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COMPARITIVE ANALYSIS OF P40 AND 34BETAE12. IMMUNOHISTOCHEMISTRY IN THE DIAGNOSIS OF PROSTATE LESIONS: INSIGHTS INTO DIAGNOSTIC UTILITY

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ABSTRACT

Introduction: Prostate carcinoma remains one of the commonly diagnosed cancers and a leading cause of morbidity and mortality worldwide. The diagnostic challenge in distinguishing benign and malignant prostate lesions remains significant, especially in

small biopsies. Immunohistochemistry(IHC) serves as a valuable adjunct tool in the diagnosis and management of prostate malignancies. This study aims to evaluate the utility of P40 expression in the diagnosis of prostate lesions and to compare with the immunohistochemical expression of 34betaE12 in benign, premalignant and malignant lesions of the prostate. **Materials & methods**: This investigation was done at the Sree Balaji Medical College and Hospital, Department of Pathology, Chennai, India. Total 41 males with prostate specimens prostatic specimens (biopsies and resections) satisfying inclusion and exclusion criteria were included in this cross-sectional research study.Initial sections weres tained with Hematoxylin and eosin stain followed by IHC staining with two markers, P40 and 34BetaE12. Data were analysed using the mean and standard deviation for quantitative variables, as well as frequency and percentage for categorical variables, for descriptive purposes. Statistical analysis was made with IBM SPSS 16.0 software and P value of <0.05 was considered significant. **Results**: Of the 41 cases examined, the most prevalent pathology was a benign lesion (51.2%), followed by 41.5% malignant and 7.3% had premalignant lesions. All patients with benign lesions and pre-malignant lesions were positive and all malignant lesions were negative for P40 staining. There was statistically significant increase in P40 and 35betaE12 staining among patients with benign and pre-malignant lesions. **Conclusion**: Our findings suggest that immunohistochemical markers 34betaE12 and p40 have been found to be of value in differentiating benign and malignant

lesions of the prostate thereby playing an important role in management of patient and therapeutic outcome.

KEYWORDS: Prostate carcinoma, Immunohistochemistry, P40, 34betaE12 & Basal cells.

ANÁLISIS COMPARATIVO DE P40 Y 34BETAE12. INMUNOHISTOQUÍMICA EN EL DIAGNÓSTICO DE LESIONES PROSTÁTICAS: PERSPECTIVAS SOBRE SU UTILIDAD DIAGNÓSTICA

RESUMEN

Introducción: El carcinoma de próstata sigue siendo uno de los cánceres más frecuentemente diagnosticados y una de las principales causas de morbilidad y mortalidad a nivel mundial. El desafío diagnóstico para distinguir entre lesiones prostáticas benignas y malignas sigue siendo significativo, especialmente en biopsias pequeñas. La inmunohistoquímica (IHQ) constituye una valiosa herramienta complementaria en el diagnóstico y tratamiento de las neoplasias malignas de próstata. Este estudio busca evaluar la utilidad de la expresión de P40 en el diagnóstico de lesiones prostáticas y compararla con la expresión inmunohistoquímica de 34ßE12 en lesiones prostáticas benignas, premalignas y malignas. Materiales y métodos: Esta investigación se realizó en el Departamento de Patología del Colegio Médico y Hospital Sree Balaji, Chennai, India. Se incluyeron en este estudio transversal 41 varones con muestras de próstata (biopsias y resecciones) que

cumplían los criterios de inclusión y exclusión. Las secciones iniciales se tiñeron con hematoxilina y eosina, seguida de tinción inmunohistoquímica (IHQ) con dos marcadores: P40 y 34BetaE12. Los datos se analizaron utilizando la media y la desviación estándar para las variables cuantitativas, así como la frecuencia y el porcentaje para las variables categóricas, con fines descriptivos. El análisis estadístico se realizó con el programa informático IBM SPSS 16.0 y se consideró significativo un valor de $p < 0,05$. RESULTADOS: De los 41 casos examinados, la patología más prevalente fue una lesión benigna (51,2%), seguida de una maligna (41,5%) y una premaligna (7,3%). Todos los pacientes con lesiones benignas y premalignas dieron positivo en la tinción de P40, y todas las lesiones malignas dieron negativo en la tinción de P40. Se observó un aumento estadísticamente significativo en la tinción de P40 y 35ßE12 entre los pacientes con lesiones benignas y premalignas. Conclusión: Nuestros hallazgos sugieren que los marcadores inmunohistoquímicos 34ßE12 y p40 han demostrado ser valiosos para diferenciar lesiones benignas y malignas de la próstata, desempeñando así un papel importante en el manejo del paciente y el resultado terapéutico.

PALABRAS CLAVE: Carcinoma de próstata; inmunohistoquímica; P40; 34betaE12 y células basales.

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INTRODUCTION

Alzheimer's disease (AD) is a complex neurodegenerative disorder that diminishes identity and autonomy through its impact on behavior, memory, and cognitive abilities. Discovered over a century ago, AD is characterized by the presence of tau protein tangles and beta-amyloid plaques, which disrupt brain function and lead to neuronal death (1). Despite its pervasive occurrence and devastating consequences, effective treatments remain elusive. As the global population ages, AD is poised to exert a significant socioeconomic burden on caregivers and healthcare systems. Advancements in genetics, neuroscience, and technology are driving ongoing progress in AD research, offering hope for mitigating its profound impact through improved early detection, enhanced diagnostic precision, and personalized interventions (1, 2).

MicroRNAs (miRNAs), small RNA molecules, modulate gene expression by binding to target messenger RNA (mRNA) molecules, either facilitating or inhibiting their translation (3, 4). Dysregulation of miRNAs significantly influences the pathogenesis of Alzheimer's disease (AD). Research suggests that specific miRNAs may regulate genes and processes associated with AD pathophysiology, such as the formation and clearance of tau protein tangles, amyloid-beta (Aβ) plaque deposition, neuroinflammation, synaptic dysfunction, and neuronal apoptosis. Dysregulated miRNAs have been

identified in various tissues and biofluids of AD patients, indicating their potential utility as biomarkers for prognosis, diagnosis, and treatment response assessment. Understanding the causal relationships between miRNAs and AD pathophysiology holds promise for early disease detection, personalized therapeutic interventions, and cognitive decline prevention (5, 6).

Graph neural networks (GNNs) represent a powerful machine-learning paradigm capable of capturing complex relationships inherent in graph-structured data (7, 8). By amalgamating principles from graph theory and neural networks, GNNs can directly process graph-structured data, exploiting its inherent structure and connectivity. In Alzheimer's disease research, graphical neural networks (GNNs) are utilized to predict causal relationships involving microRNAs (miRNAs). This approach shows potential for unraveling the underlying pathophysiology of AD and identifying viable therapeutic targets (9, 10). GNNs can integrate multi-omics data into a unified graph representation, facilitating the learning of intricate dependencies and patterns. This enables the prediction of associations between miRNAs and diseases, elucidating the causal mechanisms underlying AD pathophysiology. The GNN-based methodology encompasses data integration, graph construction, feature encoding, graph convolution, prediction, and interpretation, offering insights into the molecular mechanisms driving AD

and aiding in the development of targeted therapeutic interventions. Moreover, interpretable models can provide valuable insights into the biological mechanisms and regulatory networks underpinning AD pathophysiology, paving the way for personalized precision medicine approaches.

Aberrant miRNA expression is implicated in various diseases, and deep learning methods like ADPMDA demonstrate efficient prediction of miRNA-disease associations, achieving a mean AUC value of 94.75% in experiments (10-12). GraphTar, a novel miRNA target prediction method, utilizes a graph-based representation and word2vec encoding for RNA sequences, surpassing existing approaches, albeit necessitating expanded datasets for further exploration (13).

This study aims to elucidate the molecular mechanisms of Alzheimer's disease (AD) and identify novel therapeutic targets, with a specific focus on delineating causal associations between microRNAs (miRNAs) and AD, essential for early disease detection and monitoring. Identification of specific miRNAs holds promise for understanding disease pathogenesis and facilitating targeted interventions. Graph neural networks (GNNs) can predict causal associations between miRNAs and diseases, thereby enhancing the ability to identify miRNAs causally linked to AD. MiRNA-based therapeutics, an emerging field in AD research, have the potential to restore normal gene expression patterns

and attenuate or reverse disease progression.

Our study aims to predict miRNA-disease causal associations using graph neural network-based approaches in Alzheimer's disease.

Materials and Methods

Dataset Preparation

The study utilized HMDD V4.0 (14) to analyze the microRNA-disease association causality dataset, comprising microRNA, disease, and causality information. Nodes representing microRNAs, diseases, and causality were designated, and graph neural networks were employed to predict edge interactions as causality between microRNAs and diseases, specifically Alzheimer's disease. This methodology facilitated effective analysis and the discovery of potential causal connections within the biomedical context.

A dataset sourced from HMDD V4.0 (14) was employed, incorporating microRNA expression profiles and associated clinical data from individuals with Alzheimer's disease and healthy controls. Preprocessing steps were implemented to clean and normalize the microRNA expression data while integrating it with clinical information. The Alzheimer's disease dataset, inclusive of microRNA, disease, causality (categorized as "no" and "yes"), and primary literature references (PMIDs), was extracted from the downloaded dataset. Nodes were allocated for microRNA, disease, and

causality, serving as edges, and node features were assigned and labeled. These data were then subjected to graph neural networks (GNNs) with the aim of predicting the edge interaction of causality.

This study employs GNNs to investigate the intricate relationships between microRNAs and Alzheimer's disease, with the goal of predicting their causality using structured data. This comprehension is pivotal for understanding molecular mechanisms and identifying potential therapeutic targets.

Graph Neural Network Architecture

GNNs are deep learning models designed to utilize graph-structured data for tasks such as link prediction and node classification. They comprise multiple layers processing node and edge features, facilitating information propagation across the graph. Techniques like message passing enable nodes to capture higher-order dependencies and refine hidden states. GNNs commonly utilize the Adam optimizer for optimization. The architecture of a GNN encompasses multiple layers of graph convolutional operations, facilitating information propagation between nodes. The output of the final layer is inputted into a classification layer to predict the causality of microRNAs in Alzheimer's disease.

In addition to the number of layers and units, other hyperparameters that can be tuned include the learning rate, dropout rate, and regularization strength. The learning rate dictates the step size at

which the model updates its parameters during training. A high learning rate may cause the model to overshoot optimal values, while a low learning rate may decelerate the learning process. The dropout rate serves as a regularization technique, randomly setting a fraction of input units to 0 during training to prevent overfitting. The regularization strength governs the balance between the model's capability to fit the training data and its generalization to unseen data.

The hyperparameter selection process typically involves grid search and model evaluation. The model exhibiting the best performance on the validation set is chosen for further evaluation on the test set. By fine-tuning the hyperparameters, the performance of the GNN model can be optimized, leading to enhanced predictions of microRNA causality in Alzheimer's disease.

Results

The graph neural network model accurately predicted Alzheimer's disease, achieving a precision of 69.44%, recall of 83.33%, and an F1 score of 75.75%. This methodology demonstrates promise in the identification of potential biomarkers or therapeutic targets for Alzheimer's disease utilizing microRNA data.

The precision and recall metrics of the model are pivotal for discerning genuine associations. Precision, quantifying the ratio of true positive predictions to total positive predictions, attains an accuracy of 69.44%. Recall, or sensitivity, achieves

an accuracy of 83.33%, signifying successful identification of positive associations. The F1-score, serving as a harmonic mean of precision and recall, offers a balanced assessment of these metrics, indicating commendable performance.

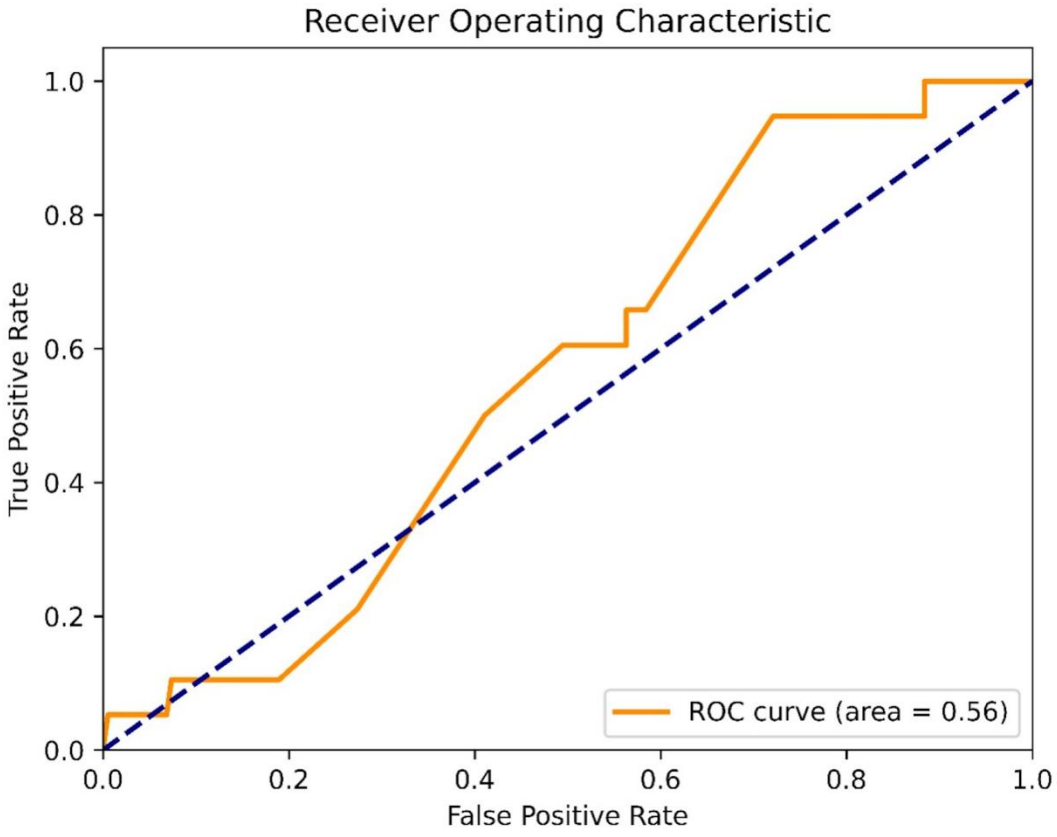

Figure 1 illustrates the ROC curve predicting the causal association between microRNAs and Alzheimer's disease. It charts the True Positive Rate (TPR) against the False Positive Rate (1-specificity) across various threshold

settings. The AUC value of 0.56 indicates that the model performs slightly better than random guessing but lacks robustness in distinguishing between positive and negative cases. The proximity of the ROC curve to the top-left corner signifies superior model performance.

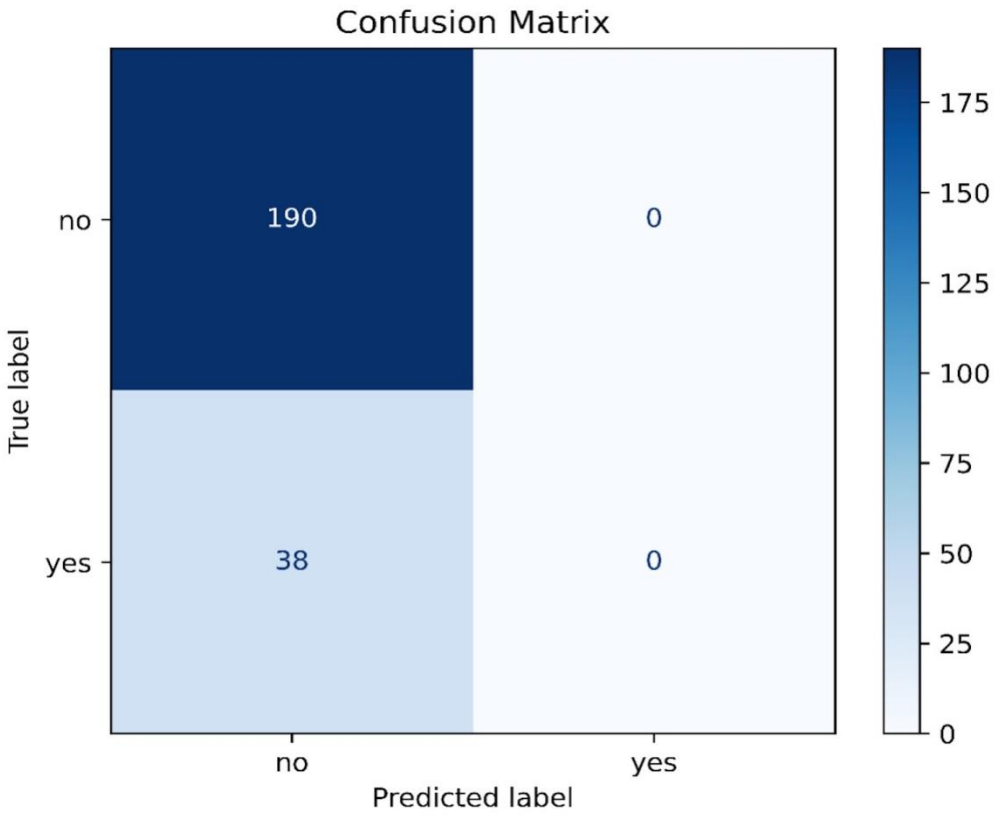

Figure 2 depicts the confusion matrix of the graph neural network model for predicting causal associations with Alzheimer's microRNA disease. It accurately recognized 190 instances of "no" cases but did not identify any "yes"

cases, resulting in 38 false negatives and zero true positives. The model effectively discerned 190 instances lacking a causal association between a microRNA and Alzheimer's disease but did not detect any instances exhibiting a causal association. While proficient in identifying cases without a causal association, the model struggled to accurately identify cases with a causal association, highlighting a significant limitation in its ability to predict microRNA-disease causal associations in the context of Alzheimer's disease.

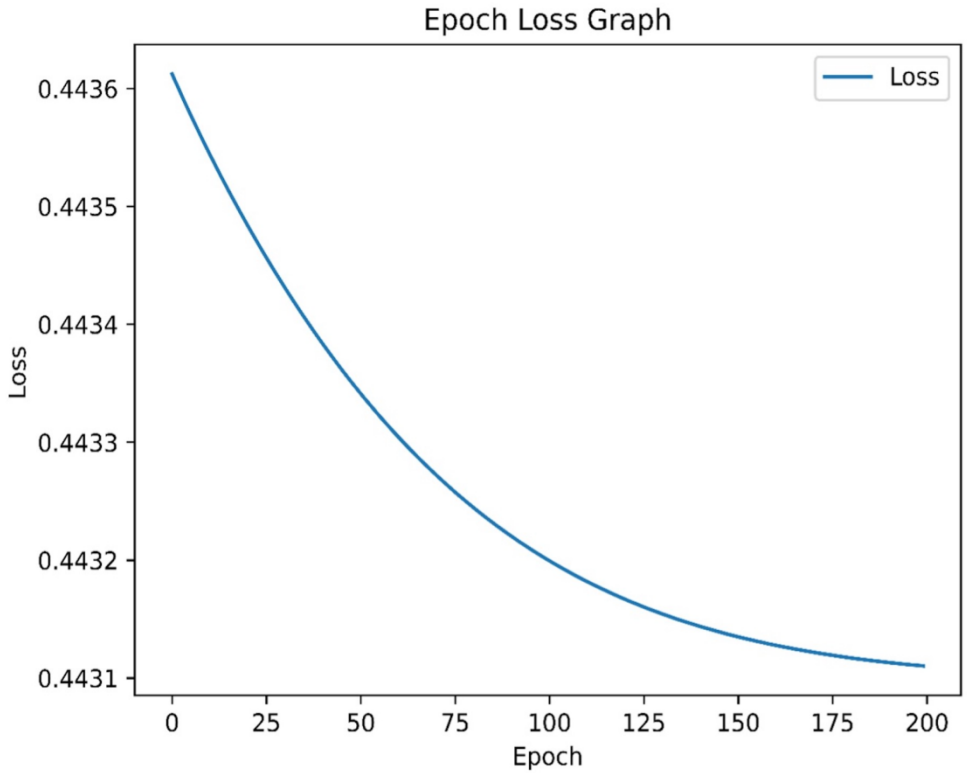

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Figure 3 illustrates the Epoch Loss Graph, demonstrating the performance of the neural network model in predicting causal associations between Alzheimer's microRNA disease and training epochs. The model's loss initiates at 0.4436 and steadily diminishes with increasing epochs, suggesting effective learning from the training data. By epoch 200, the loss decreases to 0.4431, signifying enhanced accuracy.

Discussion

Alzheimer's disease stands as a neurodegenerative condition characterized by cognitive decline and memory impairment (15,16), believed to be influenced by both genetic and environmental factors. Recent investigations have underscored the role of microRNAs (miRNAs) in the development and progression of Alzheimer's disease. Dysregulated miRNAs have been pinpointed in Alzheimer's disease, targeting genes crucial for neuronal survival, synaptic plasticity, and inflammation (17-19). A recent study employed protein-protein interaction networks and miRNA-gene interactions to link Alzheimer's disease with miRNAs, identifying 257 novel AD-related miRNAs via a one-class SVM semi-clustering method, yielding higher AUC values and reliable outcomes (2,20).

Previous research utilized a network of miRNA-target interactions (MTIs) relevant to Alzheimer's disease (AD),

sourced from data in miRTarBase. The network comprised seven MTI subnetworks and 12 MTI pairs, incorporating nodes such as APP, BACE1, NCSTN, SIRT, SP1, and specific miRNAs like miR-9, miR-16, and miR-181c. This study scrutinized the interactions of miRNA targets with proteins and their enrichment for AD-associated miRNAs, elucidating their role in gene expression regulation (20,21). Nonetheless, consensus on validation strength remains elusive, and our study endeavors to explore microRNA disease causation prediction to uncover novel targets.

MicroRNAs (miRNAs) play pivotal roles in post-transcriptional gene regulation, with implications in various diseases including cancer. Graph neural networks (GNNs) have been leveraged in drug screening for small molecules targeting miR-21, predicting potential drugs based on structural similarities and showcasing potential for discovering novel therapeutic agents. GATMDA, a computational framework (9,10), employs a graph attention network to identify miRNA-disease associations, achieving high performance with an average AUC of 0.9566 in five-fold cross-validation.

Recent investigations highlight the potential of graph neural networks (GNNs) in predicting Alzheimer's disease risk. These robust machine learning models can capture intricate biomarker relationships, offering insights into disease progression and facilitating more

accurate prognosis and earlier interventions. Incorporating time-varying information into the GNN framework could further enhance prediction accuracy (22-24). The development of explainable GNN models can furnish personalized explanations for early Alzheimer's disease diagnosis, empowering clinicians to make informed decisions and tailor treatment strategies. The graph neural network model adeptly predicts Alzheimer's microRNA disease causal associations, achieving an accuracy of 83.33%, precision of 69.44%, recall of 83.33%, and an F1-score of 75.76%, rendering it a promising tool for unraveling complex relationships.

The accuracy of a model is influenced by its proficiency in predicting cases with no causal association accurately. However, a more nuanced analysis is provided by the ROC curve and AUC value. The AUC value of 0.56 suggests the model performs slightly better than random guessing but struggles to discriminate between positive and negative cases. This disparity may arise from class imbalance, false positives, and negative costs. Therefore, the model's subpar performance in the ROC curve implies inadequate identification of cases with causal associations. The graph neural network model's accuracy in predicting Alzheimer's microRNA disease (25-27) causal associations holds promise, yet there exist limitations and potential avenues for enhancement (28,29). Dataset

imbalance, where one class outweighs the other in terms of samples, can bias the model towards predicting the majority class, resulting in higher accuracy but poorer performance in identifying cases with causal associations (30,31). The model may also prioritize minimizing false positives at the expense of higher false negatives, leading to a lower AUC value. Future endeavors encompass dataset balancing, classification threshold adjustments, and exploration of additional features or advanced GNN architectures. Extending the application to other diseases could yield valuable insights into molecular mechanisms, though limitations include data availability, heterogeneity, lack of experimental validation, and interpretability.

Conclusion

The graph neural network model for predicting causal associations between Alzheimer's disease and microRNAs exhibits promise; however, certain limitations need to be addressed. Future research endeavors should prioritize addressing dataset imbalance, fine-tuning classification thresholds, incorporating additional features, and exploring advanced model architectures. These efforts hold potential for enhancing the accuracy and robustness of the predictive model, thereby advancing our understanding of Alzheimer's disease pathophysiology and identifying novel therapeutic targets.

Conflict of Interest

The authors have no conflicts of interest to declare

Authors contribution

Pradeep Kumar Yadalam, Soundharya Manogaran, Ramya Ramadoss and Carlos M. Ardila contributed to the conception, analysis, interpretation of data, and drafting of the manuscript.

Pradeep Kumar Yadalam, Soundharya Manogaran, Ramya Ramadoss and Carlos M. Ardila: Conceptualization

Pradeep Kumar Yadalam, and Carlos M. Ardila: Methodology

Pradeep Kumar Yadalam, Soundharya Manogaran, Ramya Ramadoss and Carlos M. Ardila: Data curation

Pradeep Kumar Yadalam, and Carlos M. Ardila: Writing- Original draft preparation.

Pradeep Kumar Yadalam, Soundharya Manogaran, Ramya Ramadoss and Carlos M. Ardila: Visualization

Pradeep Kumar Yadalam, and Carlos M. Ardila: Investigation.

Pradeep Kumar Yadalam, Soundharya Manogaran, Ramya Ramadoss and Carlos M. Ardila: Validation and supervision.

Pradeep Kumar Yadalam, and Carlos M. Ardila: Writing- Reviewing and Editing.

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