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Analysis of risk factors, pathogenic bacteria of maternal sepsis in term pregnant women with positive blood culture during hospitalization

Yanqing Wen, MD, Hong Chen, MD, Xin Ming, MD, Xiaoyan Chen, MD, Wei Zhou, PhD*

Abstract

The objective of this study was to evaluate the risk factors, pathogenic bacteria and drug sensitivity of maternal sepsis, and provide evidence for clinical prevention and treatment.

A retrospective investigation of pregnant women with full-term maternal sepsis was performed to analyze the risk factors, pathogenic bacteria, and drug sensitivity of maternal sepsis.

Univariate analysis showed that temperature, serum procalcitonin (PCT) and C-reactive protein (CRP) at admission, white blood cell count (WBC), PCT, CRP and neutrophilic granulocyte percentage (N%) during fever, premature rupture of membranes (PROM), antibiotic use within 1 week, mode of production, onset and duration of fever, between groups were statistically significant ($P < .05$). Logistic regression analysis showed that cesarean section was an independent risk factor for sepsis (OR=11.839, 95%CI: 3.121–44.906). Apparent increase was found in body temperature (OR=3.664, 95%CI: 1.722–7.795), duration of fever (OR=1.953, 95%CI: 1.242–3.071), and PCT (OR=1.080, 95%CI: 1.002–1.163). Also, increasing neutrophil ratio (OR=1.180, 95%CI: 1.073–1.297) indicated a high possibility of maternal sepsis. The organism *Escherichia coli* (*E. coli*) was the most common pathogenic bacteria in the positive blood culture group (90%), and the sensitivity to carbapenems (meropenem and imipenem/cilastatin) was 100%, that to piperacillin-tazobactam and amoxicillin sulbactam was over 90%, and that to ceftazidime was 95%.

Cesarean section was an independent risk factor for maternal sepsis in term pregnant women with positive blood culture. Besides, the *E. coli* was the most common pathogenic bacteria in the positive blood culture group. Antibiotics should be used in time and reasonably when the temperature was significantly increased with elevated PCT and N% after a cesarean section.

Abbreviations: CRP= C-reactive protein, N% = neutrophilic granulocyte percentage, OR = odds ratio, PCT = procalcitonin, PROM = premature rupture of membranes, WBC = white blood cell count.

Keywords: drug sensitivity, maternal sepsis, pathogenic bacteria, risk factors

Department of Obstetrics, Chongqing Health Center for Women and Children, No. 120 Longshan Road, Yubei District, Chongqing, People's Republic of China.

* Correspondence: Wei Zhou, Department of Obstetrics, Chongqing Health Center for Women and Children, No. 120 Longshan Road, Yubei District, Chongqing 401147, People's Republic of China (e-mail: dr.zhouwei@163.com).

1. Introduction

Sepsis is an increasingly important cause of maternal morbidity in developed nations.[1] Maternal sepsis ranks the third most common direct cause of maternal mortality following maternal hemorrhage and maternal hypertension in Asia.[2,3] Death incidence rates of maternal sepsis in a country varies by development stages. Compared with developed countries, sepsis was significantly more frequent in Africa, Asia, Latin America, and Caribbean.[4] Even in developed countries, the risk of maternal death due to maternal sepsis was unacceptably high. The Confidential Inquires into Maternal Deaths of the UK, a longest-running continuous audit on maternal mortality in the world, reports the total maternal mortality of 10 per 100,000 pregnancy, and in spite of a significant fall over the past 90 years, puerperal sepsis still accounts for 15% of all maternal deaths.[5] According to the Centre for Maternal and Child Enquire, the longest running continuous series of clinical audits worldwide, deaths due to sepsis have nearly doubled over the past decade, rising from 0.65 to 1.13 per 100,000 maternities when comparing the period of 2000 through 2002 and 2006 through 2008.[6] In the United States, sepsis complicated 1/3333 deliveries, and sepsis-related deaths occurred 1/105,384 deliveries. While the overall frequency of sepsis was stable, the odds of acquiring severe sepsis increased 10% per year in the United States from 1/15,385 to 1/7246, sepsis-related death also increased 10% per year.[1]

While maternal sepsis has drawn public alertness in the UK and the United States, data is limited in China. The estimated incidence of maternal sepsis is around 6% in the Chinese population.[4] In recent years, with the implementation of the 2-child policy, the annual number of deliveries in China has reached more than 17 million. However, statistics of maternal sepsis are incomplete, inconclusive, and not well-characterized, resulting in a lack of clinical guidelines about maternal sepsis. The spectrum of pathogenic bacteria involved in maternal sepsis and their sensitivity and resistance to antimicrobial agents remains largely unknown, which makes selection of proper antimicrobial agents difficult in clinical practice. Undetected and poorly managed maternal infections lead to sepsis, death, or disability for the mother as well as an increased risk of early infection and other adverse outcomes for the neonates.

The study was to investigate the clinical records of maternal sepsis in term pregnant women occurred in hospital in the Chongqing Maternal and Child Health Care Hospital in recent 2 years, covering 25,666 births and 241 cases of maternal sepsis. The aim of this retrospective study was to explore the risk factors, route of maternal infection, pathogenic microorganism, and sensitive antibiotics. This information was necessary for improvement of clinical management of maternal sepsis, for rational use of antibiotics, and for development of new infection control strategy.

2. Material and methods

2.1. Study subject

This retrospective study covered lying-in women with fever who were admitted between January 2019 and September 2020 at the Obstetrics Department, Chongqing Health Center for Women and Children. In clinical work, Inclusion criteria were as follows:

1. Fever during hospitalization (body temperature ≥38°C for 2 times, 4 hours apart);
2. In case of cesarean section, transversal incision of the lower uterine segment and the use of combined lumbar and epidural anesthesia were performed;
3. Perioperative prophylactic use of antimicrobial agents like penicillin or cephalosporins.

   Exclusion criteria were as follows:

1. Postpartum fever (>38°C) after hospital discharge;
2. Pregnant women (gestational weeks <37 weeks) with fever before term or with fever occurred at odinopoeia;
3. Admission for diagnosis of infectious diseases of other systems;
4. Fever has existed when admitted to hospital. The current study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the Chongqing Health Center for Women and Children, Chongqing, China. Written informed consent was obtained from patient donor.

2.2. Methods

As we found that the clinical symptoms of maternal sepsis with positive blood culture were more severe than those with negative blood culture, such as higher body temperature, longer duration of fever and antibiotic application, and so on, the patients were divided into positive blood culture group and negative blood

culture group. The following data were collected retrospectively and compared between 2 groups:

(1) Demographic data: age, Body Mass Index (BMI), gestation age, gravidity, and parity;
(2) Clinical data: complications of pregnancy, premature rupture of membranes, vaginal delivery or cesarean; and frequency of vaginal examinations;
(3) Perioperative data: days in hospital before surgery, history of use of antibiotics within 1 week, amount of postpartum hemorrhage, lasting time of operation, onset, and duration of fever;
(4) Laboratory examination data: laboratory examination at admission and the beginning of fever, including white blood cell count (WBC), neutrophilic granulocyte percentage (N%), hemoglobin (HGB), albumin, serum procalcitonin (PCT), c-reactive protein (CRP), blood culture and drug sensitive test.

2.3. Statistical analysis

The patients were divided into the positive group and the negative group according to the results of blood culture. According to the results of positive blood culture, the statistical analysis of pathogenic bacterium and sensitive drugs were performed. Qualitative data were treated with the Chi-Squared test. Quantitative data was expressed as mean ± standard deviation. After distribution normality was confirmed, and a 2-group t test was used for comparison. Quantitative data with non-normal distribution were expressed as median and rank sum test was used for inter-group comparison. Logistic regression analysis was employed to analyze the correlation between each factor and positive result of blood culture. All the statistical analyses mentioned above were performed with the software SPSS 21.0. Besides, a probability value of <.05 was considered as statistical significance.

3. Results

Among 25,666 deliveries in the Obstetrics Department between January 2019 and September 2020 at Chongqing Health Center for Women and Children, patients (gestational age ≥37 weeks) with fever were studied (among which 89 cases had positive blood culture, 152 cases had negative blood culture). In these 241 cases, the mean age was 29.25 years (range 20–41), mean gravidity was 1.94 (range 1–8) and mean parity was 1.03 (range 1–3), 88% were primiparous. The results of the blood culture showed 80 cases with *E. coli*, 3 cases with *Klebsiella pneumoniae*, and 1 case for each of *Burkholderia onioniae, Staphylococcus cephalococcus, Staphylococcus cephalococcus urealytic subspecies, Staphylococcus epidermidis, Cozier's bacillus citrate,* and *Streptococcus alactiae* was detected.

There was no statistically significant difference in age, gestational age, gravidity and parity history, and Body Mass Index ($P > .05$, Table 1). The incidence of premature rupture of membranes in the blood culture positive group was evidently higher than that in the negative group, which was statistically significant ($P < .05$). Gestational diabetes, *Streptococcus* carriers, placenta previa, the number of vaginal examinations, and cervical ligation were the risk factors for infection, but there was no statistical significance between 2 groups (Table 2). Simultaneously, there were no statistically differences between the 2 groups in delayed pregnancy, amniotic hydramnios, and

Table 1

Analysis of demographic characteristics.

Characteristic	Mean (Range)	Negative blood culture Median (IQR)	Positive blood culture Median (IQR)	*P* value
Age (years)	29.25 (20–41)	29 (27,32)	28 (27,30)	.513
BMI (Kg/m^2)	27.49 (20.03–38.86)	27 (25,3)	28 (25,3)	.365
Gestation age (weeks)	39.57 (37.00–41.14)	39.71 (38.86,40.29)	39.86 (39.00,40.43)	.540
Gravidity	1.94 (1–8)	1 (1,2)	2 (1,2.25)	.546
Parity	1.03 (1–3)	1.21 (1,2)	1.52 (1,3)	.435

BMI = Body Mass Index, IQR = inter-quartile range.

Table 2

Single factor analysis of blood culture.

Characteristic	Mean (Range)/N (%)	Negative blood culture Median (IQR)/N (%)	Positive blood culture Median (IQR)/N (%)	*P* value
Times of vaginal examinations	5.7 (0–20)	6 (3,8)	6 (3,8)	.690
Days in hoslital before surgery (days)	1.8 (0–7)	1.8 (1,2)	2 (1,3)	.004
Amount of bleeding (ml)	512.26 (295–1496)	445 (400,560)	445 (405,510)	.780
Time of operation (minutes)	46.48 (21–135)	45 (38,55)	40 (35,55)	.211
Temperaure (°C)	38.97 (35–40.7)	38.7 (38.3,39)	39.3 (38.9,39.6)	.000
WBC at admission (10^{*9}/L)	9.19 (3.9–17.8)	8.5 (7,11.1)	9.3 (8,10.2)	.203
N% at admission	77.46 (52.8–144)	77.4 (71.5,81.8)	77.05 (71.6,79.7)	.401
HGB at admission (g/l)	120.33 (62~161)	122 (112,128)	121 (114,130)	.648
Albumins at admission	35.79 (26–44)	35 (34,37)	36 (33,38)	.101
PCT at admission (10^{*9}/L)	0.9 (0.05–0.30)	0.11 (0.06,0.11)	0.105 (0.05,0.11)	.001
CPR at admission (mg/L)	6.49 (1.06–113.20)	6.42 (6.42,6.42)	6.42 (1.86,6.42)	.006
WBC when fever (10^{*9}/L)	13.28 (2.9–26.2)	13.66±4.73	12.84±4.07	.046
N% when fever	87.19 (11.5–97.7)	87.9 (83.9,90.2)	89.05 (86.8,91.8)	.001
PCT when fever (10^{*9}/L)	1.61 (0.05–105.66)	0.13 (0.07,0.26)	0.44 (0.2,1.03)	.000
CRP when fever (mg/L)	75.88 (26–150)	66.47±46.18	86.92±41.20	.000
Post-term pregnancy				
No	213 (88.4%)	135 (89.4%)	78 (86.7%)	.521
Yes	28 (11.6%)	16 (10.6%)	12 (13.3%)	
PROM				
No	139 (57.7%)	98 (64.9%)	41 (45.6%)	.003
Yes	102 (42.3%)	53 (35.1%)	49 (54.4%)	
GDM				
No	201 (83.4%)	126 (83.4%)	75 (83.3%)	.982
Yes	40 (16.6%)	25 (16.6%)	15 (16.7%)	
GBS				
No	232 (96.3%)	146 (96.7%)	86 (95.6%)	.450
Yes	9 (3.7%)	5 (3.3%)	4 (4.4%)	
Oligohydramnion				
No	224 (92.9%)	139 (92.1%)	85 (94.4%)	.483
Yes	17 (7.1%)	12 (7.9%)	5 (5.6%)	
Cervical ligation				
No	240 (99.6%)	150 (99.3%)	90 (100%)	.627
Yes	1 (0.4%)	1 (0.7%)	0 (0%)	
Placenta previa				
No	237 (98.3%)	148 (98%)	89 (98.9%)	.521
Yes	4 (1.7%)	3 (2%)	1 (1.1)	
Use of antibiotics 1 week				
Yes	67 (28%)	30 (19.9%)	37 (42%)	.000
No	172 (72%)	121 (80.1%)	51 (58%)	
Delivery way				
vaginal	51 (21.3%)	47 (31.5%)	4 (4.4%)	.000
caesarean	188 (78.7%)	102 (68.5%)	86 (95.6%)	
Fever time after delivery				
0 day	31 (13.0%)	27 (18.1%)	4 (4.4%)	.000
1 day	68 (28.5%)	28 (18.8%)	40 (44.4%)	
2 days	58 (24.3%)	32 (21.5%)	26 (28.9%)	
3 days	30 (12.6%)	20 (13.4%)	10 (11.1%)	
4 days	1 (0.4%)	1 (0.7%)	0 (0%)	
predelivery	51 (21.3%)	41 (27.5%)	10 (11.1%)	
Duration of fever (days)	1.705 (0~4)	1 (4)	2 (3)	.000

WBC = white blood cell, N% = neutrophilic granulocyte percentage, HGB = hemoglobin, PCT = Procalcitonin, CPR = C-reactive protein, PROM = Premature rupture of membranes, GDM = Gestational diabetes mellitus, GBS = Group B streptococci, ICP = Intrahepatic cholestasis of pregnancy, HDP = Hypertensive disorder of pregnancy.

Multivariate logistic regression analysis of prediction of positive blood culture.

Characteristics	OR	95%CI		P value
		Lower limit	Upper limit	
Delivery way	11.839	3.121	44.906	.000
Temperature	3.664	1.722	7.795	.001
Duration of fever	1.953	1.242	3.071	.004
N% when fever	1.180	1.073	1.297	.001
PCT when fever	1.080	1.002	1.163	.043

Table 3 was only shown the indicators that enter the regression equation. Variables that did not enter the regression equation were as follows: times of vaginal examinations, amount of bleeding, time of operation, WBC at admission, N% at admission, HGB at admission, albumins at admission, post-term pregnancy, GDM, GBS, oligohydramnion, cervical ligation, and placenta previa.
OR = odds ratio, CI = confidence interval.

hypertensive disorders complicating pregnancy, pregnancy with hypothyroidism, twin pregnancy and intrahepatic cholestasis of pregnancy (ICP).

In the positive blood culture group, the average hospitalization before surgery was significantly longer, the body temperature was significantly higher than in the negative blood culture group. There was no significant difference between the 2 groups in the lasting time of operation and the amount of bleeding in 24 hours ($P > .05$, Table 2).

There was no significant difference in the results of laboratory examination (WBC, N%, PCT) between the 2 groups at admission. Although the difference in PCT and CRP at admission was statistically significant ($P < .05$), but the outcomes might have not definite clinical significance, because not all the cases were covered with PCT and CRP at admission. The N%, PCT and CRP in the positive blood culture group were significantly higher than those in the negative group during fever ($P < .05$, Table 2).

Variables with statistical significance in single univariate analysis were defined as independent variables, and the positive blood culture was defined as the dependent variable for logistic regression analysis. In the Wald test of regression coefficient and regression coefficient of independent variables, cesarean section, body temperature increased significantly and long duration of fever, neutrophils ratio and PCT were found to be significantly related to increased positive rate of blood culture during fever (Table 3).

Drug resistance analysis showed that 89 cases had positive blood culture, among which the pathogenic bacteria of 80 cases were E. coli, accounting for about 90.0% of total positive culture. The sensitivity to Meropenem and imipenem/cilastatin was 100.0%, to piperacillin tazobactam was 97.5%, to ceftazidime was 95%, and to amoxicillin clavulanic acid was 93.8%. The sensitivity to ampicillin sulbactam was only 50.0% and
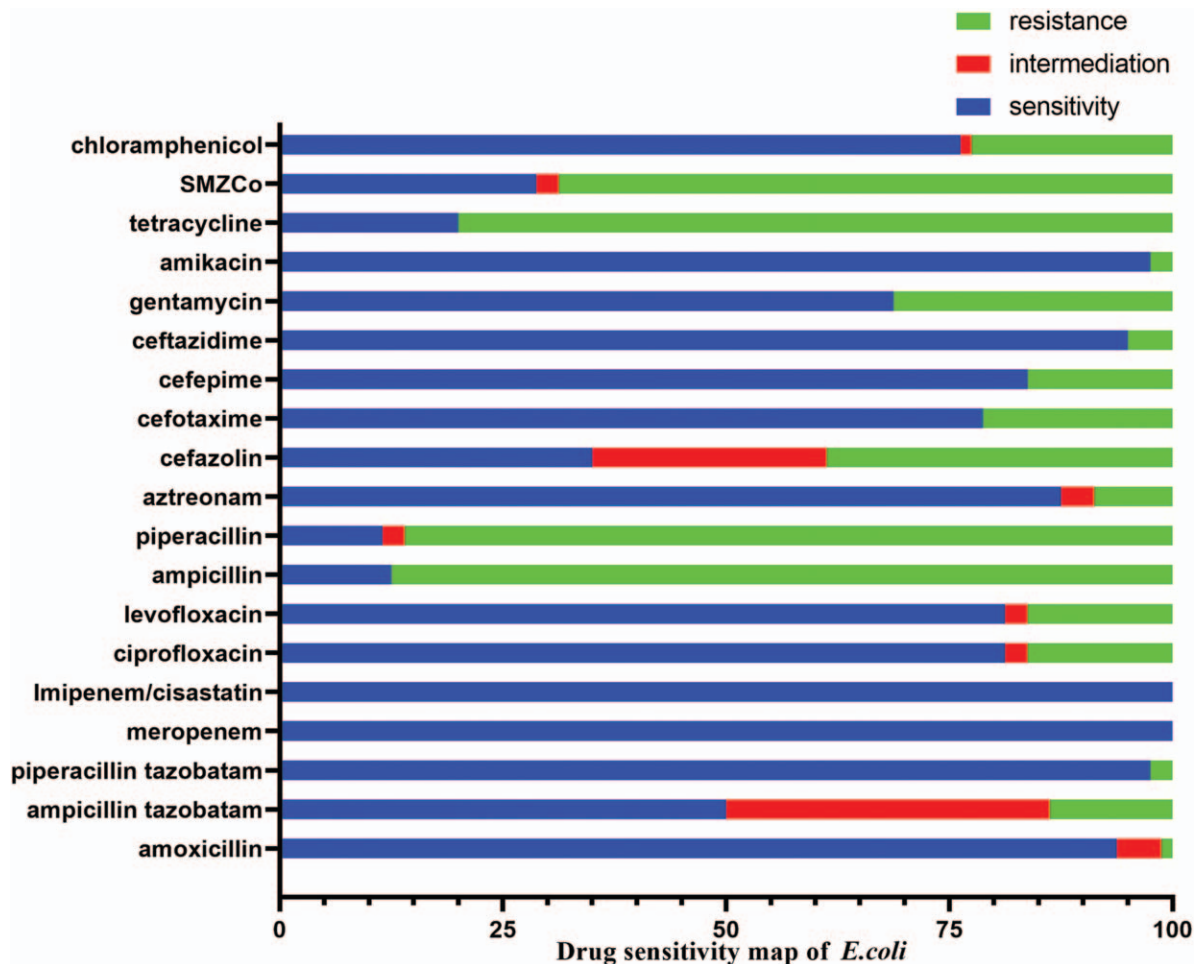
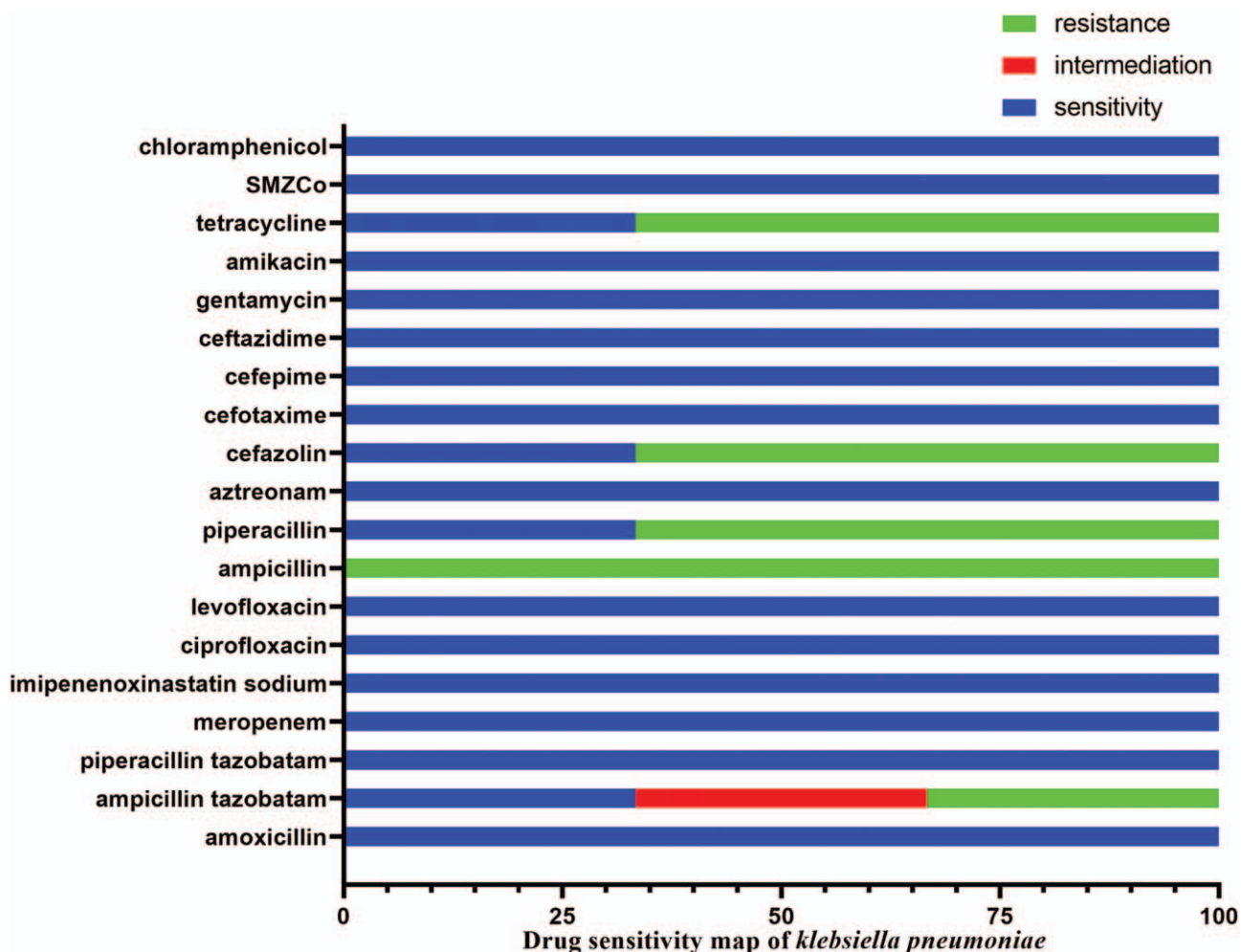

Figure 1. Drug sensitivity map of E. coli.

Figure 2. Drug sensitivity map of *Klebsiella pneumoniae*.

piperacillin was only 11.0% (shown in Fig. 1). Three cases were *Klebsiella pneumoniae*, and the sensitivity to amoxicillin, piperacillin tazobactam, tienam, and cefatadine was 100.0% (shown in Fig. 2). In addition, among the positive blood culture strains, there was 1 case of *Burkholderia onioniae,* 1 case of *Staphylococcus cephaloides*, 1 case of *Staphylococcus cephalococcus ureahydrates*, 1 case of *Staphylococcus epidermidis*, and 1 case of *Streptococcus alactiae.*

4. Discussion

Our analyses revealed that the average number of vaginal examinations in patients with fever was 6, there were 102 cases with PROM, 116 cases with induced labor history, 188 cases gave birth by cesarean. All of the above mentioned risk factors of maternal sepsis have been observed in previous studies.[1,7–9] In single factor analysis, we found that the incidence of PROM was significant higher in the positive blood group. After the PROM, induced labor was needed, which could lead to an increase in the number of vaginal examinations, which could break the balance of vaginal flora in women, leading to weakened defense and higher chance of pathogenic bacteria entering the blood, uterine cavity, and abdominal cavity through the wound of the reproductive tract, then maternal sepsis occurred.

In the multivariate logistic regression analysis, we found that the rate of cesarean was significantly higher in the positive blood culture group. Mother who gave birth by cesarean delivery had a greater incidence of maternal sepsis than mother who gave birth vaginally, especially after induced labor. Induced labor is most often associated with the prolonged labor, increased number of vaginal examinations, and the higher cesarean section rate. Prolonged labor followed by a cesarean delivery increased the incidence of postpartum sepsis to as high as 30% to 35%.[10] A study from Denmark found a 5-fold increase in risk for infection after a caesarean section compared with a vaginal birth.[11] Chaim et al observed that the rising cesarean section rate may thus contribute to maternal sepsis.[12] This is most likely due to effusion after tissue necrosis and the presence of bacteria in the surgical site and the abdominal cavity.[13–15] Also, the infection after cesarean was positively correlated with the frequency of vaginal examinations.[16] Although there was no significant difference in the number of vaginal examinations between the blood culture negative group and the blood culture positive group in our study, the average number of vaginal examinations was more than 5 times. Previous studies showed that more than 5 vaginal tests increased the risk of maternal sepsis. In the future study we need to learn more about the times of vaginal examinations in non-infected women during delivery. In clinical

work, obstetrician should improve their clinical ability to evaluate the labor process, minimize the frequency of vaginal examinations, especially for the patients with PROM. Meanwhile, obstetrician was required to correctly access whether artificial rupture of the membrane was necessary, and whether cesarean was necessary during labor.

Our study found that the average days of blood culture were 2.7 days, but the guidelines of the Surviving Sepsis Campaign[17,18] requires high-dose intravenous antimicrobial agents to be administered to any cases suspected sepsis within 1 hour. Therefore, even before the result of blood culture, timely administration of antibiotics, sepsis care bundles, multidisciplinary discussion and early involvement of senior staff members are important to improve the outcome. In the multivariate logistic regression analysis, we found that the body temperature of pregnant women after cesarean section was significantly increased, and the N% and the PCT were significantly increased in the blood culture positive group, which was helpful for clinical doctors to select the right antibiotics. The use of these indicators for infection could difficult, as the WBC might be elevated during pregnancy, and especially at birth and an increase in body temperature is commonly seen during labor. PCT is a non-hormone active precalcitonin peptide substance. Its level in plasma in healthy people is extremely low. During severe inflammation, PCT derives from almost all cell types, including monocytes and parenchymal tissues, making it a good predictive and diagnostic marker of an inflammatory state with rapidly increased serum levels in inflammation or sepsis.[19,20] It is specifically elevated in plasma during bacterial infection, sepsis, and multi-organ failure. The elevated of PCT is closely related to bacterial infection. It can rise at early stage of infection. PCT would be reduced after infection was controlled with antibiotics. Neutrophile granulocyte played an important role in the nonspecific cellular immune system of the blood, especially for infected by purulent bacterium. Elevated PCT and N%, especially PCT, may be important in predicting maternal sepsis. In our study, the PCT in the blood culture positive group was as high as 0.44 ng/L, while the PCT in the blood culture negative group was only 0.14 ng/L. Besides, the sample size of our study is relatively small, and the specific values of N% and PCT cannot be obtained. Further studies on the value of available indicators and identification of novel prognostic markers are required for more timely and efficient application of antibiotics to pregnant women with high risk of sepsis.

To investigate the susceptibility of pathogen which involved in maternal sepsis, we conducted statistics on pathogenic bacteria in the positive blood culture group and found that 80 cases of blood culture were *E. coli*, accounting for about 90.0% (80/89) of the total positive cultures. This result is consistent with the study by Colleen d. Acosta et al in the UK.[21,22] With the widespread use of antimicrobial agents, the drug resistance rate of bacteria increases year by year. We examined the drug sensitivity to *E. coli* and Klebsiella pneumoniae, and found that the sensitivity of the 2 strains to carbapenems (Meropenem and imipenem/cisastatin sodium) reached 100.0%, and the sensitivity to the beta lactam compound drug piperacillin tazobactam was more than 90.0%. However, the sensitivity to ampicillin, the drug recommended in the guidelines for premature rupture of membranes, was only 50.0%. Therefore, if high fever occurs in patients with PROM, the antimicrobial agent ampicillin should be replaced in time. Women who are allergic to penicillin may also consider ceftazidine for anti-infection treatment, and 95.0% of pathogens

are sensitive to this drug. In our hospital, if the patients had high fever with elevated PCT, especially after induced labor, most cases would use piperacillin tazobactam. All the patients mentioned above complete recovered.

Considerable efforts have been paid to discuss the risk factors, pathogenic bacteria of maternal sepsis in term pregnant women, some limitations for our present meta-analysis need to be declared. Firstly, maternal sepsis often occurs when patients have been discharged from the hospital. The data of patients with a fever after discharge were not completely obtained, for they may receive treatment in the nearby community hospital, so our study did not include patients who returned to our hospital for treatment after discharge with fever. Pregnant women with premature rupture of membranes and premature delivery, who had fever during hospitalization, began to use antibiotics immediately due to hospitalization, which reduced the positive rate of blood culture. These cases were also excluded from our study, so my results did not include all maternal sepsis. Secondly, the sample size of our study is relatively small, and the specific values of N% and PCT cannot be acquired. Available indicators and identification for novel prognostic markers are required and efficient antibiotics are applied to pregnant women with high risk of sepsis.

In conclusion, patients with PROM, induced labor, and cesarean delivery have an increased risk of severe sepsis. Prolonged labor followed by a cesarean delivery is the most important risk factor for maternal sepsis. Thus, we should strengthen the management for pregnant women with the high risks, reduce the frequency of vaginal examination as far as possible, and avoid unnecessary cesarean section. Early diagnoses and alternative antimicrobial agents are paramount to the reduction of severe sepsis, such as septic shock and multiple organ dysfunctions.

Author contributions

Conceptualization: Wei Zhou.
Data curation: Yanqing Wen, Hong Chen, Xin Ming, Wei Zhou.
Formal analysis: Hong Chen, Xiaoyan Chen.
Funding acquisition: Wei Zhou.
Investigation: Yanqing Wen, Hong Chen.
Methodology: Yanqing Wen, Xiaoyan Chen.
Project administration: Wei Zhou.
Resources: Hong Chen.
Software: Yanqing Wen, Xin Ming.
Supervision: Wei Zhou.
Visualization: Xiaoyan Chen, Wei Zhou.
Writing – original draft: Yanqing Wen, Hong Chen.
Writing – review & editing: Yanqing Wen, Xin Ming, Xiaoyan Chen, Wei Zhou.

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