

The extent of honeycombing on computed tomography cannot predict the treatment outcome of patients with acute exacerbations of interstitial lung disease (Retrospective cohort study)

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Abstract

Background: The purpose of this retrospective study was to clarify whether the presence of honeycombing on computed tomography (CT) can affect the prognosis of patients with acute exacerbations (AEs) of interstitial lung diseases (ILDs).

Methods: Clinical parameters including age, sex, Charlson Comorbidity Index score (CCIS), blood biomarkers, and 3-month mortality were retrospectively compared between the CT honeycombing present and absent groups at the diagnosis of AEs of ILDs.

Results: Ninety-five patients who were on corticosteroid pulse therapy were assessed. Though log-rank tests showed that Kaplan-Meier survival curves of the high and low ground-glass opacity (GGO) score groups differed significantly in 3-month mortality in patients with AEs of idiopathic ILDs ($P = 0.007$) and overall patients ($P = 0.045$), there was no significant difference between the CT honeycombing present and absent groups in patients with AEs of idiopathic ILDs ($P = 0.600$) and AEs of secondary ILDs ($P = 0.472$), as well as of overall patients ($P = 0.905$). In addition, whereas CCIS (OR, 1.436; 95% CI, 1.119-1.938; $P = 0.004$) and age (OR, 1.097; 95% CI, 1.119-1.212; $P = 0.026$) were significant predictors of 3-month mortality in the CT honeycombing absent group, serum lactate dehydrogenase (OR, 1.004; 95% CI, 1.002-1.007; $P = 0.001$) and sex (OR, 6.381; 95% CI, 0.821-49.602; $P = 0.023$) were significant predictors in the CT honeycombing present group.

Conclusions: The clinical features of patients with or without honeycombing may differ due to the difference in prognostic factors, but these groups were found to have similar prognoses 3 months after AE onset, and clinicopathological examinations according to these groups are essential.

Introduction

An acute exacerbation (AE) of an interstitial lung disease (ILD) is a rapid deterioration of the respiratory condition that usually requires hospitalization and is associated with high in-hospital and post-discharge mortality [1]. It is widely known to occur in idiopathic pulmonary fibrosis (IPF), but it also occurs in other ILD patients such as non-IPF idiopathic interstitial pneumonias (IIPs) or connective tissue disease (CTD)-associated ILDs [2-6]. The typical pathological findings in patients with AEs of ILDs are known to be diffuse alveolar damage (DAD) superimposed on lung fibrosis with organizing pneumonia (OP), diffuse alveolar hemorrhage (DAH), pulmonary thromboembolism, lung cancer, and bronchopneumonia [7]. The high-resolution computed tomography (HRCT) findings of lung fibrosis in AE have been reported to range widely between typical honeycomb and reticular opacity without honeycomb [8,9].

Honeycombing on HRCT is defined as clustered cystic airspaces of typically consistent diameter (3-10 mm, but occasionally larger) with thick and well-defined walls. It is usually accompanied by reticular fibrosis containing traction bronchiectasis [10]. Honeycombing has been described in diverse forms of ILDs such as chronic hypersensitivity pneumonitis, CTD-ILD, IPF, and unclassifiable/other ILDs [11]. Among ILD patients in the stable condition, the mean overall survival time has been reported to be shorter

among those with CT honeycombing than among those without CT honeycombing [11]. However, there are few reports on the effect of the presence of CT honeycombing on the prognosis after the onset of AE [8]. The purpose of this retrospective study was to clarify whether the presence of CT honeycombing can affect the prognosis of patients with AEs of ILDs.

Methods

Study location and patients

This retrospective cohort study was performed at Yokohama City University Hospital and Yokohama City University Medical Center between 2014 and 2018. The medical data of 95 patients including acute or subacute IIPs, with AE of nonspecific interstitial pneumonia and IPF, acute interstitial pneumonia, cryptogenic organizing pneumonia, drug-induced ILD, or AE of CTD-ILDs treated with corticosteroid pulse therapy were assessed. Medical records at the time of diagnosis of AE were reviewed for data including age, sex, diagnosis of ILD, Charlson Comorbidity Index score (CCIS), blood parameters such as partial pressure of oxygen in arterial blood/fraction of inspired oxygen (P/F ratio), lactate dehydrogenase (LDH; normal < 225 U/L), surfactant protein (SP)-D (normal < 110 ng/mL), Krebs von den Lungen (KL-6; normal < 500 U/mL), and treatment regimens, including anticoagulation therapy before steroid pulse therapy, steroid use before steroid pulse therapy, and macrolide therapy [12].

Diagnosis of ILDs

Subtypes of IIP were confirmed based on physical, serological, HRCT, and lung pathological findings, in accordance with the official statement for IIPs [13,14]. Patients for whom lung biopsy could not be performed due to severe hypoxemia were diagnosed based on the HRCT classification [13,14]. The CTD-ILD diagnosis was confirmed by physical, serological, and HRCT findings consistent with ILD, and lung biopsy was undertaken to exclude other pulmonary diseases. Diagnosis of drug-induced ILD was based on previously reported criteria [15]. AE of ILD was defined as: worsening of hypoxemia reflecting severely impaired gas exchange; worsening of dyspnea; newly appeared alveolar infiltration on radiography; and absence of alternative etiologies including pneumothorax, pulmonary embolism, infection, or heart failure [3-6].

HRCT score

HRCT was performed at the time of diagnosis of AE. HRCT findings including ground-glass opacity (GGO) and honeycombing were assessed independently by two pulmonologists and two radiologists. HRCT scores were calculated using the semi-quantitative scoring method described by Ooi et al. [16]. These findings were then scored based on the percentage of disease extent in each of the 6 lobes. A global score was calculated by adding the scores for each abnormality in all lobes.

Statistical analysis

Data were analyzed statistically using JMP12 (SAS Institute Inc., Cary, NC, USA) and are shown as medians with 25th - 75th percentiles or numbers (%). Groups were compared using the Wilcoxon rank-sum test or Pearson's chi-squared test. Optimal parameter cut-off values were determined from receiver operator characteristic (ROC) curves. Survival curves were generated using the Kaplan-Meier method and compared using log-rank tests. Predictors of 3-month mortality were determined using multiple stepwise regression analysis. Values with $P < 0.05$ were considered significant.

Results

Characteristics of enrolled patients

Table 1 shows the clinical characteristics of the 95 enrolled patients with AEs of ILDs, all of whom received corticosteroid pulse therapy. The diagnoses of the patients were AEs of idiopathic ILDs in 62 patients (65%) and AEs of secondary ILDs in 33 patients (35%). Idiopathic ILDs consisted of 17 IPF patients (18%) and 45 other IIP patients (47%). Secondary ILD patients consisted of 18 CTD-ILD patients (20%) and 13 drug-induced ILD patients (14%). Three-month mortality of all enrolled patients was 24%. Table 2 shows the HRCT scores at the time of diagnosis of AE. The GGO scores of patients with idiopathic ILDs and secondary ILDs were 10 points and 11 points, respectively. Honeycomb scores of patients with idiopathic ILDs and secondary ILDs were 1 point and 1 point, respectively. Total CT scores calculated by the summation of GGO and honeycomb scores in patients with idiopathic ILDs and secondary ILDs were 12.5 points and 15 points, respectively. All of these scores did not differ significantly between idiopathic and secondary ILDs.

The clinical impact of GGO and total HRCT scores

The area under the ROC curve (AUC) value was 0.600 in the evaluation of the GGO score as a predictor of 3-month mortality. The 95 patients were assigned to groups with either low GGO ($N = 42$) or high GGO ($N = 53$) scores based on the optimal cut-off (10 points). Log-rank tests showed that Kaplan-Meier survival curves of these groups differed significantly in patients with AEs of idiopathic ILDs ($P = 0.007$) and overall patients ($P = 0.045$), but not in those with AEs of secondary ILDs (Fig. 1). In addition, similar to the GGO score, the same examination was conducted for the total HRCT score. The AUC value was 0.630 in the evaluation of the total HRCT score as a predictor of 3-month mortality. The 95 patients were assigned to groups with either a low total HRCT score ($N = 80$) or a high HRCT score ($N = 15$) based on the optimal cut-off (20 points). Log-rank tests showed that the Kaplan-Meier survival curves of these groups differed significantly in patients with AEs of idiopathic ILDs ($P = 0.004$) and overall patients ($P = 0.002$), but not in those with AEs of secondary ILDs (Fig. 2).

Clinical impact of the extent of honeycombing on CT

To evaluate the clinical impact of the extent of honeycombing on CT, clinical data including age, sex, diagnosis of ILD, CCIS, P/F ratio, LDH, SP-D, KL-6, and treatment regimens were compared between the patients with and without honeycombing on HRCT (Table 3). There were no significant differences between the two groups other than in serum KL-6 and the frequency of use of macrolides. In addition,

there was no significant difference in 3-month mortality between these two groups in patients with AEs of idiopathic ILDs ($P = 0.600$), AEs of secondary ILDs ($P = 0.472$), and overall patients ($P = 0.905$) (Fig. 3). Furthermore, in patients with AEs of idiopathic ILDs, AEs of secondary ILDs, and overall patients, there was no significant difference in 3-month mortality among the groups with low (0 point), middle (1–4 points), and high (≥ 5 points) honeycomb scores (Fig. 4).

Stepwise Multiple Logistic Regression Analysis

In both patients with and without honeycombing, clinical parameters including age, sex, CCIS, diagnosis of ILDs, P/F ratio, serum LDH and KL-6, and the GGO scores were evaluated using stepwise multiple logistic regression analysis. Whereas CCIS (OR, 1.436; 95% CI, 1.119–1.938; $P = 0.004$) and age (OR, 1.097; 95% CI, 1.119–1.212; $P = 0.026$) were significant predictors of 3-month mortality in the CT honeycombing absent group, serum LDH (OR, 1.004; 95% CI, 1.002–1.007; $P = 0.001$) and sex (OR, 6.381; 95% CI, 0.821–49.602; $P = 0.023$) were significant predictors in the CT honeycombing present group (Table 4).

Discussion

Honeycombing on HRCT is defined as clustered cystic airspaces of typically consistent diameter (3–10 mm, but occasionally larger) with thick and well-defined walls [10]. In the observational cohort study of data from America, the prevalence of CT honeycombing was reported to be about 30–40% in patients with CTD-ILD, IPF, chronic hypersensitivity pneumonia (CHP), and unclassified ILD, and CT honeycombing was associated with increased long-term mortality rate compared with no honeycombing [11]. Similar to these stable ILD patients, CT honeycombing is expected to be an important prognostic predictor in ILD patients having an AE, but there are few reports examining the relationship between CT findings including honeycombing, traction bronchiectasis, GGO, and consolidation [17]. Actually, Kishaba et al. demonstrated that, in patients with AEs of IPF, the GGO and consolidation score calculated from HRCT could be a significant predictor of 3-month mortality, but the honeycomb and traction bronchiectasis score could not [17]. The purpose of this retrospective study was to clarify whether the presence of CT honeycombing affects the prognosis of patients with AEs of ILDs.

It is not clear whether the presence of CT honeycombing affects the prognosis at the onset of AE [8]. In the present retrospective study that included 107 patients with AE-IPF, Kaplan-Meier analysis did not show any difference in overall survival between the usual interstitial pneumonia (UIP) group and the possible UIP group, but the 30-day cumulative survival proportion was significantly higher in the UIP group than in the P-UIP group [8]. In the present study, there was no significant difference in 3-month mortality between the with and without CT honeycombing groups among patients with AEs of idiopathic ILDs, AEs of secondary ILDs, and overall patients. This tendency was similar 6 months after AE onset (Fig. S1). In addition, CCIS proved to be a significant prognostic factor in the former group, and serum LDH was significant in the latter group. Serum LDH has been previously mentioned as a prognostic factor in patients with AEs of IPF [17, 18]. However, the present study showed that the groups with and without

CT honeycombing had different prognostic factors. Therefore, these suggest that the mechanism of disease progression in AE patients with and without CT honeycombing may be different, and it may be necessary to select prognostic biomarkers and treatment strategies taking into account the pre-existing radiological findings of ILD in the future.

The present study has some limitations. First, the study was limited by the small number of patients and the absence of additional validation datasets. In order to generalize these findings, further validation studies are essential. Second, the clinical diagnoses of the enrolled patients were heterogeneous, but there was no significant difference in the ILD diagnoses between the groups with and without CT honeycombing. Third, both groups likely had various pathological changes other than DAD, but pathological assessment was not performed after the onset of AE in all patients due to severe respiratory failure [7]. Therefore, the credibility of this study will be increased by evaluating the relationship between clinical parameters such as blood examinations and radiographic findings and prognosis in autopsy cases only.

Conclusions

In conclusion, the clinical features of patients with and without honeycombing may differ due to the difference in prognostic factors, but these groups had similar prognoses 3 month after AE onset, and clinicopathological examinations according to these groups are essential.

List Of Abbreviations

AE, acute exacerbation

AUC, area under the ROC curve

CCIS, Charlson Comorbidity Index score

CHP, chronic hypersensitivity pneumonia

CI, confidence interval

CTD-ILDs, connective tissue disease-associated ILDs

DAD, diffuse alveolar damage

DAH, diffuse alveolar hemorrhage

GGO, ground-glass opacity

HRCT, high-resolution CT

IIPs, idiopathic interstitial pneumonias

ILD, interstitial lung disease

IPF, idiopathic pulmonary fibrosis

KL-6, Krebs von den Lungen

LDH, lactate dehydrogenase

OP, organizing pneumonia

OR, odds ratio

P/F ratio, partial pressure of oxygen in arterial blood/fraction of inspired oxygen

PSL, prednisolone

ROC, receiver operating characteristic

SP-D, surfactant protein-D

UIP, usual interstitial pneumonia

Declarations

Ethics approval and consent to participate

This research was performed in accordance with the Declaration of Helsinki and approved by the institutional review board at Yokohama City University Hospital (approval number B171100003). In this retrospective study, informed consent was obtained by disclosing the clinical study with the description of the opt-out process (https://www.yokohama-cu.ac.jp/amedrc/ethics/ethical/fuzoku_optout.html).

Consent for publication

Written consent for publication from the patients or their next of kin was obtained.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

- (I) Conception and design
- (II) Administrative support
- (III) Provision of study materials or patients
- (IV) Collection and assembly of data
- (V) Data analysis and interpretation
- (VI) Manuscript writing
- (VII) Final approval of manuscript

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TY, NR, MK, and AA: (I), (III), (V), (VI), and (VII).

TK, WK: (III), (IV), (VI), and (VII).

HN, KN, YM, KM, and KT: (I), (II), (III), (VI), and (VII).

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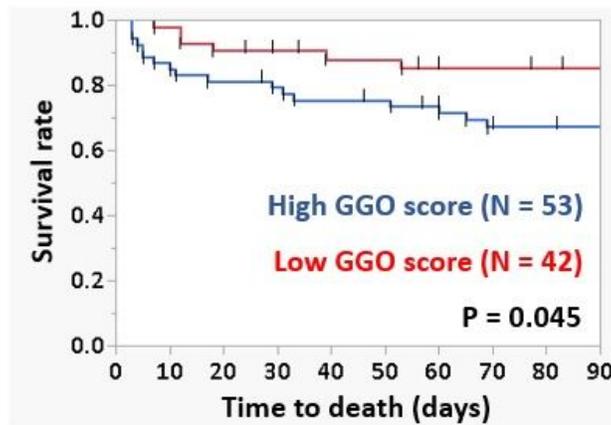
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Tables

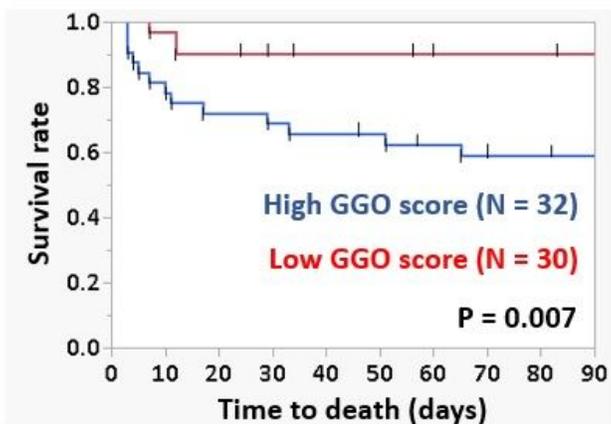
Due to technical limitations the Tables are available as downloads in the Supplementary Files.

Figures

A. Overall



B. Idiopathic



C. Secondary

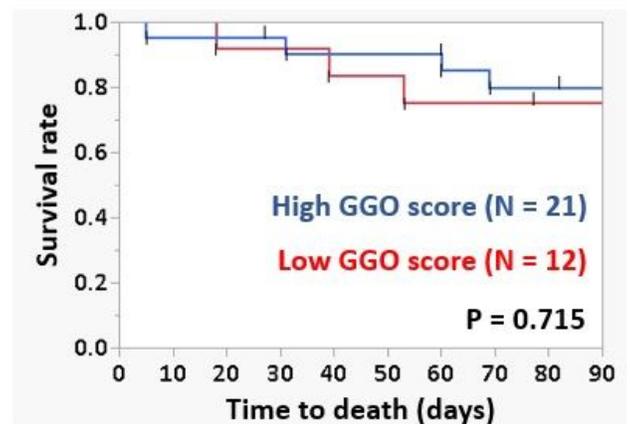
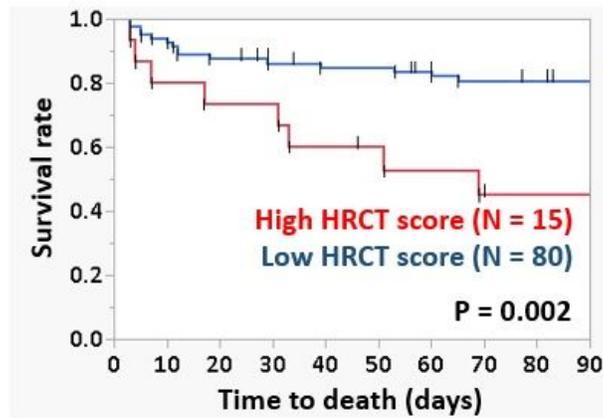


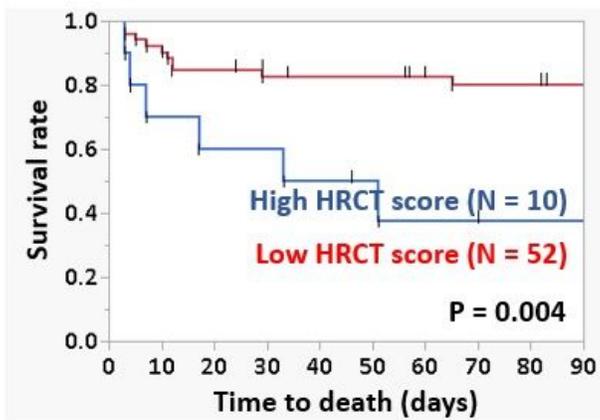
Figure 1

Comparison of patients with high and low GGO scores. The 95 patients were assigned to groups with a low GGO (N = 42) or a high GGO (N = 53) score based on the optimal cut-off (10 points). Log-rank tests show that Kaplan-Meier survival curves of these groups differ significantly in patients with AE of idiopathic ILDs and overall patients, but not in those with AEs of secondary ILDs. Abbreviations: AE, acute exacerbation; GGO, ground-glass opacity; ILD, interstitial lung disease.

A. Overall



B. Idiopathic



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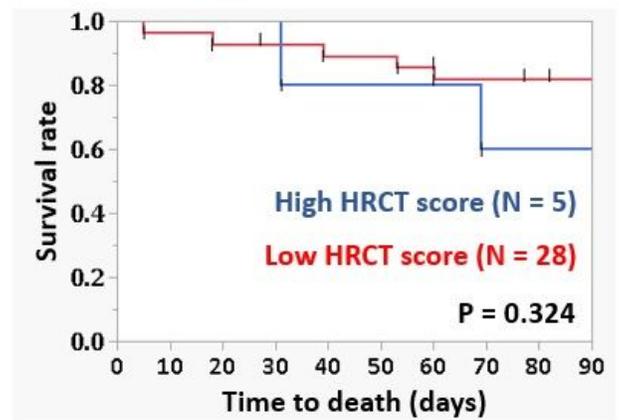
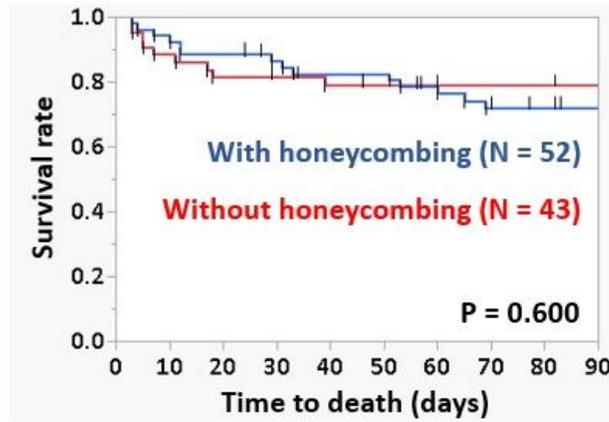


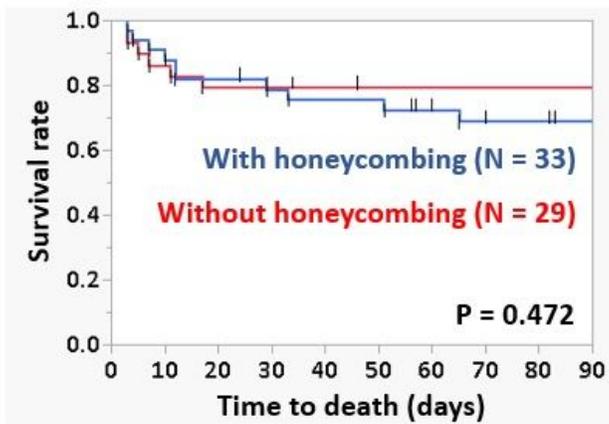
Figure 2

Comparison of patients with high and low total HRCT scores. The 95 patients were assigned to groups with a low total HRCT (N = 80) or a high total HRCT (N = 15) score based on the optimal cut-off (20 points). Log-rank tests show that the Kaplan-Meier survival curves of these groups differ significantly in patients with AEs of idiopathic ILDs and overall patients, but not in those with AEs of secondary ILDs. Abbreviations: AE, acute exacerbation; GGO, ground-glass opacity; ILD, interstitial lung disease.

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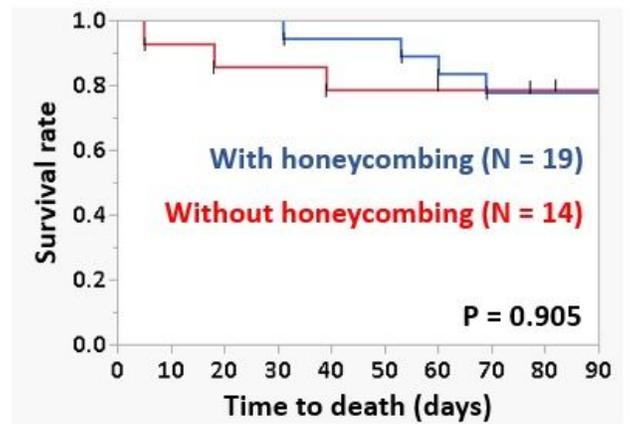
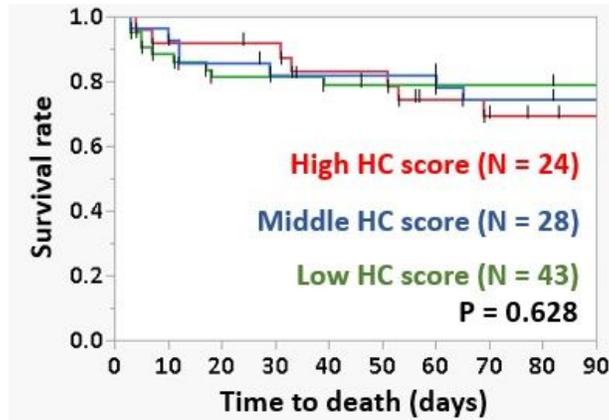


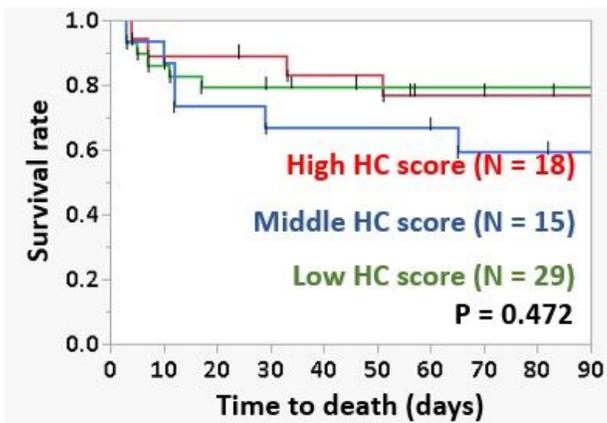
Figure 3

Comparison of patients with and without honeycombing. There is no significant difference in 3-month mortality between those with and without honeycombing in patients with AEs of idiopathic ILDs, AEs of secondary ILDs, and overall patients. Abbreviations: AE, acute exacerbation; ILD, interstitial lung disease.

A. Overall



B. Idiopathic



C. Secondary

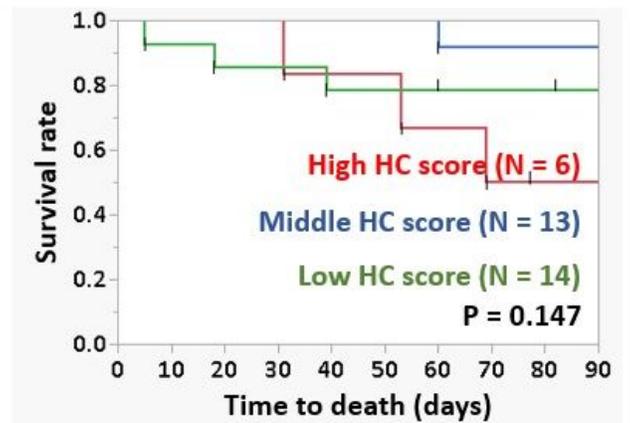


Figure 4

Comparison of patients with high, middle, and low honeycomb scores in patients with AEs of idiopathic ILDs and secondary ILDs and overall patients, there is no significant difference in 3-month mortality among the groups with low (0 point), middle (1-4 points), and high (≥ 5 points) honeycomb scores. Abbreviations: AE, acute exacerbation; ILD, interstitial lung disease.

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