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Anemia and Low Albumin Levels Are Associated with Severe Community-Acquired Pneumonia in Pregnancy: A Case-Control Study

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Community-acquired pneumonia (CAP) is the most common form of pneumonia in pregnancy and may lead to severe adverse maternal and fetal outcomes. Severe CAP (SCAP) is defined as the need for invasive mechanical ventilation and with septic shock with the need for vasopressors. This study aimed to analyze the clinical characteristics and factors associated with SCAP in pregnancy. The present study was a case-control study of pregnant women hospitalized between September 2012 and September 2017 at nine tertiary hospitals in China. Among 358,424 pregnant women, we found 35 SCAP cases and 393 common CAP cases. The 35 SCAP cases were matched 1:4 with common CAP cases (n = 140), based on patient age and gestational weeks. Infection indicators, hemoglobin, platelets, coagulation function, liver, and kidney function markers, myocardial enzyme, arterial oxygen pressure/fraction inspired oxygen (PO_2/FiO_2), and partial echocardiographic results were different between the two groups at admission (all $P < 0.05$). The univariable analyses indicated significant differences for hemoglobin, BMI, irregular obstetric examination, albumin, and white blood cells (all $P < 0.05$) between the common CAP and SCAP groups. The multivariable logistic regression analysis showed that hemoglobin (OR = 0.87, 95% CI: 0.77-0.97, P = 0.01), BMI (OR = 0.42, 95% CI: 0.22-0.81, P = 0.01), and serum albumin (OR = 0.37, 95% CI: 0.19-0.69, P = 0.002) were independently associated with SCAP. Anemia and low serum albumin are possibly associated with SCAP in pregnancy. The results indicate that anemia and albumin levels should be examined and properly treated in pregnant women with CAP.

Keywords: anemia; albumin levels; community-acquired pneumonia; pregnancy; severe
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Introduction

Community-acquired pneumonia (CAP) is one of the most common non-obstetric diseases in pregnant women (Kaunitz et al. 1985). Due to anatomical, physiological, and immunological changes, pregnant women are prone to lung infections (Brito and Niederman 2011; Frye et al. 2011). The ability to clear the airway secretions is weakened in pregnant women. These factors predispose pregnant women to complications with respiratory tract infec-

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tions (Brito and Niederman 2011; Frye et al. 2011). In the USA, the incidence of antepartum CAP is around 0.5 to 1.5 per 1,000 pregnancies (Berkowitz and LaSala 1990; Sheffield and Cunningham 2009). A study in East Asia reported an incidence of CAP in pregnancy of 0.7% over a one-year period (Chen et al. 2012). CAP in pregnancy may be associated with complications such as anemia, asthma, drug abuse, and combined immune deficiency diseases (Brito and Niederman 2011). In addition, CAP in pregnancy may lead to severe adverse maternal and fetal outcomes such as placental abruption, eclampsia, premature birth, intrauterine growth restriction, and even maternal death (Frye et al. 2011; Romanyuk et al. 2011). Currently, most studies on severe CAP (SCAP) are case series or studies with small sample size (Li et al. 2010; Liao et al. 2016; Mazlan et al. 2017). In China, there are few clinical reports on CAP in pregnancy so far.

No clinical studies on SCAP in pregnancy are available to date (both domestically and internationally), and the associated factors are still unclear. In their study on severe pneumonia, Sligl and Marrie (2013) found that 10-22% of patients with CAP required admission to the intensive care unit (ICU) and the rates of complications and mortality were significantly increased in SCAP patients.

Therefore, the present descriptive study included patients with CAP in pregnancy from nine tertiary hospitals and conducted a comprehensive assessment of the factors associated with SCAP in pregnancy. This study could identify potential factors associated with poor pregnancy outcomes and help improve the prognosis of those patients.

Materials and Methods

Study design

This was a case-control study of pregnant women hospitalized between September 2012 and September 2017 at nine tertiary hospitals in China (Foshan Women and Children Hospital; Guangdong Provincial Maternity and Child Care Center; Dongguan Women and Children Hospital; Zhuhai People's Hospital; The First People's Hospital of Zhaoqing; Peking University Shenzhen Hospital; Jiangmen Central Hospital; Lanzhou University Second Hospital; Guizhou Provincial Maternity and Child Care Center). The study was approved by the ethic committee of each participating hospital (listed above). The need for individual consent was waived by the committees because of the retrospective nature of the study.

Patients

Through the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), we searched the electronic medical record from the nine hospitals from September 2012 to September 2017. We retrieved the annual amount of deliveries, as well as the number and IDs of the patients with CAP.

The inclusion criteria were: 1) ≥ 18 years of age; 2) definite singleton pregnancy; and 3) complicated with CAP. The exclusion criteria were: 1) pregnancy complicated with pulmonary tuberculosis (diagnosed as per hospital routine examination); 2) acute lung injuries due to major obstetric surgery, massive hemorrhage, blood transfusion, etc.; 3) congenital diseases, tumors, or organ failure; 4) severe immunodeficiency such as HIV infection (diagnosed as per hospital routine examination) or organ transplantation; or 5) incomplete data.

Diagnostic criteria and grouping

For the diagnosis of CAP, we used the 2007 guidelines of the Infectious Diseases Society of America/American Thoracic Society (Mandell et al. 2007). The diagnosis of CAP is based on the presence of select clinical features (e.g., cough, fever, sputum production, and pleuritic chest pain) and is supported by chest radiography of the lung.

For the diagnosis of SCAP, two deputy chief physicians conducted a retrospective analysis of all the CAP cases using the 2007 guidelines of the Infectious Diseases Society of America/American Thoracic Society (Mandell et al. 2007). Patients who matched at least one major criterion or at least three minor criteria were confirmed as SCAP patients. The major criteria were: 1) invasive mechanical ventilation; and 2) septic shock with the need for vasopressors. The minor criteria were: 1) ≥ 30 breath/min; 2) $PaO_2/FiO_2 \leq 250$; 3) multilobar infiltrates; 4) confusion; 5) blood urea nitrogen ≥ 7.14 mmol/L; 6) white blood cell count < 4,000 cells/mm^3; 7) platelet count < 100,000 cells/mm^3; 8) core temperature < 36°C; and 9) hypotension requiring aggressive fluid resuscitation.

All patients with SCAP that could be identified from those hospitals, treated during the study period, and meeting the eligibility criteria, were included. The SCAP cases during the study period were matched 1:4 with common CAP cases based on patient age (± 2 years) and gestational weeks (within 4 weeks).

Data collection and definition

Clinical data (age, gestational week, number of pregnancies, number of deliveries, body mass index (BMI), irregular obstetric examinations (refers to patients who did not follow the recommended plan for obstetric examinations), SOFA score, and complications) were collected. Clinical manifestations included clinical symptoms (fever, cough, cough with purulent phlegm, shortness of breath, wheezing, chest pain, chest tightness, etc.), etiology, source of infection (based on the comprehensive analysis of the patient conditions by the treating physicians), biochemistry and echocardiographic findings, and fetal outcomes (abortion, stillbirth, and preterm delivery). Hemoglobin, albumin, and the other biochemical parameters were from the initial biochemical examination after the patient was hospitalized.

Low serum albumin was defined as albumin ≤ 35 g/L (Gassa et al. 2018). Low hemoglobin was defined as hemoglobin ≤ 110 g/L (World Health Organization 2011).

Statistical analysis

Stata 12.0 (StataCorp, College Station, TX, USA) was used for data analysis. Continuous data were tested using the Kolmogorov-Smirnov test for normal distribution. Continuous data were presented as means ± standard deviation and analyzed using the Student's t test (normally distributed) or presented as median (range) and analyzed using the rank sum test, as appropriate. Categorical data were presented as frequencies and analyzed by the chi-square test. As for the selection of the variables for the multivariable analysis, the principle was based on the correlation and clinical significance of the occurrence of SCAP. Univariable analyses were first performed using those factors, and the factors with P values < 0.05 were then included in the multivariable analysis. Two-sided P values < 0.05 were consid-

ered statistically significant.

Results

Characteristics of the patients

During the study period, 358,424 pregnant women were hospitalized at the nine participating hospitals. Among them, 393 had common CAP, accounting for 0.1% of all hospitalized patients, while 35 had SCAP, accounting for 0.0097% of all hospitalized patients during the study period. The 35 patients with SCAP were matched 1:4 with 140 common CAP cases. Patients' baseline data are shown in Table 1. Significant differences were observed in BMI, educational level, SOFA score, and rate of irregular obstetric examinations (both $P < 0.05$). All patients in the SCAP group (35/35, 100%) had SOFA scores ≥ 2, while only three patients (3/140, 2.1%) in the common CAP group had SOFA scores ≥ 2 ($P < 0.001$).

The rate of abortion/stillbirth was higher in SCAP than in common CAP (42.9% vs. 2.1%, $P < 0.01$), as well as the rate of preterm delivery (31.4% vs. 5.0%, $P < 0.01$) (Table 1).

Clinical symptoms and etiological findings

SCAP patients presented with fever (n = 34), shortness of breath (n = 30), cough (n = 25), cough with phlegm (n = 18), chest pain (n = 15), palpitation (n = 3), and hemoptysis (n = 1). Common CAP patients showed fever (n = 287), shortness of breath (n = 64), cough (n = 251), cough with purulent phlegm (n = 237), and chest pain (n = 55) (Table 2). In the SCAP group, microbiologic results were obtained from the upper respiratory tract infection (n = 18) and blood (n = 6, including three cases of urinary tract infections, two cases of suppurative appendicitis, and one case of gastrointestinal tract perforation).

Table 1. Characteristics of the patients.

Group	Common CAP (n = 140)	SCAP (n = 35)	P
Age (years)	30.6 ± 6.0	30.2 ± 5.5	0.707
BMI* (kg/m^2)	25.5 ± 3.4	21.7 ± 2.2	< 0.001
Gestational week (weeks)	27.8 ± 6.8	27.5 ± 7.1	0.861
Number of pregnancies	1-5	1-4	0.453
Number of deliveries	0-3	0-2	0.117
Educational level (junior high school and below), n (%)	34 (24.3)	16 (45.7)	0.020
Smoking, n (%)			0.713
Never	134 (95.7)	34 (97.1)	
Former	2 (1.4)	0	
Current	1 (0.7)	0	
Unknown	3 (2.1)	1 (2.9)	
Irregular obstetric examination, n (%)	35 (25.0)	19 (54.3)	< 0.001
Complication in pregnancy, n (%)			
Gestational diabetes mellitus	7 (5.0)	3 (8.6)	0.416
Pregnancy-induced hypertension	11 (7.9)	6 (17.1)	0.097
Chronic respiratory tract disease (asthma)	4 (2.9)	2 (5.7)	0.345
SOFA score, n (%)			< 0.001
≥ 2	3 (2.1)	35 (100)	
< 2	137 (97.9)	0	
Time of onset, n (%)			
Spring	47 (33.6)	11 (31.4)	0.810
Summer	26 (18.6)	7 (20.0)	0.847
Autumn	24 (17.1)	7 (20.0)	0.692
Winter	43 (30.7)	10 (28.6)	0.805
Fetal outcomes, n (%)			
Abortion and stillbirth	3 (2.1)	15 (42.9)	< 0.01
Preterm delivery	7 (5.0)	11 (31.4)	< 0.01

*Body mass index during pregnancy.

Table 2. Features of the disease.

Group	Common CAP (n = 140)	SCAP (n = 35)	P
Clinical symptoms, n (%)			
Fever	113 (80.7)	34 (97.1)	0.015
Short of breath	41 (29.3)	30 (85.7)	< 0.001
Cough	92 (65.7)	25 (71.4)	0.521
Cough with purulent phlegm	54 (38.6)	18 (51.4)	0.167
Chest pain	36 (25.7)	15 (42.9)	0.046
Palpitation	17 (12.1)	3 (8.6)	0.553
Hemoptysis	9 (6.4)	1 (2.9)	0.416
Proof by microbiologic results, n (%)			
Upper respiratory tract infection	86 (61.4)	18 (51.4)	0.281
Systemic blood-borne infection	9 (6.4)	6 (17.1)	0.043
Urinary tract infection	2 (1.4)	3 (8.6)	0.264
Suppurative appendicitis	3 (2.1)	2 (5.7)	1.00
Gastrointestinal tract perforation	2 (1.4)	1 (2.9)	0.792
Infections of the other sites	2 (1.4)	0	0.215
Moderate to severe pleural effusions, n (%)	12 (34.3)	7 (5.0)	< 0.001
Septic shock, n (%)	9 (25.7)	7 (5.0)	< 0.001
Bacteria, n (%)	20 (14.3)	9 (25.7)	0.271
Gram- bacillus	8	6	0.026
Escherichia coli	1	3	
Klebsiella pneumoniae	3	2	
Citrobacter freundii	0	1	
Haemophilus influenzae	4	0	
Gram+ cocci	11	3	0.889
Pneumococcus	7	2	
Staphylococcus aureus	4	1	
Virus	5 (3.6)	3 (8.6)	0.205
Influenza A virus	4	3	0.408
Adenovirus	1	0	
Fungus	3 (2.1)	2 (5.7)	0.062
Aspergillus	2	1	
Candida	1	1	
Mycoplasma	9 (6.4)	0	0.124

Etiological findings in the SCAP group were mainly based on the pathogenic culture of alveolar lavage fluid, deep phlegm fluid, pleural fluid, and blood. Five patients underwent fiberoptic bronchoscopy, and at the same time, we made alveolar lavage fluid culture in these five patients. The results of alveolar lavage fluid culture revealed one case of Pneumococcus and one case of Escherichia coli, and the other three cases were negative. Moreover, nine out of 35 patients had positive results for bacteria culture of the deep phlegm fluid, four out of 10 patients had positive results for bacteria culture of the pleural fluid, and four out of 23 patients had positive blood culture results. A total of 14 pathogens were identified in the SCAP group: nine were bacteria, three were viruses, and two were fungi; no myco-

plasma was found. Most of the bacteria were Gram-negative (G–) bacilli, such as *Escherichia coli* (n = 3), *Klebsiella pneumoniae* (n = 2), and *Citrobacter freundii* (n = 1). Three Gram-positive (G+) cocci, including two cases of *pneumococcus* and one case of *Staphylococcus aureus*, were identified. The three cases of viral infections were all from influenza A virus. The fungal infections were caused by *Aspergillus* and *Candida*. Pathogens in the common CAP group were mainly bacteria and mycoplasmas. The most frequently found bacteria were *Streptococcus pneumoniae* (n = 7), *Haemophilus influenzae* (n = 4), *Staphylococcus aureus* (n = 4), *Klebsiella pneumoniae* (n = 2), and *Escherichia coli* (n = 1). Nine patients had a mycoplasma antibody titer > 1:320 (Table 2). In the SCAP group, 12 patients suffered from moderate to severe pleural effusions and 10 of them underwent thoracic punctures, all indicating the presence of exudates. Septic shock occurred in nine patients from the SCAP group.

Biochemical and echocardiographic results

Infection indicators, hemoglobin, platelets, coagulation function, liver and kidney function markers, myocardial enzyme, arterial oxygen pressure/fraction inspired oxygen (PO_2/FiO_2), and partial echocardiographic results of patients from both groups at admission are shown in Table 3. Compared with patients with common CAP, the patients with SCAP had higher white blood cells ($P < 0.001$), higher C-reactive protein ($P < 0.001$), higher procalcitonin ($P < 0.001$), lower hemoglobin ($P < 0.001$), lower platelets ($P < 0.001$), lower PO_2/FiO_2 ($P < 0.001$), lower serum albumin (P

Table 3. Biochemical and echocardiographic results.

Group	Common CAP (n = 140)	SCAP (n = 35)	P
White blood cell (10^9/L)	12.6 ± 4.6	15.0 ± 5.7	< 0.001
C-reactive protein (mg/L)	44.7 ± 27.5	82.5 ± 37.5	< 0.001
Procalcitonin (ng/ml)	0.44 (0.22-1.19)	10.30 (1.48-18.00)	< 0.001
Hemoglobin (g/L)	110.4 ± 14.6	83.6 ± 18.1	< 0.001
Platelet (10^9/L)	242 ± 58	178 ± 55	< 0.001
PO_2/FiO_2	419 ± 36	234 ± 41	< 0.001
Albumin (g/L)	36.85 ± 3.01	27.25 ± 4.31	< 0.001
Partial prothrombin time (s)	35.57 ± 3.97	36.89 ± 6.75	0.731
Thrombin time (s)	13.01 ± 0.85	12.78 ± 1.71	0.274
Fibrinogen (g/L)	4.94 ± 1.00	4.93 ± 0.81	0.944
Urea nitrogen (mmol/L)	3.16 ± 1.11	4.52 ± 2.34	< 0.001
Creatinine (μmol/L)	45.57 ± 10.32	72.03 ± 24.45	< 0.001
Uric acid (μmol/L)	290.35 ± 81.56	336.37 ± 88.51	0.004
Aspartate aminotransferase (IU/L)	16.87 ± 9.72	23.94 ± 9.61	< 0.001
Alanine aminotransferase (IU/L)	20.58 ± 10.46	35.17 ±12.44	< 0.001
Total bilirubin (μmol/L)	10.63 ± 2.77	12.77 ± 4.18	< 0.001
Brain natriuretic peptide (pmol/L)	28.00 (20.20-49.2)	216.00 (28.50-310.00)	< 0.001
Troponin (ng/ml)	0.11 ± 0.05	0.08 ± 0.04	0.108
Creatine kinase isozyme (IU/L)	19.34 ± 4.56	19.85 ± 4.84	0.564
Cardiac output (L/min)	6.10 ± 0.76	6.35 ± 0.64	0.088
Ejection fraction (%)	62.8 ± 2.8	63.2 ± 3.1	0.538

< 0.001), higher BUN (P < 0.001), higher creatinine (P < 0.001), higher uric acid (P = 0.004), higher AST (P < 0.001), and higher ALT (P < 0.001).

No significant differences were found in the systolic or diastolic function between the two groups from the 276 patients who underwent echocardiography. There was no case of heart failure in the SCAP group.

Associated factors for SCAP

Age, irregular obstetric examination, gestational week, BMI, white blood cell, hemoglobin, and albumin were included in the univariable logistic regression analysis. The results indicated significant differences for hemoglobin, BMI, irregular obstetric examination, albumin, and white blood cells (all P < 0.05). The multivariable logistic regression analysis showed that hemoglobin (OR = 0.87, 95% CI: 0.77-0.97, P = 0.01), BMI (OR = 0.42, 95% CI: 0.22-0.81, P = 0.01), and albumin (OR = 0.37, 95% CI: 0.19-0.69, P = 0.002) were independently associated with SCAP (Table 4).

Discussion

CAP in pregnancy is associated with complications (Brito and Niederman 2011; Frye et al. 2011; Romanyuk et al. 2011). There are no reports of the factors associated with poor pregnancy outcomes of common CAP vs. SCAP. Therefore, the aim of this study was to analyze the clinical characteristics and factors associated with SCAP in pregnancy. The results may suggest that anemia and malnutrition are associated with SCAP in pregnancy. Active and effective treatment could possibly improve the prognosis of SCAP in pregnancy, but studies are necessary to verify this hypothesis.

CAP in pregnancy may lead to severe adverse maternal and fetal outcomes (Frye et al. 2011; Romanyuk et al. 2011), but it has also been reported that no significant differences were noted in the disease course or maternal/fetal prognosis in pregnant women with or without pneumonia, indicating that not all pregnant women with pneumonia would experience adverse outcomes (Jin et al. 2003; Brito and Niederman 2011). The possible reasons for these disparities may be from the different severity degrees of CAP, sample sizes of the studies, therapeutic approaches, and study populations. Graves (2010) reported a frequency of 0.078%-0.27% for pneumonia occurring during pregnancy. In our retrospective analysis of 358,424 pregnant women from nine tertiary hospitals, the frequency was 0.1%, with 0.0097% being severe pneumonia, similar to what was previously reported. In the present study, a significant longer hospital stay, a higher pre-term delivery rate, and a lower live birth rate were found in patients with SCAP compared with common CAP (data not shown).

Due to anatomical, physiological, and immunological changes, pregnant women are prone to lung infections, in part because of a weakened ability to clear the airway secretions (Brito and Niederman 2011; Frye et al. 2011). This is due to: 1) increased negative pressure within the abdominal cavity and raised diaphragm as the gestation progresses; 2) reduced functional residual capacity that hampers the respiratory compensation; 3) gradual increase of progesterone levels during pregnancy that results in the congestion and edema of the respiratory mucosa; and 4) reduced immunological functions during late pregnancy, as manifested by reduced numbers of T helping cells and decreased vitality of natural killer (NK) cells. These factors predispose pregnant women to complications from respiratory tract infections (Brito and Niederman 2011; Frye et al. 2011).

In terms of etiology, pathogens for pneumonia in pregnancy include bacteria, viruses, fungi, mycoplasma, and *Pneumocystis carinii*, with bacteria being the most common pathogens (Goodnight and Soper 2005; Brito and Niederman 2011). The commonly found pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *mycoplasma*, and *Staphylococcus aureus*. Sheffield and Cunningham (2009) found that the most common single

Table 4. Multivariable logistic regression analysis of the risk factors for SCAP in pregnancy.

	Univariable			Multivariable		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
Age	0.99	0.93-1.05	0.705			
Gestational week	1.00	0.95-1.06	0.860			
Hemoglobin	0.89	0.87-0.93	< 0.001	0.87	0.77-0.97	0.011
BMI	0.53	0.42-0.68	< 0.001	0.42	0.22-0.81	0.010
Albumin	0.45	0.34-0.60	< 0.001	0.37	0.19-0.69	0.002
Irregular obstetric examination	3.06	1.43-6.56	0.004	3.16	0.22-44.88	0.396
White blood cell	1.09	1.02-1.18	0.012	1.10	0.87-1.39	0.410

OR, odds ratio; CI, confidence interval.

pathogen was *Streptococcus pneumoniae*, which was identified in 15-20% of CAP in pregnancy. In a retrospective analysis of 1,462 patients with pneumonia in pregnancy, Chen et al. (2012) found that 93% of patients suffered from bacterial infections. In the present study, the dominant pathogen in the common CAP group was also *Pneumococcus*. Gram-negative bacteria were more commonly seen in the SCAP group, possibly because the infection sources were more commonly the urogenital system and abdominal cavity (Arancibia et al. 2002; Morgan and Glossop 2016; Inghammar et al. 2018). Previous studies showed that pregnant women represent a high-risk population for viral infections (Siston et al. 2010; Brito and Niederman 2011; Kourtis et al. 2014). Frequently observed viruses are influenza A and B, and varicella zoster virus, and the uncommon ones are adenovirus, enterovirus, and coronavirus. For viral infections, there will typically be some short-term outbreaks, such as flu or severe acute respiratory syndrome (SARS). In itself, pregnancy has been shown to be a risk factor for poor outcomes from influenza infection (Mertz et al. 2017). During the viral outbreaks, pregnant women are prone to complications with chickenpox and influenza virus infections, and their conditions can usually be critical following pulmonary infections. In the present study, two patients with SCAP had influenza A virus infection complicated with acute respiratory distress syndrome and suffered from multiple organ dysfunction syndrome. They had to receive prolonged therapy and incurred high medical expenses. In this study, the rate of pathogenic detection was 42.9% in the SCAP group, while that in the common CAP group was significantly lower, only 25%. This difference might be due to the higher disease severity, more versatile pathogens, and more specimen types in the SCAP group. We found that although SCAP patients had more severe symptoms and higher ratio of etiological examinations, their ratio of complications with resistant bacteria was low (1/14).

In the SCAP group, 12 patients suffered from moderate to severe pleural effusions and 10 of them underwent thoracic punctures, all indicating the presence of exudates. This phenomenon was possibly associated with the increased pleural effusion during pregnancy and severity of pneumonia, which induced serious inflammation leading to significantly increased pulmonary capillary leakage and eventually increased pleural effusion. In addition, no significant differences were found in the systolic or diastolic function between the two groups from the 276 patients who underwent echocardiography. Nevertheless, the cardiac output was higher in the patients from the SCAP group than those from the common CAP groups. Septic shock occurred in nine patients from the SCAP group, which may possibly result from the greater severity of infection, faster heart rate, and hemodynamic presentations of high cardiac output with low vascular resistance. In the present study, we did not observe any case of pneumonia complicated with heart failure in the SCAP group, which was due to the fact that all patients were free from congenital cardiac diseases and had good cardiac reserve during pregnancy.

At present, the commonly used criteria for the diagnosis of severe pneumonia are the 2007 guidelines of the Infectious Diseases Society of America/American Thoracic Society (Mandell et al. 2007), which include two major and nine minor criteria. In this study, 19 patients matched at least one major criterion and 16 patients matched at least three minor criteria. The two major criteria involve the therapeutic aspect for CAP patients, while the nine minor criteria address the clinical manifestations and auxiliary examinations. Previous studies showed that the major and minor criteria demonstrated excellent predictive value for determining disease severity and prognosis in CAP patients (Phua et al. 2009; Guo et al. 2011). On the other hand, the minor criteria, especially confusion, arterial oxygen pressure/fraction inspired oxygen (PO_2/FiO_2), and respiratory rate, had greater value in determining the clinical prognosis (Phua et al. 2009; Guo et al. 2011).

In the present study, the multivariable analysis suggested showed that hemoglobin, BMI, and albumin were independently associated with SCAP. This analysis has to be taken with caution because of the large number of included variables and the small number of patients with SCAP. Laibl and Sheffield (2006) found that physical weakness, malnutrition, fatigue, and combined upper respiratory tract infection were risk factors of pneumonia in pregnancy. Brito and Niederman (2011) found that smoking, anemia, asthma, drug abuse, and combined immunodeficiency diseases were risk factors for pneumonia in pregnancy. In the present study, the multivariable logistic regression analysis showed that anemia, low BMI, and hypoproteinemia were risk factors for SCAP in pregnancy, while combined upper respiratory tract infection or asthma were not. Brito and Niederman (2011) found a significantly higher chance of pneumonia in patients with anemia, supporting the present study. Anemia disturbs the immune functions of pregnant women and results in insufficient cellular immunity and insufficient tissue perfusion or hypoxia, which reduces the ability to fight pathogens. This suggests that preventing and treating anemia during pregnancy may be one of the strategies for the prevention of SCAP in pregnancy. Nutrition significantly affects the prognosis of patients with infections, and BMI is an important index for nutritional status assessment. In a prospective observational study of 1,406 CAP patients, Lee et al. (2015) observed a significant higher mortality rate in pneumonia patients with low BMI. Accordingly, in our multivariable analysis, we found that low hemoglobin, low albumin, and low BMI were independently associated with SCAP. Low hemoglobin levels are associated with weakened immunity and may aggravate an infection (Bishlawy 1999; Hassan et al. 2016). Albumin is an acute phase reactant that can be decreased in infections (Wierdak et al. 2018). The association of albumin with the nutritional status is controversial and apparently varies among patient populations (Fuhrman

et al. 2004; Kuzuya et al. 2007; Baron et al. 2010; Gama-Axelsson et al. 2012; Fruchtenicht et al. 2015; Academy of Nutrition and Dietetics 2016; Bharadwaj et al. 2016; Marcason 2017). Other laboratory parameters were also disturbed in SCAP patients (such as platelets, liver function, and natriuretic peptide), but whether they are causes or consequences of SCAP is unknown. Additional studies are necessary to examine this.

Of course, the present study has limitations. It was a retrospective study that was limited to the data recorded in the medical charts. In addition, despite the screening of all pregnant patients from nine tertiary hospitals, only 35 patients with SCAP could be identified. The regional differences could not be examined in the present study because of the small sample size. In addition, the rate of pathogenic culture was low, which could be related to the culture method. Finally, the number of variables included in the multivariable analysis was large when considering the number of patients with SCAP; therefore, this analysis should be considered exploratory at best. Additional studies are necessary to validate the associations observed here.

In conclusion, the results indicate that anemia and albumin levels should be examined and treated if needed in pregnant women with CAP, but prospective studies will be necessary since anemia and low serum albumin are possibly associated with SCAP in pregnancy. Active and effective treatment could possibly improve the prognosis of SCAP in pregnancy, but studies will have to be performed to confirm this hypothesis.

Conflict of Interest

The authors declare no conflict of interest.

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