British Journal of Hospital Medicine

Br. J. Hosp. Med. (Lond) **2026**; 87(6): 55375
https://doi.org/10.31083/BJHM55375

Review

Multimodal PET/CT Image Fusion-Derived Parameters and Biochemical Indices for Prognostic Monitoring in Nasopharyngeal Carcinoma: A Review

Qidi Hu[1], Lili Kong[2], Jing Deng[1,3,*]

[1]Department of Otolaryngology, Jiaxing University Master Degree Cultivation Base, Zhejiang Chinese Medical University, 314100 Jiaxing, Zhejiang, China
[2]Department of Otolaryngology, Jiaxing Traditional Chinese Medicine Hospital, 314199 Jiaxing, Zhejiang, China
[3]Department of Otolaryngology, The First Hospital of Jiaxing, 314000 Jiaxing, Zhejiang, China
*Correspondence: dj30590471@163.com (Jing Deng)
Academic Editor: John Alcolado
Submitted: 1 September 2025 Revised: 15 November 2025 Accepted: 18 November 2025 Published: 28 June 2026

Abstract

Nasopharyngeal carcinoma is a common Epstein-Barr virus (EBV)-associated malignant tumour of the head and neck region. Accurate prognosis evaluation, risk stratification, and follow-up monitoring are essential for improving patient survival and quality of life. Multimodal positron emission tomography/computed tomography (PET/CT) image fusion has shown considerable promise in the diagnosis, staging, response assessment, and prognostic evaluation of nasopharyngeal cancer. This review examines the application of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT)-derived parameters together with biochemical markers in prognostic models for nasopharyngeal cancer. Biochemical markers, including EBV DNA, lactate dehydrogenase, C-reactive protein, and inflammation-based indices associated with patient prognosis, are summarised. These markers may enhance the accuracy of prognostic assessment and provide critical supplementary information for imaging evaluation. Integrating imaging parameters with biochemical markers is expected to establish a more comprehensive prognostic evaluation system. Multimodal image fusion combined with systematic biochemical indicator monitoring offers novel concepts and techniques for the prognostic evaluation of nasopharyngeal carcinoma (NPC). Future research should focus on standardised PET/CT acquisition, validated segmentation methods, reliable biochemical assays, and prospective multicentre model validation to improve therapeutic outcomes and survival rates in affected patients.

Keywords: nasopharyngeal carcinoma; positron emission tomography/computed tomography; Epstein-Barr virus DNA; tumor biomarkers; prognosis; risk assessment; radiomics

1. Introduction

Nasopharyngeal carcinoma (NPC) is a common malignant tumour of the head and neck in South China and Southeast Asia, and its initiation is closely linked to infection with the Epstein-Barr virus (EBV) [1,2]. Recent single-cell and spatial transcriptomic research has further clarified the biological and immune heterogeneity of NPC [3]. Although advancements in intensity-modulated radiotherapy, induction chemotherapy, immunotherapy, and comprehensive treatment strategies have markedly improved local control rates, tumour heterogeneity, distant metastasis, and post-treatment recurrence remain major obstacles affecting long-term survival [4]. Accurate prognostic assessment is essential for implementing individualised treatment, optimising therapeutic outcomes, reducing toxicity and side effects, and improving quality of life. However, the traditional tumour node metastasis (TNM) staging system, despite being the foundation of treatment, cannot adequately represent tumour biological behaviour, dynamic changes in treatment responses, or variations in patients' inherent prognoses [1,2]. Thus, interest in multimodal prognostic models that integrate molecular biological markers and functional imaging continues to grow [5].

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT), a non-invasive functional imaging technique, can directly reflect glucose metabolic activity and anatomical localisation of tumour tissues [6,7,8]. In NPC, conventional PET parameters and volume-based metrics have been linked to survival and distant-metastasis outcomes in systematic review and multicentre evidence [9,10]. Studies combining PET parameters with plasma EBV DNA have shown complementary prognostic value [11,12]. Maximum standardized uptake value (SUVmax)-focused cohorts have reported prognostic associations in definitive radiotherapy and PET/CT staging settings [13,14]. Additional evidence from intensity-modulated radiation therapy (IMRT)-treated and long-term follow-up cohorts also supports the prognostic value of pretreatment PET/CT [15,16]. PET/CT before treatment or after radiotherapy provides information for distant-metastasis prediction and response assessment [17,18]. In recurrent or model-based settings, SU-

Vmax can complement EBV DNA and nodal classification for risk prediction [19,20]. Volume-based parameters such as metabolic tumour volume (MTV) and total lesion glycolysis (TLG) are associated with survival in metastatic or chemoradiotherapy-treated NPC [21,22]. Additional studies have reported the prognostic utility of FDG-PET parameters and MTV in locally advanced or general NPC cohorts [23,24]. In *de novo* metastatic disease, PET/CT SUVmax may provide information beyond EBV DNA [25,26]. Post-chemoradiotherapy response evaluation and neoadjuvant-response prediction are also clinically informative PET/CT applications [27,28]. Additionally, serum or plasma biochemical indicators, which reflect tumour burden, host response, and microenvironmental status, play indispensable roles in the prognostic assessment of NPC. Quantitative plasma EBV DNA was established as a tumour-burden and prognostic biomarker in early studies [29,30]. Subsequent clinical studies confirmed its utility in advanced disease and TNM-complementary prognostication [31,32]. Mid-treatment and post-chemoradiotherapy EBV DNA provide additional risk information [33,34,35]. Post-treatment follow-up and longitudinal EBV DNA analyses support dynamic monitoring [36,37,38]. Cell-free DNA/circulating tumour DNA (cfDNA/ctDNA)-based approaches further expand liquid-biopsy risk assessment [39, 40]. Systemic inflammatory and lactate dehydrogenase (LDH)-related markers also provide prognostic information [41,42]. LDH-related evidence has been evaluated in NPC cohorts [43], whereas C-reactive protein (CRP)-related prognostic evidence has been reported in separate NPC studies [44,45]. CRP kinetics and baseline CRP have also been incorporated into survival assessment [45,46,47].

Despite major progress, significant challenges persist. Variations in PET/CT data acquisition and postprocessing techniques, including reconstruction algorithms, uptake time, SUV threshold selection, MTV/TLG segmentation, and region-of-interest delineation, reduce comparability and hinder uniform application across research institutions [7,8]. Standardised image-biomarker definitions are needed to improve radiomics reproducibility [48]. Prediction models also require transparent reporting and risk-of-bias assessment [49,50,51]. Cutoff selection and clinical utility assessment should be handled cautiously [52,53]. Second, the predictive power of a single indicator (e.g., SUVmax or EBV DNA) is limited and susceptible to individual variation, therapeutic interference, assay inconsistency, and tumour heterogeneity. Therefore, developing comprehensive models that effectively integrate multimodal data (radiomics, bioomics, and clinicopathology) is urgently needed [54,55]. Recent NPC-specific multimodal and deep-learning studies have started to address these needs [56,57]. In addition, conventional integrated models combining imaging-derived tumour burden with EBV DNA have also shown prognostic value [58]. Third, large-sample, prospective, and multicentre validation studies remain scarce, as many current findings are derived from single-centre retrospective cohorts, which restricts clinical generalizability and translational potential. Furthermore, more extensive longitudinal research is needed to clarify dynamic changes in parameters such as EBV DNA, ctDNA, and MTV during the treatment course and their prognostic significance. In conclusion, effectively integrating these research findings into clinical decision support systems to accomplish dynamic, real-time prognostic risk assessment and treatment recommendations remains a crucial future direction.

The purpose of this review was to comprehensively examine recent advancements in prognostic prediction models for NPC concerning ^{18}F-FDG PET/CT metabolic parameters (including fundamental quantitative indicators and emerging radiomic features) and major serum biochemical indicators, particularly EBV DNA and other potential biomarkers [9,11]. In addition to summarising specific clinical application scenarios and evidence-based roles in pretreatment risk stratification, response assessment during treatment, and follow-up management post-treatment, this review explores the prognostic value of individual and combined indicators [20,38]. Key methodological challenges and limitations in the development and validation of current multimodal prognostic models are also analysed, including image-biomarker standardisation [48], model reporting and risk-of-bias assessment [49,50,51], and cutoff/clinical-utility issues [52,53]. Finally, future research directions are proposed, including the standardised acquisition of data, the integration of sophisticated algorithms (artificial intelligence/machine learning), the development of dynamic monitoring models, and pathways for clinical translation to optimise precise prognostic assessment and advance clinical practice in nasopharyngeal carcinoma.

2. Basic Principles and Applications of ^{18}F-FDG PET/CT

2.1 Basic Principle

^{18}F-FDG PET/CT is an imaging technique that integrates positron emission tomography (PET) with computed tomography (CT). Using ^{18}F-labeled fluorodeoxyglucose (^{18}F-FDG) as the imaging agent provides dual information on tumour metabolic activity and anatomical structure [6,7,8]. ^{18}F-FDG is a glucose analog. After intravenous administration, it is preferentially taken up by highly metabolically active tumour cells. Because phosphorylated FDG is not further metabolised in the glycolytic pathway and remains trapped for imaging, tumour sites exhibit 'hot spots' with high metabolic activity on PET images. The anatomical images provided by CT scans can be used to locate areas with high metabolic activity precisely, forming fused PET/CT images [6].

^{18}F-FDG PET/CT has significant advantages in tumour diagnosis and management. First, it can sensitively detect abnormal metabolic activity in tumours, aiding in

the identification of tumour lesions and metastatic disease [6,59]. Even in the absence of obvious anatomical abnormalities, metabolic alterations can sometimes be detected. Second, ^{18}F-FDG PET/CT plays a crucial role in tumour staging. Whole-body scanning allows comprehensive evaluation of both primary tumours and metastatic sites, providing essential information for therapeutic planning [6,7,8]. In residual or recurrent NPC, PET/CT has shown diagnostic value in meta-analyses [60,61]. PET or PET/CT also contributes to the detection of distant metastatic disease [62,63]. In terms of treatment response assessment, ^{18}F-FDG PET/CT allows evaluation of therapeutic efficacy through monitoring of tumour metabolic changes, enabling timely adjustments of treatment strategies and reducing unnecessary interventions or associated side effects. Furthermore, ^{18}F-FDG PET/CT is a valuable tool for assessing the prognosis of patients with NPC. By quantitatively evaluating metabolic parameters such as TLG, MTV, and SUVmax, valuable insights into tumour biological behaviour and patient prognosis can be obtained [9,10]. These parameters are strongly linked to outcomes, such as patient survival rates and recurrence risks, thereby providing a reliable basis for individualised treatment planning.

In summary, ^{18}F-FDG PET/CT is a sophisticated imaging method that combines metabolic and anatomical information and plays an indispensable and significant role in clinical oncology. It offers comprehensive and accurate imaging support for tumour diagnosis, staging, evaluation of treatment response, and prognostic assessment.

2.2 Parameter Introduction and NPC-Specific Prognostic Evidence

^{18}F-FDG PET/CT is an advanced imaging technology that combines metabolic and anatomical information [6,7,8]. Among its key quantitative metrics are MTV, TLG, SUVmax, and related parameters. These indicators are essential for the diagnosis, treatment, and prognostic assessment of nasopharyngeal cancer. SUVmax, which measures the maximal FDG uptake within the tumour and represents the metabolic activity of malignant cells, is a crucial metric for assessing tumour aggressiveness and determining therapeutic response. Multiple NPC-specific studies have demonstrated that high pretreatment SUVmax is associated with a poor prognosis in patients with nasopharyngeal carcinoma [13,14]. Additional studies in IMRT and distant-metastasis settings support this association [15,16]. Recurrent and metastatic cohorts have also indicated prognostic relevance for SUVmax [19,25]. Changes in SUVmax can also be utilised to monitor treatment response [27,28].

MTV represents the total volume of metabolically active tumour tissue and provides a quantitative measure of tumour burden. The higher the MTV value, the higher the likelihood of disease progression in nasopharyngeal carcinoma [21,22]. Monitoring MTV before and after treatment can help evaluate treatment response and predict the risk of recurrence. Compared with SUVmax alone, MTV more comprehensively reflects both metabolic characteristics and volumetric changes in tumours. TLG, calculated as the product of MTV and the average SUV of all metabolically active regions, integrates both metabolic intensity and tumour volume. TLG is regarded as a comprehensive parameter and shows unique advantages in prognostic assessment of nasopharyngeal carcinoma [9,10]. Additional cohort studies have supported the prognostic utility of MTV and TLG [23,24]. Elevated TLG values typically indicate higher tumour metabolic burden and invasiveness, suggesting poorer prognosis. Dynamic monitoring of TLG during treatment can assist clinicians in optimising therapeutic strategies.

By quantitatively assessing tumour burden and metabolic activity, these FDG-PET/CT-derived characteristics support research and clinical applications in nasopharyngeal carcinoma. They contribute not only to early detection and accurate staging but also to individualised treatment planning and precise prognosis evaluation (Table 1, Ref. [13,15,16,18,19,20]; Table 2, Ref. [9,11,12,21,22,25]). The current revision reconstructs these tables using NPC-specific original studies and meta-analyses in which the sample size, parameter, cutoff, endpoint, and conclusion could be traced to the cited source [9]. Studies combining PET/CT and EBV DNA were prioritized when summarising multimodal evidence [11,12]. Through comprehensive analysis of these parameters, clinicians can better identify high-risk patients, develop more individualised treatment regimens, and ultimately improve survival outcomes and quality of life. Thus, the primary ^{18}F-FDG PET/CT parameters hold substantial research value and guiding significance in the clinical management of nasopharyngeal carcinoma.

3. Biochemical Prognostic Biomarkers in Nasopharyngeal Carcinoma

3.1 EBV DNA

EBV DNA is one of the most established circulating biomarkers in NPC. Plasma EBV DNA reflects tumour burden and has been widely used for baseline risk assessment, treatment-response monitoring, and post-treatment surveillance [29,30,31,32,33,34,35,36,37,38]. Elevated pretreatment EBV DNA is associated with poorer prognosis, while persistently or recurrently detectable EBV DNA after treatment may indicate residual disease or recurrence risk [31,32,33,34,35,36,37,38]. Standardised EBV DNA assays remain important for improving comparability across institutions and supporting personalised follow-up strategies [64,65,66].

3.2 LDH, CRP, and Inflammation-Based Indices

LDH, CRP, and inflammation-based indices provide complementary information on tumour metabolism, systemic inflammation, and host response. Elevated LDH

Table 1. NPC-specific studies evaluating the prognostic value of maximum standardised uptake value (SUVmax).

First author [Ref.]	Sample size (No. of patients)	SUVmax cutoff	Endpoints	Key findings
Lee SW [13]	41	8	EFS	Higher pretreatment SUVmax was associated with poorer prognosis after definitive treatment for NPC.
Liu WS [15]	75	5	OS, DFS	Pretreatment FDG-PET SUVmax helped identify patients at higher recurrence or death risk after IMRT.
Hung TM [16]	371	Primary SUVmax = 9.3; nodal SUVmax = 7.4	EFS, OS, DMFS	Pretreatment SUVmax of the primary tumour and neck nodes was associated with distant metastasis risk in non-disseminated NPC.
Xie P [18]	62	8	EFS, OS	Pretreatment SUVmax and post-radiotherapy metabolic response predicted outcomes in locally advanced NPC.
Shen T [19]	194	8.65	OS	In recurrent NPC, SUVmax and plasma EBV DNA showed different prognostic values across recurrence patterns.
Zhang Y [20]	449	Model-based SUVmax	Distant metastasis	An integrated model incorporating SUV and N-classification improved metastasis prediction.

SUVmax, maximum standardised uptake value; OS, overall survival; EFS, event-free survival; DMFS, distant metastasis-free survival; DFS, disease-free survival; IMRT, intensity-modulated radiation therapy; FDG-PET, fluorodeoxyglucose positron emission tomography; NPC, nasopharyngeal carcinoma; EBV, Epstein-Barr virus.

Table 2. Studies evaluating volume-based PET/CT parameters and combined PET/CT-biochemical markers in nasopharyngeal carcinoma.

First author [Ref.]	Sample size (n)	PET/CT parameter(s)	Biochemical marker(s)	Key findings
Lin J [9]	1938	SUVmax, MTV, TLG	Not applicable	Meta-analysis confirmed that high SUVmax, MTV, and TLG predicted a higher risk of adverse events or death in NPC.
Chang KP [11]	108	TLG >65 g	Plasma EBV DNA	TLG correlated with EBV DNA load and independently predicted OS and DFS.
Chen WH [12]	874	Nodal SUVmax = 7.5	EBV DNA = 6220 copies/mL	Combining EBV DNA with nodal SUVmax improved distant-metastasis risk stratification.
Chan SC [21]	56	MTV = 110 cm^3; TLG = 560	Not included	Higher MTV and TLG predicted inferior survival in metastatic NPC.
Moon SH [22]	44	SUVmax = 7.8; MTV = 66; TLG = 764	Not included	Volume-based PET/CT parameters were associated with event-free outcomes after concurrent chemoradiotherapy.
Yan W [25]	86	SUVmax of metastatic lesions ≥10	LDH ≥229 U/L	High metastatic-lesion SUVmax and elevated LDH independently predicted worse OS in de novo metastatic NPC.

TLG, total lesion glycolysis; MTV, metabolic tumour volume; EBV, Epstein-Barr virus; LDH, lactate dehydrogenase; OS, overall survival; DFS, disease-free survival.

has been associated with poorer outcomes, distant metastasis, and liver metastasis in NPC [42,43,67]. CRP and CRP-related indices have also shown prognostic value, reflecting systemic inflammatory status and survival risk [44,45,46,47,68]. Other clinical biochemistry-based and nutritional-inflammatory indices may further support risk stratification in selected patient populations [69,70].

3.3 cfDNA/ctDNA and Emerging Molecular Biomarkers

Liquid-biopsy approaches, including cfDNA and ctDNA analysis, provide additional opportunities for molecular risk assessment and dynamic monitoring in NPC [39,40]. These markers may complement EBV DNA by capturing tumour-derived molecular changes during treatment and follow-up. EBV DNA methylation, serum small-molecule profiles, immune-related signatures, and other emerging molecular markers may further refine early detection, treatment-response evaluation, and prognosis prediction [71,72,73,74,75,76,77].

3.4 Integration With PET/CT-Derived Parameters

Biochemical biomarkers and ^{18}F-FDG PET/CT-derived metabolic parameters provide different but complementary dimensions of prognostic information. PET-

derived parameters such as SUVmax, MTV, and TLG reflect tumour metabolic activity and burden, whereas EBV DNA, LDH, CRP, and liquid-biopsy markers reflect circulating tumour load, systemic inflammation, and molecular dynamics. Studies combining PET parameters with EBV DNA or LDH suggest that integrated imaging-biochemical assessment may improve risk stratification and support individualised treatment planning [11,12,19,25,26]. Future models should prioritise standardised imaging acquisition, reliable biomarker assays, and prospective validation.

In summary, biochemical markers such as EBV DNA, LDH, CRP, ctDNA, and inflammation-based indices demonstrate substantial clinical value in NPC prognostic research [31,32]. In addition to their individual predictive roles, these markers can also be integrated with ^{18}F-FDG PET/CT imaging parameters to offer more comprehensive and precise prognostic assessment information [11,12]. cfDNA/ctDNA-based evidence supports molecular risk assessment [39,40], and inflammation-based markers provide complementary prognostic information [41]. By thoroughly evaluating biochemical and imaging features, clinicians can develop more personalised treatment strategies, thereby improving patient survival and quality of life. Consequently, the significance of these biochemical markers in NPC prognostic modelling should not be overlooked. Future research should explore the clinical application potential of these models and further optimise their predictive utility.

4. The Combined Application of ^{18}F-FDG PET/CT Parameters and Biochemical Indicators

4.1 The Necessity of Combined Application

In the prognostic assessment of NPC, the combined use of ^{18}F-FDG PET/CT parameters and biochemical indicators is essential. Although single imaging or biochemical indicators can provide prognostic insights, each has its inherent limitations [11,12]. ^{18}F-FDG PET/CT reflects tumour biological behaviour and metabolic activity of tumours by detecting glucose metabolism of tumour tissues. Although SUVmax has demonstrated prognostic value in NPC cohorts [13,14], reliance on a single imaging parameter may not fully capture the spatial and metabolic heterogeneity of tumours; therefore, PET/CT-derived parameters should be interpreted together with biochemical and clinical indicators. Conversely, biochemical indicators such as EBV DNA, LDH, and CRP reflect tumour molecular characteristics and the systemic physiological state of patients [31,32]. These biochemical markers offer predictive information that imaging alone cannot capture, and they correlate strongly with tumour load, invasiveness, and the host immune response. However, relying solely on biochemical markers may overlook the spatial distribution and metabolic heterogeneity of tumours.

Consequently, integrating ^{18}F-FDG PET/CT parameters with biochemical indicators yields a more comprehensive and precise prognostic evaluation, enhancing the complementary strengths of each modality while reducing their limitations [11,12]. Combining both imaging and biochemical data can significantly improve the predictive potential of prognostic models, support individualised treatment regimens, and enhance patient survival and treatment outcomes. Through the integration of multidimensional data, the combined approach strengthens the scientific quality and clinical reliability of prognostic evaluation, effectively compensating for the limitations of single-modality assessment [54,55].

4.2 Research Progress

In recent years, researchers have increasingly focused on integrating imaging parameters with biochemical indicators to enhance the accuracy and clinical applicability of prognostic models [11,12]. ^{18}F-FDG PET/CT provides detailed information on tumour metabolic activity and anatomical structure, whereas biochemical indicators, such as EBV DNA, LDH, and CRP, reflect tumour molecular characteristics and the systemic physiological status of the patients [31,32]. Radiomics and deep-learning approaches have further expanded the methodological basis for such integration [54,55].

Multiple studies have shown that the combined application of ^{18}F-FDG PET/CT parameters with biochemical indicators can improve prognostic assessment in patients with NPC. For example, integrating EBV DNA levels with PET/CT metabolic parameters allows a more accurate assessment of tumour burden and recurrence risk [11,12]. In recurrent and metastatic settings, SUVmax and EBV DNA may provide complementary information [19,26]. Moreover, the CRP/albumin ratio may contribute to prognostic assessment [68], while elevated LDH levels are associated with disease progression and poorer survival in NPC [67]. Clinical biochemistry-based and nutritional-LDH indices provide additional prognostic information [69,70].

According to these studies, combining ^{18}F-FDG PET/CT-derived parameters with biochemical indicators such as EBV DNA and LDH may provide more comprehensive prognostic information and improve risk stratification in NPC [11,12,19,25,26]. NPC-specific multimodal and deep-learning studies are beginning to clarify how such data can be translated into clinical risk stratification [56,57]. Conventional integrated models combining imaging-derived tumour burden with EBV DNA have also shown prognostic value in NPC [58]. This multifaceted evaluation strategy is expected to become a standard approach for prognostic assessment in NPC patients, promoting the development of personalised treatment and improving patient survival and quality of life.

4.3 Typical Research Cases

In research on the prognostic evaluation of NPC, representative studies combining ^{18}F-FDG PET/CT parameters with biochemical indicators have provided valuable insights and data support for advancing this field [11,12]. A notable study systematically evaluated the synergistic prognostic value of ^{18}F-FDG PET parameters and EBV DNA levels in predicting the prognosis of NPC patients [11].

In that study, NPC patients underwent pretreatment PET assessment together with plasma EBV DNA measurement. The findings indicated that combining PET/CT parameters, including TLG, MTV, and SUVmax, with EBV DNA levels improved prognostic predictions and recurrence risk assessment [11]. Another study showed that nodal SUVmax and plasma EBV DNA could jointly improve distant-metastasis risk stratification [12].

Another representative line of research investigated the prognostic value of PET-derived parameters in recurrent or de novo metastatic NPC. In recurrent NPC, SUVmax and EBV DNA showed different prognostic values across recurrence patterns [19]. In de novo metastatic NPC, PET/CT SUVmax was also compared with EBV DNA as a prognostic indicator [26]. These studies collectively highlight how combining PET/CT imaging data with biochemical markers enhances the accuracy and practical utility of prognostic models.

From these typical research cases, it is evident that the combined application of ^{18}F-FDG PET/CT parameters and biochemical indicators holds significant potential in the prognostic assessment of NPC [11,12]. This integrated approach not only provides clinicians with more comprehensive and reliable prognostic information but also supports individualised treatment planning, ultimately contributing to improved survival outcomes and quality of life of patients. These research advancements have laid a strong foundation for future exploration and point toward new directions for multidisciplinary collaboration and comprehensive prognostic assessment [54,55].

5. Construction and Validation of Prognostic Models

5.1 Model Construction Method

Improving patient survival and treatment outcomes requires the development and validation of efficient prognostic models. For this, the combined use of ^{18}F-FDG PET/CT parameters and biochemical indicators provides multidimensional data support and extensive clinical information [9,11]. Data collection, feature selection, model training, and validation are the four basic steps included in most model development strategies [49,50].

Prognostic model construction begins with the collection of data. Researchers must gather comprehensive clinical data from a large number of patients with NPC, including biochemical markers (such as EBV DNA, LDH, CRP) and ^{18}F-FDG PET/CT imaging parameters (such as SUVmax, MTV, TLG) [9,11]. These data are often obtained through multicentre, prospective, or retrospective studies to ensure sample diversity and the reliability of the results. After standardised radiomic feature extraction, candidate variables are typically reduced and selected during model development using statistical modelling or machine-learning approaches, as illustrated in NPC radiomics and multimodal artificial Intelligence (AI) studies [54,55]. Transparent reporting and risk-of-bias assessment should follow established prediction-model guidance [49,50,51]. Typical techniques include univariate and multivariate regression analyses, as well as more sophisticated machine learning algorithms such as support vector machines and random forests [54,55]. Feature selection aims to eliminate redundant or irrelevant variables to enhance model stability and predictive performance.

Model construction proceeds to the model training stage. Researchers typically divide the dataset into training and validation sets, using the training set to establish the model. Commonly used methods include Cox proportional hazards regression models, and machine learning models, such as decision trees and neural networks [49,50]. Cross-validation is frequently used to optimise model parameters during the training phase and achieve superior predictive performance. Model validation is an essential step to ensure model reliability. Separate validation sets are used to assess the performance of the model. Commonly reported model-performance measures include discrimination indices such as the C-index or area under the curve (AUC), together with calibration assessment, as recommended in prediction-model reporting guidance [49,50]. Decision-curve analysis can be used separately to evaluate the clinical utility of prediction models [53]. These indicators enable assessment of the generalisation potential of the model, predictive accuracy, and consistency.

Through systematic and well-designed model development processes, researchers can establish accurate and reliable prognostic models for NPC. These models not only provide clinicians with individualised support for treatment decision-making but also help patients better understand their prognosis, ultimately improving therapeutic outcomes and quality of life.

5.2 Model Validation

Model validation is a key step to ensure the accuracy and reliability of a prognostic model. Validation is usually performed through two approaches: internal validation and external validation. Internal validation primarily evaluates the stability and generalisation potential of the model within the same dataset using techniques such as cross-validation and bootstrap sampling [49,50,51]. By dividing the dataset into training and validation sets, cross-validation allows repeated model training and testing, thereby providing a more reliable assessment of performance. Bootstrap sampling,

through multiple iterations of resampling, can be used to evaluate model robustness and estimate prediction error.

External validation is even more crucial, particularly by using separate datasets to assess the model's accuracy and suitability for various patient populations. Separate datasets, often derived from patient information collected from multiple centres or over different time periods, are used to examine the generalisation capacity of the model. Among the commonly used evaluation metrics, the C-index reflects the discriminative ability of the model. The AUC is used to assess predictive performance at various time points. Calibration curves assess agreement between observed risk and predicted risk probability. Prognostic model reporting should follow Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) principles [49,50]. Risk-of-bias assessment should consider tools such as Prediction model Risk Of Bias ASsessment Tool (PROBAST) [51]. Cutoff selection and decision-curve analysis can further clarify model robustness and clinical utility [52,53].

5.3 Model Optimisation

Model optimisation aims to enhance model accuracy, robustness, and generalizability through feature selection, parameter adjustment, and algorithm improvement.

Candidate PET/CT-derived parameters and biochemical variables can be selected during model development using methods appropriate to the dataset, such as multivariable Cox regression, receiver operating characteristic (ROC)-based assessment, penalized regression, or machine-learning approaches. In NPC-specific PET/CT–biomarker studies, multivariable modelling and ROC-based analyses have been used to evaluate PET/CT parameters together with EBV DNA or LDH [11,12,25,58]. Transparent reporting and validation remain essential to reduce overfitting and improve model reliability [49,50,51]. Parameter adjustment is another crucial phase in model optimisation. Different model algorithms exhibit varying sensitivities to parameter settings. Optimal parameter combinations can be identified using grid search, cross-validation, or Bayesian optimisation, resulting in improved model performance. For instance, the performance of a support vector machine (SVM) is greatly influenced by the choice of the kernel function and penalty parameters. In neural networks, it is essential to adjust parameters such as the number of neurons, the number of hidden layers, and the learning rate.

Algorithm improvement is also a critical component of model optimisation. Prognostic models are being developed using increasingly sophisticated algorithms as machine learning and deep learning technologies advance. Advanced machine-learning and deep-learning approaches may improve the modelling of complex imaging, clinical, and molecular data, but their clinical application in NPC still requires transparent reporting, external validation, and risk-of-bias assessment [49,50,51,56,57]. Deep learning methods (such as convolutional neural networks and long short-term memory networks) further improve the modelling capacity for complex data by processing information sequentially and automatically extracting high-level features [56,57]. MRI habitat features and disease-specific electronic health record platforms may provide infrastructure for future real-world model development [78,79].

The robustness and generalizability of the model must also be considered during the optimisation process. To minimise overfitting, the performance of the model on various datasets is evaluated using cross-validation, bootstrap sampling, and other approaches [49,50,51]. External verification is likewise essential. Testing the model on multiple independent datasets ensures universality and reliability in real-world clinical applications.

5.4 Prospects and Challenges

It is essential to comprehensively examine potential future research directions and existing challenges when examining the application of ^{18}F-FDG PET/CT parameters and biochemical markers in prognostic models for NPC, to advance progress in this field.

Exploring novel PET/CT parameters will remain an important research direction. At present, most studies have emphasised traditional parameters such as SUV, MTV, and TLG [9,10]. However, more sophisticated and intricate metrics, such as tumour texture features, asphericity, PET radiomics, and dynamic PET parameters, have gained increasing attention with advances in imaging technology and image-processing algorithms [48,54]. MRI habitat features and disease-specific big-data platforms may complement PET/CT-based prediction [78,79]. Staging and neck-risk refinements remain important for integrating imaging markers into clinically interpretable models [80,81,82]. Another crucial research avenue is the identification and development of novel biochemical markers. Conventional biochemical indicators, including LDH, albumin, and CRP, are commonly used to evaluate patient prognosis [41,42]. CRP/albumin and LDH-related evidence provide additional inflammatory and metabolic context [67,68]. Clinical biochemistry-based and nutritional-LDH indices also support risk stratification [69,70]. However, novel biomarkers, such as circulating tumour DNA (ctDNA), microRNAs (miRNAs), methylation profiles, serum small molecules, and metabolites, have progressively emerged as research hotspots with the advancement of molecular biology and genomics [39,40]. Molecular diagnostic and early-detection biomarker studies support further investigation of these approaches [71,72]. EBV methylation and non-endemic EBV DNA data provide additional directions [73,74]. These emerging biochemical markers hold substantial promise for prognostic assessment, since they can capture the molecular characteristics and dynamic alterations of malignancies.

Additionally, research aimed at expanding the sample size is another important direction for future work. Due to the limited sample size, the universality and robustness of conclusions in many studies remain somewhat restricted. In the future, through multicentre collaboration and the establishment of large-scale prospective cohort studies, the sample size can be effectively increased, thereby enhancing the reliability of research findings and the capacity for external validation. NPC-specific multimodal and deep-learning models provide examples of how large-scale data may be used [56,57]. Treatment-individualisation and immunotherapy evidence also indicate that prognostic monitoring should be connected to therapeutic decision-making [83,84]. Systematic reviews of immunotherapy and first-line regimens support the need for treatment-adapted models [85,86]. Combination-treatment and population-outcome studies provide additional clinical context [87,88,89]. Special metastatic and nodal cohorts highlight where individualised monitoring is needed [90,91]. Quality-of-life and recurrent-disease literature provides additional clinical context [92,93]. Evidence in recurrent NPC also emphasises the importance of adaptive follow-up [94].

However, many obstacles remain in advancing these potential lines of inquiry. First, inadequate sample size continues to be a major challenge. Due to limited sample sizes, many studies lack sufficient statistical power, which makes it challenging to draw conclusions with broad applicability. Multicentre collaboration can help address this challenge by combining data resources from various institutions and regions to establish extensive joint databases. This approach will increase the sample size, improve the statistical efficiency, and enhance the validity of research findings. Additionally, certain methodological designs in current research may introduce biases, including information bias and selection bias in retrospective studies [49,50,51]. Cutoff-related bias and clinical-utility assessment should also be considered [52,53]. Furthermore, the comparability and consistency of results may be impacted by heterogeneity across studies, including differences in patient profiles, treatment planning, imaging protocols, biomarker assays, and follow-up durations. Future studies should emphasise prospective research designs, rigorously control for confounding factors, standardise data collection and analytical protocols, and ensure the accuracy and repeatability of findings to address these limitations.

Furthermore, technological and methodological advancements face additional barriers. The introduction of novel PET/CT parameters and biochemical indicators requires new detection technologies and analytical techniques, which raise the expectations for researchers' technical proficiency and equipment capacity. To overcome these obstacles, investigators should strengthen interdisciplinary collaboration, leveraging the expertise of multiple disciplines, including data science, molecular biology, nuclear medicine, radiology, oncology, otolaryngology, and medical imaging, to promote joint innovation in methodology and technology [5,48]. Emerging molecular studies on radioresistance and chemoresistance illustrate the biological heterogeneity that imaging-biochemical models should eventually capture [95,96]. Studies on metastasis and metabolism provide additional mechanistic context [97,98]. Immune escape and DNA-repair studies may also inform future biomarker development [99,100]. Drug-resistance and methylation studies offer potential future biomarkers [75,101]. Metabolomic and immune-signature studies provide additional candidate markers [76,77]. Clinical complications and experimental therapeutic pathways broaden translational directions [102,103]. Immune archetypes, metabolic-epigenetic interactions, and heat-shock proteins represent further areas for hypothesis generation [104,105,106].

The parameters and biochemical indicators derived from ^{18}F-FDG PET/CT have broad application prospects in the development of prognostic models for NPC. The accuracy and clinical utility of prognostic models can be further enhanced by standardising PET/CT-derived parameters, incorporating validated molecular biomarkers, expanding cohort sizes, and following transparent model-development and validation strategies [10,39,40,49,50,51,52,53]. EBV DNA, ctDNA, and cfDNA-related approaches provide important directions for dynamic monitoring [31,32,39,40]. Model reporting and risk-of-bias assessment should follow established methodological principles [49,50,51]. Cutoff selection and clinical-utility assessment should also be considered [52,53]. However, addressing challenges such as small sample sizes, research design constraints, cutoff heterogeneity, assay standardisation, and technical limitations will require coordinated efforts from multiple stakeholders. Multicentre collaboration and cross-disciplinary innovation will undoubtedly drive further advances in this field, providing strong support for precision medicine and the individualised treatment of patients with NPC.

6. Conclusion

^{18}F-FDG PET/CT-derived parameters, including SUVmax, MTV, and TLG, provide important information on tumour metabolic activity and burden in nasopharyngeal carcinoma. Biochemical markers such as EBV DNA, LDH, CRP, and emerging liquid-biopsy indicators further complement imaging assessment by reflecting tumour burden, systemic inflammation, and dynamic treatment response. Integrating PET/CT parameters with biochemical indicators may improve prognostic stratification, support individualised treatment planning, and facilitate follow-up monitoring. Future studies should focus on standardised imaging acquisition, validated biomarker assays, and prospective multicentre model validation to promote clinical translation.

Key Points

• PET/CT image fusion provides metabolic and anatomical information that supports NPC staging, response assessment, and prognostic monitoring.

• SUVmax, MTV, TLG, and radiomic features can improve individualised assessment of tumour burden and metabolic heterogeneity.

• EBV DNA, LDH, CRP, ctDNA, and inflammation-based biomarkers complement PET/CT findings in prognostic evaluation.

• Combining PET/CT-derived parameters with biochemical markers may improve risk stratification and follow-up management.

• Future studies should standardise PET/CT acquisition, biomarker assays, and multicentre validation of imaging-biochemical models.

Availability of Data and Materials

Not applicable.

Author Contributions

QH wrote the article and conducted the literature review; LK was responsible for data collection, reference verification, and organisation; JD was responsible for project supervision and the design of research plans. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflicts of interest.

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