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Clinical characteristics and outcome analysis of pulmonary nocardiosis in southern China: a two-center retrospective study

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Abstract

Background Pulmonary nocardiosis (PN) is a rare and opportunistic infection. This study aimed to analyze clinical, radiological, and microbiological features, treatment and outcome of PN in southern china.

Methods Clinical, laboratory, imaging, treatment and outcome data of PN patients at two tertiary hospitals from January 1, 2018, to January 1, 2024 were collected. Factors associated with clinical outcomes were determined by multivariate logistic regression analysis.

Results 67 PN patients including 53 with clinical improvement and 14 with treatment failure were enrolled. Bronchiectasis was the most common respiratory disease in patients with PN (31.3%). The major symptoms of PN were cough (89.6%) and sputum (79.1%). Lung nodules, bronchiectasis, consolidation, pleural involvement, mass, cavity, and lymph node enlargement were the frequent computed tomography findings of PN. Among the Nocardia species detected, *N. farcinica* was the most common pathogen. Neutrophil-to-lymphocyte ratio (OR = 1.052, $p = 0.010$), concurrent bacterial infection (OR = 7.706, $p = 0.016$), and the use of carbapenems (OR = 9.345, $p = 0.023$) were independently associated with poor prognosis in patients with PN.

Conclusions This study provides important insights into the clinical features of PN in southern china. neutrophil-to-lymphocyte ratio, concurrent bacterial infection, and the use of carbapenems were independently associated with poor prognosis in patients with PN.

Keywords Pulmonary nocardiosis, Prognosis, Neutrophil-to-lymphocyte ratio, Bronchiectasis

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Introduction

Nocardia is a kind of rod-shaped, weakly acid fast, aerobic Gram-positive filamentous bacterium that belongs to the actinomycetes group. Nocardia can be found in freshwater, saltwater, dust, soil, decomposing plants, and decaying organic matter, infecting the lungs, skin, central nervous system, or other organs [1]. Nocardiosis is usually considered to be a rare and opportunistic infection, estimated to occur in up to 0.87 cases annually per 100,000 individuals [2, 3]. Lung infection, resulting from direct inhalation of Nocardia, accounts for 73–82% of cases in infected patients [4, 5]. Although pulmonary nocardiosis (PN) often occurs in patients with depressed cellular immunity, such as acquired immunodeficiency syndrome (AIDS) and transplant, one-third of PN patients are immunocompetent [6].

The common clinical presentations of PN include cough, sputum production, dyspnea, hemoptysis, pyrexia, and chest pain. The radiologic findings of chest computed tomography (CT) may be variable, such as nodular, consolidation infiltrates, cavitary lesions, and pleural effusions [7]. As the clinical presentations and radiologic findings of PN are nonspecific, making it difficult to diagnose. Furthermore, the low sensitivity of the culture-based method leads to a higher likelihood of missed diagnoses [8]. Timely identification and treatment initiation play pivotal roles in decreasing mortality rates and enhancing patient prognoses. However, most previous studies focusing on PN were case reports [9, 10]. The risk factors for poor outcomes remains still unknown.

In the present retrospective study, we aimed to analyze clinical, radiological, and microbiological features, treatment and outcome of PN based on data from two tertiary hospitals in southern china. The potential risk factors associated with poor outcome were further determined in this population.

Methods

Study population

Patients with PN at two hospitals, the First Affiliated Hospital of Fujian Medical University and the Zhangzhou Affiliated Hospital of Fujian Medical University, from January 1, 2018, to January 1, 2024, were selected as the study subjects. Inclusion criteria were as follows: patients with PN, complete clinical data, and chest CT imaging before and after antimicrobial treatment. Individuals under the age of 18 were excluded in the study. The institutional review boards approved this study (2023LWB387 and [2024]610) and waived the requirement for informed consent due to its retrospective nature.

Data collection

Data including demographics, comorbid conditions, clinical symptoms, physical examination, the first time of laboratory findings during hospitalization, radiographic characteristics, treatment variables and outcomes were collected. All data were checked by a team of trained physicians.

Definitions

Cases in which Nocardia was isolated through positive culture or detected in metagenomic next-generation sequencing (mNGS) of respiratory samples, such as sputum, bronchoalveolar lavage fluid (BALF), pulmonary puncture sample with subjective and objective symptoms and imaging findings suggesting respiratory infection were defined as PN. The clinical outcomes were classified as follows: clinical improvement (clinical symptoms disappeared accompanied by radiological improvement), and treatment failure (without clinical symptoms improvement or radiological changes persisted/worsen or death after treatment) [11]. Patients with PN were followed up after discharge.

Statistical analysis

Normally distributed, skewed, and categorical data were presented using mean ± standard deviation, median (interquartile range), and number (percentage), respectively. For comparison between two groups, Student's t-test was employed when variables exhibited a normal distribution; alternatively, the Mann-Whitney test was utilized. The Chi-square test or Fisher's exact test was employed to compare categorical variables. Multivariate logistic regression model was used to determine the independent factors for clinical outcomes. A p value of <0.05 was regarded as significant. Data analyses were performed using SPSS v 22.0 (SPSS Inc., Chicago, IL).

Results

Demographics characteristics and clinical presentation

The demographics characteristics and clinical presentation were shown in Table 1. 67 patients with PN including 38 males and 29 females were included. The mean age was 63.54 ± 14.36 years (range: 22–86 years). The most common non pulmonary underlying disease was diabetes mellitus and chronic kidney disease. 31.3% of patients have been previously diagnosed with bronchiectasis. Cough (89.6%) and sputum (79.1%) were the most common symptoms followed by dyspnea (52.2%) and fever (50.7%). 53 patients underwent clinical improvement and 14 patients underwent treatment failure. No significant difference was observed between the clinical improvement and treatment failure group in age, sex ratio, underlying disease, symptoms, use of immunosuppressant agents or corticosteroids.

Table 1 Demographics characteristics and clinical presentation

Variables	Overall (*n* = 67)	Clinical improvement (*n* = 53)	Treatment failure (*n* = 14)	*p*–values
Age, years	63.54 ± 14.36	62.98 ± 14.17	65.64 ± 15.41	0.541
Male sex, n(%)	38(56.7)	27(50.9)	11(78.6)	0.064
Non-pulmonary underlying disease				
Hematologic malignancy, n(%)	5(7.5)	5(9.4)	0(0.0)	0.576
Solid tumor, n(%)	5(7.5)	4(7.5)	1(7.1)	1.000
Connective tissue disease, n(%)	6(9.0)	5(9.4)	1(7.1)	1.000
Diabetes mellitus, n(%)	7(10.4)	4(7.5)	3(21.4)	0.153
Chronic kidney disease, n(%)	7(10.4)	6(11.3)	1(7.1)	1.000
HIV, n(%)	1(1.5)	1(1.9)	0(0.0)	1.000
Pulmonary underlying disease, n(%)				
Chronic obstructive pulmonary disease, n(%)	7(10.4)	5(9.4)	2(14.3)	0.630
Interstitial pneumonia, n(%)	3(4.5)	2(3.8)	1(7.1)	0.511
Bronchiectasis, n(%)	21(31.3)	17(32.1)	4(28.6)	1.000
Bronchial asthma, n(%)	2(3.0)	1(1.9)	1(7.1)	0.377
TB, n(%)	7(10.4)	6(11.3)	1(7.1)	1.000
Immunosuppressant agents, n(%)	9(13.4)	9(17.0)	0(0.0)	0.186
Corticosteroids, n(%)	15(22.4)	13(24.5)	2(14.3)	0.719
Symptoms				
Fever, n(%)	34(50.7)	27(50.9)	7(50.0)	0.950
Cough, n(%)	60(89.6)	49(92.5)	11(78.6)	0.153
Sputum, n(%)	53(79.1)	42(79.2)	11(78.6)	1.000
Haemoptysis, n(%)	4(6.0)	4(7.5)	0(0.0)	0.572
chest pain, n(%)	14(20.9)	13(24.5)	1(7.1)	0.269
Dyspnea, n(%)	35(52.2)	26(49.1)	9(64.3)	0.310

Abbreviation: TB = tuberculosis, HIV = human immunodeficiency virus

Table 2 Laboratory finding and chest CT imaging features

Variables	Overall (*n* = 67)	Clinical improvement (*n* = 53)	Treatment failure (*n* = 14)	*p*–values
Leukocyte	12.42 ± 7.56	15.29 ± 11.66	11.65 ± 5.97	0.277
Lymphocyte	1.11 ± 0.66	1.22 ± 0.60	0.71 ± 0.76	0.010
Neutrophil	10.58 ± 7.20	9.71 ± 5.74	13.86 ± 10.81	0.055
NLR	16.39 ± 19.82	12.01 ± 12.97	32.97 ± 30.78	0.026
Hs-CRP	80.38 ± 79.03	74.33 ± 80.54	102.01 ± 71.93	0.250
PCT	1.41 ± 5.50	1.15 ± 5.86	2.38 ± 3.89	0.462
Imaging features				
Mass, n(%)	20(29.9)	17(32.1)	3(21.4)	0.528
Nodules, n(%)	40(59.7)	30(56.6)	10(71.4)	0.315
Cavity, n(%)	19(28.4)	15(28.3)	4(28.6)	1.000
Consolidation, n(%)	23(34.3)	19(35.8)	4(28.6)	0.756
Ground-glass opacity, n(%)	10(14.9)	10(18.9)	0(0.0)	0.106
Bronchiectasis, n(%)	24(35.8)	19(35.8)	5(35.7)	0.993
Pleural effusion, n(%)	22(32.8)	16(30.2)	6(42.9)	0.523
Lymph node enlargement, n(%)	19(28.4)	15(28.3)	4(28.6)	1.000

Abbreviation: NLR = neutrophil-to-lymphocyte ratio, Hs-CRP = High-sensitivity C-reactive protein, PCT = procalcitonin

Laboratory findings and chest CT imaging features

Table 2 presented the laboratory findings and chest CT imaging features. The mean leukocyte count, neutrophil count, high-sensitivity C-reactive protein, and procalcitonin were significantly higher than the normal reference values. The mean lymphocyte count of the treatment failure group was significantly lower than that of the clinical improvement group, while the neutrophil-to-lymphocyte ratio (NLR) was substantially higher in the treatment failure group. Chest CT scan was performed on all patients. Nodules (59.7%) were the most common presentations of the chest CT findings, followed by bronchiectasis (35.8%), consolidation (34.3%), pleural effusion (32.8%), mass (29.9%), cavity (28.4%), lymph node enlargement (28.4%), and ground-glass opacity (14.9%). There was no

significant difference in imaging findings between the two groups.

Diagnosis and microbiological characteristics

The diagnosis and microbiological characteristics were displayed in Table 3. In terms of diagnosis, 70.1% of patients were diagnosed based on BALF, 26.9% by sputum, 7.5% by lung tissue. 2 patients had positive test in both BALF and sputum. One patient had positive test in both BALF and lung tissue. 56.7% of patients had positive mNGS detection for Nocardia, 50.7% of patients had positive culture (Fig. 1). Among the Nocardia species detected, *N. farcinica* was the most common pathogen, *N. cyriacigeorgica* and *N.otitidiscaviarum* were emerged as the second commonest pathogen. The rate of concurrent bacterial infection in treatment failure group was significantly higher than clinical improvement group. There were no differences between the two groups in terms of test specimens, detection methods, Nocardia species, fungal coinfection, or viral coinfection. The most frequent concurrent bacterial infection was *Klebsiella pneumonia* (Figure S1).

Treatment information

59.7% of patients were treated with combination therapy while the rest were treated with monotherapy. Sulfonamides were the most commonly used agents (73.1%), followed by carbapenems (39.4%), cephalosporin (26.9%), linezolid (25.4%), aminoglycosides (19.4%), penicillin (17.9%) quinolones (13.4%), macrolides (9.0%), and tetracyclines (3.0%). The proportion of use of carbapenems and linezolid were significantly higher than in treatment failure group than those in clincial improvement group. In additon, the rate of combination therapy was similar between the two groups (Table 4).

Risk factors for outcomes

The influencing factors with a p-value of less than 0.1 were included in the multivariate logistic analysis. The results showed that NLR (OR=1.052, p=0.010), concurrent bacterial infection (OR=7.706, p=0.016), and the use of carbapenems (OR=9.345, p=0.023) were risk factors for poor prognosis in patients with PN after adjusting for sex ratio and the use of linezolid (Table 5).

Discussion

In this retrospective study, we found that bronchiectasis was the most common respiratory disease in patients with PN. The major symptoms of PN were non-specific: cough and sputum. Lung nodules bronchiectasis, consolidation, pleural involvement, mass, cavity and lymph node enlargement were the frequent CT findings of PN.

Table 3 Diagnosis and microbiological characteristics

Variables	Overall (n=67)	Clinical improvement (n=53)	Treatment failure (n=14)	p–values
Test specimens				
BALF, n(%)	47(70.1)	36(67.9)	11(78.6)	0.528
Sputum, n(%)	18(26.9)	15(28.3)	3(21.4)	0.743
Lung tissue, n(%)	5(7.5)	4(7.5)	1(7.1)	1.000
Detection methods				
Bacterial culture, n(%)	34(50.7)	26(49.1)	8(57.1)	0.590
mNGS, n(%)	38(56.7)	30(56.6)	8(57.1)	0.971
Nocardia species				
Unkown, n(%)	15(25.4)	12(22.6)	5(35.7)	0.322
N. farcinica, n(%)	16(23.9)	13(24.5)	3(21.4)	1.000
N. cyriacigeorgica, n(%)	9(13.4)	6(11.3)	3(21.4)	0.382
N. asteroides, n(%)	2(3.0)	2(3.8)	0(0.0)	1.000
N. otitidiscaviarum, n(%)	9 (13.4)	8(15.1)	1(7.1)	0.672
N. brasiliensis, n(%)	3(4.5)	3(5.7)	0(0.0)	1.000
N. gipuzkoensis, n(%)	1(1.5)	1(1.9)	0(0.0)	1.000
N. abscessus, n(%)	3(4.5)	2(3.8)	1(7.1)	0.511
N. asiatica, n(%)	2(3.0)	2(3.8)	0(0.0)	1.000
N. beijingensis, n(%)	1(1.5)	1(0.0)	1(7.1)	0.209
N. africana, n(%)	1(1.5)	1(1.9)	0(0.0)	1.000
N. terpenica, n(%)	2(3.0)	2(3.8)	0(0.0)	1.000
N.carnea, n(%)	1(1.5)	1(1.9)	0(0.0)	1.000
Co-Isolated organism	35(52.2)	25(47.2)	10(71.4)	0.106
Bacteria infection, n(%)	22(32.8)	13(24.5)	9(64.3)	0.009
Fungus infection, n(%)	17(25.4)	12(22.6)	5(35.7)	0.322
Virus infection, n(%)	9(13.4)	7(13.2)	2(14.3)	1.000

Abbreviation: BALF=bronchoalveolar lavage fluid, mNGS=metagenomic next-generation sequencing

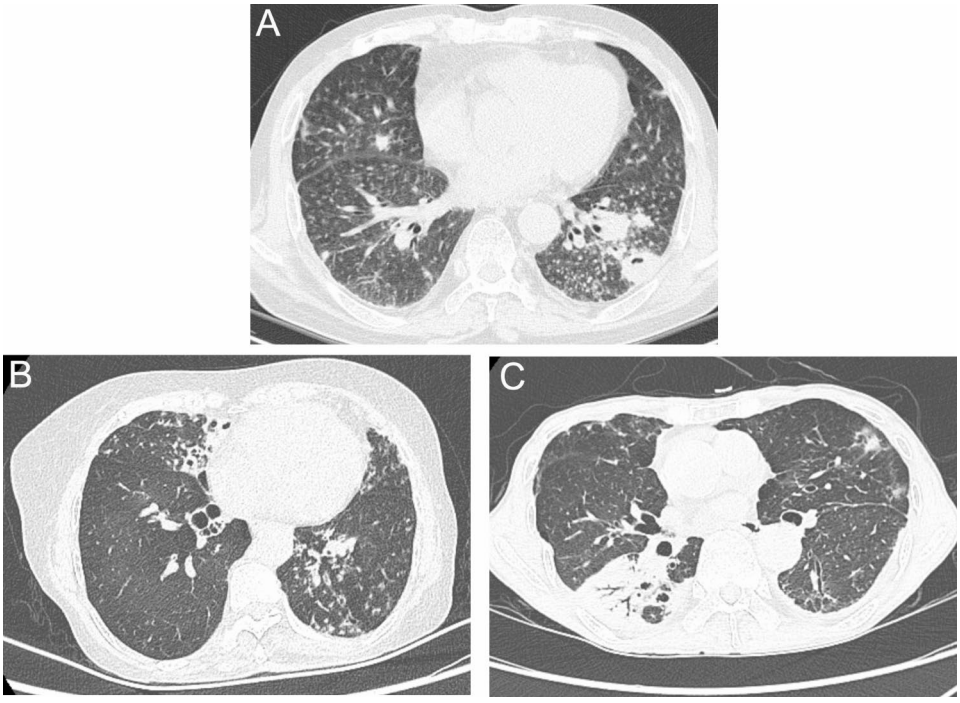

Fig. 1 **A** Chest imaging of a 74-yr-old woman with cavitary masses in left lower lobe and multiple nodules in both lungs. **B** Chest imaging of a 55-yr-old woman with bronchiectasis in the right middle lobe and multiple nodules in both lungs. **C** Chest imaging of a 76-yr-old man with segmental consolidation in the right lower lobe

Table 4 Treatment information

Variables	Overall (*n* = 67)	Clinical improvement (*n* = 53)	Treatment failure (*n* = 14)	*p*–values
Therapy				0.405
Monotherapy, n(%)	27(40.3)	20(37.7)	7(50.0)	
Combination therapy, n(%)	40(59.7)	33(62.3)	7(50.0)	
Agent				
Sulfonamide, n(%)	49(73.1)	41(77.4)	8(57.1)	0.176
Carbapenems, n(%)	26(39.4)	15(28.3)	11(78.6)	0.001
Linezolid, n(%)	17(25.4)	10(18.9)	7(50.0)	0.034
Aminoglycoside, n(%)	13(19.4)	11(20.8)	2(14.3)	0.720
Quinolone, n(%)	9(13.4)	9(17.0)	0(0.0)	0.186
Tetracyclines, n(%)	2(3.0)	1(1.9)	1(7.1)	0.377
Macrolide, n(%)	6(9.0)	6(11.3)	0(0.0)	0.330
Penicillin, n(%)	12(17.9)	11(20.8)	1(7.1)	0.435
Cephalosporin, n(%)	18(26.9)	16(30.2)	2(14.3)	0.320

Table 5 Risk factors for outcomes

Factors	Outcome	
	OR(95% CI)	*p*–values
Bacteria infection	7.706(1.472–40.341)	0.016
NLR	1.052(1.012–1.093)	0.010
Carbapenems	9.345(1.360-64.204)	0.023

Abbreviation: NLR=neutrophil-to-lymphocyte ratio, CI=confidence interval, OR=odds ratio

Among the Nocardia species detected, *N. farcinica* was the most common pathogen. Using BALF as a test specimen yielded higher sensitivity. Furthermore, NLR, concurrent bacterial infection, and the use of carbapenems were independently associated with poor prognosis in patients with PN.

Ferrer et al. [12] showed that bronchiectasis was an important risk factor for colonization by *Nocardia spp.* and for infection in patients without cystic fibrosis by analyzing 40 patients. A case series study revealed that [13] the proportion of bronchiectasis and COPD in the immunocompetent PN patients was significantly higher than immunocompromised PN patients. Another study enrolling 17 patients diagnosed as bronchiectasis complicated with PN reported that bronchiectasis combined with nocardiosis was more common in middle-aged and

elderly women without smoking and Nocardia infection might further precipitate the initiation and progression of bronchiectasis [14]. Our study corroborates this finding, indicating that underlying lung conditions like bronchiectasis play a crucial role in the susceptibility to Nocardia infections. These insights emphasize the need for heightened clinical awareness and monitoring of patients with bronchiectasis for potential Nocardia infections.

A study examining the CT findings in PN revealed that the most prevalent CT features were nodules, followed by consolidation and cavitation in PN patients. They also noted a higher frequency of cavitation and pleural effusion compared to localized infection [15]. Another study indicated that common radiological findings on CT of PN patients included consolidation, bronchiectasis, mediastinal lymphadenopathy, and nodularity [16]. Su et al. [17] also demonstrated that multiple or solitary nodules represented the most common CT features of PN and immunosuppressed patients exhibited significantly higher rates of cavitation. We found that the most common manifestations of PN were nodules, bronchiectasis, and consolidation in this study. These findings align with the typical radiological features reported in the literature. However, while these manifestations are frequently observed on CT scans, they are not unique to PN and may overlap with other pulmonary conditions. It is essential for clinicians to consider the full clinical context, including patient history, immunocompetence, and microbiological tests, alongside CT imaging.

The NLR is a biomarker that reflects two distinct aspects of the immune system: the innate immune response, primarily driven by neutrophils, and the adaptive immune response, mediated by lymphocytes [18]. Our results suggested that NLR was independently associated with poor prognosis in patients with PN. In a cohort of elderly adults with community-acquired pneumonia, Cataudella et al. [19] found that NLR predicted 30-day mortality and performed better than Pneumonia Severity Index, CURB-65, C-reactive protein, and white blood cell count to predict prognosis. Patients with NLR greater than 28.3 had the worst prognosis. NLR has also been widely validated by numerous studies for its predictive value in both COVID-19 severity [20] and mortality [21]. Two recent large meta-analyses demonstrated that on-admission NLR levels were higher in severe and non-survivor COVID-19 patients compared to those in non-severe and survivor patients [22, 23]. In PN, an elevated NLR suggests a heightened inflammatory response, which may reflect more severe infection or a greater burden of disease. High NLR values can indicate an overwhelming immune response, often associated with worse clinical outcomes.

We also found that concurrent bacterial infection and the use of carbapenems were risk factors for poor prognosis in patients with PN. Co-infections can exacerbate the severity of lung damage, lead to increased inflammatory responses, and complicate the management of the patient [24]. The dual pathogen burden can strain the immune system, making it more challenging to control the infections and increasing the risk of complications such as sepsis or respiratory failure. In the context of PN, the use of carbapenems might indicate a more severe or refractory infection. The necessity for carbapenems use could reflect the presence of severe infection or concurrent infections requiring broad-spectrum coverage. This may explain why the use of carbapenems is associated with a poorer prognosis. We recommend that carbapenem therapy in PN be guided by individual patient factors, infection severity, and the specific Nocardia species involved. Whenever possible, alternative treatments should be prioritized, with broad-spectrum antibiotics like carbapenems reserved for cases where there are clear indications and the benefits outweigh the risks. However, a study found that treatment with trimethoprim-sulfamethoxazole was independently associate with 90-day all-cause mortality in PN [25].

There are several limitations to this study. Firstly, the study's retrospective design inherently limits the ability to establish causal relationships. Secondly, the relatively small cohort size could lead to potential biases and limit the statistical power of the study. Thirdly, our follow-up was only until the point of discharge, and we did not conduct long-term follow-up, which may have provided a more comprehensive understanding of patient outcomes. Fourthly, only respiratory symptom data were collected from the patients, as a result, we were unable to assess the severity of PN. Finally, we did not conduct drug susceptibility testing for various Nocardia species in this study. However, the treatment of PN was guided by recommendations from The Sanford Guide to Antimicrobial Therapy.

Conclusions

This study provides important insights into the clinical features and prognostic factors of PN. Larger, prospective studies with longer follow-up periods are needed to confirm these findings and better guide clinical management.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-09933-6.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
L.-D.C., H.-Y. L., and K.-X. L. performed most of the experiments with assistance; J.-J.X., M.-F.H., X.-X.C., and Z.-M.C. contributed to the data analyses; L.-D.C., H.-Y. L., and K.-X. L. wrote the manuscript; X.-B.Z., G.-P.C., and L.L. edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data availability
The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Review Boards of Zhangzhou Affiliated Hospital of Fujian Medical University (2023LWB387) and the First Affiliated Hospital of Fujian Medical University ([2024]610). Because it is a retrospective study, the ethics Committees approved it without informed consent. All research data are anonymous. This study follows the Helsinki Declaration.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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