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Research Article

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Characterization of 38 Cases of Neurobrucellosis

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Abstract

Aim: *In this study, we thoroughly examine and discuss the clinical features, laboratory findings, treatment, and recovery of 38 neurobrucellosis cases. Additionally, we provide insights into the most recent research advances in the field of neurobrucellosis.*

Materials and Methods: *In this study, we collected general data, clinical characteristics, ancillary tests, and treatment plans of 38 cases of neurobrucellosis diagnosed and treated at the General Hospital of Ningxia Medical University from March 2012 to December 2022.*

Results: *Among the 38 cases, 25 were male, and 23 had a clear history of cattle and sheep exposure. The most common clinical manifestations were fever (81.58%) and headache (76.32%). Brucella agglutination test was positive in 37 patients, and 37 patients showed increased protein in the cerebrospinal fluid. All 38 patients had a complete blood routine, with 11 cases showing abnormal white blood cell counts. Among the 29 patients who underwent cranial magnetic resonance imaging, 12 showed abnormalities. There were no in-hospital deaths among the patients.*

Conclusion: *Neurobrucellosis exhibits diverse clinical manifestations and can be difficult to differentiate from tuberculous meningitis. Routine tests such as complete blood routine and cranial magnetic resonance imaging have limited diagnostic value for neurobrucellosis and are prone to clinical misdiagnosis and underdiagnosis. Patients with a history of contact with cattle and sheep in nearby grazing areas and presenting with symptoms such as fever and headache should undergo laboratory tests such as Brucella agglutination test or cerebrospinal fluid culture to establish an early and accurate diagnosis. Prompt initiation of treatment with doxycycline, rifampin, and ceftriaxone sodium triple therapy against Brucellosis is crucial in areas close to pastoral regions with potential cattle and sheep exposure.*

Keywords: Neurobrucellosis, Brucellosis, Meningitis, Cerebrospinal Fluid, Magnetic Resonance Imaging.

List of abbreviations:
Neurobrucellosis: NB
Cerebrospinal Fluid: CSF

1. Introduction

Brucellosis, also known as undulant fever, is the most common zoonotic disease affecting both humans and animals. The primary animal reservoirs for human infection are sheep, cows, and pigs [1, 2] , with higher prevalence in regions with active agricultural and pastoral activities. Each year, over 500,000 new cases are reported [1]. The countries with the highest brucellosis incidence include Syria, Mongolia, Iraq, Tajikistan, and Saudi Arabia, while the most affected countries in terms of the number of cases are Mexico, China, Greece, and Brazil [3]. Brucellosis commonly spreads in developing countries with advanced livestock farming and poor hygiene conditions. Human infections often occur through contact with infected cattle or sheep, or consumption of undercooked meat or dairy products [4]. The incidence and mortality rates of brucellosis have been gradually increasing in recent years, posing significant threats to local residents and livestock development. Approximately 5% of brucellosis patients may develop neurobrucellosis (NB), which affects the central nervous system [3].

NB exhibits severe and diverse clinical manifestations, including meningitis, encephalitis, meningoencephalitis, radiculitis, myelitis, subarachnoid hemorrhage, peripheral and cranial neuropathies, and psychiatric abnormalities [5]. This complexity makes it

challenging to differentiate NB from other neurological disorders [6]. Currently, there are no definitive diagnostic criteria for NB, and clinical diagnosis often relies on identifying Brucella in blood or cerebrospinal fluid (CSF) samples [7]. However, this approach may lead to delays in early NB treatment. This study analyzes clinical data from 38 NB cases to summarize their clinical features and laboratory characteristics, aiming to provide insights for early diagnosis and timely treatment of NB in the future.

2. Materials and Methods

in this study, we collected general information, clinical characteristics, auxiliary examinations, and treatment protocols of 38 neurobrucellosis (NB) cases diagnosed and treated at Ningxia Medical University General Hospital from March 2012 to December 2022. Ningxia Medical University General Hospital is located in Yinchuan, the capital city of the Ningxia Hui Autonomous Region in the China, in close proximity to pastoral areas.

The inclusion criteria for collecting NB cases were as follows: 1) presence of symptoms or signs indicative of central nervous system involvement; 2) positive Rose Bengal plate test/positive Brucella agglutination test (serum titer >= 1:100)/isolation and culture of Brucella from blood or cerebrospinal fluid (CSF); 3) response to specific treatment against Brucella; 4) CSF changes consistent with NB characteristics or positive findings in neuroimaging; 5) exclusion of other similar diseases.

Statistical methods involved describing continuous data using median, mean, maximum, minimum, and quartiles, while categorical variables were described using frequencies and percentages.

3. Results

General information

All 38 NB cases were hospitalized patients, including 25 males and 13 females, with ages ranging from 17 to 71 years and an average age of approximately 38 years. The duration of the illness varied from 1 week to 1 year. All patients met the diagnostic criteria for NB. Among the 38 cases, 22 had a documented history of exposure to cattle or sheep. The main clinical manifestations in the 38 patients were headache and fever, as shown in Table 1.

Symptoms / Signs	Case	Percentage
Fever	31	81.58%
Headaches	29	76.32%
Nausea and vomiting	15	39.47%
Joint pain	9	23.68%
hyperhidrosis	10	26.32%
Positive meningeal stimulation sign	11	28.95%
Decreased muscle strength	11	28.95%
Blurred vision	12	31.58%
Peripheral nerve damage	7	18.42%
Hearing loss	5	13.16%
slurred speech	4	10.53%
Mental Behavior Abnormalities	3	7.89%
delirium	3	7.89%

Table 1: Symptoms and signs in 38 patients with NB.

Auxiliary examinations

38 patients underwent lumbar puncture, with both CSF (Cerebrospinal Fluid) culture and CSF Brucella agglutination test performed in all cases. 7 patients had positive results in CSF culture, while 37 patients tested positive in the Brucella agglutination test. Additionally, 10 patients had blood cultures for Brucella, with 1 positive result. For patients who underwent multiple CSF examinations, only the results of the first CSF test after admission were considered, excluding other CSF tests to avoid interference from treatment factors. Please refer to Table 2 for specific details.

Item	Case	Percentage
Normal brain pressure（80~180 mmH_2O）	13	34.21%
brain pressure 180~330mmH_2O	16	42.11%
brain pressure >330mmH_2O	8	21.05%
brain pressure <80 mmH_2O	1	2.63%
Glucose normal（2.5-4.5mmol/L）	8	21.05%
Glucose <2.5mmol/L	30	78.95%
Normal protein（0.14-0.45g/L）	1	2.63%
Protein >0.45g/L	37	97.37%
Chloride normal（120-132mmol/L）	6	15.79%
Chloride <120mmol/L	32	84.21%
Normal white blood cell count（0-8个/mm^3）	1	2.63%
Leukocyte count 9-49个/mm^3	6	15.79%
Leukocyte count >49个/mm^3	31	81.58%
Lymphocyte-dominated（Percentage >70%）	35	92.11%
Mixed cell reaction	3	7.89%
Normal color	28	73.68%
Slightly yellow color	10	26.32%
Positive Pan's test	18	47.37%

Table 2: CSF performance in 38 patients.

All 38 patients completed the blood routine examination. Among them, 7 had increased white blood cell counts, 4 had decreased counts, and 27 had normal levels (4-10 * 10^9). Within the blood routine examination, 20 patients showed an increased percentage of neutrophils, 3 had a decreased percentage, 3 had an increased percentage of lymphocytes, 11 had normal percentages of both neutrophils and lymphocytes, and 1 had an increased percentage of monocytes.

Thirteen patients underwent blood cultures for Brucella, with 2 positive results. All 38 patients completed the Brucella agglutination test, with 37 showing positive results. Statistical data for continuous variables such as CSF, blood routine white blood cell counts, and body temperature for the 38 patients can be found in Table 3.

	Average	Median	Minimum value	Maximum value	Quartile（25%, 75%）
Maximum brain pressure mmH_2O	210.06	185.00	75.00	330.00	150.00, 300.00
CSF Protein g/L	2.92	2.03	0.20	12.00	0.72, 3.95
CSF Glucose mmol/L	2.92	2.03	0.80	3.80	1.58, 2.90
CSF chloride mmol/L	113.36	111.60	102.30	128.00	113.13, 119.33
CSF leukocytes 个/mm^3	175.14	136	0.00	420.00	68.00, 280.75
CSF monocytes 个/mm^3	6.56	4. 00	0.00	28.00	2.00, 8.00
CSF neutrophils pcs/mm3	37.30	22.00	0.00	170.00	10.50, 55.50
CSF lymphocytes pcs/mm^3	131.56	106.00	0.00	350.00	46.50, 191.25
Blood count white blood cells *10^9	7.41	6.67	2.98	22.90	5.47, 8.13
Maximum body temperature ℃	38.18	38.55	36.30	40.00	37.00, 39.00

Table 3: Selected continuous variable laboratory tests in 38patients

Twenty-nine patients underwent cranial MRI examinations. Among them, 7 had involvement of bilateral occipital lobes (Figure 1) and exhibited symptoms of meningitis, 4 had involvement of the right frontal lobe (Figure 2) and showed symptoms of brain abscess, and 1 had left thalamic infarction (Figure 3) caused by NB-induced cerebral vasculitis.

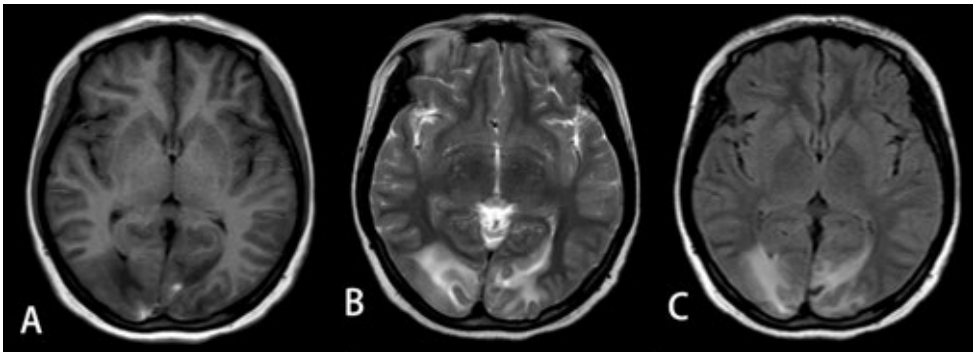

Figure 1: A - Axial T1-weighted image shows bilateral occipital lobe patchy low signal and a small amount of high signal. B - Axial T2-weighted image indicates bilateral occipital lobe patchy high signal lesions. C - Axial T2 FLAIR demonstrates bilateral occipital lobe patchy high signal lesions.

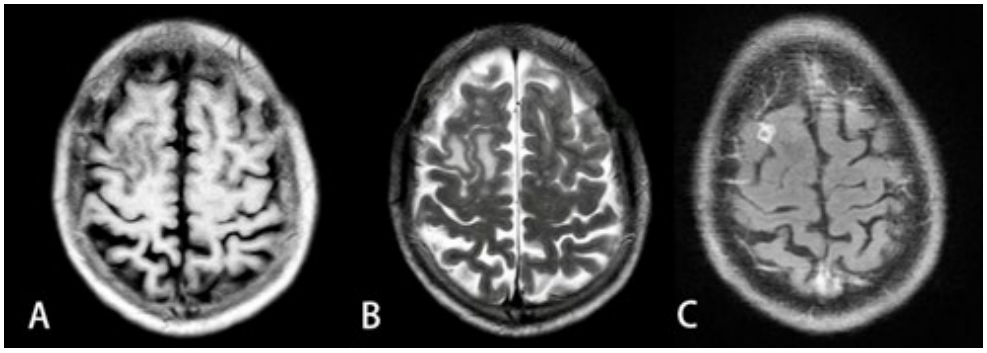

Figure 2: MRI Images of a Case of Neuroblastoma (NB) Resulting in Right Frontal Lobe Brain Abscess. A: T1-weighted image showing a low-signal lesion in the right frontal lobe. B: T2-weighted image displaying a high-signal lesion in the right frontal lobe. C: Enhanced T1-weighted image revealing a ring-enhancing lesion in the right frontal lobe.

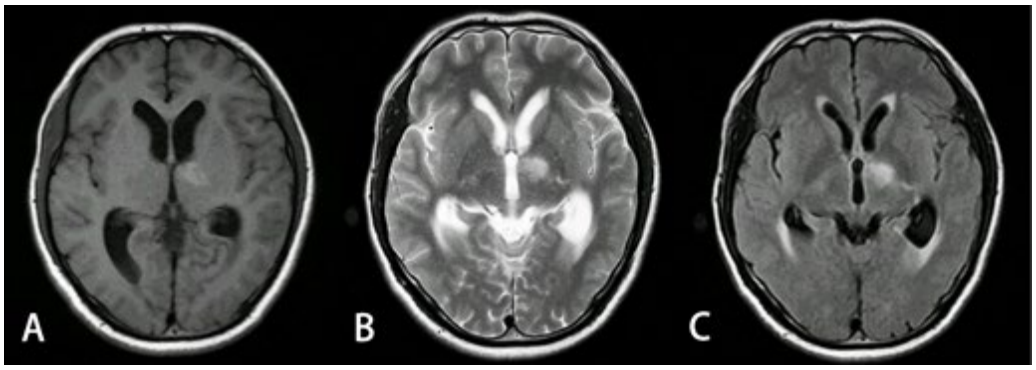

Figure 3: T1WI showing cerebral vasculitis due to NB, resulting in left thalamic infarction. Panel A shows T1WI, panel B shows T2WI, and panel C shows T2flair.

Ten individuals underwent electromyography (EMG) examinations, of whom five exhibited peripheral nerve damage. However, among these cases, the peripheral nerve damage in two individuals may not be related to the infection of neurobrucellosis.

Treatment and Outcome

Out of the 38 patients, 30 showed improvement after treatment. Seven patients requested transfer to another hospital for treatment as per the request of their families and themselves. One patient abandoned treatment due to economic reasons, and the treatment outcomes for those who transferred or abandoned treatment are unknown.

All 38 diagnosed patients received doxycycline combined with rifampicin for anti-Brucella treatment. Nineteen patients received ceftriaxone for anti-infection purposes, 5 received steroids for anti-inflammatory treatment, and 5 were administered levofloxacin for anti-infection purposes.

During the follow-up period, 12 patients were lost to contact, 2 had

residual vision impairment, 2 had residual sensorineural hearing loss, and 4 were left with limb paralysis.

4. Discussion

Our hospital is located in the Ningxia Hui Autonomous Region, near pastoral areas, which are considered high-risk regions for this disease. Among the cases in this study, 23 individuals had a clear history of contact with cattle and sheep, and 25 were males, resulting in a male-to-female ratio of 25:13, possibly due to the higher likelihood of males having contact with cattle and sheep.

The exact pathogenesis of NB remains unclear. However, Ana-M. Rodriguez et al. proposed a potential mechanism where Brucellosis triggers neuronal cell loss by activating microglia. This activation of microglia may lead to neurological deficits and ultimately contribute to the development of NB [8, 9]. Foreign scholars have put forward the hypothesis that Brucellosis induces endothelial cell activation, facilitating the transmigration of neutrophils and monocytes across the blood-brain barrier. This process may lead to intracranial inflammation, ultimately causing corresponding neurological deficits. However, it's important to note that the exact mechanisms and interactions involved in this process are still subject to ongoing research and investigation [10]. Additionally, some studies have proposed that Brucellosis may lead to the corresponding clinical manifestations by directly releasing endotoxins, which can cause damage to neuronal cells. However, further research is required to fully understand the precise mechanisms through which Brucellosis affects neuronal cells and the extent of its impact on clinical outcomes [11]. Immunocompromise is considered as one of the potential causative factors of NB. A case of neurological damage caused by Brucellosis infection in a patient with systemic lupus erythematosus, who was undergoing long-term hormone and immunosuppressive drug treatment, resulting in death, has been documented in the literature. This case highlights the importance of understanding and managing immunocompromised conditions in the context of Brucellosis infection to prevent severe neurological outcomes [12].

The clinical presentation of NB varies and often shows a subacute and chronic onset. According to some foreign scholars, fever with headache is considered the most common clinical manifestation [6], while meningitis and encephalitis are frequently observed as the main clinical features. Additionally, cerebral nerve involvement, polyneuropathy, and paraplegia are noted as the primary complications in NB patients [5, 11]. In our group of patients, fever and headache were the prevailing symptoms, accounting for approximately 3/4 of the total cases. The highest recorded temperature reached 40°C, with a mean temperature of 38.55°C. Elevated body temperature is associated with an increased risk of neurological dysfunction, necessitating early symptomatic management, such as hypothermia [13, 14]. Moreover, only 11 cases in the group displayed signs of meningeal irritation, which may not be a common clinical manifestation of NB but can serve as a characteristic indication of intracranial infection.

Peripheral nerve damage in NB patients often affects the spinal nerves, primarily involving the lower extremities. Additionally, it can also extend to brain nerves, such as the actinic, auditory, facial, and optic nerves [15, 16]. In this study, peripheral nerve damage possibly associated with NB infection was observed in three cases. The first patient was a 24-year-old male who exhibited bilateral peroneal and posterior tibial nerve damage based on electromyography. Physical examination revealed grade 5 muscle strength in both lower limbs, and rheumatology-related tests showed no significant abnormalities, suggesting the possibility of bilateral peroneal and posterior tibial nerve damage due to NB infection. The second patient, a 29-year-old male, displayed varying degrees of damage to bilateral peroneal, bilateral posterior tibial, bilateral median, and bilateral ulnar nerves based on electromyography. Despite previously being in good health, the patient had grade 5 muscle strength in the upper limbs and grade 4 in the lower limbs, with no evident abnormalities in rheumatology or tumor marker tests upon admission. The third patient, a 16-year-old female, presented with damage to bilateral posterior tibial and bilateral median nerves according to comprehensive electromyography. All her limbs exhibited grade 5 muscle strength, and she had a history of good health with no rheumatology-related diseases or diabetes.

A subset of NB patients may exhibit psychiatric behavioral abnormalities, including anxiety, depression, agitation, personality disorders, and slurred speech [15, 17, 18]. Studies suggest that the most common psychiatric behavioral abnormalities in NB patients are behavioral changes, cognitive impairment, depression, and anxiety, while apathy and mania are less frequent [19]. Importantly, depression, cognitive impairment, and psychiatric behavioral abnormalities caused by NB can often be improved through antibiotic treatment, eliminating the need for additional antidepressant or psychiatric medications [18, 20]. In our group, three cases presented with psychobehavioral abnormalities. One patient experienced intermittent episodes of slurred speech, disorientation, and difficulty recognizing relatives. Another case displayed question-and-answer incoherence, self-talk, indifferent expressions, and intermittent irritability, consistent with bipolar disorder with depression as the primary cause. The third case presented psychotic behavior abnormalities with manic episodes as the main cause. All three cases demonstrated significant improvement in their psychotic behavior abnormalities after receiving anti-Brucella treatment.

CSF examination is commonly used as an adjunctive test for NB. Some scholars suggest that in the early stages of the disease, similar to viral meningitis, elevated CSF protein is predominant, while in the later stages, similar to tuberculous meningitis, elevated CSF protein along with decreased sugar and chloride levels are more common [16, 21, 22]. In our study, we found that elevated CSF protein had higher sensitivity for diagnosing NB compared to CSF glucose and CSF chloride. The mean, median, and quartiles of CSF protein were higher than the normal range, with 97.37% of patients showing elevated CSF protein levels. However, it's crucial to note that other viral infections may also cause elevated

CSF protein, making it insufficient as a sole diagnostic criterion for NB. Therefore, it should be combined with other evidence for an accurate diagnosis. Additionally, our results indicated that most NB patients had reduced CSF sugar and chloride levels, consistent with the late stage of NB.

This observation suggests that some patients might not seek timely medical attention due to the lack of obvious symptoms in the early stage. CSF cytology showed increased leukocytes in most cases, mainly lymphocytes, which is in line with current scholarly opinions [23, 24], Furthermore, 81.58% of patients had cerebrospinal fluid greater than 49, which could be used as evidence to differentiate NB from general non-infectious encephalitis [25]. Analyzing CSF data also revealed that increased intracranial pressure may be an important manifestation of NB, with 61% of patients having cerebral pressure greater than 180 mmH2O and 19.44% having cerebral pressure greater than 300 mm H2O. Excessive intracranial pressure can lead to clinical manifestations such as headache, nausea, vomiting, and even brain herniation, which can be life-threatening [26]. Differentiating NB from tuberculous meningitis should be given high priority in clinical practice since their CSF biochemical and cytological examinations are similar [11, 23]. The positivity rates of CSF and blood culture in NB patients are generally low, being 18.4% and 21.7%, respectively [5]. The low positive CSF culture rate could be due to a low bacterial load in the patient's CSF or the prior use of antibiotics before CSF culture [15, 27]. In contrast, the positive rate of Brucellosis agglutination test can reach 97.22% and remains one of the main diagnostic bases for NB [23, 28] . Though Brucellosis CSF culture and blood culture have low sensitivity, they still hold significance in confirming the diagnosis of neurotype brucellosis due to their high specificity. Furthermore, CSF macrogenome sequencing has been reported to be a helpful tool for diagnosing NB, especially when routine infectious disease examination shows no significant abnormalities. This provides a new approach to the diagnosis of NB [29, 30] and a powerful method for differentiating NB from tuberculous meningitis [31].

Imaging, particularly MRI, holds significant value in diagnosing neurological brucellosis [32]. The MRI manifestation of NB shares similarities with general inflammatory lesions, initially showing high signal intensity in T2-weighted images (T2WI) and low signal intensity in T1-weighted images (T1WI). In later stages after enhancement, enhanced central necrotic areas may become apparent. The MRI presentation of NB is diverse, and some scholars categorize it into four groups: normal, inflammatory, white matter changes, and vascular inflammatory changes [1, 2]. In our study group, 29 patients underwent cranial MRI, where 7 demonstrated brain inflammation, 4 had white matter changes, 1 exhibited cerebral vascular changes, and the remaining 17 showed no significant abnormalities in cranial MRI. Niloofar et al. further classified the MRI manifestations of neurobrucellosis into five categories: meningitis, meningoencephalitis, inflammatory demyelination, abscess formation, and pseudotumor type. Diagnosing NB solely based on MRI findings may not be highly specific, but it can aid in differentiating it from cerebrovascular disease and cerebral demyelination changes. Moreover, MRI can help assess the extent of neurological involvement and the presence of brain abscesses, providing valuable information for subsequent treatment decisions.

The mortality rate of NB is generally low, ranging from 0% to 5%, and it is considered a curable disease with most patients showing improvement after regular antimicrobial therapy. However, there have been reported cases of death resulting from the failure of timely diagnosis and treatment [12]. Currently, the treatment for NB involves the use of powerful antibiotics, such as rifampicin, ceftriaxone, doxycycline, levofloxacin, and streptomycin. Typically, a combination of two to three antibiotics is prescribed for a period of 6 to 9 months [34-36]. In cases where Brucellosis is combined with craniocerebral infections, triple antibacterial therapy with doxycycline, rifampicin, and ceftriaxone sodium (or quinolones for those allergic to ceftriaxone sodium) is recommended. The treatment should continue until clinical manifestations and test results normalize, usually for more than 6 weeks [34, 35, 37]. In our group of patients, a total of 38 cases were treated with doxycycline combined with rifampicin for the treatment of Brucellosis, most commonly for a duration of 3 to 6 months. Additionally, 19 patients were given ceftriaxone sodium, and 5 patients received levofloxacin in combination with anti-Brucella treatment. Following the anti-Brucella treatment, 28 cases showed improvement, while the outcomes of the remaining 8 cases were unknown due to their transfer to other hospitals. It's essential to continue monitoring and ensuring proper treatment for NB patients to achieve positive outcomes and prevent complications. Timely diagnosis and appropriate therapy play a crucial role in enhancing patient prognosis and reducing the risk of adverse outcomes.

5. Conclusion

The clinical manifestations of NB can vary, making it challenging for clinicians to differentiate it from tuberculous meningitis, leading to potential missed or misdiagnosed cases. To improve early detection and accurate diagnosis, patients with a history of contact with cattle and sheep in nearby grazing areas and presenting symptoms such as fever and headache should undergo laboratory tests, such as Brucellosis agglutination test or cerebrospinal fluid culture, as soon as possible. Early and accurate diagnosis is crucial to initiate timely treatment. Therefore, if NB is suspected, clinicians should promptly begin triple antibacterial therapy with doxycycline, rifampin, and ceftriaxone sodium. This approach can help improve patient outcomes and reduce the risk of complications associated with NB.

Declarations

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Ethics approval

The study was approved by the Institutional Ethics Committee of General Hospital of Ningxia Medical University, Yinchuan, China. Ethics No：KYLL-2023-0491

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