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Clinical characteristics of refractory Mycoplasma pneumoniae pneumonia in children treated with glucocorticoid pulse therapy

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Abstract

Background: To observe the effect of corticosteroids in the treatment of children with refractory Mycoplasma pneumoniae pneumonia (RMPP) under different doses, to summarize the clinical features of children treated with glucocorticoid pulse therapy.

Methods: The clinical data of 125 children with RMPP hospitalized in Tianjin Children's Hospital from September 2018 to October 2019 were retrospectively analyzed. They were divided into two groups according to the dose of hormone. Compare the clinical features, laboratory findings, and imaging between the two groups, and use meaningful related indicators as ROC curves to find reference indicators for pulse therapy.

Results: (1)The median age of the group II was older than that of the group I(P<0.05).(2)We found more severe presentations, higher incidence of extra-pulmonary complications and more serious radiological findings in group II, which needed oxygen more often, higher the hormone, higher usage rate of gamma globulin, higher usage rate of bronchoscopy, and higher incidence of plastic bronchitis(P<0.05).(3)WBC, CRP, LDH, FER, D-D dimer, APTT, TT, PCT, IL-6 and the percentage of neutrophils in peripheral blood in Group II were higher than those in Group I(P<0.05).(4)In ROC curve analysis, CRP, LDH, FER, and neutrophils of leukocyte classification were independent related factors that could be used as valuable predictors of methylprednisolone pulse therapy for RMPP in children. The cut-off values were CRP44.45mg/L, LDH590IU/L, FER411ng/L, and neutrophils in leukocyte classification were 73.75%, respectively.

Conclusion: CRP≥44.45mg/L, LDH≥590IU/L, FER≥411ng/L, neutrophil≥73.75%, lung consolidation and pleural effusion are found in RMPP patients, which could be treated with pulse dose of methylprednisolone in time to reduce the incidence of severe RMPP and the occurrence of severe sequelae.

Introduction

Mycoplasma pneumoniae (MP) is the main pathogens of community-acquired pneumonia (CAP) in children[1]. Mycoplasma pneumoniae pneumonia (MPP) is considered as a benign and self-limiting disease. However, it has been found that some children may progress to refractory Mycoplasma pneumoniae pneumonia(RMPP) after being treated with sufficient and long-term macrolide antibiotics in timely[2], which often leads to pulmonary necrosis and pleural effusion, which may not only be difficult to treat and costing, but also leave sequelae such as bronchiectasis, necrotizing pneumonia, bronchiolitis obliteransa and so on[3-7], thus affect the quality of life. Over-immune response of host plays an important role in the development of RMPP[8, 9]. Studies have confirmed the effectiveness of glucocorticoid (GC) in the treatment of RMPP[2, 10, 11]. GC are effective in the treatment of severe RMPP by down-regulating the cell-mediated immune response associated with lung injury during infection[12-15]. Therefore, on the basis of adequate anti-infective treatment, GC has attracted more and more attention[16, 17]. It is vital for

clinicians to identify severe RMPP as early as possible and give pulse dose of hormone therapy. So, retrospective analysis was performed on 125 children with RMPP hospitalized in our hospital from September 2018 to October 2019. The purpose of this study was to compare the differences of clinical manifestations, laboratory data and imaging findings between two groups and to explore the predictive values of pulse therapy of RMPP.

Methods

Patients

This study selected 125 children with RMPP who were treated with different doses of GC at Tianjin Children's Hospital from September 2018 to October 2019. All children meet the diagnostic criteria of MPP[18, 19]: (1) Symptoms and signs of pneumonia showed on admission, including fever, cough, abnormal lung auscultation and so on; (2) Chest imaging indicated pneumonia; (3) Positive results of serologic test. Included patients underwent anti-MP IgM titrations twice, both at the time of admission and upon discharge. Patients who showed either a seroconversion (negative to positive), or four-fold or greater increase in IgM titers and who had both symptoms with≥1:640 high titers[18]. RMPP was defined as a case with persistent fever, clinical and radiological deterioration after appropriate management with azithromycin for 7 days or more[2, 20]. Clinical and radiological deterioration were described as follows[10, 17]: aggravation of clinical signs was characterized by persistent fever, severe cough, dyspnea, etc. Radiological aggravation showed enlargement of pulmonary lesions, increased density, pleural effusion, and even necrotizing pneumonia and lung abscess.

The included had the following characteristics[19, 21]: (1) Meet the diagnostic criteria of MPP; (2) Meet the definition of RMPP; (3) Age ≤16 years old. The exclusion criteria included any of the following[19, 21]: (1) Patients who had a history of tuberculosis, bronchiectasis, or lung tumors; (2) Patients who had diseases such as severe malnutrition, unconsciousness, chronic cardiac and pulmonary disease, congenital disease or immunodeficiency; (3) Patients who received GC before admission; (4) Patients who were discharged within 8 hours after admission.

Study design

The 125 children were divided into two groups. Group I was given conventional dose methylprednisolone 2mg/kg/day(<200mg/day) (n=81), and group II was treated with methylprednisolone pulse therapy ≥200mg/day(n=44).

This study was approved by the ethics committee of the Tianjin Children's Hospital (Approved No. of ethic committee: L2021-01). The ethics committee waived the need for written informed consent provided by participants due to the retrospective nature of the study, because all patient data were analyzed anonymously, and no additional informed consent was required.

Hormone grouping[22-24]

Conventional dose was defined as intravenous infusion of methylprednisolone 2mg/kg/day(<200mg/day) (or an equivalent dose of dexamethasone, hydrocortisone, prednisolone or betamethasone), and pulse therapy ≥200mg/day methylprednisolone (or an equivalent dose of dexamethasone, hydrocortisone, prednisolone or betamethasone).

Grouping[25]

All selected children were treated with routine dose of methylprednisolone intravenously within 48-72 hours after admission. According to changes in body temperature, children were divided into conventional dose group and pulse dose group:1) Conventional dose group: after given the initial of methylprednisolone 2mg/kg/day(<200mg/day), their body temperature returned to normal within 48 hours, their imaging abnormality gradually improved, CRP returned to normal, and there was no recurrence in the process of hormone withdrawal. 2)Pulse therapy: initially given methylprednisolone 2mg/kg/day, there was no significant decrease in heat peak within 48 hours. Therefore, gradually increased the dose of methylprednisolone. When the dose of methylprednisolone was increased to 200mg/day or more, their body temperature returned to normal within 48 hours.

Collection of clinical data

Collect data for each patient, including demographic characteristics, medical history, physical examination results, laboratory data, radiology results, hospital stay, fever time, etc. Record the laboratory data which were detected during hospitalization, including white blood cell (WBC) counts, neutrophil counts, and levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin (PCT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), etc[26]. Hypoxia was defined as any oxygen saturation measured by pulse oximetry in indoor air <92%[27, 28].

Statistical Analysis

Statistical analyses were performed using SPSS software (version 22.0). Normal distribution data were expressed as mean ± SD (x ± s). Independent-Samples T-test or One-way ANOVA was used to process these data. The skewed distribution data were presented as the median values (P25, P75), and comparisons were made by the Mann-Whitney U-test. Chi-squared tests were used to compare numerical data, which was presented as rate or constituent ratio. Meanwhile, we use the laboratory indicators with

significant differences as independent related risk factors to make the ROC curve, and use the area under the ROC curve (AUC) to reflect the accuracy of the diagnostic test. Take the point closest to the upper left corner of the ROC curve, which has the largest sum of sensitivity and specificity, as the optimal value of prediction. The difference was considered statistically significant at P< 0.05.

Results

General information of patients

This study included 125 children. All patients met the diagnostic criteria and were treated with macrolide antibiotics against infection. Children were divided into two groups according to GC dose. The age distribution of the subjects was shown in Fig 1. The 81 patients in group I (36 females, 45 males) had the median age of 6.54±3.03 years, and the median weight of 20.4(16.4, 28.9) kg; The 44 patients in group II (22 females, 22 males) had the median age of 7.61±2.49 years, and the median weight of 27.2(20.0, 33.5) kg, which was shown in Table 1. No difference in gender distribution was found between the two groups(P>0.05). There were significant differences between the two groups in the age and weight (P<0.05, P<0.01).

Clinical information of patients

The incidences of hypoxemia, respiratory failure were significantly higher in group II than those in group I (P<0.01, P<0.05, respectively). The incidence of extra-pulmonary complications was 75.0% in group II, and 22.2% in group I, with a significant difference (P<0.01).There were not significant differences in fever and cough among the two groups (P>0.05). The difference in the incidence of pulmonary embolism did not reach statistical significance(P> 0.05) (Table 1).

Regarding the clinical process, we found that the length of fever was 13(11, 15) days in group II, 11(8, 13) days in group I, with a significant difference (P<0.05). The days of fever before hospitalization did not differ significantly between the two groups. The meaning of fever duration at the time of corticosteroids treatment is that fever days after starting corticosteroids therapy. The days of fever after hormone administration in group II and in group I were 5.45±2.76 days and 1.95±1.91 days respectively, the difference was statistically significant. The length of stay was 13.5(11.3, 16) days in group II, and 8(7, 10) days in group I, with a significant difference (P<0.05).

Treatment of patients

All patients received macrolide therapy. There were significant differences between the two groups in the usage rate of gamma globulin, the usage rate of bronchoscopy, the incidence of plastic bronchitis (P<0.05, P<0.01, P<0.01).

Laboratory of patients

Table 2 summarized the laboratory data of patients. The median values of Fg, PT, PLT, La, ALT and AST did not differ significantly between the two groups (P >0.05). The median levels of WBC, CRP, LDH, FER, D-dimer, APTT, TT, PCT, IL-6 and the percentage of peripheral neutrophils in children with group II were significantly higher than those in children with group I(P<0.05).

Imaging findings of patients

Radiological findings in two groups of patients were summarized in Tables 3. Radiological findings were more severe in group II than those in group I. The difference in the incidence of atelectasis (25.0% versus 21.0%) and pleural thickening (68.2% versus 64.2%) did not reach statistical significance (P>0.05). And there were statistically significant differences between the two groups in the incidence of pulmonary complications, including pulmonary consolidation (93.2% versus 51.9%, P<0.01) and pleural effusion (45.5% versus 27.2%, P<0.05).

Predictive values

In order to explore the optimal values of laboratory data for group II, receiver operator characteristic (ROC) curves were made and the cut-off values with maximum sensitivities and specificities were determined. The analysis of these ROC curves shows that CRP, LDH, FER, neutrophil percentage can be used to express the clinical features of children with RMPP treated with pulse dose (Table 4). When the cut-off values for CRP, LDH, FER, neutrophil percentage were set at 44.45 mg/L, 590 IU/L, 411 ng/L, 73.75 respectively, it is helpful to guide the use of pulse dose GC in children with more severe RMPP. The sensitivity and specificity were respectively 55.0% & 85.0%, 76.3% & 47.5%, 86.4% & 68.2%, and 75.0% & 90.0%.

Discussion

One of the main pathogens of CAP in children is Mycoplasma pneumoniae. More and more RMPP have been reported[29-34]recently. Studies[35, 36] have shown that more than 90% of Mycoplasma pneumoniae infections in China are caused by drug-resistant strains. However, the latest research results of Sun et al[37] have shown that the important cause of MP resistance to macrolide antibiotics was not only related to the irregular use of antibiotics, but also related to the epidemic genotype M4-5-7-2 of Mycoplasma pneumoniae. Through the comparison of genotypes and drug resistance between Chinese, American and Australian strains, it was reasonably explained from a new perspective that the high drug resistance rate in China and even in Asia is not all caused by the abuse of antibiotics, which is closely related to the

regional differences in the epidemic genotypes of Mycoplasma pneumoniae[37]. Therefore, macrolides are still used in patients with MP in China. Only when macrolides are ineffective, antibiotics such as tetracyclines or fluoroquinolones can be used according to the condition[38-42]. Due to the influence of the pathogenesis, most of the RMPP will produce complications. The host's excessive immune response plays a key role in the development of RMPP disease[8, 9], such as cytokines (including interleukin-2, interleukin-6 and interleukin-8). Over-expression and highly activated cells (including antigen presenting cells and T cells) mediated immune response etc[43]. GC can be used to down-regulate the related cell-mediated immune response and play an effective role in severe cases of MP infection[12-14]. Early control of lung injury caused by overactive immune response by non-specific adaptive immune cells is essential for reducing the incidence of severe MPP and preventing disease progression. Because the severity of RMPP is related to the immune response, and the effect of GC is dose-dependent, higher doses may be needed in patients with severe MPP[4, 44, 45].

A number of studies have revealed that humoral and cellular immune responses[46, 47]contribute to the pathogenesis of MP infection, providing a theoretical basis for the application of GC in RMPP. Studies have shown that the addition of GC on the basis of the conventional treatment has a definite effect on RMPP, which contributes to the control of the disease progression, the improvement of the condition and the reduction of sequelae[10, 16]. So, it is very important to study the application of GC in the treatment of RMPP[2, 16, 48].

So, in this retrospective research, 125 patients of RMPP were enrolled. Among them, there were 81 cases in group I, and 44 cases in group II. First of all, this study found that there was a statistical difference in age between group I and group II (6.54±3.03, 7.61±2.49, $P<0.05$), which was similar to the previous studies[11, 17]. Children's immune system develops with age, and was prone to produce excessive inflammatory response to MP, which may lead to the deterioration of RMPP[17].

Secondly, higher incidence of hypoxemia, extra-pulmonary complications and plastic bronchitis were found in the group II than those in the group I ($P<0.05$). Moreover, the proportion of patients required oxygen therapy, gamma globulin and bronchoscopy in the group II were higher than that in the group I ($P<0.05$). The total fever days, hospital stay, fever days after hormone therapy in group II were significantly higher than in group I ($P<0.05$). In addition, our research also showed that higher incidence of pulmonary consolidation and pleural effusion were found in group II than in groups I ($P<0.05$).The imaging findings may be related to the severity of the disease. The difference of imaging is correlation to immune inflammatory response and direct damage[19]. Finally, the study also found that WBC, CRP, LDH, FER, D-D dimer, APTT, TT, PCT, IL-6, ALT and the percentage of neutrophils in peripheral blood in group II were higher than in group I ($P<0.05$). These results indicated that if RMPP was not treated effectively, the clinical course of disease maybe prolonged and the disease maybe aggravated.

In order to study the clinical characteristics that can predict the severity of RMPP disease and guide the GC pulsed dose treatment, we used the ROC curve to analyze statistically significant indicators. In ROC

curve analysis, the area under the curve of CRP, LDH, FER and white blood cell classification of neutrophils were above 0.6, which were very helpful for identifying more severe RMPP patients. The optimal cutoff value for these four factors was 44.45 mg/L,590 IU/L,411 ng/L and 73.75%, respectively. We found that CRP 44.45 mg/L, LDH 590 IU/L, FER 411 ng/L, leukocyte classification neutrophil 73.75%, lung consolidation and pleural effusion may be important clinical features of use pulsed dose hormones to treat patients of RMPP.

CRP is the most widely used acute phase inflammatory protein. CRP rises rapidly after inflammation stimulation, which value can reflect the development of the immune system. CRP levels in patients with acute infection, inflammation or trauma may increase in a short time. Liu[1] et al showed that the cutoff value of CRP for RMPP was 40mg/L. Chen et al[19, 21]. showed that when CRP was 16.5mg/L or higher, the sensitivity and specificity for diagnosing MPP with hypoxia were 74.7% and 77.2%, respectively. The cutoffs were less than that in our study. The main reason may be that our results come from a small series of cases, and our subjects are more seriously ill. In our study, the optimal cutoff point for CRP was 44.45mg/L, with a sensitivity of 55% and specificity of 85%. These indicate that CRP has a better clinical utility in identifying high-risk patients with RMPP.

LDH is an inflammatory marker. After cell damage, LDH is released into the serum and can be used to monitor tissue damage in many inflammatory processes. Studies have shown that LDH was related to many lung diseases[49, 50]. Serum LDH was a biomarker of RMPP severity[1, 11, 13, 19]. Lu et al[51].reported that serum LDH can be used as a biomarker for predicting RMPP and evaluating whether to initiate corticosteroid therapy during the initial hospitalization of patients. Chen et al[19, 21]. showed that when LDH was 417 IU/L or higher, the sensitivity and specificity for diagnosing MPP with hypoxia were 79.7% and 65.0%, respectively. In this study, the optimal cutoff for LDH was 590IU/L, with a sensitivity of 76.3% and specificity of 47.5%, which was higher than that of previous studies[13, 19].

Elevated levels of ferritin may be positively correlated with the severity of inflammation, infection, renal failure and metabolic syndrome. In lung diseases, lung inflammation and tissue damage can lead to increased ferritin levels[52]. Kawamata et al.[12] showed that serum ferritin levels were positively correlated with the severity of children's MPP, and ferritin may be a useful indicator for the initiation of glucocorticoid therapy for MPP. However, there is still no report about the correlation of ferritin in treatment of RMPP with pulse dose of GC. Choi et al.[53] reported that when ferritin was greater than or equal to 230 ng/mL, the sensitivity and specificity for diagnosing RMPP were 67% and 67%. In this study, the area under the curve for ferritin was 0.814 in the ROC curve analysis, which indicates that ferritin has a fair discriminative power in predicting the use of pulse dose to treat RMPP. The optimal cutoff for ferritin was 411 ng/mL, the sensitivity and specificity were 86.4% and 68.2%. The reasons for the difference in the studies are as follows: Firstly, it may be that the research object is RMPP, and the clinical manifestations are more serious; secondly, it may be that the research object contains unrecognized mixed infections.

Systemic GC can be considered for severe MPP with acute onset, rapid progression, especially for RMPP. However, there is no corresponding indicator for the use and timing of hormone dose. There are different opinions on the dosage of hormones in the existing article[11, 16]: You and Lee et al.[43]used intravenous infusion of methylprednisolone 10 mg/kg/day×3days for some patients who had failed oral treatment (dose reduction within 1 week). The clinical manifestations of all patients were significantly improved, and there were no related side effects. Lee [11] et al.treated 15 children with RMPP orally with prednisolone 1 mg/kg/day, and the dose was reduced after continuous use for 3-7 days, which has a significant therapeutic effect on children with RMPP. Luo et al. proved that oral prednisone (2mg/kg/day) was more effective than azithromycin alone in children with RMPP. And Tamura [2] gave 6 patients with RMPP an intravenous drip of 30 mg/kg/day×3days methylprednisolone. The body temperature of all patients returned to normal within 14 hours, and the clinical symptoms were significantly improved. They think that the combined use of hormone therapy can reduce the length of hospital stay and the occurrence of RMPP, and there is no adverse hormone response. The study implied that elder children are prone to more severe presentations, higher incidence of extra-pulmonary complications and more serious imaging. The study suggested that the severity of RMPP was related to host immune response, and the optimal values of CRP, LDH, FER and leukocyte classification neutrophils (CRP44.45mg/L, LDH590IU/L, FER411ng/L, leukocyte classification neutrophils 73.75%), lung consolidation, and pleural effusion may be the valuable predictors of the use of methylprednisolone pulse therapy for RMPP in children.

This study indicated that in the treatment of RMPP, timely use of appropriate doses of GC can reduce the intensity of local inflammation, alleviates the immune reaction, and promote disease recovery. During the treatment of RMPP with GC, blood pressure, blood glucose, blood potassium and liver function should be monitored, notice the adverse reactions such as circulatory system and gastrointestinal bleeding, and pay attention to ECG monitoring during pulse dose treatment. And be sure to: the suitable time for treatment; exclude whether there are other infections or lesions; prevent the occurrence of double infection.

The study has some limitations. Firstly, as this was a retrospective study, select bias might exist and further prospective studies are needed. However, considering that RMPP may be life-threatening, prospective study may have a harmful impact on children. So, retrospective study may still be the way to study the issues. Second, the patients come from the same region, the risk factors associated with GC resistance may not be applicable to patients in other regions, requiring multicenter studies in the future. Thirdly, our hospital is a tertiary hospital with many severely ill patients. The uneven distribution of critically ill patients in this study has a certain impact on the experimental results. Fourth, there might be some patients that were coinfected with other pathogens which could not be detected and might therefore result in the progression of RMPP. Finally, the optimal value of risk factor obtained by ROC curve may have some limitations and only guide judgment to a certain extent. More clinical data should be accumulated and further verified in clinical work to obtain more accurate reference standards.

Conclusion

This research shows that immune inflammatory response may play a vital role in the progression of RMPP. CRP≥44.45mg/L, LDH≥590IU/L, FER≥411ng/L, neutrophil≥73.75%, lung consolidation, and pleural effusion may be meaningful predictors that guide the treatment of RMPP with pulse dose of GC.

Abbreviation

MP: Mycoplasma Pneumoniae; CAP: Community Acquired Pneumonia; RMPP: Refractory Mycoplasma pneumoniae pneumonia; PCR: Polymerase chain reaction; CRP: C-reactive protein; Fer: Ferritin; D-D: D-dimer; Fg: Fibrinogen; LDH: Lactate dehydrogenase; PCT: Procalcitonin; IL: Interleukin; La: lactic acid; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ROC: Receiver operating characteristic

Declarations

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Authors' contributions

Conception and Design: ZLZ, TQZ, and YSX; Extraction of Data: ZLZ, WG, YYL, and JT; Drafting the Article: ZLZ; Revising It for Intellectual Content: ZLZ, and YSX; Final Approval of the Completed Article: ZLZ, TQZ, and YSX. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were following the Ethics Committee of Tianjin Children's Hospital (Approved No. of ethic committee: L2021-01). The ethics committee waived the need for written informed consent provided by participants due to the retrospective nature of the study, because all patient data were analyzed anonymously, and no additional informed consent was required.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Tables

Tables 1-4 are available in the Supplementary Files

Figures

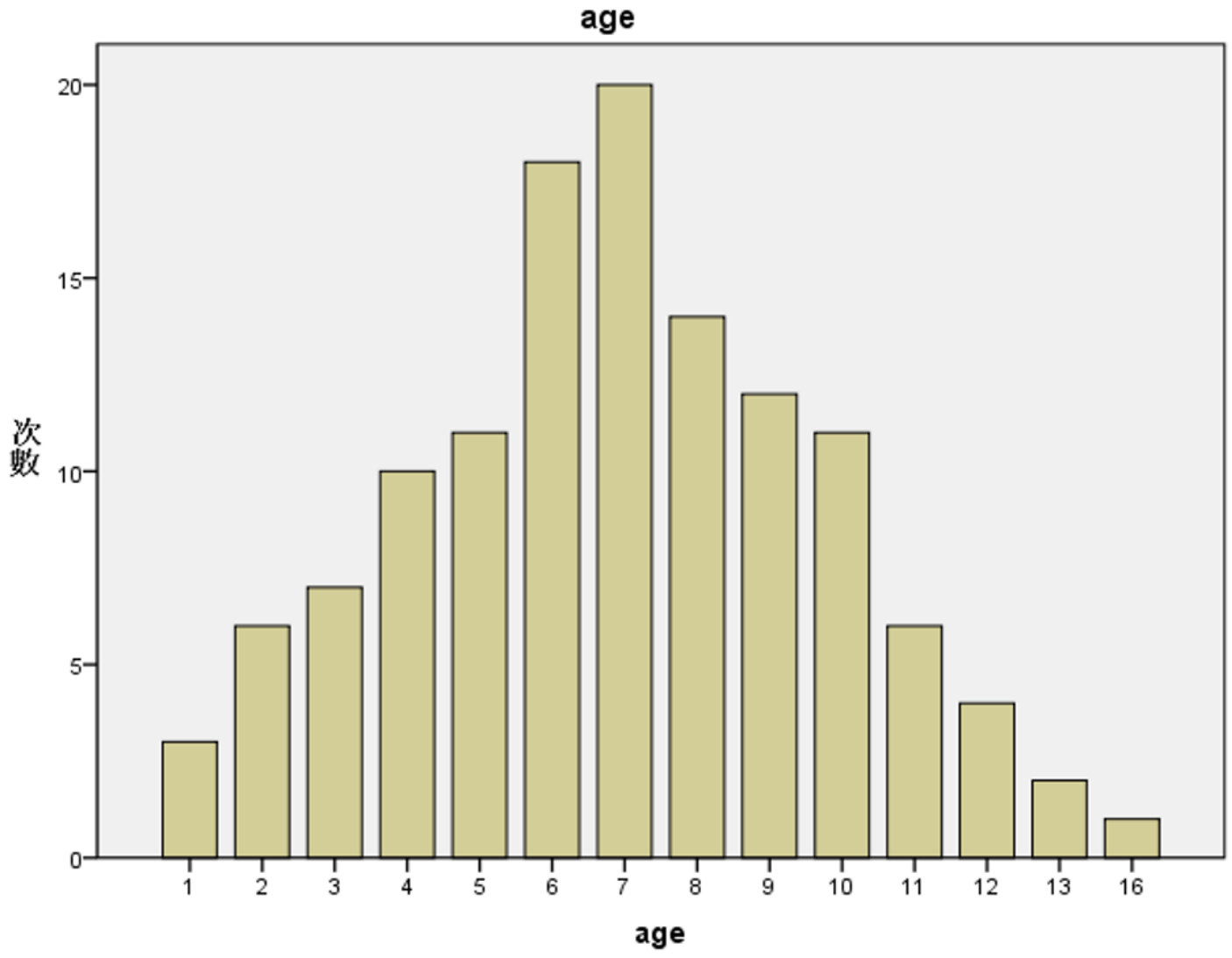

Figure 1

Age distribution of refractory Mycoplasma pneumoniae pneumonia patients.

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