Odovtos-International Journal of Dental Sciences (Odovtos-Int. J. Dent. Sc.), Online First, 2025. ISSN: 2215-3411
https://doi.org/10.15517/hz94f853

ODOVTOS
International Journal of Dental Sciences

UNIVERSIDAD DE COSTA RICA
FOd Facultad de Odontología

https://revistas.ucr.ac.cr/index.php/Odontos

BASIC RESEARCH:

Enhanced Hierarchical Attention Network-Based Drug-Gene Association for Angiotensin Receptors in Periodontal Inflammation

Red de atención jerárquica mejorada para asociaciones fármaco-gen en receptores de angiotensina en la inflamación periodontal

Pradeep K. Yadalam PhD[1] https://orcid.org/0000-0002-6653-4123
Carlos M. Ardila PhD[1-2] https://orcid.org/0000-0002-3663-1416

[1]Department of Periodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Chennai - 600 077.Tamilnadu, India.
[2]Basic Sciences Department, Faculty of Dentistry, Biomedical Stomatology Research Group, Universidad de Antioquia U de A, Medellín, 050010, Colombia.

Correspondence to: Pradeep K. Yadalam - pradeepkumar.sdc@saveetha.com
Carlos M. Ardila - martin.ardila@udea.edu.co

Received: 23-IV-2025 Accepted: 8-VII-2025

ABSTRACT: Periodontal inflammation, a chronic condition affecting teeth and supporting structures, is linked to cardiovascular disease. The renin-angiotensin system plays a crucial role in inflammation and oxidative stress, with AT1 and AT2 receptors affecting vascular functions and inflammatory responses. This study aims to utilize angiotensin receptors in periodontal inflammation through enhanced hysterical attention network-based drug-gene association. Data preprocessing is crucial for ensuring the quality and reliability of drug and gene data, particularly in research involving angiotensin receptors, by identifying duplicates and correcting inconsistent formats. Cytoscape was utilized to import drugs and genes linked to angiotensin receptors, thereby constructing and analyzing a network. The Hierarchical Attention Network is an innovative framework for processing structured data with hierarchical relationships. It is suitable for tasks where features can be organized into multi-level structures. The network, with 1,172 nodes and 4,315 edges, has efficient communication, low density, significant connectivity variance, moderate centralization, and four connected components, with a 1.531-second analysis time. The model's R^2 score is 0.3631, indicating that the features can explain 36.31% of the target variable's variance. However, the model's predictions are about 0.8013 units away from actual values, suggesting room for improvement. Integrating hierarchical attention networks in deep learning models is promising for predicting drug and gene interactions in angiotensin receptors in periodontal inflammation.

KEYWORDS: Angiotensin; Cytoscape; Cardiovascular disease; Drug-gene associations; Periodontal inflammation; Deep learning; AT1/AT2 receptors.

RESUMEN: La inflamación periodontal, una afección crónica que afecta a los dientes y sus estructuras de soporte, está vinculada a enfermedades cardiovasculares. El sistema renina-angiotensina desempeña un papel crucial en la inflamación y el estrés oxidativo, con los receptores AT1 y AT2 influyendo en las funciones vasculares y las respuestas inflamatorias. Este estudio busca utilizar receptores de angiotensina en la inflamación periodontal mediante una red de atención jerárquica mejorada para asociaciones fármaco-gen. El preprocesamiento de datos es fundamental para garantizar la calidad y fiabilidad de los datos de fármacos y genes, especialmente en investigaciones que involucran receptores de angiotensina, identificando duplicados y corrigiendo formatos inconsistentes. Se utilizó Cytoscape para importar fármacos y genes asociados a receptores de angiotensina, construyendo y analizando una red. La Red de Atención Jerárquica es un marco innovador para procesar datos estructurados con relaciones jerárquicas, ideal para tareas donde las características pueden organizarse en estructuras multinivel. La red, con 1.172 nodos y 4.315 aristas, muestra comunicación eficiente, baja densidad, variación significativa en conectividad, centralización moderada y cuatro componentes conexos, con un tiempo de análisis de 1,531 segundos. El modelo obtuvo un puntaje R^2 de 0,3631, indicando que las características explican el 36,31% de la varianza de la variable objetivo. Sin embargo, las predicciones del modelo se desvían aproximadamente 0,8013 unidades de los valores reales, sugiriendo margen de mejora. La integración de redes de atención jerárquica en modelos de aprendizaje profundo es prometedora para predecir interacciones fármaco-gen en receptores de angiotensina en la inflamación periodontal.

PALABRAS CLAVE: Angiotensina; Cytoscape; Enfermedades cardiovasculares; Asociaciones fármaco-gen; Inflamación periodontal; Aprendizaje profundo; Receptores AT1/AT2.

INTRODUCTION

Periodontal inflammation, often resulting from periodontal disease, is a chronic inflammatory condition affecting the supporting structures of the teeth, including the gums, periodontal ligament, and alveolar bone (1, 2). Periodontitis is a chronic inflammatory disease that significantly contributes to tooth loss in adults and is linked to cardiovascular disease through an inflammatory pathway. The renin-angiotensin system (RAS), primarily regulating electrolyte balance and blood pressure, also plays a crucial role in inflammation and oxidative stress. RAS operates through a cascade involving Angiotensinogen, Angiotensin I, and Angiotensin II, which interacts with specific receptors (AT1 and AT2), affecting vascular functions and inflammatory responses (3). While AT1 receptor activation promotes vasoconstriction and inflammation, AT2 receptor activation exhibits protective effects. The overlap between inflammatory responses in periodontitis and CVD is evident, with pro-inflammatory cytokines like TNF-α, IL-1, and IL-6 being central to both conditions, highlighting a systemic link that exacerbates cardiovascular risks in individuals with periodontitis.

Angiotensin II type 1 receptor (AT1R) is a key peptide in the renin-angiotensin system (RAS) that regulates inflammation, including periodontal inflammation. Its activation can lead to increased production of pro-inflammatory cytokines and chemokines, exacerbated by osteoclast differentiation (4). It also influences vasodilation and vasoconstriction, affecting blood flow to periodontal tissues and leading to localized inflammation. It is also associated with tissue remodeling and fibrosis, potentially leading to chronic inflammatory conditions. It can also modulate the immune response (5). The role of AT1R in periodontal inflammation highlights the need for comprehensive approaches to managing periodontal diseases, including syste-

mic medications targeting the renin-angiotensin system alongside local dental therapies (6).

Drug-gene associations are crucial in pharmacogenomics, a field that studies how an individual's genetic makeup influences their medication response. Understanding these associations allows personalized medicine, improved drug efficacy, reduced adverse drug reactions, optimized drug dosing, enhanced drug development, and addressed health disparities (7, 8). Transformer models are a promising approach to predict drug-gene associations, which can significantly advance pharmacogenomics and personalized medicine. Transformers excel at processing and integrating diverse types of information, facilitating a more holistic understanding of drug-gene interactions. They can manage high-dimensional pharmaceutical and genetic datasets, identifying relevant patterns and relationships that traditional methods may overlook. Transformers also utilize attention mechanisms to capture contextual relationships between different entities, improving the accuracy of predictions regarding how specific genetic variations may influence drug response. Transformer models (9) can be trained on labeled datasets with known drug-gene associations, fine-tuning for specific tasks or datasets with limited labels, and evaluated using appropriate metrics. Once validated, the model can predict drug-gene associations for new or untested pairs, guiding researchers and clinicians in making informed decisions about drug therapies. The significance of predicting drug-gene associations using transformers lies in their potential to advance personalized medicine, reduce cost-efficiency, identify new therapeutics, spur research collaboration, and support data-driven healthcare.

Periodontal disease involves alveolar bone destruction and periodontal ligament lesions due to bacterial infection and an abnormal immune response. A study on primary hypertension (PH) and periodontitis in mice suggests Ang II may be a potential treatment target, as PH exacerbates periodontitis, causing bone resorption and ligament destruction. The study found that blocking Angiotensin II receptors leads to bone loss and increased Ang II levels in the AT2-L group, with Mas receptor expression also significantly increased. One more study showed how pulmonary hypertension (PH) worsens periodontitis in mice, finding that PH increases bone resorption and ligament destruction, which can be mitigated by losartan, and increases dendritic cell and osteoclast infiltration, suggesting targeting Ang II may be beneficial (10) Predicting drug-gene associations for angiotensin receptors in periodontal inflammation is crucial for understanding the disease, developing targeted therapies, preventing adverse effects, and improving patient outcomes. Angiotensin receptors also play a role in various biological processes, including inflammation and immune responses (11-13). Understanding how drugs targeting these receptors interact with genetic factors can provide insights into the pathology of periodontal disease.

The hierarchical network AI (14) model predicts drug responses in cancer cells at gene, molecular pathway, and drug level, outperforming state-of-the-art methods with high accuracy. It emphasizes drug-target genes and cancer-related pathways, with validation through in vitro cytotoxicity assays. Our model effectively interprets the intrinsic characteristics of cancer cells and drugs for accurate cancer-drug response predictions. An interpretable graph neural network (GNN) with a self-attention-based pooling layer (SANEpool) (15) is developed to identify therapeutic targets and synergy mechanisms, outperforming previous models in synergy score prediction. The study aimed to investigate the role of angiotensin receptor drugs and genes in periodontal inflammation, as previous studies have not addressed this issue. Identifying specific drug-gene associations can lead to more effective treatment options for patients with periodontal inflammation. Predicting drug-gene associations helps anticipate adverse

effects or ineffective therapies for patients with specific gene variations related to angiotensin receptors. Enhanced attention networks capture hierarchical relationships in data, integrate multimodal data, dynamically learn contextual relationships between genes and drugs, handle sparse data and improve predictive performance. This is vital for advancing personalized medicine, understanding disease mechanisms, developing targeted therapies, and improving patient care. The aim is to utilize angiotensin receptors in periodontal inflammation through enhanced hysterical attention network-based drug-gene association.

MATERIALS AND METHODS

Figure 1 outlines the integrated workflow employed to investigate drug-gene associations in the context of periodontal inflammation and angiotensin receptor interactions. The workflow begins with data preprocessing, which involves meticulous cleaning, standardization, and removal of inconsistencies to ensure high-quality data for analysis. By incorporating an enhanced hierarchical attention network, the framework leverages advanced computational models to analyze drug-gene interactions and identify critical biochemical pathways. This structured approach not only facilitates accurate predictions of gene expressions and drug interactions but also underscores their relevance in periodontal inflammation and related pathophysiological conditions.

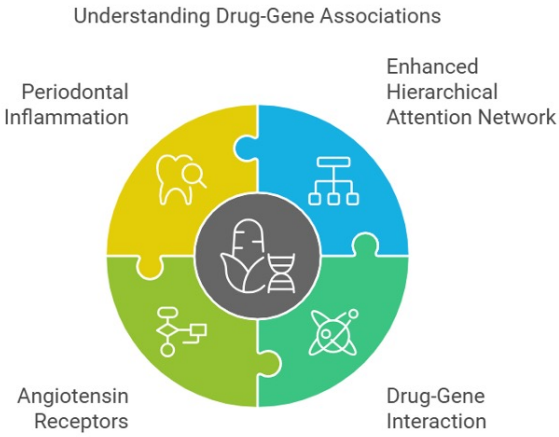

Figure 1. Workflow for Understanding Drug-Gene Associations in Periodontal Inflammation and Angiotensin Receptor Studies.

DATASET PREPARATION

Data preprocessing is crucial for ensuring the quality and reliability of drug and gene data, particularly in research involving angiotensin receptors derived from probes and drug websites (16). Data cleaning involved identifying duplicates, correcting inconsistent formats, standardizing terminology, and removing missing values to prevent biased results and ensure equal feature contribution in machine learning applications. The prepared dataset can provide reliable insights into drug interactions, gene expressions, and biochemical activities related to angiotensin receptors by applying these preprocessing methods. This meticulous preparation facilitates subsequent analysis, modeling, or machine learning tasks, enhancing

the accuracy and robustness of the results obtained from the dataset (Figure 1).

CYTOSCAPE

Cytoscape (17) was used to import drugs and genes associated with angiotensin receptors, constructing and analyzing a network.

ENHANCED HIERARCHICAL ATTENTION NETWORKS

MODEL ARCHITECTURE

The Hierarchical Attention Network (HALT) (9, 14, 18) is an innovative framework designed to effectively process structured data with hierarchical relationships, making it particularly suitable for tasks where features can be organized into multi-level structures, such as text documents, graphs, or other complex datasets. Let's delve into the components of the HALT model and the hyperparameters used, explaining the methods and their significance:

KEY COMPONENTS OF THE HALT MODEL

1. Input Layer: The input layer transforms raw features into a higher-dimensional space using a linear transformation, enhancing the model's ability to learn complex relationships in data by separating different classes or outcomes.

2. Embedding Layer: The embedding layer stabilizes training and aids representation learning through batch normalization, reducing internal covariate shift and network initialization sensitivity. The HALT model uses ReLU activation and Dropout techniques to introduce non-linearity and prevent overfitting, enhancing its robustness and generalization.

3. Hierarchical Attention Mechanism: Purpose: The hierarchical attention mechanism enables the model to focus on the most informative parts of the input data at different levels of the hierarchy. The mechanism uses multiple levels of attention to capture local and global patterns and multihead attention to jointly attend to information from different representation subspaces at each layer.

4. Output Layer: The purpose of this study is to use a fully connected network to synthesize attention outputs and make predictions for the target variable.

HYPERPARAMETERS USED IN THE HALT MODEL

1. Input Dimension (input_dim): The parameter specifies the number of features in the input data, which is crucial for correctly initializing the input layer and ensuring the model can accommodate all input features.

2. Hidden Dimension (hidden_dim): The capacity of a model is determined by the size of its hidden layers, which can capture complex patterns but also increase the risk of overfitting.

3. Number of Attention Levels (num_levels): The model's attention level, set at three, enables hierarchical data processing, allowing for meaningful information aggregation across different levels.

4. Dropout Rate (dropout_rate): The parameter, set at 0.2, regulates the percentage of neurons randomly dropped during training to prevent overfitting, balancing training capacity with overfitting prevention.

5. Optimizer: Adam is an advanced optimization algorithm, a variant of the Adam optimizer,

incorporating weight decay and a 0.001 learning rate for faster convergence and stability.

6. Loss Function: The Mean Squared Error (MSE) is a loss function used in regression tasks to measure the average squared differences between predicted and actual values.

7. Batch Size: The hyperparameter set at 32 impacts the number of samples processed before updating the model, with smaller batch sizes resulting in a noisier gradient estimate.

8. Learning Rate Scheduler: The scheduler reduces the learning rate if validation loss doesn't improve after a set number of epochs, allowing for a more refined optimization process.

9. Early Stopping: This technique stops training if validation loss doesn't improve for seven consecutive epochs, preventing overfitting and the model from learning noise in data after convergence.HALT model uses attention mechanisms and layered architecture to capture hierarchical data relationships, balancing learning complexity, convergence speed, and generalization ability, making it a powerful framework. The Enhanced HALT Model uses a hierarchical attention network with three levels of MultiheadAttention and output layers of linear (256—>128) + ReLU + Dropout (0.2) + Linear(128—>1).

Training Configuration:

- Optimizer: AdamW
- Learning Rate: 0.001
- Weight Decay: 0.01
- Loss Function: MSE Loss
- Batch Size: 32
- Early Stopping Patience: 7
- Learning Rate Scheduler: ReduceLROnPlateau
- Mode: min
- Factor: 0.5
- Patience: 3

RESULTS

The results of this study highlight the utility of a Hierarchical Attention Network (HALT) architecture in analyzing the associations between drugs and genes related to angiotensin receptors in periodontal inflammation. By employing a robust network-based approach, the study emphasizes efficient communication, structural properties, and predictive capabilities within the dataset, while also identifying areas for improvement in model performance. The following sections provide an in-depth analysis of the network characteristics and model evaluation metrics.

NETWORK ANALYSIS

The constructed network consists of 1,172 nodes and 4,315 edges, with an average of 7.261 neighbors per node. The network's diameter of six steps suggests a compact structure, while the radius of three steps indicates efficient communication. A low clustering coefficient reflects limited local interconnectedness among nodes. The network density is 0.006, confirming its sparsity, while a heterogeneity value of 2.556 suggests significant variance in node connectivity. A moderate centralization score of 0.286 indicates that some nodes have a higher influence than others. Furthermore, the network consists of four connected components, representing isolated clusters. The analysis was performed efficiently, taking 1.531 seconds (Figure 2).

These network characteristics reveal a decentralized structure with sparse connections, highlighting potential areas for targeted drug-gene

interactions. The lack of clustering and low density suggests limited tightly knit groups, while centralization and heterogeneity indicate key influential nodes within the network.

Figure 2. Network analysis of the drug and gene Association with HALT architecture.

MODEL EVALUATION

The study's predictive model was evaluated using multiple metrics.

R^2 Score: The model achieved an R^2 score of 0.3631, indicating that the features explained 36.31% of the variance in the target variable. While the model captured some relationships, its explanatory power requires further enhancement.

RMSE and MAE: The Root Mean Squared Error (RMSE) of 0.8013 and Mean Absolute Error (MAE) of 0.6116 highlight the model's prediction accuracy and error magnitude. While the RMSE reflects the error magnitude in predictions, the MAE suggests a reasonable error margin.

Training and Validation Loss: The final training and validation losses were 0.6808 and 0.6481, respectively. These values indicate a reasonable fit to the training data, with slightly better performance on the validation set.

The model was trained over 50 epochs, with early stopping and learning rate adjustments employed to prevent overfitting and enhance optimization. Although the results indicate promise, further feature engineering and tuning are needed to improve performance.

This plot depicts the progression of training and validation loss over 50 epochs. The steady decline in both losses reflects effective model learning, with no evidence of overfitting (Figure 3).

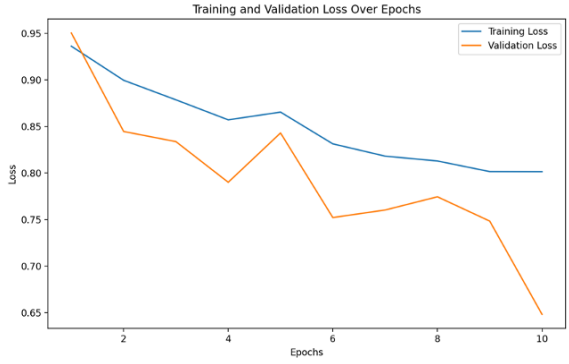

Figure 3. Training and Validation Loss Over Epochs. This plot shows the training and validation loss over epochs. The validation loss decreases steadily, indicating that the model learns effectively without overfitting.

The plot demonstrates the improvement in the model's ability to explain variance in the data. A steady increase in the R^2 score indicates enhanced alignment between predictions and actual values (Figure 4).

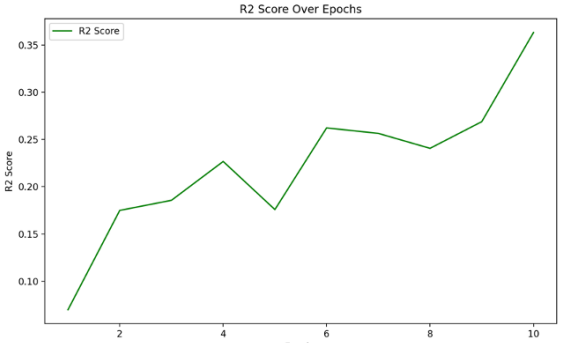

Figure 4. R^2 Score Over Epochs. The R^2 score over epochs demonstrates the model's ability to explain variance in the data. The score improves steadily, showing better alignment between predictions and actual values.

The graph shows the Root Mean Squared Error (RMSE) trend over epochs. A continuous decline reflects decreasing error magnitude and improved prediction accuracy (Figure 5).

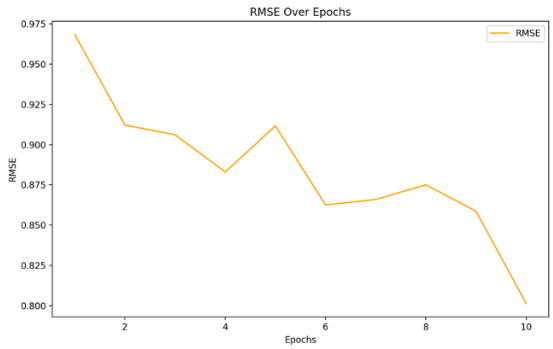

Figure 5. Root Mean Squared Error (RMSE) Over Epochs. It indicates the error magnitude. A steady decrease in RMSE reflects improved model performance.

This plot highlights the decreasing trend of Mean Absolute Error (MAE) over epochs, showcasing the model's growing precision in predictions (Figure 6).

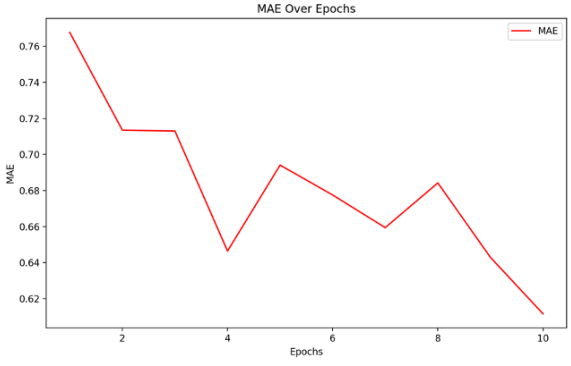

Figure 6. Mean Absolute Error (MAE) Over Epochs. The decreasing trend highlights the model's increasing accuracy.

The HALT architecture demonstrates promising potential for drug-gene association in angiotensin receptors, as evidenced by the comprehensive network analysis and model evaluation. However, the results also underscore the need for additional feature engineering and optimization to fully realize the model's predictive capabilities.

DISCUSSION

Angiotensin receptors, particularly AT1R and AT2R, are crucial in the pathophysiology of periodontal inflammation. They play a role in inflammatory responses, tissue remodeling, and vascular effects, making them potential therapeutic targets. Angiotensin II, the main active peptide of the renin-angiotensin system, binds to these receptors, promoting inflammation, fibrosis, and oxidative stress. The balance between AT1R and AT2R signaling is crucial in modulating these responses (10). Angiotensin II can enhance the production of pro-inflammatory cytokines and chemokines in periodontal tissues, leading to increased inflammation and tissue destruction. It can also affect bone resorption and remodeling processes in periodontal disease. Periodontal inflammation can lead to increased blood flow and vascular permeability, exacerbated by angiotensin II. Drugs like angiotensin receptor blockers (ARBs) and ACE inhibitors may offer protective effects against periodontal inflammation by modulating inflammatory responses and reducing oxidative stress. Genetic variations in angiotensin receptors and cytokine genes can also influence the inflammatory response in individuals with periodontal disease (19, 20).

A previous study comparing hypertensive patients on angiotensin-converting enzyme (ACE) inhibitors and those without showed lower arterial dilation post-treatment. Hypertensive patients on ACE inhibitors had less endothelial dysfunction and returned to baseline after 15 days. P. gingivalis LPS increases IL-1β and iNOS gene expression in PD groups, with AT1 receptors playing a role in blood pressure regulation (19). Silencing AT1R can affect bone tissue morphology. Healthy and inflamed human gingiva express RAS components, but inflamed tissue shows greater AT1R immunoreactivity. In rat gingiva, renin inhibition and AT1R antagonism reduce bone loss, supporting a local RAS system (21). Human and rat gingiva

express RAS components, with no differences between healthy and diseased tissue. Inflamed tissue shows greater AT1R immunoreactivity in fibroblasts. Renin inhibition and AT1R antagonism reduce EP-induced alveolar bone loss, supporting the presence and functionality of a local RAS in periodontal tissue (22-25).

In this study, the network has 1,172 nodes and 4,315 edges, with an average of 7.261 neighbors. It has a compact structure with a radius of 3 steps away, suggesting efficient communication. The network has a low density, significant variance in connectivity, and moderate centralization (Figure 2). It has four connected components, suggesting isolated clusters or groups. The model's R^2 score is 0.3631, indicating that the features can explain 36.31% of the target variable's variance. However, the model's predictions are about 0.8013 units away from actual values, suggesting room for improvement. The model fits the training data well but could benefit from further tuning or feature engineering (Figures 3- 6) similar to A new HANN model that identifies drug resistance-related genes and variants, capturing interactions among mutated genes. It achieves optimal ROC curve areas for isoniazid, rifampicin, ethambutol, and pyrazinamide, with sensitivities of 94.63%, 96.31%, 92.56%, and 87.05% (26,27). Future directions for angiotensin receptors in drug-gene associations using hierarchical attention networks in periodontal inflammation include enhanced feature engineering, integrating multi-omics data, and improving deep learning models. These include exploring advanced architectures like Convolutional Neural Networks and Graph Neural Networks, cross-validating models with diverse cohorts, conducting longitudinal studies to monitor gene expression and angiotensin receptor activity, and developing algorithms for personalized treatment plans based on genetic predispositions and receptor status. These advancements could lead to improved patient outcomes in periodontal disease management. Hierarchical attention networks, a type of deep learning model, have limitations due to factors such as data quality, complexity of biological systems, interpretability of deep learning models, limited understanding of mechanisms, potential overfitting, and ethical considerations. These limitations can hinder the model's ability to learn meaningful patterns and the potential for misleading conclusions about the generalizability of findings. Developing personalized treatment algorithms based on genetic information raises ethical issues, such as privacy and potential discrimination in treatment access. Addressing these limitations can lead to better-targeted therapies and improved patient care (28).

CONCLUSIONS

The model's R^2 score is modest, but the prediction error suggests room for improvement. The integration of hierarchical attention networks is promising for associated drugs and genes in angiotensin receptors in periodontal inflammation. However, as we advance, it's crucial to address the inherent limitations of deep learning models, including data quality issues, the complexity of biological systems, and ethical considerations surrounding patient data. Ensuring these models are interpretable and generalizable will be vital in establishing trust in predictive algorithms, particularly those guiding personalized treatment strategies. By proactively tackling these challenges, we can move closer to developing targeted therapies that significantly improve patient outcomes in managing periodontal disease and related conditions.

CONFLICTS OF INTEREST: The authors declare no conflicts of interest.

FUNDING: This research did not receive grants.

AUTHOR CONTRIBUTIONS STATEMENT

Conceptualization: P.K.Y. and C.M.A.
Data curation: P.K.Y. and C.M.A.
Formal analysis: P.K.Y. and C.M.A.
Funding acquisition: P.K.Y.
Investigation: P.K.Y. and C.M.A.
Methodology: P.K.Y. and C.M.A.
Project administration: P.K.Y.
Resources: P.K.Y.
Software: P.K.Y.
Supervision: P.K.Y. and C.M.A.
Validation: P.K.Y. and C.M.A.
Visualization: P.K.Y. and C.M.A.
Writing-original draft: P.K.Y. and C.M.A.
Writing-review & editing: P.K.Y. and C.M.A.

All authors have read and agreed to the published version of the manuscript.

REFERENCES

1. Sanz M., Marco Del Castillo A., Jepsen S., Gonzalez-Juanatey J.R., D'Aiuto F., Bouchard P., et al. Periodontitis and cardiovascular diseases: Consensus report. J Clin Periodontol. 2020; 47: 268-88.
2. Kornman K.S. Mapping the pathogenesis of periodontitis: a new look. J Periodontol. 2008; 79 (8 Suppl): 1560-8.
3. Li J., Xiao X., Wei W., Ding H., Yue Y., Tian Y., et al. Inhibition of angiotensin II receptor I prevents inflammation and bone loss in periodontitis. J Periodontol. 2019; 90: 208-16.
4. Lima M.L. de S., Martins A.A., Medeiros CACX de, Guerra G.C.B., Santos R., Bader M., et al. The Receptor AT1 Appears to Be Important for the Maintenance of Bone Mass and AT2 Receptor Function in Periodontal Bone Loss Appears to Be Regulated by AT1 Receptor. Int J Mol Sci. 2021; 22: 12849.
5. Santos C.F., Morandini A.C., Dionísio T.J., Faria F.A., Lima M.C., Figueiredo C.M., et al. Functional Local Renin-Angiotensin System in Human and Rat Periodontal Tissue. PLoS One. 2015; 10: e0134601.
6. Saravi B., Lang G., Ülkümen S., Burchard T., Weihrauch V., Patzelt S., et al. The tissue renin-angiotensin system (tRAS) and the impact of its inhibition on inflammation and bone loss in the periodontal tissue. Eur Cell Mater. 2020; 40: 203-26.
7. Yadalam P.K., Natarajan P.M., Mosaddad S.A., Heboyan A. Graph neural networks-based prediction of drug gene association of P2X receptors in periodontal pain. J Oral Biol Craniofac Res. 2024; 14: 335-8.
8. Yadalam P.K., Ardila C.M. Artificial Intelligence-Driven Multiomics Network Analysis Reveals Resistance Mechanisms in Oral Cancer. Int Dent J. 2024 ; 74: 1180-1.
9. Bi H., Lu L., Meng Y. Hierarchical attention network for multivariate time series long-term forecasting. Applied intelligence (Dordrecht, Netherlands). 2023; 53: 5060-71.
10. Lima M.L. de S., Medeiros CACX de, Guerra G.C.B., Santos R., Bader M., Pirih F.Q., et al. AT1 and AT2 Receptor Knockout Changed Osteonectin and Bone Density in Mice in Periodontal Inflammation Experimental Model. Int J Mol Sci. 2021; 22: 5217
11. Trivandrum Anandapadmanabhan L., Ramani P., Ramadoss R., Panneerselvam S., Sundar S. Effect of COVID-19 on Dental Education: A Review. Cureus. 2022; 14 (4): e24455.
12. Moovarkumudalvan B., Geethakumari A.M., Ramadoss R., Biswas K.H., Mifsud B. Structure-Based Virtual Screening and Functional Validation of Potential Hit Molecules Targeting the SARS-CoV-2 Main Protease. Biomolecules. 2022; 12: 1754.
13. Sundar S., Ramadoss R., Shanmugham R., Anandapadmanabhan L.T., Paneerselvam S., Ramani P., et al. Salivary Antibody Response of COVID-19 in Vaccinated and Unvaccinated Young Adult Populations. Vaccines (Basel). 2022; 10: 1819.

14. Gao S., Young M.T., Qiu J.X., Yoon H.J., Christian J.B., Fearn P.A., et al. Hierarchical attention networks for information extraction from cancer pathology reports. J Am Med Inform Assoc. 2018; 25: 321-30.
15. Mousavi S., Afghah F., Acharya U.R. HAN-ECG: An interpretable atrial fibrillation detection model using hierarchical attention networks. Comput Biol Med. 2020; 127: 104057.
16. Skuta C., Popr M., Muller T., Jindrich J., Kahle M., Sedlak D., et al. Probes & Drugs portal: an interactive, open data resource for chemical biology. Nat Methods. 2017; 14: 759-60.
17. Shannon P., Markiel A., Ozier O., Baliga N.S., Wang J.T., Ramage D., et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res. 2003; 13: 2498-504.
18. Li X., Lu R., Liu P., Zhu Z. Graph convolutional networks with hierarchical multi-head attention for aspect-level sentiment classification. J Supercomput. 2022; 78: 14846-65.
19. Saravi B., Lang G., Ülkümen S., Burchard T., Weihrauch V., Patzelt S., et al. The tissue renin-angiotensin system (tRAS) and the impact of its inhibition on inflammation and bone loss in the periodontal tissue. Eur Cell Mater. 2020; 40: 203-26.
20. Santos C.F., Morandini A.C., Dionísio T.J., Faria F.A., Lima M.C., Figueiredo C.M., et al. Functional Local Renin-Angiotensin System in Human and Rat Periodontal Tissue. PLoS One. 2015; 10: e0134601.
21. Lin E.C., Chiang Y.C., Lin H.Y., Tseng S.Y., Hsieh Y.T., Shieh J.A., et al. Unraveling the Link between Periodontitis and Coronavirus Disease 2019: Exploring Pathogenic Pathways and Clinical Implications. Biomedicines. 2023; 11: 2789.
22. Rubio M.C., Lewin P.G., De la Cruz G., Sarudiansky A.N., Nieto M., Costa O.R., et al. Effect of angiotensin-converting enzyme inhibitors on vascular endothelial function in hypertensive patients after intensive periodontal treatment. Acta Odontol Latinoam. 2016; 29: 60-7.
23. Santos C.F., Morandini A.C., Dionísio T.J., Faria F.A., Lima M.C., Figueiredo C.M., et al. Functional Local Renin-Angiotensin System in Human and Rat Periodontal Tissue. PLoS One. 2015; 10: e0134601.
24. Saravi B., Lang G., Ülkümen S., Burchard T., Weihrauch V., Patzelt S., et al. The tissue renin-angiotensin system (tRAS) and the impact of its inhibition on inflammation and bone loss in the periodontal tissue. Eur Cell Mater. 2020; 40: 203-26.
25. Pasini A.F., Garbin U., Nava M.C., Stranieri C., Pellegrini M., Boccioletti V., et al. Effect of sulfhydryl and non-sulfhydryl angiotensin-converting enzyme inhibitors on endothelial function in essential hypertensive patients. Am J Hypertens. 2007; 20: 443-50.
26. Yang Y., Walker T.M., Kouchaki S., Wang C., Peto TEA, Crook D.W., et al. An end-to-end heterogeneous graph attention network for Mycobacterium tuberculosis drug-resistance prediction. Brief Bioinform. 2021; 22: bbab299.
27. Jiang Z., Lu Y., Liu Z., Wu W., Xu X., Dinnyés A, et al. Drug resistance prediction and resistance genes identification in Mycobacterium tuberculosis based on a hierarchical attentive neural network utilizing genome-wide variants. Brief Bioinform. 2022; 23: bbac041.
28. Dong Z., Zhang H., Chen Y., Payne PRO, Li F. Interpreting the Mechanism of Synergism for Drug Combinations Using Attention-Based Hierarchical Graph Pooling. Cancers (Basel). 2023; 15: 4210.