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Red cell distribution width in acute pulmonary embolism patients: A simple aid for improvement of the 30-day mortality risk stratification based on the pulmonary embolism severity index

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ABSTRACT

Background: Pulmonary embolism (PE) severity index (PESI) well predicts 30-day mortality in acute PE patients, yet improvements have been advocated.
Objectives: To evaluate predictivity of the red cell distribution width (RDW) through a comparison with PESI and to explore their interaction as a potential improvement in this respect.
Methods: Retrospective analysis of consecutive adult PE patients.
Results: Of the 299 patients, 19 severely unstable died within 48 h. Among the stabilized patients, 30-day mortality was 12.1% (34/280). With PESI ≤125, mortality was 4.9% (9/185), but it was 0.7% (1/140) if RDW ≤15.0% and 17.8% (8/45) if RDW >15.0%; with PESI >125, mortality was 26.3% (25/95), but it was 15.9% (7/44) if RDW ≤15.0% and 35.3% (18/51) if RDW >15.0%. Adjusted relative risk with PESI >125 vs. ≤125 was 17.5 (95%CI 2.37–129) at RDW ≤15.0% and 1.60 (0.76–3.36) at RDW >15.0%.
Conclusions: Thirty-day mortality predictions based on the PESI score may be improved by accounting for RDW.

Introduction

Acute pulmonary embolism (PE) is among leading causes of morbidity and mortality in middle-aged and older adults. It induces a variable degree of respiratory and circulatory instability, and damage to the right ventricle that may be aggravated by predisposing conditions and comorbidity. Very early mortality is cardio-respiratory in nature and deaths directly attributable to PE or not explainable by other reasons typically occur within the first several weeks, the period of highest mortality.[1,2] Patients in whom the initial respiratory/circulatory stabilization is achieved have a generally good prognosis. Longer-term mortality is mainly driven by comorbidities (largely cardiovascular, malignancy, infections), less so by recurrent events or bleedings determined by (in)adequacy of a prolonged anticoagulation, or by development of chronic thromboembolic pulmonary hypertension.[2] Hence, estimation of the 30-day mortality risk that would guide the monitoring and therapeutic decisions has attracted much attention. A number of clinical signs, biochemical markers, ultrasound or other imaging methods reflecting the respiratory status, systemic and pulmonary hemodynamics, coagulation and fibrinolytic system, and dysfunction of the right ventricle have been evaluated in this respect.[2] Pulmonary Embolism Severity Index (PESI)[3] is a 30-day mortality risk score based on bedside-assessable clinical signs that defines five levels of risk (from "very low" to "very high"). Its simplified version distinguishes between a "low" and a "high" risk.[4] The two are the most extensively evaluated risk stratification tools in this setting, both shown to well predict 30-day mortality.[5] The updated risk stratification algorithm by the European Society of Cardiology (ESC)[2] defines four risk levels ("low", "intermediate low or high" and "high") based on the PESI score, presence of shock/hypotension and of echocardiographic/laboratory cardiac markers. As compared with the previous version, it puts more emphasis on clinical signs favoring a possibility of avoiding the need for right ventricle echocardiography and/or the use of biochemical markers.[6] Still, a need for further improvement particularly regarding identification of the "intermediate risk" patients has been pointed-out.[6] A recent evaluation of the PESI scoring systems suggested overestimation of the risk by the simplified version.[7] Therefore, there is a tendency towards simplification of the

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risk stratification procedures (focus on clinical, simpler, quicker, "bedside" markers) and improvement of accuracy.

Red cell distribution width (RDW) measures the extent of anisocytosis, i.e., variability in red blood cells size (volume) and is expressed in percentages (coefficient of variation). It is a routine laboratory parameter reported as a part of the complete blood cell count analysis and is primarily used in evaluation of hematological diseases.[8] It physiologically increases with age, physical exercise and pregnancy but independent associations have been repeatedly reported between increased RDW and the risk of all-cause mortality, cardiovascular mortality and respiratory disease mortality in the general population, occurrence of or adverse outcomes (early or late) of a number of diseased conditions – coronary artery disease, heart failure, atrial fibrillation, peripheral arterial disease, pulmonary hypertension, venous thromboembolism, diabetes, kidney and liver disease, acute poisoning or trauma, inflammatory bowel disease, malignancies or chronic obstructive pulmonary disease.[8] In one retrospective univariate analysis focused on 129 acute PE patients without relevant comorbidity or malignancy, RDW was higher in subjects with massive PE (vs. non-massive), those with pulmonary obstruction index >60% vs. <40% and those with the right-to-left ventricle ratio >1.5 vs. <1.0, indicating association of higher RDW with a more severe PE at presentation.[9] Several studies evaluated RDW in the context of mortality risk stratification in acute PE, however they observed RDW either alone or as a "by-marker" in association with other radiological, echocardiographic or laboratory parameters.[10–13] It was also shown to improve the short term mortality prediction of simplified sPESI score in patients with acute PE in a single center.[14] We aimed to evaluate the prognostic value of RDW regarding 30-day mortality in patients with acute PE specifically through a comparison with PESI and to explore their interaction as a potential improvement in the risk stratification.

Patients and methods

Design

This was an analysis of a prospectively kept database that embraced all consecutive adults (≥18 years of age) with verified acute pulmonary embolism admitted to a single institution between January 2014 and January 2017. All demographic, clinical, laboratory and imaging data were collected using a protected hospital information system and all patients provided an informed consent for the use of data for research purposes.

Diagnosis of pulmonary embolism, patient management and follow-up

Pulmonary embolism was diagnosed in line with the standard criteria[2] either by multiple slice computed tomography (MSCT) pulmonary angiography, or by bedside echocardiography or deep vein ultrasound. Stable patients were treated in line with the guidelines, either with short-acting intravenous unfractionated heparin (UFH) or with low molecular weight heparins (LMWH) with weight-based dosing.[2] The post-acute and post-discharge anticoagulation was based exclusively on titrated warfarin. Follow-up (up to 30 days) was based on clinical visits.

PESI score

The original PESI score was calculated on admission using 11 demographic and clinical variables[3]: age, gender (+10 points to age for men), history of malignancy (+30 points), heart failure or chronic lung disease (+10 points each), heart rate >110 beats/minute (+20 points), systolic blood pressure <100 mmHg (+30 points), respiratory rate >30 breaths/minute (+20 points), body temperature <36 °C (+20 points), altered mental status (+60 points) and oxyhemoglobin saturation <90% (+20 points). The 30-day mortality risk is classified as very low (score ≤65), low (66–85), intermediate (86–105), high (106–125) or very high (score >125).[3]

Complete blood cell count, RDW and other laboratory tests on admission

Complete blood cell count and RDW were determined on admission from peripheral venous whole blood samples collected in the Greiner Vacuette System (Greiner Bio-One Gmbh, Kemsmunster, Austria) with EDTA as an anticoagulant, in an automated blood counter (Advia 21201i analyzer, Siemens Healthcare Diagnostics, Tarrytown, NY, USA). Serum creatinine used to estimate creatinine clearance by the Cockcroft-Gault formula was determined using an isotope dilution mass spectrometry-validated enzymatic assay (standardized creatinine) on AU2700 plus analyzer (Beckman Coulter, Miami, FL, USA). Over the years, standard routine quality control checks at the central institutional laboratory consistently showed <5% intra- and inter-assay variability for all measured parameters.

Data analysis

All patients were considered for evaluation of the relationship between PESI score and RDW values. However, those presenting with a severe respiratory/hemodynamic disturbance that could not be managed and hence died within the first 48 h since admission were not considered for the analysis of 30-day mortality having in mind that risk stratification is of a primary interest for patients who survive the peracute phase (hemodynamic/respiratory stabilization is achieved). In the primary analysis, logistic models (to generate predicted probabilities) and modified Poisson regression models with robust error variance (to generate relative risks, RR) were fitted to proportion of patients who died within 30 days since the index event. PESI score and RDW were considered as continuous variables (ln-transformed) and were also dichotomized: PESI >105 ("high or very high risk") vs. ≤105 or PESI >125 ("very high risk") vs. ≤125; RDW >14.5% ("high", i.e., above the upper limit or normal) vs. ≤14.5%, or >15.0% vs. ≤15.0%. For illustrative purposes, PESI was also considered as a 5-level categorical variable (see: *PESI score*). Correspondingly, RDW was collapsed to 5 levels with limits defined in respect to distribution of patients across the levels of PESI score. In the secondary analysis, time-to-event data were summarized by Kaplan-Meier product-limit curves and were analyzed by fitting proportional hazard regression models. In all models, covariates were selected through stepwise selection process with the "entry" and "stay" criterion of $P \leq 0.1$. We used SAS 9.4 for Windows (SAS Inc., Cary, NC) statistical software.

Results

Patient disposition and univariate relationship between PESI score and RDW

A total of 299 patients with acute PE were admitted during the index period (Fig. 1A). Their PESI scores (Fig. 1B) and RDW values (Fig. 1C) showed a right-tailed distribution. RDW values consistently increased across the categories of PESI score (Fig. 1D) and proportion of subjects with RDW >14.5% ("high") steadily increased across the PESI score categories (Fig. 1E).

Nineteen (6.4%) patients died within 48 h since admission (resuscitated before or immediately upon admission and/or ventilated) and were excluded from further analysis (Fig. 1A). Their PESI scores ranged 125–276 (median 206), RDW was ≤14.5% in 3 patients (13.8%, 14.3%, 14.5%), one patient had RDW 14.7%, and 15 had values ranging from 15.3% to 19.7% (median 16.5%). The remaining 280

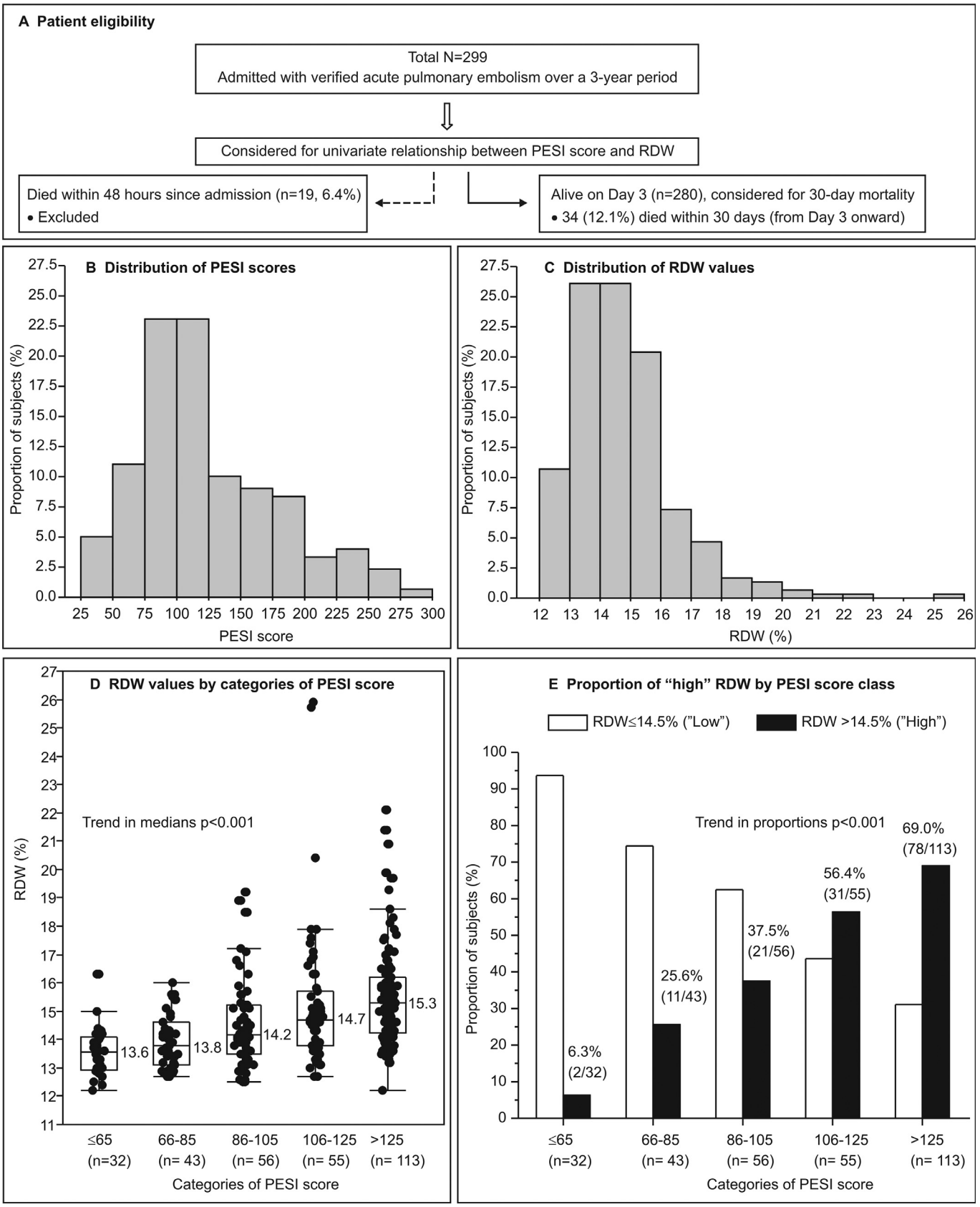

Fig. 1. Patient eligibility (**A**), their PESI scores (**B**) and RDW values (**C**) and univariate relationship between RDW and PESI scores (**D, E**). Trend in medians was by Jonckheere–Terpstra test, trend in proportions by Cochrane–Armitage test. PESI score ≤65 = "very low mortality risk", 65–85 = "low mortality risk", 86–105 = "intermediate mortality risk", 106–125 ="high mortality risk", >125 ="very high mortality risk".[3]

PESI – pulmonary embolism severity index; RDW – red cell distribution width.

Table 1
Subject characteristics [count (%) or median (range)], overall and by 30-day outcome

	All patients	Survived 30 days	Died within 30 days
N	280	246	34
Age (years)	73 (21–93)	72 (21–93)	81.5 (44–92)
Men	109 (38.9)	102 (41.5)	7 (20.6)
Deep vein thrombosis	91 (32.5)	82 (33.3)	9 (26.5)
Previous antiplatelet use	18 (6.4)	14 (5.7)	4 (11.8)
Previous anticoagulant use	60 (21.4)	45 (18.3)	15 (44.1)
Atrial fibrillation	87 (31.1)	72 (29.3)	15 (44.1)
Chronic heart failure	66 (23.6)	53 (21.5)	13 (38.2)
Chronic obstructive pulmonary disease	36 (12.9)	30 (12.2)	6 (17.7)
Malignancy	46 (16.4)	38 (15.5)	8 (23.5)
Diabetes mellitus	37 (13.2)	27 (11.0)	10 (29.4)
Chronic kidney disease	60 (21.4)	46 (18.7)	14 (41.2)
Estimated creatinine clearance (mL/min)	78.1 (21.9–145)	79.2 (21.9–145)	64.2 (21.9–93.9)
Main artery is affected	119 (42.5)	101 (41.1)	18 (52.9)
Mental status is altered	48 (17.1)	30 (12.2)	18 (52.9)
Systolic blood pressure (mmHg)	120 (60–180)	125 (80–180)	105 (60–160)
Respiratory rate ≥30/min	76 (27.4)	54 (22.2)	22 (64.7)
Heart rate (beats/min)	107 (45–180)	105 (49–180)	119 (45–180)
Temperature (°C)	36.6 (35.6–37.3)	36.6 (35.7–37.3)	36.8 (35.6–37.3)
O_2 saturation (%)	93 (68–98)	93 (68–98)	88.5 (69–96)
Pulmonary embolism severity index (PESI)	109 (31–279)	104 (31–261)	186 (81–279)
≤65	32 (11.4)	32 (13.0)	0
66–85	43 (15.4)	42 (17.1)	1 (2.9)
86–105	56 (20.0)	53 (21.5)	3 (8.8)
106–125	54 (19.3)	49 (19.9)	5 (14.7)
>125	95 (33.9)	70 (28.5)	25 (73.5)
PESI >105	149 (53.2)	119 (48.4)	30 (88.2)
Erythrocytes (x 10^{12}/L)	4.4 (3.2–5.7)	4.5 (3.2–5.7)	4.3 (3.6–5.0)
Hemoglobin (Hb) (g/L)	135 (71–171)	135 (71–171)	124 (105–150)
Anemia: Hb <130 in men or <120 women	83 (29.6)	72 (29.3)	11 (32.3)
Red cell distribution width (RDW) (%)	14.3 (12.2–25.9)	14.2 (12.2–25.9)	15.7 (13.5–21.4)
RDW >14.5%	127 (45.4)	98 (39.8)	29 (85.3)
Platelets (x 10^9/L)	231 (55–602)	231 (80–602)	235 (55–416)
Mean platelet volume (fL)	7.8 (5.9–11.8)	7.8 (5.9–11.8)	7.7 (6.8–11.0)
Leukocytes (x 10^9/L)	9.6 (3.1–29.6)	9.5 (3.5–19.9)	9.8 (3.1–29.6)
Lymphocytes (x 10^9/L)	1.7 (0.4–23.9)	1.7 (0.4–23.9)	1.2 (0.4–6.3)
Neutrophils (x 10^9/L)	6.5 (1.3–84.8)	6.4 (1.3–84.8)	7.2 (1.6–28.4)
Neutrophils/lymphocytes ratio	3.61 (0.35–35.5)	3.50 (0.76–16.9)	5.30 (0.35–35.5)
Platelets/lymphocytes ratio	142 (1.7–625)	135 (1.7–625)	194 (24–548)
Fibrinogen (g/L)	4.0 (1.0–8.8)	4.0 (1.6–8.8)	4.5 (1.0–7.3)
C-reactive protein (mg/L)	17.7 (0.2–61.3)	16.4 (0.2–61.3)	20.7 (3.1–42.2)
D-dimer (mg/L)	7.6 (0.4–36.4)	7.2 (0.4–36.4)	12.9 (0.8–34.0)
Troponin positive	97 (34.6)	81 (32.9)	16 (47.1)

patients (stable) were considered for 30-day mortality analysis (Fig. 1A). Their characteristics are summarized in Table 1.

Predicting 30-day mortality by PESI score or by RDW

Of the 280 patients who were alive on day 3, 34 (12.1%) died within the first 30 days post-index event (Fig. 1A). Those who died and survivors differed largely in respect to distribution across the PESI score levels, the latter less frequently having high PESI scores (Table 1). Similarly, survivors less frequently had RDW >14.5% (Table 1). Conversely, 30/149 (20.1%) patients with PESI >105 died vs. 4/131 (3.1%) of those with PESI ≤105; 29/127 (22.8%) patients with RDW >14.5% died vs. 5/153 (3.3%) of those with RDW ≤14.5%. In both cases, positive predictive values were low (20% for PESI, 23% for RDW), but negative predictive values were almost absolute: 97% (95%CI 92–99) for PESI ≤105 and 97% (95%CI 93–99) for RDW ≤14.5%. In contrast to the difference in prevalence of RDW >14.5%, proportions of anemic patients (hemoglobin <130 g/L in men or <120 g/L in women) were closely similar among survivors and those who died within the first 30 days. In reverse, 23/197 (11.7%) of the non-anemic patients died vs. 11/83 (13.2%) of the anemic ones. Positive predictive value of anemia was low (13.2%), while negative predictive value appeared reasonably high, but lower than for RDW (88%, 95%CI 83–92).

In the multivariate analyses, we first considered PESI as a continuous variable and all other variables in Table 1 showing a trend of numerical differences between patients who died and survivors, except for the elements of PESI score and RDW, were considered as potential covariates. The multivariate model included estimated creatinine clearance (eCrCl) and platelet-to-lymphocyte ratio (Table 2): higher PESI (by 10%) was associated with a 26% higher risk of death. When PESI was replaced with RDW, D-dimer was also included in the model, and higher RDW (by 10% relatively) was associated with a 44% higher risk of death (Table 2). Adjusted predicted probabilities of 30-day mortality associated with the increasing PESI or RDW are shown in Fig. 2A and B. Next, PESI score was considered as a 5-level categorical predictor (from "very low" to "very high" risk) – Fig. 2C depicts adjusted predicted probabilities of 30-day mortality by PESI level. When it was replaced by RDW as a 5-level categorical predictor (RDW category limits were based on patient distribution across the PESI categories), practically identical predictions were observed (Fig. 2D). When PESI was dichotomized to >105 and ≤105, high PESI was associated with 3.94-fold higher risk of 30-day mortality (Table 2). When RDW dichotomized to >14.5% and ≤14.5% was used instead of PESI, high RDW was associated with 4.44-fold higher risk of death (Table 2). Neither hemoglobin level (continuous or dichotomized as anemia/no anemia) nor the erythrocyte count were included in any of the models in Table 2 based on the criterion of

Table 2
Summary of the multivariate analyses evaluating association between on-admission PESI score or RDW and 30-day mortality. Effects are presented as relative risks (RR) with 95% confidence intervals (CI)

Models with PESI score and RDW as continuous variables					
Models for PESI score	RR (95% CI)	P	*Models for RDW*	RR (95% CI)	P
PESI (by 10%)	1.26 (1.16–1.37)	< 0.001	RDW (by 10%)	1.44 (1.20–1.73)	< 0.001
eCrCl (by 5 mL/min)	0.95 (0.88–1.01)	0.088	eCrCl (by 5 mL/min)	0.91 (0.85–0.97)	0.002
Plat/lympho (by 50)	1.16 (1.03–1.32)	0.017	Plat/lympho (by 50)	1.19 (1.05–1.34)	0.005
			D-dimer (by 1 mg/L)	1.04 (1.01–1.07)	0.002
Models with PESI score and RDW as categorical variables					
PESI >105 (vs. ≤)	3.94 (1.37–11.2)	0.011	RDW >14.5% (vs. ≤)	4.44 (1.73–11.4)	0.002
eCrCl (by 5 mL/min)	0.91 (0.85–0.97)	0.004	eCrCl (by 5 mL/min)	0.93 (0.88–0.98)	0.009
Plat/lympho (by 50)	1.17 (1.03–1.32)	0.014	Plat/lympho (by 50)	1.17 (1.04–1.31)	0.008
D-dimer (by 1 mg/L)	1.03 (1.01–1.05)	0.032	D-dimer (by 1 mg/L)	1.04 (1.01–1.06)	0.003

The first step was to evaluate the independent effect of PESI score as a continuous variable. Potential covariates were all variables depicted in Table 1, except for PESI score elements and RDW, and the final model was selected through a stepwise procedure with the "entry" and "stay" criterion P ≤ 0.1. In the next step, the same procedure was repeated, except that PESI score was replaced by RDW (continuous). Both PESI and RDW were ln-transformed, hence effects (RR) are expressed by (relative) 10% increase: $RR=exp[\beta \times \ln(1.1)]$. In the next step, the effect of PESI dichotomized as >105 or ≤105 was evaluated using the same methodology, and then PESI was replaced by dichotomized RDW (>14.5% or ≤14.5%).****
eCrCl – estimated creatinine clearance (by Cockroft–Gault formula); lympho – lymphocyte count; PESI – pulmonary embolism severity index; plat – platelet count; RDW – red cell distribution width.

P ≤ 0.1 to enter/stay. Forced adjustments for hemoglobin and/or erythrocyte counts did not relevantly affect the estimates in Table 2 (not shown).

Predicting 30-day mortality simultaneously considering PESI and RDW and their interaction

With both PESI score >105 and RDW >14.5%, 25/93 (26.9%) patients died. Mortality was considerably lower in patients with PESI >105, but RDW ≤14.5% (5/56, 8.9%), or RDW >14.5%, but PESI ≤105 (4/34, 11.8%). None of the 97 patients with PESI ≤105 and RDW ≤14.5% died. This indicated that the association between PESI score and 30-day mortality was conditional on RDW values, and *vice-versa*.

In the multivariate analyses, PESI and RDW were first considered as continuous variables, with the same adjustments as in Table 2, and the models included also their interaction. As depicted in Table 3: a) in patients with "average RDW", by 10% higher PESI was associated with a 31% higher risk of death, while in patients with "average PESI", by 10% (relatively) higher RDW was associated with a 72% higher risk of death; b) the PESI*RDW interaction was significant with a negative coefficient (RR<1.0) indicating that the association of higher PESI with 30-day mortality declined with increasing RDW and *vice-versa*. To illustrate the interaction (Fig. 3), the model was re-fitted with dichotomized PESI and continuous RDW and *vice-versa*: at high RDW values, PESI >105 ("high or very high") was only weakly or not at all associated with a higher risk of 30-day mortality (Fig. 3A); at high PESI values, RDW >14.5% was only weakly or not at all associated with a higher risk of death (Fig. 3B). Since no patient with PESI score ≤105 and RDW ≤14.5% died, multivariate models including their interaction would not converge, hence patients were re-classified as those with PESI score ≤125 (9/185, 4.9% died) and >125 ("very high", 25/95, 26.3% died) and/or RDW ≤15.0% (8/184, 4.4% died) and >15.0% (26/96, 27.1% died). With both PESI≤125 and RDW ≤15.0%, only 1/140 patients died (0.7%); with PESI≤125 but RDW >15.0%, 8/45 (17.8%) died; with PESI>125 and RDW≤15.0%, 7/44 (15.9%) died; while with both PESI>125 and RDW>15%, 18/51 (35.3%) patients died. As shown in Table 3, high PESI and high RDW were both strongly (and comparably) associated with a higher mortality. The interaction term was significant and Fig. 3C depicts predicted probabilities by PESI level, RDW level and by PESI-by-RDW level, and RRs from the interaction term: at RDW ≤15.0%, PESI >125 was associated with a 17.5-fold higher risk of death (vs. ≤125), while no significant association was seen at RDW >15.0%. In reverse, RDW >15.0% was associated with an 18.8-fold higher risk of death (vs. ≤15.0%) at PESI ≤125, while no clear association was seen at PESI >125.

For the secondary analysis, time-to-death is summarized by Kaplan-Meier curves by PESI level (≤125 or >125) (Fig. 4A), RDW level (≤15.0% or >15.0%) (Fig. 4B), and by PESI-by-RDW subset (Fig. 4C). We fitted two proportional hazard regression models with the same covariates as in the primary analysis: the first one without- and the second one with the PESI*RDW interaction (Table 4). In the first model (Model 1, Table 4), PESI >125 and RDW >15.0% were each independently (and comparably) associated with a higher mortality risk. Adjusted cumulative mortality curves (PESI, Fig. 4D; RDW, Fig. 4E) slightly differed from the unadjusted curves as a result of covariate effects. In the second model (Model 2, Table 4), the interaction between PESI score and RDW was significant: a) PESI score >125 was associated with a markedly higher risk of death than PESI ≤125 in patients with RDW ≤15.0%, but not in patients with RDW >15.0% (Table 4: b) conversely, RDW >15.0% was associated with a considerably higher risk of death than RDW ≤15.0% in patients with PESI ≤125 but not in patients with PESI >125. Fig. 4F depicts adjusted survival curves by PESI-by-RDW subset illustrating how PESI score >125 ("very high 30-day mortality risk") might actually be associated with the same risk as PESI score ≤125 if combined with RDW ≤15.0% compared to the latter combined with RDW >15.0% - in both cases, the risk would fit the definition of "intermediate".

Overall, data suggest that "high or very high" (>105) or "very high" PESI score (>125) is associated with a considerably different risk of 30-day mortality conditional on the level of RDW and *vice-versa*.

Discussion

PESI score is an extensively validated tool for stratification of the 30-day mortality risk in acute PE patients that is based on simple bedside-assessable signs and has proven clinical utility, alone or combined with echocardiographic or cardiac biochemical markers.[2–7] Still, a need for further improvement that could possibly enable avoidance of echocardiography/cardiac biochemistry and would thus contribute to simplicity and general applicability has been suggested.[6,7] In this respect, we considered it reasonable to explore a possibility that RDW – a readily available, cheap and quick laboratory parameter – might contribute to improvement of risk stratification based on clinical signs (the original PESI). The rationale is based on

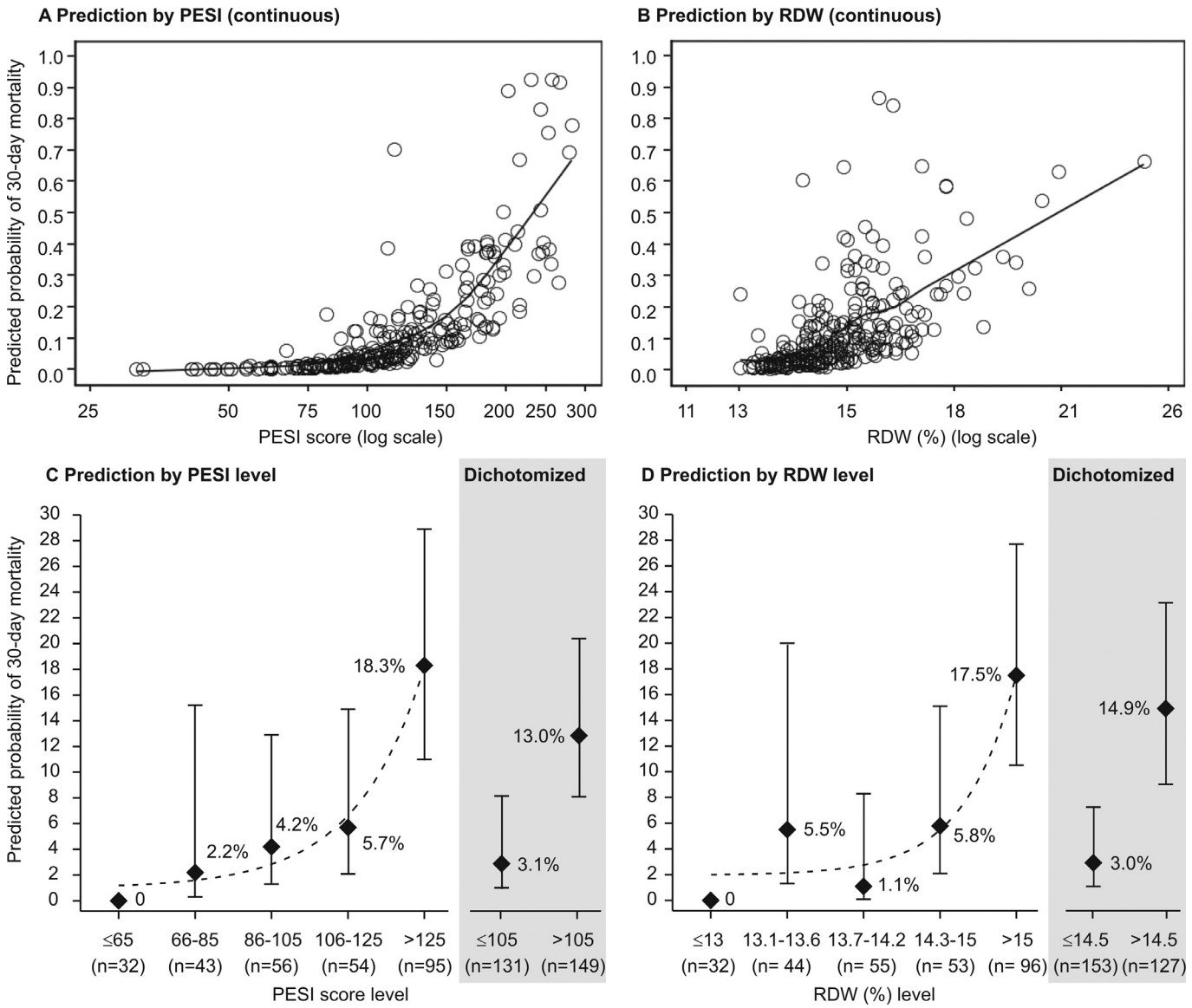

Fig. 2. Predicted adjusted probabilities of 30-day mortality from models in Table 2. **A**. Prediction by continuous PESI score (ln-transformed) adjusted for estimated creatinine clearance (eCrCl) and platelet-to-lymphocyte ratio. **B**. Prediction by continuous RDW (ln-transformed) with additional adjustment for D-dimer concentration. **C**. Prediction by 5-level categorical and dichotomized (shaded; model in Table 2) PESI score adjusted for eCrCl, platelet-to-lymphocyte ratio and D-dimer. **D**. Prediction by 5-level and dichotomized (shaded; model in Table 2) RDW with the same adjustments. The levels of RDW were defined according to the centiles of distribution of patients across PESI levels. Black diamonds in C and D are prediction point-estimates and vertical bars are 95% confidence intervals. PESI score ≤65 = "very low mortality risk", 65–85 = "low mortality risk", 86–105 = "intermediate mortality risk", 106–125 ="high mortality risk", >125 ="very high mortality risk".[3]

PESI – pulmonary embolism severity index; RDW – red cell distribution width.

Table 3
Summary of the multivariate analyses evaluating simultaneous association between on-admission PESI score and RDW and 30-day mortality. Effects are presented as relative risks (RR) with 95% confidence intervals (CI)

PESI score and RDW continuous			PESI score and RDW dichotomized		
	RR (95% CI)	P		RR (95% CI)	P
PESI (by 10%)	1.31 (1.12–1.43)	<0.001	PESI >125 (vs. ≤)	5.29 (1.86–15.1)	0.002
RDW (by 10%)	1.72 (1.30–2.26)	<0.001	RDW >15.0 (vs. ≤)	5.69 (1.89–17.1)	0.002
PESI*RDW	0.37 (0.17–0.82)	0.013	PESI*RDW	0.09 (0.01–0.80)	0.031
eCrCl (by 5 mL/min)	0.95 (0.89–1.02)	0.186	eCrCl (by 5 mL/min)	0.94 (0.89–1.00)	0.057
Plat/lympho (by 50)	1.18 (1.03–1.34)	0.015	Plat/lympho (by 50)	1.19 (1.06–1.33)	0.003
D-dimer (by 1 mg/L)	1.01 (0.98–1.03)	0.561	D-dimer (by 1 mg/L)	1.02 (1.00–1.05)	0.043

The first step was to evaluate the effects of PESI score and RDW as continuous variables and their interaction (both geometric mean-centered). Covariates were included based on P-values ≤0.1 in models in Table 2. Both PESI and RDW were ln-transformed, hence RRs are expressed by (relative) 10% increase: $RR=exp[\beta \times \ln(1.1)]$ .The analysis was repeated with dichotomized PESI score (>125 or ≤125) and RDW (>15.0% or ≤15.0%). These cut-offs were used since there were no deaths in the PESI ≤105 and RDW ≤14.5% subset.

eCrCl – estimated creatinine clearance (by Cockroft–Gault formula); lympho – lymphocyte count; PESI – pulmonary embolism severity index; plat – platelet count; RDW – red cell distribution width.

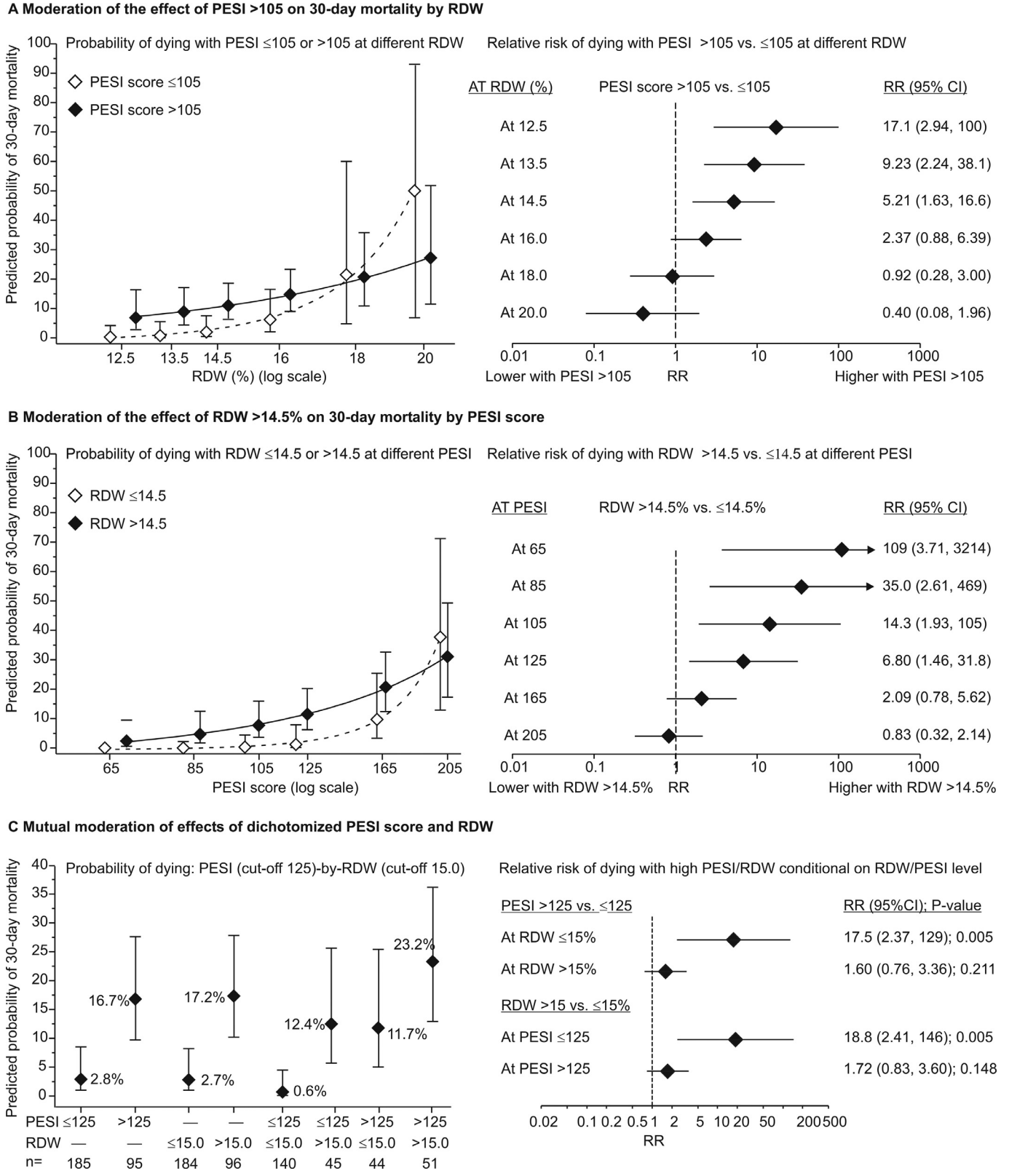

Fig. 3. Interaction between PESI score and RDW – mutual moderation of association with 30-day mortality. **A**. Predicted probabilities of death in patients with PESI score >105 and ≤105 at different values of RDW (left) and corresponding relative risks (RR) of death (right) (model in Table 3 re-fitted with dichotomized PESI and continuous RDW, interaction P = 0.006). **B**. Predicted probabilities of death in patients with RDW >14.5% and ≤14.5% at different values of PESI score (left) and corresponding RRs of death (right) (model re-fitted with dichotomized RDW and continuous PESI score, interaction P = 0.007). **C**. Predicted probabilities of death in patients with PESI score >125 or ≤125, RDW >15% or ≤15% and in PESI-by-RDW subsets (left) and RRs of death for higher vs. lower level of each factor at different levels of the other one (right) (model in Table 3 with categorical PESI and RDW). These cut-offs were used since there were no deaths among patients with PESI ≤105 and RDW <14.5%. Diamonds are point-estimates, bars are 95% confidence intervals.

PESI – pulmonary embolism severity index; RDW – red cell distribution width.

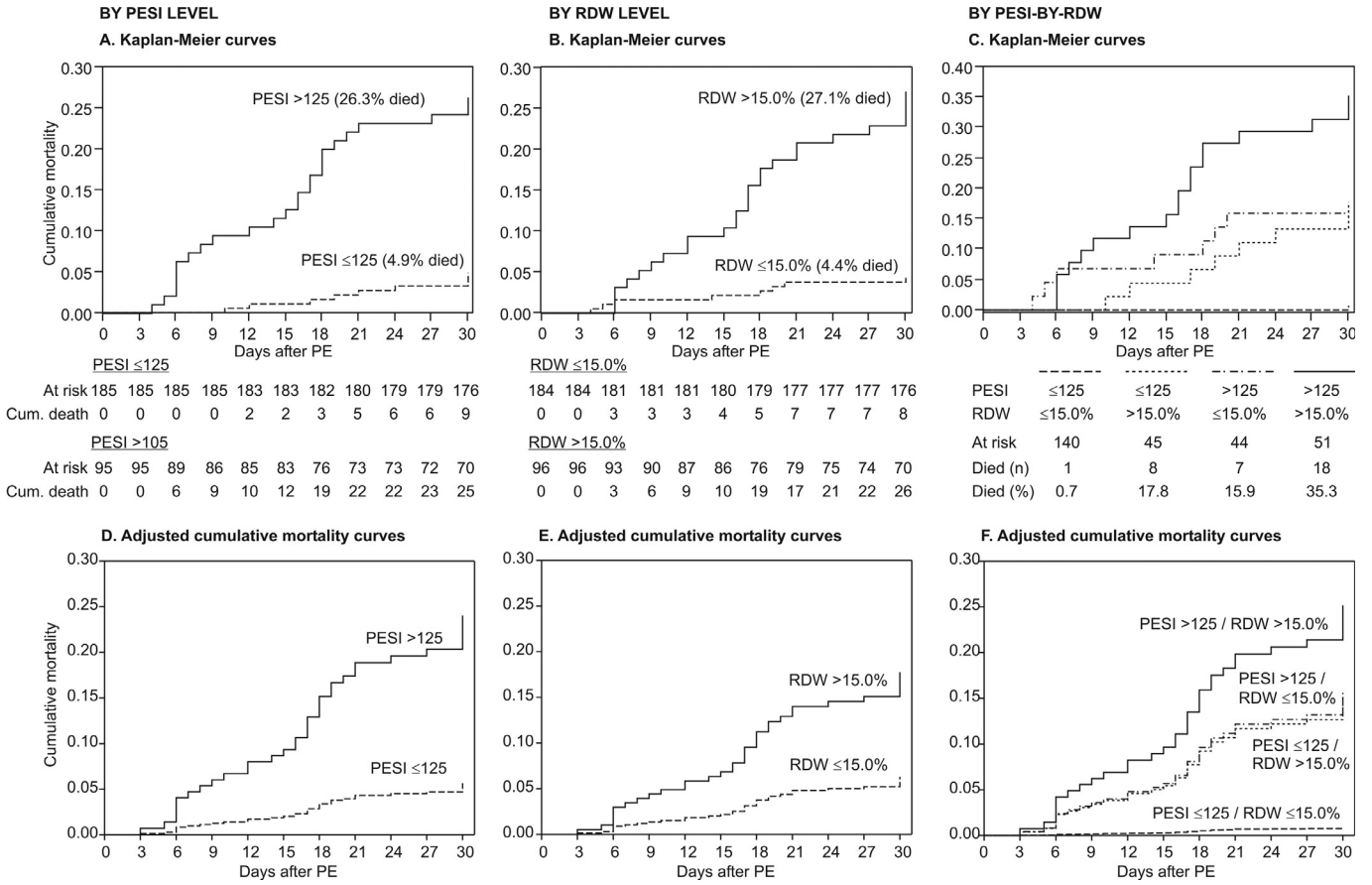

Fig. 4. Time to death by PESI score level (left column), RDW level (middle column) and by PESI-by-RDW levels (right column). Cumulative mortality data are summarized by Kaplan–Meier curves for PESI score >125vs. ≤125 (**A**), RDW >15.0% vs. ≤15.0% (**B**) and by PESI-by-RDW (**C**). Adjusted survival curves from the Cox proportional hazard regression Model 1 in Table 4 are shown for PESI score levels (**D**) and RDW levels (**E**). Adjusted survival curves for PESI score-by-RDW level subsets from the Cox proportional hazard regression Model 2 in Table 4 are also shown (**F**).

Table 4
Summary of the multivariate analyses of time to death evaluating simultaneous association between on-admission PESI score (>125 or ≤125) and RDW (>15.0% or ≤15.0%) and 30-day mortality. Effects are expressed as hazard ratios (HR) with 95% confidence intervals (CI)

	HR (95% CI)	P
Model 1: categorical PESI and RDW, no interaction		
PESI >125 vs. ≤125	3.36 (1.50–8.15)	0.003
RDW >15.0 vs. ≤15.0	3.47 (1.56–8.54)	0.002
eCrCl (by 5 mL/min)	0.92 (0.85–0.99)	0.043
Platelet-lymphocyte ratio (by 50)	1.27 (1.09–1.47)	0.003
D-dimer (by 1 mg/L)	1.04 (1.00–1.07)	0.048
Model 2: categorical PESI and RDW + interaction[1]		
PESI*RDW interaction	–	0.014
PESI >125 vs. ≤125 at RDW ≤15.0	20.8 (2.90–729)	–
PESI >125 vs. ≤105 at RDW >15.0	1.88 (0.71–5.58)	–
RDW >15.0 vs. ≤15.0 at PESI ≤125	19.8 (2.93–685)	–
RDW >15.0 vs. ≤15.0 at PESI >125	1.80 (0.67–5.52)	–
eCrCl (by 5 mL/min)	0.92 (0.84–0.99)	0.037
Platelet-lymphocyte ratio (by 50)	1.29 (1.10–1.49)	0.002
D-dimer (by 1 mg/L)	1.04 (1.00–1.07)	0.041

[1] Confidence intervals for the contrasts arising from the PESI*RDW interaction are 97.5% CI.Covariates were taken as "fixed" from the primary analysis. All effects in both models met the assumption of proportional hazards.eCrCl – estimated creatinine clearance (by Cockroft-Gault formula); PESI – pulmonary embolism severity index; RDW – red cell distribution width.

repeatedly shown independent association between increased RDW and poorer early or late outcomes in a range of cardiovascular conditions including venous thromboembolism,[8] and with more severe clinical presentation in acute PE patients.[9] It is unclear whether increased RDW is a true risk factor or (just) a marker of an underlying biological imbalance. In respect to cardiovascular conditions, there has been mechanistic evidence supporting both possibilities[8] largely converging to inflammatory process, particularly regarding thrombotic incidents.[15,16] Increased RDW might actually subsume a variety of underlying disturbances.[8] In a recent study[17] in 4273 consecutive unselected adults admitted to a hospital through an emergency department, higher RDW was independently associated with higher odds of 30-day mortality but the strength of association progressively decreased with gradual progressive adjustments for demographics + comorbidities + primary diagnosis + a variety of laboratory parameters, and eventually (with full-scale adjustments) the association disappeared. Higher RDW strongly correlated with the clinical and laboratory parameters defining components named "inflammation", "diseases of blood", "nutritional status", "kidney disease", "malignancy", "cardiovascular disease" or "lung disease".[17] Hence, RDW was a strong surrogate marker of mortality with concentrated prognostic information contributed to by different disease factors. In this respect, RDW is in a way similar to PESI score in the acute PE setting – PESI sums-up the risk determined by demographics, comorbidities and the level of respiratory and circulatory distress. It appears plausible that RDW might contribute complementary information to PESI.[14]

In the present cohort, high(er) RDW was a strong independent predictor of 30-day mortality in a way closely similar to the prediction by PESI, but the main finding is a marked moderating effect of RDW on the risk estimated by the PESI score. This was observed regardless of whether the two were considered as continuous or as categorical variables (the latter being more intuitive for interpretation), and may help improve the accuracy of predictions by the PESI score. Two potential weaknesses have been suggested for the PESI score-based risk stratification: inaccuracy in identification of the intermediate-risk patients[2] and a tendency to overestimate the risk of early mortality.[7,14] In the present analysis, 30-day mortality in patients with PESI score >105 (high or very high risk) was 20.1%, and it was 26.3% in patients with PESI score >125 (very high risk). However, when these two PESI levels were combined with RDW ≤14.5% or ≤15.0%, respectively, mortality was considerably lower (8.9% and 15.9%, respectively), i.e., closer to the description of an intermediate risk (or intermediate-high as suggested by ESC).[2] In reverse, 30-day mortality in patients with PESI score ≤105 (includes very low, low and intermediate risk PESI levels) was 3.1%, and it was 4.9% in patients with PESI score ≤125 (includes very low, low, intermediate and high risk PESI levels). When combined with RDW >14.5% or >15.0%, respectively, these PESI levels were associated with a considerably higher mortality (11.8% and 17.8%, respectively) that again would be closer to the intermediate-high risk. These findings exemplify the potential of RDW to improve the accuracy of predictions based on PESI by correcting both the underestimates and overestimates. The latter in particular could have straightforward implications in daily practice. For example, a combination of the PESI score ≤105 (mortality 3.1% if not accounting for RDW) with RDW ≤14.5% resulted in no deaths (0/97), whereas a combination of PESI score ≤125 (mortality 4.9% if not accounting for RDW) with RDW ≤15.0% resulted in one death among 140 subjects (0.7%), i.e., in a negligibly low risk. The patient (an 86-year old man with coronary artery disease, deep vein thrombosis, main pulmonary artery embolism and hemoglobin 121 g/L) had PESI score 116 (age + male sex + heart rate 130 beats/min) and RDW 14.0%, and died on day 6 since admission. Data indicate the potential of RDW to enable recognition of a low 30-day mortality risk in patients without a relevant hemodynamic/respiratory imbalance but with an intermediate or even high PESI score driven mainly by demographics and comorbidity who would be eligible for a safe ambulatory treatment. These observations remained unchanged in multivariate models. In this respect, it should be noted that we did not attempt to define the best set of explanatory variables for variability of the 30-day mortality but to evaluate independent effects of RDW and its interaction with the PESI score within the eligible cohort. Adjustments were selected from a range of potential confounders. Although the selection was based on a statistical criterion, all of the included covariates (eCrCl, D-dimers, platelet-to-lymphocyte ratio) have been suggested to have a certain predictive value for all-cause 30-day mortality in PE.[2,18] The observations, however, have been variable[2,18] and the present results should be viewed as potentially informative by-findings.

The present study has several limitations. A moderately-sized single-center sample precluded a more detailed analysis across the original five levels of the PESI score. Another important limitation is the absence of echocardiographic parameters that could be included in the multivariate analyses. On the other hand, we did not consider the lack of data on specific causes of death to be a relevant drawback. In a practical clinical context, 30-day all-cause mortality risk is of a primary interest as it guides the decisions on length of hospitalization, diagnostic and monitoring procedures, and even in patients with very advanced comorbidities it is difficult to exclude at least a contribution of this acute condition to the lethal outcome. The validity of the present analysis is in a way supported by the following: a) as in a similar recent study,[6] we excluded patients presenting with a severe respiratory and/or hemodynamic deterioration in whom initial stabilization was impossible and who died shortly upon admission. Inclusion of these patients did not relevantly change the results of the analysis (not shown). They were characterized by very high PESI scores and their RDW values were in line with those reported[9] in patients with massive PE, right-to-left ventricle ratio >1.5 or pulmonary artery obstruction index >60%; b) 30-day all-cause mortality in the entire cohort was well within the range of values identified in a recent meta-analysis of similar studies in PE[5]; c) 30-day mortality by PESI score levels was in line with the expectations.[2,3,5]

In conclusion, present data strongly suggest that RDW might serve as an aid to improve accuracy of the PESI score-based 30-day mortality risk stratification in PE patients. It appears to correct both the underestimates and the overestimates by PESI, which might help in identification of the intermediate-risk patients. In particular, it might simplify identification of patients eligible for ambulatory treatment without a need for echocardiographic/cardiac markers that differ in availability in different health care systems and clinical settings. Considering the limitations of the present work, this potential should be evaluated in larger prospective studies assessing the contribution of RDW specifically in comparison to echocardiographic and/or biochemical cardiac markers.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.hrtlng.2019.02.006.

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