Potential interaction between sepsis and acute respiratory distress syndrome and effect on the 6-month clinical outcomes: A preliminary secondary analysis of a prospective observational study

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Abstract

Background The effect of the interaction between sepsis and acute respiratory distress syndrome (ARDS) on the clinical outcomes is unclear. Therefore, this study aimed to investigate the effect of the potential interaction between the two conditions on mortality and the occurrence of post-intensive care syndrome (PICS). Methods This secondary analysis of a prospective multicenter observational study included patients who were expected to receive mechanical ventilation for more than 48 h. Patients were stratified based on the incidence of sepsis and further subdivided according to the presence of ARDS. The primary endpoints for patients whose follow-up information was available included mortality (n=162) and the occurrence of PICS (n=96) at six months. The diagnosis of PICS was based on any of the following criteria: (1) decrease ≥ 10 points in the physical component score of the 36-item Short Form (SF36) questionnaire; (2) decrease ≥ 10 points in the mental component score of the SF-36; or (3) decline in the Short Memory Questionnaire (SMQ) score and SMQ score < 40 at six months after ICU admission. We conducted multivariate logistic regression analyses to assess the effect of the potential interaction between ARDS and sepsis on the 6-month clinical outcomes. Result The mortality in the ARDS sub-group was higher than that in the non-ARDS subgroup [47% (7/15) versus 21% (18/85)] in the non-sepsis group. However, the mortality in the ARDS and non-ARDS subgroups was similar in the sepsis group. Multiple logistic regression analyses revealed that ARDS was significantly associated with mortality in the non-sepsis group (adjusted OR: 5.25; 95% CI: 1.45–19.09; p = 0.012), but not in the sepsis group (P-value for the interaction=0.087). Multiple logistic regression analyses showed ARDS was not associated with PICS occurrence in the non-sepsis and sepsis groups (P-value for the interaction=0.039). Conclusions Our findings suggested that the effect of ARDS on the 6-month outcomes depended on the presence or absence of sepsis. The findings of this hypothesis-generating study should be validated by future studies.

Background

Long-term outcomes have gained more importance with the improvement in the short-term mortality in patients admitted to the intensive care unit (ICU)[1–3]. Follow-up data have revealed that critically ill survivors are at an increased risk for severe disability as well as long-term mortality[1–6]. New or worsening physical, cognitive, or mental health problems that occur after critical illness and persist beyond acute hospitalization are termed as post-intensive care syndrome (PICS)[7]. Exploring and implementing interventions during and after ICU admission that are directed toward preventing PICS constitute an urgent issue for all medical personnel involved in intensive care. The first essential step in this endeavor is to identify patients who are at a high risk for developing PICS.

Acute respiratory distress syndrome (ARDS) is a life-threatening disease [8]. Moreover, ARDS can result in serious sequelae[9] and is considered to be a risk factor for PICS [10]. On the other hand, several studies have shown that ARDS is not independently associated with higher mortality and greater deterioration in the quality of life compared to other critical illnesses[11–14]. Therefore, there exists a controversy regarding whether or not ARDS itself worsens patient prognosis. Furthermore, sepsis is one

of the most common conditions underlying ARDS[9], which is simultaneously recognized as a risk factor for PICS and ARDS[10]. Thus, although sepsis and ARDS are closely related, the interaction effect of these two conditions on the clinical outcomes is unclear.

Therefore, this study aimed to investigate the potential interaction between ARDS and sepsis and its effect on mortality and the occurrence of PICS.

Methods

Study design and setting

This investigation entailed a secondary analysis of the Japanese PICS (J-PICS) study[15], which was a prospective multicenter observational study, conducted at 16 ICUs across 14 hospitals in Japan between April 01, 2019, and September 30, 2019 (UMIN000034072). The J-PICS study included critically ill adult patients who were expected to receive mechanical or non-invasive ventilation for longer than 48 h. The exclusion criteria for the current study were as follows: (1) primary brain injury that was likely to result in a consciousness or cognitive disorder (e.g., traumatic brain injury, subarachnoid hemorrhage, acute stroke, post-cardiac arrest, meningitis, and encephalitis); (2) pre-existing dementia; (3) home ventilation before admission; (4) end-stage cancer; (5) withholding or withdrawal of medical therapy; (6) expected death within 24 h; (7) readmission to the ICU during the study period; (8) patients lacking family members; (9) non-Japanese speakers; and (10) patients who could not be followed-up (e.g., patients who did not live in Japan and/or were homeless). The eligibility criteria were assessed at 8:00 am on the day after admission to the ICU. The patient underwent baseline evaluation with the 36-item Short Form (SF-36) questionnaire and Short-Memory Questionnaire (SMQ) by proxy (4-week recall assessment before the patient's current acute illness) at enrollment.

The institutional review board of each participating hospital approved the protocol and written informed consent was obtained from all patients or authorized surrogates. The J-PICS study has been described in detail previously[15].

Study participants

The mortality-assessment cohort included patients enrolled in the J-PICS study and excluded those who could not be followed up at six months. The PICS assessment cohort included patients who were alive at six months and excluded those who had not completed the SF-36 questionnaire and SMQ.

Data collection

The following baseline data were collected: age, sex, body mass index, Acute Physiology Chronic and Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment score obtained within 24 h of ICU admission, Charlson Comorbidity Index (CCI), Clinical Frailty Scale, do not attempt resuscitation status at ICU admission, duration of education, employment status (student, employed or self-employed, unemployed, homemaker, retired), marital status (married, separated or divorced, widowed, unmarried),

residential living arrangement (lived alone at home, lived with someone else, nursing home), Physical Component Scale (PCS), Mental Component Scale (MCS), SMQ before ICU admission, sepsis (diagnosed on the basis of Sepsis-3[16]), ARDS (diagnosed on the basis of the Berlin definition[17]), prescription of benzodiazepines, prescription of steroid, source of ICU admission (emergency department, hospital floor, another hospital, operating room after elective surgery, operating room after emergency surgery), and primary diagnosis at ICU admission (cardiogenic, acute respiratory failure, infection, trauma, etc.). The PCS and MCS are components of the SF-36 questionnaire. Moreover, we recorded treatment-related data in the ICU, including vasopressor use, paralytic agent use, renal replacement therapy, extracorporeal membrane oxygen, intra-aortic balloon pump, and tracheostomy. We also collected data related to the following outcomes: delirium during the first four days, duration of invasive mechanical ventilation, length of ICU stay, ICU mortality, duration of hospitalization, in-hospital mortality, outcome at hospital discharge (death, shifting to another facility, or nursing home, or returning home), six-month mortality, and PICS occurrence at six months.

Exposure and outcome measures

Patients were divided into the sepsis and non-sepsis group, depending on the presence or absence of sepsis, respectively. They were further subdivided into the ARDS and non-ARDS subgroups, according to the presence or absence of ARDS, respectively.

The six-month mortality was the primary outcome for the mortality-assessment cohort. The occurrence of PICS at six months was the primary outcome for the PICS-assessment cohort. The diagnosis of PICS was based on any of the following criteria: (1) decline in physical status defined as a decrease of ≥ 10 points in the PCS score; (2) decline in mental status defined as a decrease of ≥ 10 points in the MCS; or (3) cognitive function impairment defined as a decline in the SMQ score and SMQ score < 40 six months after ICU admission. A 10-point change was considered clinically meaningful in the ICU setting, as per a previous study[15].

The SF-36 questionnaire is a comprehensive 36-item survey that assesses the health-related quality of life (HRQOL) using two summary scales, the PCS and MCS, with scores ranging from 0 to 100. The higher the score, the better the mental and physical function. Both scales were transformed into a normalized scale using norm-based scoring: 50 points were designated as the mean of the population and 10 points as one standard deviation. We treated the scores according to the standard methods[18]. Missing data were processed using standard methods. If a patient responded to more than half of the subscale, the missing data were replaced by the mean of the subscale. On the other hand, we invalidated the responses if the patient answered less than half of items in the subscale[18]. The SMQ is an a 12-item instrument with scores ranging from 4 to 46 that is used to assess cognitive function[19]. It is the only proxy-completed questionnaire that has been translated and validated in Japanese[20,21]. The responses to the SF-36 questionnaire and SMQ were obtained from the patients or their proxies at six-month follow-up via mail.

Statistical analysis

Continuous variables were expressed as the median and interquartile range, and compared using the Mann–Whitney *U* test. Categorical variables were expressed as numbers with percentages, and compared using the Fisher's exact test.

We divided the participants into the sepsis and non-sepsis groups. Patients in the sepsis and non-sepsis groups were further subdivided into the ARDS and non-ARDS subgroups, respectively, and their baseline characteristics, management, and outcomes were compared. We conducted multivariate logistic regression analyses to examine the association between ARDS and the 6-month outcomes between patients with or without sepsis. The APACHE II and CCI scores were adjusted for the logistic regression analysis of 6-month mortality, while the Clinical Frailty Score and education period > 9 years were adjusted for PICS. These factors were chosen based on clinical persuasion and a previous study[15]. The potential interaction between sepsis and ARDS was calculated by adding an item (sepsis * ARDS) to each logistic regression analysis. Except for the SF-36 questionnaire data, the missing data were imputed using the R package "mice." We created 50 datasets and integrated each result according to Rubin's rule.

Two-sided P-values of less than 0.05 were considered statistically significant. All statistical analyses were conducted using R (version 4.0.3).

Results

A total of 192 patients were registered with the J-PICS study. Thirty patients were excluded from the mortality-assessment cohort due to loss to follow-up. Furthermore, 48 and 18 patients were excluded from the PICS-assessment cohort due to death at six months and incomplete SF-36 questionnaire or SMQ, respectively (Figure 1).

Sixty-two (38%) of the 162 patients enrolled in the mortality-assessment cohort developed sepsis. ARDS was observed in 15 patients (15%) in the non-sepsis group and 17 patients (27%) in the sepsis group. The baseline characteristics, ICU management, and outcomes of patients with and without ARDS were almost similar in the non-sepsis and sepsis groups (Table 1), with the exception that paralytic agents were frequently administered to patients who developed ARDS.

The results of multiple logistic regression analyses for 6-month mortality are summarized in Figure 2. The odds ratio (OR) of 6-month mortality for the development of ARDS was significant in the non-sepsis group [adjusted OR: 5.25; 95% confidence interval (CI): 1.45–19.09; $p = 0.012$], but not in the sepsis group (adjusted OR: 0.82; 95% CI: 0.22–3.08; $p = 0.767$). The OR for the interaction was 0.21 (95% CI: 0.03–1.26; $p = 0.087$).

Thirty-one (32%) of the 96 patients enrolled in the PICS-assessment cohort developed sepsis. ARDS was observed in 8 patients (12%) in the non-sepsis group and 9 patients (29%) in the sepsis group. The baseline characteristics, ICU management, and outcomes stratified by sepsis and ARDS are summarized in Table 2. Patients who developed ARDS were treated with extracorporeal membrane oxygen more

frequently than those who did not have ARDS in the non-sepsis group. There was a significant difference in the source of ICU admission in the sepsis group.

The features of PICS are illustrated in Figure 3. No significant differences were observed with respect to PICS, each component of PICS, and concomitance of PICS in the non-sepsis and sepsis groups.

Figure 4 depicts the results of the multiple logistic regression analyses for PICS. The ORs of PICS for the development of ARDS was not significant in the non-sepsis (adjusted OR: 0.47; 95% CI: 0.10–2.31; $p = 0.350$) and sepsis groups (adjusted OR: 9.56; 95% CI: 0.80–114.69; $p = 0.073$). However, the P-value for interaction was 0.039 (adjusted OR: 20.00; 95% CI: 1.17–339.80).

Discussion

Key findings

We assessed the interaction effect between sepsis and ARDS on the 6-month outcomes in this secondary analysis of a previous multicenter prospective cohort study. ARDS was associated with a higher risk of mortality in patients without sepsis but not in patients with sepsis. Furthermore, although ARDS was not a significant factor associated with PICS incidence in patients with and without sepsis, the interaction effect reached a substantial level, as patients with sepsis were more strongly affected by ARDS.

Relationship with previous studies

A meta-analysis and systematic review found that ARDS was associated with a higher risk of mortality[22]. Additionally, a retrospective analysis of two prospective sepsis cohorts showed the same association[23], which differed from our findings in patients with sepsis. This discrepancy may be attributed to the differences in the timing of outcome assessment. The previous study's primary endpoint[23] was in-hospital mortality, and the median length of hospitalization was approximately 8 days. The median length of ICU stay was 8 days in patients with sepsis in this study, and although not statistically significant, ICU mortality was considerably higher in the ARDS group than that in the non-ARDS group (24% versus 9%, Table 1). Subsequently, the 6-month mortality, which was our primary endpoint, was substantially higher than ICU mortality, even in the non-ARDS group, although the difference was insignificant between the ARDS and non-ARDS subgroups in our sepsis cohort (35% versus 38%). Previous studies have observed high long-term mortality in patients with sepsis[24–28], implying that the long-term mortality rate of sepsis itself, with or without ARDS, is high. Therefore, we believe that the effect of ARDS on the 6-month mortality in patients with sepsis was weaker than that in those without sepsis and did not attain statistical significance.

A few studies have explored whether critically ill survivors who developed ARDS had worse long-term outcomes than those who did not have ARDS[13,14,29]. A prospective cohort study showed that ARDS was significantly associated with a reduction in the quality of life in patients with sepsis[29],

consistent with our results in patients with sepsis. On the other hand, that study found the same association in patients without sepsis[29], which is inconsistent with our results. However, while the non-sepsis cohort in this prior study included only trauma patients, we included a variety of patients without sepsis, and trauma patients accounted for only 17% of the non-sepsis cohort. This difference in patient population may have been responsible for the differences in the results. Two other studies did not find an association between ARDS, and a reduced quality of life and functional status[13,14]. The proportion of patients with and without sepsis included in these studies is unknown, making it difficult to determine whether their results support or differ from our results. Our results showed that the effect of ARDS on the incidence of PICS in non-sepsis patients was lower than that in sepsis patients. Although the precise reason is unclear, it may be attributed to survival bias. While the mortality rates were similar in the ARDS and non-ARDS subgroups in the sepsis group (35% versus 38%), the mortality in the ARDS subgroup was more than twice that in the ARDS subgroup (47% versus 21%) in the non-sepsis group. It is possible that vulnerable patients did not survive, and therefore, the difference in the PICS incidence between patients with and without ARDS in the non-sepsis cohort did not attain significance. Conversely, if future interventions to reduce mortality in ARDS are discovered, the incidence of PICS would probably appear to rise, because the number of patients in a vulnerable state would increase, despite the increase in survival.

Significance and implications

The principal findings of the current study have important implications for the management of critically ill patients after ICU discharge. The association of ARDS with the 6-month outcomes depended on the presence or absence of sepsis. The development of ARDS was associated with the risk of death at six months in patients without sepsis but not in those with sepsis. However, the development of ARDS might drive a stronger trend toward an increased occurrence of PICS in patients with sepsis than those without sepsis. These findings would clarify the purpose of follow-up and help physicians provide patient-specific management after ICU discharge. For example, more stringent follow-up would be implemented for non-sepsis patients with ARDS to prevent post-ICU death or to prevent PICS in patients with sepsis who developed ARDS. Theoretically, although individualized post-intensive care and therapeutic management that account for the impact of the interaction between sepsis and ARDS on the prognosis could improve clinical outcomes and help redistribute healthcare-related costs efficiently, further studies are needed to establish these protocols.

Strengths and limitations

The strengths of our study are that we used data from a well-managed prospective multicenter study that conducted a baseline assessment of the quality of life, in addition to being the first study to report on the interaction effect between sepsis and ARDS on the 6-month outcomes.

On the other hand, this study also has several limitations. First, this hypothesis-generating study was a secondary analysis of a multicenter prospective cohort study with a relatively small sample size. Thus, although we performed multiple logistic regression analyses, we cannot eliminate the possibility of selection biases and uncontrolled confounding factors. Furthermore, we could not infer the causal

relationship due to the observational nature of the study. Second, although the effect of ARDS on the outcomes may have depended on its severity[22,23], we did not take ARDS severity into account in our analyses. In addition to the effect of the small sample size, differences in ARDS severity that were not identified in this study could have resulted in an unexpectedly higher mortality rate in the non-sepsis ARDS group than that in the sepsis ARDS group. Third, there were no specific management protocols for treatment in the ICU, after ICU discharge, and during outpatient follow-up after hospital discharge. They depended heavily on each physician or each institution, which could have introduced other biases. Fourth, we did not perform multiple follow-up assessments, and changes over time were unknown. However, a systematic review of the recovery trajectory after ICU showed that the HRQOL, cognitive function, and return to work rapidly improved during the first six months[30], whereas the improvement after one year was limited[4,31,32]. Therefore, we deemed that a single follow-up at six months was appropriate for assessing PICS symptoms. Finally, the J-PICS study was conducted only in Japan, and we could not determine whether our findings can be extrapolated to other regions.

Conclusions

Our findings suggested that the effect of ARDS on the 6-month outcomes depended on the presence or absence of sepsis. The findings of this hypothesis-generating study should be validated by future studies.

Abbreviations

ICU: intensive care unit, PICS: post-intensive care syndrome, *ARDS:* acute respiratory distress syndrome, *J-PICS study:* Japanese post-intensive care syndrome study, *SF-36:* 36-item Short Form, *SMQ:* Short-Memory Questionnaire, *APACHE*: Acute Physiology Chronic and Health Evaluation, *CCI:* Charlson Comorbidity Index, *PCS:* Physical Component Scale, *MCS:* Mental Component Scale, *HRQOL:* health-related quality of life

Declarations

Ethics approval and consent to participate

The institutional review board of each participating hospital approved the protocol. Written informed consent was obtained from all patients or authorized surrogates.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

All the authors declare that they have no competing interests.

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Authors' contributions

TO has full access to all the data and takes responsibility for the integrity of the data. Study concept and design: TO, DK; acquisition of data: DK, SF; analysis and interpretation of data: TO, DK, SF, NS, KK, YK; drafting of the manuscript: TO; and critical revision of the manuscript for important intellectual content: TO, DK, SF, NS, KK, YK

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Tables

Table 1 Characteristics and outcomes of the 6-month mortality cohort stratified by sepsis and ARDS

	Non-sepsis group				Sepsis group			
Characteristic	Overall n = 100	No ARDS n = 85	ARDS n = 15	P value	Overall n = 62	No ARDS n = 45	ARDS n = 17	P value
Age, years, median (IQR)	74 65-79	74 60-81	73 67-78	0.84	76 64-83	77 64-84	74 63-79	0.19
Male sex, n (%)	69 (69)	58 (68)	11 (73)	0.77	38 (61)	28 (62)	10 (59)	>0.99
Body mass index, kg/m, median (IQR)	21.6 [a] 19.4-25.0	21.5 [a] 19.5-24.6	23.2 18.9-25.2	0.73	22.3 19.6-24.9	22.6 19.8-25.1	21.2 19.6-23.1	0.46
APACHE II score, median (IQR)	22 17-26	22 16-26	21 18-26	0.93	24 20-31	25 21-28	23 19-31	0.83
SOFA score, median (IQR)	8 5-9	7 5-9	8 5-9	0.95	11 9-13	11 9-13	11 8-14	0.73
Charlson comorbidity index, median (IQR)	1 0-3	1 0-3	1 0-3	0.32	2 0-3	2 1-3	1 0-2	0.28
DNAR status at ICU admission, n (%)	7 (7)	6 (7)	1 (7)	>0.99	6 (10)	5 (11)	1 (6)	>0.99
Prescribed benzodiazepines, n (%)	10 (10)	9 (11)	1 (7)	>0.99	4 (7)	1 (2)	3 (18)	0.059
Prescribed steroid, n (%)	8 (8)	7 (8)	1 (7)	>0.99	13 (21)	11 (24)	2 (12)	0.49
Source of ICU admission, n (%)				0.78				0.008
Emergency department	49 (49)	43 (51)	6 (40)		27 (44)	21 (47)	6 (35)	
Hospital floor	28 (28)	23 (27)	5 (33)		15 (24)	6 (13)	9 (53)	
Another hospital	1 (1)	1 (1)	0 (0)		1 (2)	1 (2)	0 (0)	
Operating room (elective)	3 (3)	3 (4)	0 (0)		0 (0)	0 (0)	0 (0)	
Operating room (emergency)	19 (19)	15 (18)	4 (27)		19 (31)	17 (38)	2 (12)	

Primary diagnosis at ICU admission, n (%)				0.18				0.18
Cardiogenic	20 (20)	18 (21)	2 (13)		4 (7)	3 (7)	1 (6)	
Acute respiratory failure	47 (47)	36 (42)	11 (73)		12 (19)	6 (13)	6 (35)	
Infection	4 (4)	4 (5)	0 (0)		40 (65)	32 (71)	8 (47)	
Trauma	13 (13)	11 (13)	2 (13)		0 (0)	0 (0)	0 (0)	
Others	16 (16)	16 (19)	0 (0)		6 (10)	4 (9)	2 (12)	
Management in ICU								
Vasopressor use, n (%)	74 (74)	63 (74)	11 (73)	>0.99	55 (89)	41 (91)	14 (82)	0.38
Paralytic agent use, n (%)	43 (43)	32 (38)	11 (73)	0.022	24 (39)	13 (29)	11 (65)	0.022
Renal replacement therapy, n (%)	11 (11)	8 (9)	3 (20)	0.36	23 (37)	18 (40)	5 (29)	0.63
Extracorporeal membrane oxygen, n (%)	5 (5)	3 (4)	2 (13)	0.16	2 (3)	0 (0)	2 (12)	0.072
Intra-aortic balloon pump, n (%)	5 (5)	5 (6)	0 (0)	>0.99	1 (2)	0 (0)	1 (6)	0.27
Tracheostomy, n (%)	19 (19)	17 (20)	2 (13)	0.73	8 (13)	6 (13)	2 (12)	>0.99
Outcomes								
Delirium, n (%)	27 (27)	23 (27)	4 (27)	>0.99	24 (39)	19 (42)	5 (29)	0.53
Length of invasive MV, days, median (IQR)	5 3-10	5 2-12	7 5-8	0.19	5 3-10	5 3-7	6 3-11	0.25
ICU length of stay, days, median (IQR)	8 5-13	7 5-14	9 8-10	0.37	8 6-15	8 5-15	9 7-14	0.60
ICU mortality, n (%)	7 (7)	6 (7)	1 (7)	>0.99	8 (13)	4 (9)	4 (24)	0.20
Hospital length of stay, days, median (IQR)	32 19-60	28 18-60	38 28-60	0.28	34 20-62	31 20-53	39 20-73	0.59
Hospital mortality, n (%)	16	12	4	0.25	17	13	4	0.76

	(16)	(14)	(27)		(27)	(29)	(24)	
Outcome at Hospital discharge, n (%)				0.19				0.52
Death	16 (16)	12 (14)	4 (27)		17 (27)	13 (29)	4 (24)	
Another facility	44 (44)	36 (42)	8 (53)		26 (42)	19 (42)	7 (41)	
Nursing home	0 (0)	0 (0)	0 (0)		1 (1.6)	0 (0)	1 (5.9)	
Home	40 (40)	37 (44)	3 (20)		18 (29)	13 (29)	5 (29)	
Six-month mortality, n (%)	25 (25)	18 (21)	7 (47)	0.051	23 (37)	17 (38)	6 (35)	>0.99

ARDS acute respiratory distress syndrome, *IQR* interquartile range, *BMI* body mass index, *APACHE* Acute Physiology Chronic and Health Evaluation, *SOFA* Sequential Organ Failure Assessment, *DNAR* do not attempt resuscitation, *ICU* intensive care unit, *MV* mechanical ventilation

[a] one missing datum

Due to technical limitations, Table 2 is only available as a download in the Supplemental Files section.

Figures

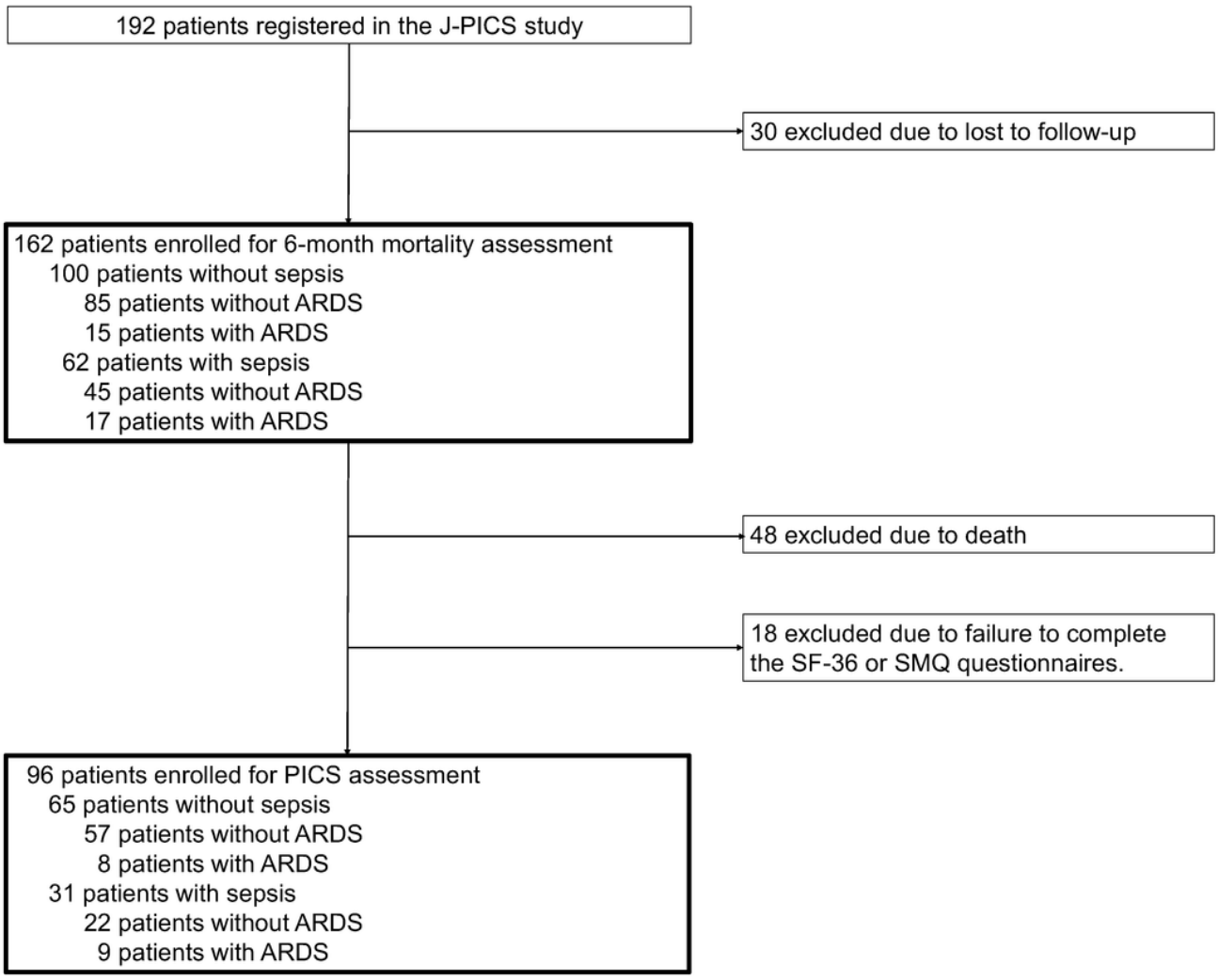

Figure 1

Flowchart showing participant enrollment in the study J-PICS study: the Japanese post-intensive care syndrome study, ARDS: acute respiratory distress syndrome, PICS: post-intensive care syndrome

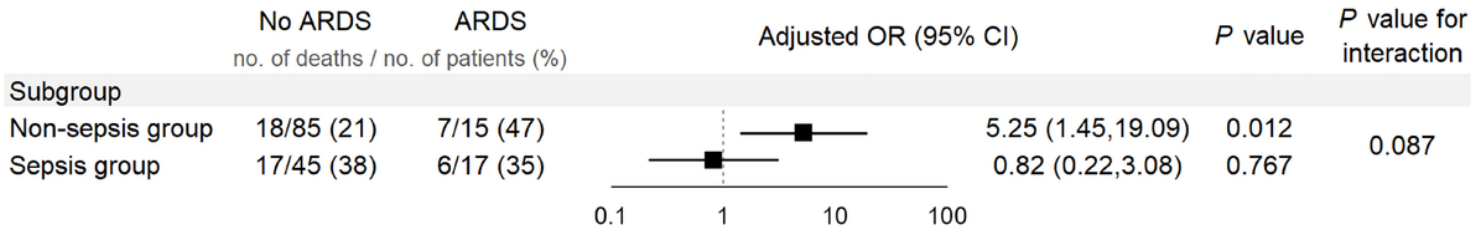

Figure 2

Multivariate logistic regression analyses for 6-month mortality Each multivariate logistic regression analysis was adjusted for the Acute Physiology Chronic and Health Evaluation II score and Charlson comorbidity index.

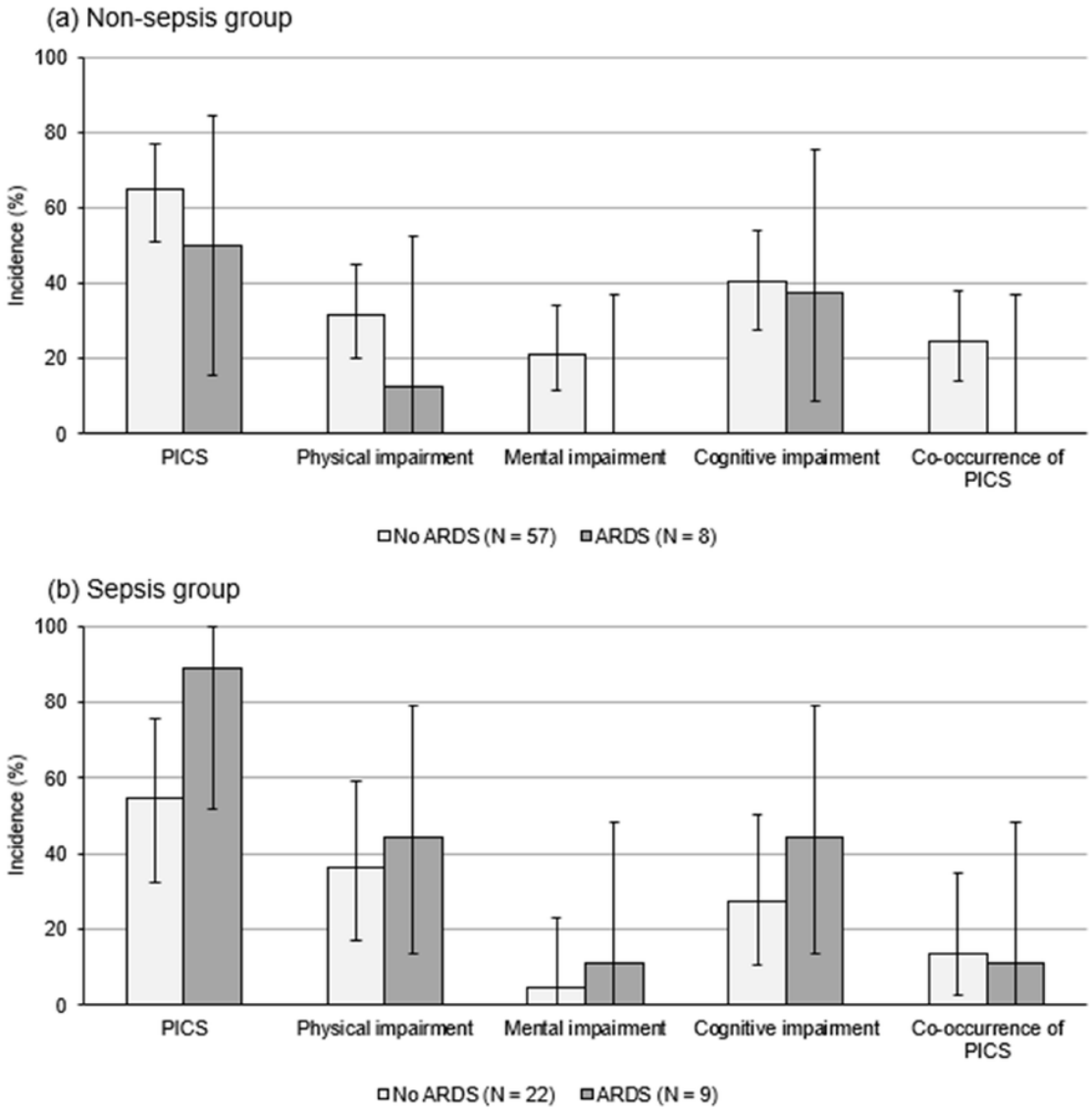

Figure 3

Details of post-intensive care syndrome PICS: post-intensive care syndrome, ARDS: acute respiratory distress syndrome

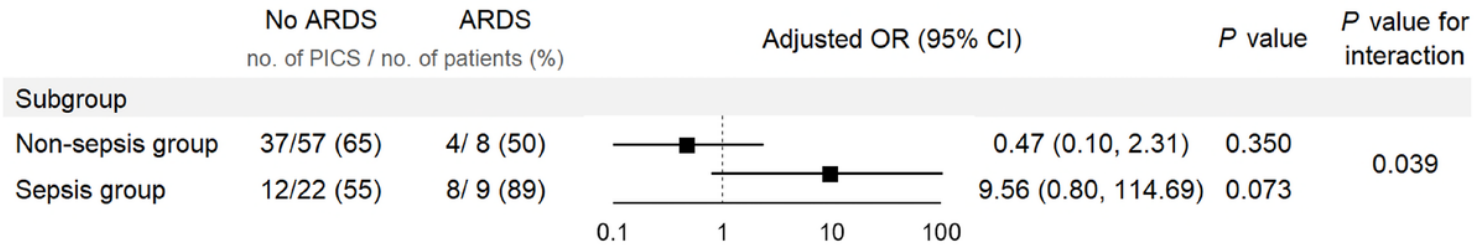

Figure 4

Multivariate logistic regression analyses for post-intensive care syndrome Each multivariate logistic regression analysis was adjusted for the Clinical Frailty Scale and education period >9 years.

Supplementary Files

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

- Table2CharacteristicsandoutcomesofthePICS.docx