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To What Degree Could Clinical Trials in Evidence Based Medicine Reflect The Real World in The Treatment of Pneumonia?

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Abstract

Background

Evidenced based medicine (EBM) is necessary to standardize treatments for infections because EBM has been established based on the results of clinical trials. Since entry criteria for clinical trials are very strict, it may cause skepticism or question whether the results of clinical trials reflect the real world of medical practice.

Methods

To examine how many patients could join any randomized clinical trials for the treatment of community-onset pneumonia, we reviewed all the pneumonia patients in our institute during 2014-2017. The patients were divided into two groups: patients who were eligible for clinical trials (participation possible group), and those who were not (participation impossible group). Exclusion criteria for clinical trials were set based on previous clinical trials.

Results

A total of 406 patients were enrolled in the present study. Fifty-seven (14%) patients were categorized into the participation possible group, while 86% of patients belonged to the participation impossible group. Patients in the participation possible group had less comorbidities and more favorable outcomes than those with the participation impossible group. As for the outcomes, there were significant differences in the 30-day and in-hospital mortality rates between the two groups. In addition, the participation possible group showed a longer overall survival time than the participation impossible group (p<0.001 by *Log-Rank* test).

Conclusion

There is a difference in patients' profile and outcomes between clinical trials and the real world. Though EBM is essential to advance medicine, we should acknowledge the facts and the limits of the clinical trial.

Background

Evidence-based medicine (EBM) aims to assist physicians in making rational decisions in general practices. As EBM is established according to the results of clinical trials, clinical trials are considered to be one of the most important undertakings and are put at the top of priority among physicians in constructing therapeutic strategies [1]. There is no room for doubt that current medicine is based on EBM. However, we skeptically think about that when we consider eligibility of pneumonia patients for EBM guidelines/recommendations in actual practice. Entry criteria for any clinical trial are generally very strict, and most patients might not be suitable for the studies. Thus, it is reasonable to doubt if the results of clinical trials reflect the real world in general practice. We already reported that only 24 % of candidemia patients could be eligible in a clinical trial [2]. Pneumonia remains a leading cause of infection deaths

worldwide [3, 4]. Especially, elderly patients with pneumonia tend to have more comorbidities than young patients and the mortality rate is higher than other groups [4, 5]. We have suspected that there might be a distinct difference of clinical pictures (characteristics) between the patients eligible in the study and those who were excluded from the study and decided to perform this study. This is the first report demonstrating to what degree clinical data on which EBM is based on, reflects the real world patients.

Methods

Study design

Our institute is a 900-bed tertiary care center and is located in the countryside at Aichi prefecture in central Japan. For the purpose of how many community-onset pneumonia patients in our institute could join any randomized clinical trials for the treatment of candidemia, we reviewed all community-onset pneumonia patients who were admitted in our hospital between September 2014 and May 2017. Pneumonia was diagnosed according to the previously published international guidelines [6]. Community-acquired pneumonia (CAP) and healthcare-associated *pneumonia (*HCAP) were categorized based on the criteria published by the American Thoracic Society/ Infectious Diseases Society of America (ATS/IDSA) in 2006 [7,8]. Severity of pneumonia was evaluated by A-DROP [8], CURB-65 [9], Pneumonia Severity Index (PSI) [10], I-ROAD [11] and SOFA score [12]. Comorbidity was evaluated by the Charlson comorbidity index (CCI) [13]. The patients were divided into two groups: patients who were eligible for clinical trials (participation possible group), and those who were not (participation impossible group). Then, patients' characteristics (age, sex), pathogens isolated, clinical outcomes such as the treatments, 30-day, or in-hospital mortality and the reasons of exclusion from the clinical trial were evaluated.

Patient selection

Exclusion criteria commonly used in the many past ordinary clinical trials are as follows; [14-16]

1. Age 18 years, >80 years
2. Coexisting comorbidities or medical conditions which are difficult to evaluate for the pneumonia such as severe liver dysfunction, severe renal dysfunction or HIV/AIDS (Severe liver dysfunction was defined as serum total bilirubin, or aspartate aminotransferase/alanine aminotransferase >the upper limit of the normal reference range×3. Severe renal dysfunction was defined as Creatinine clearance <30ml/min). Unassessable pulmonary diseases include viral pneumonia, pneumocystis pneumonia [17,18], mycobacterium infections, eosinophilic pneumonia and interstitial pneumonitis. Unassessable malignancies were defined as any malignancy terminated stage or the one with any metastatic lesion to the lung and/or receiving palliative therapy. Unassessable diabetes mellitus was defined as serum-hemoglobin A1c (NGSP) ≧7.0%.
3. Aspiration pneumonia [19,20]
4. Receiving immunosuppressive therapy due to any cause
5. Receiving chemotherapy for malignancy

6. Receiving hemodialysis due to any cause
7. Poor activities of daily living (ADL) or requiring any help [Eastern Cooperative Oncology Group (ECOG)-performance status (PS)≧3] such as needing tube feeding or home oxygen therapy
8. Having other complicated infection
9. Requiring mechanical ventilation and/or requiring treatments in the intensive care unit
10. Poor prognosis (anticipated life expectancy < 90 days or patients who are not expected to survive until the end of the trial)
11. Pregnancy

This study was approved by the Institutional Review Board of Aichi Medical University Hospital.

Microbiological evaluation

A sputum sample and two sets of blood were collected from each patient for microbiological examination. Serological tests were performed to detect antibodies against *Mycoplasma pneumoniae* [21] and *Chlamydophila pneumoniae* [22]. Additionally, Legionella pneumophila serogroup 1 antigen in the urine was tested by immunochromatography. The antimicrobial susceptibility of isolated bacterial pathogens was assessed on the basis of the minimum inhibitory concentration according to the Clinical and Laboratory Standards Institute guidelines [23]. Methicillin-resistant *Staphylococcus aureus*, *P. aeruginosa*, *Acinetobacter baumannii*, and extended-spectrum β-lactamase-producing organisms were defined as potentially drug-resistant (PDR) pathogens based on ATS/IDSA guidelines [24].

Definition of appropriate and inappropriate treatment, initial treatment failure

Antibiotic treatment was classified as appropriate or inappropriate according to whether the identified pathogens were sensitive or resistant, respectively, to the initially prescribed antibiotics. Initial treatment failure was defined as death during the initial treatment or a change in the antibiotic regimen from the initial agents within 72 hours after starting the treatment due to a lack of response or clinical deterioration (e.g. worsening of fever, respiratory condition or radiologic status; requiring mechanical ventilation, aggressive fluid resuscitation or vasopressors).

Statistical analyses

The data for categorical variables are expressed as percentages and continuous variables as mean ± standard deviation (SD). Chi-square or Fisher's exact test (two-tailed) was used to compare categorical variables and unpaired Student's *t* test or Mann–Whitney *U* test to compare continuous variables. Statistical analyses involved use of SPSS version 26 for Windows (SPSS Inc., Chicago, IL, USA). A *p-value* <0.05 was considered statistically significant.

Result

A total of 406 patients were enrolled in the present study. Table 1 shows the patients' characteristics and clinical outcomes. Fifty-seven (14%) patients were categorized into the participation possible group, while 86% patients were the participation impossible group. Comparing the two groups, patients with the participation possible group have less comorbidities than those with participation impossible group. The severity of pneumonia was much more severe in patients within the participation impossible group than in those with the participation possible group. As for the outcomes, the patients with the participation possible group had favorable outcomes than those within the participation impossible group. Mechanical ventilations and do not attempt resuscitation (DNAR) orders were frequently seen in participation impossible group than participation possible group. PDR pathogens were seen more frequently in the participation possible group than in those within the participation impossible group (5% v.s. 16%, p = 0.032). There were no significant differences in the frequency of anti-pseudomonal agents use as the initial treatment between the two groups. The duration of antibiotics use was longer in patients within the participation impossible group than in those with the participation possible group, while there was no difference of duration of admission between the two groups. As for pathogens isolated, MRSA is more frequently seen in participation impossible group than in participation impossible group (0% v.s. 20%, p = 0.013), while *Haemophillus influenzae* was seen more frequently in participation possible group than in participation impossible group (35% v.s. 8%, p = 0.042).

Table 1
Comparison of patients' characteristics and outcomes among the RCT appropriate group and inappropriate group.

Variables	All patients (n = 406)	RCT appropriate group (n = 57)	RCT inappropriate group (n = 349)	*p*-value
Mean age (years ± SD)	75.4 ± 14.8	54.9 ± 17.6	78.8 ± 11.2	< 0.001
Median age (years, range)	79 (18–103)	56 (18–79)	81 (37–103)	-
Male gender (n,%)	257 (63)	28 (49)	229 (66)	0.017
Smoking history (n,%)	36 (9)	11 (19)	25 (7)	0.003
Current smoker	205 (50)	24 (42)	181 (52)	0.172
Ex-smoker	135 (33)	21 (37)	114 (33)	0.535
Never smoker	30 (7)	1 (2)	29 (8)	0.079
Unknown				

DNAR, Do Not Attempt Resuscitation; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* PDR, potential drug resistant; RCT, randomized control trial; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, SOFA, sequential organ failure assessment.

* These denominators whose blood cultures obtained, are 230, 27 and 203. **Denominator is 192. Only cases with causative pathogens isolated were analyzed.

, *, ***** these denominators whose numbers are positive sputum cultures, are 196, 17 and 179. They were calculated up to the first digit of the minority.

Variables	All patients (n = 406)	RCT appropriate group (n = 57)	RCT inappropriate group (n = 349)	*p*-value
Underlying diseases (n,%)	126 (31)	4 (7)	122 (35)	< 0.001
Heart disease	175 (43)	20 (35)	155 (44)	0.187
Chronic pulmonary disease	61 (15)	1 (2)	60 (17)	0.001
Diabetes mellitus	51 (13)	0	51 (15)	0.002
Chronic kidney disease	16 (4)	0	16 (5)	0.099
Hemodialysis	14 (3)	0	15 (4)	0.111
Hepatic disease	41 (10)	0	41 (12)	0.006
Collagen vascular disease	100 (25)	0	100 (29)	< 0.001
Cerebrovascular disease	74 (18)	0	75 (21)	< 0.001
Malignancy	74 (18)	2 (4)	72 (21)	< 0.001
Dementia	14 (3)	3 (5)	11 (3)	0.002
Gastroesophageal reflux disease	122 (30)	5 (9)	117 (34)	0.418
Proton pump inhibitor use	60 (15)	0	60 (17)	< 0.001
Sleep agents use	2.1 ± 1.8	0.4 ± 0.5	2.4 ± 1.9	< 0.001
Charlson comorbidity index (mean ± SD)	120 (30)	0	121 (35)	< 0.001
Charlson comorbidity index ≧ 3 (n,%)				< 0.001
				< 0.001
Category of pneumonia (n,%)	177 (44)	51 (89)	126 (36)	< 0.001
Community-acquired pneumonia	229 (56)	6 (11)	223 (64)	
Healthcare-associated pneumonia				

DNAR, Do Not Attempt Resuscitation; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* PDR, potential drug resistant; RCT, randomized control trial; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, SOFA, sequential organ failure assessment.

* These denominators whose blood cultures obtained, are 230, 27 and 203. **Denominator is 192. Only cases with causative pathogens isolated were analyzed.

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Variables	All patients (n = 406)	RCT appropriate group (n = 57)	RCT inappropriate group (n = 349)	*p*-value
Severity of pneumonia (mean ± SD)	2.0 ± 1.3	0.7 ± 1.0	2.2 ± 1.2	< 0.001
A-DROP score	1.8 ± 1.1	0.6 ± 0.8	2.0 ± 1.0	< 0.001
CURB-65 score	105.9 ± 42.3	45.9 ± 34.9	115.8 ± 34.8	< 0.001
PSI score	2.1 ± 0.9	1.2 ± 0.6	2.3 ± 0.8	< 0.001
I-ROAD score	2.7 ± 1.9	1.3 ± 1.1	2.9 ± 1.9	< 0.001
SOFA score	0.6 ± 0.5	0.6 ± 0.5	0.6 ± 0.5	< 0.001
Conditions of the patients (mean ± SD)	0.3 ± 0.5	0.1 ± 0.2	0.3 ± 0.5	< 0.001
SIRS score	26 (11)	1 (4)	25 (13)	0.566
Quick SOFA				< 0.001
Bacteremia (n,%)*				0.14

DNAR, Do Not Attempt Resuscitation; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* PDR, potential drug resistant; RCT, randomized control trial; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, SOFA, sequential organ failure assessment.

* These denominators whose blood cultures obtained, are 230, 27 and 203. **Denominator is 192. Only cases with causative pathogens isolated were analyzed.

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Variables	All patients (n = 406)	RCT appropriate group (n = 57)	RCT inappropriate group (n = 349)	*p*-value
Treatment (n,%)	15 (4)	3 (5)	12 (3)	0.471
ICU admission	77 (19)	0	77 (22)	< 0.001
DNAR order	19 (5)	0	19 (5)	0.071
Mechanical ventilation	11 (3)	0	11 (3)	0.174
Vasopressor use	196 (48)	16(28)	180 (52)	0.001
Initial antibiotic therapy (n,%)	58 (14)	7 (12)	51 (15)	0.641
Penicillins alone	70 (17)	7 (12)	63 (18)	0.285
Cephems alone	26 (6)	13 (23)	13 (4)	< 0.001
Carbapenems alone	0	0	0	-
Fluoroquinolones alone	22 (5)	10 (17)	12 (3)	< 0.001
Macrolides alone	11 (3)	3 (5)	8 (2)	0.2
β-lactams plus fluoroquinolones	23 (6)	1 (2)	22 (6)	0.168
β-lactams plus macrolides	5 (1)	0	5 (1)	0.363
Others	52 (13)	15 (26)	37 (11)	0.001
Combination plus anti-MRSA agents	247 (61)	34 (60)	213 (61)	0.843
Any combination antibiotic therapy				
Anti-pseudomonal agents use (n,%)				
Duration of	18.6 ± 16.1	12.9 ± 10.2	19.5 ± 16.8	0.004
hospital stay (mean days ± SD)	13.7 ± 10.8	12.5 ± 9.1	13.9 ± 11.1	0.385
antibiotics use (mean days ± SD)				

DNAR, Do Not Attempt Resuscitation; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* PDR, potential drug resistant; RCT, randomized control trial; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, SOFA, sequential organ failure assessment.

* These denominators whose blood cultures obtained, are 230, 27 and 203. **Denominator is 192. Only cases with causative pathogens isolated were analyzed.

, *, ***** these denominators whose numbers are positive sputum cultures, are 196, 17 and 179. They were calculated up to the first digit of the minority.

Variables	All patients (n = 406)	RCT appropriate group (n = 57)	RCT inappropriate group (n = 349)	*p*-value
Outcome	19 (5)	0	19 (5)	< 0.001
Mortality (n,%)	23 (6)	1 (2)	22 (6)	
30-day mortality	37 (9)	5 (9)	32 (9)	< 0.001
In-hospital mortality	42 (22)	1 (6)	41 (24)	0.924
Initial treatment failure (n,%)	59 (14)	3 (5)	56 (16)	0.32
Inappropriate treatment (n,%) **				0.032
Isolating PDR pathogens (n,%)				
Gram positive (n)	***	****	*****	0.831
Streptococcus pneumoniae	32 (16.3)	4 (23.5)	28 (15.6)	0.381
Streptococcus non-pneumonia	19 (9.7)	0	19 (9.7)	0.083
Staphylococcus aureus	30 (15.3)	1 (5.9)	29 (16.2)	0.013
Methicillin-resistant *Staphylococcus aureus*	35 (17.9)	0	35 (19.6)	0.689
Coagulase-negative Staphylococci	1 (0.5)	0	1 (0.6)	0.571
Corynebacterium species	2 (1)	0	2 (1.1)	0.689
Enterococcus species	1 (0.5)	0	1 (0.6)	

DNAR, Do Not Attempt Resuscitation; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* PDR, potential drug resistant; RCT, randomized control trial; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, SOFA, sequential organ failure assessment.

* These denominators whose blood cultures obtained, are 230, 27 and 203. **Denominator is 192. Only cases with causative pathogens isolated were analyzed.

, *, ***** these denominators whose numbers are positive sputum cultures, are 196, 17 and 179. They were calculated up to the first digit of the minority.

Variables	All patients (n = 406)	RCT appropriate group (n = 57)	RCT inappropriate group (n = 349)	*p*-value
Gram-negative (n)	***	****	*****	0.042
Haemophillus influenzae	21 (10.7)	6 (35.3)	15 (8.4)	0.3
Esherichia coli	18 (9.2)	1 (5.9)	17 (9.5)	0.416
Pseudomonas aeruginosa	15 (7.7)	1 (5.9)	14 (7.8)	0.422
Klebsiella pneumonniae	26 (13.3)	1 (5.9)	25 (14)	0.127
Klebsiella oxytoca	4 (2)	0	4 (2.2)	0.663
Moraxella catarrahis	11 (5.6)	2 (11.2)	9 (5)	0.682
Serratia macescens	5 (2.6)	1 (5.9)	4 (2.2)	0.319
Acinetobacter species	3 (1.5)	1 (5.9)	2 (1.1)	0.422
Proteus mirabilis	4 (2)	0	4 (2.2)	0.573
Stenotrophomonas maltphilia	2 (1)	0	2 (1.1)	0.012
Legionella pneumoniae	1 (0.5)	1 (5.9)	0	0.609
Enterobacteriacea	13 (6.6)	0	13 (7.3)	

DNAR, Do Not Attempt Resuscitation; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* PDR, potential drug resistant; RCT, randomized control trial; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, SOFA, sequential organ failure assessment.

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Table 2 shows comparison of patients' characteristics and outcomes between participation possible and impossible group among CAP patients. Fifty-one patients (29%) were participation possible group. Participation possible groups are older and have more cormobidities than participation impossible group. All severity scores of pneumonia were higher in participation impossible group than in participation possible group. There was no differences of 30-day and in-hospital mortality rates in between the two groups. Mean duration of antibiotic therapy was shorter in participation possible group than in participation impossible group (12.4 ± 10.5 v.s. 17.5 ± 16.0 days, $p = 0.025$), while duration of hospital stay did not differ between the two groups.

Table 2
Comparison of patients characteristics and outcomes between participation possible and impossible group among CAP patients

Variables	All patients (n = 177)	RCT appropriate group (n = 51)	RCT inappropriate group (n = 126)	*p*-value
Mean age (years ± SD)	71.9 ± 18.3	53.2 ± 17.7	79.5 ± 12.2	< 0.001
Median age (years, range)	76 (18–103)	53 (18–79)	82 (37–103)	-
Male gender (n,%)	109 (62)	27 (53)	82 (65)	0.133
Smoking history (n,%)	26 (15)	11 (22)	15 (12)	0.1
Current smoker	82 (46)	20 (39)	62 (49)	0.227
Ex-smoker	61 (34)	20 (39)	41 (33)	0.397
Never smoker	8 (5)	0 (2)	8 (6)	0.066
Unknown				

CAP, community-acquired pneumonia; DNAR, Do Not Attempt Resuscitation; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* PDR, potential drug resistant; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, SOFA, sequential organ failure assessment.

*Patients who obtained a blood culture were evaluated. Then, the denominators are 107, 25, and 82 in all patients, the RCT appropriate group and RCT inappropriate group, respectively.

**Patients who had causative pathogens identified were evaluated. Then, the denominators are 70, 15, and 55 in all patients, the RCT appropriate group and RCT inappropriate group, respectively.

, *, ***** These denominators whose number are positive sputum cultures, are 71, 14, and 57, respectively. They were calculated up to the first digit of the minority.

Variables	All patients (n = 177)	RCT appropriate group (n = 51)	RCT inappropriate group (n = 126)	*p*-value
Underlying diseases (n,%)	51 (40)	4 (8)	47 (37)	< 0.001
Heart disease	63 (50)	16 (31)	47 (37)	0.001
Chronic pulmonary disease	31 (25)	0	31 (25)	< 0.001
Diabetes mellitus	14 (11)	0	14 (11)	0.013
Chronic kidney disease	0	0	0	-
Hemodialysis	4 (3)	0	4 (3)	0.198
Hepatic disease	1 (1)	0	1 (1)	0.523
Collagen vascular disease	28 (22)	0	28 (23)	< 0.001
Cerebrovascular disease	10 (8)	0	10 (8)	0.038
Malignancy	23 (13)	1 (2)	22 (17)	0.005
Dementia	4 (3)	2 (4)	2 (2)	0.344
Gastroesophageal reflux disease	37 (21)	4 (8)	33 (26)	< 0.001
Proton pump inhibitor use	23 (13)	0	23 (18)	0.001
Sleep agents use	1.2 ± 1.1	0.3 ± 0.5	1.6 ± 1.1	< 0.001
Charlson comorbidity index (mean ± SD)	23 (13)	0	23 (18)	0.001
Charlson comorbidity index ≧ 3 (n,%)				

CAP, community-acquired pneumonia; DNAR, Do Not Attempt Resuscitation; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* PDR, potential drug resistant; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, SOFA, sequential organ failure assessment.

*Patients who obtained a blood culture were evaluated. Then, the denominators are 107, 25, and 82 in all patients, the RCT appropriate group and RCT inappropriate group, respectively.

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, *, ***** These denominators whose number are positive sputum cultures, are 71, 14, and 57, respectively. They were calculated up to the first digit of the minority.

Variables	All patients (n = 177)	RCT appropriate group (n = 51)	RCT inappropriate group (n = 126)	*p*-value
Severity of pneumonia (mean ± SD)	1.7 ± 1.2	0.5 ± 0.8	2.1 ± 1.1	< 0.001
A-DROP score	1.5 ± 1.1	0.5 ± 0.7	1.9 ± 1.0	< 0.001
CURB-65 score	88.5 ± 44.4	42.5 ± 34.6	107.2 ± 33.1	< 0.001
PSI score	1.8 ± 0.9	1.2 ± 0.6	2.1 ± 0.9	< 0.001
I-ROAD score	2.1 ± 1.5	1.3 ± 1.1	2.5 ± 1.5	< 0.001
SOFA score	0.6 ± 0.5	0.6 ± 0.5	0.7 ± 0.5	< 0.001
Conditions of the patients (mean ± SD)	0.2 ± 0.4	0.0 ± 0.2	0.3 ± 0.4	< 0.001
SIRS score	9 (8)	0	9 (11)	0.208
Quick SOFA				< 0.001
Bacteremia (n,%)*				0.113

CAP, community-acquired pneumonia; DNAR, Do Not Attempt Resuscitation; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* PDR, potential drug resistant; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, SOFA, sequential organ failure assessment.

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Variables	All patients (n = 177)	RCT appropriate group (n = 51)	RCT inappropriate group (n = 126)	*p*-value
Treatment (n,%)	6 (3)	3 (6)	3 (2)	0.23
ICU admission	23 (13)	0	23 (18)	0.001
DNAR order	7 (4)	0	7 (6)	0.086
Mechanical ventilation	4 (3)	0	4 (3)	0.198
Vasopressor use	70 (40)	11 (22)	59 (47)	0.002
Initial antibiotic therapy (n,%)	30 (17)	7 (14)	23 (18)	0.467
Penicillins alone	26 (15)	7 (14)	19 (15)	0.818
Cephems alone	22 (12)	13 (25)	9 (7)	0.001
Carbapenems alone	0	0	0	-
Fluoroquinolones alone	16 (9)	9 (18)	7 (6)	0.011
Macrolides alone	7 (4)	3 (6)	4 (3)	0.403
β-lactams plus fluoroquinolones	6 (3)	1 (2)	5 (4)	0.504
β-lactams plus macrolides	0	0	0	-
Others	27 (15)	14 (27)	13 (10)	0.004
Combination plus anti-MRSA agents	95 (54)	30 (59)	65 (52)	0.382
Any combination antibiotic therapy				
Anti-pseudomonal agents use (n,%)				

CAP, community-acquired pneumonia; DNAR, Do Not Attempt Resuscitation; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* PDR, potential drug resistant; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, SOFA, sequential organ failure assessment.

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, *, ***** These denominators whose number are positive sputum cultures, are 71, 14, and 57, respectively. They were calculated up to the first digit of the minority.

Variables	All patients (n = 177)	RCT appropriate group (n = 51)	RCT inappropriate group (n = 126)	*p*-value
Duration of hospital stay (mean days ± SD)	16.3 ± 14.7	12.8 ± 9.6	13.6 ± 8.8	0.557
antibiotics use (mean days ± SD)	13.4 ± 9.0	12.4 ± 10.5	17.9 ± 16.0	0.025
Outcome	3 (2)	0	3 (2)	0.266
Mortality (n,%)	5 (3)	1 (2)	4 (3)	0.659
30-day mortality	10 (6)	4 (8)	6 (5)	0.421
In-hospital mortality	5 (7)	1 (7)	4 (7)	0.988
Initial treatment failure (n,%)	10 (6)	2 (4)	8 (6)	0.526
Inappropriate treatment (n,%) **				
Isolating PDR pathogens (n,%)				
Gram positive (n)	***	****	*****	0.415
Streptococcus pneumoniae	19 (26.8)	4 (28.6)	15 (26.3)	0.575
Streptococcus non-pneumonia	5 (7)	0	5 (8.8)	0.131
Staphylococcus aureus	11 (15.5)	1 (7.1)	10 (17.5)	0.11
Methicillin-resistant *Staphylococcus aureus*	6 (8.5)	0	6 (10.5)	-
Coagulase-negative Staphylococci	0	0	0	-
Corynebacterium species	0	0	0	-
Enterococcus species	0	0	0	

CAP, community-acquired pneumonia; DNAR, Do Not Attempt Resuscitation; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* PDR, potential drug resistant; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, SOFA, sequential organ failure assessment.

*Patients who obtained a blood culture were evaluated. Then, the denominators are 107, 25, and 82 in all patients, the RCT appropriate group and RCT inappropriate group, respectively.

**Patients who had causative pathogens identified were evaluated. Then, the denominators are 70, 15, and 55 in all patients, the RCT appropriate group and RCT inappropriate group, respectively.

, *, ***** These denominators whose number are positive sputum cultures, are 71, 14, and 57, respectively. They were calculated up to the first digit of the minority.

Variables	All patients (n = 177)	RCT appropriate group (n = 51)	RCT inappropriate group (n = 126)	*p*-value
Gram-negative (n)	12 (16.9)	5 (35.7)	7 (12.3)	0.311
Haemophillus influenzae	4 (5.6)	1 (7.1)	3 (5.3)	0.859
Esherichia coli	2 (2.8)	1 (7.1)	1 (1.8)	0.509
Pseudomonas aeruginosa	7 (9.9)	1 (7.1)	6 (10.5)	0.38
Klebsiella pneumonniae	2 (2.8)	0	2 (3.5)	0.363
Klebsiella oxytoca	4 (5.6)	1 (7.1)	3 (5.3)	0.859
Moraxella catarrahis	2 (2.8)	1 (7.1)	1 (1.8)	0.509
Serratia macescens	0	0	0	-
Acinetobacter species	0	0	1 (1.8)	0.522
Proteus mirabilis	0	0	0	-
Stenotrophomonas maltphilia	1 (1.4)	1 (7.1)	0	0.116
Legionella pneumoniae	7 (9.9)	0	7 (12.3)	0.332
Enterobacteriacea				

CAP, community-acquired pneumonia; DNAR, Do Not Attempt Resuscitation; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* PDR, potential drug resistant; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, SOFA, sequential organ failure assessment.

*Patients who obtained a blood culture were evaluated. Then, the denominators are 107, 25, and 82 in all patients, the RCT appropriate group and RCT inappropriate group, respectively.

**Patients who had causative pathogens identified were evaluated. Then, the denominators are 70, 15, and 55 in all patients, the RCT appropriate group and RCT inappropriate group, respectively.

, *, ***** These denominators whose number are positive sputum cultures, are 71, 14, and 57, respectively. They were calculated up to the first digit of the minority.

Table 3 shows comparison of patients' characteristics and outcomes between participation possible and impossible group among HCAP patients. Only 6 patients (3%) were participation possible group among HCAP patients. Although there were no significant differences on age and all pneumonia severity scores in between the 2 groups, CCI was higher than in participation impossible group than in participation possible group (0.8 v.s. 2.8, $p = 0.022$). There was no differences of 30-day and in-hospital mortality rates in between the two groups. There was no differences of duration of hospital stay or antibiotic treatment between the two groups. As for pathogens isolated, isolation of MRSA and *Pseudomonas aeruginosa* did

not differ between the two groups. On the other hand, *H. influenza* and *Moraxella catarrahis* tended to isolate more often in participation possible group than in participation impossible group.

Table 3
Comparison of patients characteristics and outcomes between RCT appropriate group and RCT inappropriate group among HCAP patients

Variables	All patients (n = 229)	RCT appropriate group (n = 6)	RCT inappropriate group (n = 223)	*p*-value
Mean age (years ± SD)	78.1 ± 10.6	69.5 ± 6.4	78.4 ± 10.6	0.304
Median age (years, range)	80 (42–99)	69 (62–78)	80 (42–99)	-
Male gender (n,%)	148 (65)	1 (17)	147 (66)	0.013
Smoking history (n,%)	0	0	10 (4)	0.596
Current smoker	123 (54)	4 (67)	119 (53)	0.519
Ex-smoker	74 (32)	1 (17)	73 (33)	0.406
Never smoker	22 (10)	1 (17)	21 (9)	0.552
Unknown				

DNAR, Do Not Attempt Resuscitation; HCAP, healthcare-associated pneumonia; ICU, intensive care unit; MRSA, m*ethicillin-resistant Staphylococcus aureus;* PDR, potential drug resistant; RCT, randomized control trial; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

*Patients who obtained a blood culture were evaluated. Then, the denominators are 122, 2, and 120 in all patients, the RCT appropriate group and RCT inappropriate group, respectively.

**Patients who had causative pathogens identified were evaluated. Then, the denominators are 118, 3, and 115 in all patients, the RCT appropriate group and RCT inappropriate group, respectively.

, *, ***** These denominators whose number are positive sputum cultures, are 125, 3, and 122, respectively. They were calculated up to the first digit of the minority.

Variables	All patients (n = 229)	RCT appropriate group (n = 6)	RCT inappropriate group (n = 223)	*p*-value
Underlying diseases (n,%)	75 (33)	0	75 (34)	0.083
Heart disease	112 (49)	4 (67)	108 (48)	0.378
Chronic pulmonary disease	29 (13)	0	29 (13)	0.345
Diabetes mellitus	37 (16)	0	37 (17)	0.276
Chronic kidney disease	15 (7)	0	15 (7)	0.511
Hemodialysis	11 (5)	0	11 (5)	0.577
Hepatic disease	40 (17)	0	40 (18)	0.253
Collagen vascular disease	72 (31)	0	72 (32)	0.093
Cerebrovascular disease	65 (28)	0	65 (29)	0.118
Malignancy	51 (22)	1 (17)	50 (22)	0.738
Dementia	10 (4)	1 (17)	11 (5)	0.135
Gastroesophageal reflux disease	85 (37)	1 (17)	84 (38)	0.293
Proton pump inhibitor use	37 (16)	0	37 (17)	0.273
Sleep agents use	2.7 ± 2.0	0.8 ± 0.4	2.8 ± 2.1	0.022
Charlson comorbidity index (mean ± SD)	98 (43)	0	98 (44)	0.032
Charlson comorbidity index ≧ 3 (n,%)				

DNAR, Do Not Attempt Resuscitation; HCAP, healthcare-associated pneumonia; ICU, intensive care unit; MRSA, m*ethicillin-resistant Staphylococcus aureus;* PDR, potential drug resistant; RCT, randomized control trial; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

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Variables	All patients (n = 229)	RCT appropriate group (n = 6)	RCT inappropriate group (n = 223)	*p*-value
Severity of pneumonia (mean ± SD)	2.3 ± 1.3	1.8 ± 1.8	2.3 ± 1.2	0.154
A-DROP score	2.1 ± 1.0	1.5 ± 0.8	2.1 ± 1.0	0.648
CURB-65 score	119.4 ± 35.2	75.0 ± 23.3	120.6 ± 34.8	0.219
PSI score	2.3 ± 0.8	1.5 ± 0.8	2.4 ± 0.8	0.685
I-ROAD score	3.2 ± 2.1	1.7 ± 1.4	3.2 ± 2.2	0.193
SOFA score	0.6 ± 0.5	0.7 ± 0.5	0.6 ± 0.5	0.162
Conditions of the patients (mean ± SD)	1.2 ± 0.8	0.2 ± 0.4	0.4 ± 0.5	0.001
SIRS score	17 (14)	1 (50)	16 (13)	0.26
Quick SOFA				
Bacteremia (n,%)*				

DNAR, Do Not Attempt Resuscitation; HCAP, healthcare-associated pneumonia; ICU, intensive care unit; MRSA, m*ethicillin-resistant Staphylococcus aureus;* PDR, potential drug resistant; RCT, randomized control trial; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

*Patients who obtained a blood culture were evaluated. Then, the denominators are 122, 2, and 120 in all patients, the RCT appropriate group and RCT inappropriate group, respectively.

**Patients who had causative pathogens identified were evaluated. Then, the denominators are 118, 3, and 115 in all patients, the RCT appropriate group and RCT inappropriate group, respectively.

, *, ***** These denominators whose number are positive sputum cultures, are 125, 3, and 122, respectively. They were calculated up to the first digit of the minority.

Variables	All patients (n = 229)	RCT appropriate group (n = 6)	RCT inappropriate group (n = 223)	*p*-value
Treatment (n,%)	9 (4)	0	9 (4)	0.615
ICU admission	54 (24)	0	54 (24)	0.168
DNAR order	12 (5)	0	12 (5)	0.559
Mechanical ventilation	7 (3)	0	7 (3)	0.659
Vasopressor use	126 (55)	5 (83)	121 (54)	0.158
Initial antibiotic therapy (n,%)	28 (12)	0	28 (13)	0.354
Penicillins alone	44 (19)	0	44 (20)	0.226
Cephems alone	4 (2)	0	4 (2)	0.741
Carbapenems alone	0	0	0	-
Fluoroquinolones alone	6 (3)	1 (17)	5 (2)	0.029
Macrolides alone	4 (2)	0	4 (2)	0.741
β-lactams plus fluoroquinolones	17 (7)	0	17 (8)	0.482
β-lactams plus macrolides	5 (2)	0	5 (2)	0.711
Others	25 (11)	1 (17)	24 (11)	0.647
Combination plus anti-MRSA agents	152 (66)	4 (67)	148 (66)	0.998
Any combination antibiotic therapy				
Anti-pseudomonal agents use (n,%)				
Duration of	20.4 ± 16.9	16.7 ± 7.4	20.5 ± 17.2	0.284
hospital stay (mean days ± SD)	14.0 ± 12.0	10.8 ± 4.0	14.0 ± 12.2	0.349
antibiotics use (mean days ± SD)				

DNAR, Do Not Attempt Resuscitation; HCAP, healthcare-associated pneumonia; ICU, intensive care unit; MRSA, m*ethicillin-resistant Staphylococcus aureus;* PDR, potential drug resistant; RCT, randomized control trial; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

*Patients who obtained a blood culture were evaluated. Then, the denominators are 122, 2, and 120 in all patients, the RCT appropriate group and RCT inappropriate group, respectively.

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Variables	All patients (n = 229)	RCT appropriate group (n = 6)	RCT inappropriate group (n = 223)	*p*-value
Outcome	16 (5)	0	16 (7)	0.456
Mortality (n,%)	18 (6)	0	18 (8)	0.468
30-day mortality	27 (9)	1 (17)	26 (12)	0.924
In-hospital mortality	37 (31)	0	37 (32)	0.559
Initial treatment failure (n,%)	49 (14)	1 (17)	48 (22)	0.775
Inappropriate treatment (n,%) **				
Isolating PDR pathogens (n,%)				
Gram positive (n)	***	****	*****	0.584
Streptococcus pneumoniae	13 (10.4)	0	13 (10.7)	0.571
Streptococcus non-pneumonia	14 (11.2)	0	14 (11.5)	0.5
Staphylococcus aureus	19 (15.2)	0	19 (15.6)	0.391
Methicillin-resistant *Staphylococcus aureus*	29 (23.2)	0	29 (23.8)	0.883
Coagulase-negative Staphylococci	1 (0.8)	0	1 (0.8)	0.835
Corynebacterium species	2 (1.6)	0	2 (1.6)	0.883
Enterococcus species	1 (0.8)	0	1 (0.8)	

DNAR, Do Not Attempt Resuscitation; HCAP, healthcare-associated pneumonia; ICU, intensive care unit; MRSA, m*ethicillin-resistant Staphylococcus aureus;* PDR, potential drug resistant; RCT, randomized control trial; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

*Patients who obtained a blood culture were evaluated. Then, the denominators are 122, 2, and 120 in all patients, the RCT appropriate group and RCT inappropriate group, respectively.

**Patients who had causative pathogens identified were evaluated. Then, the denominators are 118, 3, and 115 in all patients, the RCT appropriate group and RCT inappropriate group, respectively.

, *, ***** These denominators whose number are positive sputum cultures, are 125, 3, and 122, respectively. They were calculated up to the first digit of the minority.

Variables	All patients (n = 229)	RCT appropriate group (n = 6)	RCT inappropriate group (n = 223)	*p*-value
Gram-negative (n)	***	****	*****	0.055
Haemophillus influenzae	9 (7.2)	1 (35.3)	8 (6.6)	0.569
Esherichia coli	14 (11.2)	0	14 (11.5)	0.584
Pseudomonas aeruginosa	13 (10.4)	0	13 (10.7)	0.5
Klebsiella pneumonniae	19 (15.2)	0	19 (15.6)	0.835
Klebsiella oxytoca	2 (1.6)	0	2 (1.6)	0.022
Moraxella catarrahis	7 (5.6)	1 (11.2)	6 (4.9)	0.798
Serratia macescens	3 (2.4)	0	3 (2.5)	< 0.001
Acinetobacter species	3 (2.4)	1 (5.9)	2 (1.6)	0.798
Proteus mirabilis	3 (2.4)	0	3 (2.5)	0.836
Stenotrophomonas maltphilia	2 (1.6)	0	2 (1.6)	-
Legionella pneumoniae	0	0	0	0.717
Enterobacteriacea	6 (4.8)	0	6 (4.9)	

DNAR, Do Not Attempt Resuscitation; HCAP, healthcare-associated pneumonia; ICU, intensive care unit; MRSA, m*ethicillin-resistant Staphylococcus aureus;* PDR, potential drug resistant; RCT, randomized control trial; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

*Patients who obtained a blood culture were evaluated. Then, the denominators are 122, 2, and 120 in all patients, the RCT appropriate group and RCT inappropriate group, respectively.

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, *, ***** These denominators whose number are positive sputum cultures, are 125, 3, and 122, respectively. They were calculated up to the first digit of the minority.

As for overall survival times, the participation possible group displayed a longer overall survival times (OSs) than the participation impossible group (median OS not reached v.s. 43.3 months, $p < 0.001$ by *Log-Rank* test) as shown in Fig. 1A. In the sub-analysis of OSs among CAP and HCAP, participation possible group among CAP patients showed a longer OSs than participation impossible group among those (Median OSs not reached v.s. 53.9 months, $p < 0.001$ by *Log-Rank* test) (Fig. 1B), while there was no differences in the participation possible and impossible group among HCAP patients (Fig. 1C).

In terms of reasons for not being able to join a clinical trial, underlying diseases or conditions which could not be assessed correctly was the most commonly seen in 254 (73%) patients, followed by age in 180 (52%) patients (Table 4).

Table 4
Reasons of clinical trials of which is inappropriate (n = 349)

Factors	n (%)
1. Age (< 18, > 80 years old)	180 (52)
2. Underlying disease which could not be assessed	254 (73)
Heart disease	106 (30)
Pulmonary disease	74 (21)
Kidney disease	37 (11)
Hepatic disease	15 (4)
Cerebrovascular disease	19 (5)
Diabetes mellitus	39 (12)
Collagen vascular disease	41 (12)
Malignancy	63 (18)
Mental disorder	12 (4)
3. Aspiration pneumonia	196 (56)
4. Immunosuppressor agents use	44 (13)
5. Chemotherapy	25 (7)
6. Hemodialysis	18 (5)
7. Poor ADL or required any help	111 (32)
ECOG-PS ≧ 3	20 (6)
Tube feeding	28 (8)
Home oxygen therapy	
8. Other infections complicated	11 (3)
9. Requiring mechanical ventilation and/or ICU admission	20 (6)
10. Poor life expectancy	20 (6)
11. Pregnancy	0

ADL, activities of daily living; ECOG-PS, Eastern Cooperative Oncology Group-performance status; ICU, intensive care unit.

Discussion

Patients in the real world are quite different from those who can participate in a clinical trial. We already reported that only 24% of candidemia patients could participate in a clinical trial. Patients who can participate in a clinical trial have better PSs and longer overall survival times than those seen in actual medical practice [2]. Like the study, community-onset pneumonia patients with participation possible group showed lesser severity of pneumonia and fewer comorbidities than those with the participation impossible group. We found the participation possible group had higher mortality rates of 30-day and in-hospital than the participation impossible group. However, identification of PDR pathogens, mechanical ventilation and Do Not Attempt Resuscitation (DNAR) order were more frequently seen in the participation possible group than in the impossible group. In Japan, discussing DNAR order with Japanese family members is still considered to be taboo [25]. Therefore, these results could suggest that patients in the participation impossible group have a worse prognosis than those in the participation possible group do. It is well known that HCAP patients are more likely to have worse PSs and more comorbidities than those with CAP [4, 5, 7].

Outstandingly, the OSs in the participation impossible group with CAP were significantly shorter OSs than those in the participation the impossible group, while 30-day and in-hospital mortality rate did not differ between the two groups. More comorbidities could affect the prognosis among the participation impossible group. Physicians should pay attention to them after discharge. Besides, 97% of HCAP patients in the studies [4, 5, 7] was excluded from the clinical trial. In addition, HCAP patients in the participation possible group had much shorted durations of antibiotic treatment and admission than those in the participation impossible group. An appropriate duration of antibiotics is said to be 5–7 days. The result of our study also suggests that 5–7 days is long enough to treat HCAP. The therapeutic strategy for HCAP patients in the participation impossible group might have to be reconsidered due to the poor general conditions.

There are several limitations in our study. First, this is a retrospective study in a small population. Thus, there might be a bias in data selection and analysis such as the severity of pneumonia. Second, we evaluated only patients who were admitted to our institute. There might be possibility that patients in this study could not reflect the whole of pneumonia patients.

Conclusion

In conclusion, 14% patients could join the clinical trial, while 86% patients could not. There is a difference in patients' profile and outcomes between the real world and the clinical trial. Though EBM is very important and essential to advance medicine, we should acknowledge the facts and limits of clinical trials. Every physician should not be overconfident in EBM based on the results of a clinical trial.

Abbreviations

ADL: activities of daily living, ATS/IDSA: American Thoracic Society/ Infectious Diseases Society of America, CAP: community-acquired pneumonia, CCI: Charlson comorbidity index, DNAR: do not attempt resuscitation, EBM: evidenced based medicine, ECOG: Eastern Cooperative Oncology Group

HCAP: healthcare-associated *pneumonia,* OS: overall survival time, PDR: potentially drug-resistant

PS: performance status, SD: standard deviation

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the local regulations, and was approved by the Institutional Review Board of Aichi Medical University Hospital. Informed consent was waived, since only leftover materials, otherwise discarded, were used, and no additional intervention or change in treatment plan was implemented.

Consent to publish

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

None declared.

Funding

None declared.

Author contribution statement

NA contributed to the study conceptualization, methodology, and writing. HM supervised the study and edited the draft. NA, YS, DS, HK, MH, YK, and YY performed data collection. DS, HK, MH and HS performed microbial testing and analyzing data. AS provided a soft ware to analyze the data. All authors read and approved the final manuscript.

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References

1. Evidence-Based Medicine Working Group: Evidence-based medicine. A new approach to teaching the practice of medicine. JAMA 1992;268:2420–5.
2. Asai N, Sakanashi D, Suematsu H, Kato H, Hagihara M, Shiota A, et al. To What degree could clinical trials in Evidence Based Medicine reflect reality in the treatment of candidemia? J Microbiol Immunol Infect 2020 in press.
3. Welte T, Torres A, Nathwani D. Clinical and economic burden of community acquired pneumonia among adults in Europe. Thorax 2012;67:71–9.
4. Asai N, Watanabe H, Shiota A, Kato H, Sakanashi D, Hagihara M, et al. Efficacy and accuracy of qSOFA and SOFA scores as prognostic tools for community-acquired and healthcare-associated pneumonia. Int J Infect Dis 2019;84:89–96.
5. Matsunuma R, Asai N, Ohkuni Y, Nakahsima K, Iwasaki T, Misawa M, Kaneko N. I-ROAD could be efficient in predicting severity of community acquired pneumonia or healthcare-associated-pneumonia. Singapore Med J 2014;55:318–24.
6. Metlay JP, Schulz R, Li YH, Singer DE, Marrie TJ, Coley CM, et al. Influence of age on symptoms at presentation in patients with community-acquired pneumonia. Arch Intern Med 1997;157:1453–9.
7. Shindo Y, Sato S, Maruyama E, Ohashi T, Ogawa M, Hashimoto N, et al. Health-care-associated pneumonia among hospitalized patients in a Japanese community hospital. Chest 2009;135:633–40.
8. Miyashita N, Matsushima T, Oka M. Japanese Respiratory Society. The JRS guidelines for the management of community-acquired pneumonia in adults: an update and new recommendations. Intern Med 2006;45:419–28.
9. British Thoracic Society Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults. Thorax 2001;56 (Suppl 4):1–64.
10. Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001;163:1730–54.
11. Seki M, Watanabe A, Mikasa K, Kadota J, Kohno S. Revision of the severity rating and classifi cation of hospital-acquired pneumonia in the Japanese Respiratory Society guidelines. Respirology 2008;13:880–5.
12. Raith EP, Udy AA, Bailey M, McGloughlin S, MacIsaac C, Bellomo R, et al. Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit. JAMA 2017;317:290–300.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373–83.
14. Kollef MH, Nováček M, Kivistik Ü, Réa-Neto Á, Shime N, Martin-Loeches I, et al. Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a

randomised, controlled, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis 2019;19:1299–311.

15. Yamamoto Y, Izumikawa K, Morinaga Y, Nakamura S, Kurihara S, Imamura Y, et al. Prospective randomized comparison study of piperacillin/tazobactam and meropenem for healthcare-associated pneumonia in Japan. J Infect Chemother 2013;19:291–8.
16. Awad SS, Rodriguez AH, Chuang YC, Marjanek Z, Pareigis AJ, Reis G, et al. A phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia. Clin Infect Dis 2014;59:51–61.
17. Thomas CF Jr, Limper AH. Pneumocystis pneumonia. N Engl J Med 2004;350:2487–98.
18. Asai N, Motojima S, Ohkuni Y, Matsunuma R, Nakashima K, Iwasaki T, et al. Early diagnosis and treatment are crucial for the survival of Pneumocystis pneumonia patients without human immunodeficiency virus infection. J Infect Chemother 2012;18:898–905.
19. Japanese Respiratory Society. Aspiration pneumonia. Respirology 2009; 14(Suppl 2):S59-64.
20. Ranzani OT, Prina E, Menéndez R, Ceccato A, Cilloniz C, Méndez R, et al. New Sepsis Definition (Sepsis-3) and Community-acquired Pneumonia Mortality: A Validation and Clinical Decision-making Study. Am J Respir Crit Care Med 2017;10:1287–97.
21. Miyashita N, Ouchi K, Kishi F, Tabuchi M, Tsumura N, Bannai H, et al. Rapid and simple diagnosis of Chlamydophila pneumoniae pneumonia by an immunochromatographic test for detection of immunoglobulin M antibodies. Clin Vaccine Immunol 2008;7:1128–31.
22. Ishida T, Hashimoto T, Arita M, Osawa M. Etiology of Community-Acquired Pneumonia in Hospitalized Patients: A 3-year Prospective Study in Japan. Chest 1998;6:1558-93.
23. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. 21st informational supplement. M 100-S21. Wayne, PA:CLSI;2011.
24. American Thoracic Society. Infectious Disease Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am Respir Crit Care 2005;4:388–416.
25. Asai N, Ohkuni Y, Ashworth L, Kaneko N. Implementation of do not attempt resuscitate orders in a Japanese nursing home. Am J Hosp Palliat Care 2014;31:27–32.

Figures

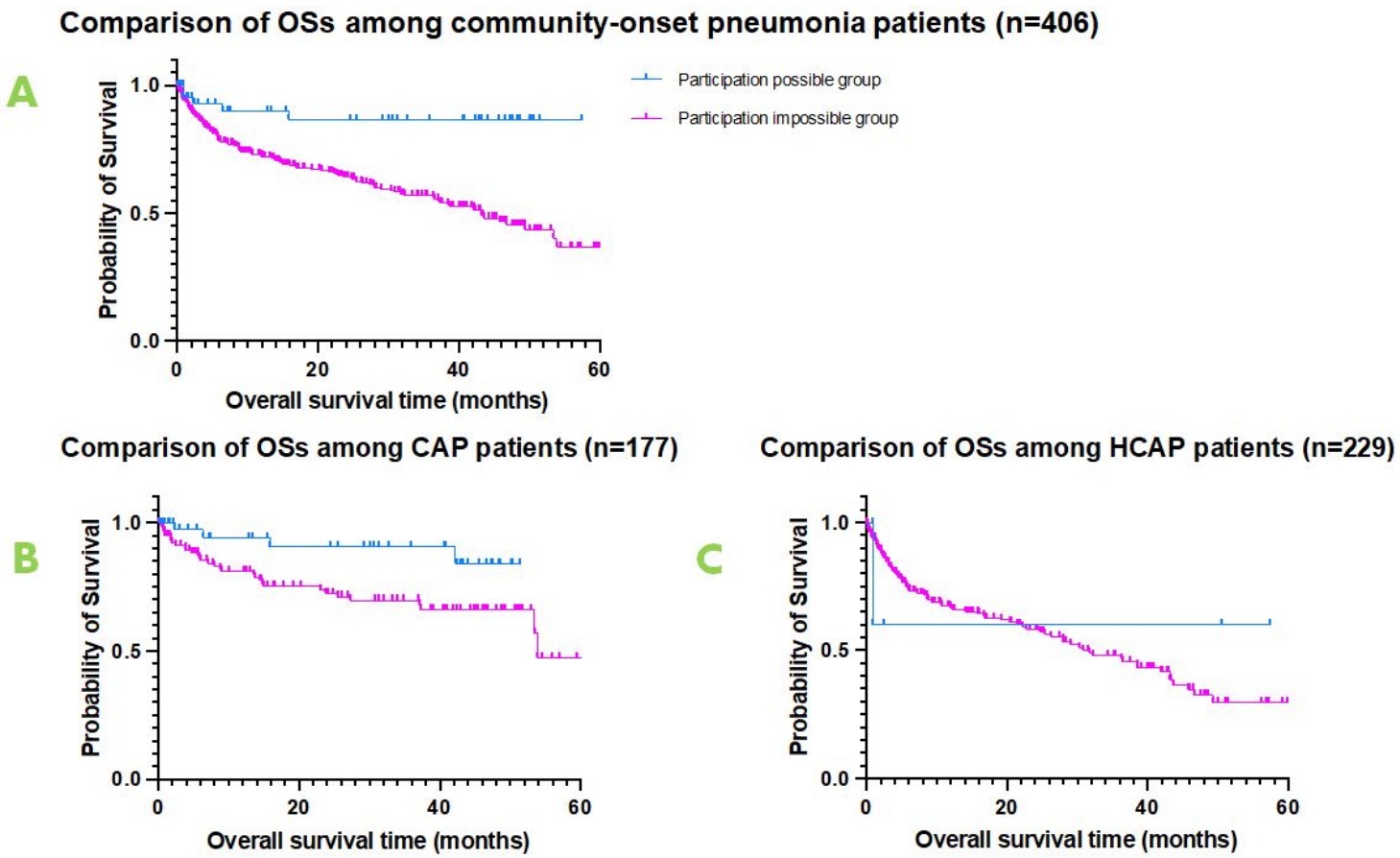

Figure 1

As for overall survival times, the participation possible group displayed a longer overall survival times (OSs) than the participation impossible group (median OS not reached v.s. 43.3 months, $p<0.001$ by Log-Rank test) as shown in Figure 1A. In the sub-analysis of OSs among CAP and HCAP, participation possible group among CAP patients showed a longer OSs than participation impossible group among those (Median OSs not reached v.s. 53.9 months, $p<0.001$ by Log-Rank test) (Fig 1B), while there was no differences in the participation possible and impossible group among HCAP patients (Fig 1C).