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Characteristics of Fever and Response to Antipyretic Therapy in Military Personnel with Adenovirus Positive Community-Acquired Pneumonia

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ABSTRACT

In 2014, the outbreak of adenoviral pneumonia occurred in Korean military training center. However, there is limited data on characteristics of fever and its response to antipyretics therapy in immunocompetent adults with adenoviral positive community acquired pneumonia (CAP). Medical records of patients who were admitted to Armed Forces Chuncheon Hospital for treatment of CAP between January 2014 and December 2016 were retrospectively analyzed. We evaluated demographics, clinico-laboratory findings and radiologic findings at admission were compared between adenovirus positive (Adv) group and adenovirus negative (Non-Adv) group. Out of 251 military personnel with CAP during the study periods, 67 were classified into Adv group while 184 were Non-Adv group. Patients with Adv group had longer duration of fever after admission and symptom onset. Adv group patients had higher mean temperature at admission, and more observed over 40 and 39 to 40℃. Adv group patients had more commonly observed no response to antipyretic treatment and adverse events after antipyretics use. Length of hospital stay had no significant difference between two groups and no patient died in both groups. In our study, Adv positive CAP in patients with immunocompetent military personnel had distinct characteristics of fever and response to antipyretic treatment.

Keywords: Adenovirus, Pneumonia, Fever, Response to antipyretic treatment

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Introduction

Adenovirus (Adv) are non-enveloped, double-stranded DNA viruses and can present as upper and lower respiratory tract infection either in sporadic fashion or as epidemics. Currently, 49 distinct Adv serotypes have been isolated from humans. Adv usually causes mild self-limited respiratory and gastrointestinal infection. Adv may case a variety of clinical manifestations, however, in immunocompromised patients, adenovirus infection leads to often fatal outcome. For example, in immunodeficiency states such as solid organ or stem cell transplantation, severe adenovirus infection may occur with mortality up to 80% [1-4].

Fatal adenovirus respiratory infection in immunocompromised patients has been described in several case reports or literatures. Adenoviral pneumonia is rare in the general population, but outbreaks have been occasionally reported in young adult women or military personnel [5-9]. Respiratory tract infection is the leading cause for hospitalization of military trainees in medical field. US military study showed that 10 % of recruits at boot camp were infected Adv, and 90% of patients with pneumonia were identified with adenovirus [10, 11]. In 2006, a study from the South Korean military reported that prevalence of Adv was 61% among military recruits with acute respiratory symptoms [12-16]. Upper or lower respiratory tract infection of Adv may also progress to pneumonia. These days, several case series were reported that recruits in boot camp were death caused by severe adenoviral pneumonia in South Korea since 2012 [13, 15-17]. Even if the results of mortality or clinical outcome of Adv infection could be affected by selection bias, it is reported that Adv infection may be severe with higher incidence of progression to respiratory failure and multi-organ failure compared to other viral etiologies. Thus, some clinical data were reported to predictive factors of respiratory failure in Adv infection [18, 19].

If Adv infection can be estimated early, increased monitoring and early applied organ

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support may improve clinical outcome of these patients, but there is no abundant data on distinctive characteristics in immunocompetent patients. We experienced that adenovirus positive CAP patients have high fever and different response to antipyretic treatment in other bacteria or virus positive CAP patients. Therefore, in this study, we aimed primarily to compare the clinical characteristics of Adv and Non-Adv positive CAP patients with immunocompetent military personnel and identified to distinctive findings.

Materials and Methods

Study design and definition

This study was a single center, retrospective cohort study. We reviewed the medical records of patients who were admitted to the Armed Forces Chuncheon Hospital (Gangwon province, South Korea, in which referral hospital in Gangwon province) for treated CAP between January of 2014 and December of 2016. Based on the unique characteristics of the Korean military medical system, all military personnel were treated initially in military hospital despite to lack of diagnostic modalities. Ethical approval was obtained from The Institutional Review Board of The Armed Forces Medical Command (AFMC-16051-IRB-16-041), which waived the need for informed consent because of the retrospectively observational nature of the study.

The patients were included in this study when they 1) were admitted for treatment of CAP, 2) had virus polymerase chain reaction (PCR) tests performed on upper respiratory specimen. Exclusion criteria were as follows; 1) respiratory virus PCR test was not done, 2) they had incomplete records, 3) they were immediately transferred to tertiary hospital for advanced care, and 4) primary reason for admission was to manage co-morbid diseases.

CAP was defined using the definition set forth by Infectious Society of

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America/American Thoracic Society Consensus Guidelines [20]. In short, CAP was diagnosed when the patients had symptoms associated with respiratory tract infections and had new onset lung infiltration or pleural effusion on chest X-rays or chest computed tomography scans. We defined fever as any temperature greater than or equal to 38 degree Celsius recorded by tympanic route. All patients checked the body temperature every one hour at admission day. However, the body temperature was often measured within a 1 hour when patients had febrile sense or worsening signs of inflammation. We also recorded body temperature at the beginning of antipyretics administration. There was no standardized antipyretic treatment protocol for fever control. In our study, antipyretic therapy was administered upon reaching a body temperature ≥ 38 degree Celsius (°C). Interval of antipyretics administration was according to pharmacodynamics, however we performed additional antipyretics when patients had fever (two consecutive measurements ≥ 38°C) and deterioration of clinical symptoms including myalgia, general weakness, cough, nasal congestion, or dyspnea within 6 hours after antipyretics administration. Responsiveness to antipyretic treatment was classified as followed; complete response is body temperature drop below 38°C after antipyretics and sustained throughout, partial response is body temperature drop below 38°C but resurge during observation or need for additional antipyretics, and no response is body temperature sustained above or equal to 38°C after antipyretics use. Unresponsive to initial antibiotic treatment was defined as had deterioration as evidenced by worsening of clinical symptoms signs and/or progression of lesions on radiologic studies after 48 to 72 hours of initial antibiotics treatment.

Data collection and patient management

All data include age, sex, smoking history, co-morbid conditions, symptoms and clinical signs, initial laboratory and radiologic findings, culture results, pneumonia severity

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index, clinical course, length of hospital stay, and survival outcome were collected from electronic medical records. We evaluated etiologies by sputum, nasopharyngeal or oropharyngeal secretions, blood, and urine using microbiological culture. Respiratory specimens were usually obtained from self-extracting sputum. When sputum specimen could not be obtained, upper respiratory tract specimens, such as oropharyngeal or nasopharyngeal swab were used for virus PCR test. Multiplex real-time PCR was performed using a Real-Q RV Detection Kit (BioSewoom, Seoul, Korea) on a Roche Light Cycler 480 II instrument (Roche Diagnostics, Mannheim, Germany). Respiratory viruses included in this test are as follows; adenovirus, rhinovirus, influenza virus A/B, respiratory syncytial virus A/B, metapneumovirus, bocavirus, coronavirus, and parainfluenza virus 1/2/3. All patients were given chest X-rays and/or high resolution computed tomography (HRCT) at the time of our emergency department visit. Initial antibiotic agents were given by intravenously in all the patients. Initial antibiotics regimens were followed by "Treatment Guidelines for Community-acquired Pneumonia in Korea: An Evidence-based Approach to Appropriate Antimicrobial Therapy" from The Korean Academy of Tuberculosis and Respiratory Diseases [21]. The antipyretic agents were as follows. Propacetamol was administered intravenously at a dose of 1 to 2 gram as needed to maximum of 8 gram per day. Acetaminophen was given orally at a dose of 2 tablets every eight hours up to 6 tablets per day. Physical cooling methods were applied to all febrile patients included external air, ice bag, or water blanket techniques.

Statistical analysis

Data are presented as mean ± standard deviation or median [interquartile range] for continuous variables and as numbers and percentages for categorical variables. The data were analyzed using Kolmogorov-Smirnov tests for normal distribution. Data were compared

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using the Mann–Whitney U-test or student t test for continuous variables and the χ 2 or Fisher's exact test for categorical variables. Statistical analyses were performed using the SPSS version 23.0 (SPSS Inc., Chicago, IL, USA) a two-sided P value < 0.05 was considered to indicate statistical significance.

Results

Study participants

During the study period, a total of 445 cases of CAP patients admitted to the Armed Forces Chuncheon Hospital (Figure. 1). All patients were admitted via emergency department. Out of 445 cases, 194 cases were excluded. The reasons for exclusion were as follows; no respiratory virus PCR test in 170 patients, incomplete data in twenty patients, transferred to tertiary medical center within 72 hours in two patients, and admission for treatment of underlying diseases in two patients. Two patients who were admitted suspicious combined to underlying disease managed to acute asthma exacerbation. Consequently, 251 patients were enrolled this study. Among of them, patients with virus PCR positive for adenovirus (Adv group) were 67, and 184 with virus PCR negative for adenovirus (Non-Adv group). In Non-Adv group patients, 50 patients were no identified pathogen in all culture study and 134 patients were identified other viruses, bacteria, and combined pathogens.

Comparison of baseline characteristics

Table 1 describes baseline characteristics of Adv group and Non-Adv group patients at admission. The median age was 21.6 years and all patients were previously healthy males. Current smokers were significantly higher in the Adv group (22.2% vs 5.4%) and among of them, recent smokers (< 30 days) were identified only Adv group (n=4). Few patient had

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underlying disease, such as asthma (n=3), allergic rhinitis (n=3), pneumothorax (n=2), and tuberculosis (n=2). Duration of symptom, time from symptom onset to admission, was no difference between two group (3.6 ± 1.8 vs 3.2 ± 2.3 days, $p = 0.224$). All patients had clinical symptoms and signs of upper or lower respiratory tract infection. Adv group patients showed more symptomatic instabilities, such as fever, cough, myalgia, headache, and nasal congestion. At admission, initial vital signs and pneumonia severity index (PSI) score were not significant difference between two groups.

The results of laboratory and radiologic findings between Adv and Non-Adv group

We compared laboratory and radiologic findings between Adv and Non-Adv group (Table 2). The percentage of patients having leukopenia and thrombocytopenia were higher in Adv patients (all $p < 0.001$), and leukocytosis was more common in Non-Adv group patients ($p = 0.035$). Infection markers, such as C-reactive protein (CRP) and procalcitonin were no difference between two groups. Also total bilirubin and creatinine showed no significant difference between two groups.

Possible causative agents were identified in 100 % in Adv group and 72.8% (134/184) in Non-Adv group. Adv group patients had co-infection with viruses, such as rhinovirus (n=5), influenza A virus (n=4), respiratory syncytial virus (n=1), and parainfluenza virus (n=1). Bacteria or combined etiologies were more common in Non-Adv group patients. Rhinovirus (40/184, 21.7%) was most commonly identified pathogen in Non-Adv group patients. Most common bacterial pathogen is *Streptococcus pneumoniae* in Adv group patients (11/67, 16.4%) and *Haemophilus influenzae* in Non-Adv group patients (52/184, 28.3%).

Most common radiologic feature was ground glass opacity with consolidation in Adv groups and consolidation in Non-Adv group ($p < 0.001$). Unilateral distribution was

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dominant in both groups (83.5% vs 72.7%), however multi-lobar (≥ 3 lobes) involvement was more common in Non-Adv group (9.0% vs 22.3%, $p = 0.015$). Presence of pleural effusion was no significant difference between two groups.

Comparisons of fever and response to antipyretics

Figure 2 was presented to the alternation of mean body temperature at admission and during 7 days after admission between Adv and Non-Adv group patients. And also, we compared the fever and response to antipyretic treatment between Adv, Non-Adv, and no pathogen group in table 3. In generally, Adv group patients comparatively had much longer duration of fever after admission (3.2 ± 1.6 vs 1.9 ± 1.2, 2.2 ± 1.5 days, $p = 0.018$) and symptom onset (5.8 ± 2.2 vs 3.9 ± 2.5, 3.7 ± 2.0 days, $p = 0.006$). To evaluate the degree of fever, we check the mean body temperature and number of patients to maximal temperature at admission. Adv group patients had higher mean body temperature at admission (37.8 ± 0.3 vs 37.3 ± 0.3 vs 37.3 ± 0.2℃, $p = 0.005$), and more observed over 40 and 39 to 40℃ ($p < 0.001$). Adv group patients took longer to maximal falls their body temperature than Non-Adv and no pathogen group patients at admission (10.2 ± 5.6 vs 8.0 ± 4.5 vs 8.6 ± 5.5, $p = 0.015$).

Approximately 18% of Adv group patients had no response to antipyretic treatment, which represented a higher proportion compared with Non-Adv or no pathogen group patients ($p < 0.001$). Proportion of complete response to antipyretic treatment, on the other hand, had comparatively lower in patients with Adv group than Non-Adv or no pathogen group.

Comparison of clinico-laboratory findings between Adv and Non-Adv group in patients

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with unresponsive to initial antibiotics treatment

Physician suspected of having atypical pathogens when patients had persistent or deteriorated symptoms or signs in despite of appropriate empirical antibiotics for 2–3 days. Thus, we compared the clinico-laboratory findings between Adv and Non-Adv group patients with unresponsive to initial antibiotics treatment (Table 4). The number of patients who did not response to initial antibiotics treatment was 47 in Adv group and 50 in Non-Adv group. The percentage of patients having leukocytosis and monocytopenia were higher in Adv patients, while there was no statistically difference in white blood cell and platelet count between two groups. Leukopenia and thrombocytopenia, which were statistically significant difference in all study patients, were no difference in patients with unresponsiveness to initial antibiotics treatment ($p = 0.720$, $p = 0.733$, respectively).

Adv group patients represented a higher in no response to antipyretic treatment compared with Non-Adv group patients (25.5% vs 10.0%, $p = 0.045$) and also more observed in number of patients to over 40 and 39 to 40 degree Celsius ($p = 0.003$). In addition, Adv group patients had higher mean body temperature at admission (37.8 ± 0.3 vs 37.3 ± 0.2, $p = 0.005$).

Comparison of treatment outcome

All patients received empirical antibiotics treatment (Table 5); a 3rd generation cephalosporin plus and azithromycin was the most common regimen (n = 243, 96.8%), followed by piperacillin/ tazobactam plus respiratory quinolone (n = 5, 2.0%). The Change of antibiotics regimen was more frequently in Adv group patients (70.1% vs 27.2%, $p = 0.024$). Duration of antibiotics had no significant difference between two groups. In our study, we did not perform to administration of cidofovir or adjuvant intravenous immunoglobulin (IVIG). In addition, there were no patients who received mechanical ventilation or extracorporeal

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membrane oxygenation support.

At admission, mean dose of antipyretics was higher in Adv group patients (5.52 vs 4.30 gram, $p = 0.032$), however overall duration of antipyretics had no significant difference between two groups. In this study, we identified to adverse events after antipyretics administration such as hypotension, gastrointestinal trouble, skin rash, and elevated liver enzyme, and Adv group patients were commonly observed ($p = 0.005$).

Time to overall clinical stabilization from admission was significantly longer in the AdV group patients than in the Non-AdV group patients (4.3 ± 2.8 vs 2.9 ± 1.8 days, $p = 0.034$). Length of hospital stay had no significant difference between two groups and no patient died in our study.

Discussion

In our study, we described clinical characteristics of Adv positive community acquired pneumonia in immunocompetent military trainee patients. The most important findings were that Adv group patients had longer duration of fever after symptom onset and admission, higher mean body temperature at admission, higher number of patients had over 39°C at admission, longer duration of maximal falls in temperature at admission, and higher no response to antipyretic treatment at admission compared to Non-Adv group patients. In addition, leukopenia and thrombocytopenia were identified higher in Adv group patients, however in patients who unresponsiveness to initial antibiotics treatment, there were no difference between two groups.

There was some epidemiologic study of Adv in South Korea military trainees and personnel. Yoo et al. found that adenovirus was identified 33.0% of all specimens in febrile respiratory illness (FRI) or pneumonia patients [15]. In this study was a reviewed military

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patient with FRI or pneumonia that tested for respiratory viruses from October 2014 to May 2016. The proportion of patients with pneumonia and the hospitalization rate did not differ between those with and without adenovirus infection. However, adenovirus-infected patients had a significantly higher risk of requiring intensive care or mechanical ventilator support. These notable findings mean that adenovirus infection has been occasionally associated with mortality and morbidity with loss in combat strength and increasing in cost of care.

To date, there was rarity data on characteristics of fever in Adv infection, especially in immunocompetent patients. We compared the characteristics of fever in Adv and Non-Adv group patients. Adv group patients had longer duration of fever and higher proportion of peak body temperature than other various viral respiratory infected or no pathogen group patients. Somewhile, Ho and colleagues [22] found that viral mono-pathogen patients had higher mean body temperature than bacterial mono-pathogen patients. In addition, dual-pathogen patients, such as *Streptococcus pneumoniae* with either influenza A or B, had higher mean body temperature, although these were not significant different from respective mono-pathogens. However, there is still lack of data on the detailed specific pathogen related clinical characteristic such as fever in immunocompetent patients. Thus, our data would be more likely to help to provide the physician to determine further diagnostic or therapeutic consideration at the time of admission.

We also referred to response to antipyretic treatment between Adv and Non-Adv group patients. Our data showed that Adv group patients represented a higher proportion of no response to antipyretic treatment compared with Non-Adv or no pathogen group patients. Weisse et al. mainly deal with effect of acetaminophen on fever in bacterial vs viral infection was tested in 100 children [23]. They concluded that there is no correlation between a fever response to acetaminophen and the etiology of the fever so no usefulness of response to

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antipyretic treatment in predicting etiologies of pneumonia. However, our data suggest that there may be difference in antipyretic response to AdV compared to other etiologies and this is first data on immunocompetent adults.

Our study had several limitations. First, our study was retrospective design in single center, so confounding variables, for example antibiotics regimen or inconsistent timing of antipyretics administration, might be had possible effects of clinical course of fever or response to antipyretic treatment. Second, our study had shortly reflect to unmeasurable variables, such as genotype of adenovirus, so difference in severity of illness between AdV vs. Non-AdV might be led to difference in characteristics of fever and its response to antipyretics. Third, we conducted our study in military hospital, so our cohort was not represent to general population because military environment had different condition such as living environment, nutrition/immune status, and mode of pathogen spread. Forth, the reason is selection bias that all patients admitted with CAP could not performed the respiratory PCR test, the examination limited to an upper respiratory tract, and did not performed Adv serotype or viral burden.

Conclusions

To the best of our knowledge, this study is the first to analyze characteristics of fever and response to antipyretic therapy in immunocompetent adult patients with adenovirus infected CAP. A significant difference of patients with Adv group have some clinical characteristics that longer duration of fever, high fever (over 39 degree Celsius), and higher proportion of no response to antipyretic treatment at admission compared to Non-Adv group at this study.

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We thank all the patients involved in the current study.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Abbreviations: Adv; adenovirus, CAP; community acquired pneumonia, PCR; polymerase chain reaction, HRCT; high resolution computed tomography, CPR; C - reactive protein, FRI; febrile respiratory illness

Ethics approval and consent to participate

The institutional review board of The Armed Forces Medical Command (AFMC-16051-IRB-16-041) approved this study and waived the requirement for informed consent because of the observational nature of the study.

Consent for publication

Not applicable.

Availability of data and material

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

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Author contributions

Conception and design: CP; Data analysis and interpretation: CP; Drafting the manuscript for intellectual content: CP; Revision of the manuscript: CP.

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Figure Legends

Fig. 1 Study flow diagram

Fig. 2 Comparison to the alternation of mean body temperature between Adv positive and negative group patients at admission day (a) and within 7 days after admission (b). (a) Alternation of mean temperature in four hours apart between Adv and Non-Adv group patients within 24 hours at admission (37.8 ± 0.3 vs 37.3 ± 0.3, $p = 0.005$), (b) Comparison of the mean daily temperature between Adv and Non-Adv group patients for a week ($p = 0.156$)

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Figure 1. study flow diagram

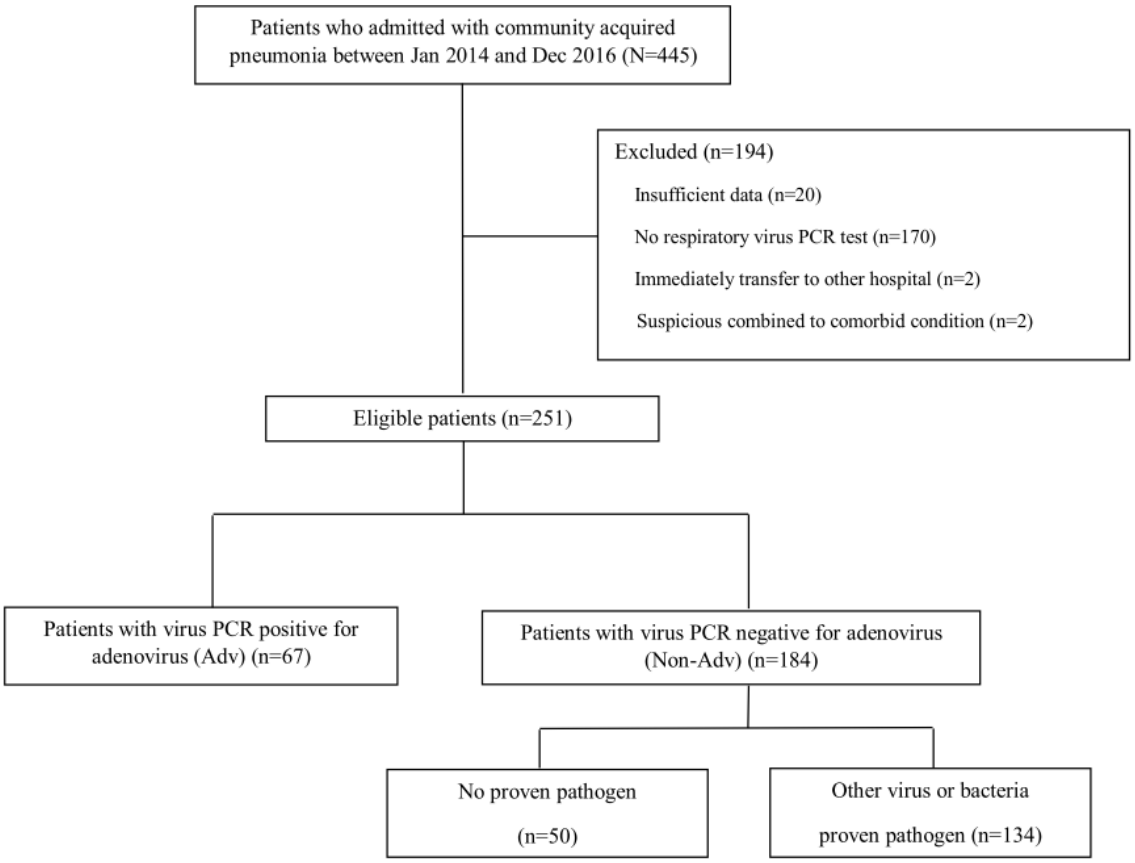

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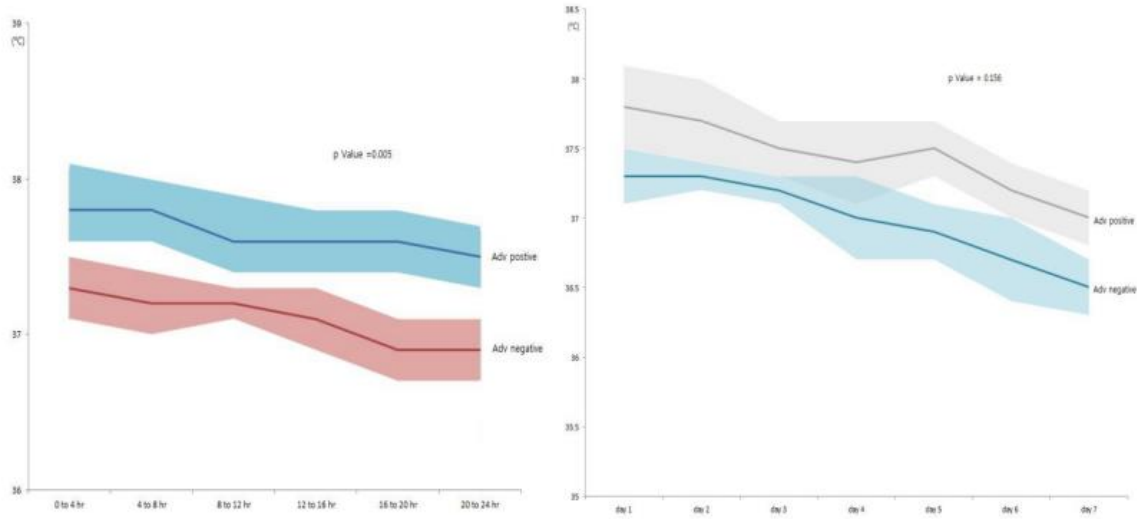
Figure 2. Comparison to the alternation of mean body temperature between Adv positive and negative group patients at admission day (a) and within 7 days after admission (b).

(a) (b)



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1 **Table 1** Comparisons to baseline characteristics of study patients at hospital admission

Characteristics	**Adv (n = 67)**	**Non-Adv (n = 184)**	**Total (n = 251)**	***p* value**
Age ,years	21.5 [20.0-22.0]	21.6 [20.0-22.0]	21.6 [20.0-22.0]	0.559
Male	67 (100)	184 (100)	251 (100)	NA
Smoking				< 0.001
Never smoker	45 (67.1)	125 (67.9)	170 (67.7)	
Ex-smoker	7 (10.4)	49 (26.6)	56 (22.3)	
Current smoker	15 (22.4)	10 (5.4)	25 (9.9)	
Recent smoker (< 30 days)	4 (6.0)	0 (0)	4 (1.6)	
BMI, kg/m^2	23.6 ± 4.3	23.2 ± 3.3	23.3 ± 3.6	0.664
Underlying condition				0.575
Asthma	3 (4.5)	2 (1.1)	5 (2.0)	
Allergic rhinitis	2 (3.0)	1 (0.5)	3 (1.2)	
Pneumothorax	1 (1.5)	1 (0.5)	2 (0.8)	
Previous history of tuberculosis	0 (0)	2 (1.1)	2 (0.8)	
Symptom duration, days (Time from symptom onset to admission)	3.6 ± 1.8	3.2 ± 2.3	3.3 ± 2.1	0.224
Symptom and sign				
Fever	66 (98.5)	157 (85.4)	223 (88.8)	0.021
Cough	65 (96.9)	157 (85.4)	222 (88.4)	0.025
Myalgia	31 (46.5)	56 (30.4)	87 (34.7)	0.001
Dyspnea(> mMRC scale II)	5 (7.7)	11 (6.1)	16 (6.4)	0.286
Purulent sputum	23 (33.8)	58 (31.7)	81 (32.3)	0.335
Headache	48 (72.2)	96 (52.4)	144 (57.4)	0.014
Nasal congestion/rhinorrhea	44 (65.3)	103 (55.8)	147 (58.6)	0.015

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Initial vital signs				
Systolic blood pressure, mmHg	125.4 ± 12.5	124.7 ± 13.1	124.9 ± 13.0	0.598
Heart rate, beats per minute	92.5 ± 14.6	91.2 ± 15.2	91.7 ± 14.9	0.335
Respiratory rate, breaths per minute	18.5 ± 3.2	18.3 ± 3.8	18.3 ± 3.6	> 0.999
SpO2 on room air, %	97.5 ± 2.3	96.8 ± 2.0	97.0 ± 2.1	0.679
Pneumonia Severity Index (PSI) score	71.0 [61.0-95.0]	75 [60.0-96.0]	74 [60.5-95.9]	0.204

Data are shown as mean ± standard deviation, median [interquartile range] or number (%).

Adv adenovirus, *NA* not applicable, *mMRC* modified Medical Research Council, *SpO_2* stands for peripheral capillary oxygen

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4 **Table 2** Comparisons of laboratory and radiologic parameters between Adv and Non-Adv groups

	Adv (n = 67)	Non-Adv (n = 184)	Total (n = 251)	*p* value
Results of laboratory study				
WBC count, 10^9/L	6.02 ± 4.15	8.13 ± 4.05	7.57 ± 4.08	0.020
Leukopenia (< 4x10^9/L)	21 (31.3)	10 (5.4)	31 (12.4)	< 0.001
Leukocytosis (> 10x10^9/L)	8 (11.9)	52 (28.0)	60 (23.9)	0.035
Lymphocyte, %	22.15 ± 8.23	18.62 ± 9.15	19.56 ± 8.90	0.054
Monocyte, %	12.05 ± 2.72	11.02 ± 3.45	11.49 ± 3.26	0.202
Platelet count, 10^9/L	136.3 ± 52.7	184.6 ±63.3	171.7 ± 61.2	< 0.001
Thrombocytopenia (< 150x10^9/L)	22 (32.8)	17 (9.2)	39 (15.5)	< 0.001
Total bilirubin, mg/dL	0.6 ± 0.3	0.6 ± 0.2	0.6 ± 0.2	0.715
Creatinine, mg/dL	0.57 ± 0.14	0.64 ± 0.14	0.62 ± 0.14	0.442
C-reactive protein, mg/dL	5.24 ± 2.94	6.02 ± 3.11	6.00 ± 3.05	0.411
Procalcitonin, ng/mL	0.04 [0.00-0.08]	0.06 [0.00-0.10]	0.05 [0.00-0.08]	0.635
Results of etiologic study				
No pathogen	NA	50 (27.2)	50 (20.0)	NA
Viral etiology				< 0.001
Adv	67 (100)	NA	67 (26.7)	NA
Rhinovirus	5 (7.5)	18 (9.8)	23 (9.2)	
Influenza A/B virus	4 (6.0)	22 (12.0)	26 (10.4)	
HMPV	(-)	1 (0.5)	1 (0.4)	
RSV	1 (1.5)	3 (1.6)	4 (1.6)	
Parainfluenza virus	1 (1.5)	3 (1.6)	4 (1.6)	
Bacterial etiology				< 0.001
S. pneumoniae	3 (4.5)	19 (10.3)	22 (8.8)	
H. influenzae	3 (4.5)	12 (6.5)	15 (6.0)	
M. pneumoniae	5 (7.5)	8 (4.3)	13 (5.2)	
K. pneumoniae	(-)	2 (1.1)	2 (0.8)	
Combined etiologies				< 0.001
S. pneumonia plus H.pneumoniae	7 (10.4)	14 (7.6)	21 (8.4)	
Rhinovirus plus H.pneumoniae	(-)	22 (12.0)	22 (8.8)	

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Influenza A/B virus plus S.pneumoniae	1 (1.5)	6 (3.3)	7 (2.8)	
Influenza A/B virus plus H.influenzae	(-)	2 (1.1)	2 (0.8)	
RSV plus H.influenzae	(-)	2 (1.1)	2 (0.8)	
Results of radiologic study				
Dominant pattern				< 0.001
GGO	3(4.5)	6 (3.3)	9 (3.6)	
Consolidation	23 (24.3)	103 (56.0)	126 (50.2)	
GGO plus consolidation	41 (61.2)	75 (40.7)	116 (46.2)	
Distribution				0.015
Unilateral	56 (83.5)	133 (72.2)	189 (75.3)	
Bilateral	5 (7.5)	10 (5.4)	15 (6.0)	
Multi-lobar (≥ 3 lobes)	6 (9.0)	41 (22.3)	47 (18.7)	
Pleural effusion	2 (3.0)	8 (4.3)	10 (4.0)	0.483

Data are shown as mean ± standard deviation, median [interquartile range] or number (%).

Adv Adenovirus, *RSV* Respiratory syncytial virus, *HMPV* Human metapneumovirus, *GGO* Ground glass opacity, *S. pneumoniae* Streptococcus pneumoniae, *H. influenzae* Haemophilus influenzae, *M. pneumoniae* Mycoplasma pneumoniae, *K. pneumoniae* Klebsiella pneumoniae

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Table 3 Characteristics of fever and response to antipyretics between Adv, Non-Adv, and no pathogen group

	Adv (n = 67)	**Non-Adv (n = 134)**	**No pathogen (n = 50)**	***p* value**
Duration of fever after admission, days	3.2 ± 1.6	1.9 ± 1.2	2.2 ± 1.5	0.018
Duration of fever after symptom onset, days	5.8 ± 2.2	3.9 ± 2.5	3.7 ± 2.0	0.006
Mean temperature at admission day, ℃	37.8 ± 0.3	37.3 ± 0.3	37.3 ± 0.2	0.005
Numbers of patients to maximal temperature at admission				< 0.001
Over 40℃	10 (14.9)	3 (2.2)	2 (4.0)	
39-40℃	24 (35.8)	5 (3.7)	3 (6.0)	
Time of maximal falls in temperature at admission, hours	10.2 ± 5.6	8.0 ± 4.5	8.6 ± 5.5	0.015
Mean change of temperature at one hour after administrated antipyretics, ℃	1.1 ± 0.7	1.2 ± 0.6	1.0 ± 0.7	0.645
Responsiveness to antipyretics at admission				<0.001
Complete response	30 (44.8)	84 (62.7)	38 (76.0)	
Partial response	25 (37.3)	48 (35.8)	12 (24.0)	
No response	12 (17.9)	2 (1.5)	(-)	

Data are shown as mean ± standard deviation, median [interquartile range] or number (%).

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Table 4 Comparison of clinico-laboratory findings between Adv and Non-Adv patients in whom unresponsive to initial antibiotics treatment

	Adv (n = 47)	**Non-Adv (n = 50)**	**Total (n = 97)**	***p* value**
WBC count, 10^9/L	5.89 ± 3.75	6.05 ± 3.54	5.95 ± 3.66	0.720
Leukopenia (< $4x10^9$/L)	21 (44.7)	20 (40.0)	41 (42.3)	0.435
Leukocytosis (> $10x10^9$/L)	8 (17.0)	15 (30.0)	23 (23.7)	0.015
Lymphocyte, %	22.15 ± 8.23	18.62 ± 9.15	19.56 ± 8.90	0.054
Monocyte, %	8.05 ± 3.72	11.02 ± 3.45	9.65 ± 3.56	0.002
Monocytopenia (< 150/μL)	8 (17.0)	2(4.0)	10 (10.3)	0.005
Platelet count, 10^9/L	128.5 ± 62.5	125.5 ±59.5	126.7 ± 61.5	0.335
Thrombocytopenia (< $150x10^9$/L)	25 (53.2)	26 (52.0)	51 (52.6)	0.736
Responsiveness to antipyretics at admission				0.045
Complete response	4 (8.5)	5 (10.0)	9 (9.3)	
Partial response	31 (66.0)	40 (80.0)	71 (73.2)	
No response	12 (25.5)	5 (10.0)	17 (17.5)	
Numbers of Maximal temperature at admission				0.003
Over 40℃	8 (17.0)	3 (6.0)	11 (11.3)	
39-40℃	21 (44.7)	6 (12.0)	27 (27.8)	
Mean temperature at admission day, ℃	37.8 ± 0.3	37.3 ± 0.2	37.5 ± 0.2	0.005
Duration of fever after admission, days	3.3 ± 1.5	2.8 ± 1.6	3.0 ± 1.5	0.156

Data are shown as mean ± standard deviation or number (%).

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Table 5 Comparisons of treatment outcomes between Adv and Non-Adv group

	Adv (n = 67)	Non-Adv (n = 184)	Total (n = 251)	*p* value
Initial antibiotics regimen				0.781
3rd cephalosporin plus azithromycin	65 (97.0)	178 (96.7)	243 (96.8)	
Respiratory quinolone	(-)	1 (0.5)	1 (0.4)	
Piperacillin/tazobactam plus quinolone	1 (1.5)	4 (2.2)	5 (2.0)	
Piperacillin/tazobactam	(-)	1 (0.5)	1 (0.4)	
Carbapenem	1 (1.5)	(-)	1 (0.4)	
Treatment regimen change (Antibiotics escalation)	47 (70.1)	50 (27.2)	97 (38.6)	0.024
Duration of antibiotics use, day	12.32 ± 2.76	11.64 ± 2.89	11.85 ± 2.83	0.114
Mean antipyretics dose at admission, gram	5.52 [3.45-6.91]	4.30 [3.14-6.55]	4.85 [3.21-6.75]	0.032
Duration of antipyretics use, days	10.5 ± 2.7	10.6 ± 3.1	10.6 ± 3.0	0.892
Adverse event after antipyretics use				0.005
Hypotension	10 (14.9)	4 (2.2)	14 (5.6)	
GI trouble	6 (9.0)	2 (1.1)	8 (3.2)	
Skin rash	1 (1.5)	(-)	1 (0.4)	
Elevated liver enzyme	4 (6.0)	2 (1.1)	6 (2.4)	
Length of hospital stay	15.0 ± 2.3	14.8 ± 2.1	14.9 ± 2.2	0.407
Time from admission to improvement of discomfort , day	4.3 ± 2.8	2.9 ± 1.8	3.2 ± 2.0	0.034
In-hospital mortality	0 (0)	0 (0)	0 (0)	> 0.999

Data are shown as mean ± standard deviation, median [interquartile range] or number (%).