The Role of Hyperleukocytosis in Predicting the Severity of Pertussis

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Research article

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Abstract

Background: Few reports have described the relationship between WBC count and the severity of pertussis or the timing of ET in patients with hyperleukocytosis.

Methods: A retrospective clinical analysis of infants with pertussis and a WBC exceeding 30*10^9/L was performed.

Results: A total of 158 patients were enrolled in the study. There were significant differences in the clinical manifestations of cyanosis, fever, highest respiratory rate, and highest heart rate. There were significant differences in all complications except for pulmonary hypertension. In laboratory findings, there were significant differences in organ damage (myocardial markers, ALT), increased inflammation indicators (CRP, PCT), and the incidence of combined bacterial infections. There were significant differences in ICU stay length, mechanical ventilation use, days hospitalized, days until cough relief and days until the WBC fell below 25*10^9/L. A WBC count >55.38 *10^9/L was calculated as the cutoff value with 88.2% sensitivity and 23.4% specificity in predicting ET. A respiratory rate of 59 breaths/min had 94.1% sensitivity and 36.7% specificity in predicting ET. A heart rate of 159 beats/min had 100% sensitivity and 38.1% specificity in predicting ET.

Conclusion: WBC count is related to the severity of pertussis. We recommend that ET is considered when the patient's WBC count exceeds 55*10^9/L, breathing exceeds 60 breaths/min, and/or heart rate exceeds 160 beats/min.

Impact Of This Article:

- The WBC count is related to pertussis severity.
- The higher the WBC count, the more severe the disease, the greater incidence of complications, the higher the occurrence of combined organ dysfunction, the higher the risk of combined bacterial infection, the slower the recovery and the worse the prognosis.
- We recommend that ET be considered for infants under 1 year old, patients with a WBC count that has reached or exceeded 55*10^9/L, patients with a respiratory rate that has exceeded 60 (breaths/min), and/or patients with a heart rate that has exceeded 160 (beats/min).

Background

Pertussis is a highly contagious respiratory illness. Severe pertussis is the leading cause of death in children with pertussis. The occurrence of severe pertussis is affected by many factors, such as pneumonia, pulmonary hypertension and hyperleukocytosis. Leukocytosis is a predictor of mortality in patients with severe pertussis infection. Kathleen Winter's research has shown that WBC counts > 30*10^9/L are strongly associated with fatal pertussis in infants[1];research conducted by Berger[2] showed that children with a WBC count greater than 50 *10^9/L had a nearly ten times higher risk of

death. WBC counts > 70*10^9/L are strongly associated with death[1],and hyperleukocytosis [WBC count > 100*10^9/L] is a rare complication that strongly predicts mortality in cases of severe pertussis[3]. Research indicates that elevated WBC counts are associated with increased mortality risk. However, there has been no systematic research analyzing the ability to predict the severity and risk of death by WBC count in patients with pertussis. The purpose of exchange transfusion (ET) is to lower the WBC count, and ET can reduce blood viscosity, pertussis toxin levels, and the pulmonary small blood vessel obstruction caused by white blood cells. In recent years, ET has been widely used in hyperleukocytosis treatment, but there is no unified understanding of the effect and standard use of ET in patients with pertussis. Cherry et al[4] suggested exchange blood transfusion and monitoring criteria for infants with pertussis who are ≤ 60 days of age. Tian et al[3] summarized the literature on ET from 2004 to 2017, and the survival rate of pertussis patients with hyperleukocytosis was significantly higher when ET therapy was used. However, the scattered ET reports have different conclusions. Therefore, we wanted to compare the relationship between disease severity and risk of death at different WBC count by collecting patients with WBC ≥ 30*10^9/L; at the same time, we also analyzed the data in transfusion and nontransfusion patients. We assessed WBC levels in relation to the severity of pertussis and the timing of ET.

Methods

Patients

A total of 158 patients under 1 year old who were diagnosed with pertussis from January 2018 to December 2019 at the Children's Hospital of ChongQing Medical University were enrolled in this study. The WBC count of all patients exceeded 30*10^9/L. The diagnosis of pertussis was based on clinical findings and confirmed by PCR. Clinical data and laboratory data were collected and analyzed. This study was approved by the Ethics Committee of Children's Hospital of ChongQing Medical University. The patients were categorized into three groups according to their WBC count: those with 30*10^9/L ≤ WBC < 50*10^9/L were categorized to group A, those with 50*10^9/L ≤ WBC < 70*10^9/L were categorized to group B, and those with 70*10^9/L ≤ WBC were categorized to group C.

Statistical Analysis

Statistical analyses were performed using SPSS software version 25. Descriptive analyses for nonnormally distributed data are presented using the median (interquartile range); comparisons between two groups were calculated using the Mann-Whitney test and multigroup comparisons were conducted using the Kruskal-Wallis rank test. Count data are expressed as the rate (%), and the difference between groups was calculated using the chi-square test. Receiver operating characteristic curve (ROC) analyses and sensitivity and specificity values were calculated by using Med Calc version 14. A P value < 0.05 was considered statistically significant.

Results

1. Study Population

During the study period, 158 patients were enrolled in this study. All patients had B pertussis DNA detected by PCR in nasopharyngeal secretions or in sputum. The demographic, clinical, and laboratory data of the study patients are shown in Table 1.

Table 1
patients data

Group	Group A	Group B	Group C	total(n = 158)	P-value
WBC(*10^9/L)	**30 ≤ WBC＜50 (n = 80)**	**50 ≤ WBC＜70 (n = 55)**	**70 ≤ WBC(n = 23)**		
Demographics					
Gender(male,n,%)	42(52.5%)	24(43.6%)	5(21.7%)	71(44.9%)	0.032
Death(n,%)	0(0%)	2(3.6%)	10(43.5%)	12(7.6%)	0.000
Any DTaP	0(0–3)	0(0–3)	0(0–1)	0(0–3)	0.479
Age of onset(d)	150(88-285.25)	136(69–435)	134(84–300)	145.5(81.5–318)	0.78
days from onset to admission(d)	15(11.25–19.75)	14(7–19)	15(6–18)	15(10–19)	0.312
Clinical Characteristics and Complications					
whooping(n,%)	28(35%)	20(37%)	13(56.5%)	61(38.9%)	0.166
Cyanosis(n,%)	36(45%)	32(58.2%)	18(78.3%)	86(54.4%)	0.015
Wheezing(n,%)	34(42.5%)	31(56.4%)	15(65.2%)	80(50.6%)	0.091
Fever(n,%)	33(41.3%)	33(60%)	21(91.3%)	87(55.1%)	0.000
Highest Temperature (°Celcius)	38.35(37.8–39)	38.4(37.975–38.925)	38.9(38.3-39.05)	38.5(38–39)	0.114
Highes heart rate(beats/min)	144(136.5–161)	157(148.75-172.25)	187.5(166.75-201.25)	158(140.5–180)	0.000
Highes respiratory rate(breaths/min)	53.9 ± 11.46	59.4 ± 12.33	69.04 ± 14.08	58.94 ± 13.46	0.000
Pneumonia (n,%)	42(52.5%)	29(52.7%)	3(13%)	74(46.8%)	0.002
Severe pneumonia(n,%)	16(20%)	23(41.8%)	20(87%)	59(37.3%)	0.000
Respiratory failure(n,%)	15(18.8%)	23(41.8%)	20(87%)	58(36.7%)	0.000
Lung consolidation or atelectasis(n,%)	14(20.6%)	21(39.6%)	16(69.6%)	51(35.4%)	0.000
Pulmonary hypertension(n,%)	2(6.7%)	3(10.3%)	5(26.3%)	10(12.8%)	0.190
Heart faliure(n,%)	2(2.5%)	2(3.6%)	13(56.5%)	17(10.8%)	0.000
Pertussis encephalopathy(n,%)	1(1.3%)	7(12.7%)	6(26.1%)	14(9%)	0.000

Group	Group A	Group B	Group C	total(n = 158)	P-value
WBC(*10^9/L)	30 ≤ WBC＜50 (n = 80)	50 ≤ WBC＜70 (n = 55)	70 ≤ WBC(n = 23)		
Laboratory Findings					
Abnormal myocardial markers(n,%)	11(13.8%)	12(21.8%)	10(43.5%)	33(20.9%)	0.013
elevated alanine aminotransferase(n,%)	16(20%)	9(16.4%)	18(78.3%)	43(27.2%)	0.000
Increased C-reactive protein(n,%)	5(6.3%)	14(25.5%)	16(69.6%)	35(22.2%)	0.000
Increased procalcitonin(n,%)	33(44%)	27(50%)	18(81.8%)	78(51.7%)	0.007
Days to highest WBC count, median (IQR)	15(13.25-20)	14(10–17)	15(7–18)	15(11–19)	0.043
Combined bacterial infection(n,%)	28(35.9%)	25(46.3%)	19(82.6%)	72(46.5%)	0.000
Combined virus infection(n,%)	14(17.9%)	16(29.1%)	8(34.8%)	38(24.4%)	0.152
Treatment					
days from illness onset to Macrolide plus treatment (d)	12(7–15)	12(8–15)	10(5–15)	12(7–15)	0.465
Total course of macrolides(d)	8(6–9)	8(7–11)	9(6–11)	8(6–10)	0.366
Received Gamma globulin(n,%)	14(17.7%)	27(49.1%)	12(52.2%)	53(33.8%)	0.000
Received steroids(n,%)	18(22.5%)	18(32.7%)	8(34.8%)	43(27.2%)	0.31
Received Vasoactive drugs(n,%)	1(1.3%)	4(7.3%)	14(60.9%)	19(12%)	0.000
Received Other antibiotics(n,%)	50(62.5%)	44(80%)	22(95.7%)	116(73.4%)	0.003
Received Exchange transfusion(n,%)	0(0%)	5(9.1%)	12(52.2%)	17(10.8%)	0.000
ICU admission(n,%)	5(6.3%)	10(18.2%)	21(91.3%)	36(22.8%)	0.000
48 hours of ICU admission(n,%)	2(40%)	6(60%)	15(71.4%)	23(63.9%)	0.380
ICU length of stay (days)	9(5.5–16)	17(5.5–23.5)	7(2.5–17.5)	9(3–18)	0.218

Group	Group A	Group B	Group C	total(n = 158)	P-value
WBC(*10^9/L)	**30 ≤ WBC＜50 (n = 80)**	**50 ≤ WBC＜70 (n = 55)**	**70 ≤ WBC(n = 23)**		
Mechanical ventilation use(n,%)	6(7.7%)	16(29.6%)	19(82.6%)	41(26.5%)	0.000
Intubation(n,%)	4(66.7%)	8(47.1%)	18(85.7%)	30(68.2%)	0.033
Length of invasive ventilation (hours)	212.5(156.25-295.75)	330(96-457.5)	151.5(40-343.5)	160(53–330)	0.371
Improvement after treatment					
Days hospitalized, median (IQR)	9(6–13)	12(9–16)	16(3–27)	10.5(7–15)	0.011
Days until cough relief, median (IQR)	23(17-27.75)	25.5(21–31)	29(24.5–37)	25(19-30.5)	0.013
Days until the WBC fell below 25*10^9/L, median (IQR)	6(4–7)	9(7-12.75)	12(9-13.25)	7(5–10)	0.013

There were 80 (50.6%) patients with 30*10^9/L ≤ WBC < 50*10^9/L, 55 (34.8%) patients with 50*10^9/L ≤ WBC < 70*10^9/L, and 23 (14.6%) patients with WBC ≥ 70*10^9/L. There were 52.5% males in group A, 43.6% in group B, and 21.7% in group C, and there were significant differences among the three groups (P = 0.032).

There were 12 patients who died in the study, 10 (43.5%) patients in group C, and only 2 (3.6%) patients in group B. No patient died in group A. There were significant differences in the mortality rate among the three groups (P = 0.000).

In the three groups, there were no significant differences in the times of vaccination, age of onset, or time from onset to admission (P = 0.479, 0.78, 0.312, respectively).

2. **Clinical manifestations and complications**

Clinical manifestations and complication data are shown in Table 1. Regarding the clinical manifestations, there were no significant differences in the incidence of whooping and wheezing (P = 0.166, 0.091). The incidence of cyanosis was 36 (45%) in group A, 32 (58.2%) in group B, and 18 (78.3%) in group C, with significant differences (P = 0.015). There were significant differences among the three groups (P = 0.015). The incidence of fever in group A was 33 (41.3%), the incidence in group B was 33 (60%), and in the incidence in group C was 21 (91.3%); there was a significant difference (P = 0.000). However, there were no significant differences in the highest temperature of fever among the three groups (P = 0.114). The highest heart rate (beats/min) in group A was 144 (136.5–161), in group B was 157 (148.75-172.25), in group C was 187.5 (166.75-201.25); the difference was statistically significant (P =

0.000). The highest respiratory rate (breaths/min) in group A was 53.9 ± 11.46, group B was 59.4 ± 12.33, and group C was 69.04 ± 14.08; the difference was also statistically significant (P = 0.000).

Regarding complications, the number of pneumonia cases was 42 (52.5%) in group A, 29 (52.7%) in group B and 3 (13%) in group C; the difference was statistically significant (P = 0.002). The number of severe pneumonia cases in group A was 16 (20%), that in group B was 23 (41.8%), and that in group C was 20 (87%); the difference was statistically significant (P = 0.002). The incidence of pneumonia and severe pneumonia was 72.5% in group A, 94.5% in group B, and 100% in group C. The incidence of complications such as respiratory failure, pulmonary consolidation or atelectasis, pulmonary hypertension, heart failure, and pertussis encephalopathy all increased with the increased WBC. The incidence rates of all complications were significantly different among the three groups (P = 0.000, 0.000, 0.000, 0.000, respectively), except for pulmonary hypertension among the three groups (P = 0.190).

3. Laboratory Data

Laboratory data are presented in table 1. On organ function assessment, the incidence of abnormal myocardial markers in group A was 13.8% (n=11), the incidence in group B was 21.8% (n=12), and the incidence in group C was 43.5% (n=10); the incidence of abnormal liver function in group A was 20% (n=16), the incidence in group B was 16.4% (n=9), and the incidence in group C was 78.3% (n=18). The incidence of myocardial and liver function abnormalities in the three groups were significantly different (P=0.013, 0.000).

In the examination of inflammatory indicators, the number of patients with increased CRP in group A was 5 (6.3%), in group B was 14 (25.5%), and in group C was 16 (69.6%); the number of patients with increased procalcitonin (PCT) in group A was 33 (44%).), in group B was 27 (50%), and in group C was 18 (81.8%). of the incidence of increased CRP and PCT were significantly different among the three groups (P=0.000, 0.007).

In the pathogenic examinations, 28 (35.9%) cases in group A were combined with bacterial infection and 14 (17.9%) were combined with viral infection; the numbers of cases combined with bacterial infection and viral infection were 25 (46.3%) and 16 (29.1%) in group B, and 19 (82.6%) and 8 (34.8%) in group C, respectively. The difference in combined bacterial infections among the three groups was statistically significant (P=0.000), but there was no significant difference in the incidence of combined viral infections (P=0.152).

4. Treatment

There was no significant difference in the days from illness onset to macrolide plus treatment or the total course of macrolides among the three groups of patients (P=0.465, 0.366). The incidence of gamma globulin, steroids, vasoactive drugs, other antibacterial drugs, and ET increased gradually with increasing WBC levels among the three groups, with the exception of steroid use (P=0.31), there were significant differences among the groups (P =0.000, 0.000, 0.003, and 0.000).

The number of patients admitted to the ICU was 5 (6.3%) in group A, 10 (18.2%) in group B, and 21 (91.3%) in group C. There was a significant difference in the rate of ICU admission within 48 hours of hospital admission among the three groups (P=0.000). Although the rate of admission to the ICU within 48 hours after hospital admission also increased with the increase in white blood cell count, there was no significant difference in the rate of admission to the ICU within 48 hours of hospital admission among the three groups (P=0.380).

5、Improvement after treatment

The length of hospital stay in group A was 9 days (6-13), in group B was 12 days (9-16), and in group C was 16 days (3-27). The number of days until cough relief in group A was 23 (17-27.75), in group B was 25.5 (21-31), and in group C was 29 (24.5-37). The number of days until the WBC fell below 25*10^9/L in group A was 6 (4-7), in group B was 9 (7-12.75), and in group C was 12 (9-13.25). The length of the hospital stay, the number of days until cough relief and the number of days until the WBC fell below 25*10^9/L were all prolonged as the WBC level increased, and the difference was statistically significant (P=0.011, 0.013, 0.013, respectively), as shown in Table 1.

6. Timing of Exchange transfusion

Seventeen patients received exchange transfusion, 12 (52.2%) patients had WBCs exceeding 70*10^9/L, and 5 (9.1%) patients had 50*10^9/L≤WBC≤70*10^9/L. No patient received exchange transfusion in the 30*10^9/L≤ WBC<50*10^9/L group.

The area under the receiver operating characteristic (ROC) curve (AUC) value for WBC count with the cutoff point of 55.38 *10^9/L was 0.899 (95% confidence interval (CI), 0.834~0.963，*P*＜0.000) in predicting exchange transfusion. When applying the ROC curve with the WBC count cutoff point of 55.38 *10^9/L, the analysis yielded 88.2% sensitivity and 23.4% specificity (Figure 1). The area under the receiver operating characteristic (ROC) curve (AUC) value for respiratory rate with a cutoff point of 59 breaths/min was 0.795 (95% confidence interval (CI), 0.699~0.891，*P*＜0.000) in predicting exchange transfusion. When applying an ROC curve with the respiratory rate cutoff point of 59 breaths/min, the analysis yielded 94.1% sensitivity and 36.7% specificity (Figure 2). The area under the receiver operating characteristic (ROC) curve (AUC) value for heart rate with a cutoff point of 159 beats/min was 0.813 (95% confidence interval (CI), 0.731~0.895，*P*＜0.000) in predicting exchange transfusion. When applying the ROC curve with heart rate at the cutoff point of 159 beats/min, the analysis yielded 100% sensitivity and 38.1% specificity (Figure 3).

Discussion

Pertussis is a highly contagious and vaccine-preventable respiratory illness. In the past few decades, immunization has greatly reduced the incidence of the disease[5]. However, pertussis has not disappeared due to widespread vaccination; it continues to threaten the health and even lives of humans, especially young children. In 2010, Black et al[6]. reported that 16 million cases of pertussis occurred in 2008

worldwide, resulting in 195,000 deaths. In our study, there were 12 patients who died among the 158 patients included. Ten (43.5%) patients had WBC counts exceeding 70*10^9/L, and only 2 (3.6%) patients in the 50*10^9/L ≤ WBC < 70*10^9/L group had WBC counts exceeding 70*10^9/L. No patient died in 30*10^9/L ≤ WBC < 50*10^9/L group. This shows that when the WBC counts is below 50*10^9/L, the risk of death is low. The risk of death is mainly in patients with WBC ≥ 70 *10^9/L. In our research, we also noticed that there was a significant difference in the sex ratio among the three groups of patients (P = 0.032). When the WBC counts was 30*10^9/L ≤ WBC < 50*10^9/L, there was no significant difference in sex, but when the WBC counts was ≥ 50*10^9/L, the higher the WBC count, the higher the proportion of female patients. When the WBC count was ≥ 70*10^9/L, the proportion of female patients was 78.3%. However, Haberling et al showed that among severe pertussis and pertussis-related deaths, the rate of female patients may not be as high as stated in other reports[7].

Severe pertussis is related to many factors, especially hyperleukocytosis[2, 8]. In our study, according to the patient's WBC count, we divided the patients into three groups: 30*10^9/L ≤ WBC□50*10^9/L, 50*10^9/L ≤ WBC□70*10^9/L, and 70*10^9/L ≤ WBC. We found that the three groups of patients had significant differences in many clinical symptoms, such as the incidence of cyanosis (P = 0.015), the probability of fever (P = 0.000), the highest respiratory rate (P = 0.000), and the highest heart rate (P = 0.000). The results suggest that the higher the WBC count is, the more severe the disease may be. However, the highest temperature was not significantly different among the three groups (P = 0.114), indicating that the highest temperature does not necessarily reflect the severity of the disease. The incidence of complications such as severe pneumonia, respiratory failure, lung consolidation or atelectasis, pulmonary hypertension, heart failure, and pertussis encephalopathy in the three groups of patients all increased with increasing WBC count. The higher the WBC count was, the more severe the disease.

Comparing the laboratory findings of patients with different WBC counts, we found that the incidence of organ damage (liver and heart) was also significantly different among the three groups of patients (P = 0.013, 0.000), which may be related to the severity of the disease. In the comparison of inflammatory indicators, the incidence of increased peripheral blood C-reactive protein (CRP) and procalcitonin (PCT) increased with the increase in white blood cell count, with significant differences (P = 0.000, 0.007). This may be caused by the presence of a combined bacterial infection because we also found that the three groups of patients had a significant difference in the incidence of combined bacterial infection (P = 0.000). The results still showed that the incidence of increased CRP, PCT and combined bacterial infections increased with the increased WBC count.

In addition, the patient's ICU admission rate, days hospitalized, days until cough relief (days), and days until the WBC fell below 25*10^9/L were significantly different at different WBC levels (P = 0.000, 0.011, 0.013, 0.013, respectively). This relationship is also consistent with the increase in the white blood cell count.

At present, people have recognized the effects of hyperleukocytosis in pertussis[9–10]. The most widely used treatment for hyperleukocytosis is ET. It can reduce the WBC count and improve the survival rate of patients. It is very important for the treatment of severe pertussis[11].Although ET has been used in the treatment of patients with hyperleukocytosis for many years, there has been no systematic study to analyze the timing and indicators of ET. We drew the ROC curves using transfusion and nontransfusion data, and we found that ET may be considered for infants under 1 year old, patients with a WBC count that reached or exceeded 55*10^9/L, patients in whom the highest respiratory rate exceeded 60 (breaths/min), and/or patients in whom the highest heart rate exceeded 160 (beats/min).

Conclusion

Taken together, the level of WBCs is related to disease severity. The higher the WBC count, the more severe the disease, the greater incidence of complications, the higher occurrence of combined organ dysfunction, the higher risk of combined bacterial infection, the slower the recovery and the worse the prognosis. We recommend that ET is considered for infants under 1 year old, patients with a WBC count that has reached or exceeded 55*10^9/L, patients in whom the highest respiratory rate exceeded 60 (breaths/min), and/or patients in whom the highest heart rate exceeded 160 (beats/min).

Abbreviations

WBC: White blood cell; ET: exchange transfusion; CRP: C-reactive protein; PCT: procalcitonin; ALT: alanine aminotransferase.

Declarations

Acknowledgments

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Authors' contributions

Dr. Wu XY contributed to data collection and writing; Dr. Gan C. contributed to the conception and design of the work. All authors contributed to the acquisition, analysis and interpretation of data.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval statement

This study was approved by the Ethics Committee of Children's Hospital of ChongQing Medical University. As it is a retrospective clinical analysis, it was decided by the ethics committee granted an exemption for informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

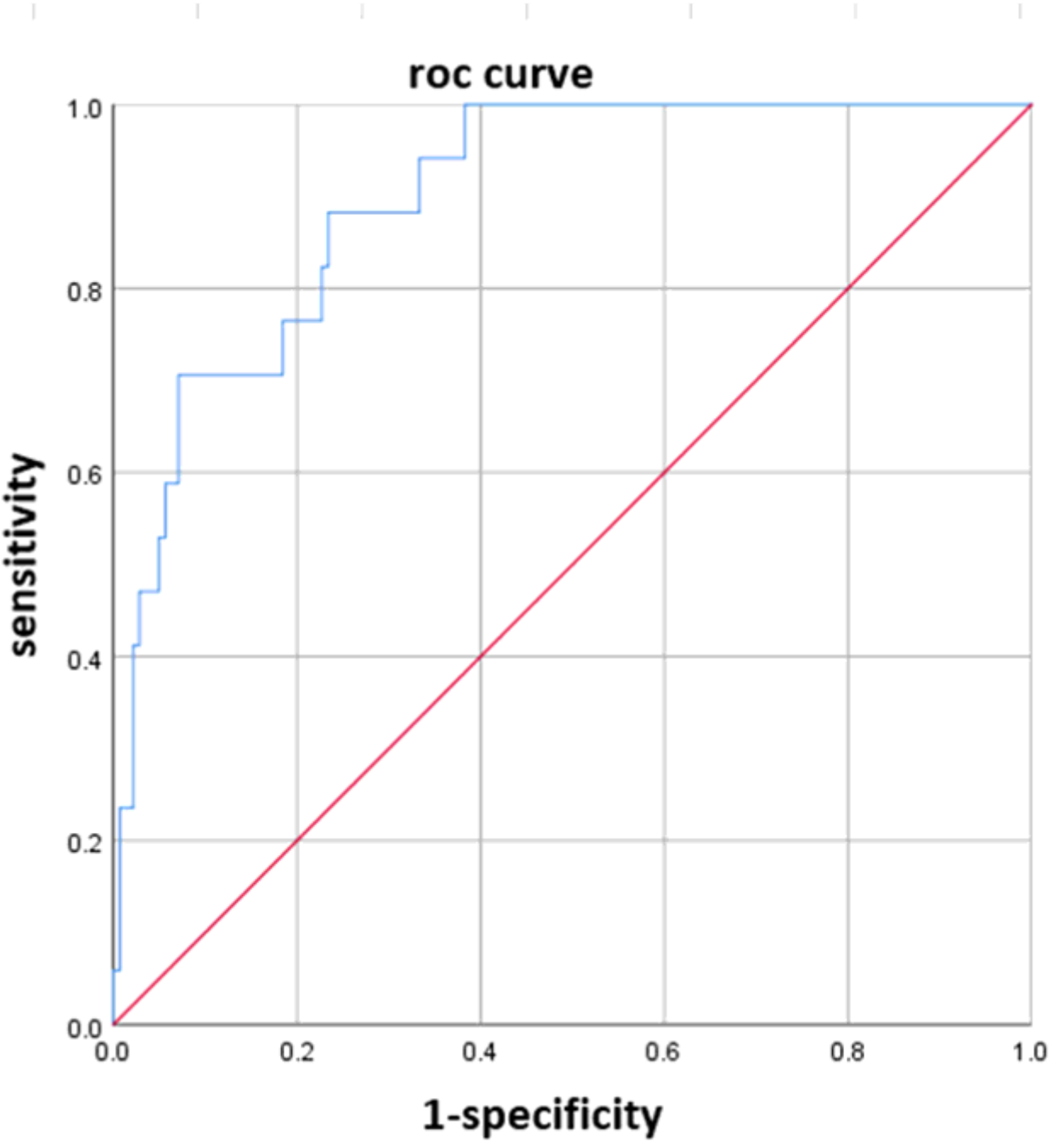

Figure 1

The receiver operating characteristic (ROC) curve (AUC) value for WBC count with the cutoff point of 55.38 was 0.899 (95% confidence interval (CI), 0.834~0.963，P＜0.000) *10^9/L in predicting exchange transfusion.

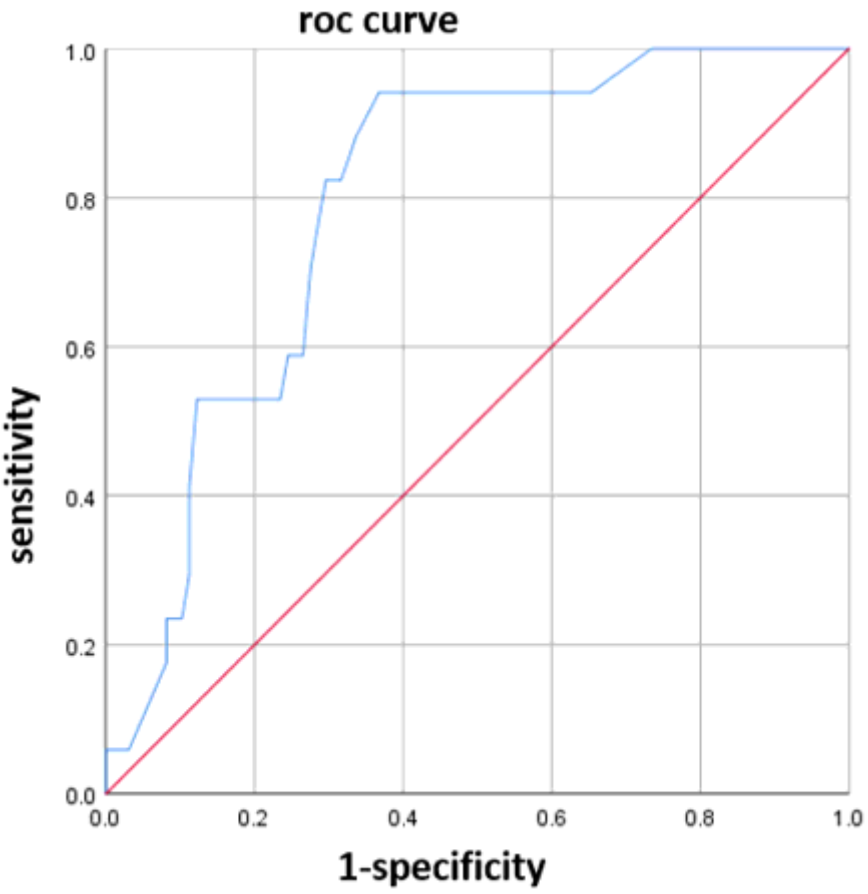

Figure 2

The receiver operating characteristic (ROC) curve (AUC) value for respiratory rate with the cutoff point of 59 (breaths/min) was 0.795 (95% confidence interval (CI), 0.699~0.891，P＜0.000) in predicting exchange transfusion.

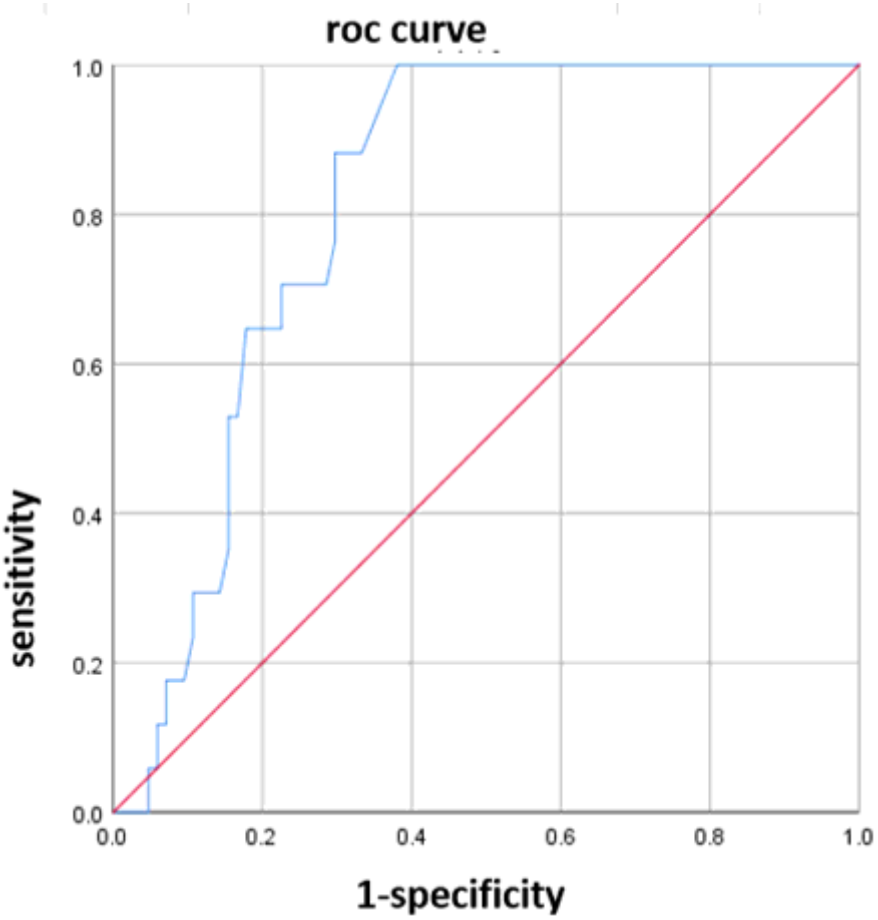

Figure 3

The receiver operating characteristic (ROC) curve (AUC) value for heart rate with a cutoff point of 159 beats/min was 0.813 (95% confidence interval (CI), 0.731~0.895，P＜0.000) in predicting exchange transfusion.