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ORIGINAL PAPER

Clinical features, treatment and prognosis of patients with endogenous infectious endophthalmitis

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Abstract

Purpose To investigate whether the clinical characteristics, treatment and prognosis of endogenous infectious endophthalmitis (EIE) have changed over the past 5 years.

Methods Retrospectively analyze all articles about EIE published in the PubMed, Web of Science, and Embase databases from 2017 to 2021.

Results A total of 128 patients and 147 eyes (46 left and 60 right) were included in the study. The mean age at diagnosis was 51 ± 19 years. The most common risk factors were diabetes and intravenous drug use. From 2017 to 2021, *Klebsiella* was the most common pathogenic microorganism (22%), and vitreous culture had the highest positivity rate. The most common complaint was blurred vision. The mean visual acuity (logMAR) at onset was 2.84, and the clinical symptoms were vitreal inflammation and opacity (63%), ocular pain (37%), and conjunctival congestion (36%). The ocular inflammation could be reduced by intraocular antibiotics or vitrectomy. However, the visual prognosis, with a mean logMAR of 2.73; only 50% of the eyes reached a visual acuity level of finger count and above. Changes in diagnostics over the past 5 years have mainly manifested as more diverse microorganism culture methods. In addition to conventional culture methods, PCR, sputum culture and aqueous humour culture are also commonly used for the diagnosis of pathogenic bacteria, improving the positive culture rate and visual prognosis.

Conclusion The prognosis of EIE is poor. It is recommended to pay attention to the pathogenic bacteria culture results and accompanying systemic diseases and to diagnose and treat patients as soon as possible.

Keywords Endogenous infectious endophthalmitis · Pathogenic microorganism · Microbial culture · *Klebsiella* · Prognosis

Introduction

Infectious endophthalmitis is a rare but serious inflammation of the eye that affects the retina, uvea, and optic nerve. The inflammation progresses rapidly and often leads to irreversible vision loss. According to the transmission route of the infection source, infectious endophthalmitis can be divided into exogenous and endogenous types. Exogenous infectious endophthalmitis is often caused by the direct entry of pathogenic microorganisms into the eye through puncture wounds, eye surgery, corneal ulcers and perforation. Endogenous infectious endophthalmitis is relatively rare. In 2020, the authors reported that this disease accounted for 2–8% [1] of all endophthalmitis cases. Endogenous infectious endophthalmitis refers

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to the infection of other parts of the body and the entry of pathogenic microorganisms, such as fungi or bacteria, into the eye through the blood, thus causing extensive ocular inflammatory reactions, such as conjunctival congestion, anterior chamber cells, retinitis, and anterior chamber pus. Endogenous infectious endophthalmitis is often accompanied by inflammatory lesions in other parts of the body. The disease may be associated with an underlying, potentially life-threatening systemic infection or risk factor for infection, including recent hospitalization or indwelling catheter or intravenous drug use, and is more commonly seen in patients with one or more immunosuppressive factors. Endogenous infectious endophthalmitis is mainly diagnosed by microbial culture. However, due to the low positive culture rate of microorganisms, approximately 50% [2], endogenous infectious endophthalmitis diagnosis can be delayed. Recent progress has been made in improving methods for detecting microorganisms, including aqueous humour culture, vitreous culture, and PCR. However, there is no consensus regarding which of these detection methods yields a higher positivity rate. Systemic static or intravitreal injection of antibiotics and surgical removal of severely infected lesions are the main treatment methods for infectious endophthalmitis, including endogenous endophthalmitis. *Klebsiella pneumoniae*, *Escherichia coli* and *Staphylococcus aureus* were the most common pathogens since 2000 [3, 4]. In our study, *Klebsiella* was the main cause of endogenous bacterial endophthalmitis. The pathogens responsible for fungal endophthalmitis did not change, and Candida remained the most common. With the diversification of detection methods, early diagnosis, timely and effective treatment, and patient prognosis have a close relationship. To determine the latest advances in the diagnosis and treatment of endogenous infectious endophthalmitis, we reviewed the literature published in the last 5 years, detailing the most common pathogenic microorganisms primary infection site, accompanying systemic disease, diganosis methods treatment modalities, and prognosis vision.

Patients and methods

Articles published in English, German, French and other languages between 2017 and 2021 were searched in the PubMed, Web of Science and Embase databases using "endogenous infectious endophthalmitis", "endophthalmitis and infection", "endophthalmitis", "endophthalmitis and treatment", "endophthalmitis and prognosis", "panophthalmitis and clinical manifestations", "endogenous panophthalmia", "endophthalmitis and endogenous endophthalmitis" as the search terms. All articles retrieved were evaluated and selected according to the following criteria. Inclusion criteria were as follows: (1) Case reports diagnosed as endogenous infectious endophthalmitis, with complete records of case data and information of diagnosis and treatment; (2) the case reports in the review, and the medical history data were recorded completely. Exclusion criteria were: (1) animal cases with endogenous infectious endophthalmitis; (2) patients with suspected but not confirmed endogenous infectious endophthalmitis; (3) cases with incomplete patient data (diagnostic methods and test results were not recorded in detail). We collected the basic information of the patient, such as sex, age, pathogenic bacteria, and past medical history, as well as the patient's eye information, such as visual acuity at onset, intraocular pressure, changes under the anterior segmental slit lamp, changes under the fundus microscope, information on auxiliary examination and the diagnosis method, sampling site, choice of antibacterial treatment and surgical treatment, and treatment results. For the purposes of statistical analysis, Snellen vision was converted to a minimum resolution logarithm (logMAR). Nondigital vision was converted to logMAR as follows: count finger 2.0, hand motion 3.0, light sense 4.0, and light sense 5.0. Visual impairment was classified according to the scope of the definition of visual impairment in the International Classification of Diseases (9th Revision—Clinical Revision). The classification criteria were as follows: logMAR in the $[-0.2, 0.5]$ range was (near) normal vision, logMAR in the [0.6, 1.7] range was low vision, and logMAR ≥ 1.8 was (near) blind [5]. This review is in line with the tenets of the Declaration of Helsinki; since this was a retrospective review of published articles, no informed consent was required.

An independent chi-square test was used to analyse the differences among pathogenic microorganisms, eye type and patient sex, the differences in culture mode and the positive culture rate. A P value of less than 0.05 was considered statistically significant.

The statistical software used was IBM SPSS Statistics 27.0.1.

Results

Demographics

A total of 119 articles and 128 cases meeting the inclusion and exclusion criteria were included in this study. Of the 128 patients, 76 were male (59%), 50 were female (39%), and 2 were of unclear sex (2%). The ratio of males to females was 1.5–1. The ages of 2 patients were unknown, 3 were neonates, and specific age data were available for 123 cases (72 males and 50 females). The mean age of the 123 patients was 51 ± 19 years (1–88 years). The mean age for males was 52 ± 19 years (19–88 years) and 51 ± 19 years (1–88 years) for females.

Ocular clinical manifestations

The most common complaints were blurred vision (78%) and eye pain (37%). The logMAR at onset ranged from 0.1 to 5.The mean logMAR at the visit was 2.84. Fifty-four percent of the patients had normal IOP (10–21 mmHg), 28% had high IOP (> 21 mmHg), and 18% had low IOP (< 10 mmHg). Other features included vitreal inflammation and opacity (63%), conjunctival hyperaemia (36%), retinitis (28%), anterior chamber cells (19%), corneal oedema (12%), choroiditis (8%), corneal turbidity (6%), and ciliary hyperaemia (5%) (clinical features are shown in Table 1).

Table 1 Clinical features of patients with endogenous infectious endophthalmitis

Clinical features	Details (%)
Blurred vision	78
Vitreous inflammation and vitreous opacity	63
Eye pain	37
Conjunctival injection	36
Retinitis	28
Cells in the anterior chamber	19
Corneal oedema	12
Choroiditis	8
Corneal opacity	6
Ciliary hyperaemia	5

Pathogenic microorganism

The most common pathogenic organism was *Klebsiella* (28 cases, 22%). Eighteen patients (14%) were infected with (14%) *Streptococcus,* 15 (12%) with *Candida*, 11 (9%) with *Staphylococcus*, 6 (5%) with *Nocardia*, 3 (2%) each with *Cryptococcus, Meningococcus, Fusarium, Aspergillus* and *Serratia marcescens*, 2 with (2%) of *Aeromonas*, and 2 (2%) with of *Pseudomonas aeruginosa and Candida*. *Candida albicans* and *S. aureus, Enterococcus gallinis and Escherichia gallium, E. gallinis and E. gallium*, *S. aureus* and *P. aeruginosa*, and *Bacillus mirariae*, *Enterococcus faecium* and *E. coli* co-infections were each detected in 1 patient (0.78%). There was 1 case each (0.78%) of *Brucella, E. coli, Red yeast, Listeria, Haemophilus influenzae,* yolk bacteria, yeast, *P. aeruginosa, Burkholderia cepacia, Scopulariopsis, Bacillus dermatitidis, Chryseobacterium, Aspergillus fumigatus, Clostridium perfringens, Stenotrophomonas maltophilia, Enterococcus gallium, Mycobacterium tuberculosis*, amoeba and soil mould infection. Seven patients (5%) had no specific pathogenic microorganism information available.

The distribution of pathogenic microorganisms involved in endogenous infective endophthalmitis appeared to differ by sex. Of the 28 patients infected with *Klebsiella*, 68% (19) were male and 32% (9) were female. Among the 18 patients infected with *Streptococcus*, 67% (12 cases) were male, and 33% (6 cases) were female. Independent chi-square test showed no statistical difference and more data may be needed for statistical analysis. The most common primary infection site was a liver abscess. There was no significant difference in the site of primary infection between men and women.

Eye and pathogenic *bacteria*

Among the 128 patients, the left eye was affected in 46 cases (36%), the right eye was affected in 60 cases (47%), both eyes were affected in 19 cases (15%), and 3 (2%) had unknown eye information. Right eye infections are more common in both men and women. In males, 27 (37%) had left eye involvement, 31 (42%) had right eye involvement, and both eyes were involved in 15 (21%). The ratio of left to right eyes

was 0.87:1. In females, left eyes were involved in 19 patients (38%), right eyes in 28 patients (58%), and both eyes in 3 patients (6%). The ratio of left to right eyes was 0.68:1. However, no significant difference was observed by independent Chi-square tests and more data may be needed for statistical analysis (see Table 2 for information on patients and pathogenic microorganisms).

Concomitant systemic disease, past history and pathogenic bacteria

The most common concomitant systemic or pre-existing conditions in patients with endogenous infectious endophthalmitis were fever (34%) and diabetes (32%), followed by intravenous injection (including intravenous fluids) (15%), cancer (11%), liver abscess (10%), pneumonia (9%), and nephritis (2%). Thirty-seven percent of diabetic patients have abscess lesions throughout the body. Among diabetic patients, *Klebsiella* was the most common pathogenic bacterium (51%). Of the 19 patients with a history of intravenous injection (including intravenous fluids), 10 (53%) had used intravenous drugs. Among patients with a history of intravenous injection, the common pathogenic microorganisms were *Candida* (21%), *Serrella marcescens* (16%), and *Streptococcus* (16%). Among the 14 patients with cancer, 1 developed central venous catheter-related bacteremia after rectal cancer surgery, 1 had a central catheter inserted 2 months before the ophthalmology visit (PICC was suspected to be a bacterial source), 1 had pathogenic bacteria isolated from the intravenous catheter, and the rest had no information regarding infectious lesions except for the eye infection. Three patients had a history of nephritis, including pyelonephritis, membranoproliferative glomerulonephritis, and acute pyelonephritis with partial obstructive kidney stones. The relationship between common bacteria and systemic diseases such as pneumonia and liver abscess was further analysed. Liver abscess accompanied by endogenous endophthalmitis was related to *Klebsiella* infection. Among the 13 patients with liver abscesses, except for 1 with no relevant information, all had

Table 2 Basic information about the patients and pathogenic microorganisms

Feature	Details
Age	
Mean age of patients	51 ± 19 years (1–88 years)
Mean age of male patients	52 ± 19 years old (19–88 years old)
Mean age of female patients	51 ± 19 years (1–88 years)
Sex (male/female)	76/50 (59%/39%)
Eyes	
Total left eye/right eye/both eyes	46/60/19 (36%/47%15/%)
Male left eye/right eye/both eyes	27/31/15 (37%/42%/21%)
Female left eye/right eye/both eyes	19/28/3 (38%/56%/6%)
Major pathogenic bacteria	
Klebsiella	28 (22%)
Male left eye/right eye/both eyes	4/9/6 (21%/47%/32%)
Female left eye/right eye/both eyes	4/5/1 (40%/50%/10%)
Streptococcus	18 (14%)
Male/female	12/6 (67%/33%)
Candida	15 (12%)
Staphylococcus aureus	11 (9%)
Nou bacteria	6 (5%)
Cryptococcus	3 (2%)
Meningococcal bacteria	3 (2%)
Sickle bacteria	3 (2%)
Aspergillus	3 (2%)
Serratia marcescens	3 (2%)

Klebsiella. There were 12 patients with pneumonia, 1 with no relevant information, 2 were infected with *Cryptococcus*, 2 with *Candida*, 2 with *Streptococcus*, 1 with *Staphylococcus*, 1 with *Klebsiella*, 1 with *E. gallium*, 1 with *Nocardia*, and 1 with *P. aeruginosa* + *Candida* (see Table 3 for accompanying systemic disease or previous history).

Diagnostic methods

In recent years, microbial culture methods become more diverse. In addition to conventional culture methods such as blood culture, urine culture and vitreous culture, PCR, sputum culture and aqueous humour culture are also commonly used to identify pathogenic bacteria. Blood cultures were performed for 91 of the 128 patients, and 54 (59%) were positive. Sixty-nine patients underwent vitreous culture, and 47 (68%) were positive. Urine culture was performed for 23 patients, and 5 (22%) were positive. Regarding the blood culture, the positive culture rate of *Staphylococcus* was the highest (90%), followed by *Streptococcus* (76%) and *Klebsiella* (70%). In vitreous cultures, the highest positive culture rate was obtained for *Staphylococcus* (100%), followed by *Streptococcus* (90%), *Candida* (70%) and *Klebsiella* (70%). The 5 positive urine cultures were *C. albicans* in 1 patient, *C. albicans* + *S. aureus* in 1 patient, *P. aeruginosa* + *Candida* in 1 patient, *K. pneumoniae* in 1 patient and *Glucococcus aureus* in 1 patient. In addition, PCR, sputum culture, aqueous humour culture and cerebrospinal fluid culture are also used for identifying pathogenic bacteria. Of the 14 patients tested by PCR, 11 (79%) were positive, 3 had *Candida*, 2 had meningococcal infections, and 2 had *Aspergillus*. Among the 14 patients, vitreous samples were collected from 9, and aqueous humour was collected from 1. The positive rate of vitreous samples was 78%. Sputum culture was conducted on 2 patients; 1 was positive for *Nocardia*. Aqueous humour culture was performed for 5 patients, and 4 were positive, 3 for *Streptococcus* and 1 for *Aspergillus*. Cerebrospinal fluid was cultured in 3 cases, and 2 patients were positive. A total of 13 patients underwent blood culture, urine culture and vitreous culture simultaneously; vitreous culture demonstrated the highest positive culture rate (8 cases, up to 62%), and 2 patients had positive blood and urine cultures. Vitreous culture and PCR detection were performed for 8 patients, including 1 vitreous-positive and 5 PCR-positive. A total of 46 patients underwent both blood and vitreous culture, and 19 had positive blood cultures, accounting for 41%. Twenty-nine patients (63%) had positive vitreous cultures. It can be seen that the positivity rates of vitreous culture and PCR are the highest; thus, it is recommended to conduct vitreous culture and PCR detection simultaneously. There was no difference in the positive culture rate among vitreous culture, blood culture and PCR, but there were differences between vitreous culture and urine culture ($P < 0.05$). In addition, an auxiliary examination was helpful for detecting source lesions. Of the 128 patients, 61 (48%) underwent CT examination, 32 (25%) underwent MRI examination, and 73 (57%) underwent ultrasound examination (diagnostic information is shown in Table 4).

Table 3 Concomitant systemic disease or past history

Concomitant systemic disease or past medical history	Details N = 128
Fever	43 (34%)
Diabetes	41 (32%)
Intravenous injection (including intravenous fluids)	19 (15%)
Cancer	14 (11%)
Liver abscess	13 (10%)
Klebsiella	12 (92%)
Pneumonia	12 (9%)
Cryptococcus aureus	2 (15%)
Nocardia	2 (15%)
Candida fungus	2 (15%)
Streptococcus bacteria	2 (15%)
Nephritis	3 (2%)

Treatment and prognosis

There is little change in the main treatment method for endogenous infectious endophthalmitis; antibiotic therapy is necessary, and vitrectomy and enucleation are necessary for patients with severe eye involvement. All patients received antimicrobial therapy, and 70% underwent surgery. Antimicrobial treatment is divided into two categories: systemic and local. Systemic drug use included intravenous antibiotics and oral antibiotics, mainly cefin (39%), vancomycin (22%), voriconazole (20%) and fluconazole (15%).

Table 4 Diagnostic information

Feature	Details (%)
Positive rate of microbial culture	
Blood culture	59
Glucococcus aureus	*90*
Streptococcus	76
Klebsiella	70
Vitreous body culture	68
Staphylococcus	100
Streptococcus	90
Candida	70
Klebsiella	70
Urine culture	22
Auxiliary examination	
CT	48
MRI	25
Ultrasonography	57

Local administration mainly refers to the intravitreal injection of antibiotics. Vancomycin (73%), cefin (69%) and amphotericin (30%) were used.

In terms of surgical treatment, 70 patients (55%) underwent vitrectomy, 20 (16%) underwent enucleation or exenteration, and 14 (11%) underwent lens resection.

Endogenous infectious endophthalmitis has a poor prognosis, with a 1999 study [6] showing that even with aggressive treatment, only approximately 40% of patients maintain vision (i.e., finger-count or better). In our study, detailed prognostic data were obtained for 88 patients and 102 eyes. Ten patients died, 36 eyes had permanent vision loss or loss of photosensory vision, 4 eyes achieved photosensory vision, 5 eyes achieved manual vision, 6 eyes achieved finger count vision, 1 eye was restored to the healthy state, and 39 eyes had specific corrected vision information available. The mean logMAR was 2.73, the median logMAR was 2.5, and 50% of eyes could reach the finger count level or above. The main reason for the poor prognosis is the low positive culture rate of pathogenic microorganisms, which leads to delayed diagnoses. The increase in visual prognosis in recent years is directly related to empirical treatment (Fig. 1) [7–125].

In summary, endogenous infectious endophthalmitis mostly occurs around the age of 50, and the male-to-female ratio is 1.5:1. Klebsiella is the number one pathogenic organism. Diabetes mellitus is the most common comorbidity, followed by intravenous injection and liver abscess. Blood and body fluid cultures are used for diagnosis but have a low positive rate. In recent years, vitreous culture and PCR have been carried out, which has increased the positive rate. Despite aggressive treatment, only half of patients have a finger count or above visual acuity. Early diagnosis and early empiric treatment improve visual prognosis.

Discussion

Klebsiella was the most common pathogenic organism in the cases analysed; other pathogenic organisms included *Streptococcus* in 18 cases, *Candida* in 15 cases, and *Staphylococcus* in 11 cases. More males than females were affected, and the right eye was

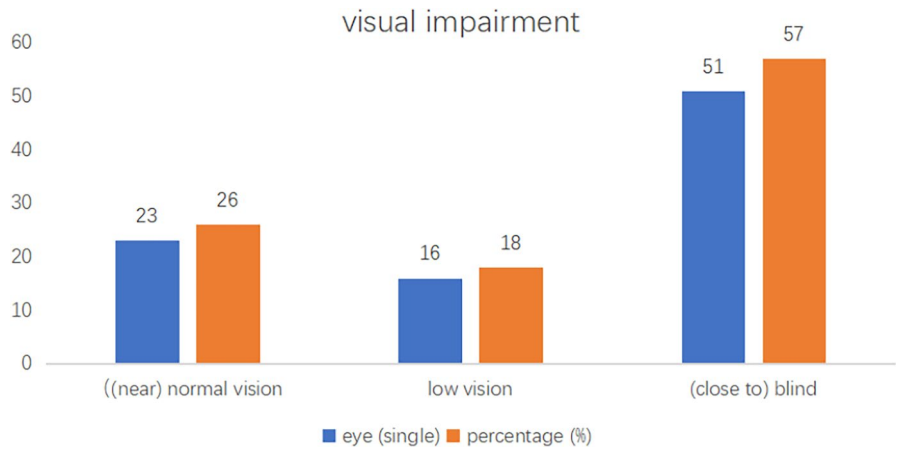

Fig. 1 The prognosis of visual acuity in patients with endogenous infectious endophthalmitis

involved more frequently than the left eye. A comprehensive analysis of the relationship between pathogenic bacteria, sex and eyes showed that *Klebsiella* infection in males mainly occurs in the right eye. The most common concomitant systemic or preexisting conditions were fever and diabetes, followed by intravenous injection (including intravenous fluids), cancer, liver abscess, and pneumonia. The most common complaints were blurred vision, vitreal inflammation and opacity, eye pain, and conjunctival congestion. Among blood, vitreous, and urine culture, the positive culture rate was highest with vitreous culture; it is recommended to perform vitreous culture and PCR detection simultaneously to improve the detection rate. The mean logMAR was 2.73, the median logMAR was 2.5, and half of the eyes reached the level of finger count or above.

Compared with previous studies, advances in endogenous infectious endophthalmitis have focused on changes in pathogenic microorganisms. In addition, the methods of bacterial culture are more diversified, which improves the early diagnosis rate, so the prognosis is improved to some extent. But with limited antibiotic options, treatment has not changed. In terms of pathogenic microorganisms, Kresloff et al. [126], the most common causes of bacterial endoophthalmitis were *Streptococcus, S. aureus*, and, in some studies, *Bacillus cereus*. The most common cause of fungal endophthalmitis is *C. albicans*. In our study, the most common pathogenic bacteria causing bacterial endophthalmitis was different, indicating that *Klebsiella* has become the main pathogenic bacteria involved in endogenous bacterial endophthalmitis. The pathogens involved in fungal endophthalmitis did not change, and *Candida* was still the most common. Other studies over the past decade have also shown that *Klebsiella* is the most common pathogen causing endogenous infectious endophthalmitis [3, 4]. Diabetes mellitus (32%) was the most common comorbidity in our patients, followed by intravenous injection, liver abscess, cancer and pneumonia. In terms of diagnostic methods, over a decade ago, the main methods relied on blood, urine, cerebrospinal fluid, wound culture and smears. In recent years, microorganism culture methods have become more diverse. In addition to conventional culture methods such as blood culture, urine culture and vitreous culture, PCR, sputum culture and aqueous humour culture are also commonly used for identifying pathogenic bacteria. In terms of treatment, antibiotic therapy is necessary, and vitrectomy and enucleation are necessary for patients with severe eye involvement. All of the patients analysed were treated with antibiotics. Romero et al. [6] empirical broad-spectrum antibiotic therapy with vancomycin and aminoglycosides or third-generation cephalosporins was necessary, and vancomycin and cephalosporin were the most commonly used antibiotics in our study. Because of the limited selectivity of antibiotics, the change in this respect is not obvious. Although inflammation can be improved with systemic or topical antibiotic treatment, these treatments are less effective. A 1999 study [6] showed that even with aggressive treatment, only approximately 40% of patients retain their vision (finger count or better). In our literature study, the mean logMAR was 2.73, the median logMAR was 2.5, and 50% of eyes reached the finger count level or above. The main reason for the low visual acuity prognosis is the low positive culture rate, which leads to delayed diagnoses. The increase in prognostic visual acuity in recent years is directly related to empirical treatment.

In summary, our literature review on endogenous infectious endophthalmitis shows that positive culture of pathogenic bacteria plays an important role, and a low positive culture rate of microorganisms leads to delayed diagnosis and treatment to some extent, which we believe is a key factor for poor prognosis. It is suggested that during the diagnosis process, in addition to conventional culture methods such as blood culture, vitreous culture and urine culture, sputum culture, pus culture and PCR detection can be performed simultaneously to improve the positive culture rate and shorten the diagnosis time. In certain cases, a diagnosis can be made by experience, and the patient's medical history should be comprehensively considered. Despite aggressive treatment, only approximately half of patients can see beyond the finger count. In the future, small-molecule drugs could be developed with improved penetration and efficacy. With the advent of new antimicrobial agents, we can expect improved vision recovery in the near future.

Author contributions Xiaoli Liu contributed to the study conception, design and and obtain of funding. Material

preparation, data collection and analysis were performed by Mingjing Hu and Mingzhu Liu. The first draft of the manuscript was written by Mingjing Hu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability All of our data are included in this manuscript.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This is a retrospective review of published articles. No ethical approval was required.

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