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Clinical analysis of 17 cases of neonatal osteomyelitis

A retrospective study

Canyang Zhan, MD[a,*], Bo Zhou, MD[b], Jing Du, MD[a], Lihua Chen, MD[a]

Abstract

Although acute osteomyelitis is rare in neonates, it might result in severe sequelae such as joint destruction and growth failure if it is not diagnosed and treated early. However, few studies have focused on the clinical features and treatment of this disease.

A retrospective review of 17 cases of neonatal osteomyelitis, for which the patients underwent medical treatment alone or combined with surgery at the Children's Hospital of Zhejiang University School of Medicine between January 2009 and September 2016, was conducted. Medical treatment included the use of antibiotics and supportive care. Surgery was performed in cases with subperiosteal abscess (>1 cm) or clinical deterioration despite antibiotic therapy.

All of the patients (11 men and 6 women) were term neonates. The main complaints were redness or swelling around the affected bone and fever. The most common sites were the femur (29.4%) and humerus (23.5%). There were 14 (82.35%) cases with positive cultures: *Staphylococcus* accounted for 71.43% (n = 10), followed by *Salmonella* (n = 1), *Streptococcus pneumoniae* (n = 1), *Klebsiella pneumoniae* (n = 1), and *Escherichia coli* (n = 1). X-rays (n = 14), ultrasound (n = 6), computed tomography (CT) (n = 5), or magnetic resonance imaging (MRI) (n = 7) were performed. Three of 14 x-rays were not pathological at the onset of the disease, while the positive rate of MRI in detecting osteomyelitis was 100%. Eleven of 17 cases underwent surgical drainage, and higher white blood cell (WBC) counts were found in patients requiring surgery ($P < .05$). The prognosis for all patients was good without severe sequelae with a mean follow-up period of 49.47 ± 23.43 months.

In conclusion, the prognosis of neonatal osteomyelitis with early active treatment is good. MRI is advocated for detecting early osteomyelitis. Additionally, neonates with higher WBC count together with osteomyelitis have an increased risk for surgery.

Abbreviations: CRP = C-reactive protein, CT = computed tomography, MRI = magnetic resonance imaging, MRSA = methicillin-resistant *Staphylococcus aureus*, WBC = white blood cell.

Keywords: clinical characteristics, neonate, osteomyelitis, sequelae, surgical intervention

1. Introduction

Osteomyelitis is an inflammation of the bone caused by infections involving the bone and/or bone marrow with bacteria or other organisms. In pediatric age groups, the incidence is 1:5000. Children <5 years old account for approximately 50% of the pediatric cases of osteomyelitis.[1] In neonates, the incidence ranges from 1 to 3 cases for every 1000 hospital admissions.[1,2] Most of the reports have been case studies. Knudsen and Hoffman[3] reported 34 cases of osteomyelitis in neonates and Hu and Chen[4] reported 7 cases of neonatal osteomyelitis. Although uncommon, it might result in severe sequelae such as joint destruction and growth failure if it is not diagnosed and treated early.[5] The diagnosis of osteomyelitis in neonates in early stages of the disease is challenging because of its nonspecific clinical presentation. As a result, the treatment is often delayed. Traditionally, the treatment of osteomyelitis in pediatric clinics is based on prolonged intravenous anti-infective therapy. Recently, more and more results from clinical trials suggest that a short course of intravenous antibiotics followed by oral therapy is safe and effective for children with uncomplicated osteomyelitis.[6–8] However, these findings do not apply to the neonates.[7] In this paper, we describe 17 cases of neonatal osteomyelitis, including their presentation, laboratory tests and treatment, and discuss the diagnosis and management.

2. Materials and methods

The cases of 17 neonates diagnosed with osteomyelitis between January 2009 and September 2016 at the Children's Hospital, Zhejiang University, School of Medicine, were retrospectively reviewed. The diagnosis was confirmed by a positive blood culture, by the finding of pus at surgery or by radiographic changes such as metaphyseal rarefaction or periosteal reaction.

Editor: Rana El Feghaly.

This work was supported by grants from the National Natural Science Foundation of China (No. 81401235), General Research Projects of the Department of Education of Zhejiang Province (No. Y201737812), and Zhejiang Province Department of Laboratory Animal Science and Technology Plan Projects (No. 2018C37115).

The authors declare no conflicts of interest.

[a] Department of Neonatology, Children's Hospital, [b] Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

[*] Correspondence: Canyang Zhan, Department of Neonatology, Children's Hospital, Zhejiang University School of Medicine, Hangzhou, 310003, China (e-mail: 6310005@zju.edu.cn).

Medicine (2019) 98:2(e14129)

Received: 3 September 2018 / Received in final form: 3 December 2018 / Accepted: 19 December 2018

http://dx.doi.org/10.1097/MD.0000000000014129

Medical treatment included the use of antibiotics and supportive care. Surgery was performed in cases with subperiosteal abscess (>1 cm) or clinical deterioration despite antibiotic therapy, and ranged from percutaneous drainage to wound debridement and irrigation. Resolution of osteomyelitis was based on improvement in the clinical signs and inflammatory markers. The clinical records of all these patients, including age, sex, manifestations, bacterial culture, management, laboratory test results, and imaging examination results, were collected retrospectively. All neonates were followed up as out-patients. Our department follows up with patients every 6 months after discharge. All parents or guardians of pediatric patients provided written informed consent. The study was approved by the Ethics Committee of the Children's Hospital of Zhejiang University School of Medicine. The study was conducted in accordance with the Declaration of Helsinki for human subjects.

All statistical analyses were performed using SPSS 16.0 software (SPSS, Chicago, IL) for Windows. The data are expressed as mean (range). Categorical data were analyzed using the chi-squared (χ^2) test. Differences between the surgical group and non-surgical group were evaluated by *t* test in the case of normally distributed variables or by the Mann–Whitney *U* test in the case of nonparametric variables. A *P* value <.05 was considered statistically significant.

3. Results

3.1. Patients' characteristics

The characteristics of the patients are shown in Table 1. All of the patients (11 men and 6 women) were term neonates. The median age was 16 days (range 1–28 days). The most common symptoms were redness or swelling around the affected bone (n = 17) and fever (n = 13). However, 1 patient was hospitalized with seizure. The most common infectious sites were femur (29.4%) and humerus (23.5%). Regarding the additional diagnosis, septic arthritis (n = 2), or cellulitis (n = 14) was also found, while none of the patient was diagnosed as myositis. For predisposing factors, there were 2 patients with chorioamnionitis, and 1 patient was delivered by vacuum extraction resulting in clavicle fracture. One case of skull osteomyelitis was caused by an infectious cephal hematoma. Most of the patients (n = 14) underwent x-ray examination. Furthermore, ultrasound (US) (n = 6), computed tomography (CT) (n = 5) or magnetic resonance imaging (MRI) (n = 7) were also performed. Typical changes included metaphyseal rarefaction, periosteal reaction, bone destruction, soft tissue enhancement, or abscess. However, 3 patients in our study presented with only slight swelling or excessive crying without fever, and there were no pathological findings on x-ray at disease onset. However, typical changes in x-ray or MRI were found after 1 to 2 weeks. The average time from onset to diagnosis was 12 days for the all patients (range: 2–24 days). Thus, diagnosis and treatment were delayed.

3.2. Laboratory examination and bacteriology

Routine blood and C-reactive protein (CRP) tests showed that most of the neonates had higher levels of white blood cells (WBC) (average: 20.53×10^9/L, range: 11.08–36.62×10^9/L), platelets (average: 506×10^9/L, range: 79–963×10^9/L), and CRP (average: 77.6 mg/L, range: 8–160 mg/L). Additionally, 7 cases (41.2%) had elevated liver enzymes, but only 1 case (5.9%) with thrombocytopenia was observed.

A blood or pus sample from all patients was sent for bacterial culture. There were 14 (82.35%) cases with positive cultures; *Staphylococcus* accounted for 71.43% (10 cases). The other bacteria were *Salmonella* (1 case), *Streptococcus pneumoniae* (1 case), *Klebsiella pneumoniae* (1 case), and *Escherichia coli* (1 case). Of the staphylococcal infections, 3 (30%) cases were resistant to oxacillin but sensitive to vancomycin (Table 1).

3.3. Management

All patients were started with intravenous combined antibiotics after admission to the hospital. Antibiotic therapy was adjusted later according to the culture and the sensitivity results. Twelve cases were treated with vancomycin or oxacillin and antibiotics for Gram-negative bacteria. Third-generation cephalosporin or meropenem were used for the neonate infected with *K pneumoniae*, *E coli*, and *Salmonella* (Table 1).

There were 11 cases (64.71%) treated with surgical drainage. Compared with patients in the non-surgical treatment group, the WBC count of patients who underwent surgery was higher ($23.39 \pm 8.66 \times 10^9$/L vs $15.28 \pm 3.95 \times 10^9$/L, $P = .04$). In addition, there was a tendency that patients undergoing surgery had shorter hospital stays than did patients without surgical treatment (21.73 ± 10.20 days vs 31.33 ± 7.05 days, $P = .06$). Other clinicopathological characteristics in the two cohorts showed no significant differences, including age, sex, platelets, CRP, hospital stays, predisposing factors, location, and culture (Table 2).

With antibiotic therapy alone or combined with surgical intervention, all patients recovered and were discharged. There were no obvious sequelae and no recurrence with a mean follow-up period of 49.47 ± 23.43 months.

3.4. Comparison of osteomyelitis findings, therapies, and outcomes in the reports by Knudsen and Hu and by our group

To further analyze the clinical features and treatment of osteomyelitis, we compared osteomyelitis findings, therapies, and outcomes in the reports by Knudsen and Hoffman[3] and Hu and Chen[4] and by our group (Table 3). We found that prematurity or chorioamnionitis was the main predisposing factors for osteomyelitis. The most common infection sites were the femur and humerus. *S aureus* was the most common bacterial agent. X-rays might be normal at disease onset, but the positive rate for detecting osteomyelitis by MRI was 100%. All patients received anti-infective treatment or surgical drainage. Eight patients had different degrees of sequelae in Knudsen paper, while there were none in the report by Hu and coworkers and the patients in our series.

4. Discussion

Osteomyelitis is uncommon in neonates. The risk factors included chorioamnionitis, perinatal asphyxia, and prolonged rupture of membranes.[9] Neonatal osteomyelitis can lead to permanent joint disability and disturbances in bone growth. To a certain degree, the outcome is dependent on rapid diagnosis and immediate initiation of treatment. Thus, early diagnosis of neonatal osteomyelitis is very important. Late diagnosis by only 4 days is a risk factor for long-term sequelae.[6] However, the diagnosis of neonatal osteomyelitis is difficult and is often delayed because of nonspecific clinical presentation and normal

Table 1

Characteristics of the neonates with osteomyelitis (n = 17).

Case	Age, d	Gender	Location	Time from onset to diagnosis, d	Imaging examination	Bacterial culture		Surgery	Empiric antibacterial treatment	Final antibiotic treatment
						Source	Result			
1	10	Male	Tibia	14	X-ray: soft tissue swelling, periosteal reaction, bone destruction in left tibia. MRI: soft tissue swelling, tibial cortex not smooth, periosteal hyperplasia, uneven medullary cavity with low T1 and T2. US: subperiosteal abscess (1.3 × 0.8 cm) in left leg.	Blood, pus	MSSA	Yes	Vancomycin + Ceftriaxone sodium	Vancomycin + Ceftriaxone sodium
2	20	Female	Humerus	20	X-ray: soft tissue swelling, metaphyseal rarefaction, periosteal reaction in left humerus.	Pus	MSSA	Yes	Vancomycin + Amoxicillin sodium sulbactam sodium	Vancomycin + Amoxicillin sodium sulbactam sodium
3	19	Male	Femur	24	X-ray: soft tissue swelling, periosteal hyperplasia, uneven bone density in left femur.	Pus	Negative	Yes	Vancomycin + Cefotiam hydrochloride	Vancomycin + Cefotiam hydrochloride
4	10	Male	Femur	14	X-ray: periosteal reaction, bone destruction in the left distal femur. US: subperiosteal abscess (3.8 × 3.1 cm) in left leg.	pus	*K pneumoniae*	Yes	Vancomycin + Meropenem	Meropenem
5	16	Male	Femur	4	X-ray: soft tissue swelling, periosteal reaction in the left femur.	Blood	*S pneumoniae*	Yes	Cefotaxime sodium + Oxacillin	Cefoperazone sodium sulbactam sodium + Oxacillin
6	19	Female	Humerus, shoulder blade	5	X-ray: no significant change in bone quality in left humerus on admission. Two weeks later, periosteal reaction was found.	Blood	MSSA	No	Vancomycin + Cefotaxime sodium	Vancomycin + Cefotaxime sodium
7	13	Female	Skull	15	CT: soft tissue swelling and gas bubbles, bone destruction in right parietal bone. MRI: soft tissue swelling, unclear signaling of partial cranial.	Pus	*E coli*	Yes	Piperacillin sodium tazobactam	Piperacillin sodium tazobactam
8	1	Male	Maxilla	17	CT: bone destruction in the right maxilla. MRI: soft tissue swelling, subcutaneous nodular abnormal signal in right face.	Blood, pus	MRSA	No	Vancomycin + Ceftriaxone sodium	Vancomycin + Ceftriaxone sodium
9	13	Male	Humerus	8	X-ray: soft tissue swelling, periosteal reaction, bone destruction in left humerus. CT: soft tissue swelling, periosteal reaction, bone destruction in left humerus. MRI: soft tissue swelling, bone destruction in left humerus.	Blood	Negative	No	Vancomycin + Meropenem	Vancomycin + Meropenem
10	15	Female	Humerus	14	X-ray: normal at admission. Twelve days later, periosteal hyperplasia of the left humerus was found. CT: soft tissue swelling, periosteal hyperplasia in left humerus. US: soft tissue swelling.	Blood	MRSA	No	Vancomycin + Meropenem	Vancomycin + Meropenem
11	19	Female	Femur	7	X-ray: soft tissue swelling, periosteal reaction, decreased bone density in left proximal femur. US: subperiosteal abscess (1.5 × 1.4 cm) in left leg. MRI: soft tissue swelling, femur cortex discontinuous, periosteal reaction in left proximal femur.	Blood, pus	MSSA	Yes	Vancomycin + Meropenem	Vancomycin + Meropenem
12	7	Male	Phalanx	11	X-ray: soft tissue swelling, bone destruction in right thumb phalanx.	Blood, pus	MSSA	Yes	Cefotaxime sodium + Amoxicillin sodium sulbactam sodium	Cefotaxime sodium + Amoxicillin sodium sulbactam sodium
13	17	Male	Iliac, fibula, tibia, ischial, radial, pubic	7	X-ray: soft tissue swelling, bone destruction in right fibula, tibia, iliac, ischial, radial, pubic, and periosteal reaction in left fibula, tibia.	Pus	MRSA	Yes	Vancomycin + Ceftriaxone sodium	Vancomycin + Ceftriaxone sodium
14	20	Male	Humerus	10	X-ray: bone destruction, periosteal reaction in left humerus. US: bone echo loss in left proximal humerus. MRI: soft tissue swelling, detach of cortical bone continuity in left humerus.	Blood	MSSA	No	Vancomycin + Ceftriaxone sodium	Vancomycin + Ceftriaxone sodium
15	28	Male	Tibia, fibula	13	X-ray: normal at admission. Ten days later, bone destruction of the right distal tibia was found. MRI: significant edema of the soft tissue and destruction of the distal tibia and periosteal reaction of the distal tibia and fibula.	Blood	Salmonella	No	Meropenem	Meropenem
16	26	Male	Maxilla	2	CT: soft tissue swelling of the right eyelid.	Blood, pus	MSSA	Yes	Vancomycin + meropenem	Vancomycin + meropenem
17	3	Female	Femur	21	X-ray: soft tissue swelling, periosteal reaction in left proximal femur. US: subperiosteal abscess (2.7 × 1.9 cm).	Pus	Negative	Yes	Cefmenoxime	Cefmenoxime

CT = computer tomography, MRI = magnetic resonance imaging, MRSA = Methicillin-resistant *Staphylococcus aureus*, MSSA = *Staphylococcus aureus*, US = ultrasound.

Table 2

Comparison of the surgical and non-surgical groups.

	Surgical group (n = 11)	Non-surgical group (n = 6)	*P*
Age, d	14.55 ± 6.65	16.0 ± 8.99	.62
WBC, 10^9/L	23.39 ± 8.66	15.28 ± 3.95	.04
Neutrophils, 10^9/L	13.24 ± 6.66	8.48 ± 3.52	.55
Lymphocytes, 10^9/L	7.14 ± 2.2	5.02 ± 1.62	.69
PLTs, 10^9/L	525.9 ± 270.89	468.47 ± 189.32	.76
NLR	1.91 ± 0.87	1.89 ± 1.11	.96
CRP, mg/L	74.52 ± 58.22	83.33 ± 40.60	.92
Hospital stays, d	21.73 ± 10.20	31.33 ± 7.06	.06
Predisposing factors			.46
Yes	3	3	
No	8	3	
Culture			.51
Positive	9	5	
Negative	2	1	
Gender			.91
Male	7	4	
Female	4	2	
Location			.57
Long bone	8	5	
Others	3	1	

CRP = C-reactive protein, NLR = neutrophil-to-lymphocyte ratio, PLTs = platelets, WBC = white blood cell.

Table 3

Comparing osteomyelitis findings, therapies, and outcomes in reports by Knudsen and Hu and by our group.

	Hu et al (7 cases)	Knudsen et al (34 cases)	Our report (17 cases)
M/F	6/1	NA	11/6
Age, d	10–23	8–28	1–28
Predisposing factors	NA	Prematurity: 7 cases Skin/umbilical sepsis: 7 cases Delivered by Caesarean section (1 premature): 6 cases Significant jaundice (2 premature): 4 cases Pneumonia: 2 cases Meningitis: 1 case	Chorioamnionitis: 2 cases Delivered by vacuum extraction and accompanied with clavicle fracture: 1 case Infectious cephal hematoma: 1 case
Symptoms	All patients had limitation of limb movement and fever	Most cases included swelling and pseudoparalysis	Most cases included redness or swelling
Location	Femur: 4 cases Humerus: 1 case Tibia and femur: 1 case Maxilla: 1 case	Proximal femur/hip: 19 cases Proximal humerus/shoulder: 8 cases Distal humerus: 1 case Olecranon/elbow: 2 cases Distal femur/knee: 6 cases Proximal tibia: 5 cases Calcaneus/subtalar: 1	Humerus: 5 cases Femur: 5 cases Tibia: 3 cases Maxilla: 2 cases Shoulder blade: 1 case Phalanx: 1 case Iliac/fibula/ischial/radial/pubic: 1 case Skull: 1 case
Blood routine	White blood cell count and neutrophil ratio were normal in 5 cases	NA	Most of the neonates had higher levels of white blood cells
Blood culture	*S aureus*: 5 cases *K pneumoniae*: 1 case *Enterobacter cloacae*: 1 case	*S aureus*: 18 cases *Haemolytic streptococcus*: 7 cases	*Staphylococcus*: 10 cases *Salmonella*: 1 case *S pneumoniae*: 1 case *K pneumoniae*: 1 case *E coli*: 1 case
X-ray	Only 2 cases had abnormal discovery on day 15	Thirty four of 42 sites of infections were noted	Three of 11 had no pathological findings on x-ray at the onset of the disease
MRI	Positive rate: 100%	NA	Positive rate: 100%
Treatment	All received anti-infective treatment, only 1 patient underwent surgical drainage	All received anti-infective treatment, and 30 patients underwent surgical drainage	All received anti-infective treatment, and 11 patients underwent surgical drainage
Follow-up	No sequelae with a follow-up period of 6 months	Eight cases had different degrees of sequelae with the average follow-up period of 43 months (range 1–12 years)	No sequelae with a mean follow-up period of 49.47 ± 23.43 months

MRI = magnetic resonance imaging, NA = not available.

plain radiographs in the early period. The manifestation of typical osteomyelitis includes redness or swelling at local sites or limited activity and fever. However, 3 patients in our study presented with only slight swelling or excessive crying without fever, and there were no pathological findings of x-ray at disease onset. Moreover, typical changes in x-ray or MRI were found after 1 to 2 weeks. The average time from onset to diagnosis was 12 days. Consequently, diagnosis and effective antibiotic treatment were delayed. Osteomyelitis should be considered in the differential diagnosis when neonatal sepsis is present, especially for neonates with local redness and swelling. Neonates whose x-rays are normal should be followed up closely.

Early changes on x-ray include periosteal reaction, lytic lesions, joint effusions, and destructive bone changes that would appear approximately 7 to 14 days after disease onset.[10,11] Similar to other reports, we found that the most common sites for neonatal osteomyelitis were the femur and humerus. There are also case reports of osteomyelitis of the mandible, iliac, rib, and vertebral bones in neonates.[12–15] Moreover, MRI is more sensitive for the early diagnosis of osteomyelitis, complicated abscesses, and related infection of soft tissues. Ultrasound evaluation is a useful diagnostic tool for identifying soft tissues swelling, periosteal elevation, and fluid collection adjacent to the affected bone.[16–18] Additionally, laboratory tests could provide more information to determine the condition of the patients. In our study, it was demonstrated that higher WBC counts were found in patients requiring surgery, indicating that we should be aware of the increased risk of surgery in neonates with high WBC count.

It has been reported that the most frequently isolated organism in neonates with osteomyelitis is *S aureus*, which is responsible for up to 70% to 90% of the cases.[8,16] Other microorganisms, including *Streptococcus agalactiae*, *E coli*, *Klebsiella*, and *Candida albicans*, are recognized as potential pathogens. In our study, we also found that the most common bacteria were in the *Staphylococcus* genus, including *S aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA), accounting for 71.43% of the cases. In addition, *Salmonella* was isolated from 1 patient, which has rarely been reported in neonates. Depending on the neonatal osteomyelitis pathogen, if neonatal osteomyelitis is suspected, combined antibiotic therapy for *Staphylococcus* and Gram-negative bacteria is recommended, while oxacillin or vancomycin are recommended for use against methicillin-resistant *S aureus* (MRSA).[19] Castellazzi et al[8] suggested that empirical treatment for neonatal osteomyelitis should include oxacillin with the addition of gentamicin.

There is no doubt that acute osteomyelitis requires prompt anti-infective treatment, starting with intravenous antibiotics. Traditionally, children with acute osteomyelitis receive intravenous antibiotic therapy for 4 to 6 weeks.[20] The duration and routes of administration of antibiotics is currently under debate. Some authors have suggested that a short course of intravenous therapy with a subsequent shift to oral administration in uncomplicated cases appears to be effective and safe.[6,7] However, there has been few randomized trials about neonatal osteomyelitis. In the randomized trial of Kaplan et al[21] including 23 children aged 1 month to 15 years diagnosed with acute osteomyelitis, they addressed that clindamycin administered intravenous until the patient was afebrile for 3 consecutive days and then orally for approximately 4 weeks was an alternative to nafcillin/methicillin in the therapy of *S aureus* osteomyelitis in children. More studies are needed to confirm these results. In our study, most of the patients underwent intravenous antibiotic therapy for >3 weeks. Of course, the duration of antibiotics should be individualized to treat bacteria in different regions and should consider patient age, clinical status, and inflammatory markers.

In addition to anti-infective treatment, surgery plays a key role in the treatment of acute osteomyelitis. Biological samples that are useful for identifying the etiologic agent can be obtained at surgery. Chou and Mahadev[22] found that early surgical intervention for acute bacterial osteomyelitis in children increased the diagnostic yield with cultures. Moreover, in cases with abscess or joint involvement, surgeons can remove the demineralized bone and clean the surrounding soft tissue; surgery can also improve the penetration of the antibiotics at the site of infection and reduce the bacterial load in surgical drainage, thereby reducing the risk of permanent damage and severe sequelae. Surgery is performed in up to 50% of osteomyelitis in children.[22] In our study, 64.7% (11/17) of patients received surgical intervention combined with antibiotics. Hospital stays for these patients were shorter than those of neonates without surgery. We believe surgical intervention is effective for patients with joint involvement or abscesses.

Our study had some limitations that must be considered. First, the present study was retrospective in nature and a single-center experience. Second, due to the limited number of patients, external validation was not performed. Therefore, future studies should be performed to evaluate the benefits of surgery and different treatment modalities for neonatal osteomyelitis.

In conclusion, awareness of osteomyelitis and knowledge of the clinical and radiographic findings at presentation allow for early diagnosis. Combination of antibiotic therapy and adequate surgical intervention is suggested for neonatal osteomyelitis, especially for patients with a high WBC count.

Author contributions

Conceptualization: Canyang Zhan.
Data curation: Canyang Zhan.
Formal analysis: Bo Zhou, Jing Du, Lihua Chen, Canyang Zhan.
Funding acquisition: Canyang Zhan, Bo Zhou.
Investigation: Bo Zhou, Lihua Chen, Canyang Zhan, Jing Du.
Methodology: Bo Zhou, Lihua Chen.
Project administration: Bo Zhou.
Resources: Jing Du.
Software: Jing Du, Lihua Chen.
Supervision: Canyang Zhan, Jing Du, Lihua Chen.
Validation: Lihua Chen.
Visualization: Lihua Chen.
Writing – original draft: Jing Du, Bo Zhou, Lihua Chen.
Writing – review & editing: Canyang Zhan.

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