table 1. Final diagnosis in 50 hospitalised HIV-infected adult patients with an elevated RDW

Elevated RDW, elevated CRP and low haemoglobin (n =27)
3 ESRF + HD (1 also had haemorrhagic gastritis, 1 also had CMV colitis & *C. difficile* diarrhoea & 1 also had CCF & CMV viraemia)
2 NHL
2 Influenza A (1 also had MAI & CMV viraemia)
2 Advanced HIV infection, not on ART (1 also had Barrett oesophagus)
2 MAI (1 also had bacterial pneumonia & CMV viraemia)
2 Disseminated TB (1 also had CMV meningo-encephalitis, 1 also had NHL)
1 PTLD, CCF
1 Mastitis
1 CMV colitis
1 Untreated hepatitis C, cellulitis, IVDU
1 Pulmonary Kaposi sarcoma
1 Infective exacerbation of COPD
1 Alcohol-induced hepatitis, UTI
1 PCP
1 Bacterial pneumonia
1 IRIS secondary to mycobacterial infection
1 MRSA Bacteraemia & endocarditis
1 VZV encephalitis, CMV retinitis
1 AIHA, avascular necrosis of hips
1 Pulmonary actinomycosis
Elevated RDW, elevated CRP and normal haemoglobin (n =14)
2 Community-acquired pneumonia (1 also had fulminant liver failure, 1 also had Chronic lung disease [“Crack lung”])
1 Flare of hepatitis B
1 Chronic hepatitis C (untreated)
1 HSV genital ulcer
1 Secondary syphilis, IVDU
1 Rhinovirus respiratory infection
1 Chronic leg ulcer, IVDU
1 Axillary and jugular vein thromboses
1 Empyema
1 CGD, COPD, pulmonary emboli
1 Poorly controlled HIV infection, detectable viral load
1 Advanced HIV infection, not taking ART
1 Self-limiting headache
Elevated RDW, normal CRP and low haemoglobin (n =4)
Advanced HIV infection, not taking ART
Hepatocellular carcinoma
PCP, AKI, Pseudomonas bacteraemia
Disseminated TB
Elevated RDW, normal CRP and normal haemoglobin (n =5)
Acquired perforating collagenosis
NHL
Ophthalmic shingles

Infective exacerbation of COPD Poorly controlled HIV infection, detectable viral load

Key: RDW: red cell distribution width; CRP: C-reactive protein; ESRF: end-stage renal failure; HD: haemodialysis; CMV: cytomegalovirus; CCF: congestive cardiac failure; NHL: non-Hodgkin lymphoma; MAI: *Mycobacterium avium-intracellulare*; ART: antiretroviral therapy; TB: tuberculosis; PTLD: post-transplant lymphoproliferative disorder; IVDU: injection drug use; COPD: chronic obstructive pulmonary disease; UTI: urinary tract infection; PCP: *Pneumocystis* pneumonia; IRIS: immune reconstitution inflammatory syndrome; MRSA: methicillin resistant *Staphylococcus aureus*; VZV: varicella zoster; AIHA: autoimmune haemolytic anaemia; CGD: chronic granulomatous disease; AKI: acute kidney injury.