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Red cell distribution width is an independent predictor of mortality in hip fracture

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Abstract

Background: the red cell distribution width (RDW), an automated measure of variability in the red blood cell size on full blood count (FBC) is an independent predictor of mortality in several disease states and in healthy older people.

Objective: we wanted to determine the prognostic value of RDW in patients following a hip fracture—a condition associated with high mortality.

Design: we examined the relationship between admission RDW and mortality in 698 consecutive patients admitted with hip fracture.

Method: regression analysis was used to examine admission RDW and subsequent mortality, adjusting for admission haemoglobin, mean corpuscular volume, age, gender, pre-morbid residence and independence level, Charlson co-morbidity index and post-operative complications.

Results: the mean age was 78 ± 13 years. Unadjusted 1-year mortality was 12, 15, 29 and 36% across quartiles of increasing RDW. Along with age and post-operative complications, RDW remained significantly associated with in-hospital, 120-day and 1-year mortality [adjusted hazard ratios: HR: 1.119, 95% CI: (1.000–1.253), P = 0.05, 1.134 (1.047–1.227), P = 0.004 and 1.131 (1.067–1.199), P < 0.001, respectively]. These relationships remained significant at all three time points on repeat analysis in non-anaemic patients (n = 548).

Conclusion: RDW, a widely available parameter on FBC, is independently associated with an increased risk of short- and long-term mortality following hip fracture.

Keywords: RDW, hip fracture, mortality, older people

Introduction

The red cell distribution width (RDW) is an automated index of red blood cell (RBC) heterogeneity performed routinely on a full blood count. High RDW indicates greater variation in the cell size. It reflects increased RBC destruction or deficient erythropoiesis resulting in the premature release of RBCs from the bone marrow. Its traditional value has been to advise on the differential diagnosis of microcytosis. Elevated RDW reflects nutritional deficiencies as well as various pathological processes including bone marrow dysfunction, systemic inflammation and oxidative stress [1–3]. Possibly through these mechanisms, RDW has become of increasing interest following its link with mortality in various
groups including subjects with heart failure, coronary artery disease, pulmonary hypertension and more recently, in large cohorts of healthy middle-aged and older individuals [4–9]. No study to date has examined the association of RDW with mortality following hip fracture, a condition associated with a high mortality burden [10].

Most studies in hip fracture patients identify age, co-morbidity burden and post-operative complications as the main mortality predictors [10–12]. Baseline anaemia has also been associated with poorer outcomes [13–15]. Our objective was to analyse the independent association of RDW and mortality following a hip fracture, to ascertain whether its known association with mortality in many other conditions, was also the case in this patient group.

Methods

We performed an analysis of 698 consecutive hip fracture cases admitted non-electively to this hospital between February 2007 and June 2010. Prospective data collection included information on demographics, fracture and operative details, comorbidities, post-operative complications and admission laboratory results. Mortality data were collected at the 4-month and 1-year time points from fracture date, by telephone clinics and/or GP records. The Charlson co-morbidity index (CCI) was used to describe co-morbidity burden. CCI considers 19 disease conditions, each assigned a weighted score [16]. It has been validated in numerous mortality studies, including in hip fracture patients [17, 18].

Post-operative complications were categorised as cardiac, respiratory, gastrointestinal, delirium, other sepsis (urinary, wound infection, cellulitis etc.).

Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>RDW category</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RDW1 (10.0–13.0%)</td>
<td>169</td>
</tr>
<tr>
<td>Age (years)</td>
<td>74 ± 15</td>
<td>78 ± 12</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>61 (36)</td>
<td>62 (33)</td>
</tr>
<tr>
<td>Used mobility aid indoors pre-fracture (%)</td>
<td>44 (26)</td>
<td>60 (32)</td>
</tr>
<tr>
<td>Care home resident (%)</td>
<td>11 (7)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Charlson index 0–1 (%)</td>
<td>112 (66)</td>
<td>118 (62)</td>
</tr>
<tr>
<td>2–5 (%)</td>
<td>50 (30)</td>
<td>63 (33)</td>
</tr>
<tr>
<td>≥6 (%)</td>
<td>7 (4)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>ASA ≥3 (%)</td>
<td>66 (39)</td>
<td>79 (42)</td>
</tr>
<tr>
<td>Post-operative cardiac complication (%)</td>
<td>13 (8)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Post-operative respiratory complication (%)</td>
<td>25 (15)</td>
<td>35 (18)</td>
</tr>
<tr>
<td>Post-operative GI complication (%)</td>
<td>5 (3)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Post-operative delirium (%)</td>
<td>17 (10)</td>
<td>21 (11)</td>
</tr>
<tr>
<td>Post-operative sepsis (other than respiratory) (%)</td>
<td>27 (16)</td>
<td>30 (16)</td>
</tr>
<tr>
<td>Admission Haemoglobin (g/dl)</td>
<td>13.1 ± 1.5</td>
<td>12.7 ± 1.5</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>94 ± 5</td>
<td>93 ± 5</td>
</tr>
<tr>
<td>Admission Creatinine &gt;120 mg/dl (%)</td>
<td>11 (6.5)</td>
<td>16 (8)</td>
</tr>
</tbody>
</table>

All values are mean ± SD, or median and range.
ASA, American Society of Anaesthesiologists; MCV, mean corpuscular volume; RDW, red cell distribution width.

Statistical analysis

For baseline patient data, we divided baseline RDW into quartiles as per Table 1. We used univariate then backward-selection multivariate Cox regression analysis to look at the association of RDW and ‘in-hospital’, 4-month and 1-year mortality. RDW had a slightly skewed distribution, normalised on log-transformation; however, repeat analysis using the untransformed values did not alter significance of its association with mortality at either of the three time points so we used untransformed values in the regression model for ease of interpretation. All variables with significant univariate association with mortality were included in the multivariate analysis. However, haemoglobin (Hb), mean corpuscular volume (MCV), age and gender were included at all steps regardless of univariate association. We grouped CCI scores into 0–1, 2–5, ≥6 given that a score of ≥6 usually implies metastatic solid tumour [16]. All analyses were repeated excluding subjects with anaemia to look at the impact of RDW in the cohort with normal admission Hb levels, though the Hb level was similarly included in all steps of the regressions models as per the main analysis. Those lost to follow-up (n = 17), they were coded as survivors with their last known contact date dictating survival time. P-values <0.05 were considered statistically significant. SPSS version 18 was used for all analyses.

Results

Baseline data are shown in Table 1. The mean age was 78 ± 13 years (median: 81 y). One-third were male. In-hospital, 120-day and 1-year mortality was 8, 14 and 23%, respectively. The mean RDW was 14.3 ± 2.2%; median: 14.1% with an inter-quartile range of 13.2–15.2%. Participants with higher RDW were more likely to be
dependent with mobility, have a greater co-morbidity burden, presented a higher anaesthetic risk and were more likely to develop post-operative complications. There was an ascending mortality rate across RDW quartiles, with 1-year mortality rate of 12, 15, 29 and 36% across quartiles, with the highest quartile of RDW having a 3-fold increase in mortality compared with the lowest.

Multivariate analysis is shown in Table 2. Significant univariate associations included in the backwards stepwise model (along with admission RDW, Hb, MCV, age and gender) were: pre-fracture residence (care home versus own home), required aid to mobilise indoors pre-fracture, ASA grade ≥3, Charlson index 2–5 or ≥6 (versus 0–1), post-operative cardiac, respiratory gastrointestinal complication, serum creatinine >120 mmol/l, Used walking aid indoors pre-fracture, care home resident, ASA grade ≥3, Charlson score 2–5 or ≥6, post-operative cardiac, respiratory gastrointestinal, delirium complications.

Table 2. Cox proportional hazards multivariate analysis showing factors significantly associated with mortality, whole group \((n = 698)\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>In-hospital mortality</th>
<th>4-month mortality</th>
<th>1-year mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.050 (1.014–1.086)</td>
<td>1.058 (1.031–1.087)</td>
<td>1.058 (1.038 1.079)</td>
</tr>
<tr>
<td>Care home resident</td>
<td>1.999 (1.093–3.655)</td>
<td>1.806 (1.013–3.550)</td>
<td>2.476 (1.540–3.980)</td>
</tr>
<tr>
<td>Used walking aid indoors pre fracture</td>
<td>4.223 (2.350–7.587)</td>
<td>3.016 (1.809–4.790)</td>
<td>1.968 (1.330–2.913)</td>
</tr>
<tr>
<td>ASA 3–4 (versus 1–2)</td>
<td>2.299 (1.291–4.094)</td>
<td>1.639 (1.048–2.562)</td>
<td>1.739 (1.236–2.445)</td>
</tr>
<tr>
<td>Charlson index ≥6</td>
<td>2.579 (1.164–5.717)</td>
<td>2.221 (1.105–4.465)</td>
<td>2.128 (1.251–3.621)</td>
</tr>
<tr>
<td>Post-operative gastro-intestinal injury</td>
<td>1.119 (1.000–1.253)</td>
<td>1.134 (1.047–1.227)</td>
<td>1.131 (1.067–1.199)</td>
</tr>
</tbody>
</table>

ASA, American Society of Anaesthesiologists; MCV, mean corpuscular volume; RDW, red cell distribution width.

Variables entered at step 1: Hb, MCV, RDW, age, gender, serum creatinine >120 mmol/l, Used walking aid indoors pre-fracture, care home resident, ASA grade ≥3, Charlson score 2–5 or ≥6 (versus 0–1), post-operative cardiac, respiratory gastrointestinal, delirium complications.

A strength of this study was that we considered all known mortality predictors from the literature, we had detailed data on post-operative complications in all, with very few patients lost to follow-up. Limitations are that we did not account for nutritional deficiencies which could modify RDW, however, previous studies which have included haematinics still found RDW to be independently

Discussion

We found an association between elevated RDW levels and both short- and long-term mortality in patients with hip fracture, which was independent of the other known mortality predictors following this event, including anaemia status, age, co-morbidities and post-operative complications. Though not a powerful predictor, it was striking in its consistent association with mortality at three different time points, particularly so when all anaemic patients were excluded, thereby supporting the hypothesis that high RDW is not linked to mortality through the function of anaemia alone.

Though RDW has been linked with mortality in several different disease states as well as healthy older adults, these studies have not shed light on how it could be linked to an increased risk of death, which remains unclear [4–9]. The main theory is through chronic inflammation, in particular, the presence of inflammatory cytokines and high oxidative stress [3, 4]. Inflammatory states and high RDW are linked through the mechanisms of myelosuppression, reduced renal erythropoietin production and increased cell apoptosis [4, 5]. These inflammatory cellular changes prevalent in chronic disease states impair red cell survival and cause release of premature red cells into the circulation, leading to an increased RDW. However, RDW may represent an integrated index of multiple pathophysiological mechanisms namely chronic inflammation, greater oxidative stress, nutritional deficiencies, organ congestion and ageing itself, resulting in anisocytosis thereby conferring a cumulative indication of high-mortality risk [8]. This is more likely the case in a broad group such as hip fracture patients whose injury is their only common entity.

Efforts to identify those at highest mortality risk following a hip fracture have been made, such as development of the NHFS (Nottingham Hip Fracture Score) and the use of the POSSUM (Physiological and Operative Severity Score for the EnUmeration of Mortality and Morbidity) score [19, 20]. Neither score incorporates post-operative complications nor does either include RDW. Though RDW is a non-modifiable factor, the findings of our study support the role of RDW in identifying a high-risk group of patients following hip fracture who could benefit from increased clinical vigilance post-admission and post-discharge which might impact their mortality risk, though there is no present evidence to support this.

A strength of this study was that we considered all known mortality predictors from the literature, we had detailed data on post-operative complications in all, with very few patients lost to follow-up. Limitations are that we
predictive of mortality [8, 21]. Secondly, our numbers for the end point of in-hospital mortality were clearly too small to draw conclusions from in isolation, but this result was included because of the clear trend in line with the associations of RDW with 4-month and 1-year mortality. It is also not clear if our result is applicable to a broader range of hip fracture patients, as our data were from a single hospital only. Studies in other centres’ hip fracture cohorts would be needed to verify our findings.

In conclusion, we have observed an independent association between admission RDW levels and short- and long-term mortality following hip fracture. The causal link between RDW and mortality is unclear but considering those susceptible to hip fracture, i.e. frail older patients with comorbidities, higher RDW is likely to represent the cumulation of several pathophysiological mechanisms in addition to ageing itself. RDW may be a useful adjunct in facilitating risk stratification of this patient group susceptible to a high mortality rate. We propose the incorporation of the widely available parameter of RDW in future larger studies on mortality risk prediction following hip fracture.

Key points

- RDW, a readily available parameter on full blood count is independently associated with mortality following hip fracture.
- This association is independent of an anaemia status, and may reflect a cumulation of pathophysiological processes of ageing itself.
- RDW may have a role in identifying high-risk patients following hip fracture.

Conflicts of interest

None to declared.

References


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