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Application value of Serum Hs-CRP, IL-6 and plasma FIB joint detection in COPD

Feng Ji^{1✉}, Ming-Kun Ge², Jian Ye¹¹Clinical Laboratory, Zhongda Hospital Southeast University (Jiangbei), Nanjing, Jiangsu 210009, China²Respiratory Medicine, Zhongda Hospital Southeast University (Jiangbei), Nanjing, Jiangsu 210009, China

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ABSTRACT

Objective: To discuss the application value of High sensitivity C-reactive protein (Hs-CRP), interleukin-6 (IL-6) and fibrinogen (FIB) joint detection in chronic obstructive pulmonary disease (COPD). **Methods:** A total of 181 COPD cases were divided to be COPD stable phase group (65 cases) and COPD acute exacerbation phase group (116 cases) per the course of disease. COPD acute exacerbation phase group was classified into grade I (39 cases), grade II (43 cases) and grade III (34 cases) based on pulmonary function. Then survival group (87 cases) and death group (29 cases) were divided based on illness transition. Meanwhile, 80 cases of healthy people at the same phase were set to be healthy group. Differences in levels of Serum hs-CRP, IL-6 and FIB in these groups were analyzed, and according to these indexes, prognostic potency of COPD acute exacerbation phase could be evaluated. **Results:** Difference in serum hs-CRP, IL-6 and FIB levels in COPD stable phase group, COPD acute exacerbation phase group and healthy group were statistical significant ($P < 0.05$). both for healthy group $<$ COPD stable phase group $<$ COPD acute exacerbation phase group. Difference in serum hs-CRP, IL-6 and FIB levels in grade I, II, III of pulmonary function in the COPD acute exacerbation phase group were statistical significant ($P < 0.05$) both for grade 1 $<$ grade 2 $<$ grade 3. Result of person analyzing showed significant positive correlation on grading of pulmonary function and serum hs-CRP, IL-6 and FIB levels, the correlation coefficient was 0.573. Differences of hs-CRP, IL-6 and FIB levels between survival group and death group were statistical significant. Serum hs-CRP, IL-6 and FIB levels were utilized respectively to evaluate area under curve of receiver operating characteristic in prognostic COPD acute exacerbation phase group, namely, 0.836, 0.815, 0.776. Sensitivities of "death", which was evaluated by the various indexes, respectively showed as: 72.41%, 65.51% and 75.86%; Specificities were 80.46%, 83.91%, 79.31%; Accuracies were 93.10%, 95.40%, 94.83%. **Conclusions:** COPD illness evolution and severity could be reflected by serum hs-CRP, IL-6 and plasma FIB all in some extent, the joint detection could be a reference on prognostic evaluation.

1. Introduction

Chronic obstructive pulmonary disease (COPD) was a common disease which could threaten the life safety of patients. Many

clinical patients had this disease. Lethality exists in acute outbreak of it to a certain extent[1], so it is important to make an accurate evaluation early on the state of COPD, which is conducive to take positive measures for suppressing the disease progression as soon as possible. So far, methods of multiple indexes joint detection were mainly used on the early clinical evaluation of COPD disease prognosis[2], but no final conclusion made to choose the most appropriate indexes. Our study had a retrospective analysis on serum hs-CRP, IL-6 and plasma FIB levels of 181 COPD patients

✉Corresponding author: Feng Ji, Clinical Laboratory, Zhongda Hospital Southeast University (Jiangbei), Nanjing, Jiangsu 210009 China.

Tel: 15851881295

E-mail: jifeng8656@163.com

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treated in our hospital from March, 2014 to March, 2016, and tried to analysis the application value on joint detection of these three indexes.

2. Materials and methods

2.1. General materials

The cases were derived from COPD patients treated in our hospital from March, 2014 to March, 2016. They all fit the diagnostic standards in China's Chronic Obstructive Pulmonary Disease Clinic guide^[3] revised in 2007. Excluded and rejected standards: (1) Patients combined Cardio-cerebral, liver-renal, endocrine systematic, autoimmune serious disease and neoplasm; (2) Patients combined pulmonary diseases, such as bronchiectasis, history of pulmonary surgery, pulmonary abscess, pneumothorax, tuberculosis and so forth; (3) Patients combined traumas such as severe extra-pulmonary infection, surgeries, etc.; (4) Patients who had incomplete clinical data. 181 COPD cases were included in this study. Based on different courses, cases were divided to be COPD stable phase group and COPD acute exacerbation phase group. There were 65 cases in COPD stable phase group, 49 male cases and 26 female cases; Ages were between 58 and 76 (67.21 ± 10.36) years old. 116 cases were in COPD acute exacerbation phase group, 89 male cases and 27 female cases; Ages were between 57 and 79 (67.43 ± 12.36) years old. COPD acute exacerbation phase group was classified into grade I, grade II and grade III based on pulmonary function^[3], 39 cases of grade I, 43 cases of grade II and 34 cases of grade III were included; And since all the death cases were in the COPD acute exacerbation phase, this group was divided to be survival group and death group based on outcome of disease. There were 87 cases in survival group, and 29 cases in death group. A total of 80 healthy people were selected from who were in the same range of age with healthy result when health examination done in our hospital in the same term, and they were created to be healthy group, 59 male cases and 21 female cases were included. Their ages were between 54 and 75 (63.21 ± 12.54) years old. Analysis of statistics indicated that there was no statistical significant difference in genders and ages among cases in COPD stable phase group, COPD acute exacerbation phase group and healthy group ($P > 0.05$); There was no statistical significant difference in genders between cases in survival group and death group ($P > 0.05$), difference in their ages was significant ($P < 0.05$).

2.2. Test method and reagent

All the involved subjects were taken 2 mL elbow venous blood without food, placed in coagulating promoting tubes, and another 2 mL placed in sodium citrate anticoagulation tubes pending inspection. COPD cases were taken before treatment. Samples

were put in centrifuge machine (3 000 r/min, 4 °C) respectively to centrifuge 8 min. After that, the upper serum and plasma were tested separately. Hs-CRP and IL-6 detect samples of serum were tested using ELISA method. The kit was purchased from Wuhan Eli Rhett Biological Technology Co., LTD; FIB samples of serum were tested by Sysmex CA7000 automatic blood coagulation analyzer.

2.3. Statistical analysis

SPSS 17.0 Software was used for analysis. Comparison in the two groups of measurement data was conducted by *t*-test; Multi-groups of measurement data were compared in pairs to analysis the advanced one-way anova. Then *SNK-q* test was utilized; Person correlation analysis was used for analyzing the data dependence, $P < 0.05$ indicated the difference was statistical significant. Receiver operating characteristic (ROC) was used to analysis hs-CRP, IL-6 and FIB single index and joint detection to evaluate the efficacy of COPD acute exacerbation phase prognosis (classified in to death and survival group), to determine AUC and sensitivity, specificity and accuracy rate at this time.

3. Results

3.1. Comparison of hs-CRP, IL-6 and FIB levels between COPD cases and healthy cases

Analysis of variance in all the 3 groups of hs-CRP, IL-6 and FIB levels showed to be equal. Hs-CRP, IL-6 and FIB levels in each group were compared in pairs, results showed statistical significant difference ($P < 0.05$), healthy group < COPD stable phase group < COPD acute exacerbation phase group (Table 1).

Table 1

Comparison of hs-CRP, IL-6 and FIB levels between COPD cases and healthy cases.

Groups	n	hs-CRP (mg/L)	IL-6 (ng/mL)	FIB (g/L)
Healthy	80	1.22±0.47	3.35±2.08	3.84±0.73
COPD stable phase	65	4.28±2.40 [△]	6.32±4.46 [△]	4.75±0.89 [△]
COPD acute exacerbation phase	116	12.71±6.58 ^{△▲}	13.34±5.14 ^{△▲}	5.60±1.09 ^{△▲}

Note: [△] $P < 0.05$ compared to healthy group, [▲] $P < 0.05$ compared to COPD stable phase group

3.2. Comparison of serum hs-CRP, IL-6 and FIB levels in different pulmonary function grades of COPD acute exacerbation phase group

Analysis of variance of hs-CRP, IL-6 and FIB levels in grade I-III showed in equal. Hs-CRP, IL-6 and FIB levels in each garde were compared in pairs, results showed statistical significant difference ($P < 0.05$), grade I < II < III. Result of person analyzing indicated negative correlation of serum hs-CRP, IL-6 and FIB levels among

pulmonary function grades ($P<0.05$), coefficient of correlation was 0.573 (Table 2).

Table 2

Comparison of serum hs-CRP, IL-6 and FIB levels among different pulmonary function grades in COPD acute exacerbation phase cases.

Pulmonary function grades	n	hs-CRP (mg/L)	IL-6 (ng/mL)	FIB (g/L)
Grade I	39	9.85±2.78	9.95±2.98	5.17±0.60
Grade II	43	12.84±3.37 [△]	13.42±3.49 [△]	5.65±0.69 [△]
Grade III	34	15.82±3.58 ^{△▲}	17.13±3.14 ^{△▲}	6.03±0.54 ^{△▲}

Note: [△] $P<0.05$ compared to grade I, [▲] $P<0.05$ compared to grade II.

3.3. Comparison of serum hs-CRP, IL-6 and FIB levels between survival group and death group

Analysis of ROC showed that AUCs of hs-CRP, IL-6 and FIB using to evaluate COPD acute exacerbation phase group prognosis were 0.836, 0.815, 0.776, sensitivities of “death” evaluated by each index were 72.41%, 65.51%, 75.86%; Specificities were 80.46%, 83.91%, 79.31%; Accuracy rates were 78.44%, 79.31%, 78.45%. When 3 indexes put into joint evaluation, AUC was 0.943, sensitivity, specificity and accuracy rate were 93.10%, 95.40%, 94.83% (Table 3).

Table 3

Comparison of hs-CRP, IL-6 and FIB levels between survival group and death group.

Groups	n	hs-CRP (mg/L)	IL-6 (ng/mL)	FIB (g/L)
Survival	87	10.36±3.14	12.16±3.45	5.44±0.96
Death	29	19.76±3.47 [△]	16.88±2.93 [△]	6.08±0.55 [△]

Note: Compared to survival group, [△] $P<0.05$.

4. Discussion

The reasonable evaluation for COPD patients could be helpful in clinic to accurately understand the criticality of disease[1], namely, essential time could be received for positive therapeutic measurements on patients in a critical condition, and excessive treatment could be diminished on patients in a rather stable disease phase, especially for patients in COPD acute exacerbation phase. It is of important significance for reasonable utilization of clinical limited medical resources[4]. Currently, there are many indexes for clinical evaluation of COPD disease severity, besides pulmonary function and blood gas indexes[5], mainly were inflammatory react indexes, such as CRP, PCT, IL-2, IL-6, IL-8 and TNF- α , *etc*[6,7], and indexes which could reflect hypercoagulable state, such as D-dimer (DD), FIB and homocysteine (Hcy), *etc*[8], since inflammatory reaction and hypercoagulable state could always bring negative effects to COPD patients[9]. Systematic and chronic inflammatory reaction is the main pathologic basis of COPD disease[10], a large-scale synthesis of inflammatory mediator in acute exacerbation phase could induce the secretion of “inflammatory waterfall”,

seriously damage pulmonary function and induce the systematic adverse reaction. It is generally recognized as an important reason leading to death of COPD patients[11]. Hypercoagulable state was also a common condition in COPD patients. Especially in an acute exacerbation phase, multiple factors could cause the aggravation of hypercoagulable degree[12]. Blood platelets activity could be increased at this time, and coagulation function could become more abnormal, they are easy to cause the generation of microthromboembolism and affect local blood circulation, and then cause the pulmonary diffusion dysfunction[13], meanwhile, the generation of microthromboembolism could further intensify the inflammatory reaction and stress reaction to damage the body, but if cardio-cerebral vascular accident is induced, conditions of patients could be suddenly aggravated, so hypercoagulable state is also recognized as an important factor for situation inconvenience of COPD patients prognosis. However, because of a numerous relevant indexes, to test all the clinical indexes is unrealistic. Therefore, 2-4 kinds of indexes selected for joint detection is a commonly used clinical method. From the previous reports[14], if indexes were reasonable selected, 3 kinds of indexes joint detection might be more appropriate, sensitivity, specificity and accuracy rate could get a best optimization this time. Hs-CRP, IL-6 and FIB selected in our study are commonly used indexes, but so far, there have been no clinical reports focusing on their joint detection to evaluate COPD disease severity and prognosis.

Hs-CRP and IL-6 are inflammatory reaction indexes, and they both belong to proinflammatory cytokines[15], which are important mediums for inducing “inflammatory waterfall”. When infection and stress activate reaction exist, they could be increased fast, and not be affected by individual differences, body conditions, *etc*[16]. Hs-CRP and IL-6 are positive correlated with tissue damage and severity of inflammatory disease[10], they could be expressed with a higher level in these patient than normal healthy people, that is the behavior of COPD chronic systemic inflammatory reaction. In the meantime, study showed their expression levels in COPD acute exacerbation phase were significantly higher than COPD stable phase, but higher expression level could cause worse pulmonary function. FIB could reflect the degree of hypercoagulable state[17], they could also reflect the levels of body inflammatory reaction in some extent[18]. Their levels are higher in COPD patients than in normal people. At the same time, they could be dramatically increased in COPD acute exacerbation phase, and they could take part in airway inflammatory response, thrombogenesis and local microcirculation disturbance[19], which could notably damage pulmonary function, so they are also considered relating with hypoxemia and hypercapnia[20]. In our study, Hs-CRP, IL-6 and FIB levels in COPD acute exacerbation phase group were higher than COPD stable phase group, and which in stable group were higher than healthy group. And as for pulmonary function grades I-III in COPD acute exacerbation phase, grade I < grade II < grade III, the higher expression levels of indexes could lead to the worse pulmonary function of patients, which

showed an obvious negative correlation, and they were conformed the documental reports[6,12]. COPD death cases were concentrated in acute exacerbation phase, our study found that all the levels of indexes in survival group were also significantly lower than death group, and all the differences had significance. ROC analyzing showed the 3 indexes joint detection could enhance efficacy to evaluate prognosis of COPD acute phase, sensitivity, specificity and accuracy rate of “death” result as: 93.10%, 95.40%, 94.83%, which were in a higher level, and better than utilizing any of the single index. So the joint detection is more valuable to evaluate prognosis of COPD.

Above all, serum hs-CRP, IL-6 and plasma FIB could reflect the COPD disease evolution and severity. The joint detection is valuable to evaluate prognosis, it might provide some clinical reference.

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