Marked Reduction in 28-Day Mortality among Elderly Patients with Severe Community-Acquired Pneumonia: Post Hoc Analysis of XueBiJing Injection Randomized Controlled Trial

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Abstract
Background There were a few studies on the case mortality of severe community-acquired pneumonia (CAP) in elderly people. Improved outcomes with XueBijing (XBJ) Injection versus placebo have been shown in overall trial populations. We investigated the efficacy and safety of XBJ versus placebo in subjects with severe CAP stratified by age (<65 and ≥ 65 years).

Methods This post hoc analysis of a large randomized trial compared data from elder and nonelderly patients with XBJ, 100 ml, q12h, or a visually indistinguishable placebo for 5-7 days.

Results Among subjects ≥65 years (n=291), 23 (16.0%) XBJ recipients and 41 (27.9%) placebo recipients (P =0.014) died within 28 days. Among subjects <65 years (n=360), XBJ still had lower mortality (XBJ 15.6% verse placebo 22.8%; P =0.082), without significantly statistical difference. Total duration of ICU stay and the time of mechanical ventilation were similar in both groups (P > 0.05).

XBJ also had a favorable safety profile, with no clinically relevant differences between two groups. The overall incidence of adverse events was similar in both groups.

Conclusions XBJ was safe and effective for reduction in 28-day mortality among elderly patients with severe CAP. Additional trials involving elderly patients are needed to further confirm the present results.

Background
Community-acquired pneumonia (CAP) represents an important threat to the health of older adults[1]. Like other respiratory infections, people at the extremes of age are at greatest risk and have worse outcomes. In adults, the incidence of CAP and related hospitalization and mortality increase steadily with age, even when these rates are adjusted for chronic health problems such as lung or heart conditions[2, 3]. Specially, the incidence of CAP in adults increases with age, with a dramatic rise after age 65. In developed countries, almost one half of the total hospitalizations for CAP occur in patients over 65 years and pneumonia is a leading cause of death among this age group[4]. The severity of CAP also increases with age, primarily due to age-related immune dysfunction, and greater likelihood of underlying comorbid factors in elderly patients[5].

However, despite the recognized importance of CAP in the elderly, there is little information about the
precise etiology and prognosis factors affecting elder patients admitted to an intensive care unit (ICU) for severe CAP although such knowledge seems basic to the most appropriate management of elder patients[6]. American Thoracic Society guidelines suggest that three criteria can be used to define appropriate empirical treatment of CAP: the severity of pneumonia at presentation, the presence of underlying disease, and age [7]. As a result, different antimicrobial strategies are proposed for outpatients according to age and/or underlying condition. Conversely, all patients with severe CAP are included in the same therapeutic group whatever their age, and the potential implications of advanced age on antimicrobial management are not mentioned. Given the morbidity and mortality of severe CAP in the elderly, new therapeutic options would be valuable[8].

XueBijing (XBJ), an herbal-based intravenous preparation approved by the National Medical Products Administration (NMPA) China in 2004, has been incorporated into routine sepsis care in China [9, 10]. Pharmacological studies have shown that XBJ has an antagonistic effect on endotoxin, and an inhibitory effect on the uncontrolled release of endogenous inflammatory mediators produced by endotoxin-stimulated monocytes/macrophages [11–13]. A recent well-done randomized study showed XBJ effective in patients with severe CAP [14]. Impressive benefit with this herbal-based medication was an 8.8% absolute reduction in mortality in patients who received XBJ. Few clinical trials have examined the safety or impact of new therapeutic options on mortality rate in an elder high-risk cohort with severe CAP, data in individuals with severe CAP in this age group is largely lacking. The present analysis evaluated the effects of XBJ and placebo in two age groups (≥ 65, < 65 years) using data from the XBJ trial. Subjects aged 65 years may represent elder patients of greatest concern to clinicians. This study provides information to clinicians on the efficacy and safety of XBJ in the elderly subjects with severe CAP.

Methods
Design Overview
A post-hoc analysis was carried out using data from the main multicenter randomized controlled trial (RCT) “XueBijing injection versus placebo for critically ill patients with severe community-acquired pneumonia: a randomized controlled trial”. Details of the XBJ trial have been previously
published. The protocol is consistent with the principles of the Declaration of Helsinki, was approved by the Medical Ethics Committee of Zhongshan Hospital, Fudan University [2011–38(3)] and the participants gave their written informed consent. The trial included 710 severe CAP patients, randomly assigned to receive XBJ (n = 334), or placebo (n = 341). The participants received the solvent only (normal saline, 200 ml, q12h) in the placebo group and the solvent plus XBJ (normal saline 100 ml + XBJ 100 ml, q12h) in the XBJ group. Both groups received a standard therapy (such as antibiotics) chosen by the attending physician according to the 2007 ATS/IDSA guideline. The primary outcome was 8-day improvement in the pneumonia severity index (PSI) risk rating. Main secondary outcomes were 28-day mortality rate, duration of mechanical ventilation and total duration of ICU stay. In this post hoc analysis of the XBJ study the primary outcome was 28-day mortality. Other secondary endpoints were the time of mechanical ventilation, total duration of ICU stay.

Statistical Analyses
Primary outcome analysis was a simple categorical frequency comparison by use of the $\chi^2$ test. For time-to-event variables, Kaplan-Meier estimates were used and the groups were compared with a log-rank test. Hazard ratio (HR) and associated 95% confidence intervals (CIs) were estimated from the Cox proportional hazards model.

The secondary outcome for the time of mechanical ventilation was analyzed by t test or the Wilcoxon rank sum test as appropriate. The same analysis was used for other continuous variables, such as total duration of ICU stay. Categorical variables were compared using the chi-square test or Fisher exact test. Descriptive statistics (number and frequency) were used to summarize all safety outcomes for each group. Safety outcomes included serious, nonserious adverse events, and laboratory measurements.

All outcomes were analyzed in the intent-to-treat population, which included all patients as randomized. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.), with a 2-sided P value of less than .05 considered significant.

Results
Demographic characteristics stratified according to age group and treatment arms are summarized in
Table 1. The mean age of elder patients (n=291) was 70.47±3.23 years; and n=190, 65.29% were male. The mean age of nonelderly patients (n=360) was 49.76±11.63 years; and n=253, 70.28% were male. The mean BMI at baseline did not differ between treatments or age groups (≥65 years P=0.929, <65 years P=0.749). Differences between age groups in baseline comorbidities, PSI score or other biological parameters were not significant.

Rate of patients with acute respiratory distress syndrome (ARDS) and septic shock, the baseline settings of mechanical ventilation, and the frequency of antimicrobial prescriptions in each age group are listed in Table 2. There were no significant differences in antimicrobial treatment (Beta-lactam, quinolones, glycopeptide, oxazolidinones, antifungal agents, tetracyclines, macrolide, aminoglycoside, nitroimidazoles, antivirals, lincomycin, and sulfanilamide) or patient parameters (septic shock and ARDS at baseline and on study) between the XBJ and placebo groups in each age group. In addition, microbiologic identification was similar in both study groups (all P > 0.05) (Table S1).

Among elder patients (n=291), 28-day mortality was significantly lower in those who received XBJ verse those who received placebo (P=0.014). No statistically significant difference in mortality between two groups was seen in younger patients (P=0.082). Both elderly and nonelderly patients experienced shorter the time of mechanical ventilation and total duration of ICU stay, however, without significantly differences. Some secondary outcomes are listed in the Table S2. Among elder patients, the XBJ group had a significantly lower pneumonia severity index (PSI) (96.0±26.18) than the control group (106.9±28.92) (P=0.001) at day 8.

Adverse events (AEs) that occurred with a frequency of >1% are summarized in Table S3. Overall, XBJ demonstrated a similar overall safety profile among the subgroups of patients aged < 65 and ≥ 65 years. In particular, very similar incidences of low red blood cell count (7.22% vs. 5.56%) and elevated aspartate amino transferase (5.56% vs. 7.64%) were seen in the subgroups aged < 65 and ≥65 years, respectively. There were no severe AEs that occurred in either elder or nonelderly patients after XBJ therapy.

Discussion
The overall results of this large trial showed that XBJ is an effective and well-tolerated therapy for patients with severe CAP [14]. With high efficacy and good tolerability, XBJ compares favorably with the placebo. Especially, there was an 8.8% absolute reduction in mortality in patients who received XBJ. In addition, with improved PSI risk score.

In the current analysis, XBJ showed a similar favorable safety profile in elder and younger patients alike, and the high efficacy of XBJ was preserved in elder patients. No clinically relevant differences in safety profile were observed between the subgroups of patients aged < 65 years and ≥ 65 years. These results suggest that there is no a priori need for upfront dose reductions when prescribing XBJ to elderly patients. Prospectively planned ongoing trial is further evaluating the efficacy and safety benefits of XBJ in elder patients.

CAP seems more severe in elder than in younger patients. Fine and colleagues’ have demonstrated that age over 65 years was one of the five predisposing factors for a complicated course. In most prognosis studies, age is a significant predictor of mortality [15]. Consequently, the mortality rate of such pulmonary infection seems high in elder people. Among elder hospitalized patients overall, the death rate was about 30%[16, 17]. When patients were admitted to an ICU, mortality was even higher [18]. In Rello’s study, the mortality rate was 40% [18]. In the present work, 94.07% of the participants were from ICUs, the 28 day mortality rate among elder patients with XBJ was 16.0%. This rate was significantly lower than the rate observed in placebo group (27.9%).

Although efficacy was not the primary end point of the original study, efficacy comparisons were undertaken to allow for a more clinically meaningful comparison of the tolerability profiles and to explore any clinically relevant differences in efficacy between younger and elder patients. One recently presented study has evaluated hydrocortisone in patients with severe CAP in the ICU setting [19]. Among patients with mean age 62 years, a continuous infusion of hydrocortisone did not result in lower 28-day mortality than placebo. We believe that this analysis is particularly intriguing: in fact, this result on mortality overcomes one of the main limitations of our previous study.

All herbal therapy requires active supervision, particularly for elderly patients, who could have other illnesses and be receiving concomitant medications[20]. Elder patients could also be at greater risk of
experiencing toxicity, particularly if their renal function is impaired. Unlike tablets at home, XBJ I.V. therapy is administered in the hospitals and the clinicians has an active role in treatment administration and the management of any toxicity.

The interpretation of this post hoc analysis has limitations to be considered. First, neither study was specifically designed to assess efficacy or in safety exclusively elder patients. Furthermore, the number of patients included in each age group was relatively small and did not allow multivariate analysis involving backward stepwise logistic regression in each group to show the exact level of significance.

Conclusions
In conclusion, XBJ treatment demonstrated similar effects in the subgroup of elder patients with severe CAP. This post-hoc analysis represents a proof-of concept study, and, this analysis found a differential effect of age on XBJ treatment in patients with severe CAP. Thus, this proof-of concept study needs to be confirmed by a large, well designed, and appropriately focused randomized clinical trial in an elder population.

Abbreviations
AE
adverse event
APACHE
acute physiology and chronic health evaluation
ARDS
acute respiratory distress syndrome
CAP
community-acquired pneumonia
CIs
confidence intervals
ICU
intensive care unit
K-M curve
kaplan-meier curve
NMPA
national medical products administration
PSI
pneumonia severity index
RCT
randomized controlled trial
SIRS
systemic inflammatory response syndrome
SOFA
sequential organ failure assessment
XBJ
Xuebijing injection

Declarations

**Ethics approval and consent to participate** The protocol is consistent with the principles of the Declaration of Helsinki, was approved by the Medical Ethics Committee of Zhongshan Hospital, Fudan University [2011-38(3)] and the participants gave their written informed consent.

**Consent for publication** Not applicable.

**Availability of data and materials** All data generated or analyzed during this study are included in this published article [XueBijing Injection Versus Placebo for Critically Ill Patients With Severe Community-Acquired Pneumonia: A Randomized Controlled Trial. Critical Care Medicine, 2019, 47(9):1].

**Competing interests:** The authors declare that they have no competing interests.

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**Authors' contributions** Yan Liu and Chi Zhang contributed equally to this work, they finished acquisition and analysis of the data, as well as wrote the manuscript. Chengyu Li participated and performed data analysis in this work. Hongcai Shang and Chunxue Bai provided critical revisions of the manuscript. All members of the writing committee read and approved the final report.

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**Tables**

TABLE 1. Comparison of Demographic and Basal Clinical Characteristics of Patients Between XueBiJing Injection and Placebo Groups
| Characteristics                              | Elder ≥65            |       | Placebo Group | Xuebijing Group | P value | Placebo Group | Xuebijing Group | P value |
|---------------------------------------------|----------------------|-------|---------------|-----------------|---------|---------------|-----------------|---------|
| **Age, yr, mean(SD)**                      | 70.4 (3.19)          | 70.6 | 70.6 (3.27)   | 0.684           | 49.1    | 126           | 111             | 23.     |
| **Men, n(%)**                              | 97 (66.0)            | 93   | 64.6          | 0.802           | 12.1    | 49.6          | 12.1            | 111.    |
| **BMI, kg/m², mean (sd)**                  | 22.4 (3.37)          | 22.4 | 3.42          | 0.929           | 23.     | 49.6          | 12.1            | 111.    |
| **Systolic blood pressure, mm Hg, mean (sd)**| 134.9 (23.86)        | 132.8| 25.20         | 0.470           | 125.    | 125.1         | 31.1            | 111.    |
| **Heart rate, beats/min, mean (sd)**       | 105.3 (19.28)        | 106.7| 20.86         | 0.564           | 111.    | 111.2         | 20.86           | 111.    |
| **Respiratory rate, breaths/min, mean (sd)**| 28.0 (6.02)          | 27.2 | 6.32          | 0.270           | 28.     | 27.2          | 6.32            | 28.     |
| **Temperature, °C, mean (sd)**             | 37.8 (1.06)          | 37.9 | 1.06          | 0.280           | 38.     | 37.9          | 1.06            | 38.     |
| **Pao2/Fio2, mean (sd)**                   | 175.3 (56.97)        | 172.4| 62.77         | 0.684           | 172.    | 172.4         | 62.77           | 172.    |
| **Glasgow score, mean (sd)**               | 11.3 (3.70)          | 11.3 | 3.35          | 0.922           | 11.     | 11.3          | 3.35            | 11.     |
| **Comorbidities, n (%)**                   |                      |      |               |                 |         |               |                 |         |
| Diabetes mellitus (any type)                | 7 (4.76)             | 5    | 3.47          | 0.580           | 1       | 7             | 4.76            | 1       |
| Chronic bronchitis                          | 4 (2.72)             | 2    | 1.39          | 0.684           | 0       | 2             | 1.39            | 0       |
| Coronary artery disease                     | 7 (4.76)             | 5    | 3.47          | 0.580           | 2       | 5             | 3.47            | 2       |
| Hypertension                                | 31 (21.09)           | 32   | 22.22         | 0.814           | 14      | 32            | 22.22           | 14      |
| Parkinson’s disease                         | 2 (1.36)             | 0    | 0.00          | 0.498           | 1       | 2             | 0.00            | 1       |
| Polytrauma                                  | 0                    |      |               |                 |         | 0             |                 |         |
| Etiological agents, n (%)<sup>a</sup>       | 57 (38.8)            | 50   | 34.7          | 0.473           | 88      | 50            | 34.7            | 88      |
| C-reactive protein, mg/L, mean (sd)         | 87.6 (95.49)         | 80.9 | 69.68         | 0.531           | 87.4    | 80.9          | 69.68           | 87.4    |
| Leucocytes, 10<sup>9</sup> cells/L, mean (sd)| 12.1 (5.98)          | 12.4 | 6.16          | 0.747           | 13.     | 12.4          | 6.16            | 13.     |
| Glucose, fasting morning, mmol/L            | 8.3 (3.82)           | 8.5  | 3.82          | 0.701           | 8.3     | 8.5           | 3.82            | 8.3     |
| **PSI score<sup>a</sup>, n (%)**           |                      |      |               |                 |         |               |                 |         |
| Class II                                    | 1 (0.7)              | 2    | 1.4           |                 | 19      | 2             | 1.4             | 19      |
| Class III                                   | 18 (12.2)            | 13   | 9.0           |                 | 39      | 13            | 9.0             | 39      |
| Class IV                                    | 80 (54.4)            | 78   | 54.2          |                 | 87      | 78            | 54.2            | 87      |
| Class V                                     | 48 (32.7)            | 51   | 35.4          |                 | 35      | 51            | 35.4            | 35      |
| **Total PSI score<sup>c</sup>, mean (sd)**  | 122.9 (28.99)        | 125.1| 31.41         | 0.521           | 106.    | 125.1         | 31.41           | 106.    |
| Sequential Organ Failure Assessment (SOFA) score, mean (sd)| 5.9 (2.66) | 5.9 | 2.59 | 0.838 | 6.5 | 5.9 | 2.59 | 0.838 |
| Acute Physiology and Chronic Health Evaluation II score, mean (sd)| 17.2 (6.35) | 16.6 | 5.88 | 0.389 | 14 | 16.6 | 5.88 | 0.389 |
| Antibiotic susceptibility testing, n (%)<sup>d</sup> | 15 (39.5) | 11 | 35.5 | 0.734 | 26 | 11 | 35.5 | 0.734 |
| Mechanical ventilation, n (%)               | 93 (63.3)            | 91   | 63.2          | 0.990           | 10.     | 91            | 63.2            | 10.     |
TABLE 2. Rate of Patients with Acute Respiratory Distress Syndrome and Septic Shock, the Baseline Settings of Mechanical Ventilation, and the Frequency of Antimicrobial Prescriptions for XueBijing Group versus Placebo Group Using Descriptive Statistics for the Intention-to-Treat Populations

| Characteristics                              | Elderly ≥65 | P value | Nonelderly65 |
|----------------------------------------------|-------------|---------|--------------|
|                                              | Xuebijing   | Placebo |              |              |
| Septic shock and ARDS, n (%)                 |             |         |              |              |
| Septic shock                                 | 8 (5.4)     | 7 (4.9) | 0.823        | 13 (7.2)     | 9 (5.0)      |
| ARDS                                         | 42 (28.6)   | 47 (32.6)| 0.452       | 60 (33.3)    | 52 (28.9)    |
| Mechanical ventilation, n (%)                | 93 (63.3)   | 91 (63.2)|            | 109 (60.6)   | 111 (61.7)   |
| Invasive ventilation, n (%)                  | 63 (67.7)   | 64 (70.3)| 0.704       | 85 (78.0)    | 82 (73.9)    |
| Tidal volume, mean (sd)                      | 457.0 (58.62)| 463.9 (74.80)| 0.486     | 469.9 (76.24)| 474.8 (92.12)|
| Positive end expiratory pressure, mean (sd)  | 6.0 (2.16)  | 6.3 (2.90)| 0.398       | 6.6 (2.76)   | 6.4 (2.72)   |
| AC, n (%)                                    | 6 (6.5)     | 9 (9.9)  | 4 (3.7)      | 5 (4.5)      |
| Bi-level positive airway pressure ventilation, n (%) | 10 (10.8)  | 14 (15.4)|            | 17 (15.6)    | 17 (15.3)    |
| Continuous positive airway pressure, n (%)   | 5 (5.4)     | 2 (2.2)  | 3 (2.8)      | 4 (3.6)      |
| Noninvasive ventilation, n (%)               | 21 (22.6)   | 11 (12.1)| 9 (8.3)      | 19 (17.1)    |
| PC, n (%)                                    | 8 (8.6)     | 9 (8.8)  | 6 (5.5)      | 14 (17.1)    |
| PSV, n (%)                                   | 6 (6.5)     | 9 (9.9)  | 11 (10.1)    | 5 (4.5)      |
| SIMV, n (%)                                  | 21 (22.6)   | 23 (25.3)| 50 (45.9)    | 38 (34.2)    |
| SIMV + PS, n (%)                             | 13 (14.0)   | 12 (13.2)| 6 (5.5)      | 7 (6.3)      |
| SIMV + SIMV/AS, n (%)                        | 0           | 0        | 1 (0.9)      | 0 (0.0)      |
| SPMV + PS, n (%)                             | 3 (3.2)     | 3 (3.3)  | 2 (1.8)      | 2 (1.8)      |
| Antimicrobial treatment, n (%)               |             |         |              |              |
| Beta-lactam                                  | 143 (97.28) | 141 (97.92)| >0.999       | 172 (95.56)  | 170 (94.44)  |
| Quinolones                                   | 51 (34.69)  | 64 (44.44)| 0.089        | 59 (32.78)   | 59 (32.78)   |
| Glycopeptide                                 | 30 (20.41)  | 20 (13.89)| 0.141        | 29 (16.11)   | 50 (27.78)   |
### Oxazolidinones
| Placebo Group | Xuebijing Group | P value |
|---------------|-----------------|---------|
| 18 (12.24)    | 17 (11.81)      | 0.908   |

### Antifungal agents
| Placebo Group | Xuebijing Group | P value |
|---------------|-----------------|---------|
| 9 (6.12)      | 10 (6.94)       | 0.777   |

### Tetracyclines
| Placebo Group | Xuebijing Group | P value |
|---------------|-----------------|---------|
| 8 (5.44)      | 7 (4.86)        | 0.823   |

### Macrolide
| Placebo Group | Xuebijing Group | P value |
|---------------|-----------------|---------|
| 4 (2.72)      | 2 (1.39)        | 0.684   |

### Aminoglycoside
| Placebo Group | Xuebijing Group | P value |
|---------------|-----------------|---------|
| 3 (2.04)      | 2 (1.39)        | >0.999  |

### Nitroimidazoles
| Placebo Group | Xuebijing Group | P value |
|---------------|-----------------|---------|
| 1 (0.68)      | 4 (2.78)        | 0.211   |

### Antivirals
| Placebo Group | Xuebijing Group | P value |
|---------------|-----------------|---------|
| 2 (1.36)      | 1 (0.69)        | >0.999  |

### Lincomycin
| Placebo Group | Xuebijing Group | P value |
|---------------|-----------------|---------|
| 1 (0.68)      | 2 (1.39)        | 0.620   |

### Sulfanilamide
| Placebo Group | Xuebijing Group | P value |
|---------------|-----------------|---------|
| 0 (0.00)      | 2 (1.39)        | 0.244   |

### Cyclic peptides
| Placebo Group | Xuebijing Group | P value |
|---------------|-----------------|---------|
| 0 (0.00)      | 0 (0.00)        | 1 (0.56) |

| Characteristics | Elderly ≥65 | Nonelderly65 |
|----------------|-------------|--------------|
| 28-d mortality, n (%) | 41 (27.9) | 23 (16.0) | 0.014 | 41 (22 |
| The time of mechanical ventilation, d, mean (std) | 14.3 (8.97) | 13.1 (8.80) | 0.422 | 10.8 (8 |
| Total duration of ICU stay, d, mean (std) | 15.6 (7.88) | 13.9 (7.84) | 0.133 | 12.3 (7 |

### Table S1. Microbiologic identification for XueBijing group vs placebo group using descriptive statistics for the intention-to-treat populations

| Characteristics       | Elderly ≥65 | Nonelderly65 |
|-----------------------|-------------|--------------|
| Microbiologic identification | Yes(%)     | 57 (38.8) | 89 (49.4) | 0.916 |
| Etiology              | Known(%)   | 38 (66.7) | 53 (59.6) | 0.128 |
| Sensitivity tests     | Known(%)   | 15 (39.5) | 30 (56.6) | 0.117 |

Table S2. Comparison of the secondary outcomes for the intention-to-treat populations

| Characteristic | Elderly ≥65 | Nonelderly65 |
|----------------|-------------|--------------|
| cs            | Placebo Group | Xuebijing Group | P value | Placebo Group | Xuebijing Group | P value |
|---------------|---------------|-----------------|---------|---------------|-----------------|---------|
| PSI score, mean(SD) |               |                 |         |               |                 |         |
| Day 4        | 108.6 (29.16) | 102.5 (26.13)   | 0.069   | 90.8 (26.56)  | 83.2 (28.14)    | 0       |
| Day 8        | 106.9 (28.92) | 96.0 (26.18)    | 0.001   | 84.8 (28.71)  | 78.3 (31.21)    | 0       |
| Sequential Organ Failure Assessment Score, mean(SD) |               |                 |         |               |                 |         |
| Day 4        | 5.3 (2.88)    | 4.5 (2.66)      | 0.017   | 4.9 (2.92)    | 4.6 (3.20)      | 0       |
| Day 8        | 4.9 (2.71)    | 3.7 (2.76)      | <0.001  | 4.2 (3.15)    | 3.7 (3.25)      | 0       |
| APACHE II score, mean(SD) |               |                 |         |               |                 |         |
| Day 4        | 5.6 (3.58)    | 3.9 (3.06)      | <0.001  | 5.5 (3.80)    | 4.8 (4.23)      | 0       |
| Day 8        | 4.9 (3.47)    | 3.6 (3.33)      | 0.001   | 5.0 (4.18)    | 4.1 (4.51)      | 0       |
| Lung Injury Score, mean(SD) |               |                 |         |               |                 |         |
| Day 4        | 7.5 (2.37)    | 6.5 (2.06)      | 0.006   | 7.3 (2.88)    | 7.2 (2.72)      | 0       |
| Day 8        | 7.4 (2.75)    | 6.4 (2.18)      | 0.029   | 7.8 (3.02)    | 7.4 (2.48)      | 0       |
| MODS score, mean (SD) |              |                 |         |               |                 |         |
| Day 4        | 6.3 (3.20)    | 5.9 (3.00)      | 0.596   | 5.0 (2.69)    | 5.1 (3.64)      | 0       |
| Day 8        | 6.2 (2.90)    | 4.7 (3.41)      | 0.056   | 4.1 (3.30)    | 3.9 (4.10)      | 0       |
| Body temperature, mean (SD) |               |                 |         |               |                 |         |
| Day 4        | 37.0 (0.69)   | 36.9 (0.59)     | 0.212   | 37.4 (0.84)   | 37.3 (0.72)     | 0       |
| Day 8        | 36.9 (0.68)   | 36.8 (0.50)     | 0.139   | 37.2 (0.78)   | 37.0 (0.62)     | 0       |
|                      | (SD)     | Placebo Group | Xuebijing Group | Placebo Group | Xuebijing Group |
|----------------------|----------|---------------|-----------------|---------------|----------------|
| **Procalcitonin**    |          |               |                 |               |                |
| Day 4                | 222.8 (87.66) | 251.1 (96.38) | 0.011 (98.72)   | 245.3 (101.90) |
| Day 8                | 243.6 (91.48) | 275.1 (98.08) | 0.007 (115.69)  | 265.1 (112.26) |
| **C-reactive protein** |          |               |                 |               |                |
| Day 4                | 4.5 (20.22)  | 5.6 (19.24)   | 0.680 (16.26)   | 5.7 (20.29)   |
| Day 8                | 1.7 (4.07)   | 2.7 (6.64)    | 0.219 (37.27)   | 2.5 (8.15)    |
| **D-dimer**          |          |               |                 |               |                |
| Day 4                | 2137 (2378.1) | 2423 (2945.5) | 0.433 (4142.3)  | 4365 (7558.4) |
| Day 8                | 2378 (3106.4) | 2474 (3599.1) | 0.836 (4837.7)  | 3121 (4762.3) |
| **Systemic Inflammatory Response Syndrome (SIRS) score, mean (sd)** |          |               |                 |               |
| Day 4                | 2.0 (1.08)   | 1.6 (1.11)    | 0.002 (1.16)    | 2.0 (1.27)    |
| Day 8                | 1.6 (1.22)   | 1.2 (1.10)    | 0.005 (1.28)    | 1.5 (1.25)    |
| **Total duration of antibiotic use, days, mean(SD)** |          |               |                 |               |
| Total                | 10.3 (4.58)  | 9.5 (4.47)    | 0.143 (4.61)    | 9.4 (4.80)    |

**TABLE S3. Adverse events and Clinically Significant Laboratory Abnormalities**

| Characteristics | Elderly ≥65 | Nonelderly65 |
|-----------------|-------------|--------------|
|                 | Placebo Group | Xuebijing Group | Placebo Group | Xuebijing Group |

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| Clinically Significant Laboratory Abnormalities | 64 (43.54) | 55 (38.19) | 68 (37.78) | 61 (33.89) |
|-----------------------------------------------|------------|------------|------------|------------|
| Elevated alanine aminotransferase              | 18 (12.24) | 12 (8.33)  | 12 (6.67)  | 18 (10.00) |
| Elevated aspartate aminotransferase            | 13 (8.84)  | 11 (7.64)  | 5 (2.78)   | 10 (5.56)  |
| Elevated blood urea nitrogen                   | 8 (5.44)   | 12 (8.33)  | 11 (6.11)  | 8 (4.44)   |
| Elevated glucose                               | 8 (5.44)   | 7 (4.86)   | 7 (3.89)   | 11 (6.11)  |
| Low red blood cell count                       | 6 (4.08)   | 8 (5.56)   | 10 (5.56)  | 13 (7.22)  |
| High white blood cell count                    | 6 (4.08)   | 6 (4.17)   | 8 (4.44)   | 10 (5.56)  |
| Elevated total bilirubin                       | 8 (5.44)   | 4 (2.78)   | 4 (2.22)   | 5 (2.78)   |
| Elevated serum creatinine                      | 6 (4.08)   | 5 (3.47)   | 4 (2.22)   | 2 (1.11)   |
| Elevated prothrombin time                     | 6 (4.08)   | 3 (2.08)   | 5 (2.78)   | 1 (0.56)   |
| Elevated plasma fibrinogen                     | 6 (4.08)   | 3 (2.08)   | 7 (3.89)   | 4 (2.22)   |
| Low white blood cell count                     | 4 (2.72)   | 4 (2.78)   | 2 (1.11)   | 1 (0.56)   |
| Elevated activated partial thromboplastin time | 5 (3.40)   | 1 (0.69)   | 3 (1.67)   | 2 (1.11)   |
| Low hemoglobin count                           | 4 (2.72)   | 1 (0.69)   | 7 (3.89)   | 1 (0.56)   |
| High platelet count                            | 3 (2.04)   | 2 (1.39)   | 4 (2.22)   | 3 (1.67)   |
| Decreased K+                                   | 1 (0.68)   | 3 (2.08)   | 10 (5.56)  | 4 (2.22)   |
| Elevated Na+                                   | 2 (1.36)   | 2 (1.39)   | 3 (1.67)   | 2 (1.11)   |
| Decreased Na+                                  | 2 (1.36)   | 2 (1.39)   | 2 (1.11)   | 0 (0.00)   |
| Elevated fibrin D-dimer                        | 3 (2.04)   | 1 (0.69)   | 3 (1.67)   | 4 (2.22)   |
| Decreased serum creatinine                     | 2 (1.36)   | 2 (1.39)   | 5 (2.78)   | 3 (1.67)   |
| Low white blood cell count                     | 1 (0.68)   | 2 (1.39)   | 2 (1.11)   | 1 (0.56)   |
| Elevated K+                                   | 1 (0.68)   | 2 (1.39)   |           |            |
| High urine white blood cell count              | 2 (1.36)   | 1 (0.69)   | 1 (0.56)   | 2 (1.11)   |
| Positive protein in urine                      | 1 (0.68)   | 2 (1.39)   | 0 (0.00)   | 1 (0.56)   |
| High urine red blood cell count                | 2 (1.36)   | 1 (0.69)   | 1 (0.56)   | 2 (1.11)   |
| Elevated urine glucose                         | 3 (2.04)   | 0 (0.00)   | 1 (0.56)   | 2 (1.11)   |
| Decreased AST                                  | 1 (0.68)   | 2 (1.39)   | 0 (0.00)   | 1 (0.56)   |
| Decreased blood urea nitrogen                  | 2 (1.36)   | 1 (0.69)   |           |            |
| Abnormal alanine aminotransferase              | 2 (1.36)   | 0 (0.00)   |           |            |
| High red blood cell count                      | 2 (1.36)   | 0 (0.00)   | 1 (0.56)   | 1 (0.56)   |
| Condition                                | Group 1 (n=58) | Group 2 (n=72) | Group 3 (n=76) | Group 4 (n=38) |
|------------------------------------------|----------------|----------------|----------------|----------------|
| Decreased plasma fibrinogen              | 1 (0.68)       | 1 (0.69)       | 2 (1.11)       | 1 (0.56)       |
| Decreased total bilirubin                | 0 (0.00)       | 2 (1.39)       | 1 (0.56)       | 0 (0.00)       |
| Positive fecal occult blood test         |                |                | 1 (0.56)       | 0 (0.00)       |
| Elevated C reactive protein              | 1 (0.68)       | 0 (0.00)       |                |                |
| Decreased activated partial thromboplastin time | 1 (0.68)       | 0 (0.00)       |                |                |
| Elevated procalcitonin                   | 1 (0.68)       | 0 (0.00)       |                |                |
| Decreased prothrombin time               | 0 (0.00)       | 1 (0.69)       |                |                |
| High hemoglobin count                    | 1 (0.68)       | 0 (0.00)       |                |                |

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Figure 1

Kaplan-Meier (K-M) survival curve of overall survival after XueBijing (XBJ) and placebo for patients in (A) elderly group: Patients with XBJ had a significantly inferior overall survival to those who with placebo. The HR of was 0.57 (95% CI, 0.34-0.95; P = 0.029), (B) nonelderly group: The HR of was 0.67 (95% CI, 0.41-1.08; P = 0.0949).