

Red cell distribution width and 5-year mortality across older adult care settings: a pooled European cohort analysis with US validation

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Abstract

Background Red-cell distribution width (RDW), generated automatically with every complete blood count, predicts mortality across multiple populations, but its independent prognostic value at a fixed cut-off across older care settings is unresolved.

Methods We pooled individual-level data from four prospective European cohorts of older adults: community-dwelling (ECHA-CP-MUSA, $n=812$), nursing home residents (SADEL, $n=813$), long-lived families with area-matched controls (GEHA, $n=579$), and hospitalized patients (REPORTAGE, $n=4,400$); total $n=6,604$, followed for 5 years. $\text{RDW-CV} \geq 15\%$ was the primary exposure and all-cause mortality the primary outcome. Multilevel Cox regression with cohort as random effect adjusted for age, sex, anaemia, albumin, neutrophil-to-lymphocyte ratio, number of chronic diseases and medications, and impaired ADL, with pre-specified stratification at age 85 years. External validation drew on 2,471 participants of the 2016 Health and Retirement Study (HRS) in the United States.

Results In European cohorts, mean age was 84.8 years (SD 9.2); 41.4% had $\text{RDW-CV} \geq 15$. Mortality rate at 5 years was 69.9%. The pooled adjusted HR for $\text{RDW-CV} \geq 15\%$ was 1.58 (95% CI 1.48–1.68; $p < 0.001$), with low between-cohort heterogeneity (Theta=0.06); the association was concordant across three of four cohorts; it was externally replicated in HRS (1.64 [1.23–2.19]; $p < 0.001$) and strongest in the oldest-old.

Conclusions $\text{RDW-CV} \geq 15\%$ independently predicts all-cause mortality during follow-up of up to five years across heterogeneous older-adult populations after adjustment for major geriatric prognostic factors. This

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association persisted after adjustment for anaemia, ADL, NLR, and albumin, suggesting that RDW captures a dimension of systemic dysregulation.

Keywords RDW · Inflammation · Ageing · Mortality · Prognosis · Oldest old

Background

Anisocytosis, the increased variability of erythrocyte volume captured by red-cell distribution width (RDW), is generated automatically with every complete blood count. Once confined to the differential diagnosis of microcytic and macrocytic anaemia, RDW has been progressively repositioned over the past two decades as a non-specific marker of systemic dysregulation. Higher values predict all-cause mortality in older adults [1] and carry prognostic weight in several chronic and acute diseases including cardiovascular diseases [2–5], sepsis [6], and cancer [7, 8]. This prognostic signal also extends to middle age: in a US cohort of adults aged 30–64 years, elevated RDW independently predicted all-cause and cardiovascular mortality [9]. Its consistency across ages and conditions reflects several distinct pathophysiological mechanisms that converge on erythrocyte heterogeneity. Pro-inflammatory cytokines suppress erythroid progenitor maturation and divert iron through hepcidin-mediated functional sequestration. Oxidative injury to the erythrocyte membrane shortens red-cell lifespan, and erythropoietin resistance compounds the disturbance in chronic kidney disease and heart failure [10–12]. These pathways operate in part independently of haemoglobin concentration and produce a wider dispersion of erythrocyte volumes, a haematological signature linked to the inflammageing pathways described for cardiovascular disease and frailty [13] and captured by RDW. In cardiovascular cohorts, RDW rises in parallel with C-reactive protein and remains an independent correlate of disease presence, consistent with an inflammatory contribution to anisocytosis [5]. The composite importance of RDW as a biological age-related signal is quantified within the PhenoAge construct, derived from nine routinely available clinical biomarkers selected by mortality modelling in NHANES III and validated in independent NHANES IV cohorts [14, 15]: RDW carries the largest hematological coefficient ($\beta = 0.3306$), underscoring its capacity to capture multisystem derangement rather than single diseases.

In older adults, RDW reflects the aggregate of several homeostatic disturbances rather than any single diagnosis. An earlier pooled individual-participant analysis of community-based older adults established the association between RDW and poor outcomes [1]. However, previous evidence was limited to studies conducted in single recruitment settings and the prognostic context of RDW may not be uniform across different settings. Furthermore, RDW might not behave uniformly across the geriatric age spectrum; especially among the oldest old, defined as those above the age of 85 [16], associations between conventional cardiovascular and metabolic risk factors and mortality are frequently attenuated or reversed, a pattern attributed to reverse epidemiology, survivor selection, and the progressive compression of heterogeneity among those reaching extreme age [16]. In this context, biological markers that reflect accumulated systemic dysregulation are expected to retain or amplify their prognostic signal precisely where conventional risk scores lose resolution. Despite previous studies having shown that RDW increased substantially with age [17], prognostic implications of such increase were not fully elucidated.

Most previous studies have analysed RDW as a continuous variable or derived study-specific optimal thresholds, limiting comparability across populations and reducing clinical applicability. By contrast, the present study evaluates the prognostic performance of the routinely reported laboratory threshold of $\text{RDW-CV} \geq 15\%$, testing whether an existing and immediately interpretable clinical cut-off can identify older adults at increased risk of mortality across heterogeneous healthcare settings. Validation of an established threshold, rather than deriving a new cohort-specific cut-off, may facilitate translation into routine geriatric practice.

To address these gaps, we conducted a pooled individual-participant analysis of four prospective European cohorts of older adults ($n=6604$) and externally validated our findings in 2,471 participants from the US Health and Retirement Study (HRS). Our primary aim was to determine whether a single RDW threshold of 15% provides

independent prognostic information for mortality, after adjusting for anaemia, serum albumin, neutrophil-to-lymphocyte ratio (NLR), number of chronic conditions, polypharmacy, age, sex, and disability. Our secondary aim was to evaluate whether observed associations differed by age group and setting of care.

Methods

European cohorts

The pooled European set comprised four analytic groupings derived from six prospective studies of older adults in Italy. ECHA-CP-MUSA ($n = 812$) aggregated three southern Italian datasets sharing a community-dwelling, family-anchored design: the European Challenge of Healthy Ageing project (ECHA) (EU-5-FP contract no. QLK6-CY-2001-00128) [18], the Carolei's Project (CP), and the Monitoring Unsuccessful and Successful Ageing study (MUSA) [19]. The other three groupings entered the pool separately: SADEL, aimed at monitoring the quality of ageing of nursing home residents recruited in Calabria ($n = 813$) [20]; the Genetics of Healthy Ageing (GEHA), including long-lived European families with younger area-matched controls ($n = 579$) [21], and REPORTAGE, an Italian registry of older adults admitted to acute care hospitals ($n = 4,400$) [22]. Detailed information on the recruitment criteria, timing of blood sampling and exclusion criteria are provided in Supplementary Table S1. All these studies were approved by relevant Ethics Committees.

External validation cohort

The US HRS, sponsored by the National Institute on Ageing, is a nationally representative longitudinal survey of adults aged 50 years or older. The 2016 Venous Blood Substudy collected blood from approximately half of the active sample [23]. We restricted the validation analysis to participants with complete data on RDW-CV, anaemia status, albumin, NLR, number of chronic diseases, drug count, age, sex and ADL ($n = 2,471$). Specifically, the survey design object was specified using the HRS-recommended strata (STRATUM) and cluster (SECU) variables together with the 2016 Venous Blood Study sub-sample respondent weight (PVBSWGTR); the latter, rather than the core HRS interview weight, was used because it corrects for the differential probability of providing a valid venous blood sample among community-dwelling 2016 h respondents, so that weighted estimates are representative of the blood-donating sub-sample. Full details of the survey design specification, including the weight, strata and cluster variables and the handling of missing data in the complete-case sample, are reported in Supplementary Table S2.

Hematological measurements and assessments

Haematology for the Italian contributing cohorts (ECHA-CP-MUSA and GEHA) was centralised at IRCCS INRCA on overnight-fasting samples; haematological measurements for SADEL and REPORTAGE were performed at the respective participating laboratories using their local analytical protocols; RDW-CV, expressed as a percentage, was the coefficient of variation of the erythrocyte volume distribution computed automatically by the haematology analyser according to this formula: $[\text{standard deviation (SD) of the mean corpuscular volume (MCV)} / \text{mean MCV}] \times 100$. Anaemia was defined by World Health Organization sex-specific haemoglobin thresholds (men < 13 g/dL; women < 12 g/dL); the neutrophil-to-lymphocyte ratio (NLR) was derived from the differential count; serum albumin was used as a proxy of nutritional status and acute inflammation, and the number of chronic conditions was retained in the principal model as cross-cohort harmonised measures of biological reserve and disease burden, respectively.

Other covariates

Functional capacity was assessed by the Katz index of basic activities of daily living (ADL) [24] in all cohorts; history of chronic diseases was extracted from medical records and prescription lists (European cohorts) or based on self-reported history (HRS). Number of medications was extracted from prescription lists and included in the study.

Outcome and follow-up

Vital status was traced through municipal Population Registries (Europe) and the National Death Index (HRS). The primary outcome was all-cause mortality at 5 years from enrolment, with right-censoring at last follow-up.

Statistical analysis

Continuous variables were summarised as mean (SD) and categorical variables as count (%). For the HRS cohort, all measures were survey-weighted to account for the complex survey design.

Kaplan–Meier survival curves stratified by RDW-CV at the 15% threshold and by age class were generated for the pooled European set and for HRS separately. The association between RDW-CV and mortality at 5 years was evaluated by fitting multivariable Cox proportional hazards models in the pooled European cohort first, with cohort entered as random effect and individual-level fixed-effect adjustment for age, female sex, RDW-CV $\geq 15\%$, ≥ 1 impaired ADL, anaemia, serum albumin, NLR, number of chronic conditions and number of medications. Analyses were repeated after stratification by age below and at or above 85 years ($n=2,752$ and $3,852$, respectively), preserving the random-effect structure. Because the primary analysis was based on a shared gamma frailty Cox proportional hazards model to account for heterogeneity across participating cohorts, the proportional hazards assumption could not be directly assessed using Schoenfeld residuals. Therefore, proportional hazards were evaluated using an equivalent Cox model stratified by cohort. Schoenfeld residuals and the corresponding statistical tests were examined to identify potential departures from proportional hazards. As a sensitivity analysis, the original shared gamma frailty Cox model was extended to account for non-proportional hazards by allowing time-varying effects for covariates that violated the proportional hazards assumption. These effects were modelled by including interactions between the corresponding covariates and the natural logarithm of follow-up time:

$$h(t) = h_0(t) \exp(\beta X + \beta_{\text{time}} X \log(t) + \sum \beta_i Z_i + b_{\text{cohort}})$$

where b_{cohort} denotes the shared gamma frailty accounting for unobserved heterogeneity across participating cohorts. All remaining covariates were modelled assuming proportional hazards. Model fit was compared with that of the primary model using a likelihood-based comparison based on the integrated penalized log-likelihood.

Multicollinearity among the fixed-effect covariates included in the multivariable shared gamma frailty Cox model was assessed by calculating variance inflation factors (VIFs) using the `vif` function implemented in the R package `car`. Because the assessment concerned only the fixed-effect predictors, VIFs were calculated from an otherwise identical Cox proportional hazards model excluding the frailty term. A $\text{VIF} > 5$ was considered indicative of potentially problematic multicollinearity.

As a sensitivity analysis, RDW was modelled as a continuous variable (per 1% increase) using the same Cox model as in the primary analysis. To evaluate the potential influence of inter-instrument analytical variability, we performed an additional sensitivity analysis restricted to the cohorts whose haematological analyses were centralized at the IRCCS INRCA Cosenza central laboratory (ECHA-PC-MUSA and GEHA). The same multivariable shared gamma frailty Cox model used in the primary analysis was fitted within this subset. Cohort-specific

Cox models without random effect were fitted for descriptive comparison and forest-plot generation. Analyses were then externally validated in the HRS cohorts by using survey-weighted Cox regression models. Statistical analyses were conducted in R (version 4.3.2); two-sided *p* values < 0.05 were considered statistically significant.

Results

Descriptive statistics of the pooled European population

The demographic and clinical characteristics of the pooled European population, overall and stratified by age and vital status, are reported in Table 1. The sample consisted of 6,604 older adults, with a mean (SD) age of 84.8 (9.2) years, 58.7% women, and more than a half of the study population was ≥ 85 years of age. Over a median (IQR) follow-up of 2.1 (0.3–5.0) years, 4,614 (69.9%) patients died, with a higher burden in oldest old (87.8%). Patients who died were older, had more impaired ADL, a higher prevalence of anaemia, as well as a higher number of chronic diseases and medications compared to survivors. They were also characterized by higher mean RDW-CV, NLR, and lower albumin, compared with survivors.

The four contributing cohorts differed significantly in their baseline profiles (Supplementary Tables S3–S6), as reflected by the study designs. REPORTAGE, the largest cohort (*n* = 4,400), had the highest mean age, the highest prevalence of increased RDW (53.7%) and anaemia (70.2%), and the highest 5-year mortality (82.3%); ECHA-CP-MUSA (*n* = 812) was the youngest and most functionally independent cohort, with a strikingly lower prevalence of increased RDW-CV (12.9%) and anaemia (16.9%), as well as a lower all-cause mortality (32.3%). SADEL (*n* = 813), the nursing home cohort, had the highest ADL impairment prevalence (62.2%) and the highest number of drugs (mean, SD: 7.2, 3.6), while GEHA (*n* = 579) had the highest proportion of oldest old (*n* = 404), given its long-lived family design.

Table 1 Demographic and clinical characteristics of the pooled European population, overall and stratified by age group and vital status

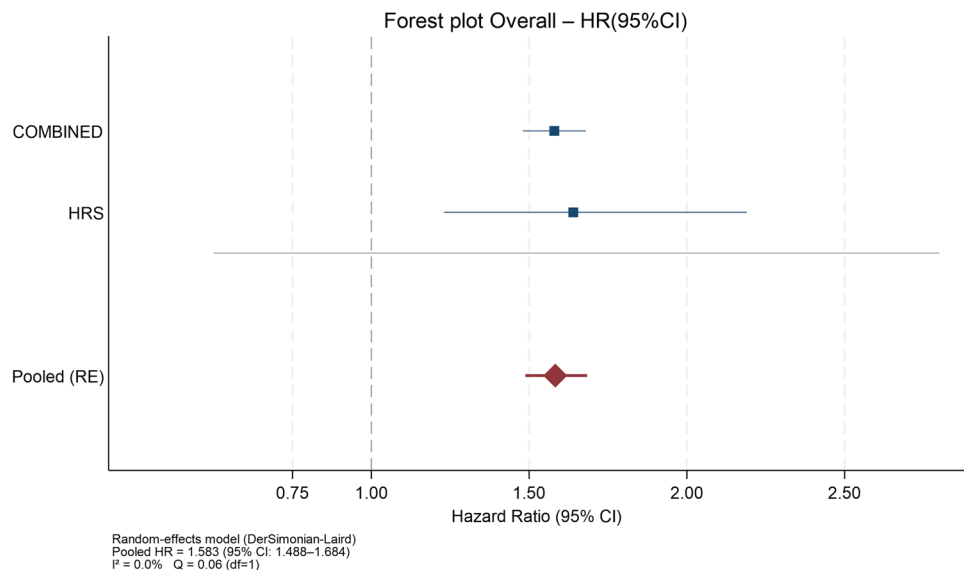
	Overall			Age < 85			Age ≥ 85		
	Total <i>N</i> = 6,604	Alive <i>N</i> = 1,990	Dead <i>N</i> = 4,614	Total <i>N</i> = 2,752	Alive <i>N</i> = 1,481	Dead <i>N</i> = 1,271	Total <i>N</i> = 3,852	Alive <i>N</i> = 509	Dead <i>N</i> = 3,343
Age, mean ± SD	84.8 ± 9.2	77.4 ± 10.0	88.0 ± 6.6	76.3 ± 7.4	73.2 ± 7.9	80.0 ± 4.6	90.9 ± 4.2	89.7 ± 3.4	91.1 ± 4.2
Gender, <i>n</i> (%)									
Male	2,724 (41.3%)	779 (39.2%)	1,945 (42.2%)	1,262 (45.9%)	627 (42.3%)	635 (50.0%)	1,462 (38.0%)	152 (29.9%)	1,310 (39.2%)
Female	3,880 (58.7%)	1,211 (60.8%)	2,669 (57.8%)	1,490 (54.1%)	854 (57.7%)	636 (50.0%)	2,390 (62.0%)	357 (70.1%)	2,033 (60.8%)
RDW-CV ≥ 15%, <i>n</i> (%)	2,731 (41.4%)	309 (15.5%)	2,422 (52.5%)	773 (28.1%)	197 (13.3%)	576 (45.3%)	1,958 (50.8%)	112 (22.0%)	1,846 (55.2%)
RDW-CV, mean ± SD	14.9 ± 2.4	13.6 ± 1.9	15.5 ± 2.4	14.2 ± 2.4	13.4 ± 1.9	15.2 ± 2.5	15.4 ± 2.3	14.2 ± 1.7	15.6 ± 2.3
1 + impaired ADLs, <i>n</i> (%)	3,979 (60.3%)	469 (23.6%)	3,510 (76.1%)	1,036 (37.7%)	236 (15.9%)	800 (62.9%)	2,943 (76.4%)	233 (45.8%)	2,710 (81.1%)
Anaemia, <i>n</i> (%)	3,724 (56.4%)	584 (29.4%)	3,140 (68.1%)	1,142 (41.5%)	358 (24.2%)	784 (61.7%)	2,582 (67.0%)	226 (44.4%)	2,356 (70.5%)
Albumin (g/dL), mean ± SD	3.4 ± 0.7	3.8 ± 0.5	3.2 ± 0.6	3.6 ± 0.6	3.9 ± 0.5	3.3 ± 0.7	3.2 ± 0.6	3.6 ± 0.5	3.2 ± 0.6
NLR, mean ± SD	7.2 ± 9.3	4.0 ± 5.7	8.6 ± 10.1	5.4 ± 8.0	3.5 ± 4.7	7.7 ± 10.2	8.5 ± 9.9	5.5 ± 7.6	8.9 ± 10.1
Number of diagnoses, mean ± SD	4.6 ± 2.3	3.4 ± 2.1	5.1 ± 2.2	4.0 ± 2.2	3.2 ± 1.9	5.0 ± 2.0	5.0 ± 2.3	4.0 ± 2.3	5.1 ± 2.3
Number of drugs, mean ± SD	5.4 ± 3.1	4.6 ± 2.9	5.8 ± 3.1	5.3 ± 3.2	4.4 ± 2.8	6.2 ± 3.3	5.6 ± 3.0	5.0 ± 3.0	5.6 ± 3.0

Abbreviations: ADL, Activities of Daily Living; NLR, Neutrophil-to-Lymphocyte Ratio; RDW-CV, Red Cell Distribution Width – Coefficient of Variation; SD, standard deviation

Table 2 Multivariable Cox proportional hazards models for all-cause mortality in the pooled European population, overall and stratified by age group

	Overall $N=6,604$		Age < 85 $N=2,752$		Age ≥ 85 $N=3,852$	
	HR (95%CI)	<i>p</i> -value	HR (95%CI)	<i>p</i> -value	HR (95%CI)	<i>p</i> -value
RDW-CV $\geq 15\%$	1.58 (1.48–1.68)	<0.001	1.52 (1.34–1.72)	<0.001	1.61 (1.49–1.73)	<0.001
1 + impaired ADLs	2.19 (2.03–2.36)	<0.001	2.42 (2.12–2.75)	<0.001	2.02 (1.85–2.22)	<0.001
Female Gender	0.71 (0.67–0.76)	<0.001	0.69 (0.61–0.77)	<0.001	0.73 (0.68–0.78)	<0.001
Age	1.06 (1.05–1.06)	<0.001	1.05 (1.03–1.06)	<0.001	1.06 (1.05–1.07)	<0.001
Anaemia	0.99 (0.92–1.06)	0.790	0.96 (0.84–1.10)	0.543	0.99 (0.91–1.08)	0.905
Albumin	0.57 (0.53–0.60)	<0.001	0.54 (0.48–0.60)	<0.001	0.57 (0.53–0.61)	<0.001
NLR	1.01 (1.00–1.01)	<0.001	1.01 (1.00–1.01)	0.007	1.01 (1.00–1.01)	<0.001
Number of diagnoses	1.00 (1.00–1.00)	0.424	1.01 (0.98–1.05)	0.434	1.00 (1.00–1.00)	0.465
Number of drugs	1.01 (1.00–1.02)	0.021	1.04 (1.02–1.07)	<0.001	1.00 (0.99–1.01)	0.738
Theta, HR (SE)	0.06 (0.05)		0.17 (0.13)		0.05 (0.04)	

Abbreviations: ADL, Activities of Daily Living; NLR, Neutrophil-to-Lymphocyte Ratio; RDW-CV, Red Cell Distribution Width – Coefficient of Variation; SD, standard deviation

Fig. 1 Forest plot showing the pooled hazard ratio for the overall association between elevated RDW-CV ($\geq 15\%$) and all-cause mortality across the pooled European populations and the HRS cohort, with random-effects meta-analytic pooled estimate

Cox proportional hazards models of the pooled European population

Kaplan-Meier survival curves for the pooled European population, stratified by RDW-CV and age class, are shown in Figure S1. Cohort-specific survival curves are reported in Figures S2–S5.

Multivariable Cox proportional hazards models for the association between increased RDW and 5-year mortality are reported in Table 2; Fig. 1. In the overall pooled analysis, increased RDW was independently associated with increased mortality. Among the other covariates, ADL impairment (HR, 95%CI: 2.19, 2.03–2.36) had the strongest association with the outcome, along with serum albumin (HR per g/dL 0.57, 0.53–0.60) and female sex (HR, 95%CI: 0.71, 0.67–0.76). Anaemia did not retain independent prognostic value. Between-cohort heterogeneity was small (theta 0.06, SE 0.05). Assessment of the proportional hazards assumption using an equivalent Cox model stratified by cohort suggested evidence of time-dependent effects for albumin, RDW and ADL limitations. Therefore, we performed a sensitivity analysis by extending the original shared gamma frailty Cox model to allow time-varying effects for these variables. The extended model provided a significantly better fit than the primary model (likelihood-based comparison: LR=220.1, $\Delta df=3$, $P<0.001$). The complete results of the extended model are presented in Supplementary Table S7. Significant time-varying effects were observed for albumin

($P < 0.001$), RDW ($P = 0.002$) and ADL limitations ($P < 0.001$), indicating that the magnitude of their associations with mortality changed during follow-up. Nevertheless, the direction of the associations remained unchanged throughout follow-up. Albumin remained consistently associated with a lower mortality risk, whereas elevated RDW and ADL limitations remained associated with an increased mortality risk at all representative follow-up times examined. Estimated hazard ratios at representative follow-up times are reported in Supplementary Table S8. No evidence of relevant multicollinearity was observed among the fixed-effect covariates included in the multivariable model, with VIF values ranging from 1.03 to 1.29, well below the predefined threshold of 5. As a sensitivity analysis, RDW was additionally analysed as a continuous variable. The association between RDW and all-cause mortality remained statistically significant after multivariable adjustment (HR per 1% increase = 1.089, 95% CI 1.077–1.100, $P < 0.001$), confirming that the observed association was not dependent on the predefined clinical cutoff of 15% (Supplementary Table S9). To investigate whether analytical variability between laboratory platforms influenced the observed association, we repeated the primary analysis after restricting the dataset to the cohorts whose haematological analyses were centralized at the IRCCS INRCA Cosenza central laboratory (ECHA-PC-MUSA and GEHA). As shown in Supplementary Table S10, elevated RDW remained independently associated with all-cause mortality (HR = 1.30, 95% CI 1.06–1.59, $P = 0.011$). Although the effect estimate was slightly attenuated compared with the primary analysis, its direction, magnitude and statistical significance remained consistent, indicating that the observed association was unlikely to be explained by inter-instrument analytical variability.

In analyses stratified by age (Table 2, Figure S6), increased RDW-CV remained independently associated with the outcome both in participants < 85 years and those 85 years or older. In both groups, ADL impairment and albumin remained the strongest independent predictors of mortality. Number of drugs reached the statistical significance only among participants younger than 85 years. Between-cohort heterogeneity was higher in younger participants, consistent with the greater structural diversity of this subgroup across the four contributing cohorts (Supplementary Tables S3–S6).

Cohort-specific analyses are reported in Supplementary Tables S11–S14. Notably, the direction of the association between RDW-CV and mortality was concordant across three out of the four cohorts. In REPORTAGE, the adjusted HR for RDW-CV $\geq 15\%$ closely reproduced the pooled estimate, with consistent effects in both age groups. In GEHA and SADEL, the association was significant only among participants aged 85 years or older, while in the ECHA-CP-MUSA cohort, the association was nonsignificant, consistent with the younger age profile, lower comorbidity burden and event rate of this cohort. Importantly, in this cohort NLR and albumin absorbed the prognostic signal.

External validation in the HRS population

The main characteristics of the external validation cohort are reported in Table 3. In survey-weighted Cox regression (Supplementary Table S15), increased RDW was independently associated with 5-year mortality, with significant effects only among those participants aged 85 years or older. In contrast with European cohorts, anaemia retained prognostic significant effects, while ADL impairment presented a more modest, despite significant, effect.

Discussion

In 6,604 European older adults pooled across four cohort designs and 2,471 US adults from HRS, RDW-CV $\geq 15\%$ independently predicted long-term mortality even after adjustment for anaemia, albumin, NLR, number of chronic diseases, medications, ADL disability and demographics. In the oldest-old, where competing causes of death and compressed life expectancy blunt conventional risk scores, RDW-CV $\geq 15\%$ retained an HR of 1.61 in the European pool and 1.74 in HRS, both highly significant. In addition, modelling RDW as a continuous variable yielded results consistent with those obtained using the clinically established 15% cutoff, indicating that the

Table 3 Descriptive statistics in HRS population

	Overall			Age < 85			Age ≥ 85		
	Total N=2,471	Alive N=2,188	Dead N=283	Total N=2,039	Alive N=1,925	Dead N=114	Total N=432	Alive N=263	Dead N=169
Age, mean±SD	72.4±8.5	70.9±6.8	83.2±11.1	69±3.1	68.9±3.1	70.5±4.1	90.4±3.9	89.4±3.5	91.5±4.1
Gender, n (%)									
Male	1,114 (46.5%)	996 (47.6%)	118 (38.3%)	1,041 (51.3%)	923 (47.9%)	64 (56.6%)	127 (26.2%)	73 (26.1%)	54 (26.3%)
Female	1,357 (53.5%)	1,192 (52.4%)	165 (61.7%)	1,052 (49.7%)	1,002 (52.1%)	50 (43.4%)	305 (73.8%)	190 (73.9%)	115 (73.7%)
RDW-CV ≥ 15%, n (%)	475 (17.9%)	385 (16.2%)	90 (30.4%)	369 (16.8%)	327 (15.7%)	42 (35.5%)	106 (24%)	58 (21.3%)	48 (27.1%)
RDW-CV, mean±SD	14±1.4	14±1.3	14.5±1.7	14±1.3	13.9±1.3	14.7±2	14.3±1.4	14.2±1.4	14.4±1.4
1+impaired ADLs, n (%)	467 (18.4%)	359 (15.2%)	108 (42.3%)	331 (15%)	295 (13.9%)	36 (32.5%)	136 (36.8%)	64 (26.8%)	72 (48.8%)
Anaemia, n (%)	510 (18.6%)	391 (15.5%)	119 (41.5%)	383 (16.7%)	331 (15%)	52 (44.2%)	127 (29%)	60 (19.8%)	67 (39.8%)
Albumin (g/dL), mean±SD	3.9±0.3	4±0.3	3.7±0.4	4±0.3	4±0.3	3.7±0.4	3.8±0.3	3.8±0.3	3.7±0.4
NLR, mean±SD	2.4±1.3	2.3±1.2	3±1.9	2.3±1.2	2.2±1.1	2.9±1.8	2.9±1.9	2.8±1.8	3±2
Number of diagnoses, mean±SD	2.5±1.5	2.4±1.5	3.2±1.6	2.4±1.5	2.3±1.5	3.4±1.7	2.8±1.4	2.7±1.3	3±1.5
Number of drugs, mean±SD	2.1±1.5	2.1±1.5	2.7±1.7	2.1±1.5	2.1±1.5	2.9±1.8	2.4±1.5	2.2±1.3	2.5±1.6

Abbreviations: ADL, Activities of Daily Living; NLR, Neutrophil-to-Lymphocyte Ratio; RDW-CV, Red Cell Distribution Width – Coefficient of Variation; SD, standard deviation

association between RDW and mortality was not driven by the chosen categorization. Although the direction of the association between elevated RDW and mortality was broadly similar across cohorts, the strength of the association differed according to the underlying population. The pooled estimate was largely influenced by the REPORTAGE cohort, which contributed most participants and events, whereas no independent association was observed in the younger and healthier ECHA-PC-MUSA cohort. These findings suggest that the prognostic value of RDW is context-dependent and becomes more evident in populations with greater clinical complexity and biological vulnerability. However, the analyses conducted in single cohorts shed light on the boundaries of the observed associations: REPORTAGE, including patients admitted to acute care hospital, was the only population where the association held in patients younger than 85 years; this may be due to the higher frailty of hospitalized populations, as confirmed by event rates in this stratum, substantially exceeding those of other cohorts even when considering patients younger than 85 years. Although the direction of the association between elevated RDW and mortality was concordant across three of the four European cohorts, statistical significance was not observed in the ECHA-PC-MUSA cohort. Importantly, this should not be interpreted as evidence of an opposite association. Rather, ECHA-PC-MUSA represents the youngest and healthiest cohort in our study, with substantially lower mortality, lower prevalence of elevated RDW, anaemia, and ADL impairment than the other cohorts. In this context, the independent prognostic contribution of RDW appeared to be largely captured by other markers of systemic dysregulation, particularly serum albumin and NLR. These patterns suggest that this biomarker may be context-sensitive: its independent signal is strongest when systemic dysregulation is already manifest (e.g. in hospitalized older patients or in nursing home residents and community-dwelling patients older than 85 years) and is attenuated in case of substantially preserved homeostasis.

The 85-year threshold was used to define the oldest-old population, consistent with demographic convention and prior work on advanced age survival [16]. In older adults, associations between conventional cardiovascular risk markers and mortality are often attenuated or reversed, as reported for blood pressure, total cholesterol, and body-mass index, a pattern consistent with reverse epidemiology and survivor-selection mechanisms in late life [25, 26]. RDW reflects inflammation, oxidative stress, and dysregulated erythropoiesis [10–13, 27, 28], retains

prognostic value across older populations [1] and is incorporated within the PhenoAge biological-age construct [14, 15].

Erythrocyte volume dispersion may reflect biological processes implicated in ageing, including chronic inflammation, oxidative stress, impaired erythropoiesis and mitochondrial dysfunction, as suggested by previous experimental and epidemiological studies [13]. Genetic evidence confirmed its importance: in 116,666 UK Biobank participants, pathway enrichment for RDW-associated variants spanned telomere maintenance, ribosomal RNA biology and apoptosis [29], core mechanisms of biological ageing. Furthermore, RDW already sits within a small family of laboratory-based measures of ageing, as it is included in the PhenoAge composite, derived from chronological age and nine routinely available blood markers (albumin, creatinine, glucose, log-transformed C-reactive protein, lymphocyte percentage, mean cell volume, RDW, alkaline phosphatase and white-cell count); this was constructed to maximise prediction of all-cause mortality in NHANES III and replicated in independent NHANES IV cohorts [5, 14] and may mediate the relationship between inflammatory markers and long-term mortality. The frailty index from blood tests (FI-Lab) aggregates routinely measured laboratory abnormalities into a deficit-accumulation score that predicts mortality in older adults independently of clinical frailty assessment [30]. The Pace of Ageing framework similarly approximates physiological decline through a small set of integrative biomarkers [31]. A recent cross-sectional study in 864 community-dwelling adults aged 70 years and older from the SOMMA cohort has shown that RDW was independently associated with decreased physical function and impaired cognition, with association partially mediated by lower muscle ATP production and oxidative phosphorylation capacity [32], thus linking RDW to age-related mitochondrial dysfunction. The observed association is consistent with the hypothesis that RDW captures aspects of biological ageing previously incorporated into laboratory-based ageing indices, although our study was not designed to directly evaluate these mechanisms. These observations suggest that RDW may represent a readily available biomarker of systemic dysregulation. However, whether it captures biological ageing processes beyond established multidimensional indices requires further investigation.

The present analysis extends the laboratory-based ageing literature into populations under-represented in the original derivations, in particular individuals aged 85 years or older, nursing-home residents and long-lived families.

The 15% cut-off is pragmatic rather than statistically optimised, and we acknowledge the loss of statistical efficiency entailed by dichotomisation of a continuous predictor; the threshold was chosen for clinical interpretability and cross-cohort reproducibility [33]. In the European pool the cut-off lies essentially at the centre of the observed distribution (mean 14.9%, SD 2.4) and stratifies participants into roughly equal halves, which limits its discriminative resolution as a stand-alone tool. External dose-response evidence corroborates the direction of the association while leaving the cut-off uninformed.

Another relevant finding is represented by the role of anaemia, that was not independently associated with mortality in the European pool, while maintaining it in the US population. A biological interpretation is that, in a sample with mean age 84.8 years and 60.3% ADL impairment, the haemoglobin-specific signal is subsumed by the broader erythrocyte heterogeneity signal; this would be consistent with the contrast against the younger HRS sample, where anaemia independently predicted prognosis alongside RDW (HR 1.70 [1.28–2.24]). Previous studies have linked RDW elevation in patients with heart failure to markers of ineffective erythropoiesis, inflammation and nutritional state rather than to anaemia per se [11, 28]; direct head-to-head comparison in haemodialysis patients had previously shown RDW to outperform haemoglobin, ferritin and transferrin saturation as a mortality predictor, with a 13.6% net reclassification improvement at 5 years over a case-mix adjusted model [34].

Among the covariates in our cohorts, ADL impairment and albumin were additionally associated with increased mortality. These results were aligned with previous evidence identifying functional disability as one of the main predictors of poor outcomes in older patients, able to subsume the cumulative effects of decreased physiological reserve, accumulation of chronic diseases, and nutritional depletion; albumin depletion is dangerous as well as it reflects both a marker of inflammation and poor nutritional reserve, both of which are triggered by senoinflammation and inflammageing. The observation that RDW retained independent prognostic weight after adjusting for

age, ADL impairment, and albumin underscores its capacity to capture a dimension of systemic dysregulation not fully expressed by functional or nutritional status alone. The pattern of risk emerging from our study is entirely consistent with the call for multidimensional biological ageing profiling [35].

Our findings support $\text{RDW-CV} \geq 15\%$ as an independent prognostic marker of 5-year mortality across heterogeneous older-adult populations. However, the present study was designed to evaluate the independent association between RDW and mortality rather than to develop or validate a clinical prediction model. Consequently, we did not assess whether RDW improves model discrimination or calibration beyond established risk factors. Future studies should determine whether RDW provides incremental predictive value over existing geriatric risk assessment tools and whether its integration into routine clinical practice improves risk stratification, clinical decision-making, and patient outcomes.

This analysis has limits. The 5-year horizon does not resolve cause-specific mortality, and incident non-fatal events were not analysed. Anaemia was operationalised through sex-specific haemoglobin thresholds, without iron-status biomarkers such as transferrin saturation or ferritin, leaving residual confounding by undiagnosed iron deficiency. More broadly, RDW is a non-specific marker, and part of its association with mortality may reflect dimensions of inflammation, nutritional status and chronic disease burden imperfectly captured by NLR [36], albumin and comorbidity count; residual confounding from biological-age axes not included in the model, including epigenetic age, telomere length and multidomain frailty indices, cannot be excluded. RDW was assessed at baseline only, so longitudinal trajectories may carry additional prognostic information. The European cohorts are predominantly Caucasian and southern European; extension to other populations remains to be established. Different analyser platforms across contributing cohorts produce documented inter-instrument bias; the random-effects structure was intended to absorb such between-cohort variability, and the stability of the pooled estimate suggests that residual measurement noise does not invalidate the principal finding. The study does not establish causality, and RDW is to be interpreted as a prognostic marker rather than a therapeutic target. The present study focused on RDW-CV because it is the index most commonly reported in routine clinical practice and was consistently available across all participating cohorts. Although RDW-SD has recently received increasing attention as an alternative measure of erythrocyte size heterogeneity, particularly because it is less influenced by mean corpuscular volume, direct comparisons between RDW-CV and RDW-SD were beyond the scope of this study. Future investigations should evaluate whether RDW-SD provides incremental prognostic information beyond RDW-CV in older adults. In addition, the present study evaluated the prognostic value of a single baseline RDW measurement because this information was consistently available across all participating cohorts and reflects routine clinical practice. However, emerging evidence suggests that RDW should not be considered solely as a static biomarker. Longitudinal changes in RDW, including temporal trajectories and ΔRDW , may provide incremental prognostic information beyond a single baseline assessment. In particular, sequential increases in RDW have been associated with progressively higher mortality risk in older adults, supporting the concept that RDW is a dynamic marker reflecting the evolution of underlying biological processes rather than a fixed characteristic [37]. Future longitudinal studies should therefore investigate whether integrating baseline RDW with its temporal evolution further improves mortality risk prediction and clinical risk stratification in older populations.

Conclusions

Across four European cohorts and a US validation sample, an RDW-CV threshold of 15% identified older adults at higher risk of all-cause mortality during follow-up of up to five years, with the strongest association observed beyond age 85. These findings support $\text{RDW-CV} \geq 15\%$ as an independent prognostic marker that may contribute to mortality risk assessment across heterogeneous older-adult populations. Future studies should determine whether RDW provides incremental predictive value beyond established geriatric risk assessment tools and evaluate its potential role within clinical risk prediction models before routine implementation.

Abbreviations

ADL	Activities of daily living
ATP	Adenosine triphosphate
CI	Confidence interval
CP	Carolei's Project
ECHA	European Challenge of Healthy Ageing project
FI-Lab	Frailty index based on laboratory tests
GEHA	Genetics of Healthy Ageing
HR	Hazard ratio
HRS	Health and Retirement Study
IQR	Interquartile range
MCV	Mean corpuscular volume
MUSA	Monitoring Unsuccessful and Successful Ageing study
NHANES	National Health and Nutrition Examination Survey
NLR	Neutrophil-to-lymphocyte ratio
RDW	Red cell distribution width
RDW-CV	Red cell distribution width coefficient of variation
REPORTAGE	Report-AGE project
RNA	Ribonucleic acid
SADEL	Nursing-home cohort (Sadel group, Calabria)
SD	Standard deviation
SE	Standard error
SOMMA	Study of Muscle, Mobility and Ageing

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Author contributions MDR, AM and LS designed the analysis and wrote the first draft of the manuscript. MDR and MAA analysed the data, conducted the literature review, and contributed to manuscript revision. GP, ACh, ACo, DS and FL provided domain expertise and critical revision of the manuscript. EP, TSC and PM contributed to data analysis, interpretation, and critical revision of the manuscript. LS and GG accessed and verified the HRS data, provided supported for the interpretation of findings and contributed to manuscript revision. GP, and FL obtained funding for the study. All authors contributed to the study design, analysis, or interpretation of the data; and critical revision of the manuscript for intellectual content. All authors could access the study data.

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Data availability European cohort data are available from the corresponding author on reasonable request, subject to the conditions of each contributing study’s data-sharing protocol and ethics approval. The HRS data, including the 2016 Venous Blood Substudy, are publicly accessible through the HRS website (<https://hrs.isr.umich.edu/>) under the standard data-use agreement. Analysis code is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate All contributing studies received approval from the relevant institutional review boards and obtained written informed consent from participants. The HRS protocol was approved by the Health Sciences and Behavioral Sciences Institutional Review Board of the University of Michigan. All procedures involving human participants

were performed in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Declaration of Helsinki and its later amendments.

Competing interests The authors have no conflict of interest to disclose.

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