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Temporal Radiographic Trajectory and Clinical Outcomes in COVID-19 Pneumonia: A Longitudinal Study

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ABSTRACT

Background: Currently, little is known about the relationship between the temporal radiographic latent trajectories, which are based on the extent of coronavirus disease 2019 (COVID-19) pneumonia and clinical outcomes. This study aimed to elucidate the differences in the temporal trends of critical laboratory biomarkers, utilization of critical care support, and clinical outcomes according to temporal radiographic latent trajectories.
Methods: We enrolled 2,385 patients who were hospitalized with COVID-19 and underwent serial chest radiographs from December 2019 to March 2022. The extent of radiographic pneumonia was quantified as a percentage using a previously developed deep-learning algorithm. A latent class growth model was used to identify the trajectories of the longitudinal changes of COVID-19 pneumonia extents during hospitalization. We investigated the differences in the temporal trends of critical laboratory biomarkers among the temporal radiographic trajectory groups. Cox regression analyses were conducted to investigate differences in the utilization of critical care supports and clinical outcomes among the temporal radiographic trajectory groups.
Results: The mean age of the enrolled patients was 58.0 ± 16.9 years old, with 1,149 (48.2%) being male. Radiographic pneumonia trajectories were classified into three groups: The steady group (n = 1,925, 80.7%) exhibited stable minimal pneumonia, the downhill group (n = 135, 5.7%) exhibited initial worsening followed by improving pneumonia, and the uphill group (n = 325, 13.6%) exhibited progressive deterioration of pneumonia. There were distinct differences in the patterns of temporal blood urea nitrogen (BUN) and C-reactive protein (CRP) levels between the uphill group and the other two groups. Cox regression analyses revealed that the hazard ratios (HRs) for the need for critical care support and the risk of intensive care unit admission were significantly higher in both the downhill and uphill groups compared to the steady group. However, regarding in-hospital mortality, only the uphill group demonstrated a significantly higher risk than the steady group (HR, 8.2; 95% confidence interval, 3.08–21.98).
Conclusion: Stratified pneumonia trajectories, identified through serial chest radiographs, are linked to different patterns of temporal changes in BUN and CRP levels. These changes can predict the need for critical care support and clinical outcomes in COVID-19 pneumonia. Appropriate therapeutic strategies should be tailored based on these disease trajectories.

Keywords: COVID-19; Pneumonia Trajectory; Critical Care Support; Clinical Outcome

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INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) began in Wuhan, China in December 2019, and it rapidly spread from then, becoming a pandemic on 11 March 2020.[1,2] As December 26, 2023, there have been over 700,000,000 laboratory-confirmed cases of COVID-19 worldwide, resulting in more than 6.9 million deaths.[1] The COVID-19 also widely emerged in South Korea in October 2020.[3]

While most cases of COVID-19 are classified as mild or moderate disease, 14% and 5% of cases can be classified as severe and critical disease, respectively.[4] In severe disease, pneumonia is usually found through abnormal chest X-ray or computed tomography, and such patients often face a substantially increased risk of developing grave complications such as severe acute respiratory distress syndrome, acute cardiac injury, acute kidney injury, and eventually mortality.[5,6]

Some previous studies have investigated risk factors for severe disease, including pneumonia, typically by using single measurements of clinical and laboratory findings.[1,7] However, that approach may not be able to fully capture the dynamic nature of the disease[8] and it may lead to potential limitations, such as the misclassification of patients into incorrect risk categories, an inability to capture changes in clinical status over time, and a limited ability to identify temporal associations between risk factors and outcomes.

COVID-19 pneumonia is known to present with radiologic findings showing a dynamic change within 2 weeks after symptom onset; in general, its extent increases within 10 days, followed by a gradual decrease thereafter.[9,10] Considering the variations in dynamic changes of pneumonia that are known to occur during the early disease course of COVID-19, investigating the relationship between these dynamic changes and clinical outcomes may aid early identification of patients at risk of progression to severe disease, and it may ultimately facilitate the development of more individually tailored treatment plans as well as optimized utilization of medical resources.[7,11] However, few studies have examined this relationship,[11,12] meaning the relationship between the dynamic nature of the disease and clinical outcomes has yet to be fully established.

Therefore, the current study aimed to identify key temporal radiographic latent trajectories based on repeatedly measured extent of pneumonia in the lungs using chest radiography, and it also aimed to elucidate differences in the temporal trends of critical laboratory biomarkers, utilization of critical care support, and clinical outcomes according to these temporal radiographic latent trajectories.

METHODS

Study population

The present study enrolled patients who were more than 19 years old and hospitalized for COVID-19 in the Seoul National University Boramae Medical Center between December 2019 and March 2022. All patients were diagnosed as having COVID-19 based on a positive real-time polymerase chain reactive assay for severe acute respiratory syndrome coronavirus-2.

Data review and classification

We reviewed the data of the enrolled patients and classified the data into the following five categories: 1) initial clinical information[13,14]; 2) initial laboratory information; 3) clinical course; 4) critical care supports; and 5) clinical outcome. The detailed items in each category are described in **Supplementary Data 1**.

Quantification of extent of COVID-19 pneumonia on chest radiographs

We used a deep learning algorithm to automatically assess the extent of pneumonia on chest radiographs by uploading anonymized DICOM files of chest radiographs to a cloud system (http://www.medicalip.com/DeepCatchX/; DeepCatch X, MEDICALIP, Seoul, Korea).[15] The extent of radiographic pneumonia was quantified as a percentage using this algorithm. The algorithm and process are described in detail in the **Supplementary Data 2**.

Data preprocessing

Our initial dataset comprised 4,937 patient samples drawn from the clinical database of Seoul National University Boramae Medical Center. The processes of subject enrollment and data preprocessing are depicted in **Fig. 1**. To refine the dataset for relevance to our study's focus, we applied several exclusion criteria. First, we excluded 497 patients who were under 19 years of age from the dataset. To capture the crucial early and critical stages of disease progression, we excluded data beyond the first three weeks of hospitalization. We then additionally refined the dataset by focusing on the severity of lung involvement in COVID-19. Patients whose maximum proportion (%) of the extent of COVID-19 pneumonia on chest radiographs was less than 1 were also excluded, resulting in the removal of 1,295 patients.[9] Moreover, to ensure a robust longitudinal analysis, patients with only a single measurement were excluded, leading to the removal of 760 more patients. Our final dataset ultimately comprised 2,385 COVID-19 patients, all presenting with pneumonia data.

Stratifying radiographic trajectory and identifying latent class

To identify the trajectories of the longitudinal extent of COVID-19 pneumonia changes during hospitalization, latent class growth analysis (LCGA) was performed.[16] LCGA analyses were conducted using the hlme function from the lcmm package in R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).[16] The process involving the LCGA analysis, optimal subgroup identification, and model fitting is described in detail in the **Supplementary Data 3**.

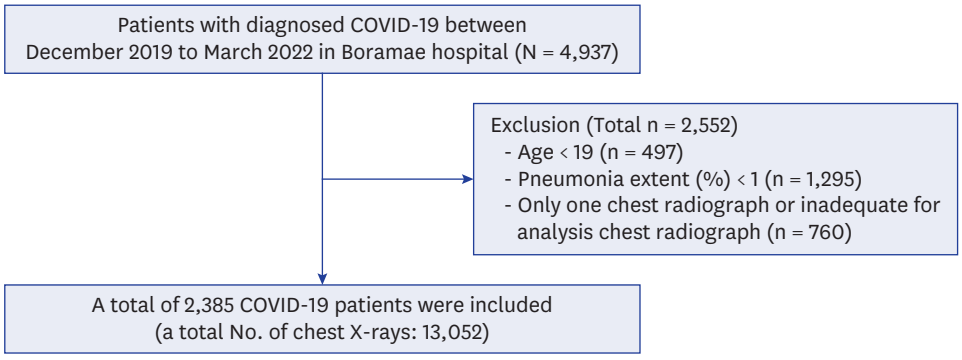

Fig. 1. Diagram of showing enrollment of study subjects.
COVID-19 = coronavirus disease 2019.

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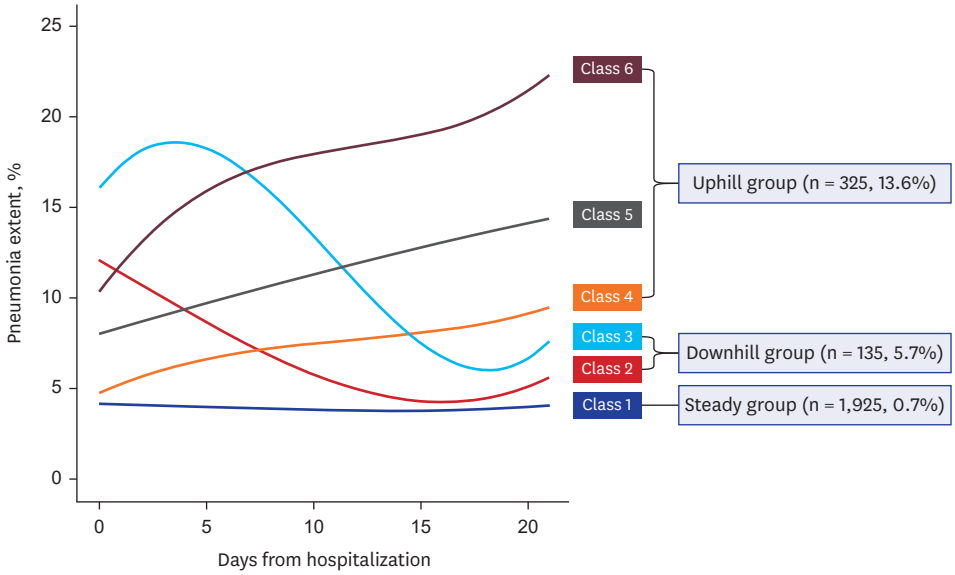

Fig. 2. Regrouping of radiographic latent classes into simplified radiographic trajectory groups for enhanced clinical interpretation. This figure illustrates the consolidation of six radiographic latent classes into three distinct trajectory groups aimed at simplifying clinical analysis and interpretation. The regrouping criteria were primarily based on the trend of slope changes in the pneumonia extent over time, facilitating a clearer comparative analysis. The purpose of this regrouping is to enhance clinical clarity and simplify the analysis, providing a more intuitive understanding of the disease progression patterns among patients.

Regrouping of radiographic latent classes into simplified radiographic trajectory group

According to the results of the latent class LCGA analyses, the radiographic trajectories of the study population were stratified into six classes: Class 1 (n = 1,925, 80.7%); Class 2 (n = 110, 4.6%); Class 3 (n = 25, 1.1%); Class 4 (n = 137, 5.7%); Class 5 (n = 142, 6.0%); and Class 6 (n = 46, 1.9%) (**Supplementary Fig. 1**).

We simplified the categorization of pneumonia progression into three main radiographic trajectory groups, as illustrated in **Fig. 2**. This regrouping was based on an analysis of the slope changes in pneumonia extent over time, and it was intended to facilitate a clearer understanding of disease progression patterns. This regrouping also aimed to enhance the interpretability of clinical data and improve the clarity of comparative analyses.

Steady group: Included only Class 1, representing 1,925 patients (80.7%). This group demonstrated a stable trajectory with minimal variation in pneumonia extent, indicating negligible disease impact throughout the hospitalization period.

Downhill group: Combined Classes 2 and 3, totaling 135 patients (5.7%). Characterized by an initial increase in pneumonia extent followed by a subsequent reduction thereof, this group depicted a trajectory from worsening to subsequent improvement.

Uphill group: Encompassed Classes 4, 5, and 6, with 325 patients in total (13.6%). This group exhibited a progressive increase in pneumonia extent, reflecting a pattern of continuous deterioration (**Fig. 3**).

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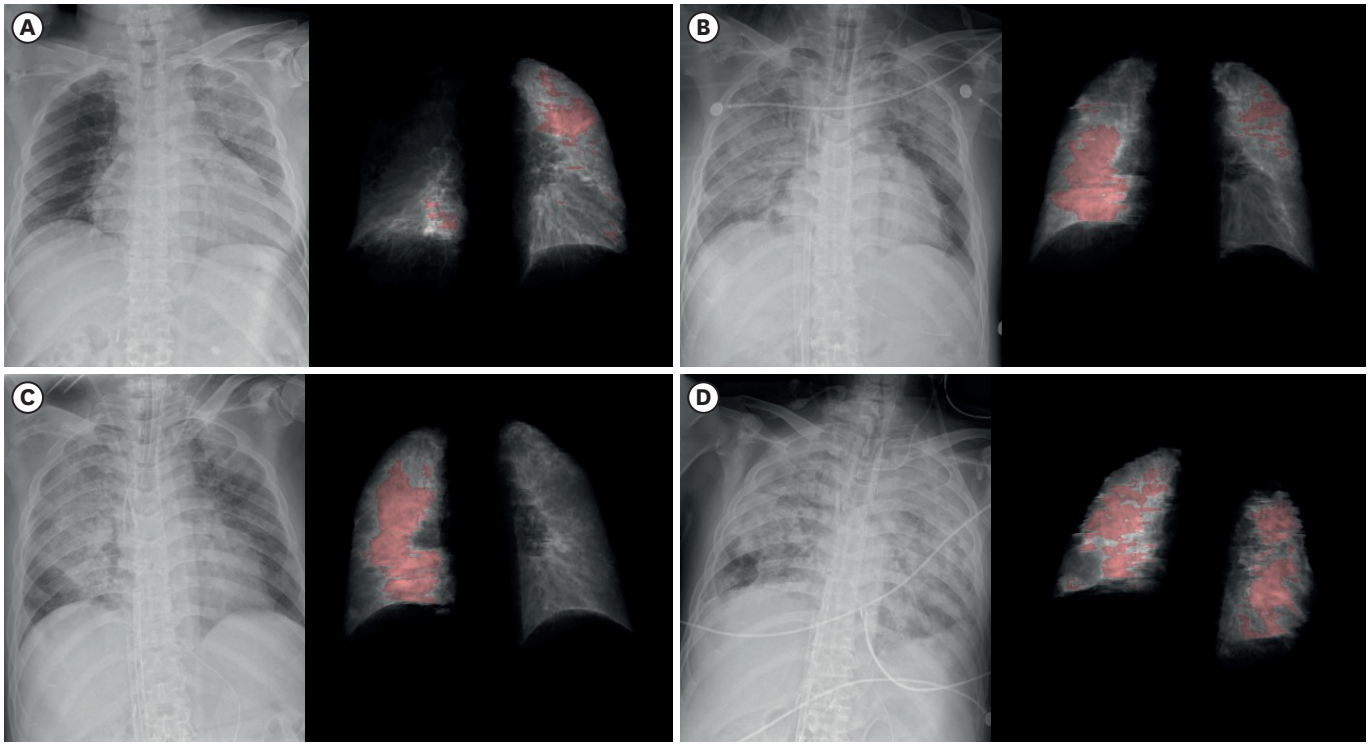

Fig. 3. Example of pneumonic extent course in uphill group. Chest radiograph progression in a patient from the uphill group: a 66-year-old male COVID-19 patient exhibited a 4.53% extent of pneumonia on an initial chest radiograph (**A**) taken on the first day after hospital admission. Subsequent chest radiographs taken 6 days (**B**), 15 days (**C**), and 51 days (**D**) after hospital admission showed a gradual increase in pneumonia extent to 15.63%, 24.49%, and 50.91%, respectively. The patient died from aggravated COVID-19 pneumonia 52 days after admission.
COVID-19 = coronavirus disease 2019.

Statistical analysis

After determining the number of latent classes, we analyzed group differences for statistical significance. Fisher's exact test or the χ^2 test was used to calculate the *P* values reflecting statistical significance for categorical variables. We tested the assumptions of normality and homogeneity of the continuous variables using the Shapiro-Wilk and Levene's tests, respectively. When these assumptions were not met, the Kruskal-Wallis test was used to assess the statistical significance of these continuous variables. After conducting the Kruskal-Wallis test as necessary, a post hoc analysis using the Bonferroni correction was conducted to verify the statistical significance between pairs of groups among the three groups. Cox regression analyses were conducted to investigate the differences in the utilization of critical care supports and clinical outcomes among the three groups. These analyses were structured into three models to elucidate the influence of different variables. Model 1 was a univariate analysis that provided a baseline hazard ratio (HR) for each group. Model 2 was adjusted for age, sex, body mass index (BMI), and number of comorbidities. Model 3 was adjusted for age, sex, BMI, number of comorbidities, C-reactive protein (CRP) level, and blood urea nitrogen (BUN) level. In Models 2 and 3, the number of comorbidities was calculated by the sum of the aforementioned comorbidities that are known to affect the severity and prognosis of COVID-19.[13,14] *P* value < 0.05 is used as the cutoff for statistical significance. All statistical analyses were conducted using R version 4.1.2 (R Foundation for Statistical Computing).

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Ethics statement

The Institutional Review Board (IRB) of Seoul National University Boramae Medical Center approved the study protocol (IRB No. 10-2022-71). Informed consent was waived due to the retrospective nature of the study, and the study was conducted in accordance with the Declaration of Helsinki.

RESULTS

Baseline characteristics of patients according to radiographic trajectory groups

The mean age of the enrolled patients was 58.0 ± 16.9 years, with 1,149 (48.2%) being male. Patients in the uphill group were significantly older than those in the steady or downhill groups. While the frequencies of dyspnea, sputum, cough, rhinorrhea, sore throat, headache, and myalgia were found to differ significantly among the three groups, there were no significant differences in the other symptoms. Among comorbidities, only the frequencies of diabetes, hypertension, and dementia were found to differ significantly across the groups. In the initial laboratory findings, there were differences in all values among the three groups. Notably, the levels of CRP and aspartate transaminase not only differed among the three groups but also between any two groups. The rate of previous COVID-19 vaccination was 10.9%, and the rate was significantly difference among three groups (**Table 1**).

Association between radiographic trajectory groups and temporal changing trends of critical laboratory biomarkers

We also explored the relationship between radiographic trajectory groups and the evolution of key laboratory biomarkers, which have previously been identified as critical factors in the literature (**Fig. 4**).[17] Our study found that the uphill group had high BUN levels throughout hospitalization, while the steady and downhill groups had normal BUN levels with minor fluctuations. CRP levels initially dropped and then rose in the uphill group, indicating increased inflammation, while they gradually declined in the other groups. White blood cell (WBC) counts in the uphill group peaked around day 14, forming an inverted U-shape, while the downhill group showed a similar pattern without exceeding normal limits, and the steady group had a slight increase in WBC counts (**Fig. 4**).

Differences in clinical courses among radiographic trajectory groups

We examined the differences in clinical courses among the radiographic trajectory groups. **Table 2** summarizes the results of the differences. All of these clinical courses showed an increasing pattern from the steady group to the downhill group, and then again to the uphill group, with statistically significant differences among the three groups ($P < 0.001$).

The results of post-hoc analyses with Bonferroni correction confirmed that there were significant differences between each pair of groups in terms of the total hospitalization days and days of high-flow oxygen supplementation. For the days of intensive care unit (ICU) stay, there were significant differences only between the steady groups and downhill groups, as well as between the steady group and uphill groups.

Differences in the utilization of critical care supports among radiographic trajectory groups

The analysis adjusted for age, sex, number of comorbidities, BUN level, and CRP level (Model 3) revealed that the rates of the application of critical care supports were found to be

Table 1. Baseline characteristics according to radiographic trajectory groups

Characteristics	Total (n = 2,385)	Steady group (n = 1,925, 80.7%)	Downhill group (n = 135, 5.7%)	Uphill group (n = 325, 13.6%)	*P* value*	Post hoc†
Demographics						
Age, yr	58 (47–70)	56 (45–68)	60 (45–70)	70 (58–80)	< 0.001	ac, bc
Male gender	1,149 (48.2)	917 (47.64)	61 (45.19)	171 (52.62)	0.195	
Anthropometrics						
BMI, kg/m^2	24.7 (22.4–27.2)	24.7 (22.3–27.2)	25.2 (23.1–28.0)	24.4 (21.9–26.9)	0.032	bc
Baseline symptoms						
Dyspnea	523 (21.9)	377 (19.6)	54 (40.0)	92 (28.3)	< 0.001	
Sputum	776 (32.5)	644 (33.5)	51 (37.8)	81 (24.9)	0.004	
Cough	1,259 (52.8)	1,046 (54.3)	79 (58.5)	134 (41.2)	< 0.001	
Rhinorrhea	102 (4.3)	93 (4.8)	4 (3.0)	5 (1.5)	0.012	
Sore throat	356 (14.9)	319 (16.6)	12 (8.9)	25 (7.7)	< 0.001	
Headache	452 (19.0)	396 (20.6)	13 (9.6)	43 (13.2)	< 0.001	
Myalgia	425 (17.8)	369 (19.2)	16 (11.9)	40 (12.3)	0.002	
Fatigue/malaise	188 (7.9)	143 (7.4)	13 (9.6)	32 (9.9)	0.242	
Nausea/vomiting	218 (9.1)	187 (9.7)	9 (6.7)	22 (6.8)	0.138	
Diarrhea	174 (7.3)	142 (7.4)	9 (6.7)	23 (7.1)	0.941	
Altered consciousness	2 (0.08)	2 (0.1)	0 (0)	0 (0)	0.787	
Underlying diseases						
Diabetes	475 (19.9)	345 (17.9)	32 (23.7)	98 (30.2)	< 0.001	
Hypertension	841 (35.3)	637 (33.1)	46 (34.1)	158 (48.6)	< 0.001	
Heart failure	97 (4.1)	75 (3.9)	4 (3.0)	18 (5.5)	0.306	
Chronic heart disease	32 (1.3)	25 (1.3)	0 (0)	7 (2.2)	0.175	
Asthma	48 (2.0)	38 (2.0)	3 (2.2)	7 (2.2)	0.962	
COPD	12 (0.5)	8 (0.4)	1 (0.7)	3 (0.9)	0.451	
Chronic liver disease	33 (1.4)	27 (1.4)	1 (0.7)	5 (1.5)	0.790	
Chronic kidney disease	30 (1.3)	23 (1.2)	1 (0.7)	6 (1.9)	0.533	
Malignancy	100 (4.2)	83 (4.3)	3 (2.2)	14 (4.3)	0.501	
Dementia	181 (7.6)	118 (6.13)	8 (5.93)	55 (16.92)	< 0.001	
Initial vital signs						
HR, /min	90 (80–101)	90 (81–101)	92.00 (82–103)	90 (78–101)	0.312	
SBP, mmHg	132 (119–146)	131 (118–145)	132. (117–147)	136 (121.5–150.0)	0.004	ac
BT, ℃	36.9 (36.5–37.4)	36.9 (36.5–37.4)	36.8 (36.5–37.6)	36.9 (36.5–37.5)	0.832	
Initial laboratory findings						
WBC, × 10^3/uL	4.86 (3.75–6.20)	4.8 (3.7–6)	5.4 (4.1–7.8)	5.2 (3.8–7.1)	< 0.001	ab, ac
Hb, g/dL	13.3 (12.2–14.4)	13.4 (12.3–14.5)	12.9 (12.1–14)	12.8 (11.6–14)	< 0.001	ab, ac
Platelet, × 10^3/uL	177 (138.5–227.0)	180 (142–230)	190 (142–250)	162 (123–206)	< 0.001	ac, bc
PT-INR, INR	1.03 (1.00–1.08)	1.03 (1–1.07)	1.06 (1–1.1)	1.05 (1.01–1.11)	< 0.001	ac
CRP, mg/dL	2.96 (0.82–6.80)	2.43 (0.66–5.81)	7.22 (3.78–12.61)	5.38 (1.53–11.59)	< 0.001	ab, ac, bc
D-dimer, mg/L‡	0.50 (0.32–0.86)	0.46 (0.30–0.76)	0.77 (0.47–1.21)	0.78 (0.45–1.46)	< 0.001	ab, ac
AST, IU/L	31 (23–46)	30 (23–42)	41 (31–69)	37 (26–53)	< 0.001	ab, ac, bc
ALT, IU/L	22 (15–36)	22 (15–35)	29 (18–53)	22 (15–37)	< 0.001	ac, bc
BUN, mg/dL	12 (9–17)	12 (9–16)	13 (10–18.5)	16 (12–25)	< 0.001	ac, bc
Creatinine, mg/dL	0.76 (0.62–0.93)	0.8 (0.6–0.9)	0.7 (0.6–0.9)	0.9 (0.7–1.1)	< 0.001	ac, bc
Previous COVID-19 vaccination	261 (10.9)	230 (11.9)	8 (5.9)	23 (7.1)	0.005	

Data are present as median (interquartile range), number of patients (percentages).
BMI = body mass index, COPD = chronic obstructive pulmonary disease, HR = heart rate, SBP = systolic blood pressure, BT = body temperature, WBC = white blood cell, Hb = hemoglobin, PT-INR = prothrombin time-international normalized ratio, CRP = C-reactive protein, AST = aspartate transaminase, ALT = alanine transaminase, BUN = blood urea nitrogen, COVID-19 = coronavirus disease 2019.
**P* values were calculated using the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables.
†To address the issue of multiple comparisons, we implemented the Bonferroni correction.
‡One hundred fifty-six patients (134 patients in the steady group, 6 patients in the downhill group, and 6 patients in the uphill group) did not have initial D-dimer data.
The steady group is notated as a, the downhill group as b, and the uphill group as c: [ab]Significant difference between the steady and downhill groups; [ac]Significant difference between the steady and uphill groups; [bc]Significant difference between the downhill and uphill groups.

significantly higher in the downhill and uphill groups than they were in the steady group. Specifically, the HRs for high-flow oxygen supplementation were 8.4 (95% confidence interval [CI], 5.89–11.83) in the downhill group and 9.1 (95% CI, 6.95–11.94) in the uphill group. For mechanical ventilation, the HRs were 51.5 (95% CI, 19.07–139.01) in the downhill

group and 51.8 (95% CI, 20.49–130.9) in the uphill group. For continuous renal replacement therapy or extracorporeal membrane oxygenation, the HRs were 56.3 (95% CI, 3.85–822.15) in the downhill group and 67.2 (95% CI, 6.71–671.85) in the uphill group, as presented in **Table 3**.

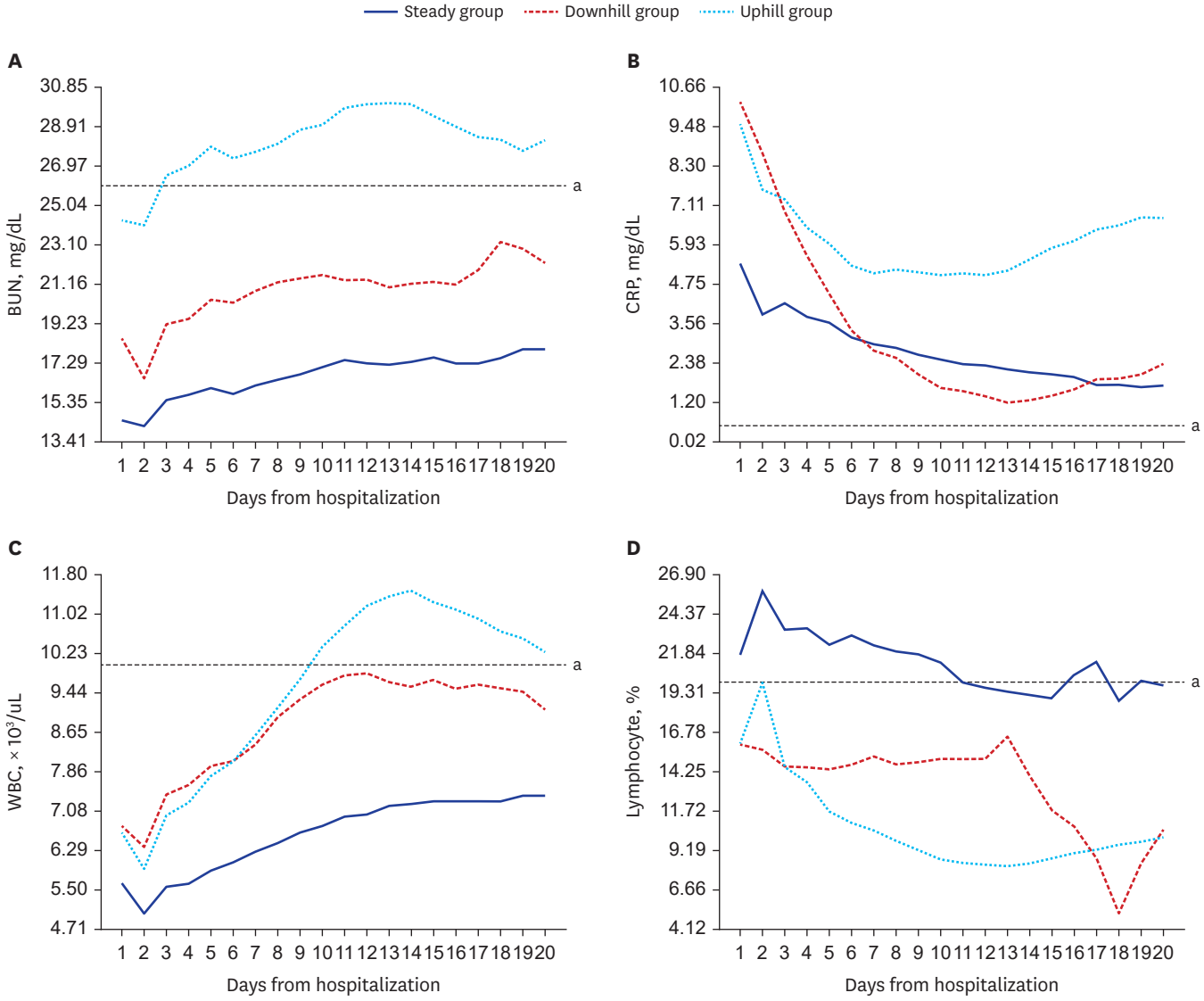

Fig. 4. Association between radiographic trajectory groups and temporal changing trends of critical laboratory biomarkers. Our findings revealed significant variances in BUN levels among the groups. Specifically, the uphill group exhibited abnormally high BUN levels for most of the hospital stay, aside from the initial phase of the clinical course. By contrast, both the steady and downhill groups exhibited BUN levels within the normal range throughout their hospitalization, albeit with some fluctuations in levels (**A**). Regarding CRP levels, all groups initially presented values at the upper limit. In the uphill group, the CRP levels initially decreased before rising again over time. This fluctuation indicates that, as the severity of pneumonia increased quantitatively in the uphill group, so did the CRP levels, thus reflecting the degree of inflammation associated with pneumonia. Meanwhile, the downhill and steady groups exhibited a gradual decline in CRP levels as time progressed (**B**). In the uphill group, the WBC counts increased sharply from the beginning of hospitalization, surpassing the upper normal limit around day 10, and continued to rise with an abruptly increased slope. It peaked around day 14 before gradually decreasing, showing an inverted U-shape pattern. In the downhill group, the WBC counts also displayed an inverted U-shape similar to the uphill group, but the peak did not exceed the upper normal limit. In the steady group, the WBC counts exhibited a slightly increased slope throughout the hospitalization period (**C**). For the lymphocyte level, there is no specific trend over the hospitalization period among the three groups (**D**). The critical laboratory tests included in this paper were measured at irregular intervals, and the mean value of the measurements taken on the same date among patients within each group was presented as the representative value for each group.
BUN = blood urea nitrogen, CRP = C-reactive protein, WBC = white blood cell.
[a]The black dashed lines in each subfigure indicate the cutoff values for the lower or upper limits of each laboratory finding.

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Table 2. Differences in clinical courses according to radiographic trajectory groups in COVID-19 pneumonia

Clinical courses	Total (n = 2,835)	Radiographic trajectory groups			*P* value*	Post hoc†
		Steady group (n = 1,925, 80.7%)	Downhill group (n = 135, 5.6%)	Uphill group (n = 325, 13.6%)		
Total hospitalization days, days	12.1 ± 8.91	10.6 ± 6.00	12.6 ± 7.61	20.6 ± 16.17	< 0.001	ab, ac, bc
Days of HF oxygen use, days	0.92 ± 3.02	0.23 ± 1.36	2.34 ± 3.63	4.40 ± 5.90	< 0.001	ab, ac, bc
Days of ICU stay, days	0.51 ± 3.24	0.01 ± 0.35	1.07 ± 2.92	3.20 ± 8.00	< 0.001	ab, ac

Data are present as mean ± standard deviation.
HF oxygen = high-flow oxygen supplement, ICU = intensive care unit.
**P* values were calculated using the Kruskal-Wallis test for continuous variables.
†To address the issue of multiple comparisons, we implemented the Bonferroni correction.
The steady group is notated as a, the downhill group as b, and the uphill group as c: [ab]Significant difference between the steady and downhill groups; [ac]Significant difference between the steady and uphill groups; [bc]Significant difference between the downhill and uphill groups.

Table 3. Differences in the utilization of critical care supports among radiographic trajectory groups, analyzed using a hierarchical Cox regression model

Variables	Total (n = 2,385)	Radiographic trajectory groups		
		Steady group (n = 1,925, 80.7%)	Downhill group (n = 135, 5.7%)	Uphill group (n = 325, 13.6%)
HF oxygen				
Event	315 (13.2)	92 (4.8)	51 (37.8)	172 (52.9)
Model 1		1.0	10.2 (7.21–14.30)	13.5 (10.48–17.43)
Model 2		1.0	10.6 (7.52–14.92)	11.2 (8.62–14.59)
Model 3		1.0	8.4 (5.89–11.83)	9.1 (6.95–11.94)
MV				
Event	94 (3.9)	5 (0.3)	19 (14.1%)	70 (21.5)
Model 1		1.0	57.7 (21.53–154.46)	77.5 (31.21–192.19)
Model 2		1.0	58.0 (21.63–155.31)	60.1 (23.97–150.77)
Model 3		1.0	51.5 (19.07–139.01)	51.8 (20.49–130.9)
CCRT/ECMO				
Event	18 (0.8)	1 (0.1)	2 (1.5)	15 (4.6)
Model 1		1.0	25.5 (2.31–281.73)	53.0 (6.84–410.51)
Model 2		1.0	27.3 (2.47–302.2)	46.7 (5.85-–72.92)
Model 3		1.0	56.3 (3.85–822.15)	67.2 (6.71–671.85)

Data are present as number (%) or hazard ratio (95% confidence interval). Comorbidities include diabetes, hypertension, heart failure, chronic heart disease, asthma, chronic obstructive pulmonary disease, chronic liver disease, chronic kidney disease, malignancy, and dementia.
Model 1: univariate analysis.
Model 2: adjusted for age, sex, body mass index, and number of the comorbidities.
Model 3: adjusted for age, sex, body mass index, and number of the comorbidities, C-reactive protein level, and blood urea nitrogen level.
HF oxygen = high-flow oxygen supplement, MV = mechanical ventilation, CRRT = continuous renal replacement therapy, ECMO = extracorporeal membrane oxygenation.

Differences in clinical outcomes among radiographic trajectory groups

The analysis adjusted for age, sex, number of comorbidities, BUN level, and CRP level (Model 3) revealed that both the downhill and uphill groups had significantly higher risks of ICU admission compared to the steady group (HR for the downhill group, 47.3 [95% CI, 18.9–118.3]; HR for the uphill group, 44.9 [95% CI, 19.15–105.29]). Regarding in-hospital mortality, only the uphill group showed a significantly higher risk compared to the steady group (HR for the uphill group, 8.2 [95% CI, 3.08–21.98]) (**Table 4**).

DISCUSSION

Our study aimed to obtain a more comprehensive understanding of how pneumonia develops and progresses in COVID-19 patients as well as to identify key temporal patterns and risk factors associated with disease worsening. To our knowledge, this is the first study to thoroughly evaluate the potential associations between radiologic pneumonia trajectories

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Table 4. Differences in clinical outcomes among radiographic trajectory groups, analyzed using a hierarchical Cox regression model

Variables	Total (n = 2,385)	Radiographic trajectory groups		
		Steady group (n = 1,925, 80.7%)	Downhill group (n = 135, 5.7%)	Uphill group (n = 325, 13.6%)
ICU admission				
Event	102 (4.3)	6 (0.3)	21 (15.6)	74 (22.8)
Model 1		1.0	53.1 (21.4–131.6)	66.5 (28.9–153.2)
Model 2		1.0	53.9 (21.7–133.6)	53.2 (22.86–123.74)
Model 3		1.0	47.3 (18.9–118.3)	44.9 (19.15–105.29)
In-hospital mortality				
Event	57 (2.4)	6 (0.3)	1 (0.7)	49 (15.1)
Model 1		1.0	1.6 (0.19–13.13)	10.0 (4.13–24.22)
Model 2		1.0	2.2 (0.25–18.28)	7.6 (3.18–18.32)
Model 3		1.0	2.6 (0.28–23.83)	8.2 (3.08–21.98)

Data are present as number (%) or hazard ratio (95% confidence interval). Comorbidities include diabetes, hypertension, heart failure, chronic heart disease, asthma, chronic obstructive pulmonary disease, chronic liver disease, chronic kidney disease, malignancy, and dementia.
Model 1: univariate analysis.
Model 2: adjusted for age, sex, body mass index, and number of the comorbidities.
Model 3: adjusted for age, sex, body mass index, and number of the comorbidities, C-reactive protein level, and blood urea nitrogen level.
ICU = intensive care unit.

and various outcome indicators, such as critical laboratory biomarkers, clinical courses, utilization of critical care support, and clinical outcomes. Our findings demonstrate a correlation between the trends of temporal changes in BUN and CRP levels and the radiologic pneumonia trajectories. Additionally, our results reveal that patients in the downhill and uphill groups have higher risks of utilizing critical care support, ICU admission, and in-hospital mortality compared to those in the steady group.

The extent of pneumonia changes over time in COVID-19 patients can be complex and varied for each individual. However, we believe that the longitudinal changes in pneumonia extent over time can be internally classified into a few latent trend groups. Therefore, in this study, we quantified the extent of pneumonia using a deep learning model, which has recently become a widely used technique in the medical field. Next, we were able to reclassify the quantified pneumonia extent into three groups using the LCGA model. Although the latent trajectory groups for radiographic analysis, estimated through LCGA, represent an optimized classification, the number of groups is quite large. Moreover, the patterns depicting the change in pneumonia extent over time are complex. This complexity hinders clinical interpretation and clear statistical analysis. Therefore, in the present study, we simplified the trajectory groups estimated by the LCGA model into three categories (steady, downhill, and uphill groups) based on the trend of slope change. We believe this regrouping may be useful for simplifying clinical interpretation and to enable a straighter comparative analysis among the groups.

In this study, we investigated the relationships among three radiographic trajectory groups and changes in the patterns of critical laboratory biomarkers that have been well established in previous research.[17] BUN levels exhibited distinct trends of change among the three radiographic trajectory groups. Previous studies have shown that continuous monitoring of BUN levels is an important factor in determining the severity of COVID-19 in patients.[18] These results indicate that differences in the severity among radiographic trajectory groups may be associated with the temporal trends in BUN levels. This fact also paradoxically suggests that close monitoring of temporal changes of BUN levels may facilitate the assessment of the pneumonia trajectories and severity of COVID-19 cases. To this point, there

has been no research establishing a relationship between the trend in pneumonia extent and the temporal change in BUN levels according to the radiologic trajectory group. A possible mechanism for this association could be the inflammatory response and cytokine storm triggered by COVID-19 infection, which could potentially lead to variations in pneumonia extent and the degree of kidney damage.[18]

In this study, we sought to examine differences in clinical courses among radiographic trajectory groups while focusing on total hospitalization days, days of high-flow oxygen use, and days of ICU stay. We found clear distinctions among the three groups, with an increasing pattern in these variables from the steady group to the downhill group, and then again to the uphill group. Multiple comparison tests were conducted to clearly identify differences between the groups, and the results revealed significant variations in total hospitalization days and days of high-flow oxygen use across all groups. We observed a trend suggesting a difference in ICU stay duration between the downhill and uphill groups, although this trend was not statistically significant. This outcome may originate from the relatively small sample sizes of the downhill and uphill groups compared to the steady group. To more comprehensively assess differences in duration of ICU stay between these groups, a larger-scale study is warranted in the future.

This study observed differences in the application of critical care support among different radiographic trajectory groups. Despite adjusting for a variety of confounding factors that could influence severity, the need for high-flow oxygen therapy in the downhill and uphill groups was found to be increased by 8–9 times compared to that in the steady group. Moreover, there was up to a 50-fold increase in the need for mechanical ventilator therapy in the downhill and uphill groups. These findings highlight the importance of considering radiographic trajectory grouping in the distribution of critical care resources.

In the present study, we identified significant differences in clinical outcomes among different radiographic trajectory groups. We found that the HR associated with ICU admission was up to 45–47 in the downhill and uphill groups. However, in terms of in-hospital mortality, only the uphill group showed an 8-fold increase in risk. These results differ from those of a previous study reporting clinical outcomes across radiographic trajectory groups.[11] That previous study reported that in-hospital mortality was higher in both the downhill and uphill groups compared to the steady group, with a risk increase of 21–26 times. However, those results were based on a small cohort (n = 200) and estimated risk using only age, sex, and diabetes as adjusting variables. By contrast, our study involved a relatively large cohort (n = 2,385) and estimated risk by adjusting for all known potential confounding factors, including age, sex, BMI, various comorbidities,[13,14] CRP level, and BUN level. The discrepancies between the findings of our study and the previous study may thus be attributable to the comprehensive adjustment for confounding variables and the larger cohort size in our study.

Our study has some limitations that should be noted. First, the retrospective design of this study inherently limits our ability to control for various biases with COVID-19 severity.[14] Secondly, the irregular intervals between chest X-ray examinations resulted in missing data points, affecting the completeness of the dataset. Lastly, we concentrated exclusively on the quantitative assessment of pneumonia extent in chest X-rays, and we did not perform an analysis of other important qualitative indicators, including opacity (reticular-nodular, ground glass), consolidation, signs of vascular congestion, and the distribution of pneumonia.[19]

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In conclusion, stratified radiographic latent trajectories that are identified through serial chest radiographs are associated with varying patterns of temporal BUN and CRP level changes, and they can also predict the necessity for critical care support and clinical outcomes in COVID-19 pneumonia. These results are expected to help inform therapeutic strategies tailored to these disease trajectories.

SUPPLEMENTARY MATERIALS

Supplementary Data 1

Data review and classification

Supplementary Data 2

Quantifying extent of coronavirus disease 2019 (COVID-19) pneumonia on chest radiographs

Supplementary Data 3

Stratifying radiographic trajectory and identifying latent class

Supplementary Fig. 1

Optimal trajectory model result within LCGA. This figure presents the results of the optimal model within the LCGA framework based on the Bayesian information criterion. Based on the LCGA, the radiographic trajectories of the study population were stratified into six classes. The x-axis represents the time duration from the date of hospital admission to the date of chest X-ray imaging for each sample. The y-axis represents the coronavirus disease pneumonia extent ratio (%). Each line represents a class pattern calculated by the LCGA model.

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