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Clinical Observation

Prognostic factors for community-acquired pneumonia in middle-aged and elderly patients treated with integrated medicine

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Abstract

OBJECTIVE: To identify prognostic factors in middle-aged and elderly patients with community-acquired pneumonia (CAP) who underwent integrated interventions involving traditional Chinese medicine (TCM) and modern medicine.

METHODS: Patients aged ≥45 years and diagnosed with CAP were divided into a middle-aged cohort (45-59 years) and an elderly cohort (≥60 years), and clinical data comprising 75 predictor variables in seven classes were collected. After replacing missing data, calibrating multicenter differences and classifYing quantitative data, univariate and multivariate analysis were performed.

RESULTS: On multivariate analysis, eight independent risk factors – respiration rate, C reactive protein (CRP), cost of hospitalization, anemia, gasping, confusion, moist rales and pneumonia severity index (PSI) – were correlated with the outcome "not cured" in the elderly cohort. Nine factors – neutrophil percentage (Neu%), blood urea nitrogen (BUN), time to clinical stability, appetite, anemia, confusion, being retired or unemployed, Gram-negative bacterial infection and educational level – were correlated with not cured in the middle-aged cohort.

CONCLUSION: Independent predictive risk factors correlated with adverse outcomes in elderly patients were higher respiration rate, CRP≥four times the mean or median for the patient's center, cost of hospitalization>11,323 RMB and PSI>II, plus anemia, gasping, confusion and moist rales; those in middle-aged patients were higher Neu% , BUN≥ mean or median, loss of appetite, anemia, confusion, being retired or unemployed and lower educational level. Gram-negative bacterial infection and time to clinical stability>9 days were protective factors.

Key words: Rrognosis; Adverse outcome; Risk factor; Community-acquired pneumonia; Middle aged; Elderly; Chinese medicine

INTRODUCTION

Community-acquired pneumonia (CAP) has high morbidity and mortality in adults and the elderly [1-3]. To improve these adverse outcomes, many studies had been performed to identify prognostic factors. Various outcomes have been used, however, including short-term mortality [3-13], long-term mortality[14], treatment failure[15-17] and other end points [18-23], and only a few studies have explored the differences between different age groups[4]. In addition, most of these prognostic factors were identified using data from patients who received modern medical treatments. Thus, the conclusions of these previous studies are of limited relevance in worldwide clinical practice. Research involving a greater number of common outcomes, comparison between different age groups and complex interventions are needed. Compared with research on end points such as mortality and treatment failure, studies focused on "not-cured" as an outcome may benefit more patients with CAP. In addition, people in different age groups differ physiologically and psychologically, and risk factors may vary between the young, middle-aged and elderly. Furthermore, traditional Chinese medicine (TCM) is thought to have advantages in improving quality of life and reducing hospitalization time and adverse effects[24]. The objective of this study was to identify prognostic factors in middle-aged and elderly patients with CAP who underwent integrated treatment involving TCM and modern medicine.

METHODS

Setting

Medical data were obtained from a multicenter clinical observation supported by a national project, A Theoretical Study on Curative Effect Evaluation Methods Based on Traditional Chinese Medical Diagnosis and Treatment for Pneumonia. Data were collected from the First Affiliated Hospital of Changchun University of Chinese Medicine (Changchun, China), the First Affiliated Hospital of Henan College of Traditional Chinese Medicine (Zhengzhou, China), the Jiangsu Province Hospital of Traditional Chinese Medicine (Nanjing, China) and the Affiliated Hospital of Shandong University of Chinese Medicine (Jinan, China) from December 17, 2006 to December 22, 2008. The study was approved by the local ethics committees.

Inclusion criteria

Patients were eligible for entry into this study if they: 1) were older than 45 years; 2) had been diagnosed with CAP; 3) had been diagnosed with the syndrome of wind-heat in the lung, the syndrome of exopathic cold and interior heat, the syndrome of accumulation of phlegm-heat in the lung, the syndrome of accumulation of phlegm-dampness in the lung, the syndrome of insufficiency of the lung and the spleen *Qi*, or the syndrome of deficiency of both *Qi* and *Yin*; and 4) had signed an informed consent form.

Exclusion criteria

Patients were excluded if they: 1) had bronchiectasis, lung abscess, postobstructive pneumonia, radiation pneumonia, HIV infection, active tuberculosis or cystic pulmonary fibrosis; 2) were taking immunosuppressive agents after organ or bone marrow transplantation; 3) had received chemotherapy or radiotherapy during the past 90 days; 4) had been hospitalized in the past 30 days; or 5) had been diagnosed with the syndrome of heat attack of the pericardium or the syndrome of exhaustion of vital-*Qi* resulting from invasion of pathogens.

Groups

After patient selection, the eligible participations were divided into two groups based on age: middle-aged (45-59 years) and elderly (≥60 years). The groups underwent the same interventions and outcome assessments, but were analyzed by cohort.

Outcome, predictor variables and quality control

The only outcome was "not cured of CAP" by the 14th day of hospitalization or the time of discharge [25]. Data on 75 predictor variables in seven classes (demographics, original disease and previous conditions, complications, symptoms and signs, auxiliary examination results, severity and other factors) were collected. Among these variables, smoking refers to the total number of cigarettes that the patient had smoked in the past, daily alcohol consumption refers to grams of absolute ethanol consumed per day, hospitalization frequency refers to the number of hospitalizations due to CAP in the past year, and cost of hospitalization refers to, for example, the costs of medicines, laboratory tests, examinations, treatments, bed and nursing. Criteria for clinical stability[1] were: CURB65 (confusion + blood urea nitrogen (BUN) >19 mg/dL + respiratory rate≥30 breaths/min + systolic blood pressure (SBP) <90 mmHg or diastolic blood pressure (DBP) ≤60 mmHg + age≥65 years)[6]; Charlson Comorbidity Index (CCI)[26]; and pneumonia severity index (PSI)[27].

The data were collected on the first day of the study, which was the day when the patients' hospitalization began and was defined as lasting from the moment that the patient arrived at the inpatient department of respiratory medicine until midnight that day. Subsequent days were the subsequent midnight – midnight 24-h periods. When more than one measurement of the same physiological variable was recorded within a

24-hour period, only the first record was included in the analysis.

Strict quality control was performed in every center involved in the data collection procedure. First, education on the background of the study, implementation protocols and standard operating procedures were provided to the clinical investigators. Second, data were collected in each center simultaneously and case report forms (CRFs) were completed within required time periods. The CRFs were reviewed and modified by the co-primary investigators in each center, then submitted to the First Affiliated Hospital of Henan College of Traditional Chinese Medicine for further data analysis.

Diagnostic criteria and treatment

Modern medical diagnostic criteria and treatments were based on the Diagnosis and Treatment Guideline of CAPby the Chinese Society of Respiratory Diseases[28]; those for TCM were based on the Diagnosis and Treatment Guideline of CAP with Traditional Chinese Medicine by the research group for the project A Theoretical Study on Curative Effect Evaluation Methods Based on Traditional Chinese Medical Diagnosis and Treatment for Pneumonia.

Statistical analysis

According to the principle[29] that difference calibration should be conducted for laboratory data obtained from different centers, and because quantitative data needed to be analyzed as qualitative data, two data transformation steps were performed. In step 1, the primary data for each patient, minus the mean or median value of the laboratory findings provided by the patient's center, were divided by the difference between the highest and lowest values of each variable to obtain standardized data for analysis[30]. In step 2, the data were classified into three groups: A, the original data; B, data that had been transformed into dichotomous variables (greater than or less than a cut-off point determined by the maximal Youden's index using the receiver operating characteristic (ROC) curve); and C, data that had been transformed to multivariate variables using a simple qualitative classification – laboratory quantitative findings were divided into three groups, less or equal to -0.5, between -0.5 and 0.5, or more than 0.5, non-laboratory data with a normal range (e.g. temperature, pulse, respiration rate) were divided according to "less than minimal value, normal range or greater than maximal value", and other data, such as age and smoking, were divided by tradition and experience.

Five methods were used for analysis. First, the one-sample Kolmogorov – Smirnov test was performed to test normality. To identify variables correlated with CAP, univariate analysis using the two independent samples *t*-test was performed on data with a normal distribution, the chi-square test with 2×2 contingency tables was used for dichotomous variables, and a two independent samples nonparametric test (Mann – Whitney U) was conducted for data with a non-normal distribution and for multivariate variables. For multivariate analysis, logistic regression analysis was used. Variables with statistically significant results at the $P<0.05$ level were considered to be risk factors. Missing quantitative data were replaced with the mean if the primary data were normally distributed or with the median if the primary data were not normally distributed. Missing qualitative data were replaced with the mode of the non-missing data for that variable.

RESULTS

Subject characteristics

Four hundred and thirteen patients met the inclusion criteria on hospitalization. Of these, seven patients who died were excluded from the analysis because their families refused permission to use their data, two were lost due to lack of contact information and four refused to complete the investigation for unclear reasons. Four hundred patients (age 67.48 ± 11.535 years, 46% female) were therefore enrolled in the outcome analysis. Two hundred and ninety-three (age 73.11 ± 7.482 years, 43% female, 219 (74.7%) not cured) were in the elderly cohort and 107 (age 52.07 ± 4.414 years, 52% female, 79 (73.8%) not cured) were in the middle-aged cohort.

Classification

The cut-off points obtained from the ROC curves were as follows: age, 69.5; smoking, 49,275; daily alcohol consumption, 53.493; body mass index (BMI), 24.384; hospitalization frequency, 0.5; temperature, 36.85; pulse, 82.5; respiration rate, 21.5; SBP, 139; DBP, 77.5; WBC, 0.123; hemoglobin, – 0.23; lymphocyte percentage (Lym%), – 0.304; neutrophil percentage (Neu%), 0.408; serum creatinine (Cr), 0.348; BUN, 0.024; C-reactive protein (CRP), 2.891; albumin, 0.154; blood glucose, 0.011; serum sodium, – 0.246; time to clinical stability, 9; CURB65, 1.5; cost of hospitalization, 11,323.245; and CCI, 3.5.

Quantitative data were divided into dichotomous variables (group B) according to whether they were greater or less than the cut-off point. They were divided into multivariate variables (group C) as follows: age (1= 45-59, 2=60-95); smoking (1=0, 2=1-105, 3=>105); daily alcohol consumption (1=0, 2=1-49, 3=>50); BMI (1=<18.5, 2=18.5-22.9, 3=≥23); hospitalization frequency (1=0 or 1, 2=≥2); temperature (1=≤37.2, 2= 37.3-38, 3=38.1-41); pulse (1£100, 2=>100); respiration rate (1=12 – 20, 2=21-29, 3=≥30); SBP (1=<140, 2=140-159, 3=≥160); DBP (1=<60, 2=60-89, 3=≥90); time to clinical stability (1=0-2, 2=3-7, 3=>7); CURB65 (1=0-1, 2=2, 3=≥3); cost of hospitalization (1=<5000, 2=5000-10,000, 3=>10,000); CCI (1=0-3, 2=4-6, 3=≥7); and laboratory findings (1=<-0.5, 2=-0.5-0.5, 3=>0.5).

Univariate analysis

In the elderly cohort, 27 variables in group A were associated with the not-cured outcome: age, hospitalization frequency, pulse, respiration rate, BUN, CRP, time to clinical stability, CURB65, cost of hospitalization, CCI, use of glucocorticoid, use of anti-infective agents, aspiration, respiratory failure, hypercapnia, hypoxemia, anemia, gasping, loss of appetite, confusion, dull reaction, cyanotic lips, moist rales, time to WBC reduced to normal, time to temperature reduced to normal, severity and PSI. Twenty-eight variables in group B associated with the not-cured outcome comprised the 27 listed above plus SBP. Twenty-one variables in group C comprised all of the variables listed for group A except age, hospitalization frequency, pulse, BUN, CRP and cost of hospitalization.

In the middle-aged cohort, 13 variables in group A were associated with the not-cured outcome: hemoglobin, albumin, blood glucose, time to clinical stability, cost of hospitalization, anemia, loss of appetite, confusion, dry rales, being retired or unemployed, Gram-negative bacterial infection, educational level less than high school and severity. Seventeen variables in group B associated with the not-cured outcome comprised the 13 listed above plus Lym%, Neu%, BUN and serum sodium. Eleven variables in group C comprised all of the variables listed for group A except hemoglobin and albumin.

Multivariate analysis

In the elderly cohort, five independent predictive factors in group A were correlated with the not-cured outcome: respiration rate, anemia, confusion, moist rales and PSI. Six independent predictive factors in group B were: CRP, cost of hospitalization, anemia, confusion, moist rales and PSI. Five independent predictive factors in group C were: anemia, gasping, confusion, moist rales and PSI. Merging the three groups, we found that eight independent predictive factors were correlated with the not-cured outcome in the elderly cohort: respiration rate, CRP, cost of hospitalization, anemia, gasping, confusion, moist rales and PSI (Table 5-1, 5-2, 5-3).

Table 5-1 Prognosis factors of no cure outcome of CAP in elderly cohort with combined treatment of TCM and modern medicine by multivariate analyses

Characters	B	S.E.	Wald	df	*P* values	Exp(B)	95.0% C.I.	
							Lower	Upper
A group								
Respiration rate	0.119	0.060	3.860	1	0.049	1.126	1.000	1.268
Anemia	1.375	0.475	8.372	1	0.004	3.957	1.559	10.046
Confusion	1.074	0.378	8.067	1	0.005	2.928	1.395	6.147
Moist rales	0.931	0.396	5.515	1	0.019	2.537	1.167	5.519
PSI	0.522	0.214	5.929	1	0.015	1.685	1.107	2.564

Table 5-2 Prognosis factors of no cure outcome of CAP in elderly cohort with combined treatment of TCM and modern medicine by multivariate analyses

Characters	B	S.E.	Wald	df	*P* values	Exp(B)	95.0% C.I.	
							Lower	Upper
B group								
CRP	1.167	0.370	9.976	1	0.002	3.213	1.557	6.630
Cost of hospitalization	0.982	0.485	4.096	1	0.043	2.669	1.031	6.905
Anemia	1.181	0.482	6.009	1	0.014	3.256	1.267	8.369
Confusion	1.069	0.383	7.794	1	0.005	2.913	1.375	6.171
Moist rales	1.008	0.393	6.586	1	0.010	2.740	1.269	5.917
PSI	0.552	0.216	6.525	1	0.011	1.738	1.137	2.655

Table 5-3 Prognosis factors of no cure outcome of CAP in elderly cohort with combined treatment of TCM and modern medicine by multivariate analyses

Characters	B	S.E.	Wald	df	*P* values	Exp(B)	95.0% C.I.	
							Lower	Upper
C group								
Anemia	1.395	0.493	8.001	1	0.005	4.036	1.535	10.613
Gasping	0.675	0.319	4.467	1	0.035	1.964	1.050	3.674
Confusion	1.119	0.376	8.853	1	0.003	3.063	1.465	6.402
Moist rales	0.914	0.395	5.339	1	0.021	2.493	1.149	5.413
PSI	0.569	0.212	7.199	1	0.007	1.766	1.166	2.676

Table 6-1 Prognosis factors of no cure outcome of CAP in middle aged cohort with combined treatment of TCM and modern medicine by multivariate analyses

Characters	B	S.E.	Wald	df	P values	Exp(B)	95.0% C.I.	
							Lower	Upper
A group								
Loss of appetite	1.661	0.636	6.815	1	0.009	5.263	1.513	18.311
Retired or unemployed	2.068	0.962	4.620	1	0.032	7.908	1.200	52.116
Gram-negative bacteria infection	-2.249	0.655	11.778	1	0.001	0.106	0.029	0.381
≤high school education	1.502	0.606	6.132	1	0.013	4.490	1.368	14.741

Table 6-2 Prognosis factors of no cure outcome of cap in middle aged cohort with combined treatment of tcm and modern medicine by multivariate analyses.

Characters	B	S.E.	Wald	df	*P* values	Exp(B)	95.0% C.I.	
							Lower	Upper
B group								
Neu%	1.610	0.724	4.945	1	0.026	5.003	1.210	20.680
BUN	2.258	0.755	8.956	1	0.003	9.567	2.180	41.989
Clinical stability time >9 days	-1.975	0.958	4.250	1	0.039	0.139	0.021	0.907
Loss of appetite	1.476	0.671	4.840	1	0.028	4.377	1.175	16.307
Gram-negative bacteria	-1.917	0.691	7.701	1	0.006	0.147	0.038	0.569

Table 6-3 Prognosis factors of no cure outcome of CAP in middle aged cohort with combined treatment of TCM and modern medicine by multivariate analyses

Characters	B	S.E.	Wald	df	*P* values	Exp(B)	95.0% C.I.	
							Lower	Upper
C group								
Anemia	2.493	1.185	4.426	1	0.035	12.100	1.186	123.475
Confusion	2.349	1.178	3.978	1	0.046	10.476	1.041	105.381
Retired or unemployed	2.364	1.003	5.556	1	0.018	10.635	1.489	75.943
Gram-negative bacteria	-2.185	0.681	10.298	1	0.001	0.112	0.030	0.427

In the middle-aged cohort, four independent predictive factors in group A were correlated with the not-cured outcome: loss of appetite, occupation, Gram-negative bacterial infection (positive factor) and educational level less than high school. Five independent predictive factors in group B were: Neu%, BUN, time to clinical stability >9 days (positive factor), loss of appetite and Gram-negative bacterial infection (positive factor). Four independent predictive factors in group C were: anemia, confusion, being retired or unemployed, and Gram-negative bacterial infection (positive factor). Merging these results, we identified nine independent predictive factors that were correlated with the not-cured outcome in the middle-aged cohort: Neu% , BUN, time to clinical stability >9 days (positive factor), loss of appetite, anemia, confusion, being retired or unemployed, Gram-negative bacterial infection (positive factor) and educational level less than high school (Table 6-1, 6-2, 6-3).

DISCUSSION

The principal findings of this study were as follows. 1) Integrated medical intervention resulted in a not-cured outcome in 73.8% and 74.7% of middle-aged and elderly patients, respectively. 2) The risk factors for not cured differed significantly between middle-aged and elderly patients. 3) Independent risk factors correlated with not cured in elderly patients were greater respiration rate, CRP, cost of hospitalization and PSI, plus anemia, gasping, confusion and moist rales. 4) Independent risk factors correlated with not cured in middle-aged patients were increased Neu% and BUN, plus loss of appetite, anemia, confusion, being retired or unemployed, and educational level less than high school; protective factors were Gram-negative bacterial infection and time to clinical stability >9 days. It should be noted that the incidence of not cured in this study was higher than that reported previously[26,31] principally due to our definition of outcome, which encompassed treatment failure, improvement followed by relapse, and abnormal radiological or laboratory findings. This definition is stricter than outcomes that are defined only by symptoms or signs, such as non-responding pneumonia [1], or treatment failure[25] or inefficacy[32].

The predictive variables for the two cohorts differed except for anemia and confusion. This may be because people of different ages differ physiologically and psychologically. Although several factors have been reported in previous studies[4-23,28,33] – including anemia, confusion, respiration rate, BUN, PSI, CRP, cost of hospitalization, education, time to clinical stability and Gram-negative bacterial infection – some of the factors in our study require further discussion.

Although the effect of abnormal respiration rate on CAP has generally been consistent in previous studies, the critical value varies, having been reported to be 30/min[4,19], 25/min[18], 24/min[6], 20/min[5] or unclear[20]. In the present study, an effect of respiration rate on prognosis appeared in the elderly cohort, and was a significant factor in the multivariate analysis, but the collected values were analyzed as consecutive quantitative data. Therefore, we were unable to identify a critical value. There was a similar problem with BUN, the reported critical value of which varies from 7 mmol/L[6], 25 mg/DL[8] and 30 mg/DL (11 mmol/L) [19-28] to 60 mg/DL[7], with no consensus. In the present study, an effect of BUN on prognosis appeared in the middle-aged cohort when the collected values were analyzed as standardized dichotomous data (group B). The original data from each center were 5.81 mmol/L, 4.71 mmol/L, 5.62 mmol/L and 4.97 mmol/L from Changchun, Zhengzhou, Nanjing and Jinan, respectively. At first glance, these are all in the normal range, so we cannot identify a critical value. However, we recommend that BUN should be considered a risk factor for not cured if it is higher than the median value for the patient's center.

Both increased[12-18] and decreased[21] CRP has been related to adverse outcome in CAP. Growing evidence [9-11] indicates that it is not a risk factor, though debate continues[34]. In this study, an effect of CRP on outcome appeared in the elderly cohort in group B. The primary data were 2.235 mg/L, 2.754 mg/L, 40.770 mg/L and 37.560 mg/L for Changchun, Zhengzhou, Nanjing and Jinan, respectively. We recommend that CRP should be considered a risk factor for not cured if its concentration is more than four times that of the median for the patient's center.

Two factors that protected against a not-cured outcome were identified in the middle-aged cohort: time to clinical stability >9 days and Gram-negative bacterial infection. The former was consistent with previous studies[22], but the latter was not[15-16]. It is possible that clinicians now pay greater attention to Gram-negative bacterial infection, intervening when infection is found and administering preventive therapy if necessary.

Some factors identified in this study, such as Neu% , moist rales, loss of appetite, gasping[5-8], educational level[14,23] and being retired or unemployed[23], have been rarely reported in previous studies. High Neu% might indicate that the infection is severe, because the elderly have a lower response to the damage caused. For this reason, we suggest considering Neu% as a risk factor for not cured if it is higher than the median or mean value for the patient's center. Moist rales may be a risk factor because secretions are difficult to discharge due to the pathological changes of pneumonia. Loss of appetite indicates poor function of the digestive or nervous system, and poor nutrition. Gasping always indicates that the patient has a primary disease, and leads to disorders the body's microenvironment due to hyperventilation. Patients with a low educational background have less knowledge of health self-care that

might aid their recovery. Retired and unemployed persons often worry about their health as a reaction to other burdens in their life, and these negative emotions may affect their outcome, though the mechanism remains unclear.

Although age[3,5-6, 9, 14, 16-17, 19, 22] and chest radiographic abnormalities [5-6, 8, 10, 13-17, 19, 22, 35] have been identified as risk factors for CAP in many studies, some researchers believe that there is insufficient evidence to support these two factors being valuable prognostic factors[18,35]. In the present study, age was not found to be a prognostic factor. However, based on our clinical experience, we suggest that age should be considered carefully before it is excluded from the list of risk factors, because the age groups in the study were probably too narrow, with 293 patients in the elderly cohort and 107 in the middle-aged cohort. As for radiographic abnormalities, we did obtain sufficient data to support these being a risk factor.

In this study, no variable related to TCM was identified as a predictive factor, which may be because of a lack of such variables among in the initial observations. However, the predictive factors that were identified reflect the constitution (anemia, PSI), cause of disease (being retired or unemployed, educational level) and disease location (respiratory rate, gasping, moist rales, Gram-negative bacterial infection, loss of appetite, confusion) in TCM theory

The incidence of the outcome "not cured" in middle-aged and elderly CAP patients following combined treatment with TCM and modern medicine was very high. The risk factors for not cured differed with age. Independent predictive risk factors correlated with no cure in the elderly were: increased respiration rate, CRP ≥four times the mean or median of that for the patient's centre, cost of hospitalization >11, 323 RMB and PSI>II, plus anemia, gasping, confusion and moist rales. In middle-aged patients, independent predictive risk factors were Neu% or BUN greater than or equal to the mean or median for the patient's center, plus loss of appetite, anemia, confusion, being retired or unemployed, and educational level less than high school. Positive factors were Gram-negative bacterial infection and time to clinical stability >9 days. To improve adverse outcomes in CAP, we must pay attention to these risk factors.

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