UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

DANIELA GIRALDO ROLDAN

INTELIGÊNCIA ARTIFICIAL NO DIAGNÓSTICO DE TUMORES ODONTOGÊNICOS

ARTIFICIAL INTELLIGENCE IN THE DIAGNOSIS OF ODONTOGENIC TUMORS

Piracicaba
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Dissertação apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestra em Estomatopatologia, na Área de Patologia.

Dissertation presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of the requirements for the degree of Master in Stomatopathology, in pathology area.

Orientador: Prof. Dr. Pablo Agustin Vargas.

Coorientador: Prof. Dr. Matheus Cardoso Moraes.

Este exemplar corresponde a versão final da dissertação defendida pela aluna Daniela Giraldo Roldan e orientada pelo Prof. Dr. Pablo Agustin Vargas.

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“Sometimes we feel that what we do is just a drop in the sea, but the sea would be less if it were missing a drop.”

Mother Teresa of Calcutta.

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RESUMO

Os tumores odontogênicos (OT) são compostos por lesões heterogêneas, que podem ser benignas ou malignas, com comportamento e histologia diferentes. Dentro dessa classificação, o ameloblastoma e o carcinoma ameloblástico (CA) representam um desafio diagnóstico na prática histopatológica diária devido às suas características semelhantes e às limitações que as biópsias incisionais representam. A partir dessas premissas, quisemos testar a utilidade de modelos baseados em Intelogencia artificial (IA) no campo da patologia oral e maxillofacial para o diagnóstico diferencial. As principais vantagens da integração do Machine Learning (ML) com imagens microscópicas e radiográficas é a capacidade de reduzir significativamente a variabilidade intra e interobservador e melhorar a objetividade e a reprodutibilidade diagnóstica. Objetivo: Este estudo tem como objetivo desenvolver um modelo de Deep Learning (LD) para analisar e diagnosticar TO com características microscópicas sobrepostas que representam desafios no diagnóstico diferencial de patologias bucais, especificamente em dois grupos de lesões: ameloblastomas e carcinomas ameloblásticos (CA). Métodos: Trinta lâminas digitalizadas foram coletadas de diferentes centros diagnósticos de patologia oral do Brasil contendo biópsias com diagnósticos de ameloblastoma e CA. Após a realização da anotação manual na região de interesse, as imagens foram segmentadas e fragmentadas em pequenos retalhos. Na metodologia de aprendizagem supervisionada para classificação de imagens, três modelos (ResNet50, DenseNet e VGG16) foram foco de investigação para fornecer a probabilidade de uma imagem ser classificada como classe 0 (ameloblastoma) ou classe 1 (CA). Com a execução dos ajustes necessários de parâmetros e hiperparâmetros, o desempenho final desses modelos no conjunto de testes foi avaliado através de métricas clássicas. Resultados: As métricas de treinamento e validação não apresentaram convergência, caracterizando overfitting. No entanto, os resultados do teste foram minimamente satisfatórios, com média para o ResNet50 de 0,75, 0,71, 0,84, 0,65 e 0,77 para acurácia, precisão, sensibilidade, especificidade e escore F1, respectivamente. Conclusões: A presente pesquisa revelou que os modelos demonstraram um forte potencial de aprendizagem, mas falta de capacidade de generalização. Os modelos aprendem rápido, atingindo uma precisão de treinamento de 98% durante algumas épocas de treinamento. O processo de avaliação mostrou instabilidade na validação; ainda com desempenho minimamente aceitável no processo de teste, o que pode indicar que o conjunto de dados precisa ser aumentado para se tornar mais representativo para treinamento e validação. Apesar de atingir desempenho minimamente aceitável, este estudo estabeleceu um ponto de partida e um caminho para o progresso contínuo.

Esta primeira investigação abre uma oportunidade para expandir a colaboração para incorporar mais dados complementares; bem como, desenvolver e avaliar novos modelos alternativos e mais adequados.

Keywords: Inteligência Artificial; Patologia bucomaxilofacial; Tumores odontogênicos; Carcinoma ameloblástico; Ameloblastoma.

ABSTRACT

Odontogenic tumors (OT) are composed of heterogeneous lesions, which can be benign or malignant, with different behavior and histology. Within this classification, ameloblastoma and ameloblastic carcinoma (AC) represent a diagnostic challenge in daily histopathological practice due to their similar characteristics and the limitations that incisional biopsies represent. From these premises, we wanted to test the usefulness of models based on artificial intelligence (AI) in the field of oral and maxillofacial pathology for differential diagnosis. The main advantages of integrating Machine Learning (ML) with microscopic and radiographic imaging is the ability to significantly reduce intra- and interobserver variability and improve diagnostic objectivity and reproducibility. Objective: This study aims to develop a Deep Learning (LD) model to analyze and diagnose OT with overlapping microscopic characteristics that represent challenges in the differential diagnosis of oral pathologies, specifically in two groups of lesions: ameloblastomas and ameloblastic carcinomas (AC). Methods: Thirty digitized slides were collected from different diagnostic centers of oral pathology in Brazil containing biopsies with diagnoses of ameloblastoma and AC. After manual annotation in the region of interest, the images were segmented and fragmented into small flaps. In the supervised learning methodology for image classification, three models (ResNet50, DenseNet and VGG16) were the focus of investigation to provide the probability of an image being classified as class 0 (ameloblastoma) or class 1 (CA). With the execution of the necessary adjustments of parameters and hyperparameters, the final performance of these models in the set of tests was evaluated through classical metrics. Results: The training and validation metrics did not show convergence, characterizing overfitting. However, the test results were minimally satisfactory, with an average for ResNet50 of 0.75, 0.71, 0.84, 0.65 and 0.77 for accuracy, precision, sensitivity, specificity and F1 score, respectively. Conclusions: The present research revealed that the models demonstrated a strong learning potential, but lack of generalization capacity. The models learn fast, achieving a training accuracy of 98% during some training seasons. The evaluation process showed instability in the validation; still with minimally acceptable performance in the testing process, which may indicate that the dataset needs to be augmented to become more representative for training and validation. Despite achieving minimally acceptable performance, this study established a starting point and a path for continued progress. This first investigation opens an opportunity to expand the collaboration to incorporate more complementary data; as well as to develop and evaluate new alternative and more appropriate models.

Keywords: Artificial Intelligence; Oral and maxillofacial pathology; Odontogenic tumors; Ameloblastic carcinoma; Ameloblastoma.

SUMÁRIO

1 INTRODUÇÃO

A inteligência artificial (IA) é a capacidade de um computador de realizar tarefas comumente associadas a seres inteligentes. Alguns programas alcançaram níveis de desempenho de especialistas humanos e profissionais em tarefas específicas, como diagnóstico médico, mecanismos de busca de computador e reconhecimento de objetos, voz ou digitação. *Machine Learning* (ML) é um subcampo da IA, que é definido como a capacidade de uma máquina de aprender, melhorando seu desempenho. O aprendizado começa com os dados que são coletados para serem usados como material de treinamento, que são as informações a partir das quais o modelo de ML será treinado; quanto mais dados, melhor o desempenho o modelo alcança. Simultaneamente, outro conjunto de dados é usado como material de avaliação, o que comprova a precisão do modelo. O resultado é um modelo que pode ser usado no futuro com diferentes conjuntos de dados. As redes neurais convolucionais [do inglês, *Convolutional Neural Network* (CNN)] consistem em uma coleção de unidades conectadas chamadas neurônios artificiais, que são equivalentes aos neurônios em um cérebro biológico. Cada conexão pode transmitir um sinal para outros neurônios. Dessa forma, um neurônio artificial recebe sinais, processa-os e pode enviá-los para os neurônios conectados a ele.[1,2]

Os avanços tecnológicos no campo de ML estão cada vez mais focados na área da saúde em geral, especialmente na capacidade de fornecer cuidados personalizados aos pacientes e, portanto, melhores resultados de saúde em geral. O potencial dessas ferramentas para gerar conhecimento a partir de grandes quantidades de dados é inigualável, podendo auxiliar na tomada de decisões, que incluem intervenções diagnósticas e tratamentos muito mais específicos.

Dentre as inúmeras aplicações possíveis da IA no campo da pesquisa para diagnóstico e prognóstico, destaca-se a análise de dados multivariados de diversos tipos de câncer, por meio da utilização de marcadores biológicos provenientes de ensaios clínicos e investigações pré-clínicas de fármacos. A principal área de particular interesse que concerne aos patologistas é a interpretação de imagens microscópicas onde, devido a origem embrionária comum de alguns tumores, existe uma sobreposição de características histopatológicas semelhantes que realmente tornam o diagnóstico desafiador, gerando uma grande necessidade de utilização de outras ferramentas como a imuno-histoquímica e, finalmente, a necessidade de revisão e confirmação diagnóstica na peça cirúrgica.

Redes neurais complexas têm sido utilizadas para distinguir tumores malignos de lesões benignas na área médica por meio da análise de imagens. Algoritmos de ML têm sido utilizados

para diferenciar alguns tipos de câncer, no campo da patologia oral e maxilofacial, especialmente o carcinoma espinocelular.[3–7] O uso da IA como auxílio diagnóstico para imagens histopatológicas e radiológicas de cabeça e pescoço visa à detecção precoce, diagnóstico preciso e predição do prognóstico dos pacientes, razão pela qual o objetivo deste trabalho é desenvolver um modelo de DL para a identificação e classificação de tumores odontogênicos, utilizando imagens de lâminas digitalizadas.

2 ARTIGO

2.1 Artigo: Deep Learning applied to the histopathological diagnosis of ameloblastomas and ameloblastic carcinomas.

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DEEP LEARNING APPLIED TO THE HISTOPATHOLOGICAL DIAGNOSIS OF AMELOBLASTOMAS AND AMELOBLASTIC CARCINOMAS

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ABSTRACT

Odontogenic tumors (OT) are composed of heterogeneous lesions, which can be benign or malignant, with different behavior and histology. Within this classification, ameloblastoma and ameloblastic carcinoma (AC) represent a diagnostic challenge in daily histopathological practice due to their similar characteristics and the limitations that incisional biopsies represent. From these premises, we wanted to test the usefulness of models based on artificial intelligence (AI) in the field of oral and maxillofacial pathology for differential diagnosis. The main advantages of integrating Machine Learning (ML) with microscopic and radiographic imaging is the ability to significantly reduce intra- and interobserver variability and improve diagnostic objectivity and reproducibility. Objective: This study aims to develop a Deep Learning (LD) model to analyze and diagnose OT with overlapping microscopic characteristics that represent challenges in the differential diagnosis of oral pathologies, specifically in two groups of lesions: ameloblastomas and ameloblastic carcinomas (AC). Methods: Thirty digitized slides were collected from different diagnostic centers of oral pathology in Brazil containing biopsies with diagnoses of ameloblastoma and AC. After manual annotation in the region of interest, the images were segmented and fragmented into small flaps. In the supervised learning methodology for image classification, three models (ResNet50, DenseNet and VGG16) were the focus of investigation to provide the probability of an image being classified as class 0 (ameloblastoma) or class 1 (CA). With the execution of the necessary adjustments of parameters and hyperparameters, the final performance of these models in the set of tests was evaluated through classical metrics. Results: The training and validation metrics did not show convergence, characterizing overfitting. However, the test results were minimally satisfactory, with an average for ResNet50 of 0.75, 0.71, 0.84, 0.65 and 0.77 for accuracy, precision, sensitivity, specificity and F1 score, respectively. Conclusions: The present research revealed that the models demonstrated a strong learning potential, but lack of generalization capacity.

The models learn fast, achieving a training accuracy of 98% during some training seasons. The evaluation process showed instability in the validation; still with minimally acceptable performance in the testing process, which may indicate that the dataset needs to be augmented to become more representative for training and validation. Despite achieving minimally acceptable performance, this study established a starting point and a path for continued progress. This first investigation opens an opportunity to expand the collaboration to incorporate more complementary data; as well as to develop and evaluate new alternative and more appropriate models.

Keywords: Artificial Intelligence; Oral and maxillofacial pathology; Odontogenic tumors; Ameloblastic carcinoma; Ameloblastoma.

INTRODUCTION

Pathological examinations constitute the gold standard in many medical protocols and play a fundamental and legal role in the diagnostic process. In conventional diagnosis, pathologists analyze biopsies to perform diagnoses and prognostic evaluations, mainly based on cell morphology and architecture distribution [8]. The use of digital systems and digital image analysis associated with the development of algorithms for image analysis has motivated the use of Artificial Intelligence (AI) adapted to the context of early and accurate histopathological diagnosis [9,10].

From the review of the current scientific literature, it was found that there are a few published researches that applied AI for diagnosis in oral and maxillofacial pathology (OMFP) with the vast majority using classical Machine Learning (ML) approaches with focus on histological diagnosis of oral squamous cell carcinoma (OSSC) [3,4], most common head and neck cancer.

Computer vision research on other tumors from OMFP complex is still uncommon. It is imperative to explore this field and increase the evidence on ML approaches, especially Deep Learning (DL) methods that have the potential to be used in the near future.

Odontogenic tumors (OT) are composed of heterogeneous lesions, which can be benign or malignant, with different behavior and histology. Within this classification, ameloblastoma and Ameloblastic carcinoma (AC) represents a diagnostic challenge in daily histopathological practice due to their similar characteristics and the limitations that incisional biopsies represent [13]. From these premises we wanted to test the usefulness of models based on AI in the field of OMFP for differential diagnosis, because despite advances in technology in terms of diagnostic aid (x-ray, tomography, magnetic resonance), the histopathological diagnosis made by a qualified professional continues to be the most reliable and accepted diagnostic method.

Ameloblastoma are benign but aggressive OT that form from odontogenic epithelium within a mature fibrous stroma with columnar and cuboidal cells with inverted polarization and islands of cystic degeneration containing loose central cells similar to stellate reticulum [14], while AC combine the histological features of Ameloblastoma with cytological atypia, abnormal mitotic activities, cellular and nuclear hyperchromatism, and focal necrosis and may show both keratinization and vascular and perineural invasion. Cytological atypia in AC favors the differential diagnosis of ameloblastoma, with some cases requiring to perform complementary studies such as immunohistochemistry with Ki67 index for better discrimination [8]. When the Ki67 staining index is high (above 10%), the diagnosis can be confirmed as AC.

The aim of this work is to develop an AI-based system to analyze and diagnose OT through a DL approach, to diagnose lesions with overlapping microscopic characteristics which represents a challenge for differential diagnosis in oral pathology, specifically focused on two specific diagnoses (AC and ameloblastoma) to provide a diagnostic aid in pathology laboratories.

MATERIALS AND METHODS

Dataset

Given the rarity of some diagnoses included in this study and the need for a multicenter sample to provide variability to the computational models, five Brazilian institutions were contacted to retrieve the whole-slide images (WSIs). This cross-sectional diagnostic study was developed using a cohort of thirty patients diagnosed in five Oral Pathology Services from different regions in Brazil, and enrolled ten patients with AC, ten patients with ameloblastoma, and ten patients with recurrent ameloblastoma, in which nineteen were retrieved from the Piracicaba Dental School, University of Campinas (FOP-UNICAMP) (Piracicaba, São Paulo),

five from the Department of Pathology and Legal Medicine, Federal University of Amazonas (UFAM) (Manaus, Amazonas), three from the Federal University of Pará (UFPA) (Belém, Pará), one from the Federal University of Rio Grande do Sul (UFRGS) (Porto Alegre, Rio Grande do Sul), and one from the State University of Feira de Santana (UEFS) (Feira de Santana, Bahia). Patients were selected according to well-established inclusion criteria (i.e., cases diagnosed by experienced pathologists with reports issued of ameloblastoma or AC, respectively). Exclusion criteria include cases in which the diagnosis is only descriptive because it shares characteristics with any other OT.

The sample consists of slides containing histological sections of 4μ m thickness, stained with hematoxylin and eosin (HE). The selection of slides was based on the clinical and histopathological diagnosis. Medical records and secondary data were not used. The slides were scanned using the Aperio Digital Pathology System (Leica Biosystems, Wetzlar, Germany) with a spatial sampling of 0.47μm per pixel, automated focus and at ×20 magnification.

There is no recommendation of a minimal nor ideal sample size for approaches using AI to process histopathological images, with some articles including only ten WSIs [19]. The most important in the WSI context is to have enough tissue in the slide for the diagnosis, and to provide enough variability of population (i. e., patients from different regions/countries), histopathological patterns (i.e. to include examples of follicular, plexiform, acanthomatous, granular, and basaloid ameloblastoma), and histotechnical variations (i.e., glass slides processed in different laboratories) [20]. Thus, we consider that despite the small size, the sample has a representative number for this type of study, as well as heterogeneity.

Histological Image Processing

The first phase of the study enrolled “clinical actions” conducted by experienced pathologists who reviewed the cases (D.G.R., A.L.D.A., P.A.V.). Once the glass slides are

digitized into a WSI, the first author (D.G.R.) made manual annotations of the regions of interest (ROI) using a Huion Inspiroy H1060P graphics drawing tablet, and the software ImageScope (Leica Biosystems, Wetzlar, Germany).

The second phase involves “computational actions”, conducted by professionals in biomedical engineering and image processing to evaluate various aspects of the training from specific methodological variations. The annotations guide the segmentation of histopathological images, in which the tumor parenchyma is separated from the stroma and the background. The segmented image is further fragmented into smaller patches of 220x220 pixels with 30% superposition. The patch size choice is guided by the minimum amount of information required for classification and the network’s kernels size. In addition, image fragmentation is required due to the excessive computational cost of feeding CNNs with the entire images. A total of 10.000 patches were non-randomly sampled into three subsets in which 80% (8.000) were used for training, 10% (1.000) for internal validation, and 10% (1.000) for testing. The non-random division seeks to avoid patches from a same WSI being “seen” in more than one step (data leaking), which could lead to overoptimistic results. [20]

DL models require a diverse range of class features during training and validation to effectively mitigate overfitting and achieve superior generalization capabilities. Consequently, data augmentation techniques were applied to the training and validation subsets, introducing complementary image variability through rotations (90°,180°, and270°), inversions (horizontal/vertical) **(Figure 1).** The utilization of 10,000 patches was both feasible and representative for this initial attempt, effectively balancing available resources and computational workload for the analysis. Future investigations will encompass a larger number of patches for more in-depth analysis.

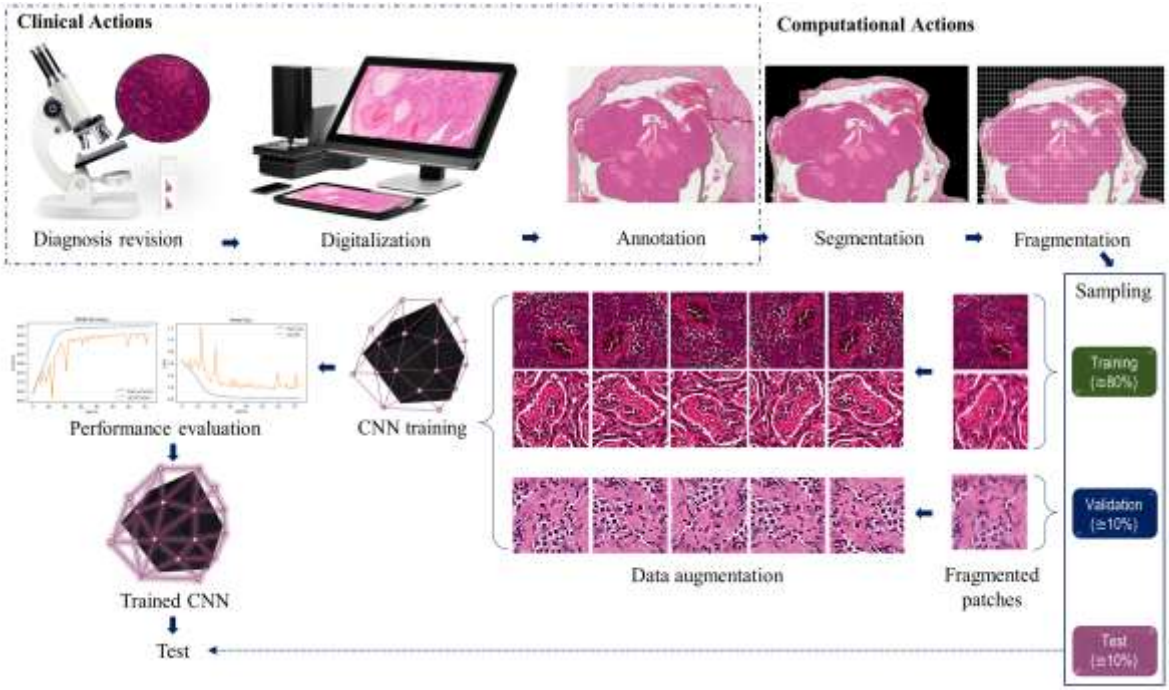

Figure 1: Methodological summary.

CNN training

In the DL methodology for image classification, the activation function approximates the inputs to the outputs (labels) to provide the probability of an image to be classified as class0 (i.e., ameloblastoma) or class1 (i.e., AC).

Three state-of-the art CNNs (Resnet50 [15], VGG16 [16], and DenseNet [17]) were implemented in an Intel CORE i7 3.50 GHz computer processor with 32GB RAM and 1TB, available at the Signal and Image Processing Laboratory at the Institute of Science and Technology, Federal University of São Paulo (ICT-Unifesp), using Python 3.6 and several open-source libraries specific to ML and image processing as TensorFlow, Keras, Scikit-Learn, and OpenCV.

CNN training was conducted for 20 epochs until accuracy stabilization using the Adam optimizer (ideal for binary classification), with an initial learning rate of 0.0001. Considering the hyperparameters of the above-mentioned models (i.e., number of neurons, number of

kernels, and the convolutional layer are the predefined structural elements), the necessary adjustments of parameters (i.e., weights, internal kernel function), were conducted during training execution. The final performance of these models in the test set was evaluated through classical metrics such as accuracy, precision, sensitivity, specificity, F1-score, loss, and confusion matrices. These metrics are regularly used in ranking problems and allow a thorough evaluation of the classifiers' performances on a given set of images. The variety of metrics should consider the influence of true positives and true negatives, as well as false positives and negatives, which brings results with specific particularity regarding the hits and misses and their interpretation within the medical context.

RESULTS

The accuracy and loss curves for training and validation are shown in **Figure 2**. It is possible to observe that the model learns correctly and fast, reaching a training accuracy of 98% during few training epochs, with a descending loss. On the other hand, the accuracy and validation loss curves present some peaks that demonstrate instability, which may indicate the available data are not fully representative for training and validation. The distance between the training and validation curves characterizes overfitting, meaning that the model can learn the training set, but the model's complexity and the dataset variety need adjustments to increase the ability to generically learn. In other words, the model learned the available and specific patterns from the training data, which, possibly, still not fully representative for the investigated models, considering the variation required in this application. We can identify the overfitting by looking at validation metrics such as loss or accuracy. As can be seen, the validation metric stops improving after a certain number of epochs and begins to decline afterward. On the contrary, the training metric continues to improve because the model seeks to find the best fit for the training data.

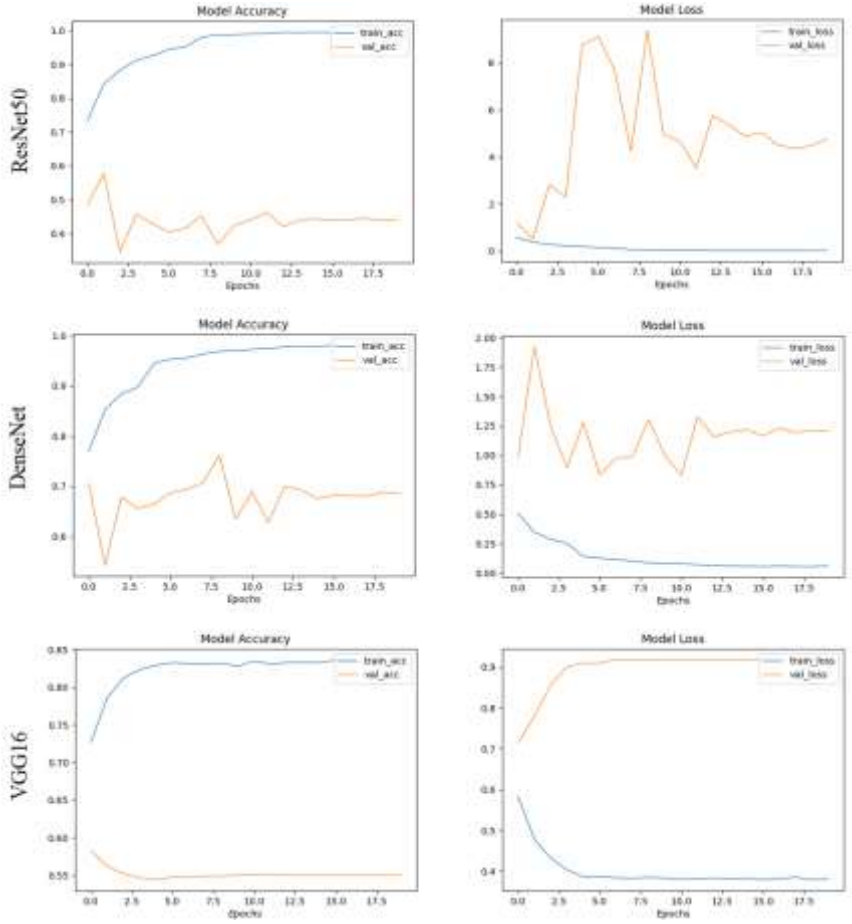

Figure 2: Training and validation accuracy and loss curves for ResNet50, DenseNet and VGG16.

The independent test metrics also reflect the overfitting (**Figure 3, Table 1**), demonstrating that the investigated trained models require adjustments to be more functional. Additionally, the test shows a good hit rate on the true negatives but requires an analysis for improvements on the true positives. In any case, for a first preliminary test, the metrics of precision and specificity indicate the potential application of this model.

Finally, the best results came from ResNet50 model, and they were 0.75, 0.71, 0.84, 0.65, and 0.77 for accuracy, precision, sensitivity, specificity, and F1-score, respectively. Although the individual performance of models is not perfect yet, they provided important level of efficacies, mainly related to True Positive of ResNet50 with 83.8%, and True Negative of

DenseNet with 78.4%. It means that, the models are individually more suitable for each one of the classes. Consequently, we have room to progress in new investigations, considering other models in literature; as well as, developing specialized models.

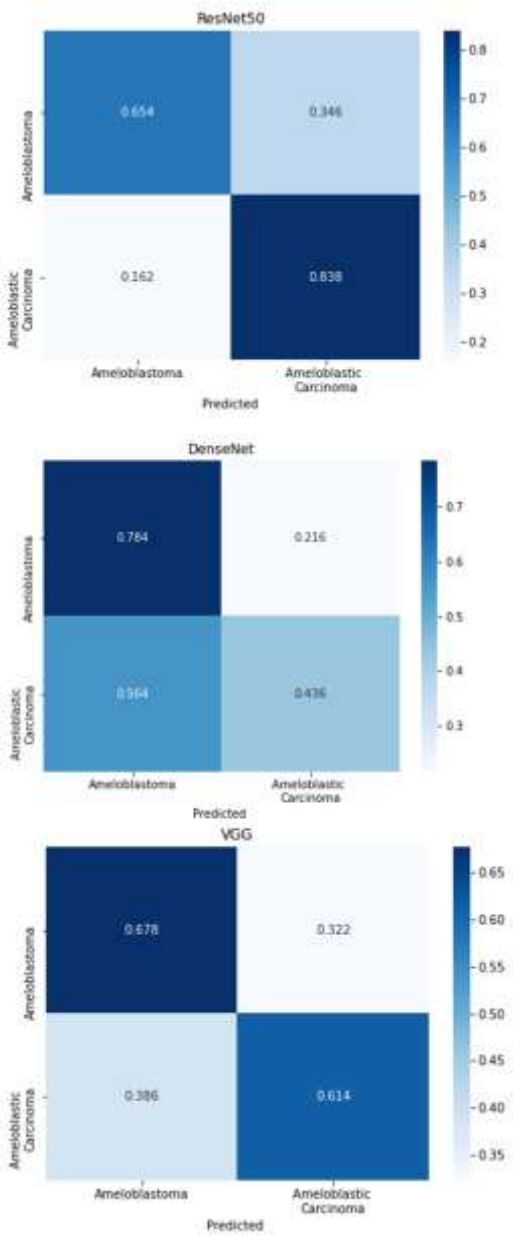

Figure 3: Confusion matrices of test sets of the ResNet50, DenseNet and VGG16.

Table 1: Evaluation metrics of the independent test set for ResNet 50, DenseNet, and VGG 16 networks.

Metrics	ResNet50	DenseNet	VGG16
Accuracy (%)	75%	61%	65%
TP-(AC) (%)	83,8%	43,6%	61,4%
FP (%)	34,6%	21,6%	32,2%
TN-(A) (%)	65,4%	78,4%	67,8%
FN (%)	16,2%	56,4%	38,6%
Precision	0,71	0,67	0,66
Sensitivity	0,84	0,44	0,61
Specificity	0,65	0,78	0,68
F1-Score	0,77	0,53	0,63

DISCUSSION

ML has played an important role over the years in almost every aspect of science and medicine [23]. ML is a branch of AI that employs a variety of statistics, probabilistic and optimization techniques that allow computers to "learn" from previous examples and detect hard-to-discern patterns from large data sets [24]. ML methods can enable automated and early identification of diseases, with performance comparable to that of human experts [3]. Professionals could use a developed algorithm with good diagnostic capacity as a valuable and cost-effective tool to assist in the diagnosis of challenging entities, allowing adequate and timely treatment. [25][26].

In the medical literature focusing on head and neck pathologies, there is some evidence of a great advance in the use of AI approaches for the diagnosis of OSCC [27–32]. Das et al. proposed a two-stage approach using CNN and a texture-based random forest classifier to detect

and segment keratin beads using texture-based characteristics, with accuracy of 96.88%.[4] Chan et al. proposed an innovative deep CNN combined with a texture map for oral cancer detection. The proposed model consists of two collaborative branches, one to perform oral cancer detection and a second to perform the marking of the region of interest (ROI) and semantic segmentation. Experimental detection results are up to 96.87% sensitivity and 71.29% specificity [7]. Fraz et al. proposed a network for simultaneous segmentation of oral cancer micro vessels and nerves. The proposed block-based pyramidal clustering deep CNN outperforms other deep CNNs in semantic segmentation [6]]. Additionally, only a few studies used radiomic data for intraosseous lesions detections, segmentation or diagnosis [33] but none investigated approaches using histopathological slides for OT diagnosis. These tumors comprise a heterogeneous group of lesions ranging from hamartomatous to benign and malignant neoplasms. [34] Given the rarity of these entities and the importance of their timely diagnosis, especially since their treatment can cause extensive mutilations in patients, in addition to recurrences and metastases, there is an immense need for personalized approaches to prevention, detection and treatment interventions.

Histologically, ameloblastomas shows anastomosed islands or cords of odontogenic epithelium delineated by peripheral cylindrical cells showing reverse polarization, and islands of cystic degeneration that contain cells like the central lax stellate reticulum. On the other hand, ACs are characterized by an ameloblastoma-like appearance with peripheral columnar cells, variable reverse polarity, cytological atypia with altered nuclear cytoplasm ratio, cell pleomorphism, atypical mitosis, neurovascular invasion, and necrosis. According to the WHO [13], the differential diagnosis is based on the histopathological morphology and, in some cases, ki67 index is required to a better characterization. However, similarities like areas of classic ameloblastomas in AC, especially in incisional biopsy, insert sampling bias that may difficult the diagnostic process even for experienced pathologists. Therefore, a computer-aided tool

would certainly incorporate this bias given the resemblance of ameloblastic and ameloblastoma-like appearance. Our results may reflect the influence of this similarity during training stage and the unfeasibility to exclude such confounding areas during the annotation process, as they are intrinsically intermingled with other important and diagnostic features. This may have provided an inconsistent ground truth diagnosis during training. Additionally, the limited number of samples may have contributed to the overfitting, which could be overcome by increasing the data set. However, it is difficult when working with extremely rare and complex tumors.

We conclude that the CNNs used in this experiment are very complex in their architecture which, in combination with limited sample variety, may have a great role in the final performance. Ideally, it would be interesting to develop and implement shallower architectures targeting one specific classification problem.

These results are consistent with several limiting factors. As mentioned above, these tumors are borderlines and difficult to diagnose, a situation that is aggravated when the biopsy is not representative. This means that there is not always a consensus among pathologists in the definition of the diagnosis, leading to the exclusion of borderline cases, which reduces the number of samples, favoring overfitting. It is also important to consider the quality of the patches, given their dimensions and the scanner used, and the correct sampling among the subsets for training, validation and testing, as well as the proportion of patches per case and the variability of patterns within the two diagnoses. Finally, it is interesting to consider whether the classes chosen in fact represent differential histopathological characteristics for classification, since there may be overlapping characteristics between the classes.

In addition, despite not having similar studies to compare our results and according to the international literature, it is not always clear if the results published to date include test metrics or only training/validation metrics. In this context, it is important to remind ourselves

that the evaluation on the learning capacity is based on several factors, and that the model seeks to find the best fit for the training data, which means it will eventually reach a good accuracy during training. Ideally, the training and validation data should be completely separated to avoid data leakage, which may be enough to some authors in terms of assessing the performance in unseen data. However, these metrics do not allow the evaluation of the generalization ability of the models and are frequently reported as an incomplete set of metrics. There is a chance that researchers are unaware of "bad results" by relying on and publishing only the "good" and overoptimistic training/validation results without performing an independent test to test the generalization of the model.

Our study and results set up a starting point and path for continuous progress of this important interdisciplinary investigation; hence, providing knowledge and motivating the continued research on different CNNs for the diagnosis of OTs. Future studies will focus on incorporating alternative models and expand dataset variation to escalate performance; in addition, we are planning to replicate this investigation on a variety of solid tumors.

CONCLUSION

The present research revealed that the models have great learning potential, but no generalization ability. Training and validation metrics show unstable convergence, characterizing a level of overfit. However, the test results showed that this research has potential to scale. Among CNN investigated, ResNet50 provided the best performance in the diagnosis of ameloblastic carcinomas, as well as DenseNet demonstrated good complementary performance for the diagnosis of ameloblastomas. Consequently, this is the first research work that integrates ML methodologies for the differential diagnosis of odontogenic tumors using histopathological laminas, future works will focus on the development of new and alternative ML models, as well as being associated with the increase in size and variation of the dataset.

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Competing Interest

The authors declare no conflict of interest.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. All authors agree to be accountable for any aspects of the work and we ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Statement

This study was performed in accordance with the Declaration of Helsinki and was approved by the Piracicaba Dental Ethical Committee, Registration number CAAE:

61732122.7.0000.5418, which also comprised Material Transfer Agreements between co-participant Institutions to share digital slides.

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3 CONCLUSÃO

- Os modelos têm potencial para aprendizagem, mas não capacidade de generalização.
- O uso de CNNs de última geração para o diagnóstico de tumores odontogênicos é promissor, especialmente para o diagnóstico histopatológico.
- As características histopatológicas dos OT sobrepõem-se frequentemente, o que pode ser um fator de confusão para a CNN.
- O diagnóstico histopatológico por patologistas especialistas continua sendo o padrão ouro em patologia oral. No entanto, novas soluções devem continuar a ser buscadas para reduzir custos e tempo de fluxo laboratorial, além de auxiliar no diagnóstico e prognóstico dos pacientes.
- Mais modelos precisam ser testados e desenvolvidos para o diagnóstico de TO para que, finalmente, estes possam ser levados para a prática clínica real.

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4 ANEXOS

Anexo 1 - Comitê de Ética em Pesquisa

UNICAMP - FACULDADE DE ODONTOLOGIA DE PIRACICABA DA UNIVERSIDADE DE CAMPINAS - FOP/UNICAMP

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: INTELIGÊNCIA ARTIFICIAL NO DIAGNÓSTICO DE TUMORES ODONTOGÊNICOS
Pesquisador: Daniela Giraldo Roldan
Área Temática:
Versão: 3
CAAE: 61732122.7.0000.5418
Instituição Proponente: Faculdade de Odontologia de Piracicaba - Unicamp
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.691.961

Apresentação do Projeto:
O parecer inicial é elaborado com base na transcrição editada do conteúdo do registro do protocolo na Plataforma Brasil e dos arquivos anexados à Plataforma Brasil. Os pareceres de retorno, emendas e notificações são elaborados a partir do último parecer e dos dados e arquivos da última versão apresentada. A EQUIPE DE PESQUISA citada na capa do projeto de pesquisa inclui DANIELA GIRALDO ROLDÁN (Cirurgiã Dentista, Mestranda no PPG em Estomatopatologia da FOP-UNICAMP, Pesquisadora responsável), PABLO AGUSTIN VARGAS (Cirurgião Dentista, Professor da Área de Patologia da FOP-UNICAMP), HELDER ANTONIO REBELO PONTES (Cirurgião Dentista, Professor associado da Universidade Federal do Pará), JECONIAS CÂMARA (Cirurgião Dentista, professor Adjunto IV do Departamento de Patologia e Medicina Legal da FM/UFAM), MANOELA DOMINGUES MARTINS (Cirurgiã Dentista, Professora e Membro do Serviço de Patologia Bucal da Faculdade de Odontologia da UFRGS), o que é confirmado na declaração dos pesquisadores e na PB.

DELINEAMENTO DA PESQUISA: Trata-se de estudo laboratorial, que envolverá 120 amostras de material biosiado e processado em 4 centros de patologia do Brasil. Este estudo tem como objetivo desenvolver um sistema baseado em Inteligência Artificial (IA) para analisar tumores odontogênicos de cabeça e pescoço por meio de uma abordagem de Deep Learning (DL), a fim de

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Telefone: (19)2106-5349 **Fax:** (19)2106-5349 **E-mail:** cep@fop.unicamp.br

Outros	carta_resposta_parecer2_DGR.pdf	13:59:51	Roldan	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO1SEP_DGR.pdf	02/10/2022 13:58:34	Daniela Giraldo Roldan	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Modelo_TCLE_CEP_FOP2.pdf	02/10/2022 13:58:14	Daniela Giraldo Roldan	Aceito
Folha de Rosto	FolhadeRosto_DanielaGiraldoRoldan.pdf	08/09/2022 18:08:05	Daniela Giraldo Roldan	Aceito
Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	BIORREPOSITORIO.pdf	05/09/2022 16:07:39	Daniela Giraldo Roldan	Aceito
Outros	Autorizacao_Uso_ArquivosUFAM.pdf	05/09/2022 15:55:58	Daniela Giraldo Roldan	Aceito
Declaração de Pesquisadores	declaracao_dos_pesquisadores_DGR.pdf	17/08/2022 13:47:03	Daniela Giraldo Roldan	Aceito
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Outros	DeclaracaoConcordanciaUFAM.pdf	15/08/2022 11:00:50	Daniela Giraldo Roldan	Aceito
Outros	AutorizacaoUsoArquivosUFRGS.pdf	15/08/2022 11:00:22	Daniela Giraldo Roldan	Aceito
Outros	AutorizacaoUsoArquivosHUJBB.pdf	15/08/2022 10:59:47	Daniela Giraldo Roldan	Aceito
Declaração de concordância	DeclaracaoConcordanciahujbb.pdf	15/08/2022 10:58:16	Daniela Giraldo Roldan	Aceito
Outros	Materialtransferagreement_UFRGS.pdf	04/08/2022 11:01:49	Daniela Giraldo Roldan	Aceito
Outros	Material_transfer_UFAM.pdf	04/08/2022 10:45:16	Daniela Giraldo Roldan	Aceito
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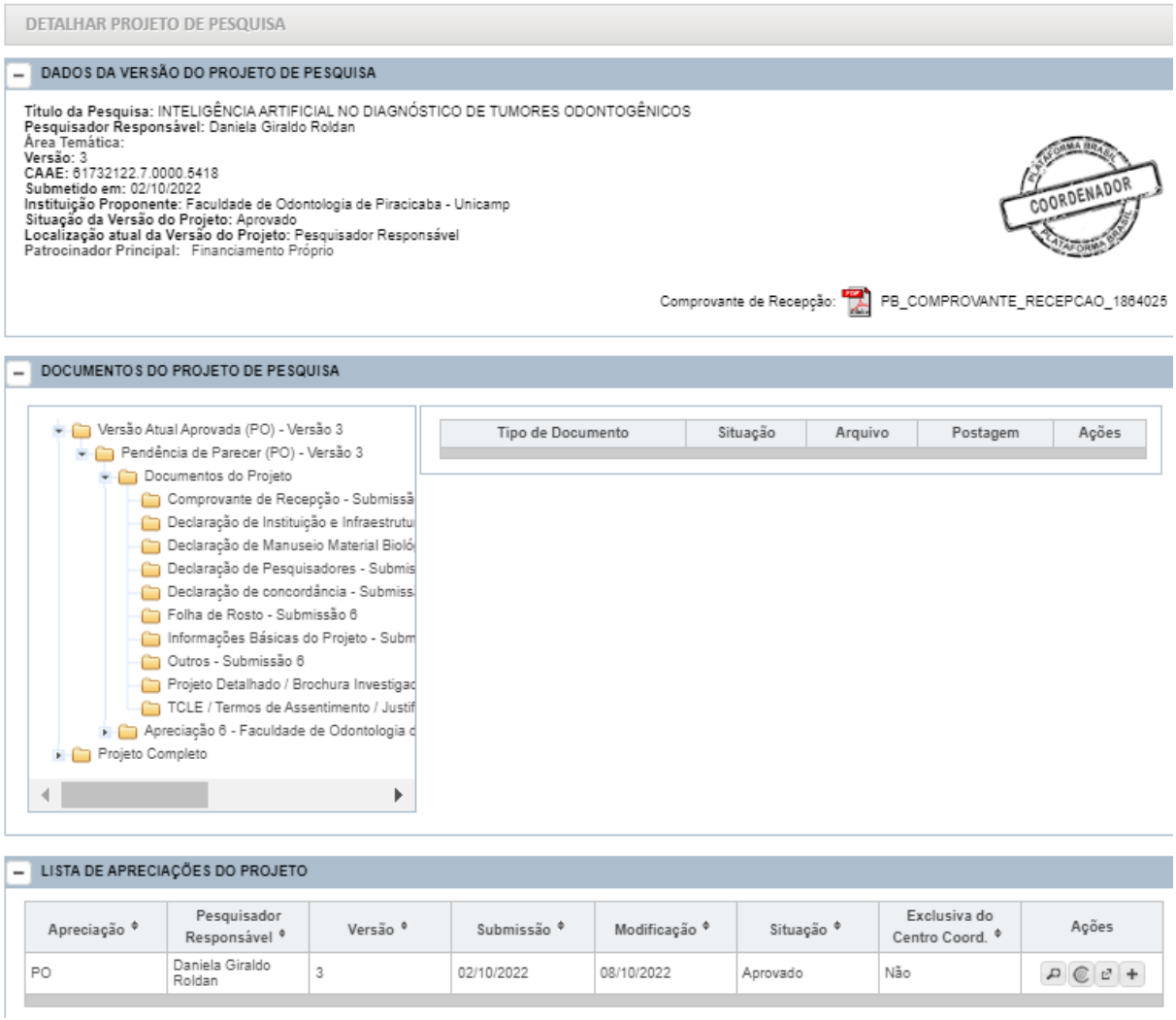
Declaração de Instituição e Infraestrutura	Declaracao_da_InstituicaoDanielaGiraldoRoldan.pdf	30/03/2022 15:05:10	Daniela Giraldo Roldan	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:

Anexo 2 - Situação do Projeto na Plataforma Brasil (print)



DETALHAR PROJETO DE PESQUISA

DADOS DA VERSÃO DO PROJETO DE PESQUISA

Título da Pesquisa: INTELIGÊNCIA ARTIFICIAL NO DIAGNÓSTICO DE TUMORES ODONTOGÊNICOS
Pesquisador Responsável: Daniela Giraldo Roldan
Área Temática:
Versão: 3
CAAE: 61732122.7.0000.5418
Submetido em: 02/10/2022
Instituição Proponente: Faculdade de Odontologia de Piracicaba - Unicamp
Situação da Versão do Projeto: Aprovado
Localização atual da Versão do Projeto: Pesquisador Responsável
Patrocinador Principal: Financiamento Próprio

PLATAFORMA BRASIL COORDENADOR PLATAFORMA BRASIL

Comprovante de Recepção: PB_COMPROVANTE_RECEPCAO_1864025

DOCUMENTOS DO PROJETO DE PESQUISA

- Versão Atual Aprovada (PO) - Versão 3
  - Pendência de Parecer (PO) - Versão 3
    - Documentos do Projeto
      - Comprovante de Recepção - Submissã
      - Declaração de Instituição e Infraestrutu
      - Declaração de Manuseio Material Bioló
      - Declaração de Pesquisadores - Submis
      - Declaração de concordância - Submiss
      - Folha de Rosto - Submissão 6
      - Informações Básicas do Projeto - Subm
      - Outros - Submissão 6
      - Projeto Detalhado / Brochura Investigac
      - TCLE / Termos de Assentimento / Justif
    - Apreciação 6 - Faculdade de Odontologia c
  - Projeto Completo

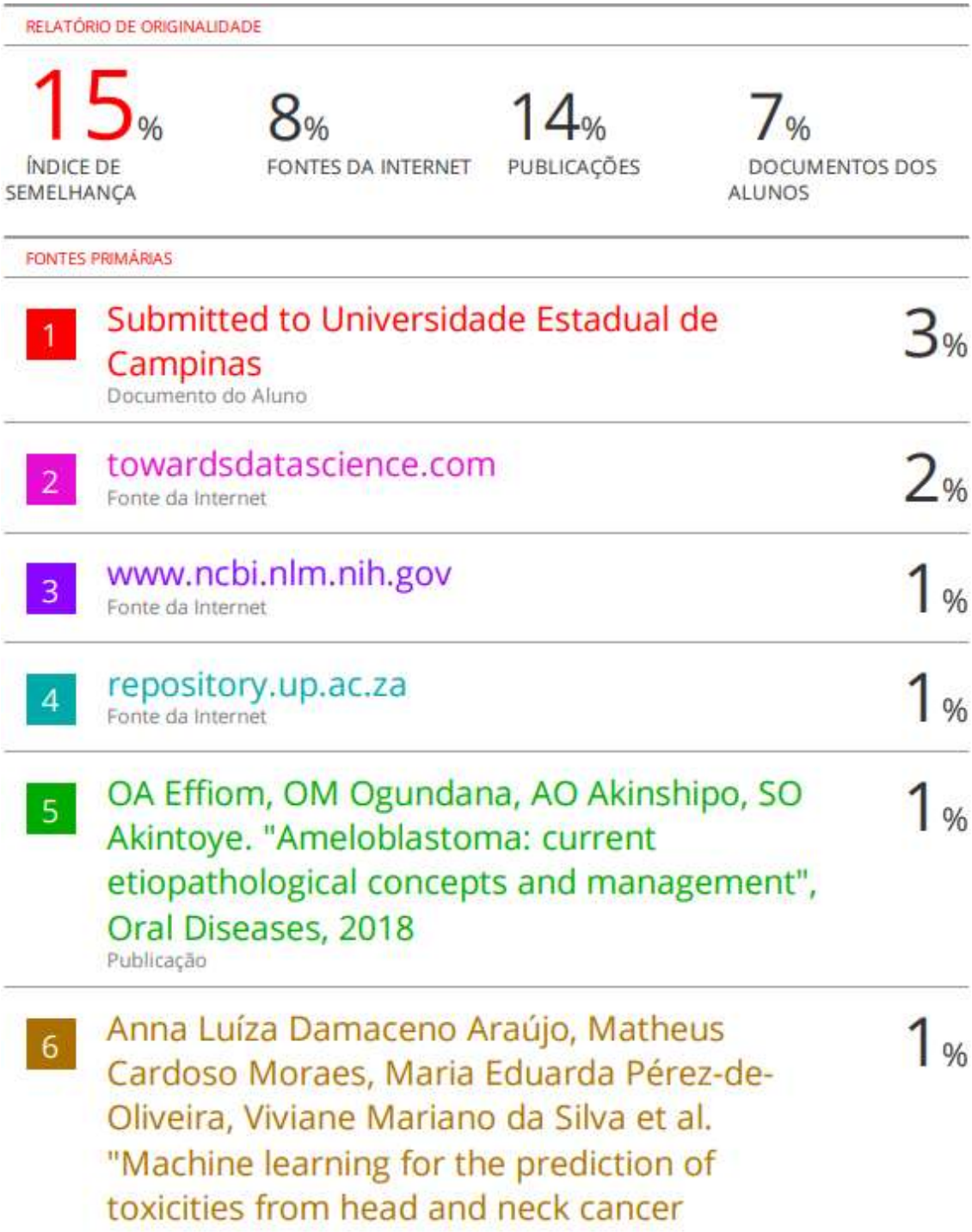
Tipo de Documento	Situação	Arquivo	Postagem	Ações

LISTA DE APRECIAÇÕES DO PROJETO

Apreciação	Pesquisador Responsável	Versão	Submissão	Modificação	Situação	Exclusiva do Centro Coord.	Ações
PO	Daniela Giraldo Roldan	3	02/10/2022	08/10/2022	Aprovado	Não	

Anexo 3 - Documento de aceite do artigo (print do sistema online de submissão)

Anexo 4 - Relatório de similaridade da Plataforma Turnitin



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