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ORIGINAL RESEARCH

Comprehensive Analysis Identifies Hsa_circ_0058191 as a Potential Drug Resistance Target in Multiple Myeloma

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Background: Multiple Myeloma (MM) is the second most common hematologic malignancy, which exhibits strong resistance to bortezomib, the first-line treatment. Circular RNAs (circRNAs) are increasingly considered as important drivers of drug resistance across various cancers, but their roles in multiple myeloma are not well understood.

Aim: To investigate and identify potential circRNA targets and their roles in the mechanisms of bortezomib resistance.

Methods: Bortezomib-resistant MM patient-specific circRNAs were screened using Arraystar circRNA microarrays. The MM circRNA dataset from the GEO database was analyzed with GEO2R to identify candidate circRNAs associated with MM progression and drug resistance. CircRNA-forming and loop-forming sites, along with their structures, were identified via Sanger sequencing. The identified circRNA was validated by qRT-PCR in MM patients with and without bortezomib resistance. Bioinformatic analysis through CircInteractome was conducted to predict potential miRNA and RBP binding for the core circRNAs. Metascape was employed to perform RBP pathway analysis to identify specific biological processes in circRNAs.

Results: The hsa_circ_0058191 was found to be overexpressed in bortezomib-resistant MM patient samples, suggesting its pivotal role in drug resistance mechanisms. The interaction of hsa_circ_0058191 with miR-660 and AGO2 as determined through bioinformatic predictions, indicated that it regulates RNA modification and mRNA regulation pathways. These molecular interactions expand our understanding of the mechanisms of drug resistance in multiple myeloma.

Conclusion: This study identified the role of hsa_circ_0058191 in the development of drug resistance in MM, which provides a theoretical foundation for designing potential therapeutic strategies to prevent drug resistance.

Keywords: circRNA, multiple myeloma, drug resistance, treatment target, bioinformatic analysis

Introduction

Multiple myeloma (MM) is a plasma cell malignancy contributing to high morbidity and mortality globally.[1] Bortezomib, as a first-line therapeutic drug for patients with MM, significantly improves the survival of patients and prolongs the remission duration.[2] However, due to bortezomib resistance, rates of relapse or disease deterioration are high in MM. This calls for deeper investigations into the molecular basis of MM resistance to identify new therapeutic targets.

Non-coding RNAs (ncRNAs) are a diverse class of RNA molecules that do not code for proteins, which include long non-coding RNAs (lncRNAs) and micro RNAs (miRNAs), which together account for more than 90% of the transcriptional output of the human genome. These molecules influence the development of MM by regulating gene expression and facilitating intercellular communication.[3] Circular RNAs (circRNAs) are unique covalent closed-loop structures formed by back-splicing and are more stable with longer half-life livcompared with linear RNAs, such as lncRNAs and miRNAs. CircRNAs are specifically expressed in specific types of cancers.[4] Based on these properties, we infer that circRNAs may serve as MM biomarkers and therapeutic targets. Several investigations have demonstrated that the

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synthesis circRNA is regulated by several RNA regulators, including miRNAs and RBPs. These factors play key roles in the emergence of MM-induced drug resistance by modulating multiple aspects of RNA splicing, modification, and translation to jointly regulate gene expression and cellular function.[5] However, the synthesis of specific circRNAs is dependent on the splicing of precursor mRNAs by specific RNA regulators. Zhu et al found that RBP EIF4A3 may accelerate MM progression by directly binding to circ_0005615.[6] miRNAs, on the other hand, bind to complementary sequences on circRNAs through their seed sequences, which alters the drug-resistance-related signaling pathways, which in turn regulate the expression of drug resistance genes.[7] Although several MM biomarkers have been identified, the circRNA biotargets of bortezomib-resistant MM patients and their underlying molecular mechanisms remain unclear. Therefore, it is imperative to study bortezomib-resistant circRNA targets and the mechanisms of MM to advance MM research and improve clinical treatment. In this study, circRNA microarray in combination with GEO database and qRT-PCR assays were performed, which identified and validated hsa_circ_0058191, a circRNA stably expressed in bortezomib-resistant MM patients. In addition, the potential binding miRNAs and RBPs of hsa_circ_0058191 were predicted, providing a preliminary theoretical basis for the molecular mechanism of MM resistance.

Materials and Methods

Arraystar circRNA Microarray

Using the Arraystar Human circRNA Array (V2.0) and Agilent Feature Extraction software (version 11.0.1.1), we performed a comprehensive array analysis on whole blood samples from five bortezomib-resistant patients and healthy donors. Total RNAs were treated with RNase R (Epicentre, Inc.) to degrade linear RNAs and selectively enrich circRNAs. The enriched circRNAs were then amplified and transcribed into fluorescent cRNA using a random priming technique (Arraystar Super RNA Labeling Kit; Arraystar). The labeled cRNAs were hybridized onto the Arraystar Human circRNA Array V2 (8x15K, Arraystar). They were then mounted onto slides, washed and then scanned using the Agilent Scanner G2505C. The resulting array images were analyzed using Agilent Feature Extraction software (version 11.0.1.1).

Data Sources

Two datasets, GSE208782 and GSE133058 were derived from the Gene Expression Omnibus (GEO) database, to explore differences in circRNA expression between patients with MM and IDA (iron deficiency anemia), as well as between MM patients and healthy donors. Differential gene expression analysis of circRNAs from the two distinct MM patient datasets was conducted using GEO2R (www.ncbi.nlm.nih.gov/geo/geo2r) to identify differentially expressed circRNAs in MM. Subsequently, the differential circRNAs from different datasets, including chip data, were intersected using a Venn diagram to identify the key circRNAs. The detailed information of hsa_circ_0058191 was derived from the circBase database (www.circbase.org).

Bioinformatics Analysis

The CircInteractome online tool was employed to predict miRNA and RBPs targets of hsa_circ_0058191 (circinteractome.nia.nih.gov). The prediction was performed by comparing the absolute values of the "context + score" from the miRNA prediction results, with a higher score signifying a higher binding likelihood. The "Seed Pairing Score" was also considered, with scores approaching 0 or being positive indicating more stable pairing. In the analysis of RBP sites corresponding to circular RNAs, the number of BindingSites and flanking regions Tags was evaluated, which identified Argonaute 2 (AGO2) as the predominant RBP. Subsequently, pathway analysis was conducted on 22 associated binding proteins using the Metascape online platform to reveal the potential biological context and functions of hsa_circ_0058191.

Sample Collection

Patients diagnosed with MM and treated with bortezomib-based therapy and healthy donors, were recruited from the Hematology Departments of the Affiliated Hospital of Guilin Medical University and the Second Affiliated Hospital of Guilin Medical University between September 2022 and December 2023. The inclusion criteria for MM patients were based on the International Myeloma Working Group diagnostic criteria.[8] Patients in the bortezomib-resistant group

exhibited disease progression during or within 60 days after receiving at least two cycles of bortezomib, either as a single agent or in combination with other drugs. Patients in the bortezomib-sensitive group met the criteria for partial response or high with reference to the standard guidelines. Exclusion criteria included patients with secondary or mixed MM, and pregnant or lactating women. All participants provided informed consent prior to blood collection. The study protocol was approved by the ethics committees of the Affiliated Hospital of Guilin Medical University and the Second Affiliated Hospital of Guilin Medical University. The study was performed following the Declaration of Helsinki guidelines.

Specimen Processing and Handling

Blood samples were immediately collected into EDTA-anticoagulated tubes. Mononuclear cells were isolated employing the standard Ficoll-Paque density gradient centrifugation method (Solarbio, Beijing, China). The isolated cells were stored at −80°C for further RNA extraction and analysis.

qRT-PCR

Total RNA was extracted from single nucleated cells using the GeneJET™ RNA Purification Kit (Thermo Fisher Scientific, Waltham, MA, USA). It was then quantified with the NanoDrop ND-1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) and then reverse-transcribed to synthesize cDNA RNA using MonScript™ RTIII All-in-One-Mix with dsDNase (Monad Biotech Co., Ltd., Wuhan, China). It was then amplified utilizing the MonadAmp™ SYBR Green qPCR Mix (Low ROX) (Monad Biotech Co., Ltd., Wuhan, China) in a total volume of 20 μL. Cycle threshold (Ct) values were obtained for each target gene, and with GAPDH gene serving as the internal control gene. The ΔCt value was calculated by subtracting the Ct value of GAPDH from the Ct value of the target gene. The ΔΔCt value was then determined by subtracting the ΔCt value of the control sample from that of the experimental sample. The relative expression level of the target gene was calculated using the $2^{-\Delta\Delta Ct}$. Primer details used in this experiment are presented in Supplementary Table 1.

Statistical Analysis

The circRNA-related data were visualized using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and related software packages. Data analysis was conducted using GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA). Normality and lognormality tests were conducted to characterize the distribution of gene expression data in the two groups. Data that followed a normal distribution, the homogeneity of variance test was performed. In cases of unequal variances, the Welch's correction was applied. For data that did not follow a normal distribution, the Mann–Whitney *U*-test was utilized. Data are expressed as the mean ± standard deviation (SD), with statistical significance set at $P < 0.05$.

Results

Hsa_circ_0058191 Is a Key Regulator of Bortezomib Resistance

To identify potential circRNAs in bortezomib-resistant MM patients, we employed the $|LogFC| \geq 1.5$ and $P < 0.05$ (Figure 1a) as the selection threshold. A total of 360 up-regulated and 438 down-regulated circRNAs were detected in bortezomib-treatment-resistant MM patients through Arraystar CircRNA Microarray. In the clustered heatmap analysis, the bortezomib-resistant samples were effectively clustered together and could be distinguished from the healthy donor samples. This observation revealed significant differences in circRNA expression patterns between the two groups (Figure 1b). In addition, we visualized the number of circRNAs on different chromosomes using the "karyoploteR" package in the R software (Figure 1c), with each horizontal line representing a single chromosome (from chr1 to chrY) and the red dots indicate circRNAs on each chromosome. This distribution analysis revealed the specific chromosomal localization of the differential circRNAs, and these mutant loci may contribute to the emergence of bortezomib resistance in MM patients.

To further identify the differentially expressed circRNAs, we analyzed the GSE208782 and GSE133058 datasets using the GEO2R online tool in the GEO database based on the criteria: $|LogFC| \geq 1$ and $P<0.05$. It was observed that 645 differentially expressed circRNAs were found between MM patients and IDA patients, and 258 differentially expressed circRNAs were found between MM patients and healthy donors. These differential circRNAs were used to construct

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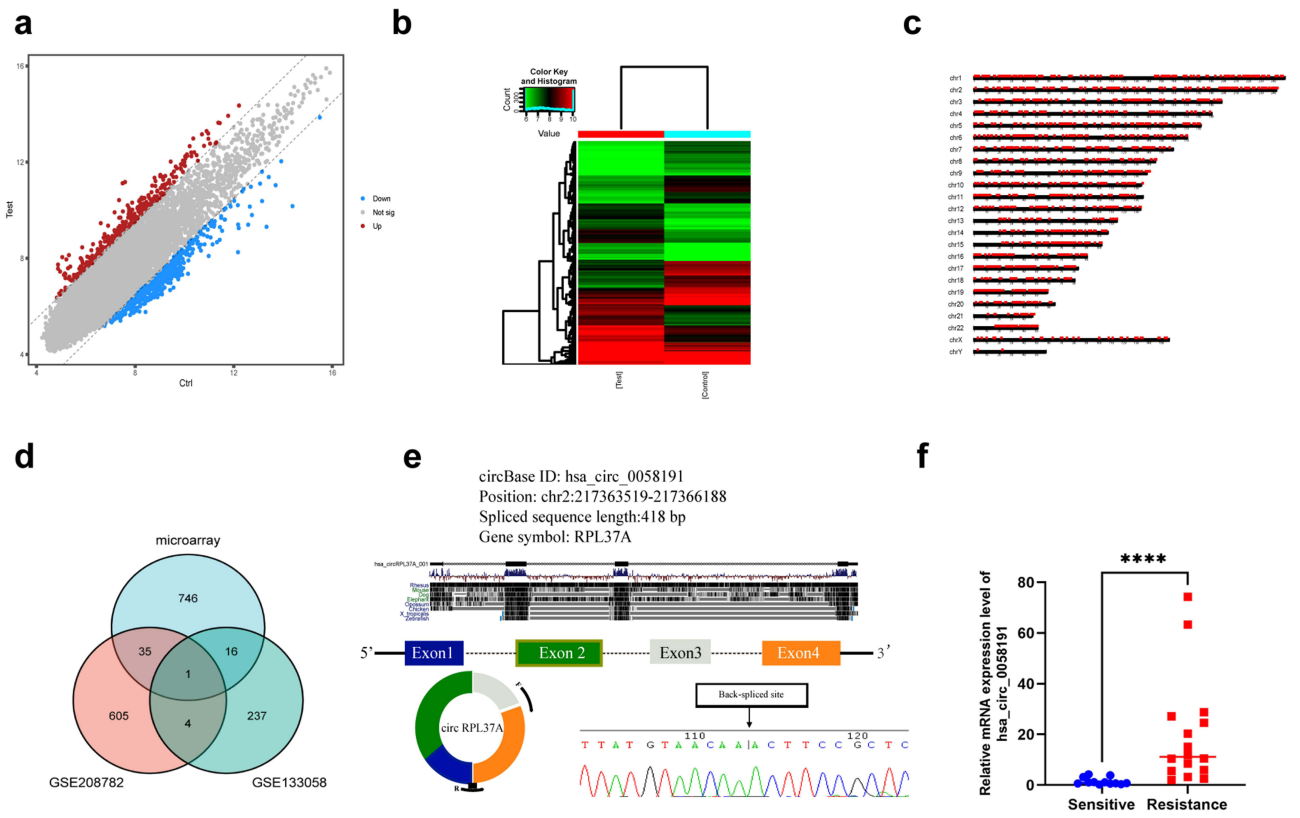

Figure 1 Screening and validation of abnormally expressed circRNAs in multiple myeloma. (**a**) A volcanic map showing 360 up-regulated and 438 down-regulated differentially expressed circRNAs in the circRNA microarray determined based on (|log2fold change|> 1.5, p < 0.05) as selection thresholds. (**b**) The clustering heatmap indicating that the bortezomib-resistant samples were clustered together, effectively separating them from healthy donor samples. (**c**) The genome map displaying the distribution of circRNAs across different chromosomes, where each horizontal line represents a chromosome, and the red dots above the line indicate the number of circRNAs on that chromosome. (**d**) The Venn diagram illustrates the intersecting genes of differentially expressed circRNAs in Multiple Myeloma from the microarray, GSE208782, and GSE133058 datasets. (**e**) The model diagram of hsa_circ_0058191. Sanger sequencing illustrating the junction point of hsa_circ_0058191. (**f**) The qRT-PCR results showing that hsa_circ_0058191 was significantly upregulated in the bortezomib-resistant group compared to the bortezomib-sensitive MM patients.
Note: ****indicates p < 0.0001.

Venn plots facilitate further identification of candidate circRNAs, which may influence MM progression and drug resistance (Figure 1d and Supplementary Table 2). As shown in Figure 1e, hsa_circ_0058191 was found to be located on chromosome 2 and consisted reverse splicing of exons 1, 2, 3 and 4 of the encoding gene RPL37A (chr2:217363519-–217366188). The splice junctions were verified through Sanger sequencing, which demonstrated the presence of a circularization site to clarify the circular structure of hsa_circ_0058191. Finally, the expression level of hsa_circ_0058191 was verified by qRT-PCR in the bortezomib-resistant and sensitive MM patients, and the results showed that it was significantly up-regulated in bortezomib-resistant MM patients (P < 0.0001) (Figure 1f), implying that it may be involved in the development of drug resistance in MM.

Identification of miRNA and RBP Targets of Hsa_circ_0058191

Given the important roles of miRNAs and RBPs in circRNA function, we predicted the miRNA and RBPs targets of hsa_circ_0058191 using the CircInteractome online tool. The prediction revealed that the hsa_circ_0058191 could potentially interact with 19 miRNAs and 22 RBPs (Supplementary Tables 3 and 4). Notably, the context+score percentile showed that the miR-660 contributed to high biological priority or importance. Among the RBPs, AGO2 had the strongest binding site and the corresponding flanking region of the circRNA (Figure 2a), suggesting that miR-660 and AGO2 may be the most significant potential binding targets for hsa_circ_0058191. Interestingly, pathway analysis for the 22 RBPs bound by hsa_circ_0058191 revealed that the most enriched processes were those associated with miRNA processing, RNA splicing, and positive regulation of translation, suggesting that the RBPs were involved in the regulation of circ RNA formation (Figure 2b).

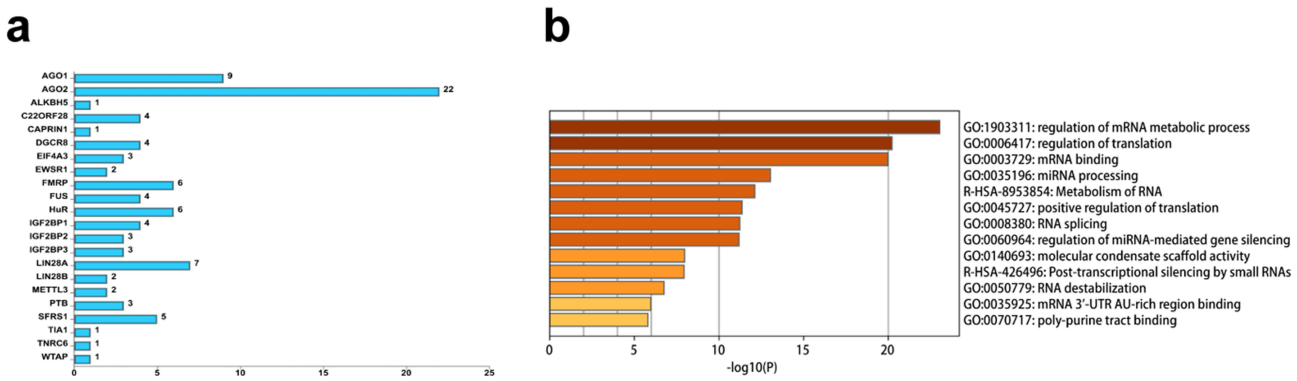

Figure 2 Prediction and functional analysis of RNA-binding proteins (RBPs) associated with hsa_circ_0058191. (**a**) Identification of RNA-binding proteins. A total of 22 RNA-binding proteins associated with hsa_circ_0058191 were identified. The bar chart displays the number of binding sites for each RBP. The x-axis represents the number of binding sites, while the y-axis shows the names of the identified RBPs. (**b**) Functional enrichment analysis of the RNA-binding proteins. The bar chart shows the results of the Gene Ontology (GO) enrichment analysis for the identified RBPs. The x-axis represents the -log10(P-value), indicating the significance of enrichment, while the y-axis lists the GO terms. The color gradient of the bars represents the range of -log10(P-values) from low to high significance.

Discussion

CircRNA has been recognized as an important MM biomarker owing to its high specificity.[9] However, for circRNAs detected in bortezomib-resistant MM patients, their molecular mechanisms have been studied, with little focus on their potential to serve as biomarkers of MM resistance. In this study, we analyzed the aberrantly expressed circRNAs in bortezomib-resistant patients through circRNA microarray and searched for their associated differentially expressed circRNAs in MM in the GEO database to determine the core circRNA that may underlie the development of drug resistance to MM. Notably, hsa_circ_0058191 was identified as the key circRNA, which may potentially play a role in MM resistance and serve as a biomarker of bortezomib resistance in MM.

Hsa_circ_0058191 is synthesized by reverse splicing of exons 1, 2, 3, and 4 of the precursor mRNA RPL37A, which encodes the ribosomal protein L37a, an important component of the 60S ribosomal subunit, and is mainly involved in the functional regulation of the ribosome during protein synthesis. Studies have shown that aberrant expression or mutation of RPL37A is associated with an increased risk of various malignant tumors and genetic diseases.[10,11] Although the specific role of RPL37A in MM remains unclear, ribosomal proteins play a critical role in regulating protein translation, particularly under conditions of cellular stress.[12] In addition, bortezomib, a proteasome inhibitor, triggers the accumulation of misfolded proteins by blocking protein degradation, which leads to over-activation of the unfolded protein response in the endoplasmic reticulum inducing apoptosis.[13] Against this background, we hypothesized that RPL37A might participate in the development of resistance to bortezomib in MM cells by regulating translation suspension or selective translation during endoplasmic reticulum stress or accumulation misfolded proteins. These mechanisms need to be further investigated.

RPL37A splicing is influenced by RNA RBPs. Studied have reported that proteins such as ADAR1 and DHX9 can bind to specific RNA sequences, thereby promote or inhibit the reverse splicing of circRNAs.[14,15] These proteins determine the selection of splicing sites and splicing efficiency by interacting with specific regions of pre-mRNAs, resulting in the formation of specific circRNAs.[16] In this study, we predicted the potential binding RBPs of Hsa_circ_0058191 were determined through the circInterncome online website, and the significance role in the circRNA formation process was clarified through pathway analysis. Among the RBPs, AGO2, which is the only catalytically active member of the Argonaute family, was associated with Hsa_circ_0058191. It is involved several gene regulatory functions, such as chromatin remodeling and alternative splicing.[17] In addition, A serum proteomics analysis which revealed that AGO2 was a potential multiple myeloma disease-activity and which is correlated with poor disease outcome.[18] Furthermore, AGO2 overexpression was significantly associated with shorter progression-free survival in MM patients treated with lenalidomide.[19] However, whether it regulates the bortezomib sensitivity remain to be clarified unknown. This study reveals the role of AGO2 in the mechanism of drug resistance in MM.

Wu et al found that AGO2 can also promote myeloma angiogenesis directly by binding to miRNAs, suggesting that RBP may also bind to miRNAs to regulate MM development and drug resistance.[20] In addition, miRNAs serve as

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circRNA sponges that modulate gene expression and various cellular functions.[21] In this study, miR-660 could bind to Hsa_circ_0058191, and miR-660 is known to influence chemosensitivity in various cancers.[22,23] However, CircRNA-mediated miRNA regulation exhibits pathway specificity, wherein distinct circRNAs preferentially influence different downstream gene networks critical for MM pathogenesis.[24] Therefore, its role in MM drug resistance and how these three modulate each other to promote bortezomib resistance in MM is largely unknown. Further studies are needed to explore these grey areas.

Although the present findings on the role of hsa_circ_0058191 are only preliminary, it carries significant potential for clinical application. As the current understanding regarding the roles of circRNA increases, the full scope of hsa_circ_0058191 will be unraveled and its role as a novel biomarker for predicting the prognosis of drug-resistant MM will be uncovered. For instance, integration of hsa_circ_0058191 expression and clinical indicators may create a multifactorial model with high prediction accuracy for disease progression. In addition, hsa_circ_0058191 can be targeted to alleviate drug resistance.

Nevertheless, this study has several limitations that should be addressed acknowledged. In the circRNA microarray screening of the samples, we did not stratify the samples into drug-resistant and sensitive groups, but rather chose samples from the drug-resistant group and healthy individuals. After careful consideration, we believe that the samples in the resistant group may contain multiple resistance mechanisms, and thus, identifying the differences in circRNA expression associated with different resistance mechanisms with reference to healthy donors will help to select the resistant and sensitive groups through validation tests. In addition, we employed a small validation sample size, which may limit the external validity of our findings. In future, we will explore the expression level of hsa_circ_0058191 in different disease states and its impact on the prognosis. Moreover, functional experiments using in vitro and in vivo models are needed to investigate its regulatory mechanisms.

Conclusion

This study identified hsa_circ_0058191 as a key factor regulating the development of bortezomib resistance in multiple myeloma. The analysis uncovered its interaction with miR-660 and AGO2, providing new insights into the molecular mechanisms underlying drug resistance. Therefore, targeting hsa_circ_0058191 may be a novel therapeutic approach for overcoming bortezomib resistance in multiple myeloma, and could be a biomarker for resistance management.

Abbreviations

MM, Multiple myeloma; CircRNAs, Circular RNAs; RBP, RNA binding protein; GEO, Gene Expression Omnibus; qRT-PCR, Quantitative real-time PCR.

Data Sharing Statement

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Approval for the study was obtained from the Ethics Committee of the Affiliated Hospital of Guilin Medical University (NO.YJS-2022016). The study was conducted in accordance with the tenets of the Declaration of Helsinki.

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Disclosure

The authors declare no competing interests in this work.

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