Intensity-Based Computation Tomography (CT) Evaluation of Temporal Changes in Lung Abnormalities During the Recovery Stage in COVID-19 In-Hospital Patients

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Abstract

Background: The coronavirus disease-19 (COVID-19) and its variants have increased rapidly worldwide since December 2019, with respiratory disease being a prominent complication. As such, optimizing evaluation methods and identifying factors predictive of disease progress remain critical. The purpose of the study was to assess late phase (≥ 3 weeks) pulmonary changes using intensity-based computed tomography (CT) scoring in COVID-19 patients and determine the clinical characteristics predicting lung abnormalities and recovery.

Methods: We conducted a retrospective study on 42 patients (14 males, 28 females; age 65 ± 10 years) with COVID-19. Only patients with at least 3 CT scans taken at least 3 weeks after initial symptom onset were included in the study. Two scoring methods were assessed: (1) area-based scoring (ABS) and (2) intensity-weighted scoring (IWS). Temporal changes in the average lung lesion were evaluated by the calculating the averaged area under the curve (AUC) of the CT score-time curve. Correlations between averaged AUCs and clinical characteristics were determined.

Results: Using the ABS system, temporal changes in lung abnormalities during recovery were highly variable ($P=0.934$). By contrast, the IWS system detected more subtle changes in lung abnormalities during in COVID-19 patients, with consistent week-to-week relative reductions in IWS ($P=0.025$). Strong relationships were observed with D-dimer and C-reactive protein (CRP) levels on admission, with hazard ratios (HR)(95%CI) of 5.32 (1.25-22.6)($P=0.026$) and 1.05 (1.10-1.09)($P=0.017$), respectively.

Conclusion: Our results suggest COVID-19-mediated pulmonary abnormalities persist well-beyond 3-weeks of symptom onset, with intensity-weighted rather than area-based scoring being more sensitive. Moreover, D-dimer and CRP levels were predictive of the recovery from the disease.

Background

The coronavirus disease of 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)[1], has been declared a global pandemic by the World Health Organization (WHO). Over a year into the pandemic, COVID-19 and its variants continue to place a significant burden on health care and economic systems worldwide, with a total of 192,284,207 cases including 4,136,518 deaths worldwide reported as of July 25, 2021 [2]. While there is increasing evidence for direct multiorgan effects and long-term sequelae of COVID-19 [3, 4], the disease primarily impacts the respiratory system [5]. Chest computation tomography (CT) imaging is critical for the clinical evaluation and guiding disease management in COVID-19 patients [6]. The characteristic patterns of the early-phase (i.e., symptom onset to ~ 3 weeks) have been thoroughly reviewed [7–9]. However, in spite of many patients being discharged within 3 weeks of symptom onset, lung abnormalities may persist and recovery may be incomplete at discharge [10], with long covid or post-covid syndrome [11, 12] being increasingly recognized but less well-defined [13, 14].

In the present retrospective study, two semi-quantitative CT grading systems were used to evaluate temporal changes and the degree of recovery of lung abnormalities during late phase (weeks 3 through 8) of disease. Our findings suggest monitoring and interpreting the long-term pattern and recovery of lung abnormalities in COVID-19 patients using intensity-based CT imaging and inflammatory markers may contribute greatly to clinical decision making on patient prognosis, discharge and follow-up.

Materials And Methods

Patient screening, management and recording

A total of 63 (31 males and 32 females) in-patients diagnosed with COVID-19 from China-Japan Union Hospital of Jilin University and Tongji Hospital of Huazhong University of Science and Technology, who were admitted between February 7th, 2020 and March 27th, 2020, were initially screened as candidates for the study. The retrospective cohort data was restricted to patients in which at least 3 CT exam images taken ≥ 3 weeks after COVID-19 symptom onset were available, resulting in 42 patients (14 males and 28 females, aged 65 ± 10 years) being included in the final study (Fig. 1). The Community-Acquired Pneumonia (CAP) Symptom questionnaire (CAP-Sym 18)[15] was used to assess symptom changes during the study period and was calculated according to the medical record by two independent investigators (YWJ and LL). The discharge criteria for our patient cohort were: 1) Complete recovery from symptoms judged by the attending doctor, with a CAP-Sym 18 score < 5 ; 2) Two negative RNA tests for COVID-19 separated by at least 24 hours; and 3) Evidence of complete control of combined diseases.

For each of the 42 patients, CT scans were evaluated using two semi-quantitative scoring systems and compared to assess the severity of lung abnormalities and the time course of recovery: (1) Area-Based Scoring (ABS) and (2) Intensity-weighted scoring (IWS)(see **Supplementary Material**). Representative CT images and score assessments for each grade are shown in Fig. 2. To assess the link between the extent of and temporal changes in lung abnormalities during the late phase of recovery and clinical biomarkers, CT imaging data was compared with individual patient characteristics on admission, including inflammatory indices such as C-reactive protein (CRP), white blood cell (WBC) count, and D-dimer.

To evaluate temporal changes in lesion burden, the average lesion burden throughout recovery was calculated. Briefly, after first generating a CT course-score plot, the area under the curve (AUC) of the mean lesion burden was calculated per assessment week (i.e., weeks 3–8) to reveal changes in the intensity of lung lesions during the late phase recovery period (Fig. 2E). An expanded Methods section is available in the **Supplementary Material**.

Statistical analysis

Continuous variables were presented as mean $\pm$ standard deviation (SD)(for normally distributed data) or median (Range)(for non-normal distribution). Categorical variables were presented as n(%). Kruskal-Wallis test was used to compare non-normalized data (i.e., symptom scores). Chi-square (χ^2) test was used to compare the data of weekly ABS and IWS changes determining the differences in the proportion

of individuals with a score change $\leq 10\%$. Violin plots were generated to visualize the distribution and probability density of ABS and IWS during the study period. A Spearman correlation test was used to determine the correlation between variables. Logistic regression analysis was used to identify predictive factors within these clinical markers. A P -value < 0.05 was considered statistically significant. Statistical analyses were done using SPSS 24 (IBM) software.

Results

Demographic, clinical and image findings on admission

63 patients that were treated between February 7th, 2020 and March 27th, 2020 were screened. Among them, 21 patients were excluded (see **Methods** and Fig. 1), resulting in a total of 42 patients being included in the final analysis. The median CT assessments per patient was 4 (range: 2–5), while the median follow-up period was 4 weeks (range: 3–6). Demographic characteristics, clinical outcomes and laboratory findings of the cohort on admission are summarized in Table 1.

Table 1. Demographic, clinical and laboratory findings of patients on admission			
Characteristics		All patients (n=42)	
Sex	Male	14 /42(33.3%)	
	Female	28/42 (66.7%)	
Age (years)		64.7 ± 10.5	
Body Mass Index (BMI) (kg/m ²)		38.4 ± 5.7	
Basic diseases	Heart disease	4/42(9.5%)	
	Chronic obstructive pulmonary disease	4/42(9.5%)	
	Hypertension	18/42(42.9%)	
	Diabetes	8/42(19.1%)	
	Cerebrovascular disease	3/42(7.1%)	
	Other diseases [#]	4/42(9.5%)	
Clinical symptoms	Fever(>37.3°C)	38/42 (90.5%)	
	Cough	39/42 (92.9%)	
	Dyspnea	29/42 (69.0%)	
	CAP-Sym 18 score (on admission) *	18.7±8.4 points	
Symptom Onset to Admission		Mean	12.6±5.5 days
		Range	2-15 days
Laboratory Findings (on Admission)	White blood cell count (x10 ⁹ per L)	<4	7/42 (16.7%)
		4–10	31/42 (73.8%)
		>10	4/42 (9.5%)
	Lymphocyte count (x10 ⁹ per L)	<1.10	19/42(45.24.4%)
		1.10-3.20	22/42(52.38%)
		>3.20	1/42(2.38)
	Platelet count (× 10 ⁹ per L)	<100	5 /42(11.9%)

	100-300	27/42 (64.3%)
	>300	10/42 (23.8%)
High-sensitivity cardiac troponin I (pg/mL)	>99% up-limit	8/42 (19.1%)
D-dimer (µg/mL)	Elevated (>0.5)	32/42 (76.2%)
C-reactive protein (CRP)(mg/L)	Elevated (>1)	38/42 (90.5%)
#: Other diseases include thyroid diseases, urinary diseases and digestive system disorders		
*:CAP-Sym score: CAP-symptom questionnaire, acquired as method mentioned		

As summarized in **Table 2**, patients typically presented with a multi-lobar involvement (more than one lobe), with most patients showing lesions in 4 (23.8%) or 5 (61.9%) lobes. Consistent with previous studies [7, 8], lung abnormalities were peripherally distributed (31.0%), with a diffuse (50.0%) and/or multifocal pattern (97.6%) frequently observed on admission.

Table 2. Chest CT image patterns on admission and discharge			
	Characteristic	Admission All patients (n=42)	Discharge All patients(n=42)
Lobes involved			
	5	26/42 (61.9%)	23/42 (54.8%)
	4	10/42 (23.8%)	9/42 (21.4%)
	3	2/42 (4.8%)	4/42 (9.5%)
	2	3/42 (7.1%)	4/42 (9.5%)
	1	1/42 (2.4%)	1/42 (2.4%)
	0	0/42 (0%)	1/42 (2.4%)
Distribution of pulmonary lesions			
	Peripheral	13/42 (31.0%)	12/42 (28.3%)
	Random	8/42 (19.0%)	9/42 (21.4%)
	Diffuse	21/42 (50.0%)	21/42 (50.0%)
Scattering			
	Focal	1/42 (2.4%)	1/42 (2.4%)
	Multifocal	41/42 (97.6%)	41/42 (97.6%)
Special signs			
Pulmonary changes			
	Vacuolar sign	3/42 (7.1%)	1/42 (2.4%)
	Cavitation	0/42 (0%)	0/42 (0%)
	Microvascular dilation sign	20/42 (47.6%)	4/42 (9.53%)
	Subpleural line	6/42 (14.3%)	7/42 (1.7%)
	Subpleural transparent line	19/42 (45.2%)	11/42 (26.2%)
	Crazy paving	34/42 (81.0%)	18/42 (42.9%)
	Interstitial fibrosis	0 (0%)	0 (0%)
Bronchial changes			

	Air Bronchogram	11/42 (26.2%)	5/42 (11.9%)
	Bronchial wall thickening	4/42 (9.5%)	2/42 (4.8%)
	Traction bronchiectasis	3/42 (7.1%)	2/42 (4.8%)
	Bronchus distortion	5/42 (11.9%)	2/42 (4.8%)
Pleural changes			
	Thickening of pleura	35/42 (83.3%)	21/42 (50.0%)
	Pleural retraction sign	31/42 (73.8%)	19/42 (45.2%)
	Pleural effusion(minor)	10/42 (23.8%)	3/42 (7.1%)
Lymphadenopathy		0/42 (0%)	0/42 (0%)
Pericardial effusion(minor)		5/42 (11.9%)	1/42 (2.4%)

To assess temporal changes in patient symptoms over the study period, CAP-sym 18 scores were evaluated from week 3 to week 8. As shown in Fig. 3, CAP-sym scores were highly variable in weeks 3 and 4 but showed a progressive decline from week 3 (median score 8, range = 0–20) to week 8 (median score 1, range = 0–4).

Temporal changes in CT-derived lung abnormalities are dependent on scoring system

To determine temporal changes in CT findings at least 3 weeks from symptom onset to patient discharge, CT scans were analyzed using two different scoring systems based on the area (i.e., ABS analysis) and intensity (i.e., IWS analysis) of lung abnormalities. Temporal changes in the two scores as well as the IWS grades (1–4) are shown in Fig. 4. Specifically, as shown in Fig. 4B, there was a clear reduction in Grades 2 through 4 over time, consistent with resolution of more severe lung abnormalities. In comparing the ABS- and IWS-scoring approaches (Fig. 4A), IWS-scores showed a consistent decrease over time in all patients, indicative of progressive resolution of lung abnormalities that aligned with symptom improvement. By contrast, rather than showing a reduction in lesion areas, ABS scores unexpectedly remained relatively stable, developing a more binary distribution in which scores remained elevated in a number of patients. Specifically, we found that in many patients the intensity of pulmonary lesions would decline throughout the study period without any change in lesion area. To determine the efficacy of the ABS and IWS systems within a given patient to track temporal changes in lung abnormalities, we compared the relative changes in ABS and IWS on a week-to-week basis. As shown in Fig. 4C, the IWS system showed more dramatic and progressive changes in lung abnormalities from week 3 post-symptom onset compared to the ABS system, suggesting the IWS system is more sensitive to detect improvements in lung

abnormalities. Thus, changes in lung abnormality scoring with the IWS system more closely tracks with improvements in symptom scores, with the ABS system showing an apparent disconnect.

Given the apparent greater sensitivity of the IWS system to assess temporal changes in lung abnormalities, an area under the curve (AUC) analysis was undertaken to further determine the average temporal changes in lesion burden during recovery by dividing the IWS-time curve by time. As shown in Fig. 5, the distribution of averaged AUC scores was 26.9 ± 16.1 (points per week), suggesting variability in the extent of pulmonary lesions persisted into the late phase of recovery. Specifically, some patients still exhibited strong pulmonary pathology at weeks 7 and 8, the long-term impact of which requires further study.

Next, we sought to determine whether temporal changes in mean lesion burden (AUC score) were linked to clinical characteristics on admission. As shown in Table 3, Spearman correlations revealed a significant relationship between white blood cell count (WBC)($p = 0.0435$), lymphocyte percentage (Lym%)($p = 0.0073$), C-reactive protein (CRP)($p = 0.0004$), and D-dimer levels ($p = 0.0039$) on admission with the average AUC level of a patient. To assess whether these four factors were predictive of mean lesion burden in our patient cohort, a Logistical regression analysis was undertaken (Fig. 6), with individuals initially grouped as high-level AUC or low-level AUC. Our results revealed that only CRP and D-dimer levels, with hazard ratio (HR) values of 5.32 and 1.05 respectively, were predictive of the AUC levels of lung lesion, despite there being no evidence of persistent interstitial fibrosis on CT images.

Table 3
Correlations between average AUC score with clinical factors on admission

	R-value	P-value
Age	-0.1168	0.4613
Gender	-0.09004	0.5707
BMI	0.1496	0.4139
WBC	0.313	0.0435*
Lym%	-0.4080	0.0073*
Platelet count	0.1492	0.3456
CRP	0.5423	0.0004*
D-dimer	0.4412	0.0039*
Numbers of combined disorders	-0.06430	0.6896
BMI: body mass index; WBC: white blood cell count; Lym%: lymphocyte percentage; CRP: C-reactive protein. *:p < 0.05		

Discussion

Chest CT images are critical for the evaluation of lung abnormalities in COVID-19 patients. While the early phase of disease progression has been well-characterized [7, 8], our study enhances our understanding the time course and pattern of lung recovery of the disease using intensity-based CT image analysis. The key findings of our study are that the IWS system more closely tracked with resolution of disease symptoms than the ABS analysis, suggesting intensity-weighted scoring is more sensitive to evaluate temporal changes in lung abnormalities during late-phase recovery in COVID-19 patients. Second, D-dimer and C-reactive protein (CRP) levels on admission were strong independent risk factors for high-level lesion burden during late-phase recovery, indicating that a strong inflammatory response to the virus may be predictive of long-lasting lesion burden in COVID-19 patients.

Chest CT imaging has become one of the most important evaluation approaches for assessing COVID-19 severity, progression, and guiding effective management [6]. The specific chest CT changes of COVID-19 patients have been described by several previous studies [6, 18, 19], with lung abnormalities including ground glass opacities, consolidation, reticular pattern and crazy paving patterns found to be common hallmarks at symptom onset into peak illness in both COVID-19 [7, 8, 20] and asymptomatic patients [21]. Our findings confirm that these typical patterns persist throughout the late-phase of the disease, even showing up in some scans in week 8, which has been observed in COVID-19 [5, 22, 23] and (commonly) SARS-CoV-1 [17, 24] patients. Indeed, the presence of ground glass opacities in the CT scans of COVID-19 patients has been linked to accumulating lung damage [22], and have been observed in asymptomatic COVID-19 patients [25]. While these lung patterns were consistent between early- and late-phase disease, their presence alone was not indicative of the time course of resolution of lung abnormalities from symptom onset. As different CT patterns and the intensity and extent of lesion burden would indicate different pathophysiological changes in the lungs [26–28], taking these factors into consideration is necessary for assessing the severity of COVID-19-mediated lung abnormalities and may be predictive of long-term adverse pulmonary consequences of COVID-19. The semi-quantitative visual CT grading approaches used in the current study have been previously indicated, with both area-based (ABS)[10, 29, 30] and intensity-weighted (IWS)[16] grading systems having been used to assess various pulmonary abnormalities. It is clear from our findings that the IWS approach aligned with symptom presentation and showed progressive reductions in lesion burden. By contrast, the ABS approach suggested less recovery over time, with the pattern and time course of changes in many patients lagging behind the recovery implied by symptom scores and the IWS approach. These differences in the ability to capture subtle changes in lung abnormalities may reflect the ability of IWS to simultaneously assess both density and range changes in pulmonary lesions, which avoids overestimation or underestimation in lesion burden scores caused by simple density and/or range constant changes [16]. Given the IWS approach encapsulates the specific nature of the lung abnormalities in its semi-quantitative scoring of lesion extent and intensity, this method is more dynamic than ABS and may possess greater sensitivity to detect subtle lesion resolution and more adequately assess recovery, especially in those patients in which lesion area remains unchanged.

The time course of resolution of pulmonary lesion burden during the late phase of recovery is of great concern in COVID-19 patients [31]. Although there is no evidence of delayed virus elimination in patients

with higher lesion burden in the current study, our data suggest that elevations in inflammatory markers on admission, specifically D-dimer and CRP, may be predictive of a higher and more prolonged lesion burden in COVID-19 patients. Indeed, elevated pro-inflammatory cytokines has been linked to impaired type 2 pneumocyte function and lung cell damage [32, 33]. The link between elevated lesion burden and inflammatory markers is not surprising [17]. Indeed, CRP levels have been shown to be elevated in the early stages of COVID-19 [34] and is being increasingly linked to clinical outcomes in COVID-19 patients [35]. Moreover, D-dimer, which has been linked to thromboembolic disease, has been increasingly recognized as a biomarker for disease severity and mortality [23, 35–37], consistent with D-dimer being a prognostic biomarker in other pulmonary diseases [38, 39]. Thus, targeting the early inflammatory response may be important to managing the long-term pulmonary effects of COVID-19.

Of concern, late pulmonary fibrosis, which is a severe complication after recovery for other coronavirus infections, is highly linked to inflammation [40–42], thus there is a concern that elevated pro-inflammatory markers and high lesion burden on admission may be a harbinger for pulmonary interstitial fibrosis and permanent lung injury in COVID-19 patients in the long-term [33, 43]. Thus, CRP and D-dimer levels may be important for risk stratification and identifying those patients that may have long-term adverse outcomes to COVID-19, which requires further study. However, there is currently limited [44, 45] evidence showing severe fibrosis in recovered COVID-19 patients, including our own patient cohort, with much of the long-term concern extrapolated from SARS-CoV-1 patients [17, 46] in which conservative estimates expect one-third of COVID-19 patients to have significant pulmonary fibrosis [24, 47]. Nonetheless, the results of our AUC analysis suggest recovery from COVID-19 is slower compared to other forms of viral pneumonia that typically resolve within 2–3 weeks [48–50], with lung abnormalities detectable in some patients 8 weeks after symptom onset. Hence, given the paucity of studies examining the long-term pulmonary effects of COVID-19 [51] and as our understanding of the complexity and pathophysiology of COVID-19 and its variants continues to evolve, late-phase CT follow-up should be indicated and a standardized approach for identifying, differentiating, and reporting interstitial lung fibrosis [52] in this cohort is needed, especially in those patients with persistent respiratory symptoms and high-levels of inflammatory markers on admission.

Limitations

The retrospective design of our study and absence of a control group may influence the accuracy of symptom scoring and lead to selection bias of our patient cohort. However, the infectious nature of COVID-19 and the sudden onset of disease outbreak in our region made a perspective study design unfeasible. While the IWS used in the current study has been prominently used to assess lung abnormalities in other types of pneumonia [16], studies are required to further confirm its utility in assessing in COVID-19 patients. As COVID-19 is a multisystem disease [11], future studies will be required to determine the interplay between our patient characteristics (i.e., BMI, hypertension, diabetes) and the pathophysiology of COVID-19 to provide a more holistic understanding of disease progression.

Conclusion

The present study analyzed chest CT images from late phase (3–8 weeks post-symptom onset) of COVID-19 patients, showing that an intensity-weighted scoring approach is more sensitive to assess temporal resolution of lung abnormalities, with the intensity and extent of lesion burden predicted by elevations in inflammatory markers on admission. As our understanding of the pathophysiology of COVID-19 continues to evolve at a rapid pace, our findings suggest that more long-term CT intensity-based assessments will only serve to enhance our insight into disease progression, patient management, and clinical improvement.

Abbreviations

ABS, area-based scoring; AUC, area under the curve; CRP, C-reactive protein; CT, computational tomography; COVID-19, coronavirus disease of 2019; CP, crazy paving; GGO, ground-glass opacity; IWS, intensity-weighted scoring

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Commission of Tongji Hospital (TJ-IRB20200345) and the Ethics Commission of China-Japan Union Hospital of Jilin University (2020032622).

Consent to Publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no conflicts of interest.

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analysis, data interpretation, or drafting.

Authors' contributions

SH, LL: study conception and design, supervision, modifying the manuscript; WYJ, RL: drafting of the manuscript, analyzing of the images, statistical analyses; JN, YB, SDY, LGH, DM, MPY: data collection; WH, GXY, YB, LJY: analyzing of the images, statistical analyses; YP, HYQ: data interpretation and supervision. All authors have read and approved the final manuscript.

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Figures

Figure 1

Flowchart of the selection strategy for the COVID-19 patient cohort.

Figure 2

CT of COVID-19 patients showing progressive increases in the extent (CT grade) of lung abnormalities. A: Representative Grade 1 CT scan showing evidence of mild ground-glass opacity (GGO)(black arrow). B: Representative Grade 2 CT scan revealing a crazy-paving (CP) pattern of lung abnormality, shown by red arrows. C: Representative Grade 3 CT scan showing a pattern of GGO with mixed consolidation (GMC) (blue arrows). D: Representative Grade 4 CT scan showing completed consolidation (yellow arrows). E: Representative example showing temporal changes in the average lesion burden (IWS) in a patient calculated by changes in the area under the curve (AUC) over the study period.

Figure 3

Temporal changes (week 3 to week 8) in symptom score (CAP-sym score) in patients with COVID-19. Weekly changes in individual symptom scores showing a gradual reduction in symptom scores on a week-to-week basis. Median CAP-sym scores are indicated in red. Statistical difference among symptom score in different weeks ($p < 0.0001$).

A

B

C

Figure 4

Temporal changes (week 3 to week 8) in intensity-weighted scoring (IWS) and area-based scoring (ABS) assessments of lung abnormalities. A: Violin plots showing temporal changes in IWS-based grades (1-4), with grading based on the following patterns: Grade 1 (GGO), Grade 2 (GGO with crazy paving), Grade 3 (GGO with consolidation), and Grade 4 (total consolidation). While Grade 1 scores were stable, reductions in Grade 2, 3, and 4 scores were observed over time. B: Violin plots showing temporal changes in ABS and

IWS scoring of lung abnormalities. IWS scoring showed a persistent reduction over time, indicative of resolution of lung abnormalities. By contrast, ABS scores were relatively consistent, with a binary distribution observed and patients clustered in high and low scores by week 8. C: Relative changes in ABS and IWS scoring from one week to the next to determine the ability to assess sensitivity of scoring systems to detect pulmonary lesion resolution. IWS scoring shows a more pronounced relative week-to-week change in lesion score compared to ABS scoring.

Figure 5

Distribution of mean pulmonary lesion strength in late-phase recovery as determined by averaged AUC score.

Figure 6

Forest plot of hazard ratios for factors predicting of the degree of lung abnormalities (average AUC score) in late-phase recovery. Only those factors determined to correlate to averaged AUC score after 3 weeks from symptom onset were analyzed. Logistical regression analysis revealed only D-dimer and C-reactive protein (CRP) were predictive factors for AUC levels.

Supplementary Files

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