Serum Heme Oxygenase-1 Measurement is Useful for Evaluating Disease Activity and Outcomes in Patients With Acute Respiratory Distress Syndrome and Acute Exacerbation of Interstitial Lung Disease

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Research article

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Abstract

Background: Oxidative stress plays an important role in acute lung injury, which is associated with the development and progression of acute respiratory failure. Here, we investigated whether the degree of oxidative stress as indicated by serum heme oxygenase-1 (HO-1) is clinically useful for the patients with acute lung injury including ARDS and AE-ILDs.

Methods: Serum HO-1 levels of newly diagnosed or untreated ARDS and AE-ILD patients were measured at diagnosis. Relationships between serum HO-1 and other clinical parameters and 1-month mortality were evaluated.

Results: Fifty-five ARDS (n = 22) and AE-ILD (n = 33) patients were assessed. Serum HO-1 level at diagnosis was significantly higher in ARDS patients than AE-ILD patients (87.8 ± 60.0 ng/mL vs. 52.5 ± 36.3 ng/mL, $P < 0.001$). Serum HO-1 correlated with serum T-bil ($R = 0.454$, $P < 0.001$) and serum LDH ($R = 0.500$, $P < 0.001$). Serum HO-1 level significantly decreased from diagnosis to 2 weeks after diagnosis (81.1 ± 9.3 ng/mL vs. 60.9 ± 52.4 ng/mL, $P = 0.016$), however normalized. Composite parameters including serum HO-1, diagnosis, partial pressure of oxygen in arterial blood/fraction of inspired oxygen ratio, and sex for prediction of 1-month mortality showed a higher AUC (0.932) than did AUCs of a single predictor or combination of two or three predictors.

Conclusion: Oxidative stress assessed by serum HO-1 is persistently high in patients with acute lung injury against intensive treatment. Also, serum HO-1 measurement could be clinically useful for evaluating disease activity and prognosis in patients with ARDS and AE-ILDs.

Background

Acute respiratory distress syndrome (ARDS) is one of the major manifestations of multiple organ failure syndrome and is a leading cause of death in intensive care units (1). Within the clinical course of interstitial lung disease (ILD), an acute exacerbation (AE) can occur at any time and is associated with significant morbidity and mortality (2). Diffuse alveolar damage (DAD) is considered the histological hallmark of the acute phase of ARDS and AE-ILDs, while alternative histological appearances comprise organizing pneumonia, alveolar haemorrhage, and unspecific inflammatory changes (3, 4). The clinical course and rate of progression of ARDS and AE-ILDs are extremely variable among patients. Therefore, biomarkers including symptoms, blood, physiological, radiological, and pathological findings and these combination may be useful in characterizing disease severity and predicting the rate of progression and response to therapies (5, 6).

Oxidative stress plays an important role in the development and progression of lung injuries including ARDS and AE-ILDs (7, 8). Heme oxygenase-1 (HO-1) is a rate-limiting enzyme in heme degradation, and is also called an oxidative stress marker (9). HO-1 expression is induced by various stimuli such as reactive oxygen species, heavy metals, cytokines, and growth factors. HO-1 converts heme into bilirubin, free iron, and carbon monoxide (CO) under the control of the microsomal nicotinamide adenine dinucleotide

phosphate-cytochrome p450 reductase (10). Mumby *et al*. reported that HO-1 protein concentrations are significantly elevated in lung tissue and bronchoalveolar lavage fluid taken from ARDS patients compared with controls, and HO-1 expression contributes to changes in iron mobilization, signalling, and regulation seen in this condition (11). We have also demonstrated the usefulness of measuring serum HO-1 in the diagnosis and prognosis of patients with ARDS and AE-ILDs (12, 13).

In the present study, we investigated whether evaluating the degree of oxidative stress by measuring serum HO-1 is useful for diagnosis and prognosis in patients with lung injury including ARDS and AE-ILDs. Also, we compared the baseline serum HO-1 and its variation during intensive treatment between ARDS and AE-ILDs.

Methods

Study location and patients

This multi-institutional prospective study was performed between 2011 and 2019. We recruited untreated ARDS patients who met the Berlin definition and AE-ILD patients defined as having unexplained worsening of dyspnoea; hypoxaemia or worsening or severely impaired gas exchange; new alveolar infiltrates on radiograph; and absence of an alternative explanation such as infection, pulmonary embolism, pneumothorax, or heart failure from Yokohama City University, Kyoto Prefectural University, and National Defense Medical College Hospital (14-16). In addition, we recruited healthy volunteers among medical personnel of Seamen's Insurance Health Management Center for health examination.

Data collection and blood sampling

Extracted data included age, sex, diagnosis including the causes of ARDS, and 1-month mortality. Blood samples were obtained at the diagnosis of ARDS or AE-ILD from each patient. We measured serum HO-1 along with serum total bilirubin (T-bil; normal range: 0.2–1.2 mg/dL), serum lactate dehydrogenase (LDH; normal range: < 225 U/L), serum C-reactive protein (CRP; normal range: ≤ 0.3 mg/dL), and partial pressure of oxygen in arterial blood/fraction of inspired oxygen (P/F) ratio.

Serum HO-1 enzyme-linked immunosorbent assay (ELISA) measurement

Serum HO-1 levels were measured at the time of ARDS or AE-ILD diagnosis (D0) and 7 (D7) and 14 (D14) days from the diagnosis using the IMMUNOSET® HO-1 (human) ELISA development set (Enzo, Farmingdale, NY, USA), according to the manufacturer's instructions. The details of this ELISA method have been described previously (12). The assay validation was performed reproducibility of ELISA standard curve for serum HO-1, the intra- and inter-assay tests, and the percentage recovery test. We confirmed all of these results were acceptable (12). Control subjects for serum HO-1 levels included 28 healthy, non-smoking adults who had been admitted to the hospital for a medical checkup.

Statistical analysis

Data are expressed as median with mean ± standard deviation (SD). Statistical analysis was performed using JMP11 (SAS Institute, Inc., North Carolina, USA). Group comparisons were made using Wilcoxon's rank-sum test or the chi-squared test, as appropriate. Spearman's correlation coefficients were calculated to assess the relationship between serum HO-1 and other clinical parameters. The applicability of serum HO-1 with or without other clinical parameters in predicting 1-month survival was evaluated using the area under a receiver operating characteristic (ROC) curve (AUC). Survival curves were generated using the Kaplan–Meier method and were compared using the log-rank test. P values < 0.05 were considered significant.

Results

Patients' characteristics

Table 1 shows the clinical characteristics of patients with acute respiratory failure. Among the 55 enrolled patients, 22 were diagnosed with ARDS and 33 were diagnosed with AE-ILDs. The causes of ARDS included infection (n = 14, 60%) and surgery (n = 5, 23%). The diagnosis of ILDs included idiopathic interstitial pneumonias (IIPs; n = 21, 64%) and collagen vascular disease-related interstitial pneumonia (CVD-IP; n = 8, 24%). A significant difference in the 1-month mortality rate was evident between ARDS and AE-ILD patients (48% vs. 9%, respectively, P < 0.001) (Fig. 1).

Baseline serum HO-1 (D0) and other blood biomarkers

As shown in Fig. 2, serum HO-1 levels were significantly higher in ARDS and AE-ILD patients than in control subjects at D0 (P < 0.001). In addition, serum HO-1 levels were significantly higher in ARDS patients than in AE-ILD patients at D0 (87.8 ± 60.0 ng/mL vs. 52.5 ± 36.3 ng/mL, respectively, P < 0.001). As shown in Table 2, serum HO-1 significantly correlated with serum T-bil (R = 0.454, P < 0.001) and LDH (R = 0.500, P < 0.001), but not with serum CRP and P/F ratio.

Variation in serum HO-1 levels (D0, D7, and D14)

Serum HO-1 levels at D0, D7, and D14 were available in 35 of 55 patients (64%). Of these 35 patients, 18 (51%) patients had ARDS and 17 (49%) patients had AE-ILDs. Eight (44%) of the 18 ARDS patients and 3 (18%) of the 17 AE-ILD patients died within a month from diagnosis. As shown in Fig. 3A (all patients), serum HO-1 levels tended to decrease over time, and serum HO-1 levels at D14 were significantly lower than those at D0 (81.1 ± 9.3 ng/mL vs. 60.9 ± 52.4 ng/mL, respectively, P = 0.016). Furthermore, as shown in Fig. 3B and 3C, significant differences were observed between serum HO-1 levels at D0 and D14 in the ARDS group (95.7 ± 61.6 ng/mL vs. 67.8 ± 61.3 ng/mL, respectively, P = 0.041). Although serum HO-1 levels in the AE-ILD group tended to decrease over time, no significant differences were observed between timepoints.

Stepwise multivariate analysis and composite parameters for predicting 1-month mortality

Variables of age, sex, ARDS (vs. AE-ILDs), serum CRP, P/F ratio, and serum HO-1 were assessed using stepwise multiple logistic regression. Diagnosis [hazard ratio (HR), 16.04; 95% confidence interval (CI), 2.717–306.787; P = 0.001], serum HO-1 (HR, 1.013; 95% CI, 1.004–1.024; P = 0.007), and P/F ratio (HR, 0.992; 95% CI, 0.983–0.999; P = 0.021) were identified as significant predictors of 1-month mortality among these patients (Table 3). Moreover, composite parameters including serum HO-1, diagnosis, P/F ratio, and sex for prediction of 1-month mortality showed a higher AUC (0.932) than AUCs of a single predictor (0.767) or combination of two (0.829) or three predictors (0.903) (Fig. 4).

Discussion

Oxidative stress plays an important role in the development and progression of lung injuries including ARDS and AE-ILDs (7, 8). HO-1, a rate-limiting enzyme in heme catabolism, has antioxidative activities in patients with diffuse parenchymal lung disease (17-19). We previously investigated whether evaluating the degree of oxidative stress by measuring serum HO-1 using the sandwich ELISA method is useful for assessing disease activities and predicting prognosis in patients with ARDS and AE-ILDs (12, 13). The present study was an integrated analysis of these. We analyzed the clinical usefulness of serum HO-1 in lung injury patients, and compared the baseline serum HO-1 and its variation during intensive treatment between ARDS and AE-ILDs.

As a protective reaction against oxidative stress, HO-1 protein has been reported to increase in lung tissue including alveolar macrophages, alveolar and bronchial epithelium, interstitium, and endothelium taken from patients with ARDS or AE-ILDs, contributing to the changes in iron mobilization, signalling, and regulation seen in these conditions (11, 13). We found that in the patient with AE of idiopathic pulmonary fibrosis (IPF), high HO-1 expression was observed mainly in alveolar macrophages, while HO-1 expression in fibrotic lesions or alveolar macrophages was not conspicuous in stable IPF (20). In our present case report, autopsy findings of patients with drug-induced ARDS (serum HO-1 = 76 ng/mL at baseline) showed no obvious HO-1 expression in the fibrotic DAD lesion. However, in the active DAD lesion, HO-1 expression was prominent in alveolar macrophages (Fig. S1, Supplementary Information). In addition, serum HO-1 significantly correlated with serum T-bil as the downstream product of active heme metabolism and serum LDH as a marker of cellular damage (21-23). Therefore, we speculate that the mechanism of HO-1 increase in the blood is as follows. High HO-1 expression in the lung, which converts heme to CO, iron, and bilirubin, is introduced into the bloodstream due to its relatively small molecular size (32 kDa), destruction of alveolar structures and enhancement of vascular permeability (24). In the present study, ARDS patients had significantly higher serum HO-1 levels at baseline compared with AE-ILD patients. Furthermore, plasma levels of oxidative stress factors including superoxide dismutase, malondialdehyde, and nitric oxide in patients with sepsis have been reported to significantly increase, which is closely related to organ damage and poor prognosis (25). Taken together, we consider that oxidative stress in ARDS is stronger than that in AE-ILDs, and the oxidative stress intensity could correlate with disease prognosis.

Ongoing and persistent oxidative stress leads to poor prognosis (22, 26). HO-1 is encoded by *HMOX1*, the transcription of which can be induced by a variety of signal transduction pathways that activate different transcription factors. Of these transcription factors, nuclear factor erythroid 2-related factor 2 (Nrf2) is possibly one of the most important regulators of the cellular stress response. Cancer cells with persistent Nrf2 activation often develop Nrf2 addiction and show malignant phenotypes, leading to poor prognoses (26). In patients with ILDs, persistently high ethane levels, a product of lipid peroxidation that has been proposed as a biomarker of oxidative stress, may correlate with poor prognosis (23). In the present study, serum HO-1 levels tended to decrease 2 weeks after the start of treatment in both ARDS and AE-ILD patients. However, HO-1 levels remained persistently elevated. Furthermore, while intravenous corticosteroid therapy is widely used in severe ARDS and AE-ILDs, serum HO-1 levels remained high even in patients treated with intravenous corticosteroids (Fig. S2, Supplementary Information) (27-30). These data suggest that corticosteroid therapy does not effectively reduce oxidative stress in patients with ARDS and AE-ILDs and specific treatments aimed at reducing oxidative stress are important for improving the prognosis of ARDS and AE-ILDs (31, 32).

Composite approaches have been developed using peripheral blood biomarkers and physiological and radiographic measurements to provide more accurate prognostic information (33-35). The acute physiology and chronic health evaluation (APACHE) II score is frequently used to measure disease severity in intensive care unit patients with ARDS (33). The composite scoring system, which is based on serum LDH, Krebs von den Lungen-6, P/F ratio, and extent of abnormal high resolution computed tomography findings, is useful for predicting 3-month mortality in AE-IPF patients (34). We previously demonstrated that the Charlson comorbidity index score, sex, and serum LDH are important for predicting 3-month mortality in AE-ILD patients (35). In the present study, we found that composite parameters including serum HO-1, ARDS diagnosis, P/F ratio, and sex had acceptable AUC for prediction of 1-month mortality in ARDS and AE-ILD patients. In addition, in ARDS patients only, these composite parameters were more accurate for predicting 1-month mortality than the APACHE II score (Fig. S3, Supplementary Information). However, this finding must be confirmed in a multi-centre prospective study.

There are several limitations to this study. First, the study enrolled only a small number of patients from a few institutions. Therefore, our findings need to be confirmed in a multi-centre, prospective study. Second, clinical diagnoses among ARDS and AE-ILD patients were heterogeneous. Future investigation to evaluate the clinical utility of serum HO-1 measurement in patients with each of the clinical diagnoses is needed.

Conclusion

Serum HO-1 may serve as a useful biomarker for evaluating the severity of oxidative stress in patients with acute respiratory failure. Ongoing and persistent oxidative stress leads to poor prognosis in patients with acute respiratory failure. Because serum HO-1 levels were found to be persistently elevated in both ARDS and AE-ILD patients, despite intensive treatment for 14 days, specific treatments aimed at reducing oxidative stress may be important for improving the prognosis of ARDS and AE-ILDs.

Abbreviations

AE, acute exacerbation

APACHE, acute physiology and chronic health evaluation

ARDS, acute respiratory distress syndrome

AUC, area under the ROC curve

CI, confidence interval

CO, carbon monoxide

CRP, C-reactive protein

CVD-IP, collagen vascular disease-related interstitial pneumonia

DAD, diffuse alveolar damage

ELISA, enzyme-linked immunosorbent assay

HO-1, heme oxygenase-1

IIPs, idiopathic interstitial pneumonias

ILD, interstitial lung disease

IPF, idiopathic pulmonary fibrosis

LDH, lactate dehydrogenase

Nrf2, nuclear factor erythroid 2-related factor 2

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

ROC, receiver operating characteristic

SD, standard deviation

T-bil, total bilirubin

Declarations

Ethics approval and consent to participate

All aspects of this research were approved by the Institutional Review Board of Yokohama City University Graduate School of Medicine (approval numbers B170900025 and A181100007). The severely ill condition or deep sedation of ARDS and AE-ILD patients precluded us from obtaining informed consent from the patients themselves. Therefore, informed consent was obtained from the patients' relatives or their legal guardians. Control subjects provided informed consent prior to participation in this study.

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

Ryo Nagasawa and Hara Y were responsible for study conception, design, data analysis, and drafting manuscript; Hara Y and Murohashi K were responsible for acquisition of data; Murohashi K, Aoki A, Kobayashi N, Takagi S, Hashimoto S, Kawana A, Kawana A, and Kaneko T were responsible for drafting and revision of the manuscript.

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Tables

Table 1. Patients' characteristics.

Characteristics	Total patients (n = 55)
Age, y	71.4 ± 9.9
Male sex	37 (73)
Blood biomarkers	
P/F ratio	204.4 ± 89.3
Serum lactate dehydrogenase, U/L	347.0 ± 168.9
Serum haeme oxygenase-1, ng/mL	66.6 ± 49.9
Serum total bilirubin, mg/dL	2.1 ± 5.0
Serum C-reactive protein, mg/dL	12.3 ± 9.3
Causes of acute respiratory failure	
ARDS	23 (40)
AE-ILDs	33 (60)
Aetiology of ARDS	
Infection	14 (60)
Surgery	5 (23)
Others	3 (17)
Diagnosis of ILDs	
IIPs	21 (64)
CVD-IP	8 (24)
Others	4 (12)
Outcome	
1-month mortality	13 (24)

Values are reported as mean ± SD or n (%).

AE, acute exacerbation; ARDS, acute respiratory distress syndrome; CVD-IP, collagen vascular disease-related interstitial pneumonia; IIPs, idiopathic interstitial pneumonias; ILDs, interstitial lung diseases; P/F ratio; partial pressure of oxygen in arterial blood/fraction of inspired oxygen; SD, standard deviation.

Table 2. Relationships between serum HO-1 and other blood parameters

Variables	N	R	95% CI	P
Serum T-bil	54	0.454	0.212–0.644	< 0.001
Serum LDH	55	0.500	0.271–0.676	< 0.001
Serum CRP	55	0.262	−0.004–0.493	0.053
P/F ratio	48	−0.159	−0.424–0.131	0.281

CI, confidence interval; CRP, C-reactive protein; HO-1, haeme oxygenase-1; LDH, lactate dehydrogenase; P/F ratio, partial pressure of oxygen in arterial blood/fraction of the inspiratory oxygen; T-bil, total bilirubin.

Table 3. Multiple stepwise regression analysis of primary predictor of 1-month mortality.

Variable	Odds ratio	95% CI	P
Sex (male vs. female)	3.940	0.681–76.78	0.141
Diagnosis (ARDS vs. AE-ILDs)	7.292	1.173–141.165	0.031
P/F ratio	0.990	0.976–1.102	0.057
Serum HO-1	1.013	1.002–1.024	0.014

AE, acute exacerbation; ARDS, acute respiratory distress syndrome; CI, confidence interval, HO-1, haeme oxygenase-1, ILD, interstitial lung disease; P/F ratio, partial pressure of oxygen in arterial blood/fraction of inspired oxygen, T-bil, total bilirubin.

Figures

Figure 1

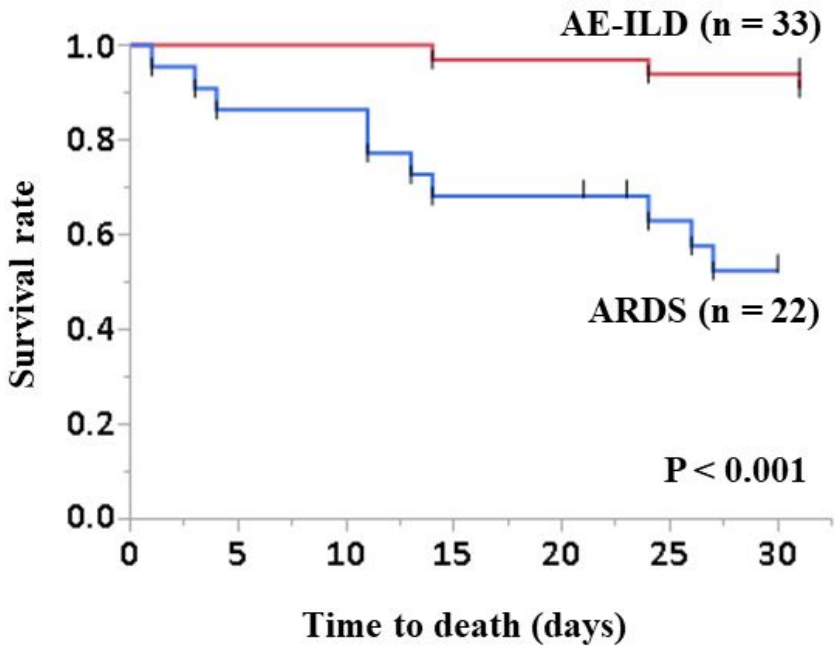

Figure 1

Comparison of 1-month mortality between acute respiratory distress syndrome (ARDS) and acute exacerbation of interstitial lung disease (AE-ILD) patients. Among the 55 enrolled patients with acute respiratory failure, 22 were diagnosed with ARDS, and 33 were diagnosed with AE-ILDs. A significant difference in the 1-month mortality rate was evident between ARDS and AE-ILD patients (48% vs. 9%, respectively, P < 0.001).

Figure 2

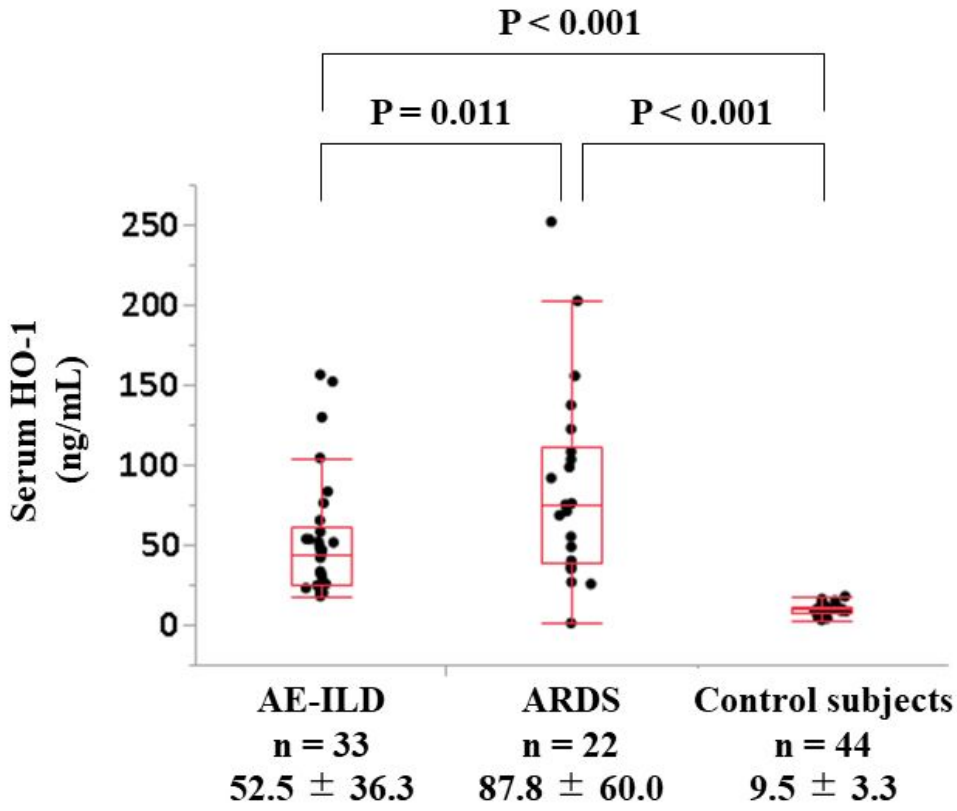

Figure 2

Serum haeme oxygenase (HO)-1 of patients with acute respiratory distress syndrome (ARDS) and acute exacerbation of interstitial lung disease (AE-ILD) patients and control subjects. Serum HO-1 levels at baseline were significantly higher in ARDS (n = 22) and AE-ILD patients than in control subjects (n = 44) (P < 0.001). In addition, mean (± standard deviation) serum HO-1 level was significantly higher in ARDS patients than in AE-ILD patients (87.8 ± 60.0 ng/mL vs. 52.5 ± 36.3 ng/mL, respectively, P < 0.001).

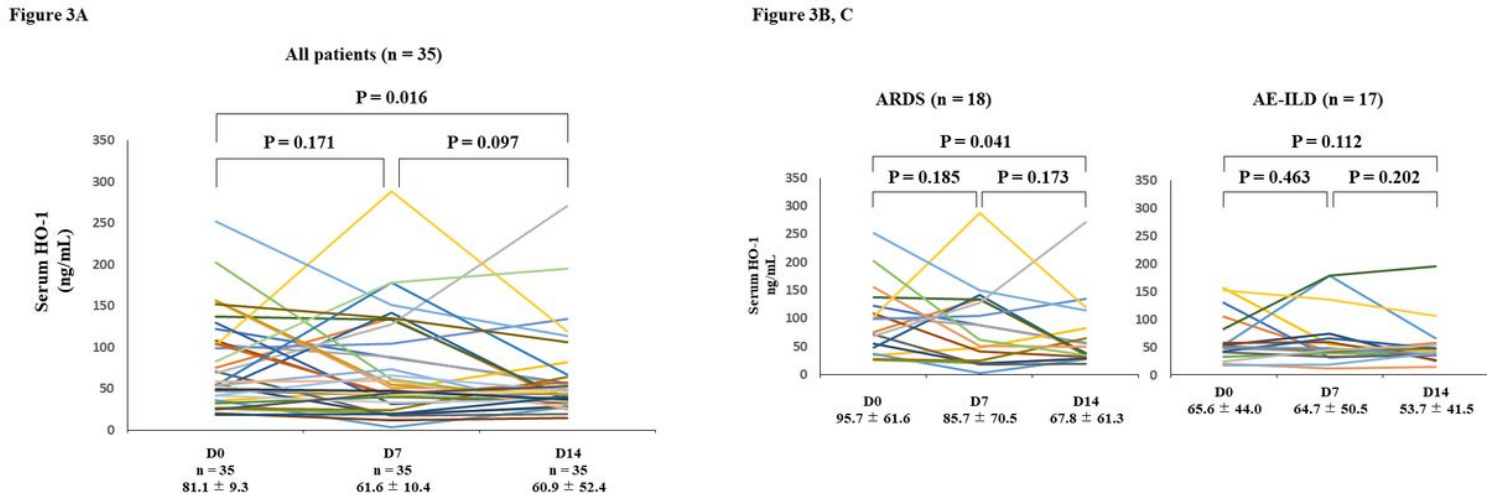

Figure 3

Variation in serum haeme oxygenase (HO)-1 levels in acute respiratory distress syndrome (ARDS) and acute exacerbation of interstitial lung disease (AE-ILD) patients and control subjects. Serum HO-1 levels were measured at the time of ARDS or AE-ILDs diagnosis (D0) and 7 (D7) and 14 (D14) days from the diagnosis. Mean (± standard deviation serum HO-1 levels at D0, D7, and D14 were available in 35 of 55 patients (64%). Of the 35 patients, 18 (51%) had ARDS and 17 (49%) had AE-ILDs. Eight (44%) of the 18 ARDS patients and 3 (18%) of the 17 AE-ILD patients died within a month from diagnosis. As shown in A (all patients), serum HO-1 at D0, D7, and D14 tended to decrease, and serum HO-1 levels at D14 were significantly decreased compared with those at D0 (81.1 ± 9.3 ng/mL vs. 60.9 ± 52.4 ng/mL, respectively, P = 0.016). Furthermore, as shown in B and C, significant differences were observed between serum HO-1 levels at D0 and D14 in the ARDS group (95.7 ± 61.6 ng/mL vs. 67.8 ± 61.3 ng/mL, respectively, P = 0.041). While serum HO-1 levels of the AE-ILD group tended to decrease, these differences were not significant.

Figure 4

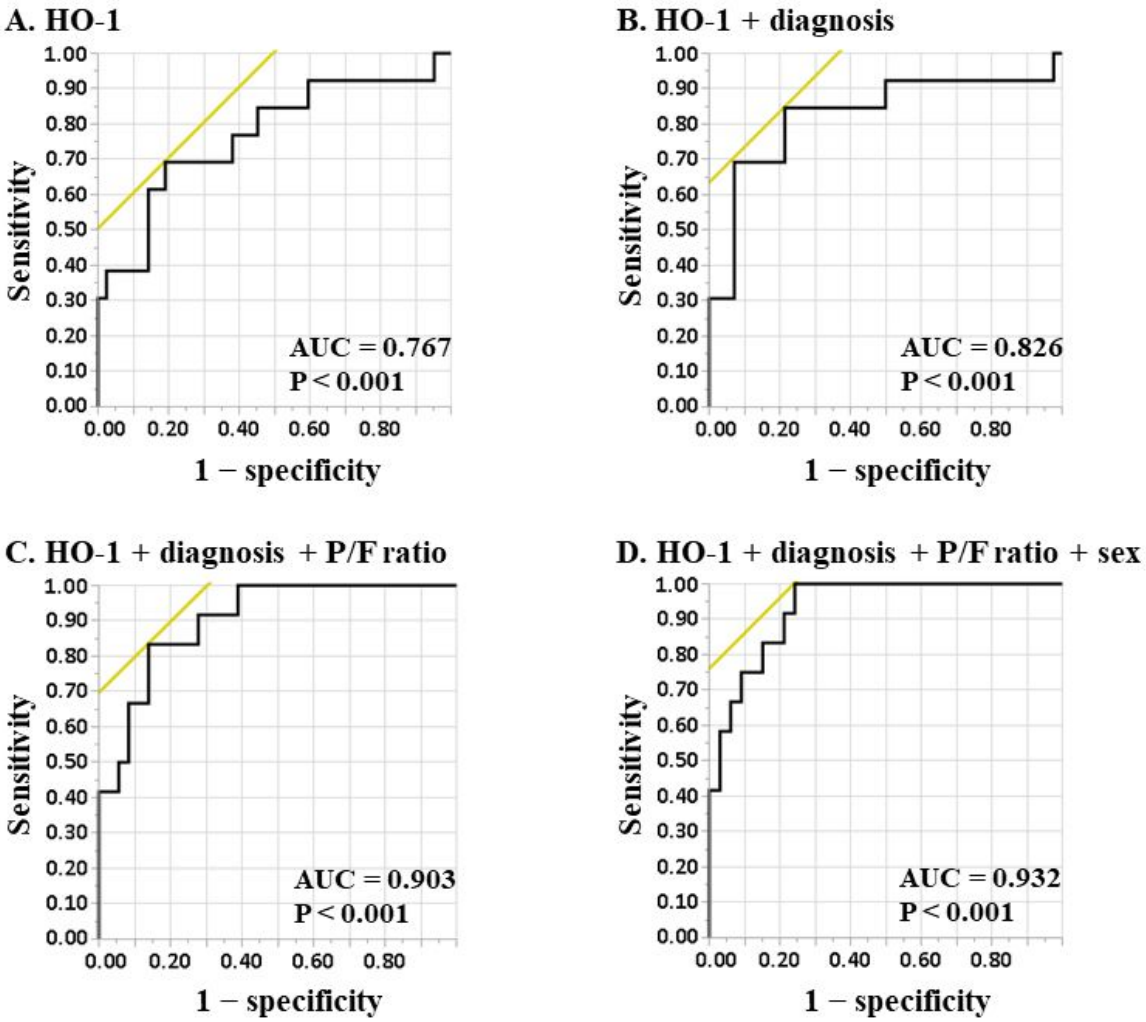

Figure 4

Analysis of receiver operating characteristic (ROC) curves to predict 1-month mortality. Composite parameters including serum haeme oxygenase (HO-1), diagnosis (acute respiratory distress syndrome or not), partial pressure of oxygen in arterial blood/fraction of inspired oxygen (P/F) ratio, and sex for prediction of 1-month mortality showed a higher area under the ROC curve (AUC) than did AUCs of a single predictor or combination of two or three predictors.

Supplementary Files

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- renameda3e02.PNG
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