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# **Revision of the severity rating and classification of hospital-acquired pneumonia in the Japanese Respiratory Society guidelines**

Masafumi Seki,<sup>1</sup> Akira Watanabe,<sup>2</sup> Keiichi Mikasa,<sup>3</sup> Junichi Kadota<sup>4</sup> and Shigeru Kohno<sup>1</sup>

<sup>1</sup>Department of Molecular Microbiology and Immunology, Nagasaki University Graduate School of Medical Sciences, Nagasaki, <sup>2</sup>Research Division for Development of Anti-Infective Agents, Institute of Development, Aging and Cancer, Tohoku University, Sendai, <sup>3</sup>Center for Infectious Diseases, Nara Medical University, Nara, <sup>4</sup>Second Department of Internal Medicine, Oita University Faculty of Medicine, Oita, Japan.

**Short title:** New criteria for severity of HAP

**Correspondence:** Masafumi Seki, MD, PhD

<sup>2</sup><sup>nd</sup> Department of Internal Medicine, Nagasaki University Hospital, Sakamoto 1-7-1, Nagasaki, 852-8501, Japan. Tel: +81-95-849-7273, Fax: 095-849-7285

E-mail: [seki@nagasaki-u.ac.jp](mailto:seki@nagasaki-u.ac.jp)

## **ABSTRACT**

**Background and objective:** Based on the results of a multicentre collaborative survey of hospital-acquired pneumonia (HAP) conducted in Japan, the severity rating and classification of pneumonia in the Japanese Respiratory Society guidelines for management of HAP were examined.

**Methods:** Parameters for the severity classification were selected from the factors associated with prognosis in the HAP survey and in other previous reports. Depending on the presence of the parameters listed below, patients with HAP were stratified into those with high, moderate, or low-risk. The high-risk group was defined as patients with three or more of the following risk factors: “malignant tumour or immunocompromised status”, “impaired consciousness”, “requiring fraction of inspired oxygen ( $\text{FiO}_2$ ) > 35% to maintain  $\text{SaO}_2$  > 90%”, “male aged 70 years or older, or female aged 75 years or older” and “oliguria or dehydration.” The moderate-risk group was defined as patients with any of the secondary risk factors as follows: “C-reactive protein  $\geq$  200 mg/L” and “extent of infiltration on CXR covers at least 2/3 of one lung”. The low-risk group was defined as all other patients.

**Results:** Application of this classification scheme to the patients enrolled in the HAP survey revealed a mortality rate of 40.8% (98/240) in the high-risk group, which was significantly higher than the mortality rates in the moderate and low-risk groups: 24.9% (69/277) and 12.1% (101/834), respectively.

**Conclusion:** These results indicate that it is possible to classify patients using these parameters as prognostic indicators.

**Key words:** guidelines, hospital-acquired pneumonia, Japan, surveillance.

## INTRODUCTION

Hospital-acquired pneumonia (HAP) is the second most common nosocomial infection, and mortality due to HAP is the highest among hospital-acquired infections.<sup>1-3</sup> Because drug-resistant pathogens are common causative organisms in compromised hosts, treatment is difficult and antibiotic selection is important. Delays in appropriate initial antimicrobial therapy have been associated with excess mortality due to HAP.<sup>4-8</sup> In the United States (US), the management of HAP has been standardized by the publication of treatment guidelines by the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA).<sup>1,2</sup>

The ATS guidelines define HAP occurring within the first 5 days of hospitalization as early-onset disease, and HAP occurring thereafter as late-onset disease. Due to differences between the health insurance systems of Japan and the US, however, patients are more likely to have near-normal immunity throughout long-term hospitalization in Japan. Thus, it would not be appropriate to apply the US treatment guidelines directly to the Japanese situation.<sup>9,10</sup>

To define the criteria relevant to the actual condition in Japan, guidelines for the management of HAP were published by the Japanese Respiratory Society (JRS) in March 2002.<sup>9</sup> In these guidelines, patients were divided into groups I, II, III and IV, ranging from mild to severe. Following the publication of these guidelines, a nationwide multicentre collaborative survey was conducted to ascertain the clinical details of HAP across Japan, with the objective of investigating the appropriateness of the guidelines.<sup>9</sup>

The results of this survey suggested a need for revision of the classification of pneumonia, because there was a remarkable disparity in the numbers of patients in each group; more than 90% of patients were stratified into Groups III or IV, while only 4 patients (0.3%) were stratified into Group I. In addition, among patients categorized in Group III, there were differences in mortality rate with the severity of pneumonia.<sup>10</sup>

The severity classification in the current JRS guidelines was based on clinical evaluation methods for new antimicrobial agents for treating respiratory infections,<sup>11</sup> with emphasis being on evaluating the efficacy of investigational drugs. Taking into account the fact that the primary endpoint of pneumonia is the prognosis (mortality rate), it is more appropriate to select parameters that are indicators of prognosis, such as the CURB-65 (confusion, urea >7 mmol/L, respiratory rate  $\geq$ 30/min, low systolic (<90 mm Hg) or diastolic ( $\leq$ 60 mm Hg) blood pressure, and aged  $\geq$ 65 years)<sup>12</sup> and A-DROP (age, dehydration, respiratory failure, orientation disturbance, shock blood pressure)<sup>13</sup> severity criteria for community-acquired pneumonia (CAP).

In this study, the factors affecting prognosis of HAP were examined, and those most relevant for severity classification of HAP in Japan were selected.

## **METHODS**

### **Subjects**

The cases used in this study were identified in a nationwide multicentre collaborative survey of HAP in Japan.<sup>10</sup> The survey was conducted during June 2002 – May 2004, and details of 1,356 patients from 254 hospitals were analyzed.

### **Selection of primary assessment parameters**

For the primary assessment parameters, starting with the parameter with the most significant effect on prognosis, we selected the following factors as prognostic indicators: “malignant tumour or immunocompromised status”, “impaired consciousness”, “requiring fraction of inspired oxygen ( $\text{FiO}_2$ ) > 35% to maintain  $\text{SaO}_2$  > 90%”, “male aged 70 years or older, or female aged 75 years or older” and “oliguria or dehydration”.<sup>10</sup> Of these factors, “malignant tumour” (odds ratio: 3.555; 95% confidence interval [CI] 2.497-5.061), “impaired consciousness” (odds ratio: 2.406; 95% CI 1.667-3.472), “requiring  $\text{FiO}_2$  > 35% to maintain  $\text{SaO}_2$  > 90%” (odds ratio: 1.567; 95% CI 1.071-2.291), and “oliguria” (odds ratio: 2.863; 95% CI 1.286-6.376) had significant effects on prognosis in the HAP survey.<sup>10</sup>

The survey showed that prognosis was poor for patients with cellular immunocompromised status, while some patients had multiple immunosuppressive states such as cellular and humoral immunosuppressive states. In addition, since there were no pronounced differences among the presumptive causative organisms (data not shown), these two conditions were merged as “immunocompromised status”, and the assessment parameter was combined with the associated disease state, malignant tumour, to yield “malignant tumour and/or immunocompromised status”.

Dehydration was not associated with prognosis in the HAP survey, but had an impact on clinical efficacy.<sup>10</sup> Thus, it was combined with the associated disease state, oliguria, to

create the assessment parameter “oliguria or dehydration”, similar to the A-DROP criterion.<sup>13</sup>

### **Selection of secondary assessment parameters**

Considering the possibility that patients with a poor prognosis may not be completely covered by the primary assessment parameters, we selected the following secondary assessment parameters as indicators of severity of pneumonia: “C-reactive protein (CRP)  $\geq$  200 mg/L” and “extent of infiltration on CXR covers at least 2/3 of one lung”. In the survey results, the factors “CRP  $\geq$  200 mg/L” (odds ratio: 1.322; 95% CI 1.072-1.630) and “extent of infiltration on CXR covers at least 2/3 of one lung” (odds ratio: 1.285; 95% CI 1.051-1.572) were found to affect prognosis.<sup>10</sup>

### **Severity rating**

The severity rating was assessed using the criteria shown in Figure 1. Patients with a specified number or more of the primary risk factors were stratified into the high-risk group. Patients with any of the secondary risk factors were stratified into the moderate-risk group. All other patients were stratified into the low-risk group.

### **Calculation of mortality rate according to severity, and statistical analysis**

Mortality rate was evaluated as all-cause death at 30 days after the start of the initial treatment, and the mortality rate was calculated according to severity. According to the IDSA/ATS HAP guidelines, the crude mortality rate for HAP may be as high as 30 to 70%.<sup>5</sup> As the mortality rate for HAP in Japan is relatively low in comparison with the US,<sup>10</sup> 30% was used as a yardstick for mortality rate in the high-risk group. Fisher’s exact test was used for statistical analysis, and a risk rate less than 5% was regarded as significant.

## RESULTS

### Characteristics of patients included in the HAP survey in Japan

Details of the patient characteristics are summarized in Table 1. Males, patients aged 65 years or older, and patients with ventilator associated pneumonia accounted for 69.2%, 81.0%, and 6.6% of the total, respectively. Early onset cases accounted for 9.2% of all cases, and cases with onset of symptoms more than 30 days after hospitalization accounted for 48.7%. The most common pathogens were *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]) (25.5%), followed by *Pseudomonas aeruginosa* (18.3%) and *Klebsiella pneumoniae* (8.2%). The 30-day mortality rate was 19.8%.

### Investigation of severity rating

#### *Stratification by primary assessment parameter*

The distribution of mortality rate by number of primary assessment parameters is shown in Table 2. When the cases were stratified by a threshold value of “3 factors”, the mortality rate for the group with “3 or more factors” was 40.8%, which was the closest to the target mortality rate (30%), and higher than the mortality rate for “2 or fewer factors” (15.3%). In the following analysis, the high-risk group was defined as the patients with “3 or more” of the primary risk factors.

#### *Threshold value for CRP*

The distribution of mortality rates by CRP value at diagnosis is shown in Table 3. When the cases were stratified by a threshold value of 200 mg/L, the mortality rate in the “ $\geq$  200 mg/L” group was 30.9%, which was the closest to the target mortality rate (30%), and higher than the mortality rate in the “ $<$ 200 mg/L” group (17.7%). In the following analysis, severity was stratified based on a CRP value of 200 mg/L.



### **Mortality rate by degree of severity**

The mortality rate in the moderate-risk group was 24.9% (69/277). This mortality rate was higher than that in the low-risk group (12.1%, 101/834) (Table 4). Among the patients in the low-risk group, 194 (34.9%) were assessed as severe under the current JRS HAP guidelines (Table 5). The mortality rate for these patients was 19.1% (37/194).

### **Comparison of the severity classification criteria evaluated in this study with CURB-65**

CURB-65 is a clinical prediction rule that has been validated for predicting mortality in CAP.<sup>12</sup> The performance of CURB-65 in predicting mortality due to HAP in Japan has been examined.<sup>10</sup> As information on blood-urea nitrogen was not collected in the HAP survey, dehydration was used as a substitute. Patients with CURB-65 scores of 0-1, 2, and 3-5 accounted for 70.3% (953/1356), 20.4% (277/1356), and 9.3% (126/1356) of the total, respectively. In comparison with the percentage of patients in the low-risk group (61.8%, 838/1356), the percentage with CURB 0-2 was slightly higher. The mortality rate increased with increasing CURB-65 scores; the mortality rates of patients with CURB-65 scores of 0-1, 2, and 3-5 were 15.1% (143/950), 27.5% (76/276), and 39.2% (49/125), respectively.

The mortality rate for patients classified by CURB-65 score was compared with that for patients classified according to the criteria used in this study (Table 6). Thirty-one patients in the high-risk group had CURB-65 scores of 0-1, and the mortality rate was 45.2%. In contrast, 15 patients with CURB-65 scores of 3-5 were categorized in the low-risk group, and the mortality rate for these patients was 13.3%.

## **DISCUSSION**

Based on the results obtained in a nationwide survey, the classification of severity of HAP in the current guidelines was reviewed, and a new classification scheme based on prognostic indicators was evaluated.

A process of scoring individual risk factors and classifying severity on the basis of those scores, similar to the PORT (pneumonia outcomes research team) classification in the IDSA CAP guidelines,<sup>14</sup> was initially considered. However, as the basic principle was to ensure that the JRS HAP guidelines would be widely used by non-specialized physicians in practical clinical settings, a classification scheme that required cumbersome calculation of scores would not have been appropriate. Therefore concise classification criteria, similar to the A-DROP criteria in the JRS CAP guidelines,<sup>13</sup> were developed.

Risk factors associated with prognosis in the HAP survey,<sup>10</sup> were selected and investigated, to identify those most relevant for severity classification. The five factors selected were very similar to the assessment factors used in A-DROP, except that “malignant tumour or immunocompromised status” was adopted instead of “blood pressure (shock)”. For the assessment of severity in HAP, the underlying disease was more important than the physical condition of the patients. Although dehydration is a subjective parameter, A-DROP includes dehydration as a severity assessment parameter that is an indicator of prognosis. As the JRS CAP guidelines are widely used and accepted in clinical settings in Japan, dehydration was similarly adopted as a severity assessment parameter for HAP. The mortality rate for the group with “3 or more factors” was 40.8%. The mortality rate for patients with five primary assessment factors was probably relatively low because only seven patients were in this category.

As some patients with a poor prognosis may be classified as “mild” on the primary criteria alone, secondary criteria for assessment of the severity of pneumonia were also

examined, and CRP and infiltrates on CXR were selected as the secondary parameters. It has been reported that there is no correlation between CRP and the prognosis of patients with CAP;<sup>15,16</sup> however, CRP was correlated with the prognosis of HAP patients.<sup>10</sup> In addition, when the mortality rate was calculated for a threshold CRP value of 200 mg/L, there was an appreciable difference in mortality rates between patients with high and low values for CRP, and it was therefore considered appropriate to include CRP as an assessment parameter.

With the classification based on the criteria used in this study (Fig. 1), the mortality rate in the high-risk group was 40.8% (98/240), which was significantly higher than the rates in the moderate and low-risk groups [24.9% (69/277),  $P < 0.001$  and 12.1% (101/834),  $P < 0.001$ , respectively]. When this severity classification was compared with that using the CURB-65 criteria, the percentage of patients classified in the low-risk group was considerably higher using CURB-65. The low-risk group, as classified by CURB-65, contained a sub-group with a high mortality rate, and CURB-65 may underestimate the number of serious HAP cases in Japan. This is probably because CURB-65 does not use factors affecting HAP prognosis, such as malignant tumour,<sup>10</sup> as evaluation parameters. Thus, these revised severity classification criteria can be more appropriately applied to HAP cases than CURB-65.

As the mortality rate in the high-risk group was high (40.8%), it seems appropriate to recommend potent combination therapy (carbapenems or other  $\beta$ -lactams with anti-pseudomonal activity, plus aminoglycosides or fluoroquinolones, etc.) for this group of patients, in accordance with the antibiotic recommendations for groups at risk for multidrug resistant pathogens in the ATS/IDSA HAP guidelines.<sup>2</sup> It would also be important to de-escalate the therapy whenever possible.

In contrast, for the low-risk group, excluding patients with risk factors for *Pseudomonas aeruginosa* pneumonia, including long-term hospitalization, prior use of third-generation cephalosporins, COPD,<sup>17-19</sup> and aspiration pneumonia involving anaerobic

organisms,<sup>20</sup> it may be appropriate to recommend monotherapy (e.g., penicillins, third-generation cepheems, etc.) rather than potent combination therapy as initial treatment.

In the ATS/IDSA HAP guidelines, if MRSA risk factors are present or recognized or if there is a high incidence locally, use of anti-MRSA drugs is recommended as initial empirical therapy.<sup>2</sup> In a survey conducted in Japan, the incidence of *S. aureus*, principally MRSA, as the presumptive causative organism was high, but initial use of glycopeptide drugs was as low as 3.8%.<sup>10</sup> Considering the fact that both clinical efficacy and prognosis are poor in MRSA pneumonia,<sup>5</sup> it may be necessary to use anti-MRSA drugs as initial therapy for patients at risk of infection with MRSA. As reported in previous studies,<sup>21-23</sup> MRSA infection should be suspected on the basis of Gram-stained specimens or other evidence such as, 1) long-term antimicrobial treatment, 2) a history of long-term hospitalization, and 3) a history of MRSA infection or colonization. As the risk of MRSA infection is significant (data not shown), initial combination therapy that includes an anti-MRSA drug may lead to improved prognoses.

Using the severity classification criteria examined in this study, we were able to definitively classify patients into three groups based on prognostic indicators. However, the low-risk group included some patients assessed as severe using the current guidelines, and it is possible that severity in these cases was underestimated (Table 5). In these cases, escalation of antibiotic therapy may be necessary.

In conclusion, clinical parameters were examined and new severity classification criteria for HAP were established. Verification of the appropriateness of these revisions under clinical conditions will be important, and it will also be essential to periodically review the classification scheme with the aim of providing appropriate guidelines.

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## **FIGURE LEGENDS**

Figure 1. Flowchart depicting new procedure for assessment and classification of severity. Patients with hospital-acquired pneumonia (HAP) were assessed according to the criteria and treatment is determined by classification into one of the three risk groups.

Table 1. Characteristics of patients with hospital-acquired pneumonia in a survey from Japan<sup>10</sup>

Characteristic	Category	Number of patients (%)
Gender	male	939 (69.2%)
Age (years)	65 years or older	1098 (81.0%)
Onset time (days)	2≤<5	125 ( 9.2%)
	>30	660 (48.7%)
Disease type	ventilator-associated pneumonia	90 ( 6.6%)
Presumed causative organism	<i>Staphylococcus aureus</i> <sup>a</sup>	208 (25.5%)
	<i>Pseudomonas aeruginosa</i>	149 (18.3%)
	<i>Klebsiella pneumoniae</i>	67 ( 8.2%)

<sup>a</sup> Including methicillin-resistant *S. aureus*

Table 2. Prognosis by the number of primary risk factors in the severity classification.

Number of risk factors	Mortality rate <sup>†</sup>	<i>P</i> value <sup>*</sup>
0	5.2% (6/115)	
1	12.5% (70/561)	15.3%
2	21.6% (94/435)	(170/1111)
3	35.6% (62/174)	] <0.001
4	57.6% (34/ 59)	
5	- (2/7)	
		(98/240)

<sup>\*</sup>Fisher’s exact test

<sup>†</sup> Mortality rate was calculated by dividing the number of deaths by the number of patients for whom prognosis was assessed.

Table 3. Prognosis by the concentration of C-reactive protein (CRP)

CRP (mg/L)	Mortality rate <sup>†</sup>	<i>P</i> value <sup>*</sup>
<50	14.6% (44/301)	
≥50, <100	16.3% (59/361)	17.7%
≥100, <150	20.5% (53/259)	(198/1119)
≥150, <200	21.2% (42/198)	
≥200, <250	26.5% (30/113)	30.9%
≥250	36.3% (33/ 91)	(63/204)

<sup>\*</sup>Fisher’s exact test

<sup>†</sup> Mortality rate was calculated by dividing the number of deaths by the number of patients for whom prognosis was assessed.

Table 4. Prognosis by severity using the revised severity classification criteria

Category	Cases	Mortality rate <sup>†</sup>	<i>P</i> -value <sup>*</sup>
Low-risk	838	12.1% (101/834)	<0.001
Moderate-risk	277	24.9% (69/277)	
High-risk	241	40.8% (98/240)	

\*Fisher's exact test

† Mortality rate was calculated by dividing the number of deaths by the number of patients for whom prognosis was assessed.

Table 5. Correlation between severity classification as assessed using the revised guidelines and the current guidelines

Category	Mortality rate by severity using the current guidelines*	
	Mild or moderate cases	Severe cases
Low-risk	10.0% (64/640)	19.1% (37/194)
Moderate-risk	16.5% (23/139)	33.3% (46/138)
High-risk	16.7% (3/18)	39.2% (95/222)

\*Mortality rate was calculated by dividing the number of deaths by the number of patients for whom prognosis was assessed.

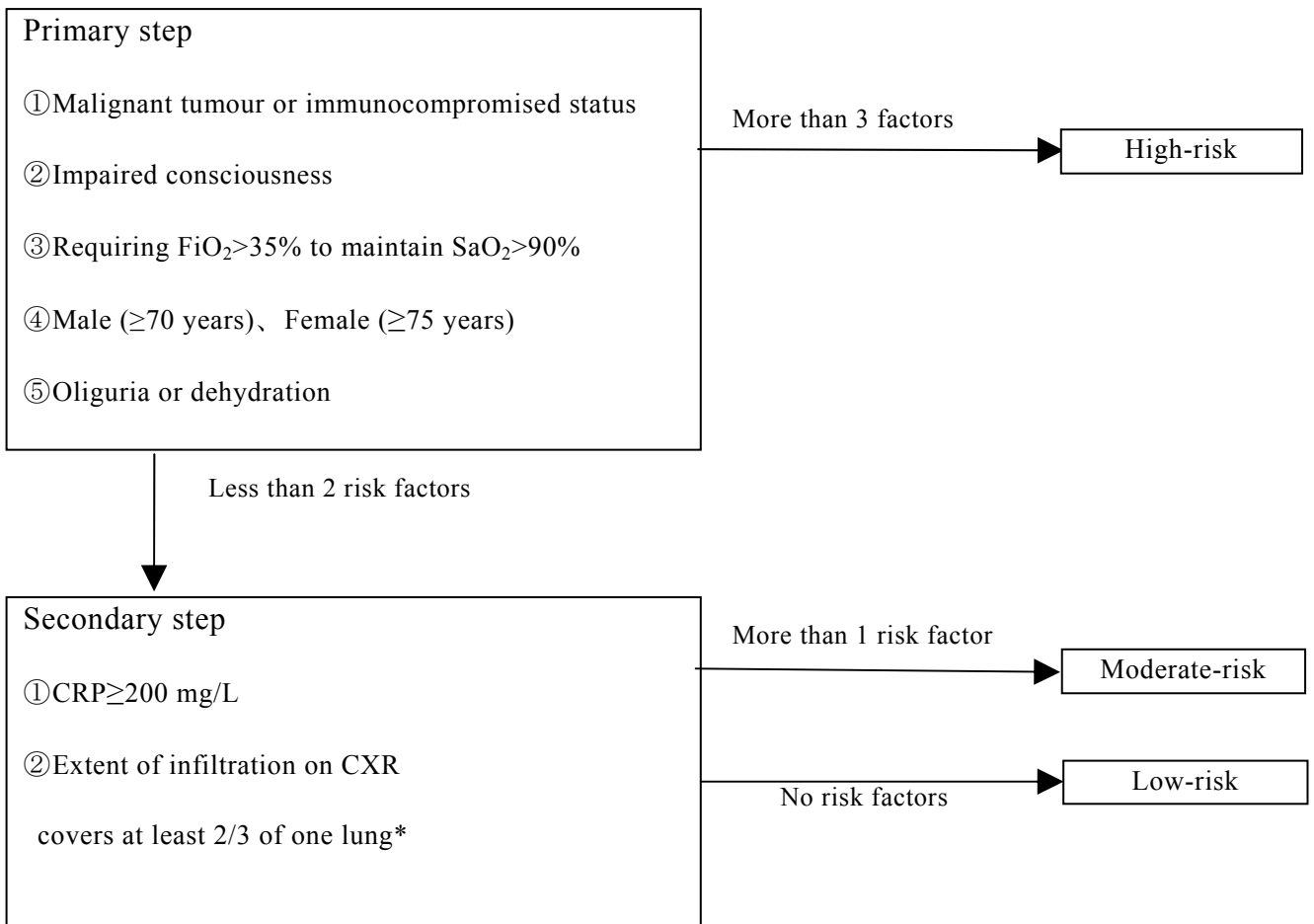
Table 6. Correlation between severity classification using the revised severity rating criteria and mortality rates for cases classified according to the CURB-65 criteria.

Category	Mortality rate according to CURB-65 scores*		
	0-1	2	3-5
Low-risk	10.9% (78/713)	19.8% (21/106)	13.3% (2/15)
Moderate-risk	24.8% (51/206)	21.9% (14/64)	- (4/ 7)
High-risk	45.2% (14/31)	38.7% (41/106)	41.7% (43/103)

\*Mortality rate was calculated by dividing the number of deaths by the number of patients for whom prognosis was assessed.

CURB-65, confusion, urea >7 mmol/L, respiratory rate  $\geq 30$ /min, low systolic (<90 mm Hg) or diastolic ( $\leq 60$  mm Hg) blood pressure, and aged  $\geq 65$  years.

Figure 1



\* If there is more than one area of infiltration, the rating is determined by the sum of all the lesions