行政院國家科學委員會專題研究計畫 成果報告

血清中鋅濃度與嚴重社區性肺炎預後之關聯
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行政院國家科學委員會補助專題研究計畫 ☑ 成 果 報 告 □期中進度報告

血清中鋅濃度與嚴重社區性肺炎預後之關聯

Association of the Serum Zinc Level and the Outcomes of Severe Community-Acquired Pneumonia

計畫類別：☑ 個別型計畫　　□ 整合型計畫
計畫編號：NSC　95－2314－B－002－091－
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中 文 摘 要

背景：社區性肺炎是一內科常見之感染疾病。大約 10%的社區性肺炎住院病患需要加護病房照護。而這群嚴重社區性肺炎之患者其死亡率可能高達 20%~50%。人體中的微量元素–鋅，在免疫系統方面扮演了重要角色。我們希望研究血清內之鋅濃度與嚴重社區性肺炎之預後關係。

材料與方法：自 2006 年 11 月至 2007 年 7 月，超過 18 歲之成人因嚴重社區性肺炎入住內科加護病房者皆接受評估。病患或其家屬同意臨床試驗者進入此研究。這些病患之臨床表徵，如：年齡、性別、過去病史、臨床症狀、疾病嚴重度、於加護病房接受之處置及併發症等，皆收集其資料以作後續分析。血清中之鋅濃度及其他發炎相關之生物標記於入住加護病房之第一天及第七天抽取。

結果：總共有 19 名病患進入此研究，平均年齡為 76.6 歲。病患入加護病房超過 14 日或於住院期間死亡者定義為預後較差者，其餘則為預後較佳者。全部病患之住院死亡率為 15.8%。預後較佳者有較高之身體質量指數(body mass index)，較少出現敗血性休克。預後較差者其較常出現意識變化且較少有咳嗽或喘鳴現象。預後較佳者有較低之 APACHE II 分數及較高之昏迷指數(Glasgow coma scale)。總共有 18 名病患(94.7%)入住加護病房第一天的血清鋅濃度呈現鋅缺乏情形。預後較佳者有較高之血清白蛋白、鋅濃度及較低之血中尿素氮(blood urea nitrogen)。血清中之鋅濃度與血清白蛋白呈正相關而與 APACHE II 分數成負相關。

結論：於嚴重社區性肺炎病患中，鋅缺乏狀況並不少見。血清中鋅濃度與病患之營養狀況，疾病嚴重度及預後有相關聯。

關鍵字：社區性肺炎、血清鋅、預後

ABSTRACT

Introduction: Community-acquired pneumonia (CAP) is a frequent severe infectious disease. About 10% of all hospitalized patients with CAP required admitted to the intensive care unit (ICU). The mortality of these patients reaches 20-50%. Zinc plays an important role in immune function. We wish to study the association between serum zinc level and severe CAP.

Material and Methods: From Nov. 2006 to Jul. 2007, patients who were over 18 years and admitted to medical intensive care unit due to severe community-acquired pneumonia were evaluated. Patients with permit sheet were enrolled in this study. Clinical characteristics, including age, gender, history of co-existing disease, presenting symptoms, disease severity, ventilator use, complications in ICU and outcomes were recorded. Serum zinc level and other inflammatory biomarker, including C-reactive protein, porcalcitonin were collected on the day 1 and day 7 of ICU admission.

Results: There were 19 patients with severe community-acquired pneumonia enrolled in the study. The mean age was 76.6 years. Patients who need ICU admission over 14 days or with hospital death were defined as poor outcome. There were 5 patients need more than 14 days ICU admission and 3 patients died in hospital. The mortality rate was 15.8%. In the clinical features, patients in the fair outcome group had higher body mass index (BMI) (p=0.02), trend of higher incidence of hypercapnic respiratory failure, and lower incidence of hypoxic respiratory failure and septic shock (p=0.02). Patients with poor outcome were more likely to present with altered mental status, less cough and wheezing (p= 0.006, 0.04, 0.02, respectively). There were also significant differences in acute physiological and chronic health evaluation (APACHE II) score and Glasgow coma scale between the two groups. There were 18 patients (94.7%) had zinc deficiency on the day of ICU admission. Higher serum albumin, zinc and lower blood urea nitrogen (BUN) level were also noted in the patients of fair outcome group. Serum zinc level was correlated with albumin level (r=0.60, p=0.02), and negative correlated with APACHE II score (r=-0.59, p=0.03).

Conclusions: Zinc deficiency is common in severe community-acquired pneumonia. The serum zinc level is related to nutritional status, disease severity and outcome.

Keywords: community-acquired pneumonia, serum zinc, outcome

INTRODUCTION

Severe community-acquired pneumonia (CAP) is now recognized as an entity of its own requiring a specific management approach [1-8]. About 10% of all hospitalized patients with CAP required admitted to the intensive care unit (ICU) [9], and the mortality of these patients reaches 20-50% [1,3-8]. The epidemiology and prognosis of severe CAP have repeatedly been investigated in the last decade [1-11], with the increasing data about the risk factors in the studies worldwide.

Zinc is an essential trace element important for growth, development, and immunity [12]. Zinc deficiency is associated with impaired immune function and an increased risk of infection, particularly diarrhea and pneumonia [13,14]. Zinc supplementation for children in resource-poor countries can reduce the incidence and duration of diarrhea and pneumonia [15,16]. Zinc might act in the acute phase response to infection, helping to boost the body's immune response through a defence cascade, rapid upregulation of immune defence-specific protein synthesis, activation of immune defence activity such as macrophage, lymphocytes, and natural killer cells, and antibody-dependent cytotoxicity [17,18]. Zinc supplementation might provide another function to protect the lung from inflammatory states, whereas zinc deficiency might enhance airway inflammation and cellular damage [19]. However, zinc nutrition status and immunity in elderly persons, another nutritionally vulnerable group of our population, have received relatively limited attention. The prevalence of zinc deficiency in healthy adult in developed country is low (<5%) [20]. However, elderly hospitalized patients had relative high prevalence (28%) of zinc deficiency and they had higher risk of respiratory tract infection and heart failure [21]. About 30% old residents in nursing home had zinc deficiency, and they had higher incidence of pneumonia and antibiotics use [22]. The prevalence of zinc deficiency elevated to 40% in hemodialysis patients [23].

There is still paucity data about the correlation between serum zinc level and severe community-acquired pneumonia. We wish to explore the role of zinc in the patients with severe community-acquired pneumonia.

MATERIAL AND METNODS

From Nov. 2006 to Jul. 2007, patients who were over 18 years and admitted to medical intensive care unit in National Taiwan University Hospital due to severe community-acquired pneumonia were evaluated. Patients with permit sheet were enrolled in this study. The diagnosis of community-acquired pneumonia was established, if chest radiographs presented with new infiltration combined with two of the following criteria: (1) fever with body temperature over 38C, (2) leukocytosis with white blood cell over 11000/mm^3 or neutropenia with neutrophil less than 3500/ mm^3, (3) cough with or without purulent sputum, (4) chest pain, (5) abnormal physical findings of breathing sounds with crackles or rales. Severe community-acquired pneumonia was defined to meet one of major criteria or two of minor criteria as followed [24,25]. Major criteria include need mechanical ventilation, increased infiltration over chest radiographs within 48 hours, septic shock or need vasopressor over 4 hours, and acute renal failure (urine output < 80 ml within 4 hours or serum creatinine > 2 mg/dL without chronic renal insufficiency). Minor criteria include respiratory rate over 30 breaths per minute, ratio of PaO_2 to fraction of inspired oxygen < 250, bilateral infiltration or multiple lobar pneumonia over chest radiographs, systolic blood pressure ≤ 90 mmHg, and diastolic blood pressure ≤ 60 mmHg. Patients would be excluded, if they had following conditions: previous admission within 14 days, ICU admission after arriving hospital over 48 hours, long-term mechanical ventilator dependent, pregnancy, and severe immunosuppression, including human immunodeficiency virus infection, solid organ or bone marrow transplantation with immunosuppressant agents, and active malignancy under chemotherapy.

Clinical characteristics, including age, gender, history of co-existing disease, presenting symptoms, disease severity, ventilator use, complications in ICU and outcomes were recorded. Serum zinc level and other inflammatory biomarker, including C-reactive protein, porcalcitonin were collected on the day 1 and day 7 of ICU admission. The normal value of serum zinc level was between 600~1000 ug/L. Zinc deficiency was defined as serum zinc level lower than 600 ug/L. All continuous data were expressed as mean and standard deviation (SD). Categorical variables were analyzed by means of Fisher exact test. Numerical variables were compared by using independent *t* test. A *p* value <0.05 was considered statistically significant.

RESULTS

From Nov. 2006 to Jul. 2007, 19 patients with severe community-acquired pneumonia were enrolled in the study. Patients who need ICU admission over 14 days or with hospital death were defined as poor outcome. There were 5 patients need more than 14 days ICU admission and 3 patients died in hospital. The mortality rate was 15.8%. The baseline characteristics of the patients were presented as Table 1. There were 68.4% male patients, and the mean age was 76.6 years. The body mass index (BMI) was relative low, especially in the poor outcome group. More hypertensive patients were noted in the fair outcome group, and no significant differences were noted in other co-morbidity.

The clinical presentations on ICU admission were presented as Table 2. Patients in the fair outcome group had trend of higher incidence of hypercapnic respiratory failure, and lower incidence of hypoxic respiratory failure and septic shock (p=0.02). Only 57.9% patients had obvious fever episode. Patients with poor outcome were more likely to present with altered mental status, less cough and wheezing (p= 0.006, 0.04, 0.02, respectively). There were also significant differences in acute physiological and chronic health evaluation (APACHE II) score and Glasgow coma scale between the two groups. Higher serum albumin and lower blood urea nitrogen (BUN) level were also noted in the patients of fair outcome group.

Most biomarkers on ICU admission day 1 and day 7 had no significant difference between the two groups (Table 3). However, serum zinc level on ICU day 1 was significant lower in poor outcome group (386.3 vs. 239.8. ug/L, p=0.03). Zinc deficiency was common in the patients with severe community-acquired pneumonia, over 90% patients presented with zinc deficiency on ICU admission. Serum zinc level was correlated with albumin level (r=0.60, p=0.02), and negative correlated with APACHE II score (r=-0.59, p=0.03). Most patients need mechanical ventilation during ICU admission, and over half patients happened acute renal failure in ICU (Table 4).

DISCUSSIONS

Our study showed that zinc deficiency is common in severe community-acquired pneumonia (CAP) patients, and zinc deficiency might be related to poor outcome in the patients. Poor outcome of severe CAP might also related to lower BMI, Glasgow coma scale, serum albumin level, and higher BUN, APACHE II score. Serum zinc level is correlated with albumin level and negative correlated with APACHE II score.

Severe zinc deficiency can impair immunity and increase susceptibility to infectious diseases, a major cause of mortality in the elderly [26,27]. Low zinc ion bioavailability and impaired cell-mediated immunity are common in ageing and may be restored by physiological supplementation with zinc for 1-2 months, impacting upon morbidity and survival [26]. Previous studies showed that near 30% elderly hospitalized patients or nursing home residents had zinc deficiency [21,22]. Low zinc consumption had been reported in elderly and it might be the cause of high prevalence of zinc deficiency in elderly [28]. Daily zinc intake lower than recommended dietary allowance (RDA) was noted in over 90% elderly [28]. Most patients in our study were elderly with mean age of 76.6 years, and they might high incidence of decreased daily zinc intake. Previous studies also showed that serum or plasma zinc level might be depressed in many infectious diseases [29,30]. Severe community-acquired pneumonia, a serious infectious disease, might contribute to the high incidence of zinc deficiency in out study.

Malnutrition associated with CAP is a very common finding in persons of advanced age [31]. Clinical features of poor nutrition in elderly CAP including lower body weight, total serum protein, albumin, and prealbumin [32]. Malnutrition with low serum zinc level was related with low serum albumin level [33]. Zinc supplementation may play an important role in the prevention and/or modulation of infectious diseases in the elderly [26]. Zinc supplementation had been known to enhance immune status, including an improved cell-mediated immune response, serum thymulin activity, and IL-2 production [34-36]. Although, there is still lack large prospective trial, zinc deficiency and zinc supply had been reported to be related to the incidence of infection in elderly [22,35]. The efficacy of zinc supplementation was demonstrated in several large prospective trials of children[15,16,37], although there were still some controversial results [38]. However, whether the experience in the children could be applied in adult patients is still uncertain.

In conclusion, zinc deficiency is common in severe community-acquired pneumonia. The serum zinc level is related to nutritional status, disease severity and outcome. Further large prospective study is necessary to explore the role of zinc supplementation in severe community-acquired pneumonia.

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Table 1. Baseline characteristics

	Total (n=19)	Fair outcome (n=12)	Poor outcome (n=7)	p value
Gender (Male)	13(68.4%)	7(58.3%)	6(85.7%)	0.33
Age	76.6±9.6	76.2±9.3	77.3±11.0	0.82
BMI	18.7±3.4	20.0±2.8	16.5±3.3	*0.02*
Diabetics mellitus	6(31.6%)	5(41.7%)	1(14.3%)	0.33
Hypertension	10(52.6%)	9(75.0%)	1(14.3%)	*0.02*
CHF	4(21.1%)	4(33.3%)	0(0.0%)	0.25
COPD	9(47.4%)	8(66.7%)	1(14.3%)	0.06
Old CVA	7(36.8%)	4(33.3%)	3(42.9%)	1.00
Liver cirrhosis	0(0.0%)	0(0.0%)	0(0.0%)	
ESRD	0(0.0%)	0(0.0%)	0(0.0%)	

BMI: body mass index, CHF: congestive heart failure,
COPD: chronic obstructive pulmonary disease, CVA: cerebral vascular accident,
ESRD: end-stage renal disease

Table 2. Initial clinical presentation on ICU admission

	Total (n=19)	Fair outcome (n=12)	Poor outcome (n=7)	p value
APACHE II score	24.2±6.9	21.5±5.7	28.7±6.8	*0.02*
Glasgow coma scale	9.4±3.6	10.8±2.9	6.9±3.4	*0.02*
Hypoxic resp. failure	8(42.1%)	3(25.0%)	5(71.4%)	0.07
Hypercapnic resp. failure	9(47.4%)	7(58.3%)	2(28.6%)	0.35
Septic shock	9(47.4%)	3(25.0%)	6(85.7%)	*0.02*
Fever	11(57.9%)	6(50.0%)	5(71.4%)	0.63
Cough	16(84.2%)	12(100.0%)	4(57.1%)	*0.04*
Altered mental status	8(42.1%)	2(16.7%)	6(85.7%)	*0.006*
Wheezing	7(36.9%)	7(58.3%)	0(0.0%)	*0.02*
Crackles	9(47.4%)	4(33.3%)	5(71.4%)	0.17
Bil. Infiltration(CXR)	10(52.6%)	5(41.7%)	5(71.4%)	0.35
MAP (mmHg)	85.3±16.9	85.6±19.9	84.8±11.5	0.92
PaO2/FiO2	212.5±101.3	227.8±105.2	186.2±95.9	0.40
WBC (/uL)	16336±21844	20430±26630	9319±6358	0.30
Hemoglobin (g/dL)	12.1±2.3	12.5±2.3	11.4±2.3	0.33
Platelet (K/uL)	235.5±139.6	237.4±159.0	232.3±109.7	0.94
Albumin (g/dL)	3.2±0.7	3.5±0.5	2.6±0.5	*0.002*
AST (U/L)	64.7±48.2	52.3±39.3	86.0±57.5	0.15

BUN (mg/dL)	32.1±16.2	26.4±14.4	41.9±15.3	*0.04*
Creatinine (mg/dL)	1.4±0.5	1.4±0.6	1.3±0.4	0.74

APACHE: Acute physiological and chronic health evaluation
MAP: mean arterial pressure, WBC: white blood cell,
AST: aspartate aminotransferase, BUN: blood urea nitrogen

Table 3. Biomarker on day1 and day7 of ICU admission

	Total (n=19)	Fair outcome (n=12)	Poor outcome (n=7)	p value
CRP D1 (mg/dL)	18.5±13.1	15.8±12.7	23.1±13.3	0.25
CRP D7 (mg/dL)	5.0±4.1	4.3±3.9	6.2±4.4	0.35
Procalcitonin D1(mg/mL)	14.7±21.2	11.8±17.0	20.1±28.8	0.51
Procalcitonin D7(ng/mL)	0.6±0.6	0.5±0.5	0.8±0.8	0.37
Zinc D1 (ug/L)	323.5±128.1	386.3±129.6	239.8±66.9	*0.03*
Zinc D7 (ug/L)	410.4±139.0	420.5±131.6	396.8±160.0	0.77
Troponin I D1 (ng/mL)	0.60±1.04	0.19±0.16	1.07±1.43	0.13
Troponin I D7 (ng/mL)	0.10±0.00	0.10±0.00	0.10±0.00	0.42

CRP: C-reactive protein

Table 4. ICU managements and complications

	Total (n=19)	Fair outcome (n=12)	Poor outcome (n=7)	p value
Need MV	16(84.2%)	9(75.0%)	7(100.0%)	0.26
Duration of MV (days)	10.8±8.7	6.8±3.5	15.9±11.0	*0.03*
GI bleeding	7(36.8%)	3(25.0%)	4(57.1%)	0.33
Acute renal failure	10(52.6%)	6(50.0%)	4(57.1%)	1.00
Positive blood culture	6(31.6%)	4(33.3%)	2(28.6%)	1.00
ICU days	11.9±6.8	8.3±3.7	18.1±6.5	*0.001*
Hospital days	26.7±17.4	19.5±9.4	39.1±21.4	*0..01*

MV: mechanical ventilation, GI: gastrointestinal, ICU: intensive care unit

計畫成果自評

此研究計畫已初步展現出血清中鋅濃度於嚴重社區性肺炎中所扮演之角色。由此研究結果我們可以了解鋅缺乏於嚴重社區性肺炎是相當常見的，而造成此現象之原因除老年人容易攝取不足外，急性感染造成的鋅濃度下降也可能是原因之一。另外，我們也可瞭解到血清中鋅濃度與病患當時之營養狀態(血清白蛋白濃度)及疾病嚴重度(APACHE II score)是有相關的。而這些病患的營養狀態及相關的鋅濃度降低可能會影響到病患最後的預後。美中不足的是本計劃由於時間及經費的限制，未能收集到較大量之樣本數，此可能會影響到某些變數統計分析之有效性。未來更進一步的大規模研究仍是值得投入的。