Research Article

Serum Galectin-3 Predicts Mortality in Venoarterial Extracorporeal Membrane Oxygenation Patients

Jianlong Zhu,1 Dehui Guo,2 Liying Liu,3 and Jing Zhong2

1Department of Critical Care Medicine, Ganzhou People’s Hospital, Ganzhou 341000, China
2Department of Critical Care Medicine, Quannan People’s Hospital, Ganzhou 341000, China
3Department of Blood Transfusion, Ganzhou People’s Hospital, Ganzhou 341000, China

Correspondence should be addressed to Jianlong Zhu; zhujianlong@mail.gzsrmyy.com

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Objective. We investigated the potential use of galectin-3 (Gal-3) as a prognostic indicator for patients with cardiogenic shock and developed a predictive mortality model for venoarterial extracorporeal membrane oxygenation (VA-ECMO).

Methods. We prospectively studied patients (survivors and nonsurvivors) who received VA-ECMO for cardiogenic shock from 2019 to 2021. We recorded baseline data, Gal-3, and B-type natriuretic peptide (BNP) before ECMO and 24–72h after ECMO. We used multivariable logistic regression to analyze significant risk factors and construct a VA-ECMO death prediction model. Receiver operating characteristic (ROC) curves were plotted to assess the predictive efficacy of the model.

Results. We enrolled 73 patients with cardiogenic shock who received VA-ECMO support; 38 (52.05%) died in hospital. The median age was 57 years (interquartile range (IQR): 48–67 years); the median duration of ECMO therapy was 5.8 days (IQR: 4.62–7.57 days); and the median intensive care unit stay was 19.04 days (IQR: 13.92–26.15 days). Compared with the nonsurvivors, survivors had lower acute physiology and chronic health evaluation (APACHE) II scores (p < 0.001), increased left ventricular ejection fraction (p < 0.05), lower Gal-3 levels at 24 and 72h (both p < 0.001), lower BNP levels at 24 and 72h (both p = 0.001), and higher platelet counts (p = 0.009). Further multivariable analysis showed that APACHE II score, BNP-T72, and Gal-3-T72 were independent risk factors for death in VA-ECMO patients. Gal-3 and BNP were positively correlated (p < 0.05) and decreased significantly during ECMO treatment. The areas under the ROC curve (AUC) for APACHE II score, Gal-3-T72, and BNP-T72 were 0.687, 0.799, and 0.723, respectively. We constructed a combined prediction model with an AUC of 0.884 (p < 0.01).

Conclusion. Gal-3 may serve as a prognostic indicator for patients receiving VA-ECMO for cardiogenic shock. The combined early warning score is a simple and effective tool for predicting mortality in VA-ECMO patients.

1. Introduction

Cardiogenic shock (CS) is a complex clinical syndrome characterized by impaired cardiac function and end-organ hypoperfusion [1, 2]. Studies have shown that cardiogenic shock develops in 5–13% of patients with acute myocardial infarction (AMI) [3]. CS can be caused by various factors, such as AMI, myocarditis, cardiomyopathy, pericardial tamponade, or postcardiac surgery. In Europe, approximately 60,000–70,000 patients experience AMI each year. Despite significant advances in interventional treatment and critical care, mortality from infarct-related CS remains high, reaching 50% within the first 30 days of hospitalization [4].

Extracorporeal membrane oxygenation (ECMO) has become the primary rescue therapy for patients with severe CS. By providing adequate blood flow and oxygen supply through venoarterial extracorporeal membrane oxygenation (VA-ECMO), the damaged heart can rest and recover, leading to improved symptoms and prognosis in patients with CS.

Galectin-3 (Gal-3) is a multifunctional protein that plays a crucial role in many physiological and pathological processes, such as cell growth, differentiation, apoptosis, cell adhesion, angiogenesis, inflammation, fibrogenesis, and tumor progression. Recent studies have shown that Gal-3 is the most overexpressed protein in heart failure (HF) [5].
It can predict the progression of HF and guide its treatment. Sharma et al. found that Gal-3 is the most differentially regulated gene associated with HF [6]. Gal-3 induces the proliferation of fibroblasts and causes heterogeneous deposition of different types of collagen, ultimately leading to loss of cardiac function. Therefore, Gal-3 may be a novel biomarker for predicting circulatory failure.

Cardiovascular disease is a specialty of our hospital, and more than half of our ECMO patients suffer from this condition. Therefore, developing a predictive model for patients with CS is crucial. The prognostic value of Gal-3 for patients with CS undergoing VA-ECMO has not yet been established. In this study, we aimed to investigate the association between Gal-3 levels and the clinical outcomes in patients receiving VA-ECMO.

2. Methods

This study was a prospective trial and all procedures followed ethical guidelines. All study subjects or their family members gave informed consent for the treatment protocol. The study enrolled patients with cardiogenic shock who received VA-ECMO at Ganzhou People’s Hospital from January 2019 to December 2021. All included subjects had class IV cardiac function according to the New York Heart Association (NYHA) classification. Our study estimated the Gal-3 levels before ECMO treatment and at 72 h for surviving and deceased patients. Based on the expected mean difference, standard deviation, and quantile values, we calculated that a total sample size of 58 was needed for our randomized controlled trial. To improve the reliability and stability of the study results, our team enrolled 73 patients. Patients were categorized into a survivor group and a nonsurvivor group based on their outcome during hospitalization.

The inclusion criteria for this study were as follows: for patients who met the diagnostic criteria for CS and received VA-ECMO at our institution: (1) patients aged over 10 years, as our hospital currently lacks a pediatric ECMO circuit and could not provide ECMO support for younger patients; (2) presence of severe underlying heart disease (such as extensive myocardial infarction, myocarditis, arrhythmia, mechanical valve failure, or post-cardiac surgery); (3) presented with typical clinical signs of shock, including persistent hypotension, oliguria, altered consciousness, and other symptoms; (4) after active fluid resuscitation, hypotension and clinical signs did not improve or worsened; or (5) hemodynamic parameters meet the following typical characteristics: (i) systolic blood pressure (SBP) ≤ 90 mmHg or mean arterial pressure drop ≥ 30 mmHg, or a decrease of 60 mmHg from the baseline systolic blood pressure in hypertension patients for at least 30 min; (ii) central venous pressure is normal or high; (iii) elevated left ventricular end-diastolic pressure or pulmonary capillary wedge pressure; and (iv) reduced cardiac output, and a cardiac index (CI) ≤ 2.2 [L/min]/m²; and (6) informed consent from the patient or their family members for VA-ECMO treatment.

The exclusion criteria were as follows: (1) age < 10 years or > 85 years; (2) chronic kidney disease, cirrhosis, or a history of malignancy; (3) infectious diseases unrelated to the heart; (4) death within 3 days; (5) voluntary withdrawal or incomplete information; and (6) VA-ECMO conversion to venoarterial-venous (VAV)-ECMO or venovenous (VV)-ECMO.

2.1. Data Collection. Basic information including gender, age, underlying disease, cause of cardiogenic shock, body mass index (BMI), and the acute physiology and chronic health evaluation (APACHE) II score were recorded for all patients before VA-ECMO. Venous blood samples were collected at three time points (before ECMO initiation, 24 h after ECMO initiation, and 72 h after ECMO initiation) to measure Gal-3, B-type natriuretic peptide (BNP), platelet, and lactate levels. The durations of ECMO support and intensive care unit (ICU) stay were recorded, and patients were followed up by telephone 28 days after ECMO discontinuation.

2.2. VA-ECMO Therapy. Before ECMO initiation, we assessed the patient’s vascular status by ultrasound to select an appropriate puncture site and catheter size. An arterial and a venous cannula were inserted under ultrasound guidance by a specialist, and the cannula positions were verified by ultrasound or X-ray. We used a standard oxygenator (MAQUET, Germany) that was primed with saline and connected in a sterile manner after successful cannulation of the artery and the vein. ECMO blood flow and oxygen sweep gas flow were adjusted according to the mean arterial pressure and peripheral oxygen saturation to maintain a mean arterial pressure above 65 mmHg. For systemic anticoagulation, the initial bolus dose of heparin sodium was 50 U/kg, and the maintenance infusion dose was 5–15 [U/kg]/h. The target range of the activated partial thromboplastin time (APTT) was 55–65 s.

2.3. Statistical Method. Statistical analysis was performed using SPSS 25.0 software. Continuous variables with normal distribution were expressed as mean ± standard deviation (mean ± SD) and were compared by the independent-samples t-test between groups. Continuous variables with non-normal distribution were expressed as median (interquartile range) and were compared by the Mann–Whitney U-test between groups. Categorical variables were tested using the chi-square test or Fisher’s exact test, as appropriate. Backward stepwise logistic regression was used for mortality risk factor analysis and predictive modeling. The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off values of the risk factors, and the accuracy of each risk factor and prediction model in predicting mortality in ECMO patients was evaluated by calculating the area under the curve (AUC). A p value < 0.05 was considered statistically significant.
3. Results

3.1. Demographics and Characteristics. A total of 78 patients with CS undergoing VA-ECMO were enrolled in this study, with one automatic dropout, two deaths within 3 days, and two cases transferred from VA-ECMO to VAV-ECMO treatment. Therefore, the final analysis included 73 cases (shown in Figure 1), with 35 (47.95%) in the survivor group and 38 (52.05%) in the nonsurvivor group. The median age of the patients was 57 (48–67) years, the median ECMO treatment time was 5.8 (4.62–7.57) days, and the median ICU stay was 19.04 (13.92–26.15) days. The top three disease categories for performing VA-ECMO were AMI (32.88%), heart valve disease (28.77%), and aortic coarctation type A (21.92%). Among them, 33 (45.21%) cases were after open-heart surgery and 17 (23.29%) were percutaneous coronary intervention patients (as shown in Table 1).

There was no statistically significant difference in age and sex between the survivor and nonsurvivor groups of ECMO patients. There was no difference in Gal-3 and BNP levels between the two groups before ECMO initiation. However, after ECMO treatment, Gal-3 and BNP levels at 24 and 72 h were lower in the survivor group than in the nonsurvivor group, which was statistically significant ($p < 0.05$). Platelet counts were below normal in both groups but were higher in the survivor group than in the nonsurvivor group, which was statistically significant ($p < 0.05$). There was no statistically significant difference between the two groups in terms of lactate levels at 72 h after VA-ECMO initiation, duration of ECMO support, and length of ICU stay ($p > 0.05$) (as shown in Table 1).

4. Effects of VA-ECMO on BNP and Gal-3

The Friedman test for repeated measures was used to compare Gal-3 and BNP levels at three time points in the study subjects. There were significant differences among Gal-3 levels at baseline, 24 h, and 72 h ($\chi^2 = 134.33, p < 0.01$), with mean ranks of 2.95, 2.03, and 1.03, respectively. There were also significant differences among BNP levels at baseline, 24 h, and 72 h ($p < 0.01$), with mean ranks of 3.00, 1.52, and 1.48, respectively. Post hoc analysis with the Wilcoxon signed-rank test showed that BNP levels decreased significantly from baseline to 24 h and from baseline to 72 h, but not from 24 h to 72 h ($p > 0.05$), as shown in Table 2.

5. The Relationship between Gal-3 and BNP

Pearson correlation analysis was used to examine the relationship between Gal-3 and BNP at three time points in the 73 patients. There was a significant positive correlation between Gal-3 and BNP at each time point ($p < 0.05$), which is consistent with the average trend results of Gal-3 and BNP (as shown in Figure 2(d)). Specifically, Gal-3-T0 (baseline) was positively correlated with BNP-T0 ($r = 0.373; p = 0.01$) (as shown in Figure 2(a)), Gal-3-T24 (24 h) was positively correlated with BNP-T24 ($r = 0.510; p < 0.01$) (as shown in Figure 2(b)), and Gal-3-T72 (72 h) was positively correlated with BNP-T72 ($r = 0.523; p < 0.01$) (as shown in Figure 2(c)).

5.1. Analysis of the Risk Factors Affecting the Prognosis of ECMO Patients. Variables with $p < 0.05$ in the univariate analysis were included in a binary logistic regression analysis using the backward stepwise method, as shown in Table 3. The results showed that APACHE II score, Gal-3-T72, and BNP-T72 were independent risk factors for death in patients undergoing VA-ECMO for CS ($p < 0.05$), while platelets were not statistically significant ($p > 0.05$).

5.2. The Predictive Value of ROC Curve Analysis of Risk Factors on the Prognosis of VA-ECMO Patients. The independent risk factors, APACHE II score, Gal-3-T72, and BNP-T72, identified by the multivariate analysis in Table 3 are plotted as ROC curves, and the area under the curve (AUC) was calculated by software. The results are shown in Figure 3, where all three risk factors had significant predictive value for mortality ($p < 0.05$). The AUCs of the APACHE II score, Gal-3-T72, and BNP-T72 were 0.687, 0.799, and 0.723, respectively. The optimal cut-off point was determined by the maximum Youden index, which corresponded to the largest AUC for Gal-3-T72. The sensitivity and specificity of Gal-3-T72 > 7.165 ng/ml were 0.895 and 0.429, respectively (as shown in Table 4).

5.3. Construction of a Prediction Model for Death in Patients Undergoing VA-ECMO for CS and Evaluation of Its Value. The APACHE II score, Gal-3-T72, and BNP-T72 were assigned based on the optimal threshold points, as detailed in Table 5. The death prediction score was constructed as APACHE II score + Gal-3-T72 + BNP-T72, with a total score ranging from 0 to 3. The ROC curve was plotted after assigning the raw data of the APACHE II score, Gal-3-T72, and BNP-T72 and calculating the death prediction score (as shown in Figure 4). The optimal threshold point was 2.5. A
score > 2.5 had 81.6% sensitivity and 70.2% specificity for predicting mortality (AUC: 0.884; 95% confidence interval (CI): 0.803–0.965; p < 0.05) with 81.6% positive predictive value, 88.5% negative predictive value, and 84.9% accuracy. Therefore, patients with CS undergoing VA-ECMO with a score > 2 were classified as high-risk for the nonsurvivor group, while those with a score ≤ 2 were classified as low-risk for the nonsurvivor group.

6. Discussion

This study found that Gal-3 can be used to determine the prognosis of patients with CS undergoing VA-ECMO. The main findings of this study were as follows: (1) BNP and Gal-3 levels decreased significantly in patients with CS after VA-ECMO initiation, indicating that the ECMO technique is effective for treating patients with CS; (2) serum Gal-3
levels correlated well with serum BNP levels, suggesting that Gal-3 may be used to predict the degree of HF; (3) Gal-3 levels in the survivor and nonsurvivor groups were statistically different, indicating that Gal-3 can be used to predict the prognosis of patients with CS; and (4) the VA-ECMO mortality risk assessment model consisting of Gal-3-T72, BNP-T72, and the APACHE II scores showed good predictive ability, with scores \(>2\) belonging to the high-risk group for mortality and scores \(\leq2\) to the low-risk group for mortality.

During VA-ECMO treatment, we observed that VA-ECMO provided arterial pressure support to the patient, which altered the original physiological circulatory structure and changed the preload and afterload of the heart [7]. This made it challenging to evaluate cardiac function using conventional examination methods. Qin et al. [8] studied the relationship between serum BNP and endothelin-1 (ET-1) levels and left atrial pump function in HF patients and found that BNP and ET-1 were negatively correlated with the left atrial ejection fraction, left atrial passive emptying fraction, and left atrial active emptying fraction (\(p < 0.05\)). Similarly, we also assessed cardiac function by BNP levels. Our study found that BNP levels at 24h after ECMO treatment decreased significantly compared to before ECMO treatment, and the difference was statistically significant, indicating that VA-ECMO was beneficial for cardiac treatment in patients with CS [9]. ECMO can provide rapid circulatory support and protect organ perfusion, allowing time for cardiac recovery and preventing multiple organ failure [10]. However, the extent of BNP reduction in the late stage of ECMO depends on the patient’s baseline cardiac function and recovery. In our sample, we observed that Gal-3 levels decreased significantly during ECMO treatment, and we hypothesized that the changes in Gal-3 might be related to the improvement of cardiac function in the patients. We further examined the relationship between BNP and Gal-3 using Pearson correlation analysis and found a strong correlation between BNP and Gal-3 at all three time points, with the strongest correlation between BNP and Gal-3 at 72h (\(r = 0.523, p < 0.01\)), implying that serum Gal-3 could predict cardiac function. These results are consistent with Mahmoud U. Sani’s observation [11]. Interestingly, despite peripheral arterial cannulation being the exclusive method
for ECMO cannulation via the peripheral arteries, a study conducted by Fausto Biancari et al. examined the cannulation methods of 1269 patients requiring postcardiotomy VA-ECMO, which found that central arterial cannulation was associated with a higher risk of in-hospital mortality compared to peripheral arterial cannulation [12]. Our ECMO team will pay attention to and collect cases with both types of cannulation in the future.

We then analyzed the basic characteristics between the survivor and nonsurvivor groups, and the results showed intergroup differences in the APACHE II score, Gal-3, BNP, and platelets. In a study by Franziska Kaestner et al. [13], they analyzed 51 ECMO cases (including 38 VV-ECMO, 11 YAV-ECMO, and 2 VA-ECMO cases) and found a statistically significant difference in lactate levels between the survivor and nonsurvivor groups. The mean value for the survivor group was 2.0 (range: 0.4–13.5) and for the nonsurvivor group it was 4.0 (range: 1–21). However, our data showed no significant difference in lactate levels at 72h between the two groups. We believe that the difference in results is related to the study subjects we included. Our 73 cases were all patients with cardiac failure without severe pulmonary failure symptoms, and VA-ECMO can quickly relieve patients’ ischemic-hypoxic symptoms with a significant treatment effect. On the other hand, the main study subjects included by Franziska Kaestner’s team were administered VV-ECMO treatment for pulmonary failure. VV-ECMO poorly relieves ischemic-hypoxic symptoms in such patients compared with patients with CS, which may have led to inconsistent results.

In the multivariate model, we selected Gal-3-T72 and BNP-T72 as risk factors for analysis. The results showed that the APACHE II score, Gal-3-T72, and BNP-T72 were independent risk factors for death in patients undergoing VA-ECMO for CS. The ROC analysis showed that all three factors had significant predictive power for VA-ECMO patients, and the AUC of Gal-3-T72 was the largest (0.799). Patients with CS are characterized by organ ischemia, hypoxia, inflammatory factor disorders, hemodynamic changes, and volume and pressure changes in the heart.

Table 4: Receiver operating characteristic (ROC) curves analyzed the predictive value of APACHE II, galectin-3 (Gal-3), and B-type natriuretic peptide (BNP).

<table>
<thead>
<tr>
<th>Source of the Curve</th>
<th>AUC</th>
<th>Cut-off values</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Youden index</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II</td>
<td>0.687</td>
<td>21.5</td>
<td>1</td>
<td>0.629</td>
<td>0.371</td>
</tr>
<tr>
<td>Gal-3</td>
<td>0.799</td>
<td>7.165</td>
<td>0.895</td>
<td>0.429</td>
<td>0.466</td>
</tr>
<tr>
<td>BNP</td>
<td>0.723</td>
<td>4461.5</td>
<td>0.868</td>
<td>0.257</td>
<td>0.611</td>
</tr>
</tbody>
</table>

Table 5: Death early warning rating table.

<table>
<thead>
<tr>
<th>Score</th>
<th>APACHE II ≤ 21.5</th>
<th>APACHE II &gt; 21.5</th>
<th>Gal-3-T72 ≤ 7.165</th>
<th>Gal-3-T72 &gt; 7.165</th>
<th>BNP-T72 ≤ 4461.5</th>
<th>BNP-T72 &gt; 4461.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 3: Receiver operating characteristic (ROC) curve of the predictive model and single index in predicting the prognosis of patients with venoarterial extracorporeal membrane oxygenation (VA-ECMO).

Figure 4: Receiver operating characteristic (ROC) curve of the death warning score in predicting the prognosis of patients with cardiogenic shock.
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Cardiac failure during the state of CS promotes the release of serum inflammatory factors, macrophage activation, and migration to cardiac tissue, leading to a significant increase in Gal-3 that promotes cardiomyocyte fibrosis [18, 19]. When patients are given VA-ECMO support therapy, ECMO shares the workload done by the heart, resulting in the alleviation of cardiac failure symptoms, a decrease in the release of inflammatory factors, and a gradual decrease in Gal-3 levels.

There are limited models for predicting ECMO outcomes, and the predictive variables differ for different populations. Because more than half of the patients in our ECMO cohort had cardiovascular disease, we sought to establish a prediction model for patients with CS. AUC of the model comprising the APACHE II score, Gal-3-T72, and BNP-T72 was 0.884, and the model showed higher predictive accuracy than each risk factor alone. Patients with CS on VA-ECMO who scored > 2 were categorized as high-risk for mortality, and those who scored ≤ 2 were categorized as low-risk for mortality. This study indicates that the combination of the APACHE II score, Gal-3-T72, and BNP-T72 can be applied to predict the outcomes of VA-ECMO and is feasible. In contrast, Franziska Kaestner included too many types of ECMO in the construction of their ECMO prediction model, including VV-ECMO, VAV-ECMO, and VA-ECMO [13]; thus, their model is not well suited for patients with CS.

Schmidt et al. developed the SAVE score to assess the prognosis of refractory CS, based on factors including the cause of CS, age, organ function, and blood pressure. They found that the SAVE score performed better than several standard ICU severity scores [20]. Mohamed Laimoud et al. found that increasing the ∆1 SOFA score (odds ratio (OR) = 2.506, 95% CI: 1.681–3.735, \( p < 0.001 \)) and increasing the blood lactate level (OR = 1.388, 95% CI: 1.015–1.898, \( p = 0.04 \)) were significantly associated with hospital mortality after VA-ECMO support for adults with CS [21].

The scoring system we used in our study is relatively simple and includes a limited number of indicators. However, it has proven to be more valuable in predicting mortality in ECMO patients than single indicators. Therefore, this scoring system may have clinical significance for patient evaluation. In future research, we hope to further investigate this by incorporating measures such as the SAVE score, SOFA score, and peak lactate levels.

There are several limitations to this study. First, our team failed to register the clinical trial, potentially leading to biased patient selection and jeopardizing the accuracy and applicability of our research outcomes. We will further improve our research process to ensure that our future studies comply with relevant regulations and ethical requirements. Second, the small sample size may cause possible bias in the statistical analysis and requires further multicenter and large sample studies to validate the results. Third, most of the models constructed by our team are based on patients with cardiovascular disease and may not be suitable for use in VV-ECMO or VAV-ECMO patients. Further studies are needed to investigate the applicability of our model in these patient populations. Unfortunately, peak lactate levels were not included as an analytical measure. Peak lactate levels are a more sensitive indicator for assessing tissue perfusion and can more accurately predict mortality in patients with VA-ECMO. Mohamed Laimoud and Mosleh Alnazi’s study also supports this viewpoint; their research has shown that peak lactate levels had better performance (AUC = 0.889; 95% CI: 0.825–0.953; \( p < 0.001 \)), and that lactate levels after 24 h of ECMO initiation performed best in terms of sensitivity and specificity for discriminating mortality (AUC 0.93; 95% CI: 0.878–0.983; \( p < 0.001 \)) [10].

7. Conclusion

Gal-3 may be used as a predictor of prognosis in patients on VA-ECMO for CS. The VA-ECMO early warning score, which includes the APACHE II score, Gal-3-T72, and BNP-T72, has greater predictive value for mortality in ECMO patients than single indicators. This scoring system has the potential to provide valuable prognostic information for VA-ECMO patients. However, further validation of its generalizability is required with a larger sample size and broader population.

Abbreviations

Gal-3: Galectin-3
CS: Cardiogenic shock
AMI: Acute myocardial infarction
ECMO: Extracorporeal membrane oxygenation
VA-ECMO: Venoarterial-extracorporeal membrane oxygenation
APTT: Activated partial thromboplastin time
AUC: Area under curve.

Data Availability

The data used to support the findings of this study are included within the article (see the link of the public database https://doi.org/10.6084/m9.Figshare.21432435.v2 for details).

Ethical Approval

The study followed the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Ganzhou People's Hospital. The study was given a reference number TY-SKY1900301.

Consent

All participants in the study provided informed consent after being fully informed of the purpose of the research.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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