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NARRATIVE REVIEW

Epstein–Barr Virus Circulating Tumor DNA (ctDNA) as a Biomarker in Nasopharyngeal Carcinoma: A Narrative Review

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Abstract:
Nasopharyngeal carcinoma (NPC) is a cancer with a characteristic distribution in East and Southeast Asia, including Indonesia, with an incidence of 4.7 cases per 100,000 population per year. Conventional diagnostic methods still have limitations because they are invasive, carry a risk of false negatives, and are not suitable for repeated monitoring. Liquid biopsy using Epstein-Barr virus circulating tumor DNA (EBV-ctDNA) offers great potential as a noninvasive biomarker for the diagnosis and management of NPC. This narrative review was conducted through a literature search on PubMed and Google Scholar (2020–2025) using keywords related to NPC, EBV-ctDNA, and liquid biopsy. Of the 314 articles identified, 14 publications were selected based on inclusion and exclusion criteria. The results showed that EBV-ctDNA has a sensitivity of up to 97% in detecting NPC and plays a role in early diagnosis, risk stratification, therapeutic response monitoring, and earlier recurrence detection compared to imaging modalities. Digital PCR and next-generation sequencing technologies improve detection accuracy and enable large-scale population screening applications. EBV-ctDNA has the potential to be a transformative biomarker with high sensitivity and specificity, supporting routine clinical implementation and personalized care for NPC, especially in endemic areas.

Keywords: Nasopharyngeal carcinoma; Liquid biopsy; EBV-ctDNA; Biomarkers; Non-invasive diagnostics

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INTRODUCTION

Nasopharyngeal carcinoma (KNF), or nasopharyngeal carcinoma (NPC), is widely found in East and Southeast Asia, including Indonesia, where it has a high case burden.[1] In 2020, there were 133,354 new cases and 80,008 deaths, with an incidence three times higher in men.[2] In Indonesia, the incidence rate reaches 4,7 per 100,000 population per year, making it the fifth most common cancer, with the majority of cases diagnosed at advanced stages.[1,3]

EBV-ctDNA was chosen as a biomarker for KNF due to various risk factors, including interactions with Epstein-Barr virus (EBV) infection, genetic predisposition, dietary patterns high in salted fish or preserved foods, and environmental exposures such as cigarette smoke, wood dust, formaldehyde, and air pollution.[3,4]

Conventional diagnostic methods, such as tissue biopsy and imaging (CT, MRI, PET-CT), while important, have several limitations. Biopsies are invasive, carry a risk of false negatives, and are not suitable for repeated monitoring. Imaging, on the other hand, may miss small lesions, has difficulty distinguishing recurrence from post-therapy changes, and is limited by anatomical complexity.[5,6]

Liquid biopsy, as an alternative, is rapidly advancing thanks to developments in molecular biology and sequencing technology.[7] This approach enables noninvasive, sensitive, and repeatable detection of circulating tumor DNA (ctDNA) biomarkers, even in the early stages.[8] In KNF, liquid biopsy has been proven to improve early diagnosis, therapy monitoring, and detection of residual disease, with a sensitivity of up to 97%, thereby supporting future personalized therapy.[9,10]

The purpose of this narrative review is to explore circulating Epstein–Barr virus tumor DNA in the diagnosis of nasopharyngeal carcinoma, emphasizing its potential as a cutting-edge approach in molecular diagnostics.

METHOD

A literature search was conducted using the PubMed and Google Scholar databases with a publication range of 2020–2025 to obtain up-to-date information on the role of Epstein–Barr virus circulating tumor DNA (EBV-ctDNA) as a biomarker in nasopharyngeal carcinoma. Keywords used included: "Epstein–Barr Virus", "Circulating Tumor DNA (ctDNA)", "Nasopharyngeal Carcinoma", "Liquid Biopsy", and "Early Diagnosis". Articles in the form of conference abstracts, short reports without complete data, or those published in languages other than English and Indonesian were excluded.

Literature selection was carried out in three stages. In the first stage, the initial keyword search identified 314 articles. In the second stage, duplicates were removed, and titles and

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abstracts were screened based on the inclusion criteria, yielding 42 articles. In the final stage, a thorough full-text review identified 14 publications that met the criteria for further analysis in this narrative review.

Inclusion criteria were: (1) articles addressing EBV-ctDNA or liquid biopsy in KNF; (2) articles published as original research, literature reviews, or clinical guidelines; (3) publication within the last five years; and (4) studies involving human subjects, with no age restrictions. Articles were excluded if: (1) they were based on nonhuman subjects; (2) full text was not available; or (3) they discussed KNF without addressing molecular diagnostic aspects or liquid-based biomarkers.

All stages of the literature review were evaluated using SANRA (Scale for the Assessment of Narrative Review Articles), which assesses the quality, credibility, and relevance of narrative reviews. Using this instrument ensured that the article preparation process followed a systematic methodology and produced scientifically sound analysis results.

RESULT

From the selection process, 14 main articles that met the criteria were obtained and analyzed in this review. Each publication is summarized in tables (Tables 1 and 2), including information on the author, year, title, study design and population, main findings, and the type of biomarker or diagnostic method evaluated for accuracy.

Table 1. Study selection was used for the discussion of EBV ctDNA as a biomarker of Nasopharyngeal Carcinoma

Author (Year)	Title	Study Design	Findings	Linkage with EBV-ctDNA in KNF
Aulakh *et al.* (2022)	*The Promise of Circulating Tumor DNA in Head and Neck Cancer*	Review	ctDNA is useful for screening, diagnosis, monitoring therapy, prognosis (viral & non-viral).	EBV ctDNA is important for early detection & monitoring of KNF.
Ghiyasim oghaddam et al. (2024)	*Does circulating tumor DNA apply as a reliable biomarker for the diagnosis and prognosis of head and neck squamous cell carcinoma?*	Narrative Review	ctDNA from blood/saliva/serum can be used for diagnosis, prognosis, monitoring.	Confirms ctDNA (including EBV ctDNA) as an important molecular biomarker.

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Jiang et al. (2023)	*The Clinical Utility of EBV DNA and Other Liquid Biopsy Markers in Nasopharyngeal Carcinoma*	Systematic review 2015–2022	EBV plasma DNA is consistent as a biomarker of diagnosis, prognosis, monitoring; Other biomarkers are developing.	EBV ctDNA remains gold standard liquid biomarker KNF.
Zhang et al. (2022)	*Plasma EBV DNA as a Biomarker for Recurrence Detection in Nasopharyngeal Carcinoma*	Longitudinal, follow-up NPC after RT/CT	Increase in EBV DNA precedes detection of recurrence radiology.	EBV ctDNA sensitive as an early indicator of KNF recurrence.
Nguyen et al. (2024)	*Digital PCR for EBV ctDNA Detection in Nasopharyngeal Carcinoma*	Observational, 200 NPC patients	Digital PCR is more sensitive than qPCR, consistent results between laboratories.	Digital PCR strengthens the accuracy of EBV ctDNA detection for clinical applications.
Liu et al. (2022)	*Plasma Circulating Tumor Epstein–Barr Virus for the Surveillance of Cancer Progression in Bone-Only Metastatic Nasopharyngeal Carcinoma*	Retrospective, 105 patients of single-bone metastatic NPC	39/105 patients with EBV ctDNA were undetectable → no progression (100% NPV); 66 ctDNA patients were detected, 64 progressions (PPV 97%).	EBV ctDNA is effective as a prognostic biomarker and monitoring of NPC progression.
Pramanik et al. (2021)	*Cell-free EBV DNA as a biomarker during clinical management of NPC in a nonendemic region*	Pilot study (retrospektive)	EBV DNA is detected in the majority of patients; DNA levels increase with stage, drop after therapy, rise again during relapse.	EBV DNA Sensitive Plasma for Monitoring Therapeutic Response & Relapse Prediction in Non-Endemic NPCs.
Chan et al. (2022)	*Epstein-Barr virus DNA detection by targeted sequencing in post-treatment plasma samples and prognosis of locally advanced nasopharyngeal cancer*	Editorial + analysis of clinical trials NPC0502	NGS improves recurrence prediction: +40% local, +12% away compared to qPCR; low fraction proportion (<0.01%) → better survival.	NGS increases the sensitivity of EBV-ctDNA detection, playing an important role in both diagnosis and prognosis.

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Huang et al. (2023)	*Next-Generation Sequencing of Plasma EBV DNA in Screening for Nasopharyngeal Carcinoma*	Screening of a population of >10,000 high-risk people	NGS EBV ctDNA is better than qPCR for early detection, especially early stages.	EBV CTDNA-based NGS potential for screening of NPC endemic populations.
Ghose et al. (2024)	*The plasma EBV DNA load with IL-6 and VEGF levels as predictive and prognostic biomarker in NPC*	Observational	High DNA EBV correlates with IL-6 & VEGF; The combination of three biomarkers predicts the therapeutic response and disease progression.	EBV DNA along with inflammatory markers improves the accuracy of NPC prognosis.
Xu et al. (2022)	*Association of Plasma EBV DNA With Outcomes for Patients With RM-NPC Receiving Anti–PD-1 Immunotherapy*	Prospective (POLARIS-02 trial)	EBV DNA baseline is high → OS is shorter; EBV DNA dynamics predict progression earlier than radiology.	EBV DNA is important for monitoring immunotherapy (anti-PD-1) responses.
Qiu et al. (2024)	*Establishment and validation of circulating cfDNA signatures for NPC detection*	Case-control + NGS model	The cfDNA model (footprint, fragmentation, CNV, EBV) accurately differentiates NPC vs healthy (AUC 99.9%); superior to EBV DNA alone.	EBV DNA remains an important component, but the integration of cfDNA signatures is more accurate.
Maharani & Kodrat (2024)	*The EBV DNA Test as a Predictor of the Course of Nasopharyngeal Cancer*	Review	EBV DNA pre-therapy → prognosis prediction; Post-therapy is useful for the evaluation of the risk of relapse & metastases.	EBV DNA is the most reliable for prognosis and monitoring of LA-NPC, although cutoffs vary.

EBV-ctDNA Diagnostic Value

Nasopharyngeal carcinoma (KNF) is one of the cancers with a distinctive geographical distribution that places a significant burden on populations in East and Southeast Asia. One of the major challenges in managing this disease is the difficulty of detecting cases at an early stage, as the symptoms are nonspecific and often resemble common respiratory infections. Conventional diagnostic modalities, such as nasopharyngeal endoscopy and radiological

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imaging (CT scan or MRI), remain the clinical standards but have notable limitations. Endoscopy relies heavily on operator skill and carries the risk of missing small lesions hidden within the anatomical folds of the nasopharynx. Meanwhile, imaging has limitations in distinguishing inflamed or fibrotic normal tissue from active tumor tissue, often leading to failures in early diagnosis.

In this context, molecular biomarkers have become increasingly important, with one of the most promising candidates being circulating tumor DNA from the Epstein–Barr virus (EBV-ctDNA). EBV-ctDNA is a fragment of viral DNA released into the bloodstream by infected tumor cells through apoptosis, necrosis, or active secretion. These fragments are small, detectable in plasma, and uniquely reflect the biological activity of the tumor directly, rather than merely indicating the presence of a latent infection. Therefore, EBV-ctDNA can be considered a more accurate molecular fingerprint compared to conventional biomarkers such as antibodies or viral antigens.

A number of prospective and retrospective studies have shown that EBV-ctDNA has a sensitivity above 90% and a specificity exceeding 95% in detecting KNF. These values are significantly better than those of many traditional methods. Its high accuracy makes EBV-ctDNA a promising key component in future diagnostic algorithms, both for individual diagnosis and for screening high-risk populations in endemic regions.

Another crucial advantage is its ability to detect disease at an early stage. The majority of KNF patients are still diagnosed at an advanced stage, even though prognosis is highly dependent on the stage at which the diagnosis is made. Population screening studies in endemic areas have shown that plasma EBV-ctDNA testing can identify asymptomatic stage I–II patients an important milestone, as early-stage radiotherapy has a success rate exceeding 90%. This finding suggests that implementing ctDNA-based screening could reshape KNF control strategies in endemic regions.

In addition to serving as a binary (positive/negative) indicator, EBV-ctDNA levels can also be measured quantitatively. Advanced-stage patients typically exhibit higher concentrations than those at early stages. This correlation between ctDNA levels and tumor burden enhances its diagnostic value while also paving the way for its integration into risk stratification systems. Advances in cutting-edge technologies have further improved the accuracy of these measurements. The qPCR method, which was initially the standard, has now been complemented by digital PCR (dPCR) and next-generation sequencing (NGS). dPCR enables absolute quantification even at very low DNA levels, while NGS can analyze fragmentation patterns, copy number

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variations, and epigenetic signatures. Recent studies have shown that NGS-based approaches can achieve near-perfect accuracy in distinguishing KNF patients from healthy individuals, opening opportunities for effective large-scale screening programs.

In addition to its high accuracy, EBV-ctDNA testing is noninvasive. Unlike tissue biopsies, which are painful and carry a risk of complications, or radiological imaging, which can be expensive and sometimes ambiguous, ctDNA testing requires only a blood sample. This makes it a safe, simple, and repeatable method for long-term monitoring as well as large-scale population screening.

However, several challenges must be addressed before EBV-ctDNA can be widely implemented. One major issue is the variation in cutoff values across studies for instance, 500 copies/mL in one study versus 1,000 copies/mL in another which complicates direct comparison of results. Preanalytical factors such as blood collection tube type, storage conditions, and DNA extraction methods also significantly affect the final outcomes. To minimize the risk of false positives caused by latent EBV infection, a two-step screening approach is recommended: initial testing with qPCR followed by confirmation using dPCR or NGS.

With all its advantages, EBV-ctDNA holds tremendous diagnostic potential and could transform the detection of KNF. Its high sensitivity, early-stage detection capability, noninvasive nature, and compatibility with advanced technologies make it superior to conventional methods. If technical and standardization challenges can be overcome, this biomarker could become a routine component of KNF screening and diagnosis, ultimately helping to significantly reduce the disease burden in the future.

The Role of Prognostic and Therapeutic Monitoring

EBV-ctDNA is not only useful as a diagnostic tool but also has prognostic value and an important role in therapeutic monitoring. As a biomarker, ctDNA can predict disease progression, assess therapeutic effectiveness, detect relapse early, and assist in personalizing treatment plans. Its main advantage lies in its noninvasive nature and its ability to reflect the tumor's biological state in real time, offering clear benefits over conventional modalities such as imaging or histopathology.

Several studies have demonstrated that pre-treatment EBV-ctDNA levels are strongly correlated with tumor stage and burden. Patients with high ctDNA levels are generally in advanced stages or have metastases, while low levels are more common in early stages. These findings establish EBV-ctDNA as a valuable risk stratification tool that helps clinicians distinguish between high-risk and low-risk patients. Such information is crucial

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for determining the optimal intensity of therapy from the outset.

During treatment, changes in EBV-ctDNA levels provide faster information than radiological imaging. Patients who respond to radiotherapy or chemoradiotherapy typically show a significant decrease in ctDNA levels within a few weeks. In contrast, patients who do not respond maintain high or rising ctDNA levels, even when imaging shows no visible change. Thus, EBV-ctDNA functions as a biological compass, enabling physicians to assess treatment efficacy more quickly and accurately.

Another major advantage is its ability to detect recurrence at an early stage. Elevated ctDNA levels often appear months before imaging can confirm new lesions. This early detection allows timely intervention, such as initiating salvage therapy, thereby increasing the likelihood of prolonged survival for patients.

Post-therapy EBV-ctDNA status also shows a strong correlation with long-term outcomes. Patients who achieve ctDNA negativity after treatment have a better prognosis, with higher overall survival, progression-free survival, and disease-free survival rates. In contrast, patients with positive ctDNA results face a higher risk of relapse or death. This finding opens the door to personalized follow-up strategies: patients with negative ctDNA results can be monitored at longer intervals, while those with positive results require closer and more intensive surveillance.

EBV-ctDNA testing also contributes to the efficient use of healthcare resources. Advanced radiological modalities such as PET-CT are expensive and expose patients to radiation, whereas ctDNA testing is relatively inexpensive, safe, and suitable for repeated use. By utilizing ctDNA as a primary monitoring tool, imaging can be reserved for patients with abnormal ctDNA results, thereby optimizing healthcare resource allocation.

In summary, the prognostic and monitoring value of EBV-ctDNA is substantial. This biomarker can predict outcomes, assess therapeutic responses faster than imaging, detect relapses early, and enable personalized therapy. If technical and standardization challenges can be addressed, EBV-ctDNA has the potential to become a key component in the implementation of precision oncology for KNF.

Comparison and Development of ctDNA Methods with Other Methods

The clinical value of EBV-ctDNA in KNF is highly dependent on the detection technology used. The three main methods currently dominating the field are quantitative PCR (qPCR), digital PCR (dPCR), and next-generation sequencing (NGS).

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qPCR is the earliest and most widely used method. Its advantages include low cost, broad availability, and rapid analysis. qPCR is particularly suitable for large-scale population screening, especially in developing countries. However, its sensitivity decreases when DNA levels are low, making it less ideal for early detection or monitoring minimal residual disease. Additionally, qPCR results are less consistent across laboratories due to variations in primers, operational standards, and cutoff values.

These limitations have driven the adoption of dPCR, which partitions the sample into thousands of reactions so that amplification occurs independently. dPCR provides absolute quantification and high sensitivity, allowing the detection of only a few copies of DNA. This makes it superior for long-term monitoring and relapse detection. Its drawbacks, however, include high costs and limited infrastructure availability.

NGS represents the next major advancement. This technology not only quantifies DNA but also analyzes fragmentation patterns, copy number variations, and epigenetic signatures. With its comprehensive data output, NGS enables recurrence prediction and early-stage detection with higher accuracy than qPCR. Nevertheless, its limitations include high cost, the need for advanced infrastructure, and specialized bioinformatics expertise. Currently, its use remains confined to major research institutions.

Globally, the choice of method is influenced by resource availability. In developing countries, qPCR remains the primary option; dPCR is increasingly used in countries with moderate technological capacity; while NGS is mostly applied in academic and research centers. A combined approach initial screening with qPCR, confirmation with dPCR, and in-depth analysis with NGS represents a practical and balanced strategy.

The evolution of these detection methods reflects the rapid progress of molecular oncology. As technological costs continue to decrease and integration with artificial intelligence advances, the future of EBV-ctDNA detection is expected to become increasingly accurate, rapid, and clinically applicable.

Combination of Biomarkers and Multi-omics Approach

Although EBV-ctDNA is a powerful biomarker, no single marker can fully capture the complexity of cancer. Therefore, a multi-omics approach that combines EBV-ctDNA with other biomarkers is gaining traction.

The integration of EBV-ctDNA with inflammatory markers such as IL-6 and VEGF has been extensively studied. EBV-ctDNA reflects tumor presence, while inflammatory markers reflect the tumor microenvironment. Combining these markers enhances the accuracy of predicting therapeutic response and disease progression.

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In addition, fragmentomics the analysis of DNA fragmentation patterns adds a new dimension to molecular diagnostics. DNA derived from cancer cells typically exhibits distinctive fragmentation patterns that differ from those of normal DNA. Integrating fragmentation analysis with ctDNA testing has been shown to improve the ability to distinguish KNF patients from healthy individuals who carry only latent EBV infections.

Other approaches include epigenetic analysis, particularly the study of DNA methylation patterns. Abnormal methylation in certain genes is a hallmark of cancer. When combined with ctDNA analysis, methylation profiling enhances both diagnostic and prognostic accuracy.

The multi-omics framework also extends to RNA and protein analysis. EBV-derived microRNAs, such as miR-BARTs, can serve as additional biomarkers, while metabolomics provides insights into the metabolic state of tumors. Integrating data across these biomolecular layers enables a more comprehensive understanding of the disease and opens new opportunities for personalized therapy.

With the support of advanced bioinformatics and artificial intelligence technologies, complex multi-omics data can be analyzed simultaneously to generate highly accurate predictive models. The future of precision oncology will likely depend on this type of integrated, multi-omics approach.

Clinical Implementation Challenges

Although the scientific evidence supporting EBV-ctDNA is very strong, its implementation in daily clinical practice still faces many challenges. The main issues include variations in cutoff values between studies, population heterogeneity, pre-analytical factors, high costs, and the lack of international standards.

Variation in cutoff thresholds makes it difficult to compare results across studies. Population heterogeneity also plays a significant role, as the prevalence of NPC and EBV infection patterns differ between regions. Pre-analytical variables, such as the type of blood collection tube and storage conditions, greatly influence test outcomes. Meanwhile, the high costs of advanced technologies like digital PCR (dPCR) and next-generation sequencing (NGS) present serious obstacles in developing countries.

Beyond technical limitations, social and ethical considerations must also be addressed. A positive result in an asymptomatic individual could cause anxiety, stigma, or even unnecessary medical interventions. Furthermore, limited laboratory infrastructure in many endemic regions contributes to disparities in access to diagnostic testing.

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To overcome these barriers, comprehensive efforts are needed standardization of methods, cross-population validation, cost subsidies, and public education so that the potential benefits of EBV-ctDNA can be realized optimally.

Clinical Implications and Future Research Directions

EBV ctDNA has wide-ranging clinical implications. As a screening tool, it can detect early-stage cases, thereby reducing NPC mortality in endemic regions. In therapy monitoring, ctDNA provides faster information than imaging methods, enabling earlier treatment adjustments. During follow-up, these biomarkers support personalized surveillance strategies, contributing to more efficient use of healthcare resources.

Future research directions include large-scale prospective clinical trials to confirm the benefits of ctDNA-based screening, establishment of universal cutoff values, standardization of pre-analytical procedures, and integration with multi-omics approaches. Furthermore, ctDNA analysis offers new opportunities to deepen the understanding of NPC pathogenesis and to identify novel therapeutic targets.

If technical, social, and economic challenges can be addressed, EBV ctDNA holds the potential to transform the management of NPC. From a cancer that is often detected late, NPC could become a disease that is more easily identified at an early stage and treated more effectively, leading to a significant reduction in mortality.

CONCLUSION

EBV-ctDNA represents a highly accurate, non-invasive biomarker with significant potential for the diagnosis, prognosis, and monitoring of nasopharyngeal carcinoma (NPC). The advancement of detection technologies such as digital PCR and next-generation sequencing (NGS) further strengthens its feasibility for routine clinical application, particularly in endemic regions. The emergence of ultra-sensitive NGS platforms and the optimization of pre-analytical processes are expected to enable large-scale population screening with high precision, thereby facilitating early-stage diagnosis, improving clinical outcomes, and reducing mortality rates.

The integration of ctDNA analysis into clinical workflows also opens new avenues for the detection of minimal residual disease, real-time monitoring of therapeutic responses, and more accurate risk stratification. Future research priorities include conducting large-scale randomized clinical trials to confirm the survival benefits of EBV ctDNA-based screening, developing universal cutoff standards for consistent interpretation, and integrating ctDNA with cost-effective multi-omics panels.

Collaborative regional efforts across Southeast Asia are essential, considering the high NPC burden in this area. With strong

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research networks and clear regulatory frameworks, EBV ctDNA has the potential to become a standard clinical biomarker enabling personalized therapy, optimizing resource allocation, and ultimately lowering NPC-related mortality.

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