



Article

Hemoglobin-to-RDW Ratio and All-Cause Mortality in Idiopathic Pulmonary Fibrosis: Complementary Value to Echocardiographic Right Ventricular–Pulmonary Arterial Coupling

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Abstract

Background: The hemoglobin-to-red cell distribution width ratio (HRR) is a composite hematologic biomarker that integrates oxygen-carrying capacity and inflammation-related erythrocyte variability. Its prognostic value in idiopathic pulmonary fibrosis (IPF), and its relationship with right ventricular (RV) function, have not been established. **Methods:** We conducted a single-center retrospective study of 198 patients with IPF. A total of 165 patients with baseline hemoglobin, red cell distribution width (RDW) and date of diagnosis available constituted the analytical cohort. An HRR cutoff (≤ 0.86) was derived by time-dependent Receiver Operating Characteristic (ROC) curve analysis at 5 years. All-cause mortality from diagnosis was assessed by Kaplan–Meier and Cox regression, with bootstrap internal validation. Associations between hematologic markers and TAPSE (Tricuspid Annular Plane Systolic Excursion), PAPs (pulmonary arterial systolic pressure) and TAPSE/PASP were examined by linear and logistic regression, followed by joint stratification of HRR and RV–PA coupling. **Results:** Over a median follow-up of 70.3 months, 57 patients (34.5%) died. Low HRR was associated with higher mortality (72.7% vs. 15.5%; adjusted HR 3.07, 95% CI 1.68–5.63; optimism-corrected HR 2.37) and improved a clinical model beyond RDW (likelihood-ratio $p = 0.012$). HRR was not associated with TAPSE, PAPs, TAPSE/PASP or RV–PA uncoupling. In exploratory joint stratification, mortality rose from 11.7% with both



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markers preserved to 100% with both abnormal (age-adjusted HR 6.47, 95% CI 2.64–15.86). At 5 years, HRR and RDW showed similar discrimination (time-dependent AUC 0.70 and 0.71), higher than TAPSE/PASP (0.61). **Conclusions:** HRR is a simple, inexpensive and independent predictor of mortality in IPF that is unrelated to RV–PA coupling. The two markers provide complementary prognostic information, and their combination identifies a subgroup at very high risk. These findings require external validation.

Keywords: idiopathic pulmonary fibrosis; hemoglobin-to-RDW ratio; red cell distribution width; right ventricular function; TAPSE/PASP; prognosis

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial lung disease of unknown etiology, histologically and radiologically characterized by a usual interstitial pneumonia (UIP) pattern [1]. The disease typically affects older adults, predominantly men with a history of smoking, and is associated with a relentlessly progressive decline in lung function and an exceptionally poor prognosis. Recent epidemiological data from European population-based registries indicate an annual incidence of approximately 4–6 cases per 100,000 inhabitants, with a five-year survival of approximately 50% from the time of diagnosis [2,3]. Although the introduction of antifibrotic therapies (pirfenidone and nintedanib) has slowed disease progression, IPF still carries a median survival of 3–5 years from diagnosis without lung transplantation, and the disease course remains highly heterogeneous and difficult to predict at the individual patient level [4,5].

Pulmonary vascular remodeling and right ventricular (RV) dysfunction are increasingly recognized as important determinants of outcome in IPF [6]. Even in the absence of overt pulmonary hypertension, progressive lung fibrosis, chronic hypoxia, and capillary rarefaction increase right ventricular afterload and impair RV–pulmonary arterial (RV–PA) coupling [7]. Echocardiographic indices of RV function—in particular, the tricuspid annular plane systolic excursion (TAPSE) and its ratio to systolic pulmonary artery pressure (TAPSE/PASP)—provide non-invasive estimates of RV–PA coupling and have been shown to carry independent prognostic information in pulmonary hypertension and chronic lung disease [6,8]. The 2025 American Society of Echocardiography (ASE) guidelines on the right heart endorse the use of TAPSE/PASP as a clinically useful index of RV–PA coupling, with values below 0.30–0.40 mm/mmHg indicating uncoupling [8,9]. Evidence from autoimmune interstitial and pulmonary vascular disease provides additional support for evaluating RV–PA coupling. In a cross-sectional cohort of patients with primary Sjögren’s syndrome, those with interstitial lung disease had higher sPAP and lower TAPSE/sPAP than those without interstitial lung disease. In systemic sclerosis with pulmonary hypertension, a TAPSE/sPAP ratio below 0.32 mm/mmHg was independently associated with cardiovascular events and mortality. Because these findings derive from distinct autoimmune populations, they cannot establish an IPF-specific cutoff; nevertheless, they support the biological and prognostic rationale for evaluating this ratio in fibrotic lung disease [10,11].

Among the routine blood-count parameters, the red cell distribution width (RDW)—a measure of erythrocyte size variability (anisocytosis)—has emerged as a marker of systemic inflammation, oxidative stress, and ineffective erythropoiesis [12,13]. Elevated RDW values have been consistently associated with adverse outcomes across a wide spectrum of cardiovascular and pulmonary conditions [12,14]. In IPF, three previous studies have shown that higher baseline RDW is independently associated with reduced survival, both

as an absolute value and as a longitudinal trajectory [15–17]. Hemoglobin (HB), reflecting oxygen-carrying capacity and overall hematologic reserve, has likewise been associated with prognosis in chronic lung and cardiovascular disease, although its prognostic role in IPF has been less consistently demonstrated. The ratio of hemoglobin to RDW (HB/RDW ratio, hereafter referred to as HRR) has been proposed as a composite hematologic biomarker that integrates the two complementary dimensions captured by HB and RDW: oxygen-carrying capacity and the inflammation- and stress-erythropoiesis-related variability of erythrocyte size [18]. A low HRR—that is, low HB combined with high RDW—has been shown to identify high-risk patients in heart failure with both reduced and preserved ejection fraction [18,19], in coronary artery disease and acute coronary syndromes [20], and in general population studies of cardiovascular and all-cause mortality [19,21]. Compared with HB or RDW alone, HRR appears to provide additive prognostic information in several of these settings, and may offer a unifying readout of the hematologic, inflammatory, and tissue-perfusion derangements that accompany chronic cardiopulmonary disease. To our knowledge, however, the prognostic value of HRR has not been formally evaluated in IPF, nor has its relationship with echocardiographic indices of RV function and RV–PA coupling been examined.

Building on this background, the present study was designed with three sequential aims, addressed in a single-center cohort of patients with IPF. First, we evaluated the prognostic value of HRR for all-cause mortality and identified an optimal cutoff using time-dependent receiver operating characteristic (ROC) analysis, comparing its discriminative performance with that of HB and RDW alone. Second, we examined whether HRR and its individual components were associated with echocardiographic indices of RV function (TAPSE, PAPs and the TAPSE/PASP ratio), to determine whether the prognostic information conveyed by HRR is related to, or independent of, RV–PA coupling. Third, we performed a joint stratification analysis combining HRR with TAPSE/PASP to determine whether these two non-invasive markers provide complementary or overlapping prognostic information, and to identify clinical subgroups at highest risk of mortality.

2. Methods

2.1. Study Design and Population

We conducted a single-center, retrospective, observational study of patients with idiopathic pulmonary fibrosis (IPF) followed at a tertiary referral center. The diagnosis of IPF was established according to international ATS/ERS/JRS/ALAT criteria. Patients were excluded if clinical records were substantially incomplete or if they had concomitant conditions likely to interfere with the assessment of right ventricular function. The source population comprised 198 patients, who formed the basis for the analysis of demographic, clinical, functional, and radiological characteristics.

Baseline hemoglobin and RDW were obtained from the complete blood count performed at the time of IPF diagnosis. All-cause mortality was the primary endpoint. Survival time was calculated from the date of IPF diagnosis to the date of death from any cause, or to the date of last follow-up for patients who remained alive (censored).

2.2. Data Collection

Demographic, clinical, laboratory, functional, and radiological data were extracted from clinical records and the electronic health record and organized in a dedicated database. Collected variables included age, sex, smoking history (current, former, never), cardiovascular risk factors and comorbidities (arterial hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease), and vital status during follow-up. Pulmonary function was characterized by forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide

(DLCO), forced expiratory volume in 1 s (FEV1), and total lung capacity (TLC), expressed as percentages of predicted values. The HRCT pattern at diagnosis was classified according to current radiological categories (definite UIP, probable UIP, indeterminate). Hemoglobin and red cell distribution width (RDW) were obtained from the baseline complete blood count and constituted the primary exposures of the study. The hemoglobin-to-RDW ratio (HRR) was calculated as hemoglobin (g/dL) divided by RDW (%). Because the numerical value of HRR depends on the unit of hemoglobin, this convention was used throughout; HRR values obtained with hemoglobin expressed in g/L are ten times higher (e.g., 0.86 corresponds to 8.6), and patients were categorized according to a cutoff derived by ROC analysis (see Statistical analysis). Mean corpuscular volume (MCV) was also recorded. Complete baseline hemoglobin and RDW were available in 169 of the 198 patients (85.4%), who constituted the analytical cohort.

2.3. Echocardiographic Assessment

Transthoracic echocardiography was performed during routine clinical care, as part of screening for pulmonary hypertension, by experienced cardiologists using Philips ultrasound systems (Philips Healthcare, Amsterdam, The Netherlands), according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging, with particular attention to the right heart chambers. Right ventricular longitudinal systolic function was assessed by tricuspid annular plane systolic excursion (TAPSE). Systolic pulmonary artery pressure (PAPs) was estimated from the peak tricuspid regurgitation (TR) jet velocity using the simplified Bernoulli equation, adding right atrial pressure inferred from the diameter and inspiratory collapsibility of the inferior vena cava; the severity and peak velocity of TR were also recorded. The TAPSE/PASP ratio (mm/mmHg) was calculated as a non-invasive surrogate of right ventricular–pulmonary arterial (RV–PA) coupling.

TAPSE and PAPs were available for all patients in the analytical cohort and were extracted from the clinical reports without re-measurement. Operators were unaware of the study hypothesis but were not formally blinded to clinical and laboratory data. For each patient, the most recent available examination was used. No maximum interval between the blood count at diagnosis and echocardiography was prespecified; the actual interval is reported in the Results.

2.4. Statistical Analysis

Continuous variables are presented as median [interquartile range], because most were not normally distributed (Shapiro–Wilk test), and categorical variables as n/N (%), with N indicating the number of patients with available data. Groups were compared with the Mann–Whitney U test for continuous variables and with the chi-square test, or Fisher's exact test when any expected count was below 5, for categorical variables.

The optimal cutoff of the hemoglobin-to-RDW ratio (HRR) was derived by time-dependent receiver operating characteristic (ROC) analysis, which accounts for the timing of death and for censoring. A prespecified horizon of 5 years from diagnosis was chosen to match the 5-year survival estimates of the Kaplan–Meier analysis. We used the cumulative/dynamic definition: cases were patients who died within 5 years of diagnosis, and controls were patients still alive at 5 years [22,23]. Patients censored before 5 years could not be classified as cases or controls. They were therefore not counted as survivors but were accounted for by inverse probability of censoring weighting, with censoring probabilities estimated by the Kaplan–Meier method [22,24]. Lower HRR values were considered indicative of higher risk. The time-dependent area under the curve, AUC(5 years), was estimated with its 95% confidence interval (CI) from 1000 bootstrap resamples. The threshold that

maximized the time-dependent Youden index (sensitivity + specificity – 1) at 5 years was taken as the optimal cutoff, and its stability was assessed across the same bootstrap resamples. As a sensitivity analysis, the procedure was repeated at a 3-year horizon. The derived threshold (0.845) was practically identical to that obtained by conventional ROC analysis (0.858); the threshold $HRR \leq 0.86$ was therefore applied in all subsequent analyses. No external validation cohort was available; the threshold was therefore evaluated by bootstrap internal validation (see below). To assess discrimination independently of any cutoff, HRR was also analyzed as a continuous variable using Harrell's concordance index (C-index) [25]. For the individual components, RDW was dichotomized at $>15.5\%$, and reduced TAPSE/PASP, an echocardiographic estimate of right ventricular–pulmonary arterial (RV–PA) uncoupling, was defined as a ratio ≤ 0.40 mm/mmHg [8].

Survival was analyzed using the Kaplan–Meier method, with curves stratified by HRR status and compared using the log-rank test; estimated median survival and 5-year survival probabilities were derived from the Kaplan–Meier estimator. The prognostic value of each hematologic marker was assessed using Cox proportional hazards regression. Univariable models were fitted for hemoglobin (per 1 g/dL), RDW (per 1% and as $RDW > 15.5\%$) and HRR (per 0.1-unit increment and as $HRR \leq 0.86$). Multivariable models were adjusted for age, sex, smoking status, DLCO and FVC as a priori clinically relevant confounders, whose number was limited to respect the events-per-variable ratio. As sensitivity analyses, diabetes, dyslipidemia, chronic kidney disease, definite UIP pattern on HRCT, antifibrotic treatment, MCV and echocardiographic pulmonary hypertension (PAPs ≥ 40 mmHg) were added one at a time to the multivariable model, and an extended model included diabetes, dyslipidemia, chronic kidney disease and antifibrotic treatment together. In addition, a propensity score for low HRR was estimated by logistic regression from age, sex, smoking status, DLCO, FVC, diabetes, dyslipidemia, chronic kidney disease and antifibrotic treatment, and used both as a covariate and for stratification by quintiles. The main model was also repeated after excluding the one patient who underwent lung transplantation. Hazard ratios (HRs) are reported with 95% confidence intervals (CI). The proportional hazards assumption was tested with scaled Schoenfeld residuals for each variable and globally; for covariates with borderline departures, models stratified on tertiles of those covariates were fitted as a sensitivity analysis. Linearity of continuous markers with the log hazard was assessed with restricted cubic splines (3 degrees of freedom). Median follow-up was estimated with the reverse Kaplan–Meier method.

To assess whether HRR provides prognostic information beyond its components, Cox models were built on a clinical base model including age, sex, smoking status, DLCO, and FVC. The model with RDW added was compared with the model with HRR added using Harrell's C-index, the Akaike information criterion (AIC), and likelihood-ratio tests for nested models (HRR added to a model containing RDW, and vice versa). Internal validation was performed by bootstrap resampling (500 samples). In each sample, the full modeling procedure, including derivation of the HRR cutoff, was repeated; the model was then applied to the original data, and the mean difference in performance was taken as the optimism (Harrell's method). Optimism-corrected C-indices and hazard ratios are reported.

The relationship between hematologic markers and right ventricular function was examined in the whole analytical cohort. Associations of hemoglobin, RDW (per 1%) and HRR (per 0.1-unit increment) as continuous predictors, and of the dichotomous $HRR \leq 0.86$ indicator, with TAPSE, PAPs and the TAPSE/PASP ratio were assessed by Spearman correlation and linear regression, reporting β coefficients with 95% CI both unadjusted and after adjustment for age, sex, smoking, DLCO and FVC. As a complementary analysis, the binary outcome of RV–PA uncoupling ($TAPSE/PASP \leq 0.40$ mm/mmHg) was modeled

by logistic regression using the same predictors and the same adjustment set, with results expressed as odds ratios (ORs) with 95% CI. As a sensitivity analysis, these associations were repeated in patients whose blood count and echocardiography were performed within ± 1 and ± 2 years of each other, using Spearman correlation and age-adjusted linear regression; effect modification by the time interval was tested with an $\text{HRR} \times \text{interval}$ interaction term.

To evaluate, in an exploratory analysis, whether HRR and RV-PA coupling provided complementary prognostic information, all patients were classified into four mutually exclusive groups defined by the prespecified thresholds ($\text{HRR} \leq 0.86$ and $\text{TAPSE/PASP} \leq 0.40 \text{ mm/mmHg}$). Mortality was compared across groups, survival was displayed by Kaplan–Meier curves with a four-group log-rank test, and the prognostic value of each group was estimated by Cox regression with the “both preserved” group as reference. Cox models were adjusted for age (Model 1) and for age, sex and DLCO (Model 2). A cumulative score (number of abnormal markers, 0–2) was also entered as an ordinal variable in both models, and multiplicative interaction was tested by adding an $\text{HRR} \times \text{uncoupling}$ product term to the age-adjusted model. Because echocardiography was performed after diagnosis, a sensitivity analysis was performed with follow-up starting at the date of echocardiography, in patients with a recorded examination date, with adjustment for age. Because of the limited number of events, the four-group Cox models and the adjusted logistic models for RV-PA uncoupling were repeated using Firth’s penalized likelihood [26,27].

Finally, the discriminative performance of HRR, RDW and TAPSE/PASP for all-cause mortality was compared in the whole analytical cohort by time-dependent AUC at 5 years and Harrell’s C-index. Pairwise differences in AUC were tested by bootstrap (1000 resamples), and sensitivity and specificity were reported at the prespecified cutoffs.

Analyses were performed on complete cases, and the number of patients included in each model is reported. After completion of data retrieval, echocardiographic data were available for all patients; missing data were limited to DLCO ($n = 8$) and smoking status ($n = 1$) in multivariable models, and to body mass index and HRCT pattern in descriptive analyses. A two-sided p -value < 0.05 was considered statistically significant. Analyses were performed using SPSS version 26 and Python 3.11 (statsmodels and SciPy); time-dependent ROC analysis used an inverse probability-of-censoring weighted estimator³.

3. Results

3.1. Study Population

Of the 198 patients with idiopathic pulmonary fibrosis (IPF) included in the registry, 169 (85.4%) had complete baseline measurements of hemoglobin (HB) and red cell distribution width (RDW), allowing calculation of the HB/RDW ratio (HRR). Of these, 165 had a recorded date of diagnosis and constituted the analytical cohort (Figure 1). During follow-up, 57 patients (34.5%) died and 108 (65.5%) were censored alive at database lock; median follow-up was 70.3 months (reverse Kaplan–Meier; IQR 47.5–92.9), and the median observed time was 53.9 months.

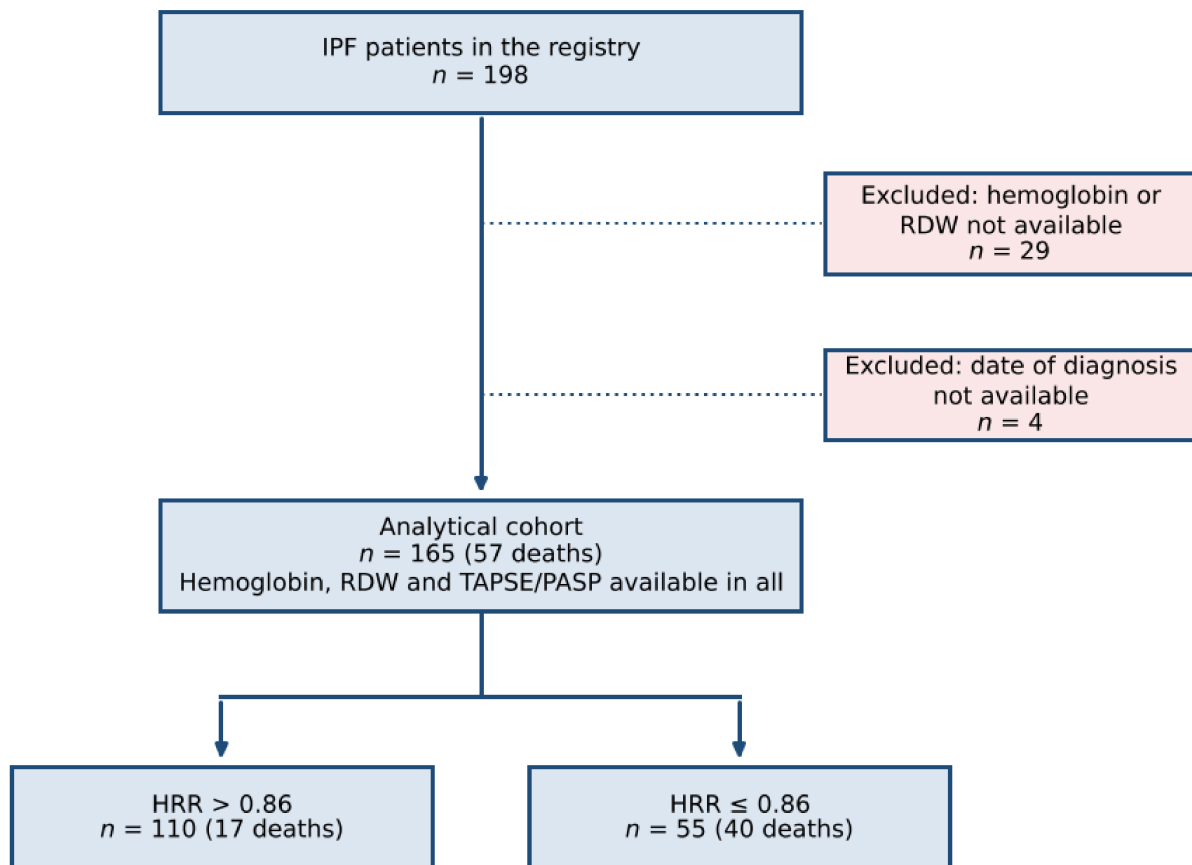


Figure 1. Diagram of subject recruitment in this study.

3.2. Baseline Characteristics by HRR Status

Baseline characteristics by HRR status are presented in Table 1. Patients with $\text{HRR} \leq 0.86$ ($n = 55$) and > 0.86 ($n = 110$) were comparable in age, sex, body mass index, smoking status and antifibrotic treatment. Diabetes mellitus (40.7% vs. 16.4%, $p = 0.001$) and dyslipidemia (72.2% vs. 49.5%, $p = 0.010$) were more frequent in the low-HRR group, whereas hypertension and chronic kidney disease did not differ. DLCO tended to be lower in the low-HRR group (median 46.5% vs. 55.0% of predicted, $p = 0.056$), while FVC, FEV1 and TLC were similar. Definite UIP was numerically more frequent in the low-HRR group (53.7% vs. 36.5%), but the distribution of HRCT patterns did not differ significantly ($p = 0.076$). As expected from the definition of the ratio, hemoglobin was lower (median 11.7 vs. 14.7 g/dL) and RDW higher (16.2% vs. 14.0%) in the low-HRR group (both $p < 0.001$), while MCV did not differ ($p = 0.40$). Echocardiographic indices were similar in the two groups: median TAPSE 20.0 vs. 20.0 mm, PAPs 33.0 vs. 30.0 mmHg, TAPSE/PASP 0.62 vs. 0.65 mm/mmHg, and RV-PA uncoupling 16.4% vs. 14.5% (all $p > 0.4$). Mortality was 72.7% in the low-HRR group and 15.5% in the preserved-HRR group ($p < 0.001$).

Table 1. Baseline characteristics by HB/RDW status (cutoff 0.86).

Variable	HRR > 0.86 ($n = 111$)	HRR ≤ 0.86 ($n = 58$)	<i>p</i> -Value
Demographics and comorbidities			
Age at diagnosis, years	72.6 [66.1–77.4]	74.5 [68.9–79.2]	0.058
Male sex	92/110 (83.6)	47/55 (85.5)	0.940
BMI, kg/m ²	26.6 [24.1–29.1]	24.9 [23.2–27.5]	0.262

Table 1. Cont.

Variable	HRR > 0.86 (n = 111)	HRR ≤ 0.86 (n = 58)	p-Value
Ever smoker	83/110 (75.5)	43/54 (79.6)	0.690
Hypertension	59/109 (54.1)	34/54 (63.0)	0.366
Diabetes mellitus	18/110 (16.4)	22/54 (40.7)	0.001
Dyslipidemia	54/109 (49.5)	39/54 (72.2)	0.010
Chronic kidney disease	6/110 (5.5)	3/54 (5.6)	1.000
Antifibrotic treatment	101/110 (91.8)	50/55 (90.9)	1.000
Pulmonary function and imaging			
FVC, % predicted	87.5 [76.0–102.8]	89.0 [78.0–99.0]	0.853
FEV1, % predicted	97.0 [80.2–107.8]	97.0 [83.5–104.5]	0.681
TLC, % predicted	83.0 [74.0–98.0]	81.0 [75.0–94.0]	0.879
DLCO, % predicted	55.0 [42.0–68.0]	46.5 [37.2–61.0]	0.056
HRCT: Definite UIP	38/104 (36.5)	22/41 (53.7)	0.076
HRCT: Probable UIP	45/104 (43.3)	16/41 (39.0)	
HRCT: Indeterminate	21/104 (20.2)	3/41 (7.3)	
Hematology			
Hemoglobin, g/dL	14.7 [13.8–15.4]	11.7 [10.9–12.4]	<0.001
RDW, %	14.0 [13.6–14.6]	16.2 [15.8–18.5]	<0.001
MCV, fL	93.0 [90.3–96.7]	91.0 [88.5–97.4]	0.399
Echocardiography			
TAPSE, mm	20.0 [18.0–22.0]	20.0 [18.0–23.0]	0.697
PAPs, mmHg	30.0 [24.0–40.0]	33.0 [25.0–44.0]	0.435
TAPSE/PASP, mm/mmHg	0.65 [0.49–0.88]	0.62 [0.47–0.89]	0.609
RV-PA uncoupling (TAPSE/PASP ≤ 0.40)	16/110 (14.5)	9/55 (16.4)	0.939
Death during follow-up	17/110 (15.5)	40/55 (72.7)	<0.001

Data presented as mean ± SD or n (%). Mann–Whitney U test and chi-square or Fisher exact test were used. BMI, body mass index; CKD, chronic kidney disease; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; TLC, total lung capacity; DLCO, diffusing capacity of the lung for carbon monoxide; HRCT, high-resolution computed tomography; UIP, usual interstitial pneumonia; RDW, red cell distribution width; MCV, mean corpuscular volume; TAPSE, tricuspid annular plane systolic excursion; PAPs, systolic pulmonary artery pressure. BMI was available in 79 patients and HRCT pattern in 145.

3.3. Derivation of the HRR Cutoff

In time-dependent ROC analysis at 5 years (32 deaths within 5 years, 77 patients alive at 5 years), HRR had an AUC of 0.70 (95% CI 0.59–0.81). The Youden-optimal threshold was 0.845 (sensitivity 68%, specificity 69%), practically identical to that obtained by conventional ROC analysis (0.858), and the same threshold was obtained at 3 years. The threshold $\text{HRR} \leq 0.86$ was therefore applied in all analyses; at 5 years it had a sensitivity of 68% and a specificity of 68%. On bootstrap resampling, the optimal threshold showed moderate variability (median 0.84, interquartile range 0.78–0.92).

3.4. Hematologic Markers as Predictors of All-Cause Mortality

In univariable Cox analysis, all hematologic markers were associated with mortality (Table 2). These included hemoglobin (HR 0.79, 95% CI 0.70–0.89 per 1 g/dL, $p < 0.001$) and RDW, both as a continuous variable (HR 1.25, 95% CI 1.14–1.36 per 1%, $p < 0.001$) and above 15.5% (HR 3.94, 95% CI 2.26–6.87, $p < 0.001$). They also included HRR, both as a continuous variable (HR 0.73, 95% CI 0.65–0.83 per 0.1 unit, $p < 0.001$) and dichotomized at ≤ 0.86 (HR 3.81, 95% CI 2.14–6.81, $p < 0.001$). After adjustment for age, sex, smoking, DLCO and FVC ($n = 156$, 55 deaths), all markers remained independently associated with mortality, including HRR per 0.1 unit (HR 0.77, 95% CI 0.67–0.88, $p < 0.001$) and $\text{HRR} \leq 0.86$ (HR 3.07, 95% CI 1.68–5.63, $p < 0.001$). The proportional hazards assumption was satisfied for all

hematologic markers (Schoenfeld $p \geq 0.30$), and results were unchanged when the model was stratified on DLCO and age tertiles. Spline analysis supported a linear association of HRR and hemoglobin with the log hazard (p for non-linearity 0.44 and 0.33), whereas the association of RDW was non-linear ($p = 0.03$), with risk plateauing above approximately 18% (Supplementary Figure S1).

Table 2. Univariable and multivariable Cox regression for all-cause mortality.

Marker	Unadjusted HR (95% CI)	p -Value	Adjusted HR (95% CI)	p -Value
Hemoglobin (per 1 g/dL)	0.79 (0.70–0.89)	<0.001	0.80 (0.69–0.91)	0.001
RDW (per 1%)	1.25 (1.14–1.36)	<0.001	1.16 (1.05–1.27)	0.003
RDW > 15.5%	3.94 (2.26–6.87)	<0.001	2.96 (1.62–5.38)	<0.001
HRR (per 0.1 unit)	0.73 (0.65–0.83)	<0.001	0.77 (0.67–0.88)	<0.001
HRR ≤ 0.86 (vs > 0.86)	3.81 (2.14–6.81)	<0.001	3.07 (1.68–5.63)	<0.001

Univariable models: $n = 169$, 57 deaths. Adjusted for age, sex, smoking (ever vs. never), DLCO and FVC.

Kaplan–Meier curves separated clearly according to HRR status (log-rank $p < 0.001$; Figure 2). Five-year survival was 57.2% in patients with HRR ≤ 0.86 and 88.1% in those with HRR > 0.86. Median survival was 74.5 months in the low-HRR group and was not reached in the preserved-HRR group. The association between low HRR and mortality was consistent in all sensitivity models (HR range 2.61–4.70, all $p \leq 0.003$), including the extended model (HR 3.32, 95% CI 1.70–6.49) and propensity-score adjustment (HR 2.66, 95% CI 1.41–5.03) (Supplementary Table S4).

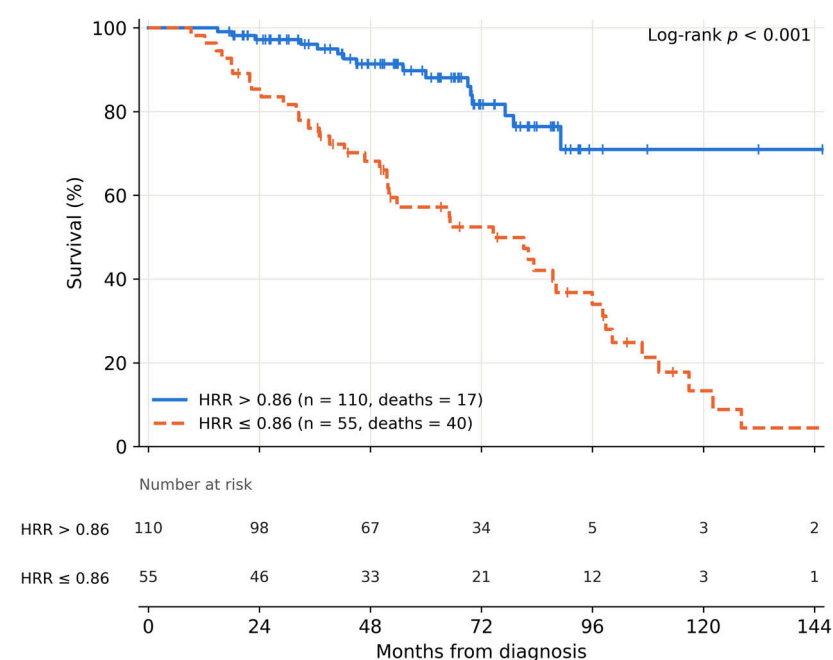


Figure 2. Kaplan–Meier survival curves stratified by HRR status in the analytical cohort ($n = 165$). Patients with HRR ≤ 0.86 ($n = 55$) had worse survival than those with HRR > 0.86 ($n = 110$; log-rank $p < 0.001$). Five-year survival was 57.2% and 88.1%, respectively; median survival was 74.5 months in the low-HRR group and not reached in the preserved-HRR group. Tick marks indicate censored observations.

3.5. Incremental Prognostic Value and Internal Validation

To determine whether HRR provides prognostic information beyond its components, RDW and HRR were each added to a clinical base model including age, sex, smoking,

DLCO and FVC (Table 3). Adding HRR improved model fit more than adding RDW (likelihood-ratio χ^2 13.98 vs. 7.83; AIC 402.7 vs. 408.9), with a higher optimism-corrected C-index (0.776 vs. 0.762; base model 0.740). In the model containing both markers, HRR remained significantly associated with mortality after adjustment for RDW (likelihood-ratio $p = 0.012$), whereas RDW added no information beyond HRR ($p = 0.70$). However, the gain in discrimination of HRR over RDW was small and not statistically significant ($\Delta C +0.014$, bootstrap 95% CI -0.013 to 0.035). On bootstrap internal validation, in which the HRR cutoff was re-derived in each resample, the optimism-corrected C-index of the model including dichotomous HRR was 0.764 (apparent 0.797), and the optimism-corrected hazard ratio for HRR ≤ 0.86 was 2.37 (apparent 3.05).

Table 3. Incremental prognostic value of RDW and HRR beyond a clinical base model, with bootstrap internal validation.

Model	C-Index (Apparent)	C-Index (Optimism-Corrected)	AIC	Likelihood-Ratio Test
Base model *	0.764	0.740	414.7	—
Base + RDW	0.787	0.762	408.9	vs base: χ^2 7.83, $p = 0.005$
Base + HRR	0.801	0.776	402.7	vs base: χ^2 13.98, $p < 0.001$
Base + RDW + HRR	0.798	0.769	404.6	HRR added to RDW: χ^2 6.30, $p = 0.012$; RDW added to HRR: χ^2 0.15, $p = 0.70$
Base + HRR $\leq$ cutoff †	0.797	0.764	—	HR 3.05 (optimism-corrected 2.37)

* Base model: age, sex, smoking status, DLCO and FVC ($n = 156$, 55 deaths). HRR entered per 0.1 unit, RDW per 1%. † Cutoff re-derived by time-dependent ROC analysis in each bootstrap sample. Optimism correction by bootstrap (500 resamples, Harrell's method). Difference in C-index between the HRR and RDW models: $+0.014$ (bootstrap 95% CI -0.013 to 0.035). AIC, Akaike information criterion; lower values indicate better fit.

3.6. Relationship Between Hematologic Markers and Right Ventricular Function

We examined the associations of hemoglobin, RDW and HRR (as continuous variables, with HRR per 0.1 unit and RDW per 1%), and of the dichotomous HRR ≤ 0.86 indicator, with TAPSE, PAPs and the TAPSE/PASP ratio. Linear regression was used, unadjusted and adjusted for age, sex, smoking, DLCO and FVC; RV-PA uncoupling (TAPSE/PASP ≤ 0.40 mm/mmHg) was modeled by logistic regression (Figure 3; Supplementary Table S1). RV-PA uncoupling was present in 25 patients (24 in the adjusted sample). In the overall cohort, none of the hematologic markers was associated with any index of RV function. In adjusted models ($n = 156$), HRR per 0.1 unit was not associated with TAPSE ($\beta +0.09$, $p = 0.48$), PAPs ($\beta -0.50$, $p = 0.35$) or TAPSE/PASP ($\beta +0.012$, $p = 0.28$), nor with RV-PA uncoupling (OR 0.89, 95% CI 0.72–1.11, $p = 0.31$). RDW showed only a non-significant trend towards lower TAPSE ($\beta -0.21$ per 1%, $p = 0.077$), and hemoglobin was not associated with any RV parameter. The correlation between HRR and TAPSE/PASP was weak and non-significant (Spearman $\rho = 0.10$, $p = 0.22$).

The blood count and echocardiography were performed a median of 2.5 years apart (IQR 1.0–5.1; $n = 138$). In patients with both measurements within 1 year ($n = 31$), higher HRR correlated with lower PAPs ($\rho = -0.43$, $p = 0.02$) and higher TAPSE/PASP ($\rho = 0.39$, $p = 0.03$); after adjustment for age, the association with TAPSE/PASP was borderline ($p = 0.08$). Within 2 years ($n = 53$), the associations were weaker (PAPs $\rho = -0.29$, $p = 0.03$; TAPSE/PASP $\rho = 0.26$, $p = 0.06$), and the interaction between HRR and the time interval was not significant ($p = 0.31$) (Supplementary Table S3). HRR and RV-PA coupling therefore appear to capture largely distinct dimensions of risk, although a relationship with contemporaneous pulmonary pressure cannot be excluded.

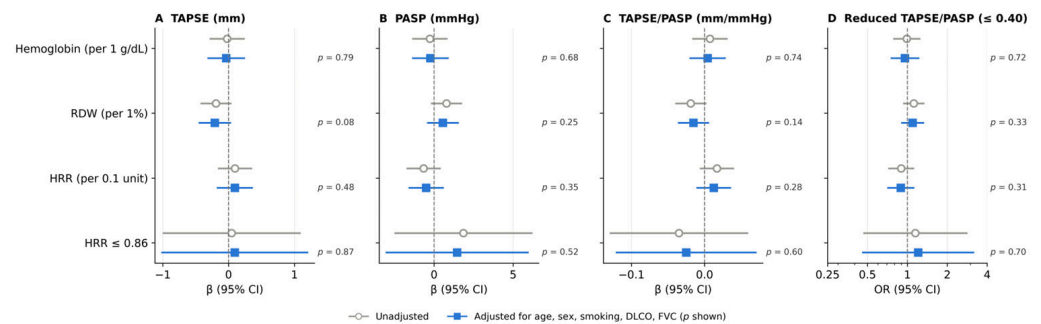


Figure 3. Associations of hematologic markers (hemoglobin, RDW, HRR as continuous and HRR ≤ 0.86 as binary) with right ventricular parameters. Panels (A–C) show β coefficients from linear regression for TAPSE (A), PAPs (B) and the TAPSE/PASP ratio (C); panel (D) shows odds ratios from logistic regression for RV–PA uncoupling (TAPSE/PASP ≤ 0.40 mm/mmHg). Open circles: unadjusted ($n = 165$); filled squares: adjusted for age, sex, smoking, DLCO and FVC ($n = 156$), with the corresponding p -values. None of the associations was statistically significant.

3.7. Joint Stratification by HRR and RV–PA Coupling Status

To assess whether HRR and TAPSE/PASP provide complementary prognostic information, patients were classified into four groups based on the prespecified thresholds (Table 4, Figure 4). Mortality increased from 11/94 (11.7%) in patients with both markers preserved to 6/16 (37.5%) with isolated RV–PA uncoupling, 31/46 (67.4%) with isolated low HRR, and 9/9 (100%) with both markers abnormal (log-rank $p < 0.001$). Compared with patients with both markers preserved, the age-adjusted HR was 2.38 (95% CI 0.87–6.48, $p = 0.090$) for isolated uncoupling, 4.00 (1.97–8.12, $p < 0.001$) for isolated low HRR, and 6.47 (2.64–15.86, $p < 0.001$) for both abnormal. Each additional abnormal marker was associated with an HR of 2.58 (1.72–3.88, $p < 0.001$). After further adjustment for sex and DLCO, isolated low HRR (HR 3.72, 1.82–7.60) and combined abnormality (HR 3.40, 1.34–8.64, $p = 0.010$) remained associated with mortality. The cumulative score also remained significant (HR 1.95 per abnormality, 1.30–2.92, $p = 0.001$). There was no multiplicative interaction between low HRR and uncoupling ($p = 0.55$).

Table 4. Cox regression for all-cause mortality by joint HRR and RV–PA coupling status.

Group	<i>n</i>	Deaths	Model 1 HR (95% CI)	<i>p</i> -Value	Model 2 HR (95% CI)	<i>p</i> -Value
Both preserved (HRR > 0.86 and TAPSE/PASP > 0.40)	94	11 (11.7%)	1.00 (reference)		1.00 (reference)	
Isolated RV–PA uncoupling (HRR > 0.86 and TAPSE/PASP ≤ 0.40)	16	6 (37.5%)	2.38 (0.87–6.48)	0.090	2.28 (0.82–6.33)	0.114
Isolated low HRR (HRR ≤ 0.86 and TAPSE/PASP > 0.40)	46	31 (67.4%)	4.00 (1.97–8.12)	<0.001	3.72 (1.82–7.60)	<0.001
Both abnormal (HRR ≤ 0.86 and TAPSE/PASP ≤ 0.40)	9	9 (100.0%)	6.47 (2.64–15.86)	<0.001	3.40 (1.34–8.64)	0.010
Per additional abnormal marker (0–2)			2.58 (1.72–3.88)	<0.001	1.95 (1.30–2.92)	0.001

Follow-up from diagnosis. Model 1: adjusted for age ($n = 165$, 57 deaths). Model 2: adjusted for age, sex and DLCO ($n = 157$, 56 deaths). Log-rank $p < 0.001$. p for HRR × uncoupling interaction = 0.55. Events per parameter: Model 1 ≈ 14, Model 2 ≈ 9. Exploratory analysis; estimates were unchanged with Firth’s penalized Cox regression (Supplementary Table S5).

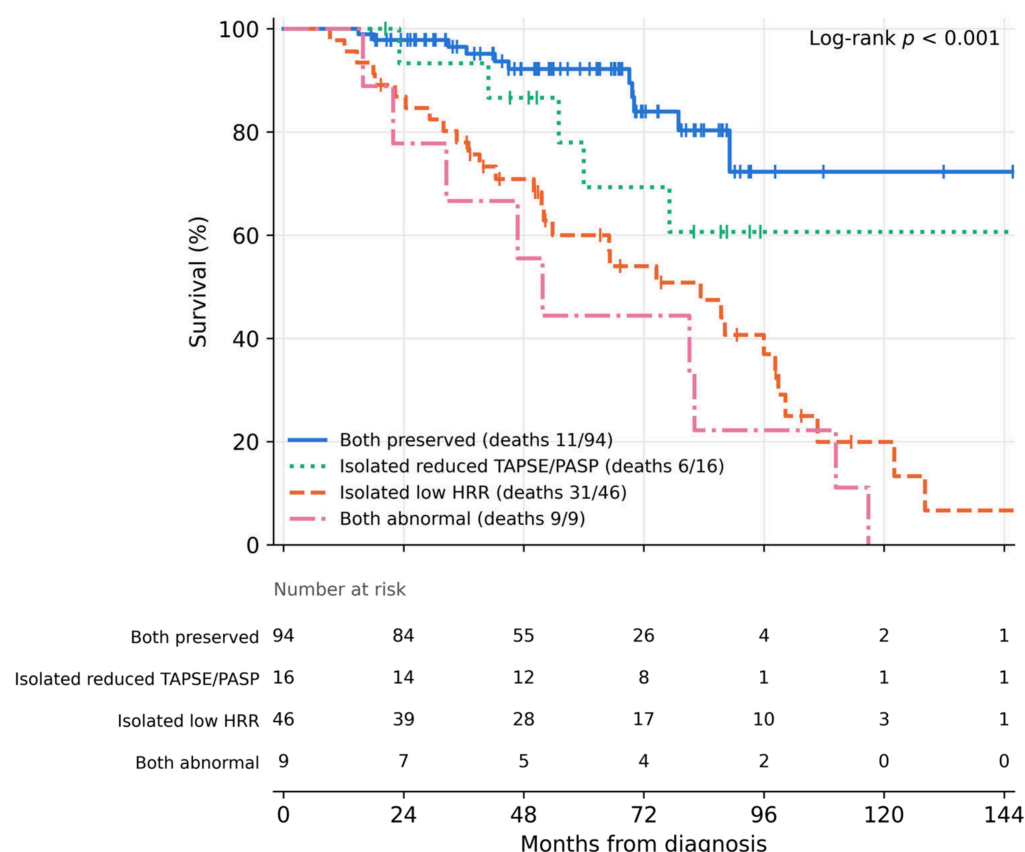
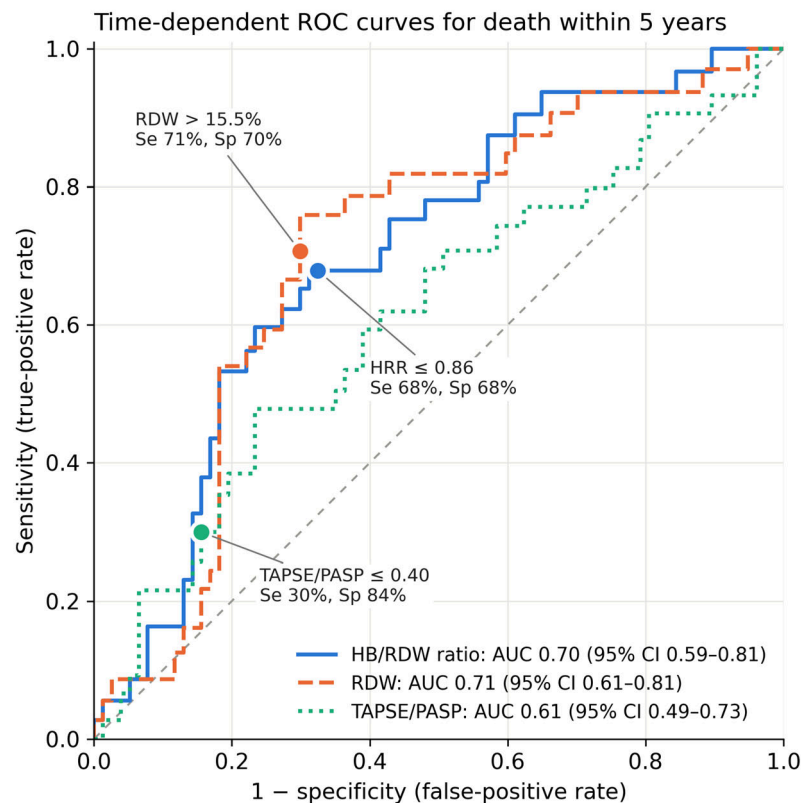


Figure 4. Kaplan–Meier survival curves by joint HRR (≤ 0.86 vs. > 0.86) and TAPSE/PASP (≤ 0.40 vs. > 0.40 mm/mmHg) status ($n = 165$). Mortality was 11.7% with both markers preserved, 37.5% with isolated RV–PA uncoupling, 67.4% with isolated low HRR and 100% with both abnormal. Log-rank $p < 0.001$.

Because echocardiography was performed after diagnosis, the analysis was repeated with follow-up starting on the date of echocardiography in 138 patients (45 deaths; median follow-up 20.5 months) (Supplementary Table S2). The gradient was consistent and steeper. Compared with the both preserved group, the age-adjusted HR was 3.41 (1.17–9.91) for isolated uncoupling, 6.32 (2.81–14.18) for isolated low HRR, and 24.35 (8.60–68.92) for both abnormal (all $p < 0.05$); the last estimate is imprecise because all 7 patients in this group died.

3.8. Comparative Discriminative Performance

In time-dependent ROC analysis at 5 years in the 165 patients (32 deaths within 5 years) (Figure 5), discrimination was similar for HRR (AUC 0.70, 95% CI 0.59–0.81) and RDW (AUC 0.71, 95% CI 0.61–0.81), and lower for TAPSE/PASP (AUC 0.61, 95% CI 0.49–0.73). None of the pairwise differences was statistically significant (bootstrap 95% CI for the difference HRR – RDW -0.07 to 0.06 , $p = 0.79$; HRR – TAPSE/PASP -0.09 to 0.27 , $p = 0.32$). Harrell’s C-indices were consistent (0.70, 0.71 and 0.60, respectively). At the prespecified cutoffs and a 5-year horizon, HRR ≤ 0.86 had a sensitivity of 68% and a specificity of 68%, and RDW $> 15.5\%$ had a sensitivity of 71% and a specificity of 70%. TAPSE/PASP ≤ 0.40 showed the highest specificity (84%) but low sensitivity (30%).



$n = 165$; 32 deaths within 5 years, 77 alive at 5 years; IPCW (Uno) estimator, 1,000 bootstrap resamples. Dots mark the prespecified cutoffs.

Figure 5. Time-dependent receiver operating characteristic (ROC) curves at 5 years from diagnosis for HRR, RDW and the TAPSE/PASP ratio for the prediction of all-cause mortality ($n = 165$; 32 deaths within 5 years, 77 patients alive at 5 years). Curves and areas under the curve were estimated with inverse probability of censoring weighting; 95% CIs from 1,000 bootstrap resamples. Dots indicate the prespecified cutoffs ($\text{HRR} \leq 0.86$, $\text{RDW} > 15.5\%$, $\text{TAPSE/PASP} \leq 0.40$ mm/mmHg) with the corresponding sensitivity (Se) and specificity (Sp) at 5 years.

4. Discussion

In this single-center retrospective cohort of patients with IPF, we evaluated the prognostic value of the hemoglobin-to-RDW ratio (HRR) and its relationship with echocardiographic indices of right ventricular (RV) function. Three main findings emerged. First, HRR was an independent predictor of all-cause mortality: patients with $\text{HRR} \leq 0.86$ had a three-fold higher adjusted hazard of death, which persisted after bootstrap correction for optimism, and HRR improved model fit beyond RDW alone. Second, HRR was not associated with RV function or RV–PA coupling, indicating that the two markers capture distinct dimensions of risk. Third, the joint assessment of HRR and RV–PA coupling identified a gradient of risk, with mortality ranging from 12% in patients with both markers preserved to 100% in the small subgroup with both abnormal.

4.1. HRR as a Prognostic Marker

Our results expand the growing body of evidence supporting the prognostic role of HRR in chronic cardiopulmonary disease. The composite ratio, originally proposed in oncology and later validated across cardiovascular populations, integrates two complementary erythrocyte parameters: hemoglobin concentration, which reflects oxygen-carrying capacity and chronic disease-related anemia, and RDW, a marker of erythrocyte size heterogeneity that captures inflammation, oxidative stress, and impaired erythropoiesis [19,21,25]. In coronary atherosclerotic heart disease, $\text{HRR} < 10.25$ was associated with a near doubling

of long-term mortality after percutaneous coronary intervention [20], and in pulmonary embolism, low HRR independently predicted both 28-day and 90-day mortality with consistently higher discriminative ability than hemoglobin or RDW alone [28]. Of note, the numerical value of HRR depends on the unit of hemoglobin. Thresholds derived with hemoglobin in g/L, as in the coronary study [20], are about ten times higher than those obtained with hemoglobin in g/dL, as in ours; our cutoff of 0.86 corresponds to 8.6 when hemoglobin is expressed in g/L. Published HRR cutoffs should therefore be compared only after harmonizing units, and even then, with caution, because thresholds also depend on the population studied and on the analyzer used to measure RDW.

In IPF, only its individual hematologic components have been explored to date. Nathan and colleagues first reported that an elevated baseline RDW (>15%) was associated with a 2.6-fold higher mortality and a substantially shortened median survival (16 vs. 43 months) in 319 IPF patients followed for up to 14 years [16]. This finding was subsequently confirmed by Gürün-Kaya and colleagues, who found that RDW remained an independent prognostic factor after adjustment for DLCO (HR 1.65, 95% CI 1.09–2.47) [15], and more recently by Ay and colleagues, who demonstrated that RDW > 13.6% and an elevated neutrophil count both correlated negatively with survival in a real-world IPF cohort [29]. Our findings extend these observations: in model comparisons, HRR improved prognostic fit beyond RDW, indicating that its hemoglobin component carries independent information, although the gain in discrimination was modest. HRR also offers a potential practical advantage: it captures the anemia-associated and inflammation-associated dimensions of the disease in a single index. Whether it is also less influenced by transient fluctuations of either component remains to be tested with repeated measurements. The cutoff was derived within our cohort by time-dependent ROC analysis at 5 years (0.845, applied as ≤ 0.86), and showed moderate variability on bootstrap resampling; as an internally derived threshold, it requires confirmation in external cohorts.

In contrast with our original hypothesis, HRR and its components were not associated with TAPSE, PAPs, the TAPSE/PASP ratio or RV–PA uncoupling in the complete cohort, and the correlation between HRR and TAPSE/PASP was weak and non-significant. In the small subgroup with contemporaneous measurements, however, HRR correlated with pulmonary pressure, suggesting that a relationship may have been diluted by the interval between blood sampling and echocardiography. This differs from observations in autoimmune disease. In primary Sjögren's syndrome, a lower HRR was associated with higher PAPs and lower TAPSE/PASP, particularly in the presence of vitamin D insufficiency, and in systemic sclerosis vitamin D insufficiency was associated with similar echocardiographic changes [28,30]. These cross-sectional, disease-specific observations may reflect the different pathophysiology of pulmonary vascular involvement in connective tissue disease. In IPF, our data suggest that the hematologic profile captured by HRR and the pulmonary vascular load reflected by TAPSE/PASP are largely independent.

The lack of association with RV function suggests that HRR conveys prognostic information through pathways other than RV afterload. IPF is characterized by chronic systemic inflammation, oxidative stress and hypoxemia, which suppress erythropoiesis and widen the red-cell size distribution. Low HRR may also reflect anemia of chronic disease, nutritional status and comorbidity burden; in our cohort, diabetes and dyslipidemia were more frequent in patients with low HRR. RV–PA uncoupling, by contrast, mainly reflects pulmonary vascular remodeling and the extent of parenchymal involvement, as suggested by its close relationship with DLCO in this cohort [7,31,32]. RDW has been associated with pulmonary hypertension in other populations [33], but in IPF the two processes appear to contribute separately to prognosis. This would explain why their combination identified the patients at highest risk.

4.2. Joint Stratification: A High-Risk IPF Phenotype

The exploratory joint assessment of HRR and RV-PA coupling showed a clear gradient of risk. Mortality was 11.7% in patients with both markers preserved, 37.5% with isolated reduced TAPSE/PASP, 67.4% with isolated low HRR and 100% in the 9 patients with both abnormal. Each additional abnormal marker was associated with a 2.6-fold higher hazard of death. There was no multiplicative interaction, indicating a cumulative rather than synergistic effect, consistent with the two markers capturing independent dimensions of risk. The gradient was also consistent, and steeper, when follow-up started at the date of echocardiography. After adjustment for sex and DLCO, however, the hazard ratio for combined abnormality was similar to that for isolated low HRR, and estimates for the combined group were imprecise because of its small size. A reduced TAPSE/PASP ratio, a strong predictor of mortality in pulmonary hypertension of various causes, has been shown to outperform either TAPSE or PASP in isolation in heart failure, pulmonary arterial hypertension, and post-cardiac-surgery cohorts [8,30,31], and the present data are consistent with its prognostic relevance in IPF, where pulmonary hypertension is a common and impactful comorbidity [32,33], although in our cohort isolated reduced TAPSE/PASP did not reach statistical significance. Alternative echocardiographic measures of right ventricular-pulmonary arterial coupling may also merit investigation in IPF. In a multicenter registry of 347 patients with incident pulmonary arterial hypertension, a lower FAC/PASP ratio was independently associated with higher 1-year and 5-year all-cause mortality. However, FAC/PASP has not been validated in IPF or group 3 pulmonary hypertension, and the analysis was not designed to establish IPF-specific thresholds [34,35].

From a clinical standpoint, the joint use of HRR and TAPSE/PASP is appealing for three reasons. First, both markers are inexpensive and broadly available: HRR requires only a routine complete blood count, and TAPSE/PASP requires a standard transthoracic echocardiogram already routinely performed in IPF for the screening of pulmonary hypertension [33,36]. More broadly, simple inflammatory indices derived from routine blood-count analysis have shown prognostic value in cardiovascular populations, for example the delta neutrophil index in patients undergoing open-heart surgery with cardiopulmonary bypass [37] and the neutrophil-to-lymphocyte ratio after coronary artery bypass grafting [38], supporting their potential for pragmatic risk stratification. These observations derive from perioperative cardiovascular settings and do not constitute direct evidence in IPF. Second, neither marker depends on advanced imaging, invasive hemodynamics, or specialized expertise beyond standard clinical practice. Third, the two markers appear to capture complementary information and, when used together, identified the patients with the worst survival in our cohort. Whether this risk stratification can usefully guide follow-up intensity, the timing of lung transplant referral or patient selection in clinical trials is a hypothesis that requires prospective validation.

4.3. Comparative Discriminative Performance

In time-dependent ROC analysis at 5 years, HRR and RDW showed similar, moderate discrimination for mortality (AUC 0.70 and 0.71), and both performed better than TAPSE/PASP (AUC 0.61), although none of the pairwise differences was statistically significant. HRR therefore does not outperform RDW as a discriminator; its added value lies in improved model fit and in combining the anemia-related and inflammation-related dimensions in a single index. $\text{TAPSE/PASP} \leq 0.40$ had high specificity (84%) but low sensitivity (30%), suggesting that it is more useful to confirm a high-risk phenotype than to screen for it. Overall, these AUC values indicate moderate discrimination, so neither marker should be used in isolation.

4.4. Strengths and Limitations

The main strengths of our study include a real-world, single-center IPF cohort with detailed hematologic and echocardiographic phenotyping, prolonged median follow-up (70.3 months), and the use of survival analysis with Cox regression rather than logistic regression alone, allowing appropriate handling of censoring and time-to-event information. The consistency of the findings across Cox regression, joint stratification, time-dependent ROC analysis and bootstrap internal validation strengthens confidence in the central finding.

Our work also has limitations. First, this is a retrospective single-center study, and the HRR cutoff was derived and evaluated in the same cohort. Although bootstrap internal validation was performed, the optimism-corrected hazard ratio was about 20% lower than the apparent estimate, and the optimal threshold varied moderately across bootstrap samples; external validation in independent IPF populations, ideally prospective and with standardized echocardiographic protocols, is required before HRR-based risk stratification can be recommended in routine practice. Second, echocardiography was performed a median of 2.5 years after the blood count at diagnosis, and the interval exceeded 1 year in most patients. This may have attenuated associations between hematologic markers and RV indices; in the small subgroup with contemporaneous measurements, HRR correlated with pulmonary pressure. For the prognostic analyses, results were consistent when follow-up started at the date of echocardiography. In addition, echocardiographic values were obtained from routine clinical reports by operators who were not formally blinded to clinical data. Third, only 9 patients had both low HRR and RV-PA uncoupling, so estimates for this group are imprecise and were attenuated after adjustment for sex and DLCO. Fourth, results were robust to additional adjustment for comorbidities, HRCT pattern, antifibrotic treatment and propensity scores. However, oxygen requirement, iron and vitamin status, inflammatory markers and transplant listing were not systematically available, so residual confounding cannot be excluded; low HRR may partly reflect comorbidity burden and anemia of chronic disease. Fifth, the marked male predominance of the cohort (84%) precluded a reliable evaluation of sex-specific effects, which should be assessed in larger IPF cohorts. Cardiometabolic phenotype may be another source of heterogeneity: in a multicenter cohort of 581 patients with incident pulmonary arterial hypertension, ESC/ERS risk-stratification tools showed numerically lower discrimination in patients with obesity, although the differences were not statistically significant. Because this evidence derives from group 1 pulmonary arterial hypertension, future IPF studies should test whether BMI and metabolic comorbidities modify the prognostic performance of HRR and TAPSE/PASP [36]. Sixth, pulmonary pressure and RV-PA uncoupling were assessed by echocardiography rather than right heart catheterization. The TAPSE/PASP threshold of 0.40 is well validated in cardiovascular populations [8,34], but echocardiographic estimation of PAPs has known limitations in advanced lung disease, and TAPSE-based indices are subject to inter-operator variability. In a standardized study of 100 patients with systemic sclerosis, TDI S' showed greater reproducibility than TAPSE, supporting standardized acquisition and multiparametric assessment of RV function [39]. Finally, we did not capture longitudinal trajectories of HRR or TAPSE/PASP; whether changes in HRR during treatment predict outcome, as previously shown for RDW, remains an attractive direction for future studies. Taken together, these limitations highlight the need for larger, prospective, multicenter studies including more diverse IPF populations, with standardized echocardiographic protocols and repeated hematologic measurements. Such studies are necessary to validate the HRR threshold externally, to confirm the complementary prognostic value of HRR and TAPSE/PASP, and to establish whether these findings can be generalized to routine clinical practice.

5. Clinical Implications and Conclusion

In summary, our findings support HRR as a simple and inexpensive hematologic biomarker that independently predicts all-cause mortality in IPF and was not associated with RV–PA coupling in the overall cohort. Because HRR is influenced by comorbidities, renal function and nutritional status, residual confounding cannot be excluded, and HRR should be regarded as a marker of risk rather than a causal factor. When combined with the echocardiographic assessment of RV–PA coupling, HRR helps identify a high-risk IPF phenotype; whether these patients benefit from intensified surveillance or earlier consideration of advanced therapies, including lung transplantation, should be tested in prospective studies. Because both measurements are already routinely performed in IPF care, integrating HRR and TAPSE/PASP into the prognostic workflow requires no additional cost or technology. Prospective multicenter validation, ideally with longitudinal sampling, is needed to confirm these observations and to define the place of HRR within the broader prognostic framework of IPF.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/jcdd13110532/s1>, Table S1: Associations of hematologic markers with echocardiographic indices of RV function; Table S2: Sensitivity analysis: joint stratification with follow-up from the date of echocardiography; Table S3: Sensitivity analysis: associations of HRR with RV indices according to the interval between blood count and echocardiography; Table S4: Sensitivity analyses for additional confounders: Cox regression for all-cause mortality; Table S5: Sensitivity analysis with Firth’s penalized likelihood for models with few events; Figure S1: Association of HRR (A), RDW (B) and hemoglobin (C) with all-cause mortality, modeled with restricted cubic splines (3 degrees of freedom) in Cox models adjusted for age, sex, smoking, DLCO and FVC ($n = 156$, 55 deaths). Hazard ratios are relative to the median value; shaded bands, 95% CI; dotted lines, cutoffs used in the analyses; rug, observed values.

Author Contributions: Conceptualization, F.C., S.D. and S.C.; methodology, F.C., S.D. and S.C.; formal analysis, S.D.; investigation, G.R., A.L., A.M., D.D.C., G.P., C.G., M.M., F.G. and F.S.; data curation, D.A. (Dario Andrisani), F.A., M.L. and D.A. (Daniela Aschieri); writing—original draft preparation, L.B., E.C., A.B. and G.P.; writing—review and editing, F.F., A.V.M. and E.C.; supervision, S.D. and S.C. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The original protocol was approved by the Ethics Committee of Area Vasta Emilia Nord (protocol No. 244/2022/OSS/AOUMO; approval letter dated 20 July 2022). All participants had provided written informed consent for the use of their clinical data for research purposes, in accordance with the approved protocol and institutional procedures. (We would also like to clarify that the 2020–2026 period reported in the manuscript refers exclusively to the dates of routine clinical assessments available in the patients’ medical records, and not to a period of prospective data collection specifically conducted for research purposes. Pulmonary function tests, echocardiographic examinations, laboratory investigations, and clinical follow-up were all performed as part of routine clinical care).

Informed Consent Statement: The study was conducted in accordance with the principles of the Declaration of Helsinki and the guidelines of Good Clinical Practice. Given the retrospective and observational nature of the study and the use of anonymized data extracted from routine clinical practice, the requirement for formal informed consent was waived according to local regulations. All data were handled in compliance with current privacy regulations (GDPR, Regulation EU 2016/679).

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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