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REVIEW

Advancements in Image-Based Artificial Intelligence in the Diagnosis and Treatment of Head and Neck Squamous Cell Carcinoma: A Narrative Review

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Abstract: Head and neck squamous cell carcinoma (HNSCC) remains a significant global health challenge. Early detection, accurate diagnosis, and individualized treatment planning are essential for improving patient outcomes and enhancing quality of life. Artificial intelligence (AI), including radiomics and deep learning, has shown substantial potential in the early screening, accurate diagnosis, and treatment response prediction of HNSCC. In this review, we summarize the commonly used types of medical imaging and outline the basic workflows of radiomics and deep learning in medical image analysis. We then review the applications of AI in the clinical diagnosis and treatment of HNSCC across various aspects, including screening, diagnosis, staging and grading, pre-treatment evaluation, and prognostic prediction. We further discuss the convergence of AI with emerging imaging modalities, including hyperspectral imaging, optical coherence tomography, and Fourier transform infrared spectroscopy. Notably, most studies included in this review are retrospective and single-center in design, with limited external validation, underscoring the urgent need for prospective, multicenter research to facilitate clinical translation.

Keywords: head and neck squamous cell carcinoma, medical imaging, artificial intelligence, deep learning, machine learning

Introduction

Head and neck cancer (HNC) ranks as the seventh most prevalent malignancy globally, with over 900,000 new cases reported worldwide in 2020, according to GLOBOCAN.[1] Major risk factors contributing to HNC incidence include tobacco use, alcohol intake, and HPV infection.[2] Notably, squamous cell carcinoma (SCC) constitutes around 90% of all head and neck malignancies.[3] Due to its often-subtle onset, early clinical symptoms of head and neck squamous cell carcinoma (HNSCC) are frequently neglected, resulting in a considerable proportion of cases being identified at advanced stages (clinical stages III or IV).[4] Despite recent therapeutic advancements for HNSCC,[5] patients continue to experience a high local recurrence rate of 60% and a limited 5-year survival rate of approximately 40%.[6]

The diagnostic and treatment workflow for HNSCC typically initiates with a preliminary clinical assessment, incorporating medical history, physical examination, and laryngoscopy. For cases suspected of malignancy, imaging modalities—such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), or Positron Emission Tomography (PET)—are employed to determine the tumor's precise location, dimensions, and degree of infiltration. Biopsy is conducted in areas with a high suspicion of malignancy, serving as the definitive method for confirming HNSCC diagnosis. Following confirmation, treatment approaches differ by tumor site: surgical resection is the primary approach for most HNSCC cases. In early-stage HNSCC, surgery is typically followed by adjuvant radiotherapy or

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chemotherapy, contingent on intraoperative findings and lymph node pathology, to reduce local recurrence risk. For advanced-stage disease (stages III or IV), neoadjuvant chemotherapy or chemoradiotherapy may be administered to reduce tumor mass before surgical intervention. Recently, immunotherapy has gained prominence as a valuable treatment modality for advanced and recurrent HNSCC, particularly in patients showing limited response to conventional surgery and chemoradiotherapy. Immune checkpoint inhibitors, specifically PD-1 inhibitors, have demonstrated substantial clinical efficacy within this patient cohort.

Nonetheless, existing diagnostic and treatment methodologies face notable limitations. For example, the screening and assessment of malignant tumors heavily depend on clinicians' expertise, leading to potential diagnostic inaccuracies in early or asymptomatic head and neck squamous cell carcinoma (HNSCC) cases, especially among less experienced physicians. Furthermore, variability in image interpretation across different hospitals or clinicians introduces an additional layer of diagnostic and therapeutic uncertainty.[7] While biopsy remains the gold standard for HNSCC diagnosis, it is inherently invasive and involves a labor-intensive and time-consuming process—from tissue preparation to staining and microscopic examination. Due to intratumoral heterogeneity, a single biopsy may fail to capture the tumor's comprehensive biological characteristics. Additionally, current prognostic evaluations primarily rely on the TNM staging system, which assesses tumor size and extent of invasion but lacks the capacity to capture intratumoral heterogeneity. This may partly explain why patients with the same TNM stage often exhibit diverse clinical outcomes in real-world practice.[8] The current HNSCC diagnosis and treatment process, its limitations, and the assistance AI can provide are shown in Figure 1.

To address these limitations, artificial intelligence (AI) systems based on medical imaging have recently been developed and implemented to enhance disease screening, diagnostic accuracy, treatment planning, prognosis prediction, and post-treatment monitoring.[9–12] Several previous reviews have summarized the application of AI in HNSCC; however, most have focused on individual imaging modalities or specific clinical tasks. This review provides a narrative synthesis of the field, covering a broader range of imaging techniques—including radiological, pathological, and endoscopic imaging—as well as emerging technologies such as hyperspectral imaging and optical coherence tomography. We conducted a comprehensive but non-systematic literature search across PubMed and Web of Science up to October 2024, using keywords including "head and neck squamous cell carcinoma," "artificial intelligence," "machine learning," "deep learning," "radiomics," and "medical imaging." Given the heterogeneity of study designs and outcome measures, a narrative review approach was adopted to provide an integrated overview of current advancements, highlight key challenges, and identify future directions.

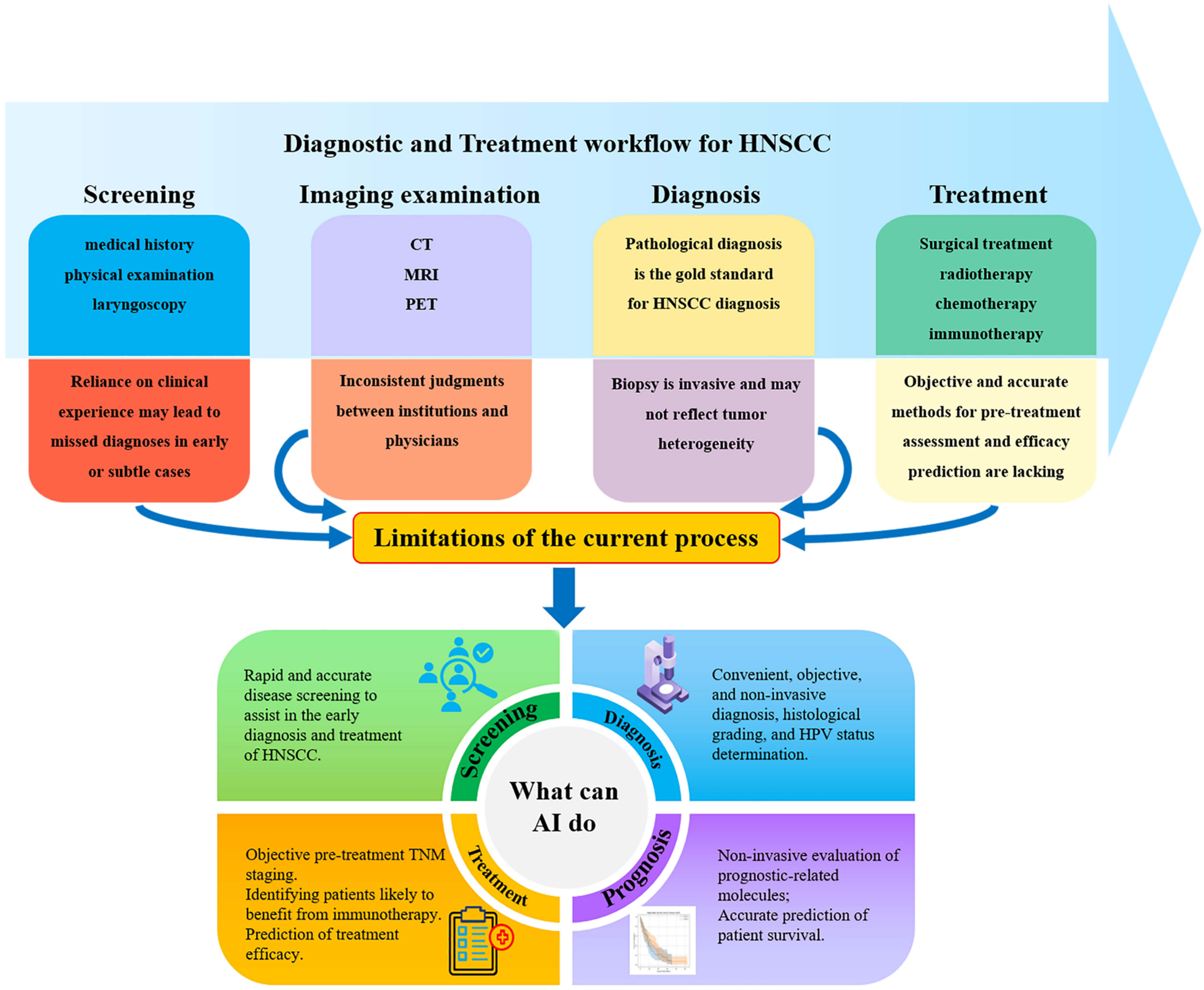
Definition of Artificial Intelligence

AI encompasses a wide range of computer science methodologies that utilize machine-based approaches to generate predictive insights.[13] Within AI, Machine Learning (ML) and Deep Learning (DL) are two key subsets.[14] ML involves algorithms that analyze input data to produce outcomes by learning from the patterns within.[15] In contrast, DL represents a more advanced iteration of ML, emerging from developments in artificial neural networks.[16] The primary distinction between ML and DL lies in data input requirements: while ML algorithms typically depend on well-labeled data for accurate predictions, DL networks employ multiple layers of artificial neurons, allowing them to autonomously identify patterns and form categories by detecting distinct features within large datasets.[14]

Widely Employed Imaging Modalities in the Diagnosis and Treatment of HNSCC

Radiological Images

The Most Common Imaging Techniques in the Diagnosis and Treatment of HNSCC. Radiomics (RDM) derives from the integration of "radiology" and "omics",[17] representing a field dedicated to extracting high-dimensional data from radiological images. Originally introduced by Lambin et al in 2012, radiomics enables the computational analysis of medical imaging to uncover intricate and clinically relevant tumor features beyond human visual perception. This non-invasive approach leverages various imaging modalities, including computed tomography (CT), magnetic resonance



Reliance on clinical experience may lead to missed diagnoses in early or subtle cases

Inconsistent judgments between institutions and physicians

Biopsy is invasive and may not reflect tumor heterogeneity

Objective and accurate methods for pre-treatment assessment and efficacy prediction are lacking

Rapid and accurate disease screening to assist in the early diagnosis and treatment of HNSCC.

Convenient, objective, and non-invasive diagnosis, histological grading, and HPV status determination.

Objective pre-treatment TNM staging.
Identifying patients likely to benefit from immunotherapy.
Prediction of treatment efficacy.

Non-invasive evaluation of prognostic-related molecules;
Accurate prediction of patient survival.

Figure 1 Diagnostic and Treatment workflow for HNSCC.

imaging (MRI), positron emission tomography (PET), and ultrasound (US),[18] to provide advanced insights into tumor phenotypes.

Pathological Images

Pathological examination is the gold standard for diagnosing HNSCC. The development of Whole Slide Imaging (WSI) has ushered pathology into the digital era, known as digital pathology.[19–21] WSI involves scanning, digitizing, and displaying entire tissue sections,[22] which pathologists can view digitally on monitors, offering enhanced storage, accessibility, and sharing advantages over traditional glass slides.[23–25] Comparative studies have validated WSI's diagnostic equivalence to conventional microscopy, supporting its use as a digital gold standard in pathology.[26–29]

Photographic Images

Photographic imaging primarily targets oral lesions, as the oral cavity is accessible and can be visually examined without specialized instrumentation.

Endoscopic Images

Endoscopy and laryngoscopy are integral for the visualization and evaluation of lesions within the larynx, oropharynx, nasopharynx, nasal cavity, and oral cavity.[30] Computer Vision (CV), an AI-based computational technology, empowers machines to analyze visual data, such as images and videos, extracting critical information for diagnostic purposes.[31] This has led to the rise of "videomics," a field that applies CV and AI to endoscopic video images, facilitating disease detection, classification, and segmentation by processing and modeling unstructured visual data.[32,33]

Application of Image-Based AI in the Diagnosis and Treatment of HNSCC

In the diagnosis and treatment of HNSCC, AI technologies are increasingly showcasing their significant potential and promising applications. Driven by the rapid expansion of medical imaging data and advancements in computational capabilities, AI has made notable strides across various clinical domains in HNSCC management. Specifically, AI has demonstrated considerable promise in early screening, pathological diagnosis, HPV infection status evaluation, pre-treatment assessment, and prognostic prediction. Its precision and efficiency provide invaluable support for clinical decision-making, offering new avenues for improving patient care and outcomes.

Early Screening

Public health screening and the early detection of precancerous lesions are foundational to primary and secondary cancer prevention efforts.[34] However, the insidious onset and non-specific diagnostic features of certain head and neck cancers (HNC) make early identification challenging.[35] Diagnostic delays elevate the likelihood of local or distant metastasis, markedly diminishing survival rates. Within anatomical regions like the larynx, oral cavity, oropharynx, hypopharynx, and nasopharynx, squamous cell carcinoma (SCC) predominantly impacts the oral cavity (44%) and larynx (31%).[36]

Emerging studies demonstrate that ML- and DL-based AI models have substantial potential for detecting oral lesions through photographic imaging.[37–42] Kouketsu et al[43] recently developed an AI model employing 1,043 lesion images from 424 patients with oral squamous cell carcinoma (OSCC), leukoplakia, and various oral mucosal disorders to accurately identify oral cancer and leukoplakia, achieving impressive sensitivity and specificity. Wuttisarnwattana et al[44] leveraged an AI model to examine 2,591 smartphone-captured images encompassing normal oral conditions, oral potentially malignant disorders (OPMDs), and OSCC, validating its effectiveness in lesion identification and segmentation. Fu et al[45] developed a cascaded convolutional neural network-based DL algorithm for detecting oropharyngeal squamous cell carcinoma (OPSCC) in photographic images, with validation across multiple centers. Their results confirmed that automated OPSCC detection through DL was comparable to expert evaluations, offering a rapid, non-invasive, cost-effective, and accessible method for early screening and detection. In another recent retrospective study, Azam et al[46] validated a DL model designed for real-time laryngeal squamous cell carcinoma (LSCC) detection under white light (WL) and narrow-band imaging (NBI) laryngoscopy. The same research team further developed a DL segmentation model utilizing video datasets of LSCC under WL and NBI to enable automatic segmentation of upper gastrointestinal malignancies in endoscopic images. The findings highlighted that automated tumor segmentation in complex and heterogeneous environments is achievable, underscoring the potential of DL models in early tumor detection and precision-guided biopsy.[47]

Pathological Diagnosis

Pathological diagnosis remains the cornerstone of qualitative assessment in head and neck tumors.[35] Accurate diagnosis and histological grading are pivotal in guiding therapeutic strategies for patients with HNSCC. Currently, these processes are predominantly based on biopsy-derived tumor samples, relying on pathologists' subjective interpretation and visual evaluation, which may introduce variability in tumor grading and prognosis.[48,49] This subjectivity underscores the demand for an objective, non-invasive method to enhance diagnostic precision and determine the histological differentiation in HNSCC.

Yang et al[50] developed a DL model to assist in the diagnosis of OSCC using 2,025 histopathological images, reporting high sensitivity (0.98), specificity (0.92), positive predictive value (0.924), and negative predictive value

(0.978). This model was further validated with a test subset, demonstrating its potential to improve diagnostic accuracy and efficiency for pathologists and clinicians. Sukegawa et al[51] demonstrated that supplementing pathologists' assessments with DL diagnostic outputs significantly enhanced diagnostic accuracy ($p = 0.031$). Similarly, Musulin et al[52] highlighted AI's potential in OSCC diagnosis. Rahman et al[53] introduced an ML approach integrating morphological and texture features to distinguish benign from malignant nuclei in OSCC biopsy images, achieving a remarkable accuracy of 99.78%. Zhang et al[54] employed a DL algorithm, introducing an innovative "onion peeling" technique to automatically count epithelial layers in digital slide images, facilitating differential diagnosis across oral disease spectra. Further advancements include Zheng et al[48] who constructed a predictive model using contrast-enhanced CT images from 204 patients with HNSCC. By combining radiomic and DL features, this model accurately predicted histological differentiation, achieving AUC values of 0.878 and 0.822 in training and testing sets, respectively. Additionally, ML techniques incorporating 18F-FDG PET, MRI, and CT radiomic features have demonstrated promising accuracy in predicting differentiation status in OSCC and locally advanced esophageal cancer.[55–57]

HPV Infection Status

Human papillomavirus (HPV) infection plays a significant role in the carcinogenic process in a subset of HNSCC cases, particularly in OPSCC.[58] Epidemiological, clinical, and prognostic differences between HPV-positive and HPV-negative HNSCC cases are notable, with distinct variations in disease progression and presentation.[59,60] Stratifying patients with HNSCC by HPV status may optimize treatment, maintaining high cure rates for HPV-positive cases while reducing the risk of overtreatment.[61,62] Currently, p16 immunohistochemistry (IHC) staining is the standard surrogate marker for assessing HPV status in patients with OPSCC. However, not all p16-positive cases indicate HPV infection; a more precise diagnosis often requires in situ hybridization (ISH) or Polymerase Chain Reaction (PCR),[63,64] both of which incur additional time and cost. This underscores the need to explore alternative objective methods for determining HPV status in patients with HNSCC.

Wang et al[58] developed a DL model based on Hematoxylin and Eosin (H&E)-stained WSI to detect HPV infection, demonstrating that digital HPV scores from H&E-stained slides significantly stratified patients by overall and disease-specific survival. In a multicenter study, Klein et al[65] constructed an HPV prediction score using DL on H&E-stained slides, achieving strong predictive performance (AUC = 0.8) for identifying HPV-positive OPSCC cases.

Sohn et al[66] developed an ML model leveraging MRI radiomic features to differentiate HPV infection status in OSCC, with findings suggesting that MRI-based radiomics could serve as potential biomarkers for HPV status identification in OSCC. Two additional studies reported similar efficacy of MRI radiomics for HPV stratification.[67,68]

Saikia et al[69] introduced DL models using CT and PET images, alongside a multimodal fusion model that integrated key features from both imaging modalities to identify HPV status in OPSCC. Results indicated that imaging-based DL models effectively distinguished HPV infection status, with multimodal models achieving superior AUC values compared to unimodal approaches. Research led by Fujima[70] and Woo[71] further indicated that AI-based analysis of FDG-PET and 18F-FDG PET/CT imaging data could serve as valuable tools for HPV status assessment in patients with OPSCC.

Pre-Treatment Assessment

TNM Staging

In the pre-treatment evaluation of HNSCC, TNM staging remains fundamental in guiding the treatment approach.[72] For instance, in laryngeal and hypopharyngeal cancers, the T classification directly influences the surgical resection extent. Early-stage (T1, T2) LSCC cases are often managed with laser resection, partial laryngectomy, or radiation therapy, whereas advanced-stage (T3, T4) cases frequently necessitate total laryngectomy, combined with adjunct therapies, resulting in substantial differences in organ function preservation and quality of life.[73–76] Over-assessment can lead to unnecessary loss of speech and swallowing functions, adversely impacting quality of life, while under-assessment may elevate the risk of tumor persistence or recurrence.[77] The N classification is critical in deciding whether to perform concurrent neck lymphadenectomy. Preoperative imaging assessments, combined with evaluations based on tumor location and biological characteristics, are used to inform decisions on lymphadenectomy. In clinical N0 HNSCC individuals with tumors in high-risk locations, neck lymphadenectomy is commonly recommended, leading to over-treatment in 60–70% of cases and subsequent functional impairments.[78–80] Thus, precise TNM staging before treatment initiation is essential.

In a recent retrospective study, Liu et al[77] developed an ML model leveraging contrast-enhanced computed tomography (CECT) to distinguish between T2 and T3 laryngeal and hypopharyngeal cancers, achieving AUC values of 0.901, 0.857, and 0.817 in training, validation, and test sets, respectively. Choi et al[81] demonstrated that DL-based AI models could reliably segment regions of oral squamous cell carcinoma in CT and MRI images, corroborated by similar findings from Outeiral et al[82] Öztürk et al[83] and Fukushima et al[84] constructed ML models using support vector machines (SVM) and XGBoost, respectively, to assess bone marrow invasion in lower gingival squamous cell carcinoma (LGSCC), achieving AUC values of 0.999 and 0.83. The eighth edition of the American Joint Committee on Cancer staging guidelines incorporated depth of invasion (DOI) into the T staging criteria for oral cancers,[72] recognizing its significance. Research by Yoshizawa et al[85] revealed a strong correlation between the invasion pattern of OSCC and DOI, with ML methods accurately identifying OSCC invasion patterns.

Several studies have highlighted the effectiveness of AI-based radiomic models in accurately classifying cervical lymph nodes in patients with HNSCC using CT, CECT, and MRI.[86–91] Chen et al[92] utilized preoperative CECT images from 100 patients with OSCC, encompassing 217 metastatic and 1,973 non-metastatic cervical lymph nodes. They developed models combining DL and ML to predict lymph node metastasis (LNM) preoperatively. The fusion model integrating DL with radiomics showed superior predictive performance in the test set, achieving 89.2% accuracy, 92.0% sensitivity, 88.9% specificity, and an AUC of 0.95, outperforming clinician assessments in sensitivity and accuracy. Yuan et al[93] demonstrated that MRI texture analysis using ML effectively predicts occult cervical lymph node metastasis in early oral tongue squamous cell carcinoma (OTSCC). In another study, Lan et al[94] extracted radiomic features and DL features (DLFs) from MRI images of 319 patients, constructing a model to predict occult cervical lymph node metastasis (OCLNM) in early oral and oropharyngeal cancers. The combined DL model incorporating radiomic and DL features performed optimally. Tang et al[95] developed an automated DL-based pathological diagnosis model for lymph node metastasis in HNSCC, achieving test set accuracy, sensitivity, and specificity of 86%, 100%, and 75.9%, respectively.

Kann et al[96] introduced a DL algorithm for identifying extranodal extension (ENE) in pre-treatment CT images of patients with HNSCC, with successful multicenter validation. This DL model outperformed head and neck radiologists in detecting ENE on pre-treatment images. Onoue et al[97] demonstrated the applicability of DL models in distinguishing pathological lymph nodes associated with thyroid papillary carcinoma (PTC), tuberculosis (TB), and HPV-positive OPSCC. Additionally, Adachi et al[98] combined AI-based histopathology analysis with clinical pathological data to create a fusion model for diagnosing lymph node recurrence in cT1-2N0 tongue squamous cell carcinoma, which achieved a remarkable AUC of 0.991, surpassing both purely clinical pathological and standalone ML models.

Screening of Patients Likely to Benefit from Immunotherapy

Immunotherapy targeting the PD-1/PD-L1 checkpoint pathway has emerged as a promising treatment option for patients with recurrent or unresectable advanced HNSCC.[99] However, this therapeutic approach appears to be most effective in a subpopulation of patients, largely influenced by PD-L1 expression levels in tumor and tumor-infiltrating immune cells.[100,101] PD-L1 expression serves as a critical biomarker for predicting response to anti-PD-1/PD-L1 inhibitors.[102,103] To quantify PD-L1 expression, three scoring systems have been developed: combined positive score (CPS), tumor proportion score (TPS), and immune cell score (ICS).[104] These scores require manual assessment by pathologists from tissue sections—a process that is both subjective and labor-intensive. AI-driven quantitative analysis of PD-L1 could offer a more convenient and objective approach, potentially enabling clinicians to better identify patients most likely to benefit from immunotherapy.

Vahadane et al[105] applied AI to calculate CPS scores for patients with HNSCC using multiplex immunofluorescence (mIF) images, demonstrating a strong correlation between AI-based CPS scores and pathologist evaluations. Puladi et al[104] developed DL algorithms to automate PD-L1 scoring on WSI from patients with HNSCC, comparing AI-generated scores with those from human evaluators. The results showed that the intra-class correlation coefficient (ICC) between AI and human CPS scores closely resembled inter-observer reliability. In a large retrospective study,[106] researchers used AI-based methods to quantify PD-L1 expression across WSIs of multiple tumor types, including HNSCC. Findings indicated that AI-based quantitative PD-L1 assessment could expand the identification of patients eligible for immunotherapy, enhancing patient selection for these targeted treatments.

Prognostic Prediction

Survival Prediction

Current prognostic methods relying on clinical pathological factors, such as demographic data and TNM staging, fail to account for the biological complexity and heterogeneity within tumors,[107] resulting in inadequate treatment stratification and less accurate prognostic predictions. This shortcoming highlights the need for more precise prognostic models to guide clinical decision-making. AI-based imaging feature analysis offers promising potential in addressing these gaps in prognostic prediction.

Naser et al[108] analyzed a large HNSCC dataset using PET/CT images to predict progression-free survival (PFS), illustrating that DL can effectively integrate imaging and clinical data to forecast outcomes in HNSCC. Similarly, Fujima et al[109] showed that DL methods offer clearer distinctions in disease-free survival (DFS) among patients with OSCC compared to traditional T and clinical staging. Tang et al[110] emphasized the predictive power of radiomic features combined with AI in forecasting 5-year survival rates for patients with HNSCC. Cheng et al[111] developed a fully automated model for predicting overall survival (OS) in OPSCC, demonstrating that these predictions could serve as an independent prognostic factor for OS, offering clinicians an objective and rapid prognosis assessment. Vollmer et al[112] collected extensive clinical, genomic, and pathological data from an OSCC cohort in the TCGA dataset, applying five ML and DL algorithms to identify key features for survival prediction. Their findings underscored that a multimodal AI model incorporating pathological features enables more accurate long-term survival predictions in patients with OSCC.

Prediction of Treatment Response and Treatment-Related Complications

In treating locally advanced HNSCC, neoadjuvant therapy and concurrent chemoradiotherapy are extensively used.[113] Although effective in clinical practice, these therapies present notable challenges. Neoadjuvant chemotherapy outcomes vary significantly among patients; predicting poor responders early could facilitate timely shifts to alternative treatments,[114] thereby improving patient outcomes. Concurrent chemoradiotherapy often involves substantial treatment-related toxicities that compromise patients' quality of life,[115] making accurate prediction of these adverse effects essential for personalized treatment planning. In this setting, AI-based imaging technologies hold considerable promise.

Research by Haider et al[116] and Fujima et al[117] has shown that ML-derived radiomic biomarkers can predict local progression in patients with OPSCC undergoing non-surgical treatments. Bos et al[118] demonstrated that an ML model integrating clinical data and MRI radiomic features effectively predicts locoregional control (LRC) and OS in patients with OSCC receiving chemoradiotherapy (CRT). Li et al[114] combined radiomic features with gene expression profiles to develop an ML model that accurately predicts the responses of patients with HNSCC to induction chemotherapy (IC).

Radiation-induced xerostomia, a frequent complication of radiotherapy, affects taste, speech, chewing, and swallowing, significantly impacting patients' quality of life.[119,120] Men et al[121] employed DL to extract spatial features from CT images, radiotherapy dose distributions, and contour images, constructing a predictive model for xerostomia with strong performance. Additionally, sarcopenia, exacerbated by treatment-related malnutrition and swallowing difficulties,[122] commonly affects patients with HNSCC and is a key component of cancer cachexia.[123] A meta-analysis indicated that sarcopenia correlates with reduced OS and DFS.[124] Naser et al[125] developed a multi-stage DL method using enhanced CT to segment the C3 vertebral region, predicting the likelihood of muscle wasting. Ye et al[126] created a model combining a 2D DenseNet regression model with a 2D U-Net to automatically segment skeletal muscle at the C3 level, calculating the skeletal muscle index (SMI) from CT images. This model, validated in a large cohort, demonstrated the capability for rapid and precise sarcopenia assessment.

Assessment of Prognostic Biomarkers

Due to the frequently overlooked early symptoms of HNSCC, a significant number of cases are diagnosed at advanced stages (III or IV). Despite considerable advancements in treatment over the past two to three decades, the prognosis for patients with HNSCC remains suboptimal.[5] In the era of precision medicine, traditional indicators such as clinical pathological features and HPV status are insufficient to fulfill the requirements for effective treatment stratification and accurate prognostic prediction in HNSCC.[127] Consequently, the identification of additional prognostic markers is essential.

In a study by Hang et al,[4] researchers validated the association between granzyme A (GZMA) expression and HNSCC prognosis, developing a radiomic ML model based on CT imaging to predict GZMA mRNA expression with notable accuracy. Prior studies have shown that mesenchymal-epithelial transition factor (MET) is highly and specifically expressed in OTSCC,[128] positioning MET as a precise diagnostic biomarker for OTSCC. Yang et al[129] demonstrated that ML could non-invasively predict MET expression levels in patients with OTSCC. The mutation status of the epidermal growth factor receptor (EGFR) has emerged as a critical prognostic factor for survival and response to chemoradiotherapy in patients with HNSCC.[130] Zheng et al[131] developed a DL radiomic nomogram (DLRN) using CECT to predict EGFR mutations, with strong predictive accuracy. Chromosomal 9p loss is recognized as a pivotal biomarker for the malignant transformation of oral leukoplakia (OLK) into HNSCC and is closely linked with HNSCC prognosis.[132,133] Cai et al[134] introduced a pathological AI model capable of rapidly predicting chromosomal 9p loss in OLK and HNSCC. The model further demonstrated robust prognostic accuracy for HNSCC survival, with AUCs of 0.739, 0.705, and 0.691 for 1-year, 3-year, and 5-year survival, respectively. In a recent multicenter retrospective study, Chen et al[7] constructed a multiparametric MRI fusion model integrating SVM-derived radiomic features with clinical data to predict Ki-67 expression in patients with HNSCC. The fusion model achieved AUC values of 0.916, 0.903, and 0.885 across the training, internal validation, and external validation sets, underscoring its efficacy in prognostic assessment.

The above studies cover diverse applications, imaging modalities, and study designs. Key characteristics of representative studies are summarized in Table 1.

Overall, while these studies demonstrate the broad potential of AI across various clinical tasks in HNSCC, most remain in early stages of validation, characterized by retrospective designs, single-center data, limited sample sizes, and a lack of external testing. These observations underscore the need for prospective, multicenter studies with standardized protocols and transparent reporting to advance clinical translation.

Application of AI in Emerging Imaging Techniques

In recent years, the integration of AI with advanced imaging technologies has gained significant attention, revealing new diagnostic and monitoring capabilities for HNSCC.

Hyperspectral imaging (HSI), an optical technique capturing wavelengths beyond the visible spectrum, has shown promise due to its ability to exploit variations in light interaction with biological tissues. Tumor cells, with molecular compositions distinct from non-tumor cells, exhibit unique absorption peaks, acting as spectral fingerprints. Research by Pertzborn et al[135] demonstrated that combining microscopic HSI of fresh, unstained frozen tumor samples with DL-based tumor classification models could potentially enhance intraoperative tumor margin assessment in OSCC surgeries. Li et al[136] found that DL-driven hyperspectral methods effectively identified tumor tissues in metastatic lymph nodes in OSCC. Zhou et al[137] further combined DL with polarized HSI, developed by their team, to automatically detect HNSCC on H&E-stained tissue slides, achieving high accuracy with an average precision of 84.2%.

Optical coherence tomography (OCT) is another non-invasive imaging technology using low-coherence near-infrared light, penetrating tissue depths of several hundred micrometers to reveal microstructural changes. James et al[138] evaluated OCT devices combined with AI algorithms for automated diagnosis in community and tertiary healthcare settings, showing that OCT images analyzed by automatic processing algorithms could reliably distinguish between benign lesions, oral potentially malignant lesions (OPML), and malignant lesions, with sensitivities of 95% and 93%. Yang et al[139] developed a DL model based on OCT and compared it with traditional ML models, demonstrating that DL algorithms for automated OCT image recognition can provide valuable decision support for effective screening and diagnosis of oral cancer.

Fourier transform infrared (FTIR) spectroscopy operates by measuring the absorption of infrared radiation at specific frequencies, resulting in unique bands in the FTIR spectrum that correspond to the vibrational energy states of a sample.[140] Prior studies have indicated that FTIR spectroscopy can detect molecular changes linked to carcinogenesis

Table 1 Key Characteristics of Representative Studies

Author, Year, Country	Sample Number	Sample Type	Learn Machine/Training Cycle and Sets	Statistical Findings (AUC, Sensitivity, Specificity, etc)	Application Area and Main Outcome
Kouketsu A et al[43] 2024, Japan	Patients: 424 Images: 1043	Photographic Images	Single Shot Multibox Detector: Pre-trained on PASCAL-VOC 2012, then retrained with 523 oral cancer images	Detection of only OSCC: Sensitivity: 93.9%, Specificity: 81.2% Detection of OSCC and leukoplakia: Sensitivity: 83.7%,Specificity: 81.2%	Early screening: The model achieves high sensitivity for detecting oral lesions requiring specialist consultation, offering a non-invasive, low-cost screening tool.
Fu Q et al[45] 2020, China	Images: 44,409	Photographic Images	Cascaded CNN: SSD for lesion localization + DenseNet121 for classification	Internal validation dataset: AUC 0.983, sensitivity 94.9%, specificity 88.7% External validation dataset: AUC 0.935, sensitivity 89.6%, specificity 80.6% Clinical validation dataset: AUC 0.970, sensitivity 91.0%, specificity 93.5%	Early screening: Automated OSCC detection from ordinary oral photos, performance comparable to oral cancer specialists.
Azam MA et al[46] 2022, Italy	Patients: 219 Images: 657	WL and NBI videolaryngoscopy frames	YOLOv5 (You Only Look Once DL detection model, an open-source software based on CNNs)	Precision 0.664, Recall 0.621	Early screening: Ensemble model demonstrated promising detection performance with low computational time, suitable for real-time clinical application.
Yang SY et al[50] 2022, China	Images: 2,025	Histopathology images	Custom 7-layer CNN (feed-forward with convolutional layers, ReLU, max pooling)	Sensitivity: 0.98, Specificity: 0.92, F1: 0.951, AUC: 0.985	Pathological diagnosis: Junior pathologists assisted by model were 6.26 min faster with improved F1 score.
Sukegawa S et al[51] 2023, Japan	Patients: 5 Images: 7918	Histopathology images	VGG16 + SAM/VGG16 + SGDM/ResNet50 + SAM	All 6 pathologists improved with AI assistance (p=0.031)	Pathological diagnosis: DL-assisted diagnosis significantly improves pathologists' diagnostic accuracy for OSCC.
Rahman TY et al[53] 2020, India	Patients: 40 Images: 40 Hand-cropped nuclei: 452	Histopathology images	Traditional machine learning; 963 features extracted (522 morphological + 441 textural); Classifiers: DT, SVM, KNN, LDA, Logistic Regression; 5-fold cross-validation	Accuracy: 99.78%, Sensitivity: 100%, Specificity:100%, AUC: 0.99	Pathological diagnosis: Traditional ML using morphological and textural features of cell nuclei achieved high accuracy for OSCC classification.
Zheng YM et al[48] 2023, China	Patients: 204 Images: 204 CECT image sets	CECT images	GoogLeNet pre-trained on ImageNet	AUC: 0.822, Sensitivity: 77.4%, Specificity: 81.6%, Accuracy: 80.0%	Pre-treatment assessment: CECT-based DLRN predicts histological differentiation grade in HNSCC.
Wang R et al[58] 2023, UK	Patients: 412 Images: 431	H&E-stained WSIs	Two-stage: (1) Weakly supervised ResNet-18 (ImageNet pretrained) + cross-entropy; (2) MIL with triplet ranking loss, Top-10% aggregation, MLP classifier; Stain augmentation + Macenko normalization	AUROC: 0.9223	HPV status prediction: DL from routine H&E WSIs predicts HPV infection without IHC/ISH/PCR
Sohn B et al[66] 2021, South Korea	Patients: 62 Images: 62 MRI image sets	MRI images: postcontrast 3D T1WI + T2WI	Traditional machine learning	Training AUC: 0.982 (95% CI 0.942–1.000); Test AUC: 0.744 (95% CI 0.496–0.991); Sensitivity: 69.2%, Specificity: 83.3%, Accuracy: 73.7%	HPV status prediction: Findings suggesting that MRI-based radiomics could serve as potential biomarkers for HPV status identification in OSCC.
Liu Q et al[77] 2024, China	Patients: 118 Images: 118 CECT image sets	CECT images	Traditional machine learning	Training AUC 0.919, Validation AUC 0.857, Test AUC 0.817; Sensitivity 65.0–97.9%, Specificity 57.1–80.0%	Pre-treatment T staging: CT radiomics model distinguishes T2 vs T3 laryngeal/hypopharyngeal SCC; helps surgical decision-making (partial vs total laryngectomy)
Yoshizawa K et al[85] 2022, Japan	Images: 101	IHC-stained digital microscopy images	Two-stage: (1) Binarization: LBP + RGB features + Random Forest to separate tumor epithelium vs stroma; (2) YK classification: 8 shape features + Random Forest	F-measure: 0.87 (Sensitivity: 87.1%, Specificity: 96.8%)	Pathological diagnosis: Machine learning-based automatic discrimination of Yamamoto-Kohama invasion classification for OSCC; provides objective, reproducible assessment of tumor invasive pattern.

(*Continued*)

Table 1 (Continued).

Author, Year, Country	Sample Number	Sample Type	Learn Machine/Training Cycle and Sets	Statistical Findings (AUC, Sensitivity, Specificity, etc)	Application Area and Main Outcome
Chen Z et al[92] 2023, China	Patients: 100 Images: 100 CECT image sets Lymph nodes: 2,190	CECT images	A multi-layer neural network model was constructed by fusing 1,454 radiomics features and 1,024 deep learning features	Test set: AUC: 0.950 (0.908–0.993), Accuracy: 89.2%, Sensitivity: 92.1%, Specificity: 88.9%	Pre-treatment assessment: The radiomics-deep learning fusion model based on imaging features enables efficient and accurate prediction of cervical lymph node metastasis in OSCC patients.
Kann BH et al[96] 2020, USA	Patients: 270 Images: 270 CECT image sets Lymph nodes: 653	CECT images	DualNet (3D CNN)	External validation: AUC: 0.84–0.90, Accuracy 83.1%-88.6%, Sensitivity 0.71–0.82, Specificity 0.85–0.91	Pre-treatment assessment: First externally validated deep learning algorithm for ENE detection on CT in HNSCC.
Vahadane A et al[105] 2023, India/ USA	Patients: 19	mIF images	QC module removes artifacts; Attention U-Net segments touching nuclei from DAPI; U-Net identifies PD-L1+ and tumor cells to calculate CPS	Cell phenotyping: PD-L1 F1=60%, PanCK F1=83%; CPS≥1 accuracy: 83.3% (10/12); Spearman correlation 78% (p=0.003)	First automated AI-based CPS scoring pipeline using mIF images; potential to reduce pathologist workload and enable scalable PD-L1 scoring.
Baxi V et al[106] 2022, USA	Training: 1,510 samples Test: 1,746 slides	PD-L1 IHC-stained WSIs	Deep learning model trained on pathologist annotations; Excludes background staining, necrosis, artifacts; Outputs AI-powered PD-L1 score; Frame-based validation	AI vs manual: higher prevalence with AI (NSCLC 90.2% vs 51.0%, UC 68.9% vs 46.8%, MEL 81.4% vs 68.7%); lower in SCCHN (42.5% vs 54.9%); ORR prediction AUC: AI 0.602 vs manual 0.596	Immunotherapy patient selection:AI-powered PD-L1 scoring identifies more PD-L1-positive patients than manual scoring across multiple tumor types; demonstrates consistent association with response and survival; high reproducibility across scanners; potential to identify low-level PD-L1 expressers missed by manual scoring.
Fujima N et al[109] 2020, Japan/USA	Patients: 113	FDG-PET/CT	ResNet-101 (transfer learning) on three slice planes	Test set: Accuracy 0.80, Sensitivity 0.80, Specificity 0.80, PPV 0.89, NPV 0.67; Training Accuracy: axial 90%, coronal 87%, sagittal 84%	Prognostic prediction: DL on FDG-PET predicts treatment outcome and DFS in OCSCC; outperforms conventional PET parameters and TNM staging.
Haider SP et al[116] 2021, USA/ Germany/Canada	Patients: 190(266 metastatic lymph nodes)	Baseline PET/CT (PET + non-contrast CT); Manual PET-guided segmentation (3D-Slicer)	Traditional machine learning: Random Survival Forest (RSF) for C-index prediction; Random Classification Forest (RCF) for risk stratification	Median C-index 0.76 (0.66–0.81, p=0.01)	Prognostic prediction: PET/CT radiomics predicts post-radiotherapy locoregional progression in HPV-associated OPSCC; outperforms clinical variables.
Men K et al[121] 2019, China/USA	Patients: 784	CT planning images	3D residual CNN	Accuracy: 0.76, Sensitivity: 0.76, Specificity: 0.76, F1: 0.70, AUC: 0.84	Treatment complication prediction: 3D rCNN predicts radiation-induced xerostomia at 12 months; outperforms logistic regression with dose/clinical variables.
Ye Z et al[126] 2023, USA	Patients: 899	Head and neck CT	Two-stage pipeline: (1) DenseNet for mid-C3 slice selection; (2) U-Net for skeletal muscle segmentation	Segmentation DSC 0.90 (0.89–0.91); External clinical acceptability 96.2% (AC1=0.94)	Treatment complication prediction: First externally validated fully automated deep learning platform for sarcopenia assessment from routine head and neck CT; fast and accurate tool for clinical integration.
Hang R et al[4] 2023, China	Patients: 139	CECT images	Traditional machine learning: GBM classifier with leave-one-out CV	Training AUC: 0.844–0.846, Validation AUC: 0.729–0.747	Prognostic prediction: CT radiomics predicts GZMA mRNA expression in HNSCC; radiomics models show good predictive performance and calibration.

before morphological changes become evident,[141] highlighting FTIR's potential in early cancer detection. Wang et al[142] demonstrated that ML algorithms could effectively classify OSCC in FTIR images and assess the risk of oral epithelial dysplasia (OED).

Ex vivo fluorescent confocal microscopy (FCM) has emerged as a promising method for rapid, automated histological analysis,[143] with studies showing high concordance between confocal and traditional histopathological images.[144] Shavlokhova et al[145] trained a convolutional neural network (CNN) using ex vivo FCM images, achieving high specificity in OSCC recognition.

Stimulated Raman Histology (SRH) employs fiber-optic stimulated Raman scattering (SRS) microscopy to produce images that resemble H&E-stained tissue sections, eliminating the need for preprocessing.[146] Weber et al[147] developed a DL model utilizing 80 SRS images from 8 patients with OSCC to classify malignant and non-malignant tissue in histological samples. Their findings indicated that DL could directly identify tissue types in SRS and SRH images, showing promise for rapid intraoperative tissue assessment in patients with OSCC.

Most of the emerging imaging techniques discussed above remain at an experimental stage. For instance, the combination of HSI or FCM with AI is currently limited to small-sample feasibility studies, lacking large-scale datasets. OCT with AI has advanced to point-of-care clinical validation, although multicenter validation is still required. SRH with deep learning has progressed to clinical application as an FDA-registered device, though most studies have focused on brain tumors rather than head and neck squamous cell carcinoma. Further exploration in this field is worthwhile and holds promise.

Discussion

AI technologies are garnering significant interest owing to their advantages of cost-effectiveness, non-invasiveness, objectivity, and reproducibility, offering transformative potential for HNSCC diagnosis and management. However, several challenges remain regarding the application of AI.

Most studies included in this review are retrospective and single-center in design with relatively small sample sizes; consequently, most lack external validation, which may lead to model overfitting and poor generalizability across different populations and clinical settings. Moreover, there is a lack of standardized imaging acquisition protocols, and nearly all studies employed manual tumor or nuclei segmentation, which introduces inter-observer variability and limits clinical scalability. In the context of HPV status prediction, most studies used p16 immunohistochemistry as a surrogate marker instead of the gold-standard HPV DNA PCR, potentially introducing classification noise. For prognostic prediction, heterogeneity in treatment regimens (eg., surgery alone vs. chemoradiotherapy, different chemotherapeutic agents) may confound outcome estimates, and overall survival is influenced by non-cancer mortality and salvage therapies. Critically, no model to date has undergone prospective external validation—a prerequisite for clinical implementation.

Across different studies, various imaging modalities—including CT, MRI, PET, and histopathological images—have demonstrated excellent application potential. However, direct comparisons of model performance across different modalities are challenging due to substantial heterogeneity in evaluation metrics, model architectures, and study designs. Nevertheless, a consistent finding across multiple studies is that multimodal fusion approaches generally outperform unimodal models, suggesting that combining complementary information from different imaging modalities may enhance predictive accuracy.

Current efforts primarily focus on applying various algorithms for feature extraction and prediction based on imaging data; however, these processes often lack interpretability. In the context of high-stakes medical decision-making, interpretability is essential for ensuring the safe, ethical, fair, and trustworthy deployment of AI.[148] Without absolute transparency, model outputs are unlikely to elicit clinical trust. The emergence of explainable AI (XAI) has made progress in addressing the "black-box" nature of AI models. Various methods have been introduced to elucidate the mechanisms and outcomes of AI systems, thus offering hope for real-world applications.[149] However, XAI remains an evolving field, with no universally accepted definitions or evaluation standards. Furthermore, the designs of many models often exclude the input of medical experts, potentially limiting their clinical relevance. Therefore, future efforts should focus on fostering collaboration among AI developers, clinicians, and regulatory authorities to establish a clear and standardized framework that encompasses imaging protocols, model development, and evaluation criteria. This approach is critical for advancing the safe and effective integration of AI into the management of HNSCC.

Conclusion

This review examines the current epidemiology of HNSCC and the limitations of existing diagnostic and therapeutic approaches. It also highlights the broad applications of AI in the screening, diagnosis, treatment, and prognostic prediction of HNSCC.

Among the applications reviewed, early screening using photographic and endoscopic images, as well as AI-assisted pathological diagnosis, are the most mature. Several models have achieved high sensitivity and specificity, with some tools (eg., smartphone-based detection) approaching clinical feasibility. HPV status prediction, pre-treatment assessment, and prognostic prediction remain at an intermediate stage, constrained by retrospective designs, small sample sizes, and lack of external validation. Emerging imaging techniques—including hyperspectral imaging, OCT, FTIR, FCM, and SRH-are still largely exploratory, with most evidence derived from small proof-of-concept studies.

To facilitate clinical translation, future efforts should prioritize prospective multicenter studies with standardized protocols, automated segmentation, and explainable AI. Rigorous external validation and demonstration of clinical utility are essential before these AI models can be integrated into routine HNSCC management.

Abbreviations

HNSCC, Head and Neck Squamous Cell Carcinoma; AI, Artificial Intelligence; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; PET, Positron Emission Tomography; HPV, Human Papillomavirus; SCC, Squamous Cell Carcinoma; TNM, Tumor, Node, Metastasis; WSI, Whole Slide Imaging; RDM, Radiomics; US, Ultrasound; CV, Computer Vision; NBI, Narrow Band Imaging; DL, Deep Learning; ML, Machine Learning; OPMDs, Oral Potentially Malignant Disorders; OPSCC, Oropharyngeal Squamous Cell Carcinoma; LSCC, Laryngeal Squamous Cell Carcinoma; IHC, Immunohistochemistry; ISH, In Situ Hybridization; PCR, Polymerase Chain Reaction; CECT, Contrast Enhanced Computed Tomography; DOI, Depth of Invasion; OCLNM, Occult Cervical Lymph Node Metastasis; LNM, Lymph Node Metastasis; IC, Induction Chemotherapy; CRT, Chemoradiotherapy; SMI, Skeletal Muscle Index; PFS, Progression Free Survival; DFS, Disease Free Survival; OS, Overall Survival; EGFR, Epidermal Growth Factor Receptor; OLK, Oral Leukoplakia; FTIR, Fourier Transform Infrared; OED, Oral Epithelial Dysplasia; FCM, Fluorescent Confocal Microscopy; SRS, Stimulated Raman Scattering; SRH, Stimulated Raman Histology; HSI, Hyperspectral Imaging; NIR, Near Infrared; PD-1, Programmed Death-1; PD-L1, Programmed Death-Ligand 1; CPS, Combined Positive Score; TPS, Tumor Proportion Score; ICS, Immune Cell Score; XAI, Explainable Artificial Intelligence; DSC, Dice Similarity Coefficient; AC1, Agreement Coefficient 1; GBM, Gradient Boosting Machine; RFE, Recursive Feature Elimination.

Data Sharing Statement

No datasets were generated or analyzed during the current study.

Ethics Approval and Consent to Participate

Not applicable, our study is based on open-source public database, and the First Affiliated Hospital of China Medical University do not require research using publicly available data to be submitted for review to their ethics committee, so there are no ethical issues and other conflicts of interest.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that they have no conflict of interests.

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