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Predictors and impact of time to clinical stability in community-acquired pneumococcal pneumonia

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Summary
Background: A clinical stability (CS) evaluation is thought to be important in community-acquired pneumonia (CAP) treatment, but evidence concerning the time to CS (TCS) remains lacking.
Methods: Among consecutive patients hospitalized with pneumococcal pneumonia, relationships between TCS and other clinical outcomes were examined, and predictors and a predictive TCS score were derived from patient characteristics on admission.
Results: A total of 144 patients were enrolled, including 46% and 27% with moderate and severe pneumonia, respectively, defined by the pneumonia severity index (PSI). The median TCS was 2 days, and was significantly correlated with the length of hospital stay ($r = 0.595$); a longer TCS was significantly associated with the more presence of poor clinical outcomes and ICU stays (adjusted odds ratios: 1.359 and 1.366, respectively). A multivariate Cox proportional hazard model revealed an absence of bilateral pneumonia (hazard rate (HR): 2.107) or bacteremia (HR: 2.520), and mild or moderate pneumonia (HR: 2.798 and 2.515, respectively, versus severe) as predictors of CS. A predictive score had moderate discriminating power for the prolonged TCS (area under the curve: 0.76), and provided similar predictive values for poor clinical outcomes and ICU stays. A score of 3 or more points indicated the prolonged TCS, with a sensitivity and specificity of 73.3% and 70.9%, respectively.

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Conclusions: Because TCS has a significant relationship with other clinical outcomes of pneumococcal CAP, the prediction of TCS might lead to the prevention of complications or an earlier transition to oral therapy. Future studies are warranted to validate these results.

Introduction

Community-acquired pneumonia (CAP) is a significant cause of morbidity and mortality worldwide; the most etiologic pathogen is thought to be *Streptococcus pneumoniae*. Therefore, it is crucial to reveal an accurate clinical picture of pneumococcal pneumonia to determine an appropriate treatment strategy for CAP. Recently, clinical stability (CS) has received attention as a clinical indicator of CAP in addition to mortality, length of hospital stay (LOS), and the use of mechanical ventilation. CS is a useful indicator of the appropriate timing to transition from intravenous to oral antibiotics and for hospital discharge [1,2]. Moreover, the time to CS (TCS) has been shown to affect clinical outcomes after discharge [3—5]. Both CS and TCS seem to play an important role in the treatment and clinical course of CAP. Up until now, the principal purpose of a primary CAP evaluation has been to predict the population with the highest mortality. In addition, it is of importance in the reduction of patient burden, medical cost, and the emerging risk of drug-resistant pathogens to switch low-risk patients to an oral therapy as early as possible. If TCS can be predicted on admission as an indicator of therapeutic efficacy, new treatment strategies for CAP might be formulated in combination with the previously existing predictive method of mortality: within the same severity category, more intensive care to prevent complications or an admission to an ICU rather than a medical ward could be indicated for patients at a high risk of a prolonged TCS, or an earlier transition to an oral therapy could be considered for those at a low risk for a prolonged TCS. However, in CAP, only some studies have reported factors affecting the TCS [6—8]; especially for pneumococcal pneumonia, few have been investigated [9].

We conducted a pilot study in patients with pneumococcal pneumonia and aimed to reveal the relationships between TCS and other clinical outcomes of CAP, and to derive the predictors and a predictive score of TCS using patient characteristics and examinations available on admission.

Methods

Patients and methods

The study population consisted of consecutive adults (aged over 18 years) admitted to our hospital with a diagnosis of pneumococcal pneumonia between January 2005 and June 2013. We excluded cases whose final diagnosis was not pneumococcal pneumonia, those who died during hospitalization, those admitted for any reason within the previous 30 days, cases diagnosed with human immunodeficiency virus infection, and those with a prescription for more than 20 mg of prednisolone or an equivalent daily. Patients with malignant disease who had received immunosuppressive treatment or who were apparent endstage were also excluded.

The patient characteristics and clinical outcomes were retrospectively collected from electronic medical records. This study was approved by the institutional review board of Komaki City Hospital (No. 131018). The requirement for informed consent was waived because of the retrospective nature of the study.

Definition and data collection

CAP was diagnosed when patients had both acute inflammatory symptoms, such as fever or severe cough, and new infiltration on a chest radiograph suggestive of pneumonia. For the diagnosis of pneumococcal pneumonia, at least one factor was needed from a specimen obtained within 24 h of admission: identification of *S. pneumoniae* from a culture of sputum or blood at $>1+$ (equivalent to 10^5 CFU/mL), identification of *S. pneumoniae* from pleural effusion, or a positive result from a urinary antigen test (UAT) (Binax NOW *S. pneumoniae* urinary antigen, Binax, Inc., Scarborough, ME, USA). The sputum was available when its Geckler grade was >3. The patients with only a positive UAT result were included unless they had an apparent respiratory infection within 3 months of admission or if any microbe other than *S. pneumoniae* was identified in the specimen.

As for the patient characteristics, age, gender, the presence of nursing home care associated pneumonia (NHCAP), comorbidities, and smoking history were recorded. Comorbidities were identified using the Charlson Comorbidity Score (CCI) [10] and the presence of chronic lung disease or diabetes was noted. The use of statins or proton pump inhibitors was also recorded.

For the severity evaluation on admission, a Simplified Acute Physiology Score 3 (SAPS 3) [11], an A-DROP scoring system (Table 1) [12] as recommended by the Japanese Respiratory Society, and a Pneumonia Severity Index (PSI) [13] were scored. The A-DROP score was classified into 3 categories as mild, moderate, or severe and extremely severe; the PSI was similarly categorized as mild (class I/II/III), moderate (class IV), or severe (class V). The value for serum C-reactive proteins (CRP) on admission was recorded as a biomarker.

An evaluation of chest radiographs on admission was performed independently by two experienced pneumologists, and the presence of pleural effusion and bilateral pneumonia were interpreted.

If *Streptococcus pneumonia* was isolated, its drug-resistance was defined by the National Committee for Clinical Laboratory Standards (NCLLS) [14], and a resistant pathogen was defined as a minimum inhibitory concentration (MIC) >0.12 μg/mL for penicillin G.

It was recorded whether the initial therapy was a combination therapy of antibiotics and whether the therapy was inappropriate with respect to the drug sensitivity of the pathogen, if available.

Table 1 The A-DROP scoring system for the severity of community-acquired pneumonia. Each factor was assigned one point, and the severity was determined by the total score calculated by adding all the points.

Factor	
Age	Male ≧ 70 y.o., female ≧ 75 y.o.
Dehydration	Blood urea nitrogen ≧ 21 mg/dL
Respiratory failure	PaO_2 ≦ 60 Torr or SpO_2 ≦ 90%
Orientation disturbance	Confusion
Blood pressure	Systolic blood pressure ≦ 90 mmHg

Severity	Total points
Mild	0
Moderate	1 or 2
Severe	3
Extremely severe	4 or 5

Outcomes

The American Thoracic Society (ATS) 2007 criteria were applied for CS [15], including all the following variables, detected during the same day after hospital admission: body temperature <37.8 °C, heart rate <100 beats/min, systolic blood pressure >90 mmHg, oxygen saturation >90% or PaO_2 >60 mmHg in room air, respiratory rate <24/min, normal mental status, and the capacity for appropriate oral intake. In cases without consecutive measurements of respiratory rate, the presence of dyspnea was substituted. All variables were assessed every day, and TCS was defined by the number of days until reaching CS.

A poor clinical outcome was defined as the need for mechanical ventilation, including non-invasive ventilation, and/or inotropic support. As for the other outcome measures, the presence of an ICU stay, including both direct admission and transfer from the general wards, and the length of hospital stay (LOS) were also collected.

Statistics

The data are presented as the median (interquartile range, IQR). TCS was related to the presence of poor clinical outcomes and ICU stay by a Mann–Whitney *U*-test, and the odds ratio (OR) was calculated and adjusted by severity on admission using a logistic regression model to examine the effect of poor clinical outcomes and ICU stay on the TCS. To investigate the relationship between the LOS and the TCS, Spearman's rank correlation test was performed.

The predictors for TCS were determined by using a multivariate Cox proportional hazard model including baseline factors with *p*-values <0.1 from the univariate analysis. To derive the predictive score for the prolonged TCS, which was defined if the TCS was over the median value, the beta-coefficient of each significant predictor was calculated using a logistic regression model and predictive scores were assigned according to their coefficients [16]. The area under the curve (AUC) of the receiver operating characteristic curve was examined to assess the discriminative ability of the predictive score for the prolonged TCS and the occurrence of poor clinical outcomes or an ICU stay.

Table 2 Patient characteristics. Data are shown as a number (%) or the median (interquartile range).

Patient characteristics	
Age (y.o.)	71 (66–81)
Gender (M/F)	87/57
NHCAP (yes)	20 (13.8)
Smoking history (yes)	84 (60.0)
Glasgow Coma Scale	15 (15–15)
Comorbidities and medications	
Chronic pulmonary disease	52 (36.1)
Diabetes	36 (25.0)
Charlson Comorbidity Index	2 (1–3)
Statin prescription	12 (8.3)
Proton pump inhibitor prescription	10 (6.9)
Examinations and therapies	
Serum C-reactive protein (mg/dL)	14.5 (9.0–25.2)
Pleural effusion	18 (12.5)
Bilateral pneumonia	41 (28.4)
Bacteremia	14 (11.7)
Mixed pathogen	10 (9.9)
Resistant pneumococcus	19 (18.8)
Combination therapy	9 (6.3)
Inappropriate therapy	19 (18.8)
Severity scores	
SAPS 3	59 (53–65)
A-DROP	
Mild	27 (18.8)
Moderate	84 (58.3)
Severe + extremely severe	33 (22.9)
PSI	
Mild	30 (27.5)
Moderate	49 (45.0)
Severe	30 (27.5)
Outcomes	
Time to clinical stability (d)	2 (1–4)
Length of hospital stay (d)	8 (6–13)
Clinical poor outcomes (yes)	14 (9.7)
ICU stay (yes)	26 (18.0)

NHCAP = nursing- and healthcare-associated pneumonia, PSI = Pneumonia Severity Index, SAPS 3 = Simplified Acute Physiology Score 3.

A *p*-value <0.05 was considered statistically significant, and the statistical analyses were performed mainly on SPSS version 20 (IBM, Armonk, NY, USA).

Results

Within the study period, 1219 consecutive patients were hospitalized because of pneumonia, of whom 164 were diagnosed with pneumococcal pneumonia. After excluding the deceased cases (mainly due to 11 dead patients), 146 patients met our criteria. In addition, two patients with discrete values resulting from prolonged enteral nutrition or mechanical ventilation (Fig. S1) were also excluded, and finally, 144 patients were included in this study and were available for an evaluation of TCS.

The patient characteristics were shown in Table 2. The median age was 71 years (IQR: 66.0–81.7) and 39.5% of the

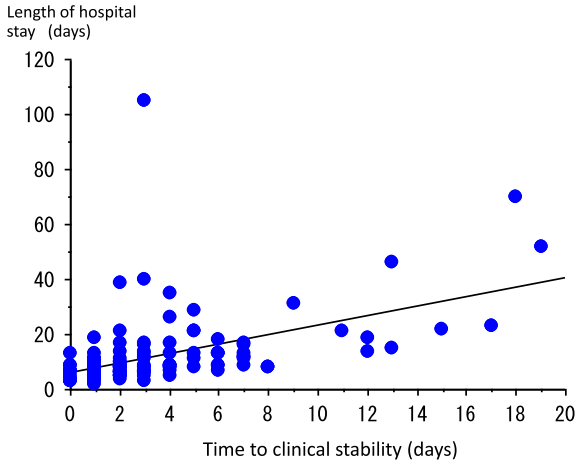

Figure 1 The relationship between the time to clinical stability and the length of hospital stay. Spearman's rank correlation test indicated a significant correlation ($r = 0.595$, $p < 0.0001$).

study population were female. The study population mainly included patients of the relatively advanced age and comorbidities with the median CCI of 2. Using A-DROP and PSI, mild and severe cases each accounted for approximately one-fifth of the cases.

The UAT had the highest performance and positive rate within the microbial examinations (Table S1). A drug-sensitivity test was obtained for 101 patients (70.1%), of whom 19 (18.8%) were considered to have resistant pathogens, with 4 cases considered highly resistant.

The median TCS value was 2 days, and poor clinical outcomes and ICU stays were detected in 14 (9.7%) and 26 patients (18.0%), respectively. The median LOS was 8 days (IQR: 6—13).

The TCS of patients with poor clinical outcomes or ICU stays were significantly longer than those of patients without (5.5 days (IQR: 2.5—15.5) versus 2.0 days (IQR: 1.0—4.0), $p < 0.001$; 5.0 days (IQR: 3.0—5.0) versus 2.0 days (IQR: 1.0—3.0), $p < 0.001$, respectively). The ORs of the prolonged TCS (defined as equal or more than 3 days) in the presence of a poor clinical outcome or an ICU stay were 1.359 (95% confidence interval (CI): 1.099—1.681, $p = 0.0047$) and 1.366 (95% CI: 1.107—1.687, $p = 0.0037$), respectively, after being adjusted by a logistic regression model using PSI, A-DROP, and SAPS 3. Moreover, the TCS was significantly correlated with the LOS ($r = 0.595$, $p < 0.0001$) (Fig. 1). The TCS was shown to have statistically significant relations to other outcome measures related to CAP, such as LOS, ICU stay and clinical poor outcomes, independently of disease severity.

The result of univariate analyses for prolonged TCS of all the variables were shown in Table S2. A multivariate analysis using six factors with p-values <0.1 from the univariate analysis revealed bilateral pneumonia, bacteremia, and PSI severity category as the significant predictors (Table 3). Those with the absence of bilateral pneumonia or bacteremia took approximately twice as early to reach CS, and cases in the moderate and mild PSI categories reached CS approximately two and three times faster, respectively, than severe cases. Specifically, the presence of bilateral pneumonia and bacteremia doubled the TCS and the TCS for mild or moderate pneumonia was one-third or one-half shorter than that of severe pneumonia. Comorbidities, resistant pathogens, and initial treatment did not affect the TCS. Using these three factors, a TCS predictive score was calculated using a logistic regression model (Table 4). This score provided moderate predictive power for the prolonged TCS, with an AUC of 0.76 (95% CI: 0.655—0.973) (Fig. 2). A total score of 3 or more points indicated the prolonged TCS with 73.3% and 70.9% sensitivity and specificity, respectively. This score was found to have similar predictive power for poor clinical outcomes and the presence of an ICU stay (AUC 0.67: 95% CI: 0.516—0.826 and 0.72: 95% CI: 0.611—0.843, respectively).

Table 3 Variables affecting the time to clinical stability. Univariate and multivariate analyses were performed using a Cox proportional hazard model. The multivariate analysis was performed using the variables with p-values <0.1 from the univariate analysis.

	Univariate			Multivariate		
	p Value	Hazard rate	95% Confidence interval	p Value	Hazard rate	95% Confidence interval
C-reactive protein (per 1 mg/dL)	0.0820	0.999	0.977—1.000	0.7224	1.000	0.998—1.002
Bilateral pneumonia (no)	0.0003	2.074	1.394—3.087	0.0209	2.107	1.119—3.965
Bacteremia (no)	0.0085	2.209	1.224—3.987	0.0100	2.520	1.247—5.090
SAPS 3 (per point)	0.0638	0.971	0.942—1.002	0.7988	1.005	0.969—1.041
A-DROP						
Mild	0.0021	2.259	1.343—3.801	0.0941	2.450	0.858—6.994
Moderate	0.1483	1.349	0.899—2.025	0.4141	1.285	0.704—2.346
Severe + extremely severe		Reference			Reference	
PSI						
Mild	<0.0001	3.243	1.845—5.701	0.0278	2.798	1.119—6.998
Moderate	0.0028	2.084	1.288—3.372	0.0069	2.515	1.288—4.911
Severe		Reference			Reference	

PSI = Pneumonia Severity Index, SAPS 3 = Simplified Acute Physiology Score 3.

Table 4 Predictive scores for the prolonged time to clinical stability. Each point was assigned by weighting it by the coefficient determined in the multivariate logistic regression analysis.

	Beta-coefficient	*p* Value	Odds ratio	95% Confidence interval	Point
PSI					
Mild		Reference	1.000		0
Moderate	1.632	0.0497	0.195	0.038–0.912	2
Severe	2.818	0.0012	0.060	0.011–0.327	3
Bacteremia	1.622	0.0271	0.198	0.047–0.832	2
Bilateral pneumonia	1.108	0.0396	0.330	0.115–0.949	1

PSI = Pneumonia Severity Index.

Discussion

TCS was evaluated among 144 patients hospitalized for pneumococcal pneumonia. A longer TCS was associated with the more presence of poor clinical outcomes and ICU stays, and significantly correlated with LOS, independent of disease severity on admission. The presence of bacteremia, bilateral pneumonia, and PSI severity category were the significant predictors of prolonged the TCS. Predictors of TCS remain unclear; especially for pneumococcal pneumonia, none have reported a predictive score.

In CAP treatment, reaching CS is important in clinical decision making. Because clinical deterioration was reported in only <1–2% of patients after reaching CS [7,17,18], it is useful as a surrogate in determining treatment duration [19,20] and when to switch to oral therapy [1,2]. Once reaching CS, oral therapy is indicated, even for bacteremic pneumococcal pneumonia [21]. Some have reported the effects of CS/TCS on CAP outcomes after discharge, reporting CS as an indicator of discharge [3–5]. This study also found a significant relationship between TCS, poor clinical outcomes, and ICU stays; both CS and TCS seem to be important indicators in CAP treatment.

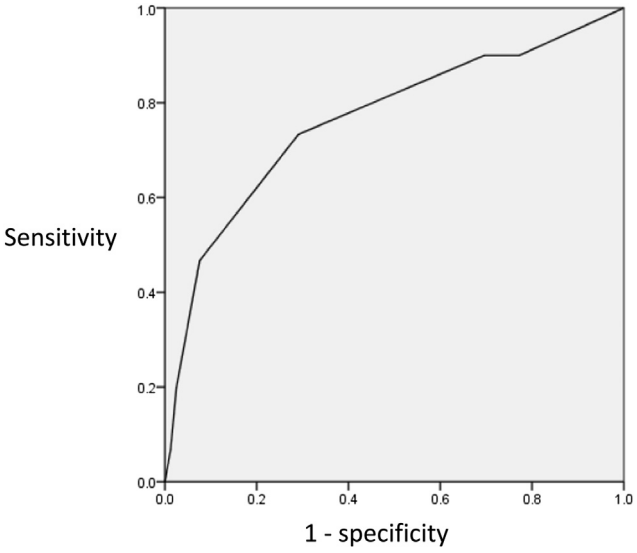

Figure 2 A receiver operating characteristic curve of the predictive score for the prolonged time to clinical stability. The area under the curve was 0.76 (95% confidence interval: 0.655–0.973).

In general, TCS is reported as 2–4 days [3,6,7], but knowledge regarding a prolonged TCS remains lacking. Using Halm's definition [7], Menendez et al. showed that dyspnea, confusion, pleural effusion, multi-lobular pneumonia, PSI classes III/IV, and adherence to CAP guideline were factors prolonging TCS in 1424 CAP patients [6]. Bordon et al. extracted pneumococcal pneumonia patients from a large CAP cohort and reported that male sex, diabetes, and HIV infection were predictors of the short TCS, and alert mental status, body temperature >104 °F or <96 °F, respiratory rate >30/min, PaO2 <60 Torr, the presence of a cavity on chest radiograph, neoplastic disease, liver disease, cerebrovascular accidents, and ICU admissions were predictors of the prolonged TCS [9]. However, they did not evaluate a general severity index or serum biomarkers, the population had a lower prevalence of 4.4% for bacteremia, and they used ATS 2001 definitions for CS criteria [22]; all these factors may have influenced the differences from the present study.

Some studies detected multi-lobular pneumonia, pleural effusion, PSI scores >90, chronic liver disease, leukocytopenia, thrombocytopenia, dyspnea academia, confusion, *Legionella* pneumonia, and higher serum CRP values as predictors of clinical failure [6,23–27]. Only one reported in a population with pneumococcal pneumonia that chronic liver disease, higher serum CRP values, and higher serum creatinine were risk factors, and that COPD was a protective factor for complicated pneumonia [28].

Previous studies rarely investigated predictors or predictions of TCS, especially for pneumococcal pneumonia; to our knowledge, this is the second such study.

Bacteremic CAP is associated with worse clinical outcomes than non-bacteremic CAP. Especially for pneumococcal pneumonia, higher rates of bacteremia of 10%–20% were identified [29], similar to the results of the present study, and longer TCS [21] and higher mortality [30] were described in bacteremic cases. However, clinical outcomes in pneumococcal pneumonia were also reported to be equivalent, whether or not bacteremia was present, and the effect of bacteremia on TCS/CS is controversial [9,31].

Bilateral pneumonia is a minor criterion for severe pneumonia in the ATS guidelines [15], and is thought to affect deterioration [6,23].

The relationship between PSI and TCS has already been described as a disease-specific severity index [6–8,32]. Confusion, Respiratory rate, Blood pressure and age ≥65

(CRB-65) score has been shown to have equivalent predictive power to PSI in discriminating the CS within 7 days [8].

Because of the lack of apparent CS definitions, a wide range of TCS values from 3 to 7 days were reported within the same populations according to different definitions [7]. However, among the recently available TCS criteria [7,15,22], a similar predictive power for clinical deterioration was reported [17,18]. Moreover, serum biomarkers such as CRP and procalcitonin were shown to have additional value than the modified Halm's criteria alone [33]. Regardless, a simple, standardized definition capable of daily evaluation is needed.

Limitations

First, this study was retrospective in nature, and has a relatively small sample size. Missing data were inevitable; especially, SAPS 3 calculations were performed for only 57% of patients. In general, CAP is thought to be a very heterogeneous disease caused by many varieties of etiologic pathogens, of which half are unknown [12], and is affected by many clinical factors such as comorbidities. Strengths of this study include that it enhances the effects of patient characteristics on the results, as it consisted of a mostly homogeneous population, including only pneumococcal pneumonia, and it examined more factors, including statin prescriptions and resistant pathogens. Regardless, our results should be validated by a prospective study in a larger population.

A second limitation concerns microbial examinations. We only included cases with only positive UAT, which may include false-positive results, with the reported specificity of 95% [34]. In addition, this study did not evaluate pneumococcal serotypes, as no commercial kit is available in Japan. Many investigations have revealed the effect of serotypes on the clinical course of pneumococcal diseases [35]; in future studies, pneumococcal serotype should be examined.

Third, we substituted dyspnea as a CS criterion in cases without consecutive respiratory rate measurements. In Japan, respiratory rate measurements are not performed frequently; therefore, respiratory rate was excluded from the A-DROP score recommended by the Japanese Respiratory Society (Table 1). To be more objective, an original Japanese definition of CS, including a respiratory rate substitute, might need to be derived and validated.

Conclusion

In this pilot study, TCS was confirmed as an important indicator relevant to LOS, poor clinical outcomes, and ICU stays. Bacteremia, bilateral pneumonia, and PSI severity category were detected as predictors prolonging TCS by two to three times. Predictive scores greater than or equal to 3 points indicated the prolonged TCS with 73.3% and 70.9% sensitivity and specificity, respectively.

The prediction of the prolonged TCS, that is, pneumonia with a high risk of complications, may lead to preventive interventions in high-risk groups and an earlier transition to oral therapy in low-risk populations. A future prospective study is warranted to validate these predictors and predictive scores among patients within a larger CAP population.

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Conflict of interest

None of the authors have any conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2014.02.007.

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