CHEST

Early Changes Over Time in the Radiographic Assessment of Lung Edema Score Are Associated With Survival in ARDS

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BACKGROUND: The Radiographic Assessment of Lung Edema (RALE) score is associated with the severity of ARDS, and treatments targeted at reducing pulmonary edema such as conservative fluid management cause a reduction in RALE score over time.

RESEARCH QUESTION: Are early changes in RALE score over time associated with survival in patients with ARDS?

STUDY DESIGN AND METHODS: Data from patients enrolled in three centers in the Lung Imaging for Ventilation sEtting in ARDS (LIVE) trial with available chest radiographs at baseline (day 0) and days 2 or 3 were used. The RALE was scored by two independent reviewers. The primary end point was death by day 90, considering RALE score both at baseline and as a time-varying covariate in a marginal Cox survival model.

RESULTS: RALE was scored from 135, 64, and 88 radiographs on days 0, 2, and 3, respectively. Both baseline RALE (hazard ratio [HR] for each one-point increment, 1.04; 95% CI, 1.01-1.08; $P = .006$) and the change in RALE over time (HR for each one-point decrease per unit of time, 0.99; 95% CI, 0.99-0.99; $P = .03$) were associated with death by day 90, even after adjustment for age, sex, BMI, Simplified Acute Physiology Score II, vasopressor use, and total volume of fluids received since study entry.

INTERPRETATION: The change in RALE during the first days after ARDS onset is independently associated with survival and may be useful as a surrogate end point in future clinical trials of new therapeutics in ARDS. CHEST 2020; 158(6):2394-2403

KEY WORDS: ARDS; radiographic score; survival; treatable trait

ABBREVIATIONS: CHU = Centre Hospitalier Universitaire; FACTT = Fluid and Catheter Treatment Trial; HR = hazard ratio; LIVE = Lung Imaging for Ventilation sEtting in ARDS; RALE = Radiographic Assessment of Lung Edema; SAPS = Simplified Acute Physiology Score; sRAGE = soluble receptor for advanced glycation end-products

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The Radiographic Assessment of Lung Edema (RALE) score has been proposed as a noninvasive tool to assess the radiographic extent of lung edema in patients with ARDS.[1] The RALE score provides a semiquantitative measure of the extent and density of alveolar opacities on the chest radiograph that correlates well with the degree of lung edema as assessed by gravimetric measurements in explanted lungs from human donors.[2] When calculated from enrollment radiographs of patients enrolled in the ARDSNet Fluid and Catheter Treatment Trial (FACTT), the RALE score was associated with both the severity and clinical outcomes of ARDS.[2] Therefore, the RALE score could be a useful addition to the currently available methods, to assess severity and prognosis in ARDS. Interestingly, in a secondary analysis of the FACTT, the change in RALE score differed by treatment arm with a significant drop in RALE from enrollment to day 3 in response to conservative fluid management. This finding suggests that the RALE score may have value to monitor therapeutic response, particularly in response to therapies that target the extent of lung edema.

Although the RALE score had prognostic value in a cohort of patients with ARDS, a recent secondary analysis of a prospective cohort study in 124 mechanically ventilated patients with either ARDS or congestive heart failure did not find any significant association between the baseline RALE score and 30- or 90-day mortality.[3] In this study, the RALE score correlated with plasma levels of soluble receptor for advanced glycation end-products (sRAGE), a marker of lung epithelial injury with prognostic value in ARDS,[4-6] but only major and late changes in RALE (as defined by a reduction of baseline RALE score of $>$ 50% by day 7 after intubation) were associated with survival at 90 days, but not at 30 days. Given these disparate findings, it is not clear whether monitoring early changes in RALE score could have value in assessing prognosis in patients with ARDS. This question requires further investigation before the RALE score could be used as a potential radiographic outcome in future clinical trials.[7,8]

We hypothesized that in addition to its association with prognosis when measured at baseline, a decrease in RALE over the first days of ARDS is associated with better survival. To test this hypothesis, we applied the RALE score to serial radiographs obtained over the first 3 days of enrollment from patients previously enrolled in the Lung Imaging for Ventilation sEtting in ARDS (LIVE) multicenter randomized controlled trial.[9]

Methods

Study Design and Data Collection

This was a secondary analysis of prospectively collected data from the LIVE multicenter, investigator-initiated, patient-blinded, stratified randomized controlled trial.[9] In the LIVE trial, patients were included within 12 h of moderate-to-severe ARDS onset, as defined using the Berlin criteria.[10] The exclusion criteria were $<$ 18 years of age, patients mechanically ventilated for $>$ 7 consecutive days during the previous 30 days, history of ARDS in the last month, intracranial hypertension, BMI $>$ 40 kg/m^2, chronic respiratory disease requiring long-term oxygen therapy, bone marrow transplantation, metastatic cancer, burns, cirrhosis with a Child Pugh score of C or greater, bronchopleural fistula, pregnancy, and enrollment in another interventional study.[11] In this trial, personalized mechanical ventilation tailored to lung morphology (focal vs nonfocal ARDS)[12,13] did not improve 90-day survival compared with a nonpersonalized control ventilation strategy of low tidal volume and low positive end-expiratory pressure.

For the current analysis, chest radiographs (at study inclusion and on day 2 and/or 3 after inclusion) were collected from medical records. According to French law,[14] the ethics committee waived the requirement to obtain signed informed consent for this additional data collection (Comité d'Ethique pour la Recherche en Anesthésie-Réanimation, Société Française d'Anesthésie et de Réanimation, Institutional Research Board No. 00010254-2018-034). All other data needed for this analysis were previously collected and were available through the LIVE study's electronic case report form. In particular, in the LIVE trial, plasma levels of sRAGE were measured in duplicate using commercially available enzyme-linked immunosorbent assay kits (RAGE Quantikine; R&D Systems). The personnel responsible for performing sRAGE assays had no knowledge of the clinical data or of the randomization group.

For practical reasons related to the collection of chest radiograph images, only patients enrolled in three participating ICUs (Centre Hospitalier Universitaire [CHU] Clermont-Ferrand, CHU Montpellier, and CHU Nîmes) were analyzed.[15] Only patients with

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FUNDING/SUPPORT: This study was supported by the French Ministry of Health (Programme Hospitalier de Recherche Clinique InterRégional 2013) and the NIH [Grants HL103836, HL126176, HL135849, HL126671].

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DOI: https://doi.org/10.1016/j.chest.2020.06.070

available radiographs at baseline (day 0, randomization) were included in this analysis.

RALE Score

As previously described,[1] the RALE score was calculated as the summed products of the consolidation and density scores for each radiograph quadrant (upper/lower right quadrants, upper/lower left quadrants), with a maximal score for each quadrant of 12 and a maximum total score of 48, in which the consolidation score is based on the extent of alveolar opacities in each quadrant (none: 0 points; < 25%: 1 point; 25%-50%: 2 points; 50%-75%: 3 points; > 75%: 4 points), and the density of alveolar opacities in each quadrant is scored as hazy (1 point), moderate (2 points), or dense (3 points).[1] In the current study, an investigator who had first proposed the RALE score (L. B. W.) and another trained investigator (M. J.) independently scored all chest radiographs.

Outcome Measures

The primary outcome was 90-day survival. Secondary outcomes were 30-day survival, indexes of ARDS severity at baseline (Pao_2/Fio_2, compliance of the respiratory system, and extent of lung epithelial injury as assessed by plasma sRAGE) and the interobserver agreement for calculating the RALE score.

Statistical Analysis

Additional details are provided in e-Appendix 1. Statistical analyses were performed using Stata software, Version 15 (StataCorp). The tests were two-sided with a type I error set at 5%. Continuous data were expressed as mean ± SD or median (interquartile range) according to statistical distribution (assumption of normality was assessed using the Shapiro-Wilk test). Survival end point was treated as right censored data. The estimation was performed using the Kaplan-Meier approach, and the comparisons were realized by log-rank test. To verify our primary hypothesis that the change in RALE score could associate with survival, the score was considered both at baseline and as a time-varying covariate. We also performed exploratory analyses aimed at further evaluating the effect on survival of the change in RALE score from baseline to day 2 and day 3 using the aforementioned methods. A marginal Cox proportional hazards model was used for multivariable analyses, considering covariates fixed according to a previous study of the RALE score[1] and clinical relevance: age, sex, BMI,[16] Simplified Acute Physiology Score (SAPS) II,[16] need for vasopressor use at baseline, and total volume of fluids received since study entry. The proportional-hazard hypothesis was verified using the Schoenfeld test and by plotting residuals, and the results were expressed as hazard ratios (HRs) and 95% CIs. The RALE scoring reproducibility was evaluated by calculating the between-observer agreement using the Lin concordance correlation coefficient and Bland-Altman plots. The relationship between the RALE score and quantitative variables, such as Pao_2/Fio_2 and the compliance of the respiratory system, was explored using correlation coefficients (Pearson or Spearman, according to the statistical distribution). A sensitivity analysis was conducted to compare the baseline characteristics of the patients from the LIVE study who were included in this secondary research with the characteristics of those who were not. A second sensitivity analysis was performed to determine the statistical nature of missing data and their potential impact on the results.

Results

Study Population

The flowchart for this analysis is presented in Figure 1. Chest radiographs were available for calculating the RALE score in 135 patients on day 0, 64 patients on day 2 (among whom three were extubated), and 88 patients on day 3 (among whom 21 were extubated and one had a tracheostomy). Among these patients, 89 survived at day 90 and 46 did not; their characteristics are described

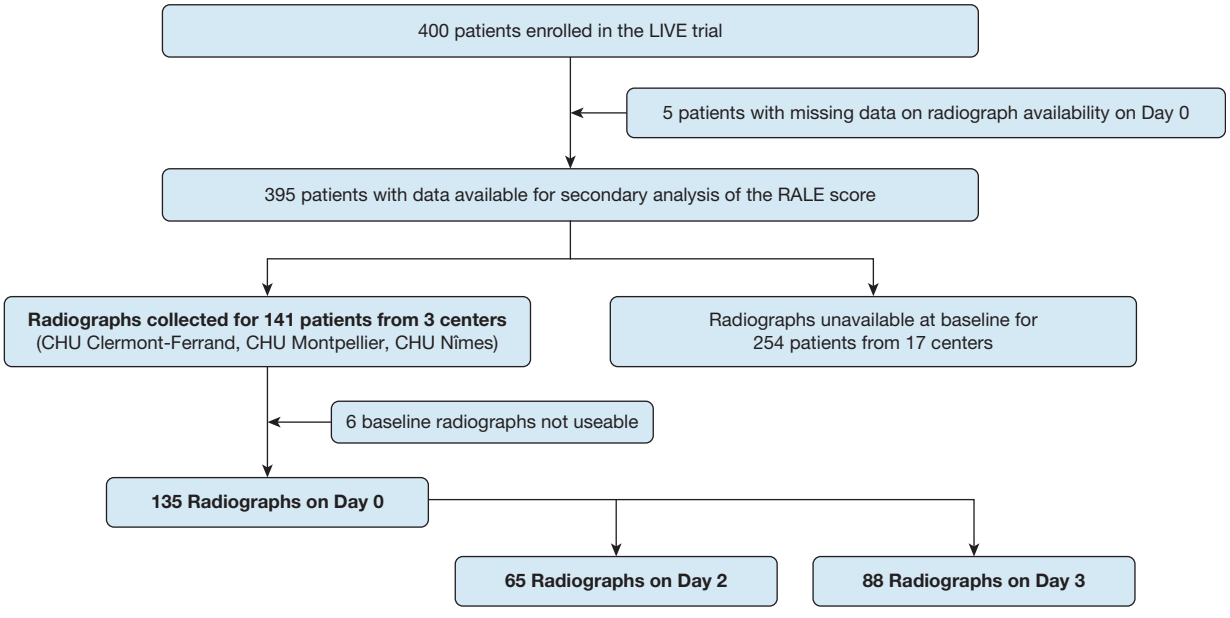

Figure 1 – *Flow of patients from the LIVE trial who were included in the secondary RALE score analysis. CHU = Centre Hospitalier Universitaire; LIVE = Lung Imaging for Ventilation sEtting in ARDS; RALE = Radiographic Assessment of Lung Edema.*

in Tables 1 and 2. Nonsurvivors were older, more severe (as assessed by higher SAPS II and Sepsis-related Organ Failure Assessment score), and more likely to have at least one comorbidity and higher $Paco_2$ or to require vasopressor support, renal replacement therapy, higher Fio_2, and respiratory rates at baseline compared with survivors. Comparisons of baseline characteristics and main clinical outcomes among patients from the LIVE study with chest radiographs available at baseline and analyzed in this study (n = 135) and those with chest radiographs unavailable at baseline (n = 254) are summarized in e-Tables 1 and 2. Patients with chest

TABLE 1] Demographic Characteristics, Coexisting Conditions at Baseline, and Radiographic Assessment of Lung Edema Scores in Survivor and Nonsurvivor Patients With ARDS at Day 90

Variable	Survivors (n = 89)	Nonsurvivors (n = 46)	*P* Value
Male sex	63 (71)	38 (83)	.10
Age, y	57 ± 15	68 ± 14	< .0001
BMI, kg/m^2	26 ± 5	26 ± 6	.60
Simplified Acute Physiology Score II score at admission	46 ± 15	57 ± 16	.0003
Sepsis-related Organ Failure Assessment score at admission	8.4 ± 3.5	10.8 ± 3.6	.0005
Time from MV initiation to study enrollment, d	0.4 ± 0.8	0.4 ± 0.8	.90
Time between ARDS onset and study enrollment, h	4.5 ± 3.8	5.2 ± 4.1	.30
McCabe score[a]			.80
A	58 (66)	24 (59)	
B	26 (30)	15 (37)	
C	4 (5)	2 (5)	
Comorbidities			
COPD	6 (7)	5 (11)	.50
Hematologic cancer	5 (6)	3 (7l)	.80
Solid cancer	0 (0)	1 (2)	.30
CKD	0 (0)	0 (0)	…
Other	61 (69)	37 (80)	.20
None	23 (26)	5 (11)	.05
Cause of ICU admission			.50
Septic shock	14 (16)	7 (15)	
Hemorrhagic shock	0 (0)	2 (4)	
Coma	8 (9)	2 (4)	
Intraabdominal sepsis	11 (12)	6 (13)	
Traumatic injuries	4 (4)	1 (2)	
Acute respiratory failure	39 (44)	23 (50)	
Acute metabolic disorders	2 (2)	2 (4)	
Elective surgery	7 (8)	1 (2)	
Urgent surgery	4 (5)	2 (4)	
Pulmonary cause of ARDS	64 (72)	30 (65)	.40
Treatments			
Norepinephrine	48 (54)	36 (78)	.008
Renal replacement therapy	2 (2)	5 (11)	.04
Antibiotics	80 (90)	42 (91)	.80
Steroids	20 (21)	17 (40)	.10
NMBA	74 (83)	39 (85)	.80

Values are reported as mean ± SD, No. (%), or as otherwise indicated. P values were calculated for comparisons between survivor and nonsurvivor patients at day 90. Percentages may not total 100% because of rounding. CKD = chronic kidney disease; MV = mechanical ventilation; NMBA = neuromuscular blocking agent.

[a]The McCabe score is a subjective score of underlying illness severity classifying patients according to a prognosis of rapidly fatal (< 1 y), ultimately fatal (1-4 y), and nonfatal (> 5 y).[17]

TABLE 2] Ventilator Settings, Respiratory System Mechanics, and Arterial Blood Gas Measurements Before Randomization in the Lung Imaging for Ventilation sEtting in ARDS Trial of Survivor and Nonsurvivor Patients With ARDS at Day 90

Variable	Survivors		Nonsurvivors		*P* Value
	No. of Available Individuals	Value	No. of Available Individuals	Value	
Ventilatory mode	89		46		.05
Controlled ventilation		81 (91)		46 (100)	
Pressure-support ventilation		8 (9)		0 (0)	
Tidal volume, mL/kg of PBW	85	6.6 ± 1.3	42	6.7 ± 1.4	.70
Respiratory rate, breaths/min	84	24 ± 5	44	22 ± 6	.02
Centimeters of water	86	10.3 ± 3.5	43	11.5 ± 4.2	.10
F_{IO_2}, %	89	73 ± 22	46	81 ± 19	.03
Pplat, cm of water	69	23.6 ± 5.9	32	24.3 ± 5.3	.50
Cst, mL/cm of water	66	35 ± 12	30	39 ± 17	.20
Driving pressure, cm of water	67	13.5 ± 5.3	32	12.6 ± 5.6	.50
Pa_{O_2}, mm Hg	89	87 ± 31	46	84 ± 31	.60
Pa_{O_2}/F_{IO_2}, mm Hg	89	124 ± 43	46	108 ± 47	.05
Pa_{CO_2}, mm Hg	89	43 ± 9	46	47 ± 12	.04
Arterial blood pH	89	7.34 ± 0.09	46	7.29 ± 0.13	.02
Sa_{O_2}/F_{IO_2}, %	88	146 ± 52	46	140 ± 51	.003
Plasma bicarbonate, mmol/L	88	24 ± 5	46	22 ± 5	.10
Lactate, mmol/L	80	2.4 ± 4.0	43	3.7 ± 3.8	.08

Values are reported as mean ± SD, No. (%), or as otherwise indicated. P values were calculated for comparisons between survivor and nonsurvivor patients at day 90. Percentages may not total 100% because of rounding. Cst = static compliance of the respiratory system; PBW = predicted body weight; Pplat = plateau pressure; Sa_{O_2} = arterial oxygen saturation.

radiographs available at baseline had slightly shorter times from onset of ARDS and mechanical ventilation to randomization, lower respiratory rates, and higher positive end-expiratory pressure levels compared with those who were not included in the study.

Changes in RALE Score and Survival

Considering RALE score at baseline and as a time-varying covariate (e-Table 3) in a marginal Cox model to evaluate the prognostic effect of its evolution over time, both baseline RALE scores (HR for each one-point increment, 1.04; 95% CI, 1.01-1.08; $P = .006$) and the change in RALE over time (HR for each one-point decrease in RALE score per unit of time, 0.99; 95% CI, 0.99-0.99; $P = .03$) were independently associated with death at day 90. These results were confirmed after adjustment for age, sex, BMI, SAPS II, need for vasopressor use at baseline, and total volume of fluids received since study entry (Table 3). Complete case analysis including only patients in whom RALE scores were available on both day 0 and day 3 showed similar results.

When considered only at baseline scores and as a continuous variable, there was no difference in the RALE score between survivors and nonsurvivors at day 90 (mean ± SD, 23.0 ± 9.7 and 24.1 ± 8.9, respectively; $P = .30$) (e-Fig 1). However, when categorizing baseline RALE score as a four-class variable according to its statistical distribution (quartiles), higher quartile of baseline RALE score was associated with higher risk of death at day 90 (HR for RALE score ≥ 30 [fourth quartile], 1.88; 95% CI, 1.02-3.49; $P = .04$; log-rank test P value = .04) (Fig 2), even after adjustment for other risk stratifiers (Table 3) or for baseline RALE score using the same multivariable time-varying model (e-Table 4).

An absolute increase, or no change, in RALE score from baseline to day 3, compared with a decrease in RALE score, was associated with a higher risk of death at day 90 (HR, 3.39; 95% CI, 1.14-10.09; $P = .03$) (Fig 3), even after adjustment for previous covariates (HR, 3.37; 95% CI, 1.11-10.26; $P = 0.03$) (Table 4). However, the change in RALE score from baseline to day 2 was not significantly associated with death at 90 days (e-Fig 2, e-Table 5).

The same overall results were found when considering 30-day survival (e-Table 6).

TABLE 3] Univariable and Multivariable Marginal Cox Survival Analyses of Death at Day 90, Considering the RALE Score at Baseline Alone or Combined With the RALE Score as Expressed as a Time-Varying Covariate

Analysis Performed	Hazard Ratio (95% CI)	*P* Value
Multivariable analysis considering the RALE score both at baseline (as expressed as a continuous variable) and as a time-varying covariate		
Baseline RALE score (hazard ratio for each one-point increment in the RALE score at baseline)	1.04 (1.01-1.08)	.006
Change in RALE score over time (hazard ratio for each one-point decrease in RALE score per unit of time)	0.99 (0.99-0.99)	.03
Multivariable analysis considering the RALE score both at baseline (as expressed as a continuous variable) and as a time-varying covariate, adjusted for other risk stratifiers		
Baseline RALE score (hazard ratio for each one-point increment in the RALE score at baseline)	1.06 (1.02-1.10)	.002
Change in RALE score over time (hazard ratio for each one-point decrease in RALE score per unit of time)	0.99 (0.99-0.99)	.022
Age, y	1.04 (1.02-1.05)	< .001
Sex (male)	1.15 (0.60-2.19)	.70
BMI, kg/m^2	1.04 (0.99-1.08)	.09
Simplified Acute Physiology Score II	1.02 (1.00-1.04)	.02
Total volume of fluids received since study entry, L	1.14 (1.01-1.28)	.04
Initial need for vasopressor use	1.47 (0.87-2.48)	.20
Univariable analysis		
Baseline RALE score ≥ 30 (fourth quartile)[a]	1.88 [1.02–3.49]	0.04
Multivariable analysis adjusted for other risk stratifiers		
Baseline RALE score ≥ 30 (fourth quartile)[a]	2.18 (1.11-4.27)	.02
Age, y	1.03 (1.01-1.06)	.007
Sex (male)	1.62 (0.67-3.96)	.30
BMI, kg/m^2	1.01 (0.96-1.07)	.60
Simplified Acute Physiology Score II	1.02 (0.99-1.04)	.07
Total volume of fluids received since study entry, L	1.18 (0.95-1.46)	.10
Initial need for vasopressor use	2.05 (0.97-4.35)	.06

RALE = Radiographic Assessment of Lung Edema.
[a]Hazard ratio is reported for a RALE score ≥ 30 at baseline, as opposed to a RALE score < 30. Number of patients available for multivariable complete case analysis: 135. Number of observations available for analysis of the RALE score as a time-varying covariate (days 0, 2, and 3): 288.

RALE Score and ARDS Severity

Higher baseline RALE score was associated with lung injury severity as measured by lower compliance of the respiratory system (Spearman $\rho = -0.41$, $P < .0001$) and extent of lung epithelial injury (as assessed by plasma sRAGE) ($\rho = 0.46$, $P < .0001$) (e-Fig 3), but there was no significant correlation between RALE score and Pao_2/Fio_2 ($\rho = -0.13$; $P = .10$).

Interobserver Agreement for RALE Scores

The RALE scores of the two independent reviewers are compared in e-Figure 4. There was excellent between-observer agreement for the total RALE score, with Lin concordance correlation coefficient ρ of 0.978 (95% CI, 0.974-0.983; $P < .0001$). Agreement was slightly better for quadrant scores calculated in upper radiographic quadrants than for scores calculated in lower radiographic quadrants ($\rho = 0.982$; 95% CI, 0.978-0.986; $P < .0001$ and $\rho = 0.935$; 95% CI, 0.921-0.949; $P < .0001$, respectively).

Discussion

The main objective of this study was to investigate whether early changes in RALE score over time are associated with clinical outcomes in patients with ARDS. In this analysis, we found that changes in RALE score over the 3 days of ARDS were independently associated with 90-day survival in ARDS, even after multivariable

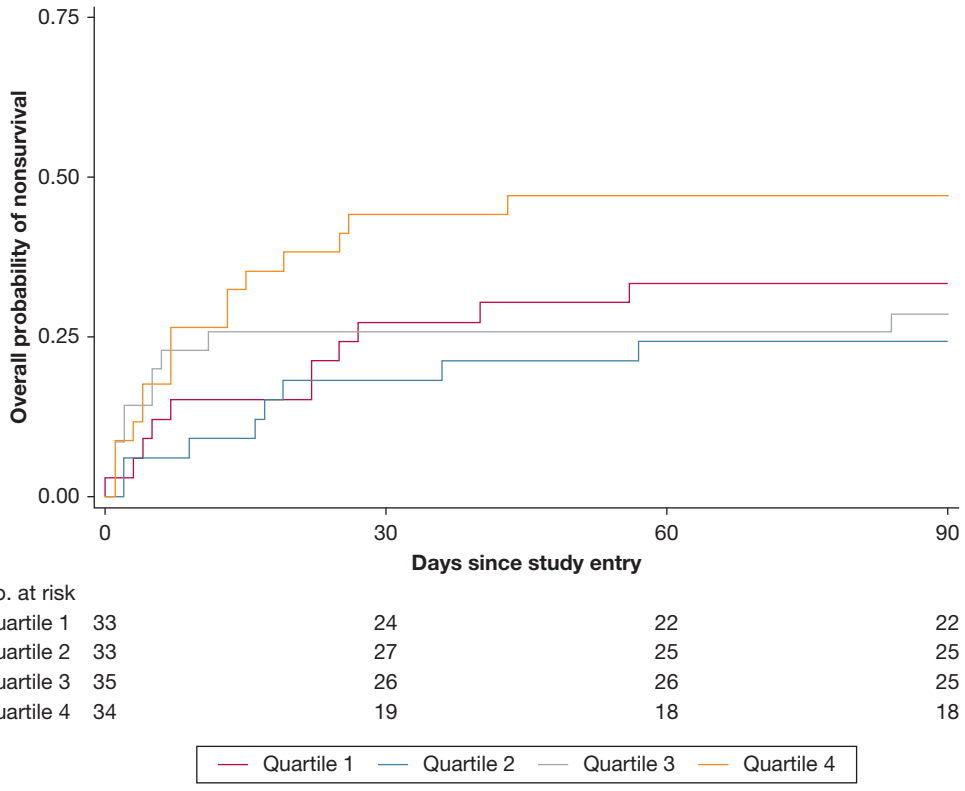

Figure 2 – *Kaplan-Meier failure estimates curves of the probability of nonsurvival from study entry to day 90, as stratified by quartiles of the RALE score. Quartile 1: RALE score < 17; quartile 2, 17 ≤ RALE score < 23; quartile 3, 23 ≤ RALE score < 30; quartile 4, RALE score ≥ 30. See Figure 1 legend for expansion of abbreviation.*

adjustment for the baseline RALE score and other risk stratifiers (eg, age, sex, BMI, SAPS II, need for vasopressor use at baseline, total volume of fluids received since study entry). A decrease in RALE score over time was associated with better survival, particularly when assessed on day 3 after ARDS,

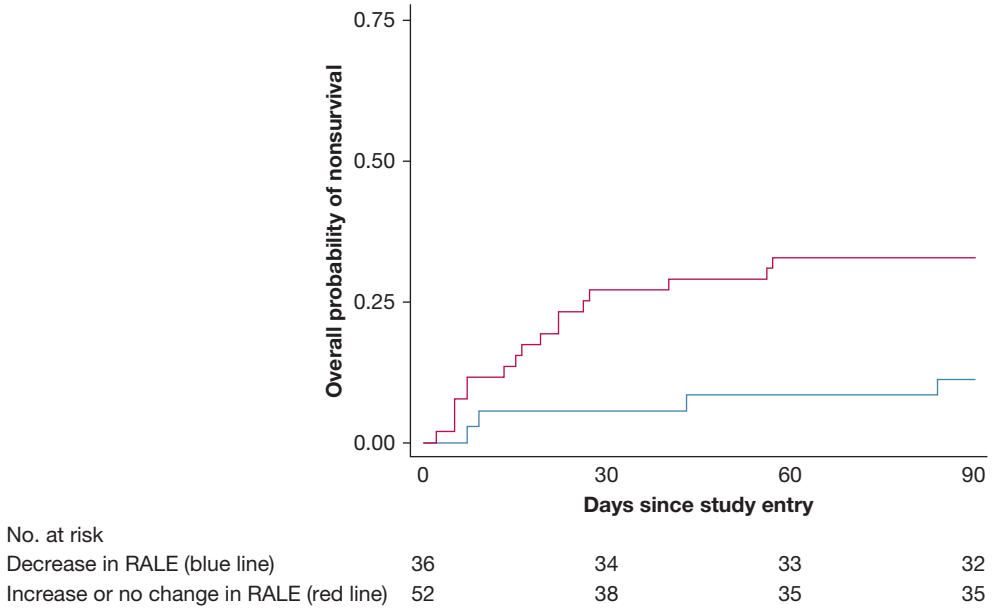

Figure 3 – *Kaplan-Meier failure estimates curves of the probability of nonsurvival from study entry to day 90, as stratified by the change in RALE score between day 0 and day 3 (decrease in RALE score [red line] vs increase or no change in RALE score [blue line]); n = 88 available for multivariable complete case analysis). See Figure 1 legend for expansion of abbreviation.*

TABLE 4] Univariate and Multivariable Marginal Cox Survival Analyses of Death at Day 90, Considering the Differences in RALE Score Between Day 3 and Baseline (Day 0)

Analysis Performed	Hazard Ratio (95% CI)	*P* Value
Univariable analysis considering the difference in RALE score between day 3 and day 0 (as expressed as a continuous variable)		
Difference in RALE score between day 3 and day 0[a]	1.05 (1.00-1.10)	.04
Univariable analysis considering the difference in RALE score between day 3 and day 0 (as expressed as an increase, or no change, compared with a decrease)		
Increase, or no change, in RALE score between day 3 and day 0[b]	3.39 (1.14-10.09)	.03
Multivariable analysis considering the difference in RALE score between day 3 and day 0 (as expressed as an increase, or no change, compared with a decrease), adjusted for other risk stratifiers		
Increase, or no change, in RALE score between day 3 and day 0[b]	3.18 (1.04-9.74)	.04
Age, y	1.03 (1.00-1.07)	.04
Sex (male)	1.14 (0.33-3.92)	.80
BMI, kg/m^2	1.06 (0.98-1.16)	.20
Simplified Acute Physiology Score II	1.00 (0.97-1.04)	.80
Total volume of fluids received since study entry, L	1.05 (0.72-1.54)	.80
Initial need for vasopressor use	1.58 (0.58-4.27)	.40

See Table 3 legend for expansion of abbreviation.
[a]Hazard ratio is reported for each one-point increase in RALE score between day 0 and day 3.
[b]Hazard ratio is reported for the increase, or no change, in RALE score between day 0 and day 3 as compared with a decrease in RALE score. Number of patients available for multivariable complete case analysis: n = 88 for the difference in RALE score between day 3 and day 0.

suggesting that serial assessment of the RALE score may have value as a surrogate outcome measure in future clinical trials.[8,18] Baseline RALE score, when considered alone and as a continuous variable, was not associated with survival; however, higher quartile of baseline RALE score was also associated with higher risk of death at days 30 and 90, even after adjustment.

Our novel findings are in contrast with those from a recent study in 124 ventilated patients with acute respiratory failure because of ARDS or cardiogenic pulmonary edema in which only large and late decreases in RALE score (> 50% reduction in baseline RALE score as assessed at 7 days) were associated with better 90-day survival.[3] In this analysis that included important variability in time intervals between available RALE scores and some clinical data, earlier changes in RALE score were not associated with outcomes, further prompting additional investigation. Although inclusion of radiographs from extubated patients and differences in selection criteria and time intervals from ARDS onset between the study from Kotok et al[3] and our current study may partially explain these discrepancies, differences in statistical analysis could also explain the differences. Because RALE scores are dynamic over time, we used a marginal Cox proportional hazards model considering the RALE score both at baseline and as a time-varying covariate to more accurately account for variation over time. In addition, here we hypothesized that earlier changes in RALE score, namely within the very first days of ARDS, might be more useful as an outcome measure for future trials than later changes that can be influenced by a variety of intercurrent events such as ventilator-associated pneumonia.

Higher baseline RALE score (≥ 30 [fourth quartile]) was associated with decreased survival, which is in line with the previous study by Warren et al.[1] In the latter, effect sizes were expressed for a five-unit, noncontinuous increase in baseline RALE score, which makes comparisons difficult; however, taken together, it can be hypothesized that higher baseline RALE values are associated with worse outcome in both the previous study[1] and the current analysis. These results are discrepant compared with those from Kotok et al,[3] possibly because of their inclusion of a more heterogeneous population of patients in whom ARDS diagnosis was made a posteriori in a secondary analysis of a prospective cohort assembled over 7 years.[3] However, a semiquantitative scoring system based only on the density of opacifications on chest radiographs was associated with clinical outcomes in a broad population of critically ill patients admitted to a medical ICU,[19] in line with our current findings in

patients with ARDS. Our results, combined with those from previous studies, confirm that the RALE is simple to calculate after minimal training and robustly reproducible when independent readings are compared.[1,3,19]

In the original report by Warren et al,[1] the RALE score provided a reliable assessment of the extent of lung edema in patients with ARDS that was reflected by the severity of hypoxemia. In contrast, in our study, as in the study from Kotok et al,[3] there was no significant correlation between higher RALE scores and lower Pao_2/Fio_2. However, the RALE score was associated with other indices of ARDS severity at baseline in the present cohort, including compliance of the respiratory system and extent of lung epithelial injury (as assessed by plasma sRAGE).[4,6,20,21] The failure to replicate previous correlations between the RALE and arterial oxygenation in patients with ARDS may be explained by different inclusion criteria of the study from Warren et al[1] and of the LIVE trial. Specifically, only patients with moderate or severe ARDS, based on the Berlin definition, were enrolled in the LIVE trial, whereas the FACTT included patients with milder severity of hypoxemia ($Pao_2/Fio_2 <$ 300 mm Hg), and the LIVE trial enrolled patients with earlier onset of ARDS (within 12 h of meeting inclusion criteria), compared with the FACTT (within 48 h).[2,9,11] This finding could also indicate that the RALE score might provide additional prognostic information about ARDS severity beyond that provided solely by the severity of arterial hypoxemia, such as lower compliance of the respiratory system and the degree of lung epithelial injury.[22]

This study has some limitations. First, there is a risk of selection bias inherent to the inclusion and noninclusion criteria used in the LIVE trial, which could hamper the generalizability of our findings to other populations of patients with ARDS. Second, we only included a relatively small sample of patients enrolled in three of the 20 centers that participated in the primary trial, and because this was a secondary analysis, no formal sample size estimation or power calculation was performed. However, with 135 patients, the statistical power was satisfactory ($>$ 80%) to highlight HRs $>$ 1.75 for Cox proportional-hazards regression Wald test, log-hazard metric (stpower command in Stata), with a two-sided type I error at 5%. Although our sensitivity analysis revealed few differences between subjects included in this analysis and those enrolled in the LIVE trial who were included in this analysis, the selection of patients to include in this study (which was made a priori because of logistical considerations related to the collection and scoring of chest radiographs) might have influenced some of the results.

This study also had several strengths. First, this study further validates excellent interobserver agreement for the RALE score among trained readers. Second, this is the first study, to our knowledge, to validate the association of the RALE score with ARDS severity and prognosis. In addition to the prognostic value of baseline RALE score, our findings support an association between changes in RALE score over the first days of ARDS and clinical outcomes. Whether the RALE could be used in future adaptive trials to selectively enroll patients with worse prognosis (prognostic enrichment) and/or serve as a treatable trait for predictive enrichment deserves further investigation.[17,23,24]

In conclusion, the change in RALE score during the first days after ARDS onset is independently associated with 90-day survival, and may be useful as a surrogate radiographic outcome in future studies. The RALE score at baseline is also associated with lung injury severity and survival in ARDS, therefore validating previous findings.

Acknowledgments

Author contributions: M. J. and L. B. W. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. J. A., B. P., C. L., J. A. B., and J.-M. C. contributed substantially to the study design, data analysis and interpretation, and writing of the manuscript. S. J., J.-Y. L., R. B., T. G., E. F., and J.-E. B. contributed to data acquisition and provided critical revisions to the manuscript. All authors reviewed several drafts of the manuscript and approved the final version.

Financial/nonfinancial disclosures: None declared.

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Role of sponsors: The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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