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Endomyocardial Biopsy: Short- and Long-Term Safety in Myocarditis Patients

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Abstract

Introduction: Aims of the study were to assess the short-term and long-term outcomes of percutaneous endomyocardial biopsy (EMB) in patients with myocarditis and to identify the risk factors for EMB-related complications in this patient population. ***Methods:*** A retrospective analysis was conducted on 294 hospitalized patients with clinically suspected myocarditis at Tongji Hospital from October 2019 to October 2023, with a median follow-up duration of 18 months. Patients were divided into an EMB group (n = 151) and a non-EMB group (n = 143) based on whether they underwent EMB procedure. The incidence of endpoints was compared between the two groups, and the Kaplan-Meier survival curve was used to assess the survival rate without endpoints. Endpoints included major adverse cardiovascular events (MACE), ventricular enlargement, and decline in cardiac function. Multivariate logistic regression analysis was employed to evaluate the risk factors for EMB-related complications. ***Results:*** The incidence of major short-term complications following EMB was 2.0% (3/151), while the incidence of minor complications was 9.3% (14/151). Multivariate risk regression analysis revealed that operative duration (OR: 1.101, 95% CI: 1.02–1.079, $p < 0.05$) and BNP levels (OR: 1.083, 95% CI: 0.931–1.26, $p < 0.05$) were associated with short-term complications following EMB. Compared to the non-EMB group, the EMB group had no significant increase in hospital stay (10 [8, 15] vs. 9 [7, 16], $p = 0.27$) and no significant decline in cardiac function. Long-term follow-up results showed that 8 patients (5.3%) in the EMB group experienced MACE, 14 patients (9.3%) had left ventricular enlargement, and 18 patients (11.9%) had a decline in left ventricular ejection fraction (LVEF) after discharge; in the non-EMB group, 12 patients (8.4%) experienced MACE, 30 patients (19.9%) had left ventricular enlargement, and 18 patients (11.9%) had a decline in LVEF after discharge. The Kaplan-Meier curve revealed a lower incidence of endpoint events in the EMB group ($p < 0.05$). ***Conclusion:*** In patients with myocarditis, EMB is associated with a risk of short-term complications, with higher levels of BNP and operative duration being independent risk factors for EMB-related complications. However, EMB does not adversely affect cardiac function or hospital stay during the inpatient period and may contribute to the improvement of long-term outcomes in patients with myocarditis.

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Introduction

Percutaneous endocardial myocardial biopsy (EMB) serves as a prevalent tool for examining cardiac transplants, evaluating the severity of drug toxicity, and identifying secondary cardiac manifestations due to systemic diseases. It is the definitive method for diagnosing cardiac rejection, myocarditis, and infiltrative or storage disorders. Moreover, EMB plays a pivotal role in the differential diagnosis of heart failure and unexplained ventricular arrhythmias. Importantly, in cases of uncertain pathological conditions, despite clinical diagnoses, EMB provides essential insights for establishing definitive diagnoses and identifying specific etiologies. This diagnostic precision is crucial for guiding treatment options, clinical management, and prognostication in conditions such as amyloidosis, hemochromatosis, Anderson-Fabry disease, and myocarditis [1]. EMB plays a key role in the differential diagnosis of heart failure and unexplained ventricular arrhythmias. It is an authoritative method for diagnosing cardiac rejection, infiltrative or storage diseases and is the gold standard for the diagnosis of myocarditis and inflammatory cardiomyopathy [2]. In the early days, the myocardial biopsy tissues were needed to be obtained by surgical thoracotomy or acupuncture. It may cause severe trauma but also followed by a high risk of complications [3, 4]. Konno and Sakakibara were the first one to perform EMB through percutaneous surgery, using a flexible biological knife with a sharp tip to clamp cardiac tissue, rather than a surgical cutting technique since 1950 [5, 6]. And then, Caves and Schultz modified the Konno-Sakakibara forceps to enable percutaneous biopsy through the right internal jugular vein under local anesthesia with a rapid tissue extraction [7]. The reusable Stanford Caves-Shulz Bioknives and their subsequent modified bioknives became standard equipment in performing EMBs for about 20 years, primarily for monitoring rejection after cardiac transplantation [8]. The use of EMBs has greatly expanded beyond the diagnosis of myocarditis, now encompassing an array of cardiac conditions such as cardiomyopathy, drug-induced cardiotoxicity, amyloidosis, invasive diseases, and cardiac tumors. The integration of molecular biology techniques – including immunohistochemistry, polymerase chain reaction (PCR), reverse transcription PCR (RT-PCR), and transmission electron microscopy (TEM) – has significantly enhanced the clinical utility of EMB in the realm of cardiac pathology. Consequently, its use has gained considerable esteem and has been widely adopted across the globe. Nevertheless, the procedure remains underutilized in practice, often due to a preference for noninvasive diagnostics like cardiac magnetic resonance imaging among clinicians, as well as concerns regarding the safety and diagnostic efficacy of endocardial biopsies. Consequently, the number of hospitals equipped to perform this operation is limited. EMB is currently only available in larger cardiovascular interventional centers. However, with the advancement of technology, the number of patients undergoing EMB has also increased in recent years [9].

In clinical practice, the methodology of choice for conducting EMBs typically involves accessing the right ventricle (RV) via the right internal jugular vein. This approach, commonly referred to as RV-EMB, has been widely adopted due to its established success in diagnosing various cardiac conditions. Alternative access routes include femoral vein, using a longer bioptome within a long sheath, and less commonly subclavian and brachial veins [10]. Left ventricular (LV) EMB (LV-EMB) is less often performed. No differences have been reported in terms of diagnostic accuracy, except that one study indicated a diagnostic superiority of biventricular EMB compared with selective LV-EMB or RV-EMB [11]. With the development of diagnostic coronary angiography and percutaneous coronary interventions, the radial artery has emerged as the preferred access site in experienced centers and is also recommended by the guidelines of the European Society of Cardiology for the interventional therapy of coronary artery disease [12, 13]. Some studies have discussed the safety of EMB [9, 14, 15]. The complications of EMB include vasovagal syncope, cardiac perforation, cardiac tamponade, etc. One study reported very low rates of major complications (i.e., 0.08% perforation with cardiac tamponade and 0.22% brain embolization) with no significant differences between LV-EMB and RV-EMB [16]. While many studies have discussed the feasibility and safety of different routes of myocardial biopsy, few have examined the long-term impacts of EMB on patients. In short, the innovation of this article lies in the discussion of risk factors for EMB-related complications and the long-term effects of EMB, both of which have been rarely covered in previous relevant studies. Our research evaluates the effect of EMB in a population with myocarditis through long-term follow-up. Additionally, there is still no consensus on whether a myocardial biopsy can affect a patient's cardiac function in the short term. Our goals were to elucidate the short-term and long-term impacts of EMB on patients and identify risk factors related to EMB complications in a patient population.

Methods

Study Population

This retrospective, single-center study encompasses a cohort of 294 patients who sought care at the Cardiology Department of Tongji Hospital, affiliated with Tongji Medical College of Huazhong University of Science and Technology in Wuhan, China, from October 2019 to May 2023. These patients were under clinical evaluation for suspected myocarditis, diagnosed based on impaired LV function, positive cardiovascular magnetic resonance findings indicative of myocarditis, along with at least two of the following criteria: (1) Clinical symptoms such as chest pain, dyspnea, or palpitations; (2) electrocardiographic anomalies that include ST-segment deviations, T-wave inversions, emergent conduction blocks, along with supraventricular and ventricular tachyarrhythmias; (3) elevated serum levels of myocardial necrosis biomarkers; (4) detection of pericardial effusion.

This investigation encompassed 294 myocarditis patients, divided into two groups: EMB group (n = 151) and non-EMB group (n = 143). Because some patients and their families are worried about the risks of EMB as an invasive procedure, they do not agree to perform EMB. We make the final decision on whether the patient should undergo EMB based on the patient's physical condition and wishes. EMB procedure exclusion criteria were as follows: (1) Hematologic disorders: hemorrhagic conditions, severe thrombocytopenia, or anticoagulant therapy; (2) presence of intracardiac thrombi in the atrium or ventricle; (3) severe LV dysfunction (ejection fraction, EF, less than 30%); (4) recent acute infections; (5) inability to remain supine or comply with the examination protocol.

The primary endpoint was the occurrence of major adverse cardiovascular events (MACE), including nonfatal myocardial infarction, stroke, or cardiovascular mortality. If the LV EF was lower than when the patient was discharged, it was defined as a decrease of EF.

Prior to undergoing endocardial biopsy, all participants provided their written informed consent. A detailed flowchart of the present study design is presented in Figure 1.

Collection of Clinical Data

Demographic data, including age, sex, and body mass index, along with New York Heart Association (NYHA) classifications and records of myocardial biopsy complications, were meticulously extracted from the electronic medical records system. Comprehensive laboratory tests conducted upon admission encompassed a broad spectrum of parameters: a complete blood count (encompassing white blood cells, platelets, and hemoglobin levels), coagulation profiles (including APTT and PT), D-dimer levels, liver function markers (alanine aminotransferase and aspartate aminotransferase), creatinine, high-sensitivity cardiac troponin I (hs-cTnI), and the concentration of N-terminal B-type natriuretic peptide (NT-proBNP). Furthermore, every patient underwent an extensive echocardiographic evaluation at Tongji Hospital's Echocardiography Department. This evaluation was designed to appraise numerous cardiac aspects: LV EF, LV chamber dimensions, diastolic function, valvular integrity, thickness of the inferolateral and interventricular septal walls, pressure gradients across the tricuspid valve, and the presence of pericardial effusion. Simultaneously, patients were meticulously screened for contraindications to LV-EMB, notably a lateral LV wall thickness less than 8 mm and noncompaction cardiomyopathy – both conditions being linked to an elevated risk of myocardial perforation. Operative metrics, including the duration of the procedure, surgical methodology, targeted ventricle for sampling, specific sampling sites, pre- and postoperative systolic and diastolic blood pressures, heart rate, and the quantity of collected samples, were systematically recorded. Post-discharge, patient follow-ups were conducted at 1, 3, and 6 months, with subsequent semiannual assessments thereafter. All patients were followed up according to this time. This timing was consistent in all patients.

Procedure of Percutaneous EMB Operation

The EMB approach based on the patient's own condition. When the patient required coronary angiography, transradial LV-EMB was performed. When the patient's condition is severe and requires IABP implantation, we carry out transfemoral LV-EMB. A small number of patients do not require either coronary angiography or IABP implantation, and transfemoral RV-EMB is performed. The specific operation process is as follows.

Transradial LV-EMB

Under local anesthesia, we inserted a 6F sheath tube (Radifocus Introducer II, 10 cm, Terumo, Japan) into the patient's right radial artery. To mitigate the risks of radial artery occlusion or spasm, the patient was preadministered 3,000 IU of standard heparin and 5 mg of verapamil prior to the arterial puncture. Subsequently, we advanced a 5F pigtail catheter (Boston Scientific, USA)

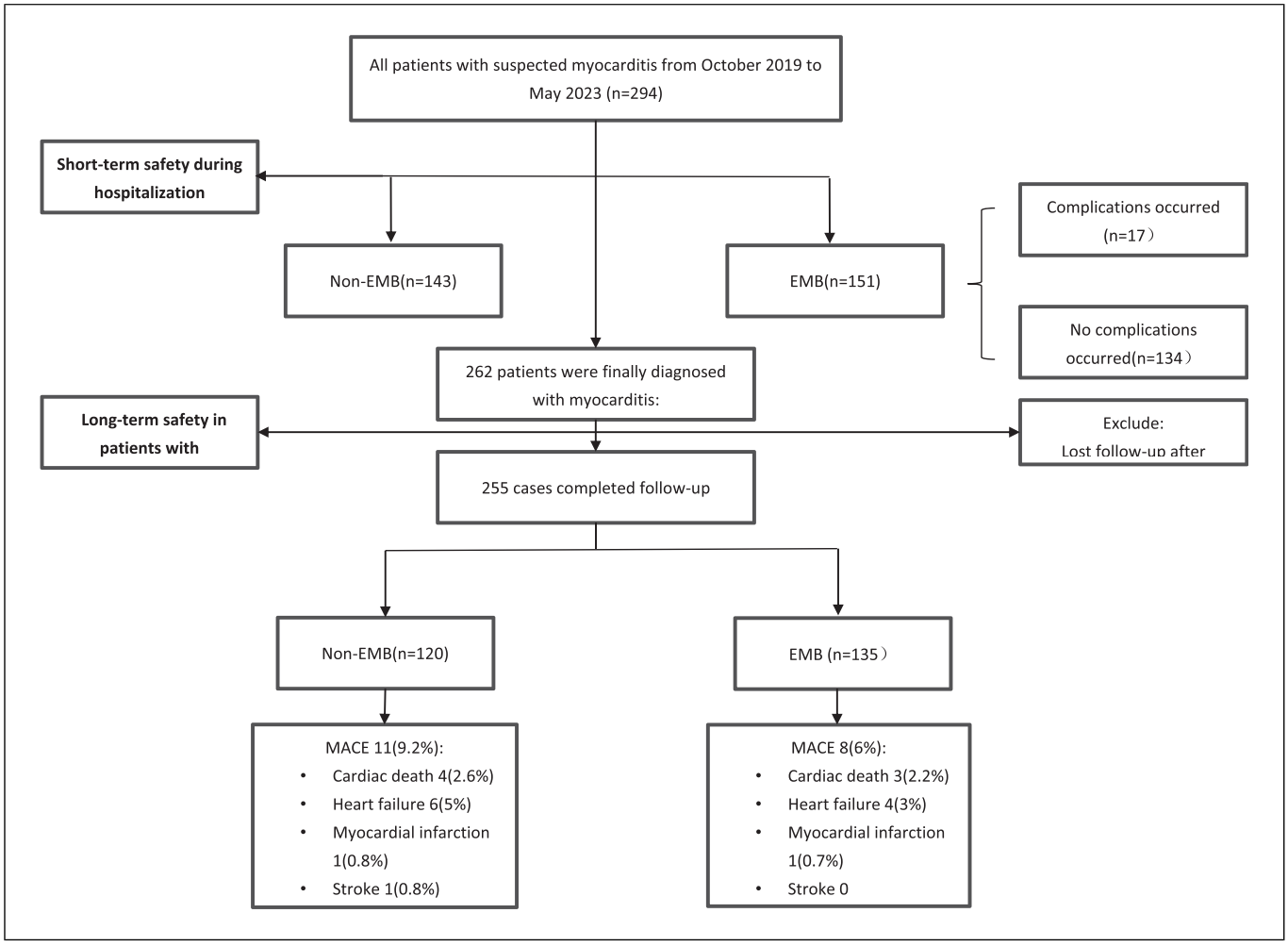

Fig. 1. Flowchart of the study. EMB, endomyocardial biopsy; MACE, major adverse cardiovascular events.

into the left ventricle using a J-guide wire (260 cm, 0.035 in), which facilitated the precise positioning within the ventricular chamber. Following the location confirmation, we withdrew both the 6F sheath tube and pigtail catheter. We introduced a 7.5F unsheathed multipurpose guide catheter (MP1.0, Asahi Intecc, Japan) over the guide wire. Upon reaching the ascending aorta, we removed the dilator. With meticulous guidance over the guide wire, the guide catheter was maneuvered into the LV cavity. After discarding the J-guide wire, we connected a Y-connector (Copilot, Abbott Vascular, USA) to the system. At 20° left anterior oblique fluoroscopy, we analyzed the positioning of the guide catheter tip to ensure that it did not make contact with the ventricular wall, as confirmed by the absence in change of the tip's reference point. A 6 mL bolus of contrast agent was then administered, allowing for a clear delineation between the catheter tip and the ventricular wall, ensuring the ideal positioning for the procedure. To prevent thrombotic complications during the protocol, we monitored the patient's active coagulation time (ACT), maintaining a range of 200–250 s. The biopsy forceps, primed in water to prevent air embolism, were introduced through the Y-connector and into the MP1.0 guide catheter. Under fluoroscopic guidance, the forceps were carefully navigated to the lateral ventricular wall. Upon encountering resistance or fluoroscopic confirmation of wall contact, the biopsy sample was promptly secured and the forceps retracted. The unsheathed guide catheter was removed following specimen retrieval, and hemostasis was achieved using a vascular closure device. Post-procedure, we prescribed a 4-week regimen of low-dose aspirin for each patient to prevent thrombus formation at the biopsy site.

Transfemoral LV-EMB

Under local anesthesia, an 8F sheath tube (Radifocus Introducer II, 10 cm, Terumo, Japan) was inserted into either the right or left femoral artery after administering 3,000–4,000 IU of standard heparin, aiming to achieve an activated clotting time (ACT) of 200–250 s. Subsequently, a 5F pigtail catheter (Boston Scientific, USA) was threaded into the left heart chamber. Through the pigtail catheter, a 260 cm J-guide wire with a 0.03500-inch diameter was placed to pinpoint the ventricle's location. Following the removal of the pigtail catheter, an 8F multipurpose guide catheter featuring side holes (MP1.0SH, Medtronic, USA) was inserted into the femoral artery. This catheter was then carefully advanced over the guide wire, reaching into the left heart cavity with precision. After removing the J-guide wire, it was connected to a Y-connector (Copilot, Abbott Vascular, USA). Fluoroscopic imaging was utilized to confirm the guide catheter's position within the heart cavity. The subsequent procedural steps mirrored those of the transradial approach for LV-EMB.

Transfemoral RV-EMB

For this procedure, we do not recommend the use of heparinization or aspirin prophylaxis. A 30 cm, 8F sheath (Arrow-Flex, Tereflex, USA) is introduced via puncture in the right or left femoral vein under localized anesthesia. We utilize flexible biopsy forceps designed to accommodate the unique anatomy of each patient. In contrast to other methods, a guiding catheter is omitted to preserve the forceps' flexibility and to minimize the risk of cardiac perforation. It is, therefore, our standing recommendation to refrain from employing any rigid or non-flexible devices for right ventricular biopsies. Under 0° right anterior oblique fluoroscopic guidance, the biopsy forceps are carefully advanced into the right atrium. They are then meticulously guided past the tricuspid valve into the RV, taking precaution to maintain control of the instrument. The ideal site for biopsy is ascertained at the 90° left anterior oblique position. Performing a biopsy in the right anterior oblique position is ill-advised due to the inability to discern the exact positioning of the forceps, specifically whether they have remained within the right atrium or made inadvertent contact with the coronary sinus. Prior to tissue sampling, it is critical to confirm that the forceps have made adequate contact with the ventricular wall. This ensures that upon opening the forceps, they are correctly situated within the RV. A slight retraction is performed to facilitate safe opening of the forceps, after which the device is directed toward the lower interventricular septum to secure several tissue samples. After all biopsy samples were taken, the 8F sheath was withdrawn and the puncture was manually pressed for minutes to stop bleeding [17].

Treatment of Myocardial Tissue

For the pathological analysis, two to four myocardial tissue samples were immersed in a 4% formaldehyde solution for standard histopathological examination. Additionally, a separate myocardial tissue sample was fixed in a 2.5% glutaraldehyde solution and subsequently stored at 4°C for detailed electron microscopic analysis. For the purpose of viral genome detection or mass spectrometry, another sample was preserved in a cryogenic environment at −80°C.

Patient Monitoring during and after the EMB Procedure

Throughout the EMB procedure, patients' heart rhythms and invasive blood pressures were meticulously monitored. Additionally, self-adhesive defibrillator pads were attached to each patient as a precautionary measure. For a minimum duration of 30 min post-procedure, patients remained under close observation within the catheterization lab, where their noninvasive blood pressure, heart rate, and oxygen saturation levels were continuously assessed. An immediate post-procedural transthoracic echocardiogram was conducted to exclude any significant pericardial effusion that could have arisen from the intervention. Patients were then transferred to the cardiology ward, where monitoring of the heart rhythm was ongoing for further assessment. Subsequent to the initial monitoring phase, a follow-up echocardiographic examination was scheduled for the next day. This follow-up aimed to reassess the presence of pericardial effusion and to evaluate the status of mitral valve regurgitation, ensuring comprehensive post-procedural care.

In addition to these monitoring protocols, all patients, irrespective of the access site used or the ventricle targeted during the biopsy (right ventricular EMB or LV-EMB), were prescribed a daily dose of 100 mg aspirin for 4 weeks. This preventive measure was intended to mitigate the risk of thrombus formation or arterial embolism stemming from the biopsy site. The only exception to this regimen was for those patients who were already on a stable regimen of oral anticoagulation therapy.

Major and Minor Complications

According to a recent expert statement [18], the following events were considered as complications. Major complications included permanent atrioventricular (AV)

block requiring pacemaker implantation, pericardial tamponade necessitating pericardiocentesis, stroke and severe valvar damage, dissection of the radial artery, access site bleeding, and ventricular fibrillation/death. Transient chest pain, non-sustained electrocardiogram abnormalities, transient AV block, cardiovascular vagal reaction, and small pericardial effusion were defined as minor complications.

Research Time Definition

To ascertain comprehensive and precise clinical follow-up data, we systematically reviewed medical records, conducted biannual interviews with outpatients, and reached out directly or via telephone to patients or their primary kin. When analyzing data, if a patient encountered multiple endpoint events during our study, only the initial occurrence was incorporated. We earmarked the study's inception from the patient's discharge date. The study concluded upon the earliest of two possibilities: the presentation of an endpoint event or the final follow-up, carried out no later than October 31, 2023.

Statistical Analysis

Continuous variables are reported as means ± SD for normally distributed data and medians with interquartile ranges for skewed data. We represent categorical data as frequencies and percentages. Group comparisons for continuous variables were conducted using the Student's *t* test (for normal distributions) or the Mann-Whitney U test (for non-normal distributions). For categorical variables, the χ^2 test or Fisher's exact test was employed as appropriate. To evaluate changes in periprocedural and postprocedural measures within subjects, we utilized the paired-sample *t* test. Survival outcomes were assessed using Kaplan-Meier analysis, with differences between the EMB group and the non-EMB group evaluated via log-rank test. We considered a two-sided *p* value of less than 0.05 as statistically significant. Logistic regression was used to identify independent risk factors for procedural complications. All statistical analyses were conducted with SPSS software, version 24 (IBM Corp., Armonk, NY, USA).

Results

Baseline Demographic Characteristics, Functional Parameters, and Laboratory Findings

This investigation encompassed 294 myocarditis patients, divided into two groups: EMB group (n = 151) and non-EMB group (n = 143). A comparative analysis of baseline demographics (age, body mass index, and gender) and clinical parameters (D-dimer levels, echocardiographic findings, complete blood count including white blood cells, hemoglobin, platelets, high-sensitivity cardiac troponin I, and brain natriuretic peptide) revealed no significant disparities between the two groups – all *p* values exceeded 0.05. These initial characteristics are meticulously outlined in Table 1.

*Comparison of Complications of Myocarditis during Hospitalization between EMB Group (*n = *151) and Non-EMB Group (*n = *143)*

In our comparative analysis of hospitalization duration, cardiac function markers, and the prevalence of myocarditis-related complications upon discharge, we observed no significant difference between EMB group (n = 151) and non-EMB group (n = 143) (as illustrated in Table 2). The median length of hospital stay was comparable (9 [7, 14] vs. 10 [8, 15]), suggesting that EMB does not prolong hospitalization. Furthermore, short-term outcomes indicate that EMB does not negatively impact cardiac function or contribute to an increased occurrence of myocarditis-related complications ($p < 0.05$). In EMB group (n = 151), 116 cases underwent EMB by transradial LV-EMB. A total of 12 patients underwent LV-EMB via the transfemoral approach, while 23 patients underwent RV-EMB via the same approach. See the details in online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000543593).

Complications Associated with EMB and Risk Factors

The procedural success rate was uniformly 100% across all groups. The average duration of the procedure was 38.7 ± 17.2 min (this assumes you meant minutes, not years as in the original text). Each patient, on average, yielded 3 myocardial tissue samples suitable for subsequent analysis. The samples obtained were sufficient in quantity and quality for pathological examination.

Our study documented a limited number of complications, both major and minor. Notably, ventricular fibrillation occurred in a single instance; two perforations resulted in hemopericardium and pericardial tamponade, necessitating pericardiocentesis (refer to Table 3). Hence, the major complication rate associated with EMB stood at 2.0% (affecting 3 out of 151 patients).

Regarding minor complications, we noted a cardiovascular vagal response and a third-degree AV block in 1 patient, which required the temporary placement of a pacemaker (see Table 3). This AV block resolved spontaneously within 2 days, allowing for the removal of the temporary pacemaker without any long-term adverse

Table 1. Baseline demographic characteristics, functional parameters, and laboratory data

Variables	Non-EMB group (*N* = 143)	EMB group (*N* = 151)	*p* value
Age, years	36.4±18.0	38.7±17.2	0.265
BMI, kg/m^2	22.8±3.7	22.7±4.7	0.732
Women, *n* (%)	52 (35.2)	67 (46.2)	0.115
Symptoms, *n* (%)			
Fever	50 (34.9)	43 (28.5)	0.232
Chest tightness	79 (55.2)	91 (60.3)	0.384
Chest pain	45 (31.5)	56 (37.1)	0.291
Shortness of breath	13 (9.1)	20 (13.2)	0.259
New York Heart Association III/IV, *n* (%)	68 (47.6)	71 (47.0)	0.736
Blood pressure, mm Hg			
Systolic BP	114.3±18.3	117.4±19.1	0.207
Diastolic BP	68.5±15.6	71.2±12.6	0.168
D-dimer			0.196
<0.5 μg/L	55 (38.7)	70 (46.4)	
>0.5 μg/L	88 (61.5)	81 (53.6)	
Echocardiography			
LVEDD, cm	4.7±0.4	4.9±0.8	0.188
RVEDD, cm	2.5±0.5	2.6±0.5	0.752
IVS, cm	1.0±0.3	1.0±0.3	0.643
EF, %	45.5±14.6	47.7±16.3	0.236
APTT ($\bar{x}$ ± s)	46.0±19.7	44.5±19.8	0.527
PT ($\bar{x}$ ± s)	16.2±7.8	15.3±7.8	0.46
White blood cells, 10^9/L	10.1±5.7	9.0±3.5	0.066
Hemoglobin, g/L	130.2±24.5	129.6±28.3	0.832
Platelet, 10^9/L	214.7±90.5	221.6±83.7	0.499
ALT (M [Q1, Q3]), U/L	37 (15, 78)	35 (17, 72)	0.491
AST, U/L	34 (19, 89)	36 (21, 90)	0.306
Creatinine, μmol/L	70.5 (56, 95)	69.5 (58, 92)	0.831
hs-cTnI, pg/mL	870.9 (103, 9,472.5)	970.2 (89.4, 10,403.0)	0.078
NT-proBNP, pg/mL	1,287.5 (288.7, 4,737)	1,187 (257, 4,469)	0.132
Vasopressors, *n* (%)	102 (71.3)	94 (62.3)	0.063
Glucocorticoid therapy, *n* (%)	138 (96.5)	148 (98)	0.491
Antiviral drugs, *n* (%)	143	151	–
t-MCS, *n* (%)	97 (67.8)	89 (58.9)	0.072

Values are expressed as *n* (%), mean ± standard deviation, or median (Q1, Q3). BMI, body mass index; LVEDD, left ventricular end-diastolic diameter; RVEDD, right ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; hs-cTnI, high-sensitivity cardiac troponin I; t-MCS, temporary mechanical circulatory support.

effects. In addition, immediate post-procedural echocardiography revealed small, asymptomatic pericardial effusions in 11 patients; these effusions were not present prior to the EMB. Consequently, the minor complication rate for EMB was registered at 9.3%.

Additionally, when analyzing the different EMB paths, transradial LV-EMB had no major complications and recorded 10 minor complications. In contrast, transfemoral LV-EMB had one major complication and two minor complications, while transfemoral RV-EMB

Table 2. Comparison of complications during hospitalization and cardiac function at discharge between non-EMB group and EMB group

Variables	Non-EMB group (N = 143)	EMB group (N = 151)	p value
Hospital stays	9 (7, 14)	10 (8, 15)	0.270
Major complication, *n* (%)			
Death	3 (2.0)	0	0.250
Acute heart failure	61 (40.4)	50 (33.1)	0.453
Ischemic stroke	3 (2.0)	2 (1.3)	0.500
Cardiogenic shock	83 (55.0)	65 (43.0)	0.453
Cardiac tamponade	0	2 (1.3)	0.333
Ventricular arrhythmias	30 (20.0)	20 (13.2)	0.415
Minor complication, *n* (%)			
Third-degree AV block	31 (20.5)	25 (16.6)	0.441
Pericardial effusion	9 (6.0)	11 (7.2)	0.545

Table 3. Complications associated with EMB

Variables	N = 151
Procedure time, min	23.7±10.3
Number of biopsy samples	3 (3, 3)
Complications, *n* (%)	17 (11.3)
Major complications	3 (2.0)
Stroke/TIA	0
Pericardial tamponade	2 (1.3)
Death	0
Permanent AV block	0
Ventricular fibrillation	1 (0.7)
Minor complications	14 (9.3)
Transient chest pain	0
Transient hypotension	0
Transient AV block	1 (0.7)
Pericardial effusion	11 (7.3)
Cardiovascular vagal reaction	2 (1.3)
Vascular access site complications	0

experienced two major and two minor complications (see online supplementary Table 1). From the overall incidence of complications, there was no statistical difference between groups. However, in terms of major complications, the complication rate of transradial LV-EMB may be better than transfemoral LV-EMB and transfemoral RV-EMB ($p < 0.05$). The EMB procedures were mainly performed by two cardiovascular professors in our center. Ultrasound examinations were performed by a sonographer.

There were 134 patients who did not experience any complications, but 17 patients experienced. There was no difference in the incidence of complications in the left and right ventricles. Compared with patients without any complications, the proportion of NYHA patients with grade III/IV heart function was higher in complication group (p = 0.048). Besides, the platelet counts at admission are lower (188.2 ± 57.3 vs. 226.7 ± 86.1, p = 0.014). At the same time, the time of the procedure (30.5 ± 15.8 vs. 24 ± 10.0, p = 0.025), heart rates (82.8 ± 15.3 vs. 74.3 ± 12.7, p = 0.024), and BNP (4,039.5 [1,829.3, 7,021.5] vs. 885 [214.8, 4,268], p = 0.014) were higher in the complication group than those in the non-complication group. Table 4 shows detailed difference.

The variables selected by regression were included in the logistic regression model (Table 5). In Table 5, ventricular biopsy means left ventricle or RV. The analysis results show that duration of surgeries (OR: 1.101, 95% CI: 1.029–1.079, p = 0.006) and high BNP levels (OR: 1.083, 95% CI: 0.931–1.258, p = 0.034) were independent risk factors for EMB complications (Fig. 2).

Final Myocarditis Diagnoses of Patients

In the EMB group, there were 99 patients with biopsy-proven myocarditis. In addition, 2 cases were diagnosed with amyloidosis, 3 cases of hypertrophic cardiomyopathy, 3 cases of restrictive cardiomyopathy, and 3 cases of myocardial infarction. The remaining patients had negative biopsy results. In the non-EMB group, combined with clinical data and cardiac magnetic resonance data, 125 cases were diagnosed with myocarditis, 3 cases with amyloidosis, 3 cases of hypertrophic cardiomyopathy, 6 cases of restrictive cardiomyopathy, and 6 cases of myocardial infarction. See online supplementary Table 2 for details.

Table 4. Comparison of baseline clinical data in patients with/without complications

Variables	Control group (N = 134)	Complication group (N = 17)	p value
Age, years	37.9±16.9	45.4±18.3	0.253
Women, *n* (%)	61 (45.5)	8 (47.1)	0.571
BMI	23.3±3.6	22.1±4.2	0.333
NYHA class, %			0.048
I/II	97	8	
III/IV	37	9	
Echocardiography			
LVEDD, mm	4.9±0.8	4.7±0.9	0.342
RVEDD, mm	2.6±0.5	2.6±0.6	0.775
IVS, mm	1.0±0.3	1.1±0.4	0.988
EF, %	48±16.3	45.3±16.2	0.489
White blood cells, 10^9/L	9±3.3	9.6±4.7	0.55
Hemoglobin, g/L	130.7±29	121.9±22.5	0.192
Platelet, 10^9/L	226.7±86.1	188.2±57.3	0.014
APTT, s	44.2±20.1	46.7±18.4	0.601
PT, s	15.2±8.3	15.9±2.6	0.714
ALT, U/L	35.5 (18, 71.3)	36.5 (14.3, 118)	0.807
AST, U/L	35.5 (21, 81.8)	47.5 (19.5, 176.8)	0.395
Creatinine, μmol/L	69 (57.8, 88.5)	93 (58, 130.5)	0.124
Hs-cTnI, pg/mL	747.4 (92.5, 8,852.3)	988.3 (68.3, 19,598.8)	0.543
BNP, pg/mL	885 (214.8, 4,268)	4,039.5 (1,829.3, 7,021.5)	0.014
Procedure time, min	24±10.0	30.5±15.8	0.025
Blood pressure, mm Hg			
Systolic BP	117.4±19.2	117.4±19.1	0.997
Diastolic BP	71.3±12.7	70.9±12.1	0.913
HR, times/min	74.3±12.7	82.8±15.3	0.024

BMI, body mass index; RVEDD, right ventricular end-diastolic diameter; LVEDD, left ventricular end-diastolic diameter.

Long-Term Safety of EMB

In this study, patients underwent follow-up evaluations at intervals of 1, 3, and 6 months post-discharge, followed by biannual assessments thereafter. Out of the 255 patients who completed the follow-up, the median duration of the follow-up was 18 months, reaching up to 48 months in the longest case. Overall, 135 participants from the EMB group and 120 participants from the non-EMB group completed their follow-up. The predefined endpoint events for this study included the occurrence of MACE, ventricular dilatation, and myocardial function deterioration. Table 6 illustrates the incidence of these endpoint events among the patients, comparing those who underwent EMB with those who did not.

The Kaplan-Meier survival curve analysis revealed a higher incidence of endpoint events in the non-EMB group compared to the patients who received EMB, with a statistically significant difference (log-rank $p < 0.05$). For a detailed depiction, refer to Figure 3.

Discussion

To our knowledge, this is one of the few studies looking into the short-term and long-term effects of EMB on patients with myocarditis. Our study also explores the risk factors for complications arising from EMB.

Table 5. Logistic univariate regression analysis about the risk factors of EMB complication

	OR (95% CI)	*p* value
Biopsy of the ventricle	0.537 (0.158–1.821)	0.318
Gender	1.064 (0.378–2.942)	0.905
Age	1.026 (0.996–1.056)	0.091
LVEDD	0.536 (0.234–1.232)	0.142
RVEDD	1.297 (0.426–3.951)	0.647
IVS	1.187 (0.266–5.927)	0.822
EF	0.98 (0.945–1.016)	0.274
APTT	1.006 (0.981–1.032)	0.614
PT	0.989 (0.919–1.063)	0.759
D-dimer	2.408 (0.665–8.719)	0.181
White blood cells	1.047 (0.906–1.211)	0.532
Hemoglobin	0.999 (0.975–1.023)	0.92
Platelet	0.994 (0.987–1.002)	0.133
Time of EMB procedure	1.075 (1.028–1.124)	0.001
Systolic BP	1.023 (0.984–1.064)	0.256
Diastolic BP	0.982 (0.926–1.041)	0.537
HR	1.053 (1.007–1.102)	0.024
cTnI >1,000 (pg/mL)	1.165 (0.423–0.768)	0.768
BNP >1,000 (pg/mL)	1.053 (0.928–1.178)	0.045

RVEDD, right ventricular end-diastolic diameter; LVEDD, left ventricular end-diastolic diameter.

In the population with myocarditis, EMB carries a risk of surgical complications in the short term. In our study, the incidence of major complications was 2%. Remarkably, none of the patients died. A patient who underwent LV-EMB developed ventricular fibrillation and 2 RV-EMB patients had cardiac perforation. In particularly, LV-EMB showed a lower incidence of cardiac perforation compared with RV-EMB, most likely because of the thinner RV wall. Several studies have already demonstrated safety and feasibility of LV-EMB compared with RV-EMB [11, 16, 19]. In a study by Chimenti and Frustaci [16], a total of 4,221 patients underwent diagnostic EMB between 1983 and 2010 performed by only two experienced interventional cardiologists, with 2,396 patients undergoing biventricular EMB, 1,153 patients undergoing selective LV-EMB, and 672 patients undergoing selective RV-EMB. In line with the results of our study, the authors reported very low rates of major complications (i.e., 0.08% perforation with cardiac tamponade and 0.22% brain embolization with transient cerebral ischemia) with no significant differences between LV-EMB and RV-EMB [16]. Perforations with cardiac tamponade as a major complication of EMB have also been reported in a prospective study of 546 patients undergoing RV-EMB investigating complications [20]. In this study, ventricle perforations were documented in 0.5% of patients and 2 patients dead. As mentioned by Chimenti and Frustaci [16], EMB should only be performed by experienced interventional cardiologists in order to reduce the risk of procedure-related complications. When compared to other studies on EMB, our major complication rate of 2% is considered high. In a retrospective study of 2,505 cases, there were 2 cases of cardiac perforation among the major complications of EMB surgery, with an incidence rate of 0.08% [21]. Our main complication rate was high due to lack of relevant experience in the initial stage of the operation, and 2 cases of cardiac perforation occurred. With the maturity and advancement of operator skills, the incidence of major complications is getting lower and lower.

Although the safety of the femoral artery access for LV-EMB has been proven, the radial artery access has gained increasing interest for LV-EMB. This is primarily based on the results of several studies involving robust evidence in favor of the transradial artery access in patients presenting with acute coronary syndrome undergoing primary percutaneous coronary intervention by experienced interventional cardiologists. For example, the Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of angioX (MATRIX) trial compared radial artery with the femoral artery access in 8,404 patients presenting with acute coronary syndrome [22]. The results of the trial revealed that the radial artery access was associated with significantly lower risks of bleeding in access site (including need for transfusion) and vascular complications. Moreover, the authors reported a significant mortality benefit in patients allocated to the radial artery access site. In addition to reducing the incidence of complications associated with the radial approach, the radial approach also enables an earlier mobilization of the patients and a potentially earlier discharge.

In our study, the rate of minor complications associated with EMB was relatively low at 9.3%, aligning with findings from several prior studies. This rate underscores the safety of EMB procedures. Specifically, we observed minor pericardial effusion in 12 patients, vasovagal reactions in two, and a transient AV block in 1 patient. The incidence of vasovagal reactions might be attributed to the excessive tightening of radial artery compression

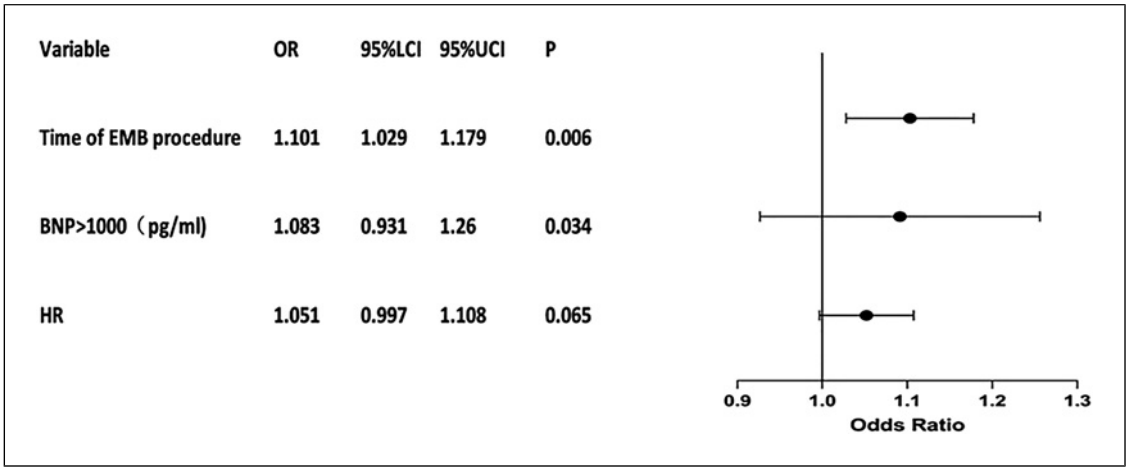

Fig. 2. Logistic multivariate regression analysis about the risk factors of EMB complication.

Table 6. Incidence of endpoint events in patients of two groups

Variables	Non-EMB group (*N* = 120)	EMB group (*N* = 135)	*p* value
MACE, *n* (%)			
Cardiac death	4 (3.3)	3 (2.2)	0.642
Heart failure	6 (5.0)	4 (3)	0.458
Myocardial infarction	1 (0.8)	1 (0.7)	0.965
Stroke	1 (0.8)	0	0.485
Dilatation of ventricles	26 (21.7)	14 (10.4)	<0.001
Decrease of EF	30 (25)	18 (13.3)	0.037

tourniquets. Notably, the occurrence of AV block was uncommon, and there were no cases of other conduction disturbances like atrial fibrillation, paralleling the results of retrospective analyses from earlier studies on post-EMB conduction abnormalities [21].

In the comparison of patients without complications and patients with complications, we found that preoperative patients with low platelet counts, high BNP, and higher NYHA class were more likely to lead to complications. Moreover, an increase in the duration of the EMB procedure can lead to a higher risk of complications. This suggests that preoperative evaluation of the above indicators should be focused, and EMB should not be performed prematurely. Also, the duration of procedure should be minimized to reduce the risk of complications in patients.

The logistic regression analysis results showed that duration of procedure and high BNP levels were independent risk factors for EMB complications. High BNP levels often imply that the patient has poorer heart function, and proceeding with the EMB diagnostic procedure for such patients is more likely to result in the occurrence of EMB complications. Also, the longer the duration of the procedure, the longer the surgical instruments operate on the endocardium and the myocardium, which may lead to adverse consequences. These conclusions are consistent with our clinical experience. Comparing to the non-EMB group, during the hospitalization period, EMB does not have adverse effects on the patients' cardiac function, does not prolong the patients' hospital stay, and does not lead to an increase in complications related to myocarditis.

In the long run, EMB may be safe for patients and does not lead to negative effects. The study's defined endpoint events encompass the incidence of MACE, dilatation of ventricles, and deterioration of myocardial performance. During the follow-up period, there were 40 endpoint events in the EMB group and 68 endpoint events in the non-EMB group. From the long-term follow-up results, the adverse events in the EMB

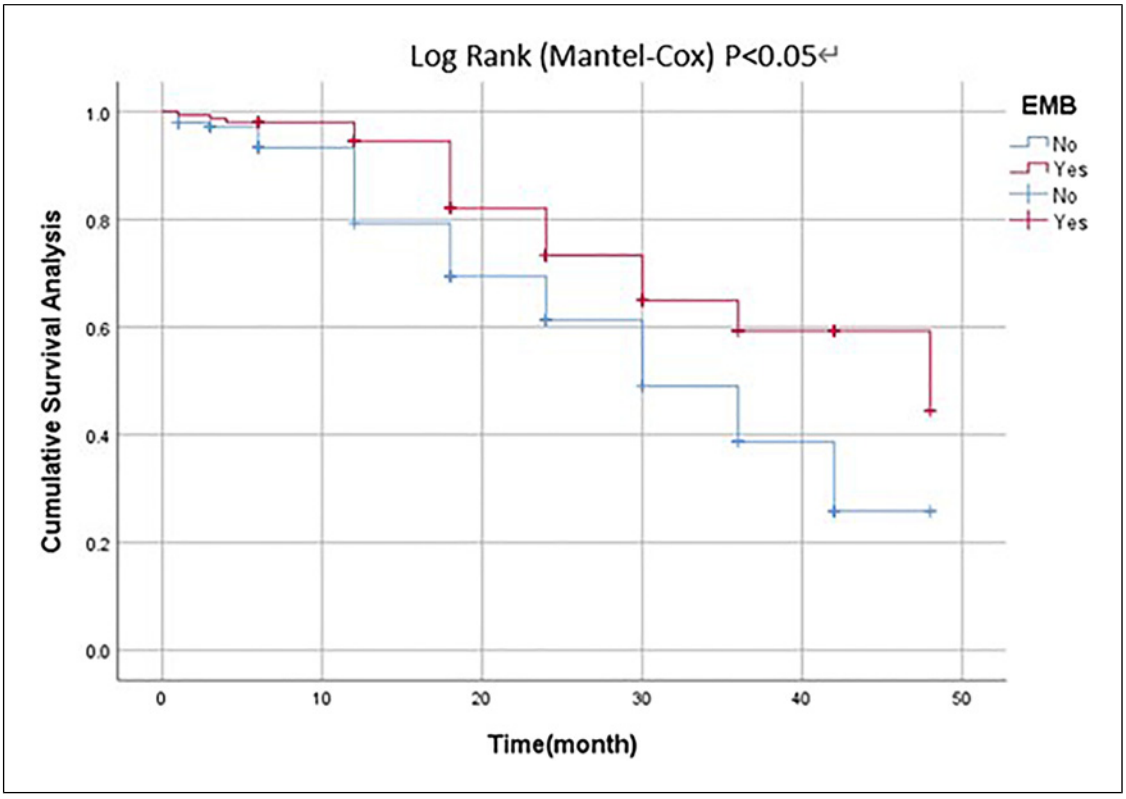

Fig. 3. Comparison of survival rates for endpoint events between EMB group (n = 130) and non-EMB group (n = 125) (Kaplan-Meier curve). The red line (yes) represents the EMB group and the blue line (no) represents the non-EMB group.

group were lower than those in the non-EMB group. Kaplan-Meier survival curve analysis showed that the incidence of endpoint events in non-EMB group was higher than that of EMB group (log-rank p = 0.001). We believe that conducting an EMB can definitively diagnose patients with clinically [23] suspected myocarditis and pathologically subtype the myocarditis of the patient. Different types of myocarditis require distinct therapeutic approaches. Following a clear diagnosis via EMB, targeted treatment can be administered to the patient, consequently improving their prognosis. Inappropriate treatment with temporary mechanical circulatory support (IMT) without systematic diagnosis confirmation by EMB may expose this population to severe infectious complications. Given that early recognition and accurate histologic identification of FM are considered cornerstones to reducing mortality, EMB is recommended in adult patients with FM [18, 23–25]. In light of our study, we recommend that an EMB diagnostic procedure be conducted on adult patients with myocarditis during their hospital stay.

Limitations

The study was conducted as a retrospective single-center cohort study. Due to the single-center design, the amount of procedure performed at different centers and the experience of the operator may have an impact on the occurrence of complications. Moreover, the study population consisted of patients with suspected myocarditis who were relatively young and had little comorbidity. The safety profile might vary in other patient populations. The safety of EMB will need to be validated with larger, more representative samples in the future. The long-term effect of EMB requires a larger follow-up sample and a longer follow-up time. In addition to histopathological analysis, modern laboratory techniques such as viral genome analysis and immunohistochemistry should be used to improve the diagnosis rate of EMB. Additionally, the reported complication rate might be underestimated due to selection bias and other confounders related to the non-prospective study design. The pathology department's limitations meant that only standard pathological analysis was conducted on the biopsy tissue, and myocarditis

was not classified. Consequently, the study's inability to classify the different types of myocarditis represents a significant limitation in understanding the disease's nuances.

Conclusions

In patients with myocarditis, EMB is associated with a risk of short-term complications, with higher levels of BNP and operative duration being independent risk factors for EMB-related complications. However, EMB may not adversely affect cardiac function or length of stay during hospitalization and does not adversely affect long-term outcomes in patients with myocarditis. This study provides a detailed dissection of EMB-related risk factors, providing clinicians with valuable insights to mitigate potential complications. As such, this research lays the groundwork for subsequent investigations aimed at optimizing EMB protocols and refining patient selection criteria to further minimize risks and maximize therapeutic efficacy.

Statement of Ethics

The written informed consent was obtained from participants to participate in the study. This study protocol was reviewed and approved by the Ethics Committee of Tongji Hospital, affiliated with Huazhong University of Science and Technology (Ethics Approval No. TJ-IRB202402093).

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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Author Contributions

Ze-Ping Li, Guang-Lin Li, Ya-Nan Wang, Hong Yang, Jian-Gang Jiang Lu-Yun Wang, Guang-Ling Cui, and Kun Miao: conceptualization. Jian-Gang Jiang: funding acquisition. Ze-Ping Li: writing – original draft. Guang-Lin Li, Ya-Nan Wang, Hong Yang, Jian-Gang Jiang, Lu-Yun Wang, Guang-Ling Cui, and Kun Miao: writing – review and editing. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author Jiang upon reasonable request.

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