Original Article

Left Ventricular Longitudinal Systolic Function in Septic Shock Patients with Normal Ejection Fraction: A Case-control Study

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Abstract

Background: Septic cardiomyopathy is a common finding in septic shock patients. The accepted definition of septic cardiomyopathy is often based on the left ventricular ejection fraction (LVEF). The aim of this study was to determine whether the left ventricular longitudinal systolic function was more sensitive than the LVEF in heart function appraisal of septic shock patients.
Methods: This was a case-control study conducted at a 40-bed Intensive Care Unit (ICU) of Peking Union Medical College Hospital. Septic shock patients admitted to the ICU were consecutively enrolled in the study group from March 1, 2016 to September 1, 2016. The control group was selected from nonsepsis patients who were admitted to the ICU and were comparable to the study group. Transthoracic echocardiography was performed to obtain the LVEF measurement, mitral annular plane systolic excursion (MAPSE), tissue Doppler velocity measurement of mitral annulus (Sa), and tricuspid annular plane systolic excursion.
Results: The study group consisted of 45 septic shock patients. Another 45 nonsepsis patients were selected as the control group. There was no difference in the LVEF between the two groups (64.6% vs. 67.2%, $t = -1.426$, $P = 0.161$). MAPSE in the study group was much lower than in the control group (1.2 cm vs. 1.5 cm, $t = -4.945$, $P < 0.001$). Sa in the study group was also lower than in the control group (10.2 cm/s vs. 11.8 cm/s, $t = -2.796$, $P = 0.014$).
Conclusions: Compared to the LVEF, longitudinal systolic function might be more sensitive in the detection of cardiac depression in septic shock patients. In the heart function appraisal of septic shock patients with a normal ejection fraction, more attention should be given to longitudinal function parameters such as MAPSE and Sa.

Key words: Cardiomyopathy; Heart Function; Systolic; Transthoracic Echocardiography

Introduction

Sepsis and septic shock are major health problems with high morbidity and mortality that affect millions of people across the globe each year.[1,2] Septic cardiomyopathy is a common finding in septic shock patients; an understanding of whether it can worsen a patient's prognosis remains elusive.[3] However, septic cardiomyopathy clearly will make hemodynamic and tissue perfusion more vulnerable in septic shock patients.[4]

Currently, the most accepted definition of myocardial dysfunction in septic shock is based on a left ventricular ejection fraction (LVEF) of <45–50%.[5,6] A meta-analysis showed that the presence of a low LVEF was neither a sensitive nor specific predictor of mortality in septic shock patients.[7] A longitudinal strain is a sensitive echocardiographic tool to evaluate LV systolic function

Access this article online
Quick Response Code:
Website: www.cmj.org
DOI: 10.4103/0366-6999.205856

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Received: 16-12-2016 **Edited by:** Ning-Ning Wang
How to cite this article: Zhang HM, Wang XT, Zhang LN, He W, Zhang Q, Liu DW, Chinese Critical Ultrasound Study Group. Left Ventricular Longitudinal Systolic Function in Septic Shock Patients with Normal Ejection Fraction: A Case-control Study. Chin Med J 2017;130:1169-74.

and is associated with hospital mortality in septic shock patients.[8,9] Carasso *et al.*[10] noted that longitudinal strain was more sensitive than LVEF in detecting abnormalities in LV systolic function. Despite the fact that strain measurement is a novel technique, there is a possibility that it is the longitudinal function rather than the strain measurement that makes this method more sensitive than the LVEF in the detection of septic cardiac depression.

The conventional longitudinal function measurement includes mitral annular plane systolic excursion (MAPSE) and tissue Doppler velocity measurement of mitral annulus (Sa). Several studies have used MAPSE as a good parameter of systolic function.[11-13] Others have used Sa to represent longitudinal systolic function.[14] However, whether longitudinal function parameters such as MAPSE and Sa will be more sensitive than LVEF when detecting cardiac depression in septic shock patients has not yet been fully analyzed. We hereby performed an observational study to investigate the LV longitudinal systolic function in septic shock patients with normal LVEF.

Methods

Ethical approval

The study was conducted according to the *Declaration of Helsinki* and was approved by the ethics committee of Peking Union Medical College Hospital (Approval Number: S617). The written informed consent was obtained from the next of kin of all of the patients.

Study population

This was a case-control study conducted at a 40-bed Intensive Care Unit (ICU) in Peking Union Medical College Hospital. Septic shock patients admitted to the ICU from March 1, 2016 to September 1, 2016 were studied. Diagnosis of septic shock was made based on the new definition that was developed by the sepsis definitions task force; the definition of septic shock included: sepsis patients with persisting hypotension requiring vasopressors to maintain mean arterial pressure ≥65 mmHg (1 mmHg = 0.133 kPa) and a serum lactate level >2 mmol/L, despite adequate volume resuscitation. Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction could be identified as an acute change in total Sepsis-related Organ Failure Assessment (SOFA) score of 2 points consequent to the infection.[15]

Patients were excluded if they had any of the following conditions: <18 years old, pregnancy, cardiac surgery, history of valvular stenosis or insufficiency, primary cardiomyopathy, acute coronary syndrome, moderate to severe pulmonary hypertension, inadequate image, or LVEF below 50%.

The control group consisted of nonsepsis patients who were age-matched, gender-matched, and cardiovascular risk factor matched with the study group. All patients who were enrolled received a transthoracic echocardiographic evaluation within 24 h of ICU admission. In order not to interfere with the initial salvage measures and to avoid a hypovolemic state, all of the echo examinations were performed after early resuscitation when the patients' hemodynamics were relatively stable. Physiologic parameters, including hemodynamic data and current vasoactive medications, were recorded at the time of echocardiography.

Echocardiography

Heart rate and blood pressure were obtained from the monitor at the onset of examination. Images were recorded for offline analysis. Two intensivists who were experienced with echocardiography performed the echo examination. To reduce the interobserver variability, both of the performers were present during each echo examination to double check the results, and a third echocardiographer was consulted if there was disagreement.

Echocardiograms were performed using an echocardiograph (Sonosite, M-Turbo, California, USA) with a 2.5-MHz phased-array probe. Electrocardiograph was recorded continuously during the echo examination. Three cardiac cycles were analyzed and averaged. Patients were in the semi-left lateral position during the examination. Echocardiographic M-mode and Doppler measurements were taken in a standard manner.

LVEF was obtained using the modified biplane Simpson's method from apical two- and four-chamber views. Indexes of longitudinal systolic function measurements were taken from the apical four-chamber view. MAPSE was obtained by putting the cursor along the mitral ring and measuring the difference between the highest and lowest point of the M-mode sinusoid wave. A value of lower than 10 mm represented systolic dysfunction.[16] Tricuspid annular plane systolic excursion (TAPSE) was obtained by putting the M-mode cursor along the lateral part of the tricuspid valve ring. Sa was performed in the apical four-chamber views by placing a 5-mm sample volume at the lateral site of the mitral annulus in accordance with the American Society of Echocardiography recommendations.[17] The e' was the annular motion of the mitral valve in early diastole using tissue Doppler imaging. Filters and gains were adjusted to achieve the optimal signal-to-noise ratio.

Statistical analysis

Statistical analysis was performed using the SPSS version 13.0 statistical software package (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as the mean ± standard deviation (SD) or median (inter-quartile range). Categorical variables were presented as the number and the percentages. Continuous variables were compared with the use of Student's *t*-test or Mann-Whitney *U*-test. Categorical variables were compared with Chi-square test or Fisher's exact test. Statistical significance was defined as a value of $P < 0.05$.

Results

General characteristics of all patients

Sixty-two consecutive septic shock patients who were admitted to the ICU were screened for enrollment. Seven were excluded because of poor image quality, six were excluded because of an LVEF below 50%, three were excluded because of valvular disease, and one was excluded because of acute coronary syndrome. Ultimately, 45 septic shock patients were selected as the study group. Another 45 nonsepsis patients were selected as the control group. The mean ages of the two groups were 62.5 ± 13.8 years old and 59.7 ± 15.6 years old, respectively, and 48.9% vs. 46.7% were men. No difference was found in cardiovascular risk factors between the two groups. The study group had higher Acute Physiology and Chronic Health Evaluation (APACHE II; 22.3 ± 10.7 vs. 12.4 ± 3.9, t = 2.765, P = 0.003) and SOFA scores (11.2 ± 3.2 vs. 2.5 ± 0.9, t = 14.560, P < 0.001). Ten patients in the study group died in the hospital, while no deaths were found in the control group [Table 1].

Respiratory support and hemodynamic data

The proportion of patients on ventilation in the two groups was similar (86.7% vs. 75.6%, χ^2 = 1.813, P = 0.178). The positive end-expiratory pressure (PEEP) level (6 ± 2 cmH_2O vs. 5 ± 1 cmH_2O, t = 1.538, P = 0.125) and plateau pressure (18 ± 5 cmH_2O vs. 17 ± 3 cmH_2O, t = 1.505, P = 0.140) in the two groups were not significantly different. The study group had a higher heart rate than the control group (99 ± 20 beats/min vs. 81 ± 17 beats/min, t = 4.376, P < 0.001). No patients in the control group were prescribed norepinephrine, while all patients in the study group were infused with norepinephrine with a median dose of 0.26 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The mean arterial blood pressure between the two groups was not significantly different (86 ± 14 mmHg vs. 91 ± 14 mmHg, t = −1.736, P = 0.086) [Table 1].

Echocardiographic measurements

There were no differences found between the two groups in terms of LV diastolic internal diameter and systolic internal diameter (47.6 ± 6.2 mm vs. 47.9 ± 2.7 mm, t = −0.220, P = 0.826; 29.8 ± 6.5 mm vs. 28.4 ± 3.8 mm, t = 1.105, P = 0.274, respectively). There was also no difference in the LVEF in the two groups (64.6% ± 9.3% vs. 67.2% ± 8.8%, t = −1.426, P = 0.161). No significant difference was found on the E-wave peak velocity, A-wave peak velocity, or e' between the two groups (73.4 ± 20.9 cm/s vs. 73.7 ± 20.1 cm/s, t = −0.016, P = 0.961; 84.8 ± 24.2 cm/s vs. 80.2 ± 12.1 cm/s, t = 0.842, P = 0.518; and 9.8 ± 3.0 cm/s vs. 10.8 ± 2.3 cm/s, t = −1.812, P = 0.073, respectively).

MAPSE in the study group was much lower than in the control group (1.2 ± 0.4 cm vs. 1.5 ± 0.2 cm, t = −4.945, P < 0.001). In the study group, Sa was lower than in the control group (10.2 ± 2.7 cm/s vs. 11.8 ± 2.9 cm/s, t = −2.796, P = 0.014). In the study group, TASPE was also significantly lower than in the control group (1.9 ± 0.4 cm vs. 2.3 ± 0.4 cm, t = −4.216, P < 0.001) [Table 2 and Figures 1a-1d].

Discussion

The present study found that the values of MAPSE and Sa were lower in septic shock patients with normal LVEF than in nonsepsis patients. The result indicates that for septic shock patients, longitudinal systolic function, such as MAPSE and Sa, might already have been compromised before an obvious low ejection fraction emerges.

Although no evidence confirmed the association between septic cardiomyopathy and mortality, it would precipitate the hemodynamic instability of septic shock patients.[7,18] Thus, the detection of cardiac depression should be an integral part of hemodynamic management in septic shock patients. The finding in this study was worth considering in the management of hemodynamics in septic shock. First, we could have a better chance to discover the LV dysfunction

Table 1: General characteristics of the sepsis shock group and nonsepsis group (n = 45)

Items	Study group	Control group	t or χ^2	P
Age (year)	59.7 ± 15.6	62.5 ± 13.8	−0.901*	0.370
Sex (male), n (%)	22 (48.9)	21 (46.7)	0.044	0.833
APACHE II	22.3 ± 10.7	12.4 ± 3.9	2.765*	0.003
SOFA	11.2 ± 3.2	2.5 ± 0.9	14.560*	<0.001
Cardiovascular risk factors, n (%)				
Hypertension	12 (26.7)	16 (35.6)	0.829	0.362
Diabetes mellitus	6 (13.3)	10 (22.2)	1.216	0.114
Coronary heart disease	3 (6.7)	1 (2.2)	1.047	0.306
Chronic renal failure	5 (11.1)	4 (8.9)	0.123	0.725
Patients on ventilation, n (%)	39 (86.7)	34 (75.6)	1.813	0.178
PEEP (mmHg)	6 ± 2	6 ± 1	1.538*	0.125
Pplat (mmHg)	18 ± 5	17 ± 3	1.505*	0.140
Oxygen saturation (%)	98 ± 2	99 ± 1	−1.065*	0.293
NE ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.26 (0.06–2.60)	–		
HR (beats/min)	99 ± 20	81 ± 17	4.376*	<0.001
MAP (mmHg)	86 ± 14	91 ± 14	−1.736*	0.086
Prognosis, n (%)				
In-hospital mortality	10 (22.2)	0	11.250	<0.001

The data were presented by mean ± standard deviation, median (inter-quartile range) or n (%).*t value. NE: Norepinephrine; PEEP: Positive end expiratory pressure; Pplat: Plateau pressure; APACHE: Acute Physiology and Chronic Health Evaluation; HR: Heart rate; MAP: Mean arterial pressure; SOFA: Sepsis-related Organ Failure Assessment.

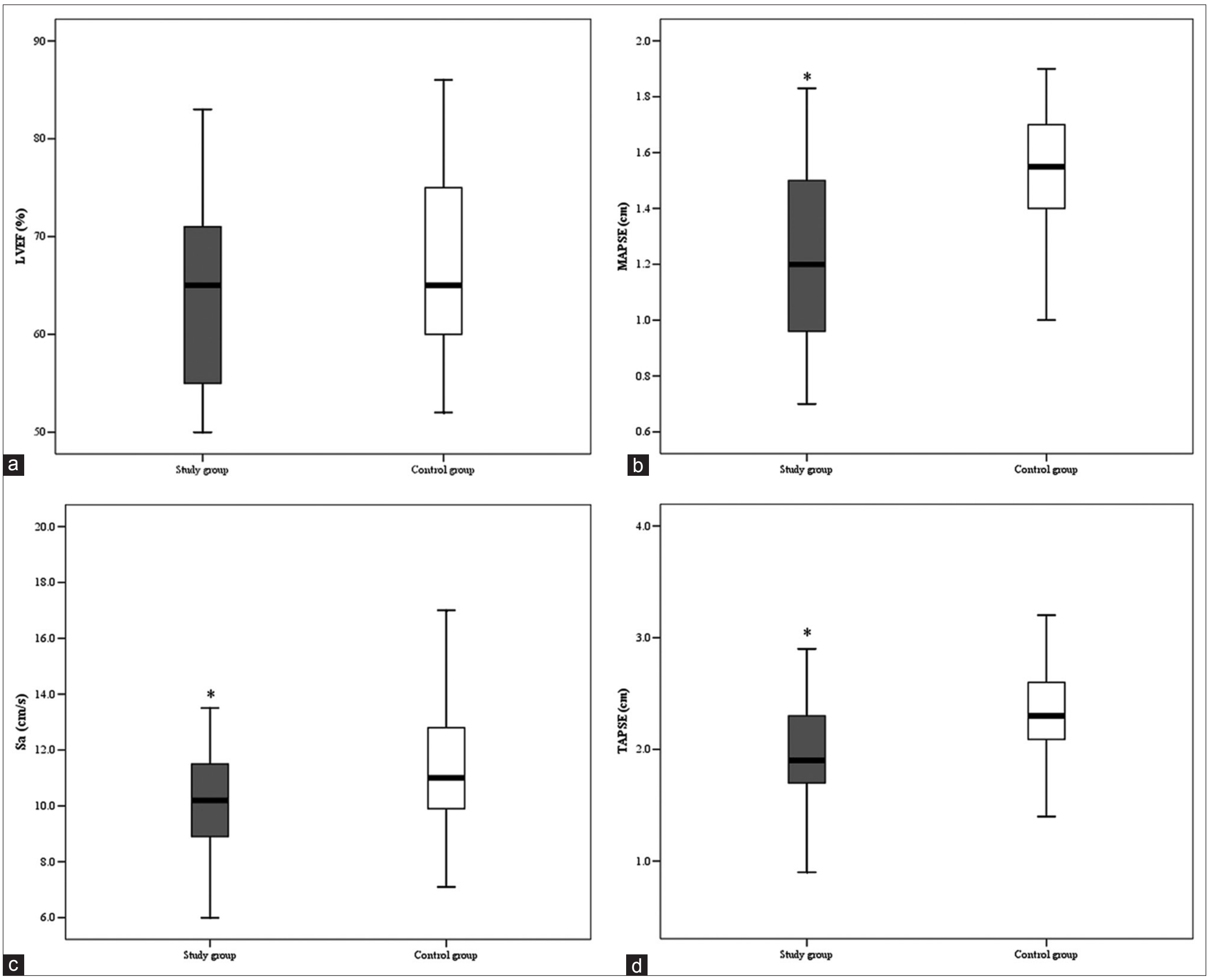

Figure 1: Left ventricular ejection fraction (LVEF) of the sepsis shock group and nonsepsis group ($n = 45$). No difference was found between two groups (64.6 ± 9.3% vs. 67.2 ± 8.8%, respectively, $P = 0.161$) (a). Mitral annular plane systolic excursion (MAPSE) of the sepsis shock group and nonsepsis group ($n = 45$). *Compared with the control group, the study group had a lower mitral annular plane systolic excursion value (1.2 ± 0.4 cm vs. 1.5 ± 0.2 cm, respectively, $P < 0.001$) (b). Tissue Doppler velocity measurement of mitral annulus (Sa) of the sepsis shock group and nonsepsis group ($n = 45$). *Compared with the control group, the study group had a lower Sa value (10.2 ± 2.7 cm/s vs. 11.8 ± 2.9 cm/s, respectively, $P = 0.014$) (c). Tricuspid annular plane systolic excursion (TAPSE) of the sepsis shock group and nonsepsis group ($n = 45$). *Compared with the control group, the study group had a lower tricuspid annular plane systolic excursion value (1.9 ± 0.4 cm vs. 2.3 ± 0.4 cm, respectively, $P < 0.001$) (d).

earlier. Second, this method was much easier than LVEF measurement in the critical care setting.

It is well known that the LVEF cannot only be influenced by intrinsic contractility but can also be affected by the preload and afterload of the heart during the examination. However, we performed the echo after initial resuscitation; thus, the possibility of hypovolemia could be ruled out. Vieillard Baron *et al*.[19] found in their study that after early resuscitation, the LV volume remained in a normal range, and the stroke index was uniquely determined by the systolic function. No difference in MAP was found between the two groups, indicating that there was little chance for afterload to influence the LVEF. Thus, the LVEF of the two groups were mainly the reflection of LV contractility.

Although the majority of myocardial fibers are arranged circumferentially, longitudinal fibers also play an important role in maintaining normal function. During ventricular contraction, the base of the heart moves toward the apex; the magnitude of the movement is believed to be proportional to systolic function. Therefore, the assessment of long-axis function provides a simple and fast evaluation of the LV systolic function that is especially useful for ICU patients without an optimal image.[20] The value of MAPSE in the study group, although still within the normal range, was much lower than that in the control group.[21] Because the echo examination can be performed at least once per day, continuous monitoring of MAPSE to detect a decrease in the value is completely feasible in the critical care setting. If we can discover a decreasing trend in MAPSE, irrespective of whether it is within the normal range, care should be taken that myocardial depression might have already occurred.

Subendocardial muscle fibers that are longitudinal and responsible for long-axis function are more susceptible

Table 2: Echocardiographic parameters the sepsis shock group and nonsepsis group (*n* = 45)

Categories	Study group	Control group	*t*	*P*
LVDD (mm)	47.6 ± 6.2	47.9 ± 2.7	−0.220	0.826
LVSD (mm)	29.8 ± 6.5	28.4 ± 3.8	1.105	0.274
LVEF (%)	64.6 ± 9.3	67.2 ± 8.8	−1.426	0.161
E-wave (cm/s)	73.4 ± 20.9	73.7 ± 20.1	−0.016	0.961
A-wave (cm/s)	84.8 ± 24.2	80.2 ± 12.1	0.842	0.518
e' (cm/s)	9.8 ± 3.0	10.8 ± 2.3	−1.812	0.073
E/e'	7.7 ± 2.1	8.1 ± 2.1	−0.506	0.614
TAPSE (cm)	1.9 ± 0.4	2.3 ± 0.4	−4.216	<0.001
Sa (cm/s)	10.2 ± 2.7	11.8 ± 2.9	−2.796	0.014
MAPSE (cm)	1.2 ± 0.4	1.5 ± 0.2	−4.945	<0.001

All data were presented by mean ± SD. LVDD: Left ventricular diastolic internal diameter; LVSD: Left ventricular systolic internal diameter; LVEF: Left ventricular ejection fraction; E-wave: Early wave of mitral inflow detected by pulse Doppler; A-wave: Mitral inflow occurs with atrial systole detected by pulse Doppler; e': The annular motion of the mitral valve in early diastole using tissue Doppler imaging; TAPSE: Tricuspid annular plane systolic excursion; Sa: Tissue Doppler velocity measurement of mitral annulus; MAPSE: Mitral annular plane systolic excursion; SD: Standard deviation.

to ischemia and injury.[22] Although no evidence support reduced overall coronary perfusion during septic shock, microvascular alteration may be associated with focal ischemia. Certainly, the most vulnerable part would be the subendocardial fiber.[23] This can explain why the longitudinal function would be more easily affected in septic shock patients.

Several studies found that global longitudinal strain measured through the speckle tracking method can detect LV impairment.[8,9] Nevertheless, in a critical care setting where patients are predominantly ventilated, obtaining optimal image quality for strain measurements can be challenging. Consequently, the longitudinal strain value obtained based on poor image quality may not accurately reflect actual LV deformation. In addition, reproducibility and standardization of reference values are not uniform across echocardiography systems because manufacturers use different algorithms.[24] However, MAPSE, also representing longitudinal function, will be easier to obtain and will be less influenced by the image and technology.

TAPSE is a good marker of the right ventricular systolic function.[25,26] Singh *et al.*[27] stated in their study that TAPSE was reflective of biventricular function in critically ill patients. A prior study demonstrated that the proportion of the right heart dysfunction in septic shock patients was approximately 31%.[28] In this study, TAPSE in the study group, also within the normal range, decreased significantly, indicating that the right heart was also affected when LV longitudinal function was impaired. Positive ventilation might influence the TAPSE by way of increasing right ventricular afterload.[29] However, in this study, the PEEP and plateau pressures were not different between the two groups. Thus, the possibility of ventilator-related TAPSE decreasing in septic shock patients could be ruled out. The ventricular interdependence might also play a role in the decrease of TAPSE. A previous study demonstrated that 30% of the contraction force of the RV comes from the left ventricle.[30] When the left ventricle is affected in septic shock, the right ventricle is as well.

This study had several limitations. First, this was a single-center case-control study, selection bias was not impossible. Second, instead of being a serial observation, echocardiographic measurements were performed only once for each patient. Therefore, we were not able to acquire the time point when longitudinal function recovers. If more time points were evaluated, the result would be more robust and clinically meaningful. Third, we did not investigate the longitudinal function of septic shock patients whose LVEF was below 50%; therefore, we failed to explain if the MAPSE and Sa would continue to decrease to an even lower level as the LVEF drops to a value of <50%. Age might also be a confounding factor in this study. Patients in both groups almost reached 60 years old, thus, the results of this research might not be applicable to younger patients.

In conclusion, compared to LVEF, the longitudinal systolic function might be more sensitive in the detection of cardiac depression in septic shock patients. In the heart function appraisal of septic shock patients with normal LVEF, more attention should be given to longitudinal function parameters such as MAPSE and Sa.

Acknowledgments

We are very appreciated for the help from Dr. Li-Xia Liu from Fourth Hospital of Hebei Province.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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