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Chest Radiograph Severity and Its Association With Outcomes in Subjects With COVID-19 Presenting to the Emergency Department

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BACKGROUND: Severity of radiographic abnormalities on chest radiograph in subjects with COVID-19 has been shown to be associated with worse outcomes, but studies are limited by different scoring systems, sample size, subject age, and study duration. Data regarding the longitudinal evolution of radiographic abnormalities and its association with outcomes are scarce. We sought to evaluate these questions using a well-validated scoring system (the Radiographic Assessment of Lung Edema [RALE] score) using data over 6 months from a large, multihospital health care system. METHODS: We collected clinical and demographic data and quantified radiographic edema on chest radiograph obtained in the emergency department (ED) as well as on days 1–2 and 3–5 (in those admitted) in subjects with a nasopharyngeal swab positive for SARS-CoV-2 by polymerase chain reaction (PCR) visiting the ED for coronavirus disease 2019 (COVID)-19-related complaints between March–September 2020. We examined the association of baseline and longitudinal evolution of radiographic edema with severity of hypoxemia and clinical outcomes. RESULTS: Eight hundred and seventy subjects were included (median age 53.6; 50.8% female). Inter-rate agreement for RALE scores was excellent (interclass correlation coefficient 0.84 [95% CI 0.82–0.87], $P < .001$). RALE scores correlated with hypoxemia as quantified by S_{pO_2}/F_{IO_2} ($r = -0.42$, $P < .001$). Admitted subjects had higher RALE scores than those discharged (6 [2–11] vs 0 [0–3], $P < .001$). An increase of RALE score ≥ 4 was associated with worse 30-d survival ($P = .006$). Larger increases in the RALE score were associated with worse survival. CONCLUSIONS: The RALE score was reproducible and easily implementable in adult subjects presenting to the ED with COVID-19. Its association with physiologic parameters and outcomes at baseline and longitudinally makes it a readily available tool for prognostication and early ICU triage, particularly in patients with worsening radiographic edema. *Key words: chest x-ray; pulmonary edema; COVID-19; RALE.* [Respir Care 0;0(0):1–●. © 0 Daedalus Enterprises]

Introduction

The significant morbidity and mortality associated with the coronavirus disease 2019 (COVID-19) pandemic have resulted in expedited research and development of preventive, diagnostic, and therapeutic strategies to decrease the incidence and severity of disease associated with SARS-CoV-2.[1,2] The ability to provide accurate prognosis at time of diagnosis remains limited and relies mostly on baseline patient characteristics such as age and known comorbidities.[3-5] Combined radiographic, biomarker, and artificial intelligence methods are emerging to assist with more accurate prognostication and identification of biologic phenotypes.[6,7]

Of the available diagnostic tools, plain chest radiograph remains a simple and readily available tool that is accessible even in low-resource areas, some of which have been severely affected with extreme rates of infection and mortality.[8] The Radiographic Assessment of Lung Edema (RALE) has been shown to be accurate and reliable between observers with baseline assessment of chest radiograph in subjects with COVID-19 and non-COVID-19 ARDS.[9-11] Although baseline radiographic edema has been shown to be associated with worse outcomes, whether the longitudinal evolution of radiographic edema as quantified by the RALE score is predicative of need for ICU admission, mechanical ventilation, and 30-d survival remains largely unexplored.

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We sought to independently evaluate the utility of the RALE score in a multi-center cohort of adult subjects diagnosed with COVID-19 early in the pandemic, examine its association with severity of hypoxemia at baseline, and to assess its ability to predict clinical outcomes at time of emergency department (ED) evaluation and in the early post-hospitalization period in those requiring hospital admission.

Methods

Subject Population

From March 2020–October 2020, we collected data from the electronic medical records within the Cleveland Clinic system from 18 different clinical sites. We included all patients 18 y or older diagnosed with COVID-19 using nasal-swab polymerase chain reaction (PCR). Patients with prior tracheostomy or those for whom the duration of symptoms associated with COVID-19 was unclear were excluded. The Cleveland Clinic Institutional Review Board (IRB) exempted the study from IRB approval (FLA 20–038).

We collected baseline clinical data obtained at the time of ED visit (including demographics, comorbidities, and physiologic and laboratory variables). We collected chest radiographs at time of ED evaluation. For subjects admitted to the hospital, we also collected chest radiographs at 2 additional time periods: early (1–2 d) and late (3–5 d) after admission to the hospital. F_{IO_2} was calculated using 1 L/min supplemental O_2 to 3% F_{IO_2} conversion. The resultant F_{IO_2} was used for subsequent analysis involving this value. For oxygen flow levels $>$ 15 L/min as documented in subjects' charts, the F_{IO_2} used to analyze was set to 100% (ie, 1.0) as this would imply subjects either being transitioned to a non-rebreather mask, a high-flow nasal cannula with high F_{IO_2} and flow requirements, or a combination of the two. We examined the association of radiographic edema with hypoxemia, need for hospital admission, ICU admission, need for mechanical ventilation within 7 d of admission, and 30-d mortality. For those admitted, we examined the association of worsening radiographic edema with 30-d survival and need for mechanical ventilation.

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Supplementary material related to this paper is available at http://rc.rcjournal.com.

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QUICK LOOK

Current knowledge

The Radiographic Assessment of Lung Edema (RALE) score is easily implementable with high rates of inter-rater agreements between studies. Baseline radiographic edema in subjects with coronavirus disease 2019 (COVID-19) was predictive of outcomes in small studies.

What this paper contributes to our knowledge

The RALE score has higher inter-rate agreement and was easily implementable in subjects with COVID-19 pneumonia. Quantification of baseline radiographic edema using the RALE score was predictive of clinical outcomes in a large, multi-center cohort. Longitudinal assessment of lung edema may assist in prognostication in patients with COVID-19.

RALE Score Calculation

We quantified the radiographic edema by calculating the RALE score as originally described by Warren and colleagues.[9] Briefly, the RALE score assesses 2 aspects of pulmonary edema in 4 quadrants divided horizontally by a line through the first branch of the left main bronchus and vertically by the spinal column: consolidation extent (quantified as percent of chest radiograph quadrant involved: 0% = 0; < 25% = 1; 25−50% = 2; 50−75% = 3; > 75% = 4) and density (1 = hazy, 2 = moderate, 3 = dense). Edema extent and density are multiplied for each quadrant, and the total RALE score is obtained by addition of all quadrant scores (0–48) (Fig. 1). Two independent reviewers (DK and SG) scored all chest radiographs.

Statistical Analysis

We assessed inter-rater agreement (DK, SG) using the interclass correlation coefficient (ICC) with a 2-way mixed-agreement model.[12,13] We compared baseline characteristics using Wilcoxon signed-rank and Fisher exact tests for continuous and categorical variables, respectively. We applied Pearson correlation test to examine for baseline association between the RALE score and oxygenation status as captured by the S_{pO_2}/F_{IO_2}.

To establish quartiles to be used for analysis, we first identified the median RALE score for the cohort. We then distinguished the first quartile from the second based on the complete absence of radiographic abnormalities (ie, RALE score of 0 in the first quartile) from the presence of mild radiographic abnormalities (ie, RALE score of 1 to median RALE score for the entire cohort). The third and fourth quartiles were derived using the 75th percentile as the

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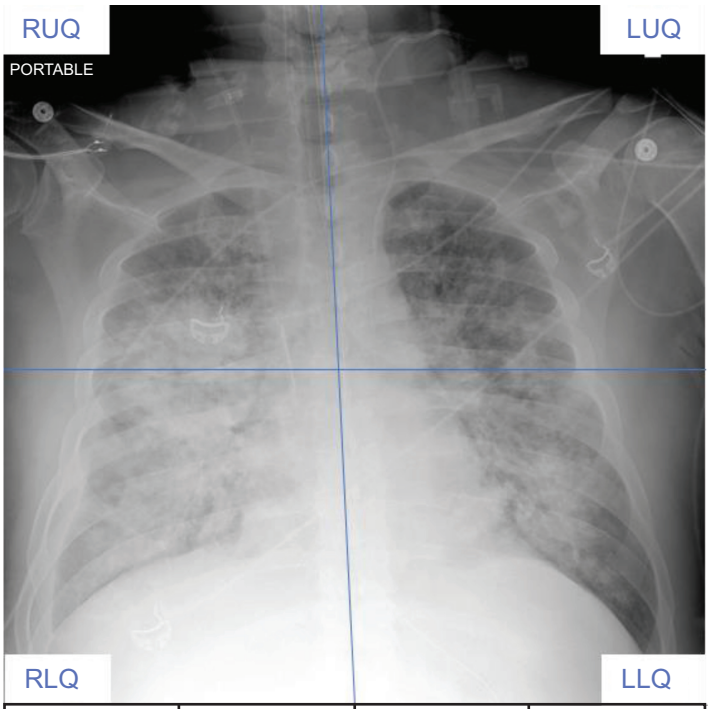

Quadrant	Extent	Density	Total
RUQ	3 (50-75%)	2 (moderate)	3 x 2 = 6
LUQ	4 (>75%)	1 (hazy)	4 x 1 = 4
LLQ	3 (50-75%)	2 (moderate)	3 x 2 = 6
RLQ	4 (>75%)	2 (moderate)	4 x 2 = 8

Total RALE : 24

Fig. 1. Radiographic Assessment of Lung Edema (RALE) score calculation from a chest radiograph. First, the radiograph is divided in 4 quadrants defined by a drawing a horizontal line from the first branch of the left main bronchus and a vertical line through the spinal column separating the left and right lungs. Each quadrant is scored separately based on consolidation extent and density, which is then multiplied. The total RALE score is obtained by simple addition of all 4 quadrant scores (0–48).

cutoff value. We then used Cox proportional hazard models adjusting for age, severity of hypoxemia, and history of diabetes to examine the effects of baseline RALE scores on 30-d survival and need for intubation within 7 d of admission. To assess for the impact of radiographic edema worsening on outcomes, we considered different thresholds of RALE score increase from baseline chest radiograph and then compared outcomes for subjects with versus without worsening edema. All statistical analyses were performed with the R statistical software version 4.1 (R Foundation for Statistical Computing, Vienna, Austria).[14]

Results

We reviewed the electronic medical records of 949 patients based on eligibility criteria. Twenty-one patients did not have chest radiographs done on ED evaluation, whereas 58 had incomplete baseline and/or outcome data (Fig. 2). A total of 870 subjects were subsequently included in the study (Table 1). Three hundred and seventy-six (43%) subjects had a normal chest radiograph (RALE = 0). The median RALE score was 2. There were 78 subjects in the second quartile (RALE score 1–2), 216 in the third quartile (RALE score 3–7), and 200 in the fourth quartile (RALE score 8–32). We further examined baseline characteristics of subjects based on RALE quartiles (Table S1, see related supplementary materials at http://www.rc.rcjournal.com).

Inter-Reviewer Agreement for RALE Score

A total of 1,185 of chest radiographs were reviewed from different study periods. Inter-rate agreement between the 2 reviewing clinicians (DK, SG) for the RALE score was excellent (ICC 0.84 [95% CI 0.82–0.87], $P < .001$).

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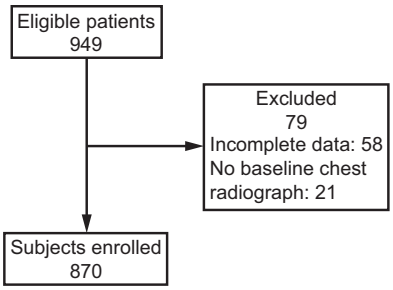

Fig. 2. Flow chart. We included subjects ≥ 18 y old diagnosed with coronavirus disease 2019 (COVID-19) using nasal-swab polymerase chain reaction. Patients with prior tracheostomy or those for whom the clinical course and duration of symptoms associated with COVID-19 were unclear were excluded.

Table 1. Baseline Characteristics of Included Subjects at Time of Emergency Department Evaluation

	$N = 870$
Female	442 (50.2)
Age, y	53.6 (39.0–66.3)
BMI	30.5 (26.0–35.6)
Symptom duration, d	4.0 (2.0–7.0)
History of diabetes	183 (21.1)
History of tobacco use	318 (37.0)
S_{pO_2}/F_{IO_2}	461.9 (452.4–471.4)
RALE score	2.0 [0–7.0]
30-d mortality	65 (7.5)

Data are shown as *n* (%) or median (interquartile range).
BMI = body mass index
RALE = Radiographic Assessment of Lung Edema

Association With Baseline Demographic and Clinical Variables

Subjects in the higher RALE quartiles were more likely to be male, older, and have history of obstructive sleep apnea, heart failure, hypertension, hyperlipidemia, chronic kidney disease, lung disease, diabetes, and immunosuppression ($P < .05$ for all, Table S1) but not tobacco use ($P = .28$). Ethanol consumption was less common in the higher RALE quartiles ($P = .002$). They were also more likely to be tachypneic, have lower hemoglobin levels, and higher neutrophil-to-lymphocyte ratios. At baseline, there was a significant association between severity of hypoxemia and RALE score (Pearson r = −0.42, $P < .001$; Figure S1, see related supplementary materials at http://www.rc.rcjournal.com).

Association With Clinical Outcomes

The RALE score was significantly higher in subjects requiring hospitalization (2 [6–11]) compared to those who were discharged home (0 [0–3], $P < .001$) (Fig. 3A). In those subjects requiring admission, a higher RALE scored was observed in those requiring ICU admission (4 [8–14]) compared to those that did not (5 [0–9], $P < .001$) (Fig. 3B). A higher baseline RALE score was associated with unadjusted 30-d mortality (5 [8–15] vs 0 [1–6], $P < .001$) and need for mechanical ventilation (8 [5–16] vs 0 [1–6], $P < .001$). In a multivariate Cox-proportional hazards model adjusted for age, severity of hypoxemia, and history of diabetes, we found baseline RALE scores to not be associated with 30-d survival when the first 2 quartiles were compared (hazard ratio [HR] 1.5 [0.13–16.6], $P = .74$). However, we found 30-d survival to be significantly lower in the third and fourth quartiles when compared to the first RALE quartile (HR 11.6 [2.7–49.3], $P < .001$ and 10.1 [2.3–43.0], $P = .002$, respectively) (Fig. 4). Similar results were observed with regard to the need for intubation and mechanical ventilation within 7 d of admission (Q3 vs Q1 and Q4 vs Q1; HR 6.49 [1.86–22.54] and HR 9.48 [2.76–32.56], $P = .003$ and $P < .001$, respectively) (Figure S2, see related supplementary materials at http://www.rc.rcjournal.com).

Longitudinal Evolution of Radiographic Edema in Hospitalized Subjects and Its Association With Outcomes

Among hospitalized subjects, 408 had baseline, 91 had early-period, and 123 had late-period chest radiographs. There were significant differences between baseline and early-period (6 [2–11] vs 14 [5–20], $P < .001$) as well as baseline and late-period (6 [2–11] vs 11 [5–20], $P < .001$) RALE scores. There was no difference between the early and late period ($P = .51$) (Figure S3, see related supplementary materials at http://www.rc.rcjournal.com). A ≥ 4-point increase in RALE score from baseline to early period was associated with worse 30-d survival (HR 2.1 [1.2–3.5], $P = .006$) (Fig. 5). This was also true for increase from baseline to late period (HR 2.7 [1.7–4.2], $P = .002$). Further increase in the RALE score was associated with worse survival (Table 2). Although we did not observe identical trends in need for mechanical ventilation, a larger increase in the RALE score from baseline to early (≥ 6) or a later increase in the RALE score of ≥ 4 (baseline to late) was associated with higher likelihood of requiring mechanical ventilation (HR 2.2 [1.1–4.3], $P = .02$ and HR 6.1 [3.4–10.7], $P < .001$, respectively) (Table 2).

Discussion

In this multi-center, retrospective, broadly inclusive study of 870 subjects presenting to the ED with symptoms concerning for and diagnosed with COVID-19 using nasal-swab PCR between March–September 2020, we examined

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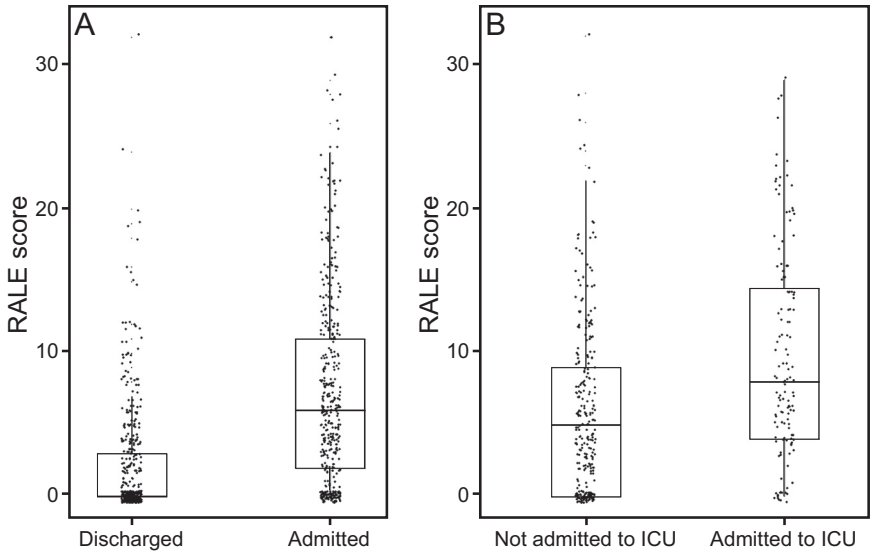

Fig. 3. Comparison of median Radiographic Assessment of Lung Edema (RALE) score by need for hospital and ICU admission. Subjects requiring hospital admission had a higher median RALE score compared to those discharged home ($P < .001$) (A). Similarly, in subjects admitted to the hospital, those who required ICU admission had a higher median RALE score compared to those who did not (B) ($P < .001$).

the association of radiographic edema on chest radiographs using the RALE score with physiologic parameters and clinical outcomes. Subjects with worse radiographic edema as quantified by the RALE score on admission were more likely to be hypoxemic, require hospital admission, ICU admission, mechanical ventilation, and had higher 30-d mortality. In addition to these baseline associations, we were able to demonstrate that progressive worsening of radiographic edema over the course of hospitalization for those requiring admission conferred a higher risk of death and need for intubation. This risk increased with worsening of radiographic edema even after adjustment for variables commonly associated with worse outcomes in subjects with COVID-19 such as history of diabetes, age, and baseline hypoxemia.

The association between baseline radiographic edema and worse outcomes has been consistently demonstrated in a multitude of smaller studies using several scoring scores demonstrating an association between chest radiograph severity and clinical outcomes.[15-21] Our study is the largest to date utilizing

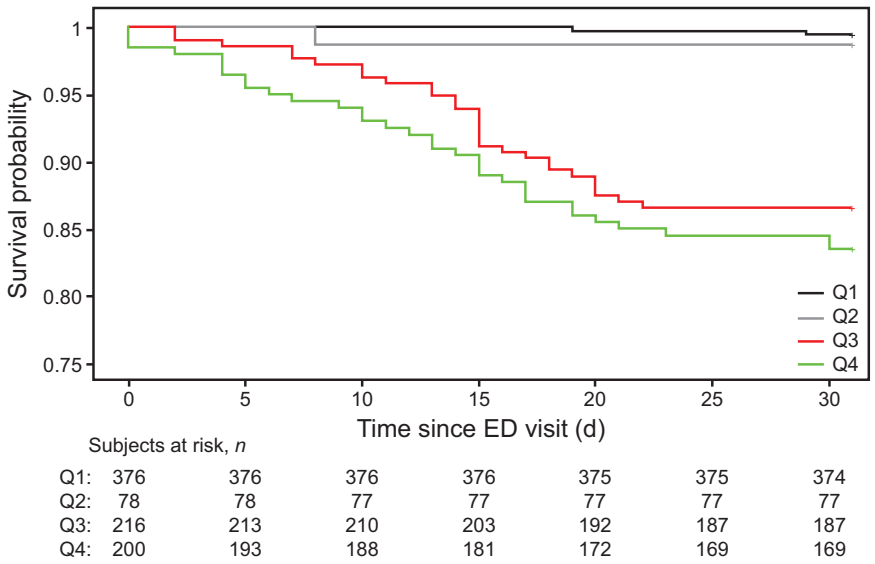

Fig. 4. Kaplan-Meier estimates of 30-d survival comparing Radiographic Assessment of Lung Edema score quartiles. We observed significantly lower likelihood of survival at 30 days when Q3 and Q4 were compared to Q1 ($P = .002$ and $P < .001$, respectively). There was no significant difference in survival when Q1 and Q2 were compared. ED = emergency department.

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Table 2. Cox Regression Analysis for Progressive Increases in Radiographic Assessment of Lung Edema Score, 30-Day Survival, and 7-Day Likelihood of Requiring Mechanical Ventilation

Examined Parameter	RALE Score Increase (≥)	Hazard Ratio (95% CI)	*P*
Likelihood of mortality at 30 d			
Baseline to early	4	2.07 (1.23–3.49)	.006
	5	2.26 (1.35–3.79)	.002
	6	3.06 (1.81–5.16)	< .001
	7	3.58 (2.08–6.14)	< .001
	8	3.87 (2.26–6.63)	< .001
Baseline to late	4	2.67 (1.69–4.22)	< .001
	5	2.57 (1.63–4.04)	< .001
	6	2.65 (1.69–4.16)	< .001
	7	2.83 (1.8–4.46)	< .001
	8	2.9 (1.85–4.55)	< .001
Early to late	4	0.97 (0.36–2.65)	.96
	5	0.58 (0.18–1.89)	.36
	6	0.62 (0.18–2.13)	.45
	7	1.20 (0.38–3.82)	.76
	8	0.98 (0.29–3.37)	.98
Likelihood of requiring mechanical ventilation at 7 days			
Baseline to early	4	1.58 (0.82–3.04)	.17
	5	1.79 (0.93–3.46)	.08
	6	2.20 (1.14–4.27)	.02
	7	2.38 (1.21–4.69)	.01
	8	1.99 (1.04–3.80)	.037
Baseline to late	4	6.06 (3.44–10.67)	< .001
	5	5.59 (3.26–9.56)	< .001
	6	5.89 (3.45–10.07)	< .001
	7	6.61 (3.89–11.26)	< .001
	8	6.85 (4.06–11.57)	< .001
Early to late	4	0.79 (0.37–1.67)	.53
	5	0.64 (0.28–1.46)	.29
	6	0.76 (0.33–1.78)	.53
	7	0.69 (0.28–1.67)	.41
	8	0.59 (0.22–1.55)	.28

A RALE score increases of at least 4 points from baseline to either early or late periods was associated with worse 30-d survival. A larger early increase (baseline to early ≥ 6) or a later (baseline to late ≥ 4) increase in the RALE score was associated with higher probability of requiring mechanical ventilation. All analyses were done after adjustment for baseline hypoxemia, age, and history of diabetes.
RALE = Radiographic Assessment of Lung Edema

the RALE score, which has been previously shown to have high rates of inter-observer agreement across different diseases including pneumonia, ARDS, and heart failure.[10,11,21] In addition to redemonstrating previously reported data (ie, worse radiographic edema being associated with worse outcomes), we were also able to demonstrate very low mortality in those with minimal radiographic edema (Q1 and Q2 with RALE score ≤ 2). This finding further reinforces the notion that screening chest radiographs in patients with asymptomatic or mild COVID-19 disease is not required.[22] However, if performed, a normal chest radiograph at time of ED visit is an indicator of a favorable prognosis. The ability of chest radiograph to identify patients who are at low risk for progression to severe disease while also providing prognostic value for those with moderate-severe radiographic edema (Q3 and Q4, RALE score ≥ 3) provides a readily available tool at time of ED evaluation. Lastly, it provides evidence for the continued use of chest radiograph in the evaluation of COVID-19 pulmonary disease in addition to (or instead of) ultrasonography, being the other low-cost, widely available modality. This is not only for the purpose of identifying lung disease, for which ultrasonography has been showed to be more sensitive when compare to noncontrast computed tomography (CT),[23] but also to identify clinically meaningful disease as it pertains to outcomes. The ability of lung ultrasound to provide prognostic value is highest in the presence of significant disease burden as captured by a high lung ultrasound score (LUS), raising questions about the interpretation of relatively mild abnormalities captured by ultrasonography.[24-26] It therefore appears that either modality would provide some degree of valuable information on initial evaluation, with a normal

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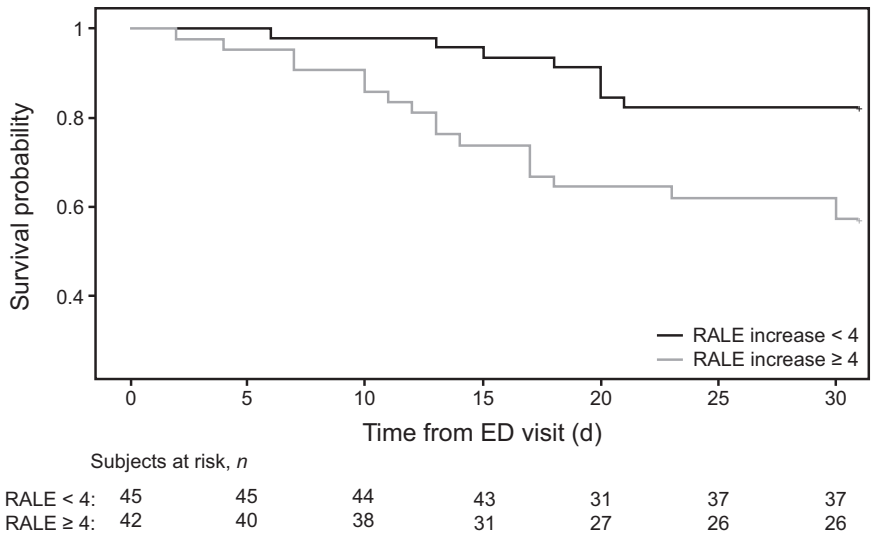

Fig. 5. Kaplan-Meier estimates of 30-day survival based on the longitudinal evolution of Radiographic Assessment of Lung Edema (RALE) score over time. A 4-point increase in RALE score or more from baseline to early period was associated with worse 30-day survival ($P = .002$). ED = emergency department.

chest radiograph providing a simpler (compared to obtainment and calculation of LUS) method of assigning low risk of progression.

Although baseline radiographic edema has been repeatedly shown to be of predictive value, the value of longitudinal evaluation using chest radiograph in patients with COVID-19 shortly after admission remains largely unclear. Small studies examining the evolution of CT abnormalities in COVID-19 showed mixed results. This was likely due to a combination of heterogeneity in disease severity and timing of CT imaging.[16,27] Studies examining the association of baseline and longitudinal evolution of radiographic edema on chest radiograph in subjects with non-COVID-19 ARDS showed mixed results. This is attributable, at least in part, to physiologic derangements present in "extrapulmonary" non-COVID-19 ARDS that are not captured by chest radiograph but result in similar outcomes as in "pulmonary" ARDS, in addition to variability in agreement between clinicians with regard to what is labeled as ARDS.[10,11,28] In the case of COVID-19 (with or without ARDS), where initial pathology requiring hospital admission is often confined to the lungs, we hypothesized that tracking radiographic edema may provide prognostic information outside of clinical monitoring. The significant association between worsening radiographic edema with worse outcomes even after adjustments for confounding factors suggests that progression of COVID-19 pulmonary disease is adequately captured on chest radiograph and periodic radiography may assist in prognostication in hospitalized patients with COVID-19.

Our study has several limitations. The time frame during which the study was performed did not allow for adjustment for antiviral treatments (such as dexamethasone) that have been shown to decrease severity of radiographic edema[29] as these were introduced later during the study period within the healthcare system from which the cohort was derived (late August–September). We were also not able to adjust for any variables other than those obtained at baseline when performing the longitudinal analyses, raising the question of whether other organ failure outside of the pulmonary system (eg, renal failure) and fluid status have contributed to radiographic deterioration that is not directly associated with COVID-19 pulmonary disease. Lastly, whereas the study is a multi-center study across multiple hospitals and states in the United States, practices and procedures early in the pandemic were often institution based and not necessarily guided by the Centers for Disease Control and Prevention and/or the World Health Organization. As such, institutional standards of treatment may not have been reflective of other health care systems around the same time period. Despite these limitations, we excluded patients for which there were incomplete data that would otherwise require imputation and potentially affect our analyses. Instead, the study protocol structured the chest radiograph sampling periods to provide early, standardized meaningful clinical data that may assist clinicians in prognostication and decision making in patients with COVID-19.

Conclusions

We were able to demonstrate the pragmatism and reproducibility of the RALE score in subjects with COVID-19 that showed significant associations between severity of radiographic edema and clinical outcomes both at baseline and longitudinally. The degree of progression as dictated by the

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RALE score was linked to worse outcomes. Furthermore, our study demonstrates that longitudinal assessment of radiographic edema may provide prognostic value and assist clinicians in prognostication in subjects with COVID-19. The effect of antiviral therapy on these findings is unclear and requires further investigation.

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