Lung Contractive Change in Severe Acute Respiratory Failure Requiring Invasive Ventilation; A Comparison of Features Between Interstitial Lung Disease and Severe Infection

Kentaro Nagaoka (knagaoka@pop.med.hokudai.ac.jp)
Hokkaido University Hospital: Hokkaido Daigaku Byoin https://orcid.org/0000-0003-3484-4554

Yu Yamashita
Hokkaido University Hospital: Hokkaido Daigaku Byoin

Akira Oguma
Hokkaido University Hospital: Hokkaido Daigaku Byoin

Hirokazu Kimura
Hokkaido University Hospital: Hokkaido Daigaku Byoin

Kaoruko Shimizu
Hokkaido University Hospital: Hokkaido Daigaku Byoin

Masaru Suzuki
Hokkaido University Hospital: Hokkaido Daigaku Byoin

Satonori Tsuneta
Hokkaido University Hospital: Hokkaido Daigaku Byoin

Noriko Oyama-Manabe
Hokkaido University Hospital: Hokkaido Daigaku Byoin

Ryo Takagi
Hokkaido University Graduate School of Medicine School of Medicine: Hokkaido Daigaku Daigakuin Igakuin

Isao Yokota
Hokkaido University Graduate School of Medicine School of Medicine: Hokkaido Daigaku Daigakuin Igakuin

Hitoshi Saito
Hokkaido University Hospital: Hokkaido Daigaku Byoin

Takeshi Wada
Hokkaido University Hospital: Hokkaido Daigaku Byoin

Hiroki Kato
Hokkaido University Hospital: Hokkaido Daigaku Byoin

Yuji Morimoto
Hokkaido University Hospital: Hokkaido Daigaku Byoin

Satoshi Konno
Hokkaido University Hospital: Hokkaido Daigaku Byoin

Research

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Lung contractive change in severe acute respiratory failure requiring invasive ventilation; a comparison of features between interstitial lung disease and severe infection

Kentaro Nagaoka,[1]* Yu Yamashita,[1] Akira Oguma,[1] Hirokazu Kimura,[1] Kaoruko Shimizu,[1] Masaru Suzuki,[1] Satonori Tsuneta,[2] Noriko Oyama-Manabe,[2] Ryo Takagi,[3] Isao Yokota,[3] Hitoshi Saito,[4] Takeshi Wada,[4] Hiroki Kato,[4] Yuji Morimoto,[4] and Satoshi Konno.[1]

[1]Department of Respiratory Medicine, [2]Department of Diagnostic and Interventional Radiology, [3]Department of Biostatistics, [4]Department of Anesthesiology and Critical Care Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Hokkaido, Japan.

*Address correspondence to Kentaro Nagaoka, First Department of Internal Medicine, Hokkaido University Hospital, Hokkaido, Japan. E-mail: knagaoka@med.hokudai.ac.jp

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23

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Abstract

Background: Generally, the incidence of irreversible lung injury is considered to be higher in acute respiratory failure due to interstitial lung disease (ILD), compared to those due to severe infection. However, those sub-phenotypes, which follow irreversible lung injury, remain poorly characterized. We aimed to examine their clinical and radiological features, in patients who could not withdraw from ventilation after receiving any treatment (defined as "irreversible respiratory failure").

Methods: Retrospective study including all patients receiving CT evaluation at onset and invasive mechanical ventilation for severe infection or acute ILD, who admitted our institution from April 2013 to May 2019. Participants were divided into Infection group and ILD group according to the dominant cause, and predictors of irreversible respiratory failure were examined among those subjects. In addition, we quantitatively evaluated the changes in lung region volumes and dispersion of grand glass opacity, using automated methods.

Results: 31 patients were subdivided to ILD group, whereas 139 patients were subdivided to Infection group. Significantly more subjects in ILD group developed irreversible respiratory failure (n=22; 70.9%), compared to those in

Infection group (n=27; 19.4%; p<0.001). With validation of radiological features in those subjects, distinct CT findings, including lung contractive change and non-edematous lung injury (NE-LI), were found in both groups. Lung contractive change was observed with 23 subjects in ILD group (74.2%) and 7 subjects in Infection group (5.0%). Among those, >10% lung volume reduction was confirmed by CT analysis with 19 subjects in ILD group and 4 subjects in Infection group. By multivariate logistic regression analysis, the following factors were found to be strong predictors of irreversible respiratory failure; lung contractive change (odds ratio [OR]=32.6; 95% confidence interval [CI], 7.1-150), NE-LI suspicious lesion (OR=13.3; 95% CI [2.9-59]), ILD-dominant respiratory failure (OR=18.4; 95% CI, 4.3-79), multidrug-resistant bacterial- or fungal-infection (OR=6.4; 95% CI, 1.3-31).

Conclusions: We demonstrated the presence of sub-phenotypes in acute respiratory failure due to ILD and severe infection, which followed an irreversible course with distinctive radiological features including lung contractive changes.

Introduction

Acute respiratory distress syndrome (ARDS) is a lung injury that results from excessive inflammation induced by various causes [1]. The leading cause of ARDS is severe infection, pneumonia or extrapulmonary sepsis, and the mainstay of treatment is early diagnosis followed by the initiation of appropriate antibiotic therapy [2]. Controversially, there still remain cases, that follow a fatal course with irreversible respiratory failure, even after infectious inflammation has been adequately controlled [3,4]. Conventionally, the most prevalent pathologic finding in ARDS is diffuse alveolar damage (DAD), which follows irreversible change [5], however, several autopsy studies have revealed that the pathology of ARDS is not limited to DAD, but includes various findings, such as potentially reversible lesions [6, 7]. There are few descriptive data available that examine the detailed features of irreversible respiratory failure in infectious ARDS.

Recently, distinct ARDS subtypes which lack exposure to common risk factors (CRFs) have been gaining increasing attention [8, 9]. Gibelin et al. reported that 7.5% of all ARDS patients in their institution had ARDS without CRFs [8]; the etiologies of these subtypes included immune, drug-induced,

79 malignant and idiopathic ARDS. To date, it has become more difficult to
80 precisely distinguish those sub-phenotypes from acute respiratory failure due
81 to interstitial lung disease (ILD), which frequently follow irreversible course
82 refractory to steroid/immunosuppressive therapy [10]. Thus, further study is
83 considered necessary, that investigate detailed features of those cases.
84 Given that lung transplantation has recently been considered as a salvage
85 therapeutic option in patients with end-stage lung disease, including ARDS
86 due to infection or ILD, the decision regarding the reversibility of lung
87 function has become a crucial issue [11]. Herein we sought to examine the
88 clinical and radiological feature of subtypes in severe acute respiratory failure
89 requiring invasive ventilation, which followed irreversible respiratory failure.
90 In this study, "irreversible respiratory failure" was defined as respiratory
91 failure which could not be withdrawn from invasive ventilation after
92 receiving any treatment including antibiotics and corticosteroid therapy.
93 Generally, the incidence of irreversible lung injury is considered to be higher
94 in acute respiratory failure due to ILD, compared with those due to severe
95 infection. Thereby, we adopted the comparison of two groups, ILD vs Infection,
96 to extract a predictor of irreversible respiratory failure. The primary end-

point of the study was extraction of predictors associated with acute irreversible respiratory failure due to ILD or infection.

Material and Methods

Study design

We conducted a retrospective study including all consecutive patients receiving invasive ventilation in our tertiary hospital (ICU or the hospital ward of respiratory medicine) from April 2013 to May 2019. This observational, non-interventional analysis of medical records was approved by the Human Subjects Review Committee of the Hospital (019-0304). As per Japanese law, no informed consent was required for this type of study.

Study participants and protocol

Participants were divided into two groups according to the dominant cause of acute respiratory failure. The participants whose dominant cause were diagnosed as infection were assigned to the Infection group, and those diagnosed as ILD were assigned to the ILD group. For the subjects whose ILD was exacerbated after infection, the group were selected according to the

115 initiated-timing of ventilation: those during infection were included in the
116 Infection group, and those after the control of infection were included in the
117 ILD group.
118 In the Infection group, patients with an initial diagnosis of infectious
119 pneumonia were defined as the pneumonia group, and the others were
120 defined as the non-pulmonary infection group. Pneumonia was classified as
121 community-acquired pneumonia, nursing and health-care associated
122 pneumonia (NHCAP), or hospital-acquired pneumonia according to the
123 American Thoracic Society guidelines [12, 13] and the Japanese criteria to
124 NHCAP [14].
125 In the ILD group, those without any previously known ILD were defined as
126 ARDS without CRFs, when its deterioration period was within 7 days, and
127 the others were defined as acute interstitial pneumonia. The diagnosis of ILD
128 was made using the relevant society's diagnostic criteria [1, 15–19].
129 Patients without a computed tomography (CT) scan from onset until the
130 initiation of ventilation were excluded, because initial evaluation of the lung
131 lesion was unavailable.
132

Radiological examination

Previous chest CT scans were reviewed retrospectively and evaluated by two experienced physicians (KN and ST/NO). Radiological findings were categorized based on the patterns seen on a CT scan performed at the onset of respiratory failure, according to the Fleischner Society Glossary of Terms for Thoracic Imaging [20]. In this study, the dominant distribution pattern of grand glass opacity (GGO) was also categorized as follows (Figure 1A-D); non-segmental, peribronchovascular, perivascular, periconsolidation pattern. We determined the GGO distribution-pattern according to the presence of gradient change around the bronchovascular bundle, vascular or consolidation, intending to assess whether the lesion affected from blood flow (increased vascular permeability, pulmonary congestion) or extended inflammation around pneumonia.

Most of the patients with irreversible respiratory failure showed loss of lung-compliance as well as lung contractive changes, reduction of aeration area, and appearance of traction bronchiectasis, on follow-up CT. Thus, we quantitatively evaluated the changes in lung areas using SYNAPSE VINCENT volume analyzer (FUJIFILM Medical Co., Ltd., Tokyo, Japan.)

Briefly, three CT slices were selected from high resolution CT images, following the modified method of Matsuoka et.al [21]; the upper cranial slice was approximately 1 cm above the upper margin of the aortic arch, the middle slice approximately 1 cm below the carina, and the lower caudal slice was at the level of the right inferior pulmonary vein. Then, the lung margins were manually traced (Figure 1E, F), and the lung areas were calculated as the sum of those in the three images. The lung contraction rate was determined by ratio relative to the lung-areas from onset-CT. We defined 10% of lung contraction as CT-confirmed lung contraction, to avoid effects of respiratory fluctuation.

Among radiological findings in the cases with lung contractive changes, we had experienced a precedented appearance of non-segmentally distributed GGO with the specific feature. Those findings were characterized as uniformly distributed GGO extending to the pleura with a poor reticular pattern, which was considered to reflect parenchymal interstitial abnormality with less edematous change. We defined the radiological pattern as “non-edematous lung injury (NE-LI) suspicious lesion” (Figure 1G), and evaluated its frequency in this study. In order to confirm uniformity of the GGO lesion,

we also validated dispersion of GGO density by using XTREK view (J-MAC SYSTEM Inc., Sapporo, Japan), and compared those of NE-LI suspicious lesion with the other GGO lesions. Briefly, regions of interest were manually selected from the representative area of GGO, avoiding vessels and trachea, and CT density of GGO was calculated. We defined "non-uniformity index" as ratio of standard deviation to absolute value of CT density.

Statistical analysis

Background factors were expressed as median (interquartile range) or number (percentages). To evaluate differences between patients' groups, the Wilcoxon test and Pearson's Chi-squared test were utilized to compare continuous and nominal variables, respectively. Predictors associated with irreversible respiratory failure were determined by logistic regression model, adjusted for several clinical indexes, within the whole cohort of patients (Infection group and ILD group). P values <0.05 were considered to be statistically significant. The JMP 11 statistical program (SAS Institute Inc, Cary, NC) was used for statistical analysis.

Results

Diagnosis of the patients in this study

The distributions of patients in this study are shown in Figure 2. In the study period, 2,439 patients received invasive ventilation, mostly for post-operative management without any complication (n=1,088). Among those in the ILD group (n=31), 15 patients were clinically diagnosed as ARDS without CRFs (10 were post-operative-, 4 had chemotherapy-induced ARDS), and 6 patients were diagnosed as AIP. Among Infectious pneumonia group (n=89), 56 patients (61% of pneumonia group) were confirmed to have bacterial pneumonia, 10 patients (11%) had viral pneumonia, and 4 patients (3%) for fungus infection. For those in the non-pulmonary infection group (n=50), 45 patients (90% of non-pulmonary infection group) were confirmed as having a bacterial infection. More detailed diagnosis for each group are described in the supplemental data (Supple Table S1-3).

Clinical characteristics and laboratory findings

The clinical characteristics, laboratory findings, and the treatment and outcomes of ILD groups and Infection groups are summarized in Table 1. The

clinical features were significantly different between Infection group and ILD group, including their simplified acute physiology score (SAPS) Ⅱ score [22] and sequential organ failure assessment (SOFA) score [23]. Notably, significantly higher patients could not withdraw from ventilation in ILD group, compared with those in Infection group.

Radiological findings

The radiological findings of patients in this study are summarized in Table 2. There existed 4 patients in the ILD group and 3 patients in the Infection group, whose lung contractive change could not be confirmed by CT analysis due to the following factors; lung contraction was partial, moderate pleural effusion was found at onset CT, and a lack of follow-up CT (X-ray was available). The representative image of NE-LI suspicious lesion is described in Supple Figure S1A. In contrast, the GGO lesion, which was not correspond to NE-LI lesion, is described in Supple Figure S1B. The non-uniformity index in NE-LI suspicious lesion were significantly lower than those in the other GGO area ($p<0.0001$; Supple Figure S1C).

Predictors of irreversible respiratory failure

Table 3 shows the results of multivariate analyses performed to determine the predictors of irreversible respiratory failure in this study. The strongest predictors of irreversible respiratory failure were lung contractive change, followed by ILD-dominant respiratory failure, the presence of a NE-LI suspicious lesion, and infection due to an antibiotic-resistant pathogen (multidrug-resistant bacteria or fungus). Additional analysis revealed that those other than NE-LI lesion were also significant increased risk of in-hospital mortality in this study, as well as routine corticosteroid use (Supple Table S4).

Characteristics of the patients who presented with lung contractive change in follow-up CT

The clinical feature of the patients who presented with lung contractive changes in follow-up CT are shown in Table 4. The representative images of the lung contraction pattern were described in Supple Figure S2A-F. The time for initial diagnosis of lung contractive change were mostly around 2-4 weeks after onset, and lung contraction rates were similar among infectious ARDS,

ARDS without CRFs, and AE-ILD (Supple Fig S3A, B). While the majority (76.7%) of lung contractive change could also be confirmed by CT analysis, for those in the remaining cases, lung contractive change in partial lung lesions was not possible to confirm with CT analysis. Therefore, we determined the cases with lung contractive changes, and not limited to those within the CT analysis-confirmed cases group.

Discussion

In the present study, we demonstrated that the respiratory prognosis of acute respiratory failure in ILD was significantly worse than those in severe infection. Lung contractive change was frequently observed with those who followed irreversible respiratory failure, mostly confirmed by CT analysis. Further, we found the frequent appearance of non-edematous GGO preceding lung contraction, which is likely to be a novel predictor of irreversible respiratory failure.

In this study, we re-considered the suitability of the ARDS criteria for the inclusion of subjects, in line with the study aims. For the ILD group, we included ARDS without CRFs, AIP, and AE-ILD, together with the ILD group.

Although diagnostic criteria for each disease is different, the appearance of clinical/radiological features of those in the acute phase were substantially similar, which predominantly results from acute interstitial abnormalities of autoimmune origin. Since the exacerbation period in those cases mostly extended to 1-4 weeks (Supple Figure S3A), it was difficult to categorize those subjects merely into ARDS criteria, which define the exacerbation period within one week from onset. For the Infection group, 131 patients (92.3% of Infection group) developed hypoxemia within ARDS criteria, however, the accompaniment of bilateral infiltration (bilateral lung lesions, non-infectious) was only confirmed in 51 patients (35.9% of the Infection group) during CT scan evaluation. Since we strictly evaluated initial lung abnormality with CT scan, ARDS due to severe infection in this study was possibly underdiagnosed compared to those studies diagnosing ARDS by chest X-ray. On the basis of these points, we enrolled the patients in this study, not limited to those meeting the ARDS criteria.

In our study, acute respiratory failure in the ILD group presented different pathogenic characters from those in the Infection group. Several lines of evidence support this notion. First, exacerbated periods of respiratory

277 symptoms from onset until ventilation were significantly longer in ILD group,
278 compared with Infection group. Second, PCT and lactate were significantly
279 higher in the Infection group than those in the ILD group. These data suggest
280 that the characteristics of the initial inflammation were different between the
281 two groups. Third, creatinine was also significantly higher in the Infection
282 group than in the ILD group, possibly reflecting higher vascular permeability
283 in the Infection group. Accordingly, severity score (SOFA, SAPS Ⅱ) at
284 initiation of ventilation were significantly higher in the Infection group than
285 in the ILD group. Fourth, the majority of GGO distribution in the Infection
286 group was categorized as peribronchovascular/perivascular pattern or
287 periconsolidation pattern, which predominantly reflected pulmonary
288 edematous changes. Taken together, acute respiratory failure due to
289 interstitial lung disease is characterized by milder inflammation than those
290 due to severe infection, which results in subacute progression with less
291 vascular permeability and systemic dysfunction. These results were
292 compatible with those described in a previous report [8].
293 In this study, we proposed NE-LI suspicious lesion as a novel predictor of
294 irreversible respiratory failure. Previously, several studies reported an

295 association between extensive pulmonary lesions, increased GGO and
296 excessive lung edema, and poor clinical outcome in acute respiratory failure
297 including ARDS [24, 25]. Contrary, NE-LI suspicious lesion was frequently
298 confirmed in ILD group, which possibly correspond to the initial phase of lung
299 injury with mild inflammatory change, frequently advanced to lung
300 contractive change after 2-4 weeks (Supple Table S4A). We could at least
301 suggest that additional caution would be necessary for non-edematous GGO
302 lesions in acute respiratory failure, in particular with acute ILD.
303 In our study, the most significant predictor of irreversible respiratory failure
304 was lung contractive change. Lung contractive change, reduction of lung
305 compliance and lung-volume, are universally accepted phenomena in chronic
306 ILD, dominantly induced by fibrotic change in the parenchymal interstitium
307 and evaluated by a decrease in forced vital capacity, total lung capacity, or
308 presentation of traction bronchiectasis [26–28]. Recently, a few studies have
309 shown correlations between lung volume and the prognosis of ARDS, using
310 automated CT analysis with relatively small numbers of subjects [29, 30]. As
311 shown in Table 4, lung contraction mostly occurred with ILD cases, after
312 preceding infection, exposure to pressure injury during general anesthesia, or

cytotoxic chemotherapy. Of note, our study demonstrated a high prevalence of subjects who were post-operative or on cancer chemotherapy treatment, which amounted to 48.4% of subjects with lung contractive change. From these results, it was felt that the incidence of lung contractive change was based on severe interstitial lung injury by complex insults, represented by direct pressure or chemical reaction. In contrast, the effect of infectious inflammation on lung injury might be mild, given the lower incidence of lung contractive changes in the group of severe infections in this study. However, in five cases of severe infection, lung contractive changes had progressed after adequate control of infectious inflammation. Taken together, once lung contractive change was confirmed after the onset of acute respiratory failure, irreversible respiratory failure can develop with high frequency. Thus, we propose that detection of lung contractive change would be a crucial predictor of irreversible respiratory failure in severe acute respiratory failure.

Our study has several limitations. First, we used a single center retrospective design, which may have resulted in a selection bias. Second, several important laboratory findings, such as BNP and PCT, were not examined in all the subjects, thus, could not be included to analyze all of the predictors.

Third, the small numbers of patients within the ILD group may have limited our ability to show differences among clinical or laboratory features. Fourth, we did not include COVID-19 cases in Infection group, which has been worldwide concern with unfavorable outcome. However, we believe our work has several important clinical implications, which would be contributive to the management of a range of intractable acute respiratory failure cases.

Conclusion

This study demonstrated the presence of sub-phenotypes in acute respiratory failure due to ILD and severe infection, which followed irreversible respiratory failure. Comparison of ILD group and Infection group extracted the sub-phenotypes with lung contractive changes, which were mostly observed in ILD group, and, interestingly, in part of Infection group. The distinct CT findings, including lung contractive change and NE-LI, were considered to be potential predictive factors of irreversible respiratory failure. Further investigation concerning the characteristics of these subjects might contribute to guiding clinical decision-making in intractable acute respiratory failure.

ABBREVIATIONS: AE-ILD = acute exacerbation of interstitial pneumonia; AIP = acute interstitial pneumonia; ARDS = acute respiratory distress syndrome; CT = computed tomography; CRFs = common risk factors; DAD = diffuse alveolar damage; ECMO = extracorporeal membrane oxygenation; GGO = grand glass opacity; ILD = interstitial lung disease; IPAF = interstitial pneumonia with autoimmune features; NE-LI = non-edematous lung injury; NHCAP = nursing and health-care associated pneumonia; SAPS = simplified acute physiology score; SOFA = sequential organ failure assessment

Declarations

Ethical Approval and Consent to participate: This study was approved by the Human Subjects Review Committee of Hokkaido University Hospital (approval number: 019-0304). As per Japanese law, no informed consent was required for this type of study.

Consent for publication: Not applicable.

Availability of supporting data: All data generated or analyzed during this study are included in this article and its supplemental data.

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Authors' contributions: KN designed and interpreted clinical data, radiological findings, and prepared the manuscript. KN and YY, with assistance of HK, HS and MS, collected the clinical data. AO and KS contributed analysis of lung-contraction rate. KN, ST and NO contributed analysis of the radiological findings and non-uniformity index. Appropriateness of statistical analysis was confirmed by RT and IY. All the author contributed discussions throughout the work.

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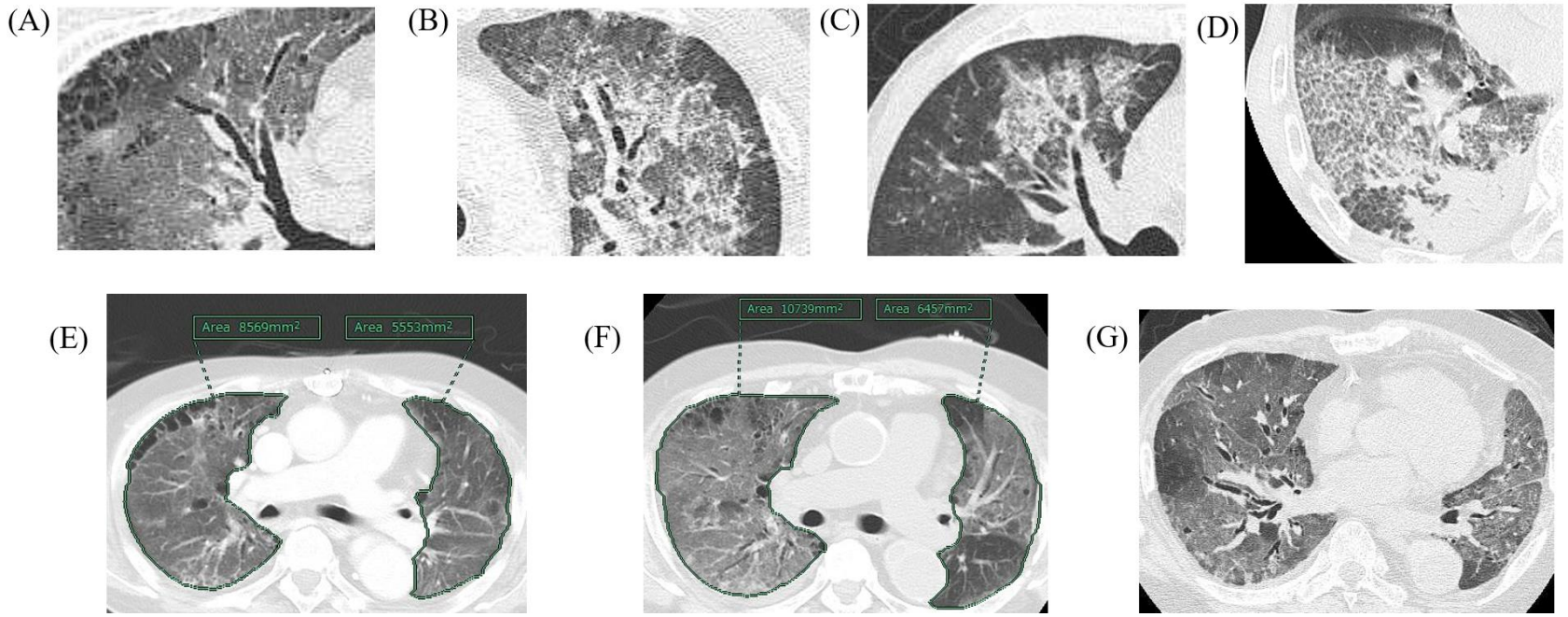
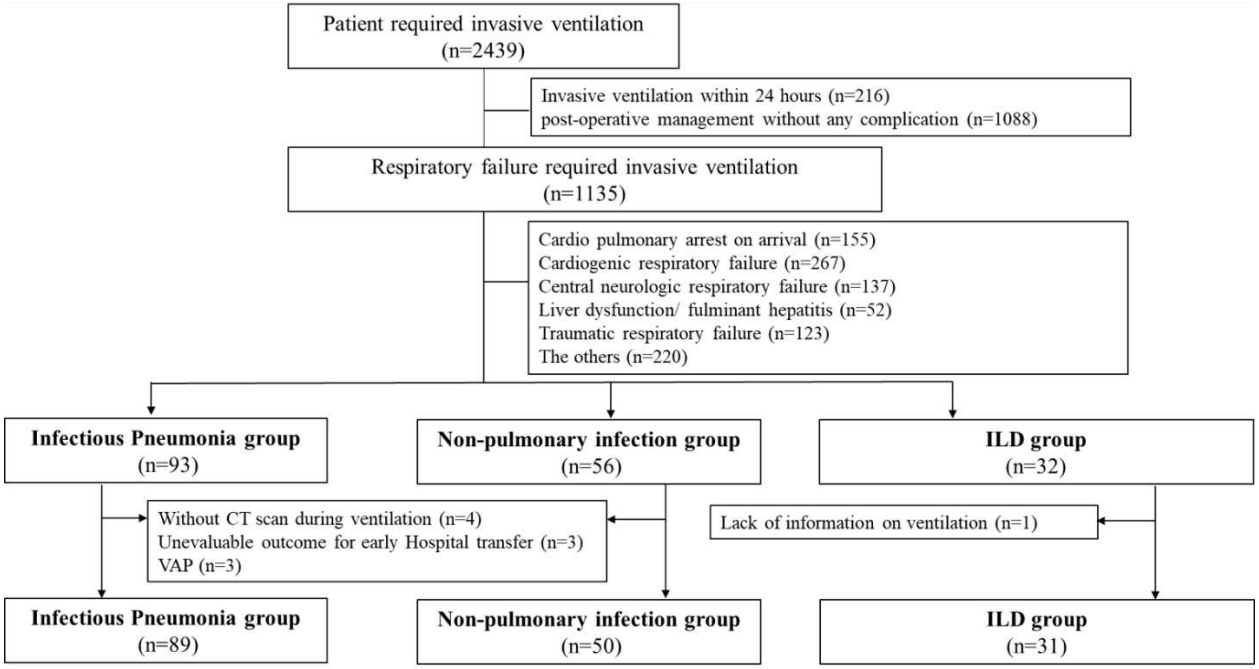
Figure 1



Definition of CT manifestations in this study. Dominant distribution pattern of grand-glass opacity; non-segmental (A), peribronchovascular (B), perivasucular (C), peri-consolidation pattern (D). Quantitative analysis of lung contraction by CT analysis; contraction rate was calculated by the ratio of lung capacity of follow up CT (E) to initial CT (F). Representative manifestation of non-edematous lung injury suspicious lesion (G).

514 Figure 2



515

516 Flow chart illustrating the distribution of patients in this study. Participants were divided into two groups according to

517 the dominant cause of acute respiratory failure; ILD for ILD group or severe infection for Infection group (subdivided

518 with focus of infection into pneumonia group or non-pulmonary group). Abbreviations: CT, computed tomography; ILD,

519 interstitial lung disease; VAP, ventilator-associated pneumonia.

Table

Table 1. Clinical feature, severity, laboratory findings, the treatment and outcomes of patients in this study.

	ILD group (n=31)	Infection group			P value[f]
		Total (n=139)	Pneumonia group (n=89)	Non pulmonary group (n=50)	
Age (years)	67 [58-73]	71 [64-79]	72 [64-79]	68 [63-76]	0.2
Male gender, n (%)	22 (70)	84 (60)	63 (70)	21 (42)	0.17
Community onset, n (%)	17 (54)	92 (66)	59 (66)	33 (66)	0.43
Underlying Disease					
Chronic respiratory disease[a]	15 (48)	36 (26)	32 (35)	4 (8)	<0.05
Diabetes Mellitus	5 (16)	38 (27)	24 (26)	14 (28)	0.34
Malignant disease[b]	16 (51)	42 (30)	29 (32)	13 (26)	0.07
Routine use of corticosteroid	12 (38)	23 (17)	14 (15)	9 (18)	<0.05
Perioperative period (within two weeks)	9 (29)	13 (9)	8 (8)	5 (10)	0.08
General anesthesia within 1 year	13 (41)	27 (19)	16 (17)	11 (22)	<0.05
Days from onset to intubation	4 [1-12]	1 [1-3]	2 [1-3]	1 [1-3]	<0.01
P/F ratio matching to ARDS severity[c]					
P/F >300	1 (3)	11 (8)	4 (4)	7 (14)	0.39
Mild (P/F 200< <300)	4 (13)	32 (23)	21 (24)	11 (22)	0.34
Moderate (P/F 100< <200)	20 (65)	66 (47)	41 (46)	25 (50)	0.05
Severe (P/F <100)	6 (19)	30 (22)	23 (26)	7 (14)	0.39
WBC[d] (10^9/L)	13.3 [8-19]	9.7 [6-16]	9.1 [5-16]	10.3 [5-18]	0.07
CRP[d] (mg/dL)	9 [4-16]	15 [6-22]	12 [6-20]	16 [8-25]	0.08
PCT[e] (ng/mL)	0.3 [0.1-0.9]	8.3 [1-39]	2.5 [0.8-11]	39.2 [9-100]	<0.001
BNP[d] (pg/mL)	104 [48-360]	230 [84-662]	210 [71-466]	513 [176-1016]	0.09
BMI[c] (kg/m^2)	23.4 [21-26]	21.4 [19-26]	21.1 [17-23]	22.9 [20-27]	0.07
Lac[d] (mmol/L)	1.4 [1-2]	3.5 [2-6]	2.6 [1.7-4.5]	4.6 [2.6-8.4]	<0.001
SOFA score[d]	5 [4-8]	9 [7-12]	8 [7-11]	12 [9-13]	<0.001

SAPSII score[d]	35 [29-44]	56 [44-66]	56 [43-66]	53 [47-66]	<0.001
Cre[d] (mg/dL)	0.7 [0.6-0.9]	1.3 [0.8-2]	1.2 [0.8-1.7]	2.0 [0.9-2.7]	<0.001
Alb[c] (g/dL)	2.5 [2.1-2.9]	2.5 [2.2-2.9]	2.5 [2.2-2.9]	2.4 [2.1-2.7]	0.42
Systemic antibiotics administration	30 (96)	139 (100)	89 (100)	50 (100)	0.05
Systemic steroid therapy					
Steroid pulse (1 g/day)	27 (87)	15 (11)	13 (14)	2 (4)	<0.001
High dose (PSL, 1mg/kg/day)	3 (9)	16 (12)	14 (15)	2 (4)	0.93
Low dose (PSL, 0.5mg/kg/day or less)	0 (0)	67 (48)	40 (44)	27 (54)	<0.001
Immunosuppressant therapy	14 (15)	2 (1)	2 (2)	0 (0)	<0.001
Tidal volume (mL/kg IBW)[g]	7.9 [6-10]	8.1 [7-9]	8.1 [6-9]	8.0 [7-9]	0.52
PEEP (mmHg)[g]	8 [6-10]	8 [6-10]	10 [8-10]	8 [6-10]	0.94
Peak inspiratory pressure (mmHg)[g]	21 [17-25]	21 [17-25]	21 [18-25]	21 [16-25]	0.64
Compliance (Cdyn)[g]	40 [21-77]	39 [29-34]	39 [30-60]	36 [25-47]	0.95
CRRT	1 (3)	48 (35)	20 (22)	28 (56)	<0.001
ECMO	7 (22)	15 (11)	14 (15)	1 (2)	0.13
Complication during ventilation	15 (48)	10 (7)	9 (10)	1 (2)	<0.001
Unable to withdraw from ventilation	22 (70)	27 (19)	20 (22)	7 (14)	<0.001
Tracheostomy	17 (54)	43 (31)	34 (38)	9 (18)	<0.05
Prolonged dysphagia until discharge	9 (29)	35 (25)	25 (28)	10 (20)	0.36
In hospital mortality	19 (61)	32 (23)	21 (23)	11 (22)	<0.001

Continuous variables are reported as median [interquartile range (IQR) 25-75]. Categorical variables are reported as number (percentages). Each laboratory data was available for all the patients, except for BNP and PCT. BNP was validated within 48 h of ventilation in 25 patients (80.6%) of ILD group and 90 patients (64.7%) of Infection group. PCT was validated within 1 week of ventilation in 29 patients (93.5%) of ILD group and 107 patients (77.0%) of Infection group. The records of ventilation-settings were available

in 29 patients (93.5%) of ILD group and 132 patients (95.0%) of Infection group. ARDS acute respiratory distress syndrome, BMI body mass index, CRRT continuous renal replacement therapy, ECMO extracorporeal membrane oxygenation, IBW ideal body weight, ILD interstitial lung disease, PEEP positive end-expiratory pressure, PCT procalcitonin, PSL predonisolone.

[a] Chronic respiratory disease included any respiratory disease required clinical follow-up.

[b] Malignant disease included any present/previous history of malignant tumor or hematological malignancies.

[c] Based on the lowest value within 48 h of invasive mechanical ventilation.

[d] Based on the highest value within 48 h of invasive mechanical ventilation.

[e] Based on the highest value within 7 days of invasive mechanical ventilation.

[f] Infection group vs ILD group

[g] Based on the initial setting of invasive mechanical ventilation within 24 h.

547 Table 2. CT manifestation, GGO feature, dominant distribution pattern, lung
548 contraction changes of patients in this study.

	ILD group (n=31)	Infection group			P value[a]
		Total (n=139)	Pneumonia group (n=89)	Non pulmonary group (n=50)	
Consolidation	8 (25)	105 (76)	85 (95)	20 (40)	<0.001
Pleural effusion	7 (22)	35 (25)	12 (13)	23 (46)	1.00
GGO	30 (96)	49 (35)	36 (40)	13 (26)	<0.001
Diffuse area	25	30	22	8	0.08[b]
Intralobular line	14	35	29	6	<0.05[b]
Intralobular septa thichening	7	31	21	10	<0.001[b]
Traction bronchiectasis	22	6	6	0	<0.001[b]
Dominant distribution of GGO					
Non-segmental	15	7	7	0	<0.005[b]
Peribronchovascular bundle/perivascular	13	32	19	13	0.06[b]
Periconsolidation	1	10	10	0	<0.05[b]
Lung contraction confirmed by CT analysis	19 (61)	4 (3)	4 (4)	0 (0)	<0.001
Lung-contraction rate (%)	22.5 [15-29]	–	39.1 [31-41]	–	–
Non edematous lung injury suspicious lesion	16 (51)	2 (1)	2 (2)	0 (0)	<0.001

549

550 Categorical variables are reported as number (percentages). Continuous
551 variables are reported as median [interquartile range (IQR) 25-75]. For
552 evaluation of dominant characteristics of lung lesion, CT scan performed for
553 initial evaluation after onset, within 48 hours of intubation, was selected for
554 26 patients in ILD group and 139 patients in Infection group. Meanwhile, CT
555 scan at onset, which were performed 7-21 days before ventilation, were
556 selected in remaining cases (6 patients in ILD group). CT computed

tomography, GGO ground-glass opacity, ILD interstitial lung disease.

[a] Infection group vs ILD group, [b] Comparison of the subjects with GGO lesion between Infection group and ILD group.

560 Table 3. Factors associated with irreversibile respiratory failure in this study.

	Withdrawal from ventilation		Multivariate analysis[a]	
	Achieved (n=121)	Impossible (n=49)	AOR (95% CI)	P
Lung contractive change with respiratory failure-progression	4 (13)	26 (87)	32.6 (7.1-150)	<0.001
Interstitial lung disease-dominant respiratory failure	9 (29)	22 (71)	18.4 (4.3-79.1)	<0.001
The presence of NE-LI suspicious lesion	3 (16)	16 (84)	13.3 (2.9-59.7)	<0.001
Multidrug-resistant bacterial/ fungal infection	2 (15)	11 (85)	6.4 (1.3-31.6)	<0.001
Routine corticosteroid use	27 (60)	18 (40)	5.2 (1.9-14)	<0.005
Male	71 (66)	37 (34)	3.2 (1.2-8.6)	<0.05
Complication during mechanical ventilation	10 (42)	14 (58)	2.9 (0.9-9.4)	0.06
Age >75	41 (67)	20 (33)	2.6 (1.1-6.5)	<0.05
ARDS Berlin Criteria >severe	22 (61)	14 (39)	2.4 (0.8-6.4)	0.09
Malignant disease	35 (60)	23 (40)	1.9 (0.8-4.8)	0.13
BMI <22 kg/m^2	58 (67)	28 (33)	1.5 (0.6-3.5)	0.33
Chronic respiratory disease	30 (58)	22 (42)	1.2 (0.5-3)	0.63
Hospital-acquired onset	40 (66)	21 (34)	1.0 (0.4-2.7)	0.96
SAPS2 >50	63 (72)	24 (28)	0.85 (0.4-2.1)	0.72
General anesthesia within 1 year	28 (70)	12 (30)	0.7 (0.2-2.2)	0.51
CRP >10 mg/dL	78 (74)	27 (26)	0.4 (0.2-0.9)	<0.05

561

562 Categorical variables are reported as number (percentages). AOR adjusted

563 odds ratio, ARDS acute respiratory distress syndrome, BMI body mass index,

564 CI confidence interval, CT computed tomography, GGO ground-glass opacity,

565 ILD interstitial lung disease, NE-LI non-edematous lung injury, OR odds

566 ratio.

567 [a] Adjusted by age >75, sex (Male), BMI <22 kg/m^2, routine steroid therapy,

present/previous history of malignant disease, chronic respiratory disease, general anesthesia within 1 year, complication during ventilation, in-hospital onset, severe ARDS, SAPS Ⅱ score >50, CRP >10mg/dL.

571 Table 4. The feature of the patients who presented lung contraction with
572 progressive respiratory failure.

	Infectious group (n=7)	ILD group (n=23)	Total (n=30)
ARDS/AIP	7 (100)	15 (65)	22 (73)
Risk factor, insult			
Precedent infection before/at onset			
Bacterial-	4 (57)	8 (35)	12 (40)
Viral-/ pathogen not detected	3 (43)	5 (22)	8 (27)
Pneumocystis-	—	3 (13)	3 (10)
Post-operation or Cancer Chemotherapy	3 (43)	12 (52))	15 (50)
CT feature			
NE-LI suspicious lesion	2 (21)	16 (70)	18 (60)
Lung-contraction confirmed by CT analysis (>10%)	4 (57)	19 (83)	23 (77)
Response to treatment			
Did not response to steroid therapy	6 (86)	10 (43)	16 (53)
Did not response to steroid and IVCY	—	7 (30)	7 (23)
Improved with steroid therapy	0 (0)	2 (9)	2 (7)
Improved with IVCY	—	4 (17)	4 (13)
Improved with rituximab	1 (14)	—	1 (3)
Pattern of Lung-contractive area			
diffuse	4 (57)	16 (70)	20 (67)
partial	2 (21)	7 (30)	9 (30)
consolidation	1 (14)	0 (0)	1 (3)
Time for initial diagnosis of lung-contractive change			
within 2 weeks	1 (1)	5 (22)	6 (20)
2-4 week	4 (57)	18 (78)	22 (73)
>4 week	2 (21)	0 (0)	2 (7)

573

574 Categorical variables are reported as number (percentages). The radiological
575 patterns of lung-contraction were categorized to 'diffuse' and 'partial',
576 according to contracted GGO area. The lung-contraction limited to

577 consolidation area was observed in 1 case in Infection group, which was
578 defined as ‘consolidation’ patterned lung-contraction. AIP acute interstitial
579 pneumonia, ARDS acute respiratory distress syndrome, CT computed
580 tomography, ILD interstitial lung disease, IVCY intravenous
581 cyclophosphamide, NE-LI non-edematous lung injury.

582 Online Depository

583 Supplementary Figure Legend

584 **Lung contractive change in severe acute respiratory failure requiring**

585 **invasive ventilation; a comparison of features between interstitial lung**

586 **disease and severe infection**

587 Kentaro Nagaoka,[1]* Yu Yamashita,[1] Akira Oguma,[1] Hirokazu Kimura,[1]

588 Kaoruko Shimizu,[1] Masaru Suzuki,[1] Satonori Tsuneta,[2] Noriko Oyama-

589 manabe,[2] Ryo Takagi,[3] Isao Yokota,[3] Hitoshi Saito,[4] Takeshi Wada,[4] Hiroki

590 Kato,[4] Yuji Morimoto,[4] and Satoshi Konno.[1]

591

592 [1]Department of Respiratory Medicine, [2]Department of Diagnostic and

593 Interventional Radiology, [3]Department of Biostatistics, [4]Department of

594 Anesthesiology and Critical Care Medicine, Faculty of Medicine and

595 Graduate School of Medicine, Hokkaido University, Hokkaido, Japan.

596

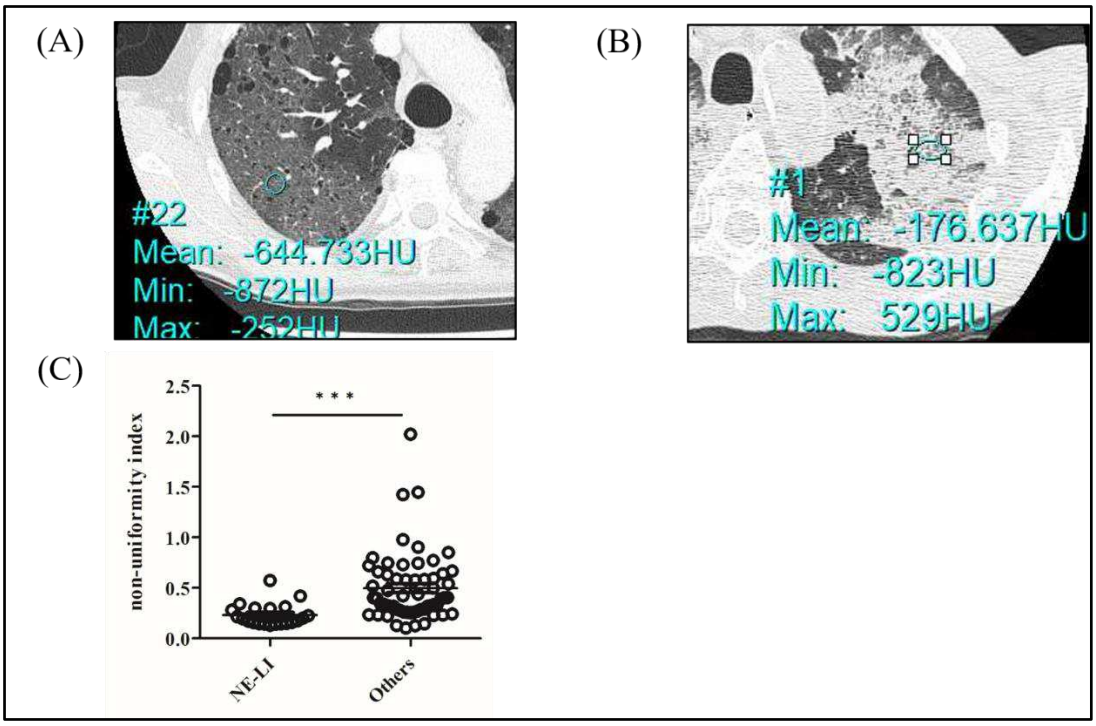
597 *Correspondence and requests for reprints should be addressed to Kentaro

598 Nagaoka, Department of Respiratory Medicine, Hokkaido University

599 Hospital, Japan. E-mail: knagaoka@med.hokudai.ac.jp

600 **Supplemental Figure**

601 Figure S1



602
603

604 Fig S1. Representative manifestation of non-edematous lung injury (NE-LI)

605 suspicious lesion (A). The regions of interest were manually selected from the

606 representative area of GGO; non-uniformity index = 0.17. The manifestation

607 of GGO lesion, which did not correspond to NE-LI (B); non-uniformity index

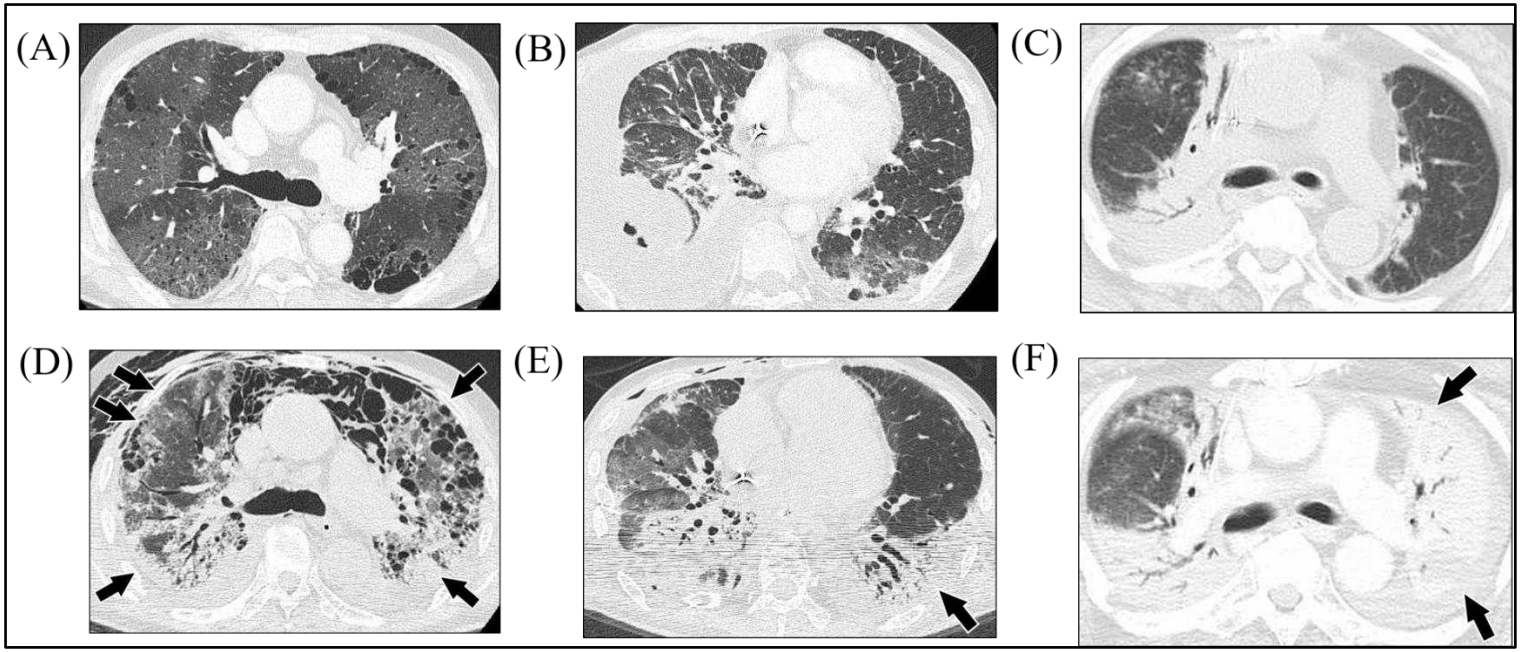
608 = 1.4. Non-uniformity index (dispersions of GGO density) in NE-LI suspicious

609 lesion compared with those in the other GGO area (C). Statistically

610 significant differences are indicated as follows: **, $P < 0.005$.

611

612 Figure S2



613

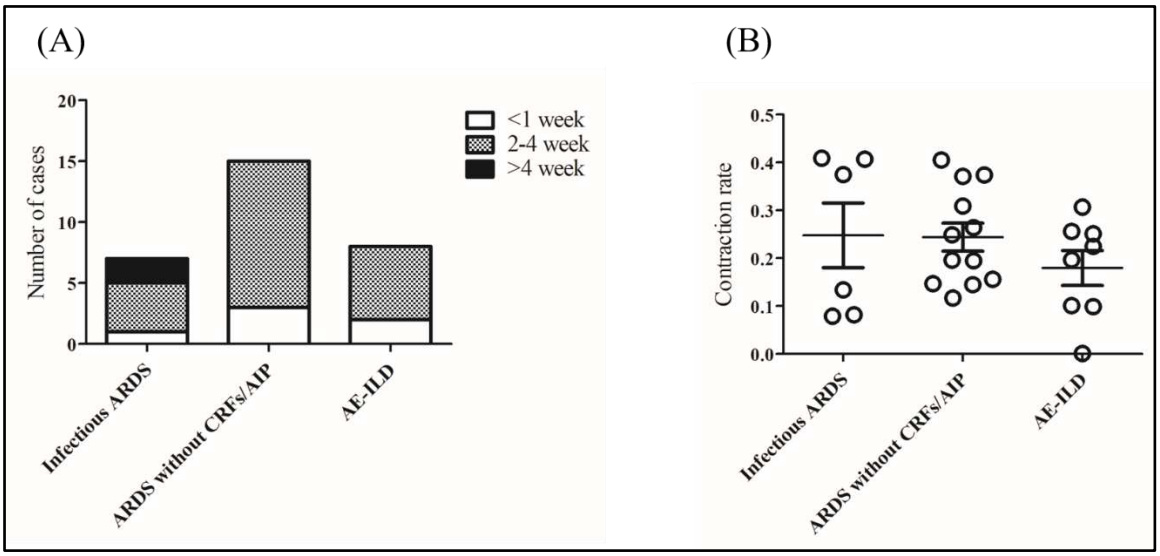
614 Fig S2. Representative manifestation of lung contractive change; diffuse (A, D), partial (B, E), and consolidation pattern

615 (C, F). Contraction was determined with distinct CT findings, appearance of reduction of aeration area and appearance

616 of traction bronchiectasis, in comparison between CT manifestation performed at onset (A-C) and during the follow-up

617 period (D-F).

618 Figure S3



619

620 Fig S3. The time for initial diagnosis of lung contractive change (A) and lung
621 contraction rate among ARDS due to infection, ARDS without CRFs/AIP and
622 AE-ILD. Abbreviations: AE-ILD, acute exacerbation of interstitial lung
623 disease; AIP, acute interstitial pneumonia; ARDS, acute respiratory distress
624 syndrome; CRFs, common risk factors.

625

Supplemental Table

Table Supple 1. Clinical diagnosis of Interstitial lung disease group in this study.

Clinical diagnosis of ILD group	Total n=31
ARDS without CRFs/ AIP	n=22 (71)
Post-operative	10
Cancer chemotherapy-induced	7
Drug induced (other than cancer chemotherapy)	2
Post-infection	2
Post-burn	1
Acute exacerbation of previously known ILD	n=9 (29)
UIP	2
NSIP	1
IPAF	3
RA-related ILD	1
PPFE	1
iLIP	1

Categorical variables are reported as number (percentages). A patient who developed acute respiratory failure after burn was included for AIP, because respiratory condition exacerbated after 2 weeks from burn, which was unusual course of typical ARDS due to burn. AIP acute interstitial pneumonia, ARDS Acute respiratory distress syndrome, CRFs common risk factors, ILD interstitial lung disease, iLIP idiopathic lymphatic interstitial pneumonia, IPAF interstitial pneumonia with autoimmune features, NSIP nonspecific interstitial pneumonia, PPFE pleuroparenchymal fibroelastosis, RA-related ILD rheumatoid arthritis related interstitial lung disease, UIP usual interstitial pneumonia.

639 Table Supple 2. Clinical diagnosis of Infectious pneumonia group in this study.
640

Types of pneumonia	total n=89
CAP	48 (54)
NHCAP	11 (12)
HAP	30 (34)
Dominant causative pathogen	
Bacteria	n=54 (61)
Streptococcus pneumoniae	14
Enterobacteria (*Escherichia coli* + *Klebsiella* spp.)	15
Staphylococcus aureus (MSSA/MRSA)	6
Pseudomonas aeruginosa	7
Hemophilus influenzae	3
Mycoplasma pneumoniae	2
Other bacteria	7
Virus	n=10 (11)
Influenzae virus	8
Cytomegalovirus	2
Fungus	n=3 (3)
Aspergillus fumigatus	3
The others	n=3 (3)
Pneumocystis jirovecii	3
Pathogen not detectable	n=20 (22)

641

642 Categorical variables are reported as number (percentages). CAP community-
643 acquired pneumonia, HAP hospital-acquired pneumonia, MRSA methicillin-
644 resistant *Staphylococcus aureus*, MSSA methicillin-susceptible
645 *Staphylococcus aureus*, NHCAP Nursing and HealthCare Associated
646 Pneumonia.

647 Table Supple 3. Clinical diagnosis of Non pulmonary infection group in this
648 study.
649

Type (Location) of infection	total n=50
Urinary tract	18 (36)
Enteral/intra-peritoneal	15 (30)
Hepatobilliary/pancreatic	8 (16)
Necrotizing fasciitis/endocarditis	1 (2)
Lateral cervical abscess	1 (2)
Focus unknown (bacteremia)	7 (14)
Dominant causative pathogen	
Escherichia coli + *Klebsiella* spp.	21 (42)
Enterobacteria (*Salmonella* spp., *Citrobacter* spp., *Serratia* spp., *Enterobacter* spp., *Providencia* spp.)	10 (20)
Obligate anaerobe (*Bacteroides* spp., *Clostridium* spp., *Prevotella* spp.)	6 (12)
Gram-positive bacterium (*Streptococcus* spp., *Enterococcus* spp., *Staphylococcus* spp.)	8 (16)
Pathogen not detectable	5 (10)

650
651 Categorical variables are reported as number (percentages).
652

653 Table supple 4. Factors associated with in-hospital mortality in this study.
654

	In-hospital mortality		Multivariate analysis[a]	
	Alive (n=120)	Dead (n=50)	AOR (95% CI)	P
Lung contractive change with respiratory failure-progression	8 (27)	22 (73)	16.9 (4.6-60)	<0.001
Interstitial lung disease-dominant respiratory failure	12 (40)	18 (60)	13.3 (3.3-52)	<0.001
Multidrug-resistant bacterial/ fungal infection	1 (8)	12 (92)	12.8 (2.4-68)	<0.001
Routine corticosteroid use	16 (46)	19 (54)	6.92 (2.5-18)	<0.005
The presence of NE-LI suspicious lesion	7 (37)	12 (73)	4.91 (1.3-17)	<0.005
Complication during mechanical ventilation	11 (44)	14 (56)	3.7 (1.3-11)	<0.05
SAPS2 >50	31 (61)	20 (39)	2.4 (1-5.5)	<0.05
ARDS Berlin Criteria >severe	22 (61)	14 (39)	2.1 (0.8-5.4)	0.13
Malignant disease	34 (59)	24 (41)	1.9 (0.4-2.4)	0.92
Chronic respiratory disease	30 (59)	21 (41)	1.7 (0.7-3.9)	0.21
BMI <22 kg/m^2	56 (64)	31 (36)	1.4 (0.7-3.1)	0.36
Hospital-acquired onset	41 (67)	20 (33)	1.2 (0.5-3)	0.65
Male	73 (69)	33 (31)	1.1 (0.5-2.5)	0.81
Age >75	41 (67)	20 (33)	1.0 (0.4-2.4)	0.92
General anesthesia within 1 year	28 (72)	11 (28)	0.5 (0.2-1.5)	0.21
CRP >10mg/dL	76 (73)	28 (27)	0.5 (0.2-1.1)	0.07

655

656 Categorical variables are reported as number (percentages). AOR adjusted
657 odds ratio, ARDS acute respiratory distress syndrome, BMI body mass index,
658 CI confidence interval, CT computed tomography, GGO ground-glass opacity,
659 ILD interstitial lung disease, NE-LI non-edematous lung injury, OR odds
660 ratio.

661 [a] Adjusted by age>75, sex (Male), BMI<22, present/previous history of

662 malignant disease, chronic respiratory disease, general anesthesia within 1
663 year, complication during ventilation, in-hospital onset, severe ARDS, SAPS
664 Ⅱ score >50, CRP >10mg/dl.
665

Supple Table S5. Histopathological and cytological diagnoses of the patients with lung-contractive change.

Cases	Clinical diagnosis	Lung tissue specimen	Cytological/Histopathological patterns
ILD groups (n=7/23)			
Case 1	AE-ILD (iLIP)	Autopsy	Malignant lymphoma (Hodgkin lymphoma)
Case 2	AIP (chemotherapy induced)	Autopsy	DAD, organizing phase
Case 3	AE-ILD (IPAF)	Autopsy	UIP, IPA
Case 4	AIP (chemotherapy induced)	Autopsy	DAD, organizing phase
Case 5	AE-ILD (UIP)	Autopsy	Pulmonary tumor thrombotic microangiopathy
Case 6	ARDS (post-operative)	Autopsy	DAD, organizing phase
Case 7	ARDS (post-operative)	Autopsy	DAD, organizing phase
Infection group (n=2/7)			
Case 1	ARDS (pneumococcal pneumonia)	Autopsy	DAD, organizing phase
Case 2	ARDS (severe HAP)	OLB	Organizing pneumonia, lung abscess

AE-ILD acute exacerbation of interstitial lung disease, AIP acute interstitial pneumonia, ARDS acute respiratory distress syndrome, DAD diffuse alveolar damage, HAP hospital acquired pneumonia, ILD interstitial lung disease, iLIP idiopathic lymphatic interstitial pneumonia, IPA invasive pulmonary aspergilloma, IPAF interstitial pneumonia with autoimmune features, OLB open lung biopsy, UIP usual interstitial pneumonia.

Figures

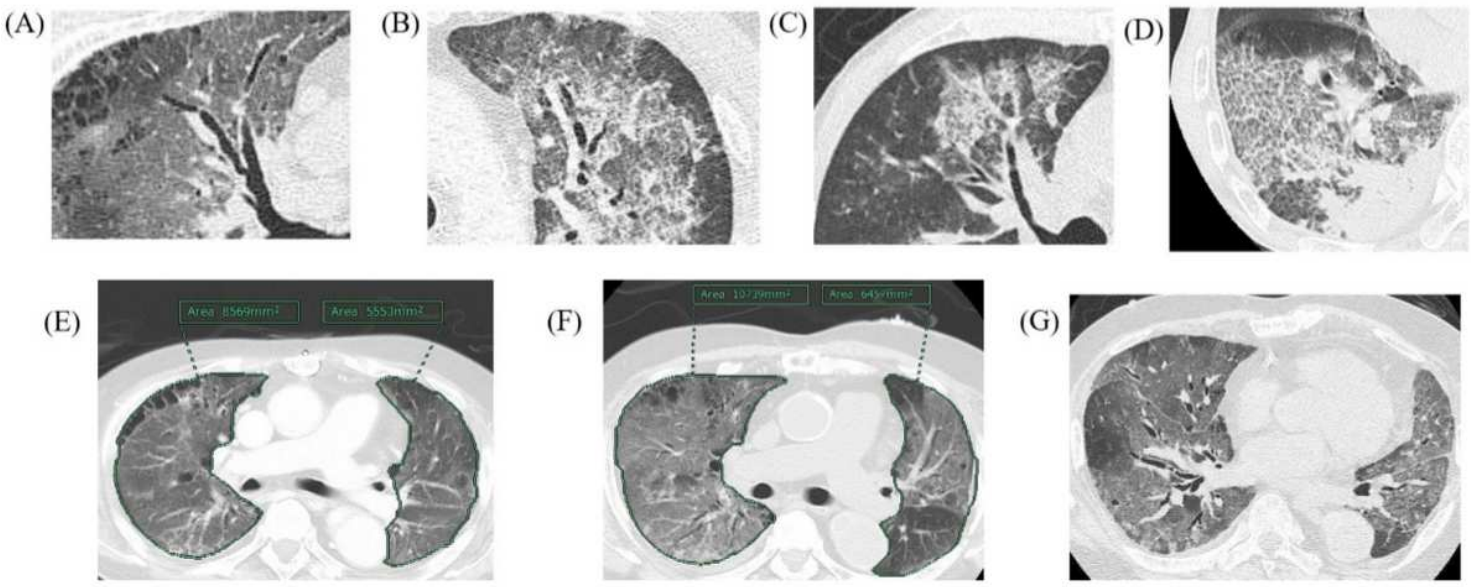


Figure 1

Definition of CT manifestations in this study. Dominant distribution pattern of grand-glass opacity; non-segmental (A), peribronchovascular (B), perivasucular (C), peri-consolidation pattern (D). Quantitative analysis of lung contraction by CT analysis; contraction rate was calculated by the ratio of lung capacity of follow up CT (E) to initial CT (F). Representative manifestation of non-edematous lung injury suspicious lesion (G).

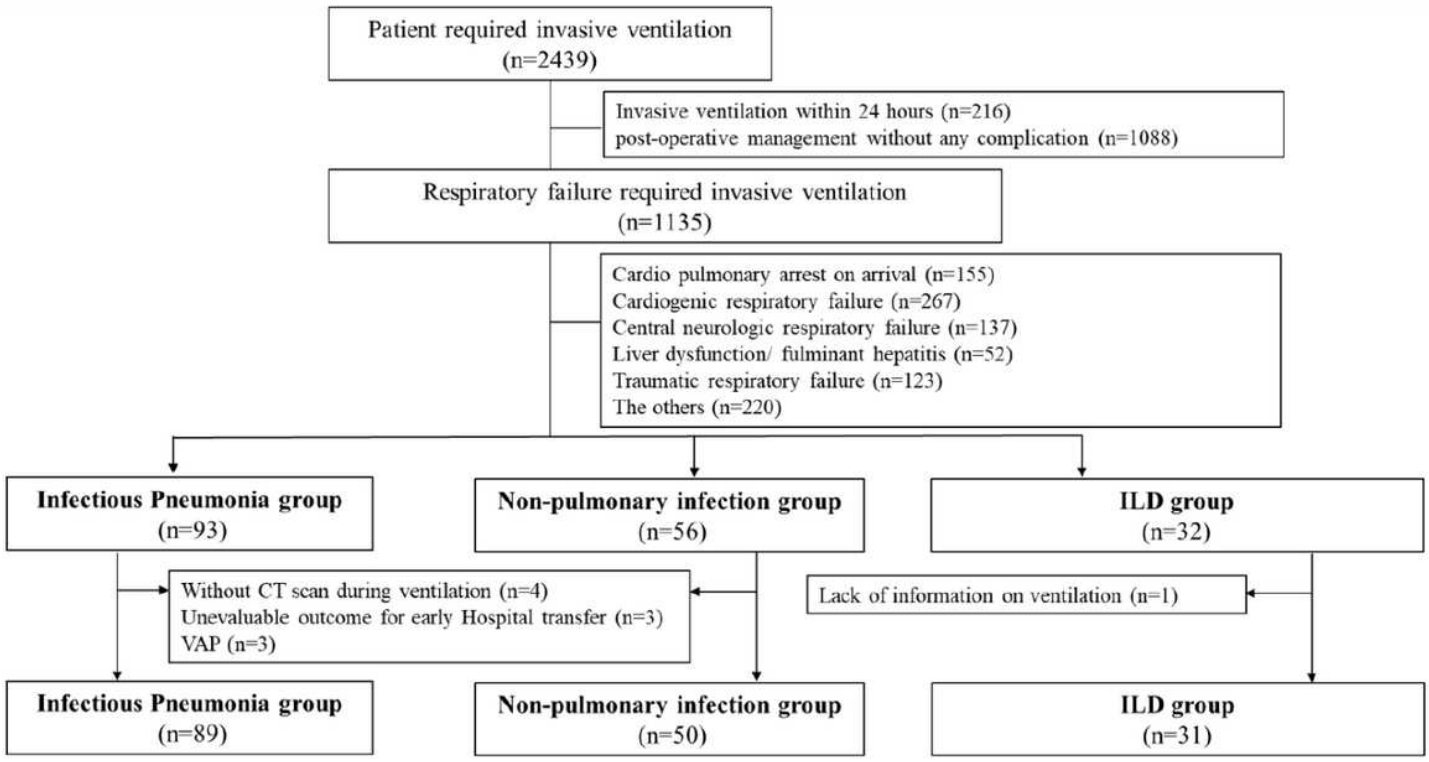


Figure 2

Flow chart illustrating the distribution of patients in this study. Participants were divided into two groups according to the dominant cause of acute respiratory failure; ILD for ILD group or severe infection for Infection group (subdivided with focus of infection into pneumonia group or non-pulmonary group). Abbreviations: CT, computed tomography; ILD, interstitial lung disease; VAP, ventilator-associated pneumonia.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementary.pdf