REVIEW ARTICLE

Epstein–Barr Virus Latent Membrane Protein-1 (EBV LMP-1) in Nasopharyngeal Carcinoma: Immune Correlates and Potential as A Clinical Outcome Biomarker

Jajah Fachiroh[1,*], Fitriya Ramadhani[1], Nayaka Bagus Wahyu Agung Hertanto[2], Dewi Kartikawati Paramita[1]

[1]Department of Histology and Cell Biology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Jl. Farmako, Sekip Utara, Yogyakarta 55281, Indonesia
[2]School of Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Jl. Farmako, Sekip Utara, Yogyakarta 55281, Indonesia

*Corresponding author. Email: jajahfachiroh@ugm.ac.id

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Abstract

In endemic populations, nasopharyngeal carcinoma (NPC) is associated with epstein-barr virus (EBV) infection, with latent membrane-1 (LMP-1) playing a major role as an oncoprotein. Despite this well-established biological role, the clinical use of LMP-1 remains limited; therefore this review aimed to discuss the potential use of LMP-1 as clinical biomarker. Based on systematic searching results in two major biomedical journal databases, in this review, only a small number of studies that evaluated LMP-1 as a clinical outcome. Studies examining the relationship between LMP-1 and its related biomarkers in clinical samples were particularly scarce. By mapping the existing literature, this scoping review highlights mechanistic linking of LMP-1 to specific biomarker, such as interferon gamma (IFN-γ), leukemia inhibitory factor (LIF), chemokine (C-X-C motif) ligand 9 (CXCL9), programmed cell death ligand-1 (PDL-1), and had a positive regulatory loop with EBV-encoded small RNA (EBERs) serving to amplify inflammatory signals that facilitates NPC progression. A clear gap between evidence mechanism of LMP-1 and clinical research practice was observed. This may related to several reasons, including low detectability, a heterogeneous expression in tumor tissue; hence shifted into surrogated biomarkers that reflected LMP-1 signalling than the protein itself. Future studies should focus on combining LMP-1 with related inflammatory or immune markers, and conducting well-designed clinical studies to better define the potential role of LMP-1 within clinically relevant biomarker strategies for NPC.

KEYWORDS: oncoprotein, stage, malignancy of nasopharynx, prognosis, survival, inflammation

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Introduction

Nasopharyngeal carcinoma (NPC) is a form of squamous cell carcinoma (SCC) that arises from the nasopharyngeal epithelium.(1) It is endemic to parts of Asia and Africa. According to the Global Cancer Observatory, approximately 120,434 new cases of NPC were reported globally in 2022, with more than 80% of the new cases reported in Asia, while 8.9% of cases are found in Africa.(2) The World Health Organization (WHO) classifies NPC into three histopathological subtypes, including keratinizing SCC, non-keratinizing SCC, and basaloid SCC. Non-keratinizing NPC is further classified into differentiated and undifferentiated tumors.(3) In its regions of endemicity, most NPC cases are non-keratinizing SCC (WHO type 3) and are predominantly associated with Epstein-Barr virus (EBV) infection.(4-6) Therefore, EBV infection is believed to be involved in the pathogenesis of NPC.

EBV is a human oncogenic virus that causes various types of cancer, including NPC, Burkitt's lymphoma, Hodgkin's lymphoma, and EBV-associated gastric

carcinoma.(7,8) In NPC, the EBV infection is influenced by factors such as host, environment, genetic and epigenetic, lifestyle including smoking habits, thereby promoting to malignancies.(6,9,10) This virus is transmitted by using saliva to the mucosa of the Waldeyer's ring. Infection of the epithelial cells become the primary vehicle to further infecting the underlying B lymphocytes. Once infection established, EBV can undergo lytic replication or latent infection depending on different circumstances. However, the establishment of latent infection by EBV has been considered as distinctive feature for malignant transformation.(7)

During the latent stage of EBV, several genes that may be play role in oncogenic role are expressed. They were latent membrane proteins (LMPs), EBV-encoded nuclear antigens (EBNAs), BamH1-A region rightward transcript (BARTs) RNAs, and EBV-encoded small RNAs (EBERs).(7,8) Among those EBV-encoded gene products expressed in NPC, LMP-1 has been well-defined as a potent oncogenic protein, which is closely involved in NPC pathogenesis. LMP-1 belongs to the tumor necrosis factor receptor superfamily and is an integral membrane protein.(11) LMP-1 contributes to NPC development and progression through multiple mechanisms.

Through activation of the signal transducer and activator of transcription 3 (STAT3), nuclear factor-kappaB (NF-κB), and other signaling pathways, LMP-1 induces the expression of a variety of inflammatory cytokines that involved in cancer cell growth, angiogenesis, epithelial-mesenchymal transition (EMT), migration, invasion, and chemotaxis of immune cells such as natural killer (NK) cells, macrophage, neutrophil, lymphocytes, myeloid derived suppressor cells (MDSC), and Regulatory T-cells (Tregs) to the tumor site.(11) Tregs through the secretion of immunosuppressive cytokines such as transforming growth factor (TGF)-β and interleukin (IL)-10, as well as upregulation of programmed death-ligand 1 (PDL-1) and programmed cell death protein 1 (PD-1) by LMP-1. LMP-1-containing exosomes may as well be released into the tumor microenvironment (TME) to induce the expansion of Tregs, MDSCs and tumor-associated macrophages (TAMs), creating an immunosuppressive TME that promotes tumor evasion.(11,12)

Reports showed that NPC with LMP-1 positive status tends to be aggressive and easily invade lymph nodes.(8) NPC with LMP-1 positive showed a low survival rate; thus, the detection of LMP-1 in NPC tumors is often associated with a poor prognosis.(13-15) On the other hand, NPC patients with negative LMP-1 status are expected to have a better prognosis. So far, LMP-1 status in tumors has not been used in the management of NPC in endemic areas, including as biomarker for prognosis, predictive or survival. With regards to the work of LMP-1 to modulate immune response, several cytokines have been associated either with the work of LMP-1 and severity of NPC, which merit to visit as potential targets for biomarkers and understanding of LMP-1 role in severity and survival of NPC.

This review focused on the use of LMP-1 and or cytokines as biomarkers in clinical settings, including type of specimens used, point of clinical determination and impact of its use for tertiary prevention. The gap in the use of LMP-1 as tumor marker and subsequently other biomarkers reflecting the burden of treatment will be further discussed.

Methods

Scoping Literature Review Searching Strategy

The literature for established scoping review was collected using two major electronic bases *i.e.*, PubMed and Scopus with range published from 2011 to 2025. The search of article focused on LMP-1-EBV in nasopharyngeal carcinoma to predict cancer severity and survival. Thus, the keywords and search terms consisting of "nasopharyngeal cancer", "Epstein-Barr virus", "latent membrane protein 1", "cytokine", "plasma", "tissue", and variations thereof. Boolean operators were used to refine the search results, and the final keywords obtained are listed in Table 1.

Eligibility Criteria

Relevant articles included in this study were selected according to the Population, Intervention, Comparator, Outcome, and Study Design (PICOS) criteria. The PICOS framework employed were as follows: studies involving patients with a confirmed NPC diagnosis (P); the articles were related with investigating plasma or tissue biomarkers for cancer prognosis, predictive, and survival (I); studies comparing the effectiveness of different biomarkers (C); the articles had outcomes related to biomarker clinical utility (O); and studies limited to original research articles (S). Exclusion criteria included studies unrelated to NPC or based on animal or *in vitro* models.

Study Selection and Data Extraction

All the retrieved articles were compiled and saved in Google Drive. Next, the selection process involved screening the titles and abstracts to identify potentially relevant articles according to inclusion and exclusion criteria. The

Table 1. The keywords and terms utilized for scoping review article search related with EBV LMP-1 in NPC.

PubMed	Scopus
((((Nasopharyngeal Cancer[Title/Abstract]) OR (NPC[Title/Abstract])) OR (Nasopharyngeal Neoplasia[Title/Abstract])) OR (Nasopharyngeal Neoplasma[Title/Abstract])) OR (Nasopharyngeal Carcinoma[Title/Abstract])	TITLE-ABS-KEY ("Nasopharyngeal Cancer" OR NPC OR "Nasopharyngeal Neoplasia" OR "Nasopharyngeal Neoplasma" OR "Nasopharyngeal Carcinoma")
AND	AND
(((Epstein-Barr Virus[Title/Abstract]) OR (EBV[Title/Abstract])) OR (Latent Membrane Protein 1[Title/Abstract])) OR (LMP1[Title/Abstract])	TITLE-ABS-KEY ("Epstein-Barr Virus" OR EBV OR "Latent Membrane Protein 1" OR LMP1)
AND	AND
(((((((((Cytokine[Title/Abstract]) OR (Interleukin[Title/Abstract])) OR (IL[Title/Abstract])) OR (Interferon[Title/Abstract])) OR (IFN[Title/Abstract])) OR (Tumor Necrosis Factor[Title/Abstract])) OR (TNF[Title/Abstract])) OR (Transforming Growth Factor Beta[Title/Abstract])) OR (TGF-β[Title/Abstract])) OR (Chemokine[Title/Abstract])	TITLE-ABS-KEY (Cytokine OR Interleukin OR IL OR Interferon OR IFN OR "Tumor Necrosis Factor" OR TNF OR "Transforming Growth Factor Beta" OR TGF-β OR Chemokine)
AND	AND
((Plasma[Title/Abstract]) OR (Serum[Title/Abstract])) OR (Tissue[Title/Abstract])	TITLE-ABS-KEY (Plasma OR Serum OR Tissue)

flowchart illustrated in Figure 1. Next, selected articles were independently extracted by two reviewers (JF and NH) and confirmed by the other authors (FR and DK) through providing agreement or disagreement notes. Later, a standard table was created from extracted data was created. The table classified into two sub-categories, including: a) study characteristics (first author and year of publication, study design, study population, and source of samples); b) study outcome (first author and year of publication input, biomarker measured, detection methods, outcome, and presence/absent of LMP-1).

Results

Study Characteristics and Outcomes

After screening a total of 214 articles from Website PubMed and Scopus, 47 duplicate articles were removed and 133 abstracts was excluded for not fulfilling the inclusion criteria (Figure 1). We obtained a total of 28 comprehensive full-text original articles.

Most of the study designs that emerged were retrospective study (n=17), followed by experimental study using *in vitro* and/or *in vivo* (n=9). Four studies using case-control study approach, two which were accompanied with nested case-control study design. Three studies used prospective study design, and one was using cross-sectional study design (Table 1).

Tissue was the most abundant sample used, with a total of 22 articles. Serum was the second most utilized source (n=13), followed by plasma (n=12), cell line (n=9), and peripheral mononuclear cell (PBMC) (n=2). The peripheral blood leukocytes included in one article (Table 2).

The various types of biomarkers, detection methods used, and outcome were shown in Table 3. Not all biomarkers were obviously described in the article; hence, we summarized the final profile of categorized biomarkers in Figure 2. Cytokines and chemokines were most observed (n=19), followed by EMT-related protein (n=9), growth factors (n=8), other markers (n=7), EBV-genes or protein-related markers (n=6), receptors and immune-checkpoint

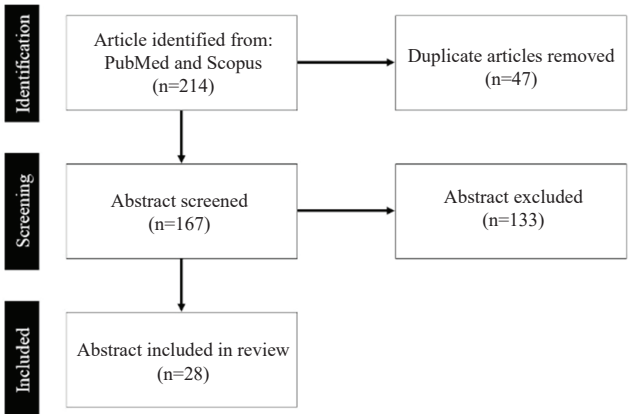

Figure 1. Selection of publication process that includes identification, screening and full paper inclusion.

Table 2. Study characteristic comprised of 28 full articles retrieved for the study. (cont.)

No.	References	Study Design	Study Population	Source of Samples
1.	Li *et al.* (16)	• Retrospective • Experimental (*in vitro*)	• Healthy controls (n=215) • NPC patients (n=232) • NPC cell lines CNE1, C6661, and MRC5	• Serum • Tissue • Cell line
2.	Liou *et al.* (17)	• Retrospective • Prospective	• NPC tissue samples (n=50) • Newly diagnosed NPC patients (n=10) • NPC tissue samples (n=50)	• Serum • Tissue
3.	Xing *et al.* (18)	• Case-control • Nested case-control	• 190 NPC patients (n=190) • Cancer-free with positive VCA-IgA (VP) patients (n=72) • Normal with negative VCA-IgA (VN) patients (n=219) • NPC patients before and after radiotherapy (n=10) • Patients with NPC and different types of cancer for preliminary screening (n=20)	• Plasma • Serum • Tissue
4.	Wang *et al.* (19)	• Retrospective	• NPC biopsy samples patients (n=45) • 45 chronic nasopharyngitis (n=45)	• Tissue
5.	Ruan *et al.* (20)	• Retrospective	• NPC patients (n=37) • Healthy control patients (n=40)	• Plasma
6.	Xue *et al.* (21)	• Retrospective • Experimental (*in vitro*)	• NPC patients (n=146) • Healthy patients with positive IgAEBV (n=108) • Healthy control patients with EBV VCAIga negative (VN) (n=127) • Culture cells (Immortalized nasopharyngeal epithelial cell lines (NPEC1, NPEC2, N5Tert) and NPC cell lines (SUNE2, CNE1, S18, S26, 58F, and 610B)	• Plasma • Tissue • Cell line
7.	Yang *et al.* (22)	• Case-control • Nested case-control	• NPC patients (n=150) and controls (n=150) (case-control) • NPC patients (n=60) and controls (n=120) (nested case-control)	• Serum
8.	Mao *et al.* (23)	• Prospective	• NPC patients (n=124) • Healthy donor patients with VCA-IgA-positive (n=132) • Normal subjects with VCA-IgA-negative (n=140)	• Plasma • Tissue
9.	Huang *et al.* (24)	• Retrospective • Experimental (*in vitro* and *in vivo*)	• Nondistant metastatic NPC patients (n=580) • Cell culture (CNE2, HNE1, HK1), and EBV+NPC cells result of coculturing parental cell lines with surface IgG crosslinked EGFPneo'EBVinfected Akata cells • Humanized mouse model (NOD/SCID mice)	• Serum • Tissue • Cell line
10.	Feng *et al.* (25)	• Retrospective • Experimental	• NPC patients (n=172) • Healthy volunteers (n=138) • NPC cell lines CNE1 and HK1,3 poorly differentiated NPC cell lines	• Plasma • Serum • Tissue • Cell line
11.	Al-Kholy *et al.* (26)	• Prospective	• Patients with biopsy-confirmed NPC who received chemoradiotherapy (n=35) • Healthy volunteers as control (n=10)	• Serum • Plasma
12.	Wang *et al.* (27)	• Prospective	• Metastatic NPC patients (n=178) • Patients with local recurrence (n=28) • Control volunteers (n=20)	• Plasma • Tissue
13.	Savitri and Haryana (28)	• Prospective	• NPC patients (n=39) • Healthy controls (n=29)	• Plasma
14.	Hsin *et al.* (29)	• Prospective	• 291 NPC patients (n=291) • Healthy patients (n=231)	• Serum • Tissue
15.	Zhang *et al.* (30)	• Retrospective	• Normal nasopharyngeal epithelia (NPEs) patients (n=7) • NPC patients (n=760)	• Tissue
16.	Chang *et al.* (31)	• Prospective	• 132 NPC patients (n=132) • 169 Healthy patients (n=169) • Chronic rhinosinusitis (CRS) patients (n=32)	• Plasma • Tissue
17.	Budiani *et al.* (32)	• Cross sectional	• EBV-positive NPC patients (n=32) • EBV-positive IM patients (n=5) • EBV-seronegative patients as control (n=10)	• Serum • PBMC

(cont.) **Table 2. Study characteristic comprised of 28 full articles retrieved for the study.**

No.	References	Study Design	Study Population	Source of Samples
18.	Mahajan *et al.* (33)	• Prospective • Retrospective	• Cohort 1 : NPC patients (n=24) • Cohort 2 : NPC patients (n=28)	• Plasma
19.	Zhang *et al.* (34)	• Retrospective • Experimental (*in vitro* and *in vivo*)	• NPC patients (n=106) • NPC cell lines S18 and 58F • 5-weeks old male nude mice	• Serum • Plasma • Tissue • Cell line
20.	Li *et al.* (35)	• Retrospective	• Stage III NPC patients (n=562) (Underwent IMRT and cumulative cisplatin dose ≥200mg/m^2)	• Serum
21.	Li *et al.* (36)	• Retrospective • Experimental (*in vitro* and *in vivo*)	• NPC patients (n=502) • Cell lines C6661, NPCB13, HK1 • NOD/SCID mice	• Plasma • Tissue • Cell line
22.	Muraro *et al.* (37)	• Retrospective	• Consecutive EBV-positive UNPC patients (n=63)	• PBMC • Tissue
23.	Niu *et al.* (38)	• Case-control	• NPC patients (n=593) • Cancer-free controls (n=480)	• Peripheral blood • Tissue
24.	Li *et al.* (39)	• Case-control	• NPC patients (n=102) • Chronic nasopharyngitis as controls (n=80)	• Tissue
25.	Li *et al.* (40)	• Retrospective • Experimental (*in vitro* and *in vivo*)	• 60 NPC patients (n=60) • Nontumor tissues (n=15) • NPC cell lines (HNE2 and C6661), human monocytic cell line • Female nude mice, Pathogenfree female C57BL/6 mice (wildtype or TLR3 knockout)	• Tissue • Cell line
26.	Zhang *et al.* (41)	• Retrospective	• Retrospective	• Tissue
27.	Fang *et al.* (42)	• Retrospective • Experimental (*in vitro*)	• Consecutive NPC patients (n=34) • NPC patients (n=139) • NPC cell lines, including EBV-negative lines (610B, SUNE1, 58F, CNE1, CNE2, TWO3, HNE1) and an EBV-positive line (C6661)	• Serum • Tissue • Cell line
28.	Liu *et al.* (43)	• Retrospective • Experimental (*in vitro* and *in vivo*)	• Pretreatment NPC patients (n=161) • Healthy donor patients (n=28) • NPC patients (n=106) • NPC cell lines C6661, CNE1, TW01, and TW06 • NOD/SCID mice	• Serum • Tissue • Cell line

(n=5), immune cells and matrix metalloproteinases (MMPs) (n=3). All biomarkers were detected with diverse detection methods, including polymerase chain reaction (PCRs) *e.g.* reverse transcriptase (RT)-PCR, realtime quantitative (RT-q)PCR (n=21), immunohistochemistry (IHC) (n=16), enzyme-linked immunosorbent assay (ELISA) (n=13), Western-blot detection (WB) (n=9), cytokine array (n=7), immunofluorescence (IF) (n=5), flow cytometry or multiplex assay (n=4), immunoblotting (n=2), and detection methods other than the already mentioned (n=35).

Biomarkers observed were proposed for different roles in patient care. Most of the articles mentioned prognostic indicators and correlation with other biomarkers with 17 and 14 studies respectively. Seven studies observed diagnostic value, six studies analyzed molecular mechanisms, and the remaining of three studies using NPC biomarker expression, predictive indicator, or NPC risk biomarkers approach to describe the outcome of NPC biomarkers impact. Particularly for LMP-1, only 4 of 28 articles included detection of LMP-1, and others were absent (Table 3).

NPC Biomarkers and Its Relationship with Emerging Roles

A. Immune components

Within this review, we discuss several immune components related with reported articles using the following classifications: a) Cytokines (Interleukins (ILs), Tumor Necrosis Factor Alpha (TNF-α), Interferon Gamma (IFN-γ), and other types of cytokines), b) Chemokines, c) Growth factors, d) Immune checkpoint, e) Immune cells, f) Receptors, and g) MMPs.

a) Cytokines

Various ILs have been reported among studies of nasopharyngeal cancers, with pro-inflammatory IL-6 being

the most examined (n=5). In clinical studies, the IL-6 had a high expression in NPC patients detected using serum (n=2), plasma (n=3), or tissue samples (n=3). Elevated IL-6 was associated with advanced stages of disease, EBV-DNA load, a predictive indicator, and treatment response. (20,26,31,34,40) The clinical staging and EBV DNA plasma

Table 3. Summary of study outcome. (cont.)

No.	References	Biomarkers	Detection Methods	Proposed Roles	Present/Absent of LMP-1 Measurement
1.	Li *et al.* (16)	• MMP-3	• Cytokine array • IHC • RT-PCR • WB • ELISA • MMP-fluoresence activated substrates	• Diagnostic value • Interaction with other biomarkers • NPC expression biomarker	Absent
2.	Liou *et al.* (17)	• NK Cell in TIL • PD1 • Tim-3 • IL-18	• IHC • Flowcytometry • RT-PCR • Multiplex immunoassay	• Prognostic indicator • NPC expression biomarker	Absent
3.	Xing *et al.* (18)	• MIC-1	• IHC • Flowcytometry • RT-PCR • Multiplex immunoassay	• Diagnostic value • Treatment role • Interaction with other biomarkers • NPC expression biomarker	Absent
4.	Wang *et al.* (19)	• IL-17A	• IHC • RT-PCR • WB	• Prognostic indicator • NPC expression biomarker	Absent
5.	Ruan *et al.* (20)	• BTLA • GITR • HVEM • LAG-3 • sPD-1 • sPDL-1 • sPDL-2 • CD28 • CD80 • CD137 • CD27 • CD152 • IFN-γ • IL-12p70 • IL-2 • IL-5 • IL-6 • TNF-α • IL-10 • IL-17A • IL-22 • IL-27 • IL-9 • EBV-DNA	• Luminex • RT-qPCR	• Interaction with other biomarkers • Diagnostic value • Prognostic indicator • Therapeutic response	Absent
6.	Xue *et al.* (21)	• 174 soluble cytokines • MIF • CCL3	• Cytokine array • RT-PCR • WB • ELISA • IHC • Immunoenzymatic assay	• Interaction with other biomarkers • Diagnostic value	Absent

(cont.) **Table 3. Summary of study outcome.** (cont.)

No.	References	Biomarkers	Detection Methods	Proposed Roles	Present/Absent of LMP-1 Measurement
7.	Yang *et al.* (22)	• 33 inflammatory cytokines	• Multiplex assay • ELISA	• NPC risk biomarker	Absent
8.	Mao *et al.* (23)	• CCL27	• ELISA • IHC	• Interaction with other biomarkers • NPC expression biomarker • Diagnostic value	Absent
9.	Huang *et al.* (24)	• CCL18+ of TAM	• Double immunostaining • Cytokine array • ELISA • Transwell cocultured system • NF-κB activation in NPC • Macrophage morphological changes • NPC cell motility • Tumor volume measurement • Metastatic colonies count in • Human hypoxanthine phosphorribosyl transferase (HPRT) mRNA expression • Double immunostaining	• Interaction with other markers • Molecluar mechanism • Diagnostic value • Prognostic indicator • NPC biomarker expression	Absent
10.	Feng *et al.* (25)	• IGF-1 • IGF-2 • IGF-1SR • IGFBP-1 • IGFBP-2 • IGFBP-3 • IGFBP-4 • IGFBP-6	• Cytokine array • RT-qPCR • WB • IHC • ELISA	• Prognostic indicator • NPC expression biomarker	Absent
11.	Al-Kholy *et al.* (26)	• IL-1β • IL-6 • TNF-α • EBV DNA	• PCR • ELISA • PCR	• Treatment role • Predictive indicator	Absent
12.	Wang *et al.* (27)	• CXCL10/IP10 • CCL2/MCP1 • EBV DNA	• Cytokine array • RT-qPCR • ELISA • IHC • In situ TUNEL assay	• Prognostic indicator	Absent
13.	Savitri and Haryana (28)	• IgA (VCA-p-18+EBNA1) • IL-8 • IL-10	• ELISA • RT-PCR	• Prognostic indicator	Absent
14.	Hsin *et al.* (29)	• CXCL9 • **LMP-1** • EBV DNA	• RT-PCR • PCR • WB • IHC • ELISA	• Interaction with other biomarker • Prognostic indicator • NPC biomarker expression • Interaction with other biomarker • Prognostic indicator	Present
15.	Zhang *et al.* (30)	• ALK1 • TGF-βR2	• RT-qPCR • Microarray • IHC	• Interaction with other biomarkers • Prognostic indicator • NPC biomarker expression	Absent
16.	Chang *et al.* (31)	• IL-2 • IL-4 • IL-6 • IL-8 • IL-10 • IP-10 • CCL4	• Multiplexed suspension array • Single plex assay • ELISA • IF • RT-qPCR	• Interaction with other biomarkers • Prognostic indicator • NPC biomarker expression • Diagnostic value	Absent

(cont.) **Table 3. Summary of study outcome.** (cont.)

No.	References	Biomarkers	Detection Methods	Proposed Roles	Present/Absent of LMP-1 Measurement
		• TNF-α • VEGF • SCF • MIP-3α • MIF • MIG • EBV VCA IgA • EBV DNA			
17.	Budiani *et al.* (32)	• IL-4 • IFN-γ	• ELISA • qPCR colorimetric dot blot • ELISA	• NPC biomarker expression	Absent
18.	Mahajan *et al.* (33)	• Circulating T-cell • CCL2 • CCL3 • CCL4 • CCL5 • CCL8 • CCL11 • CCL13 • CCL14 • CCL15 • CCL17 • CCL22 • CCL23 • CXCL9 • CXCL10 • CXCL11 • CXCL13 • BamHIW gene of EBV (EBV DNA titers)	• RT-qPCR • Flowcytometry	• Predictive indicator • Treatment response • Interaction with other biomarkers • Molecular mechanism	Absent
19.	Zhang *et al.* (34)	• Adiponectin • MMP-2 • MMP-9 • Snail • Ecadherin • Ncadherin • Slug • Claudin1 • Vimentin • STAT3 • p65 • IκBa • NF-κB • RLTK • Leptin • IL-6 • TNF-α • AdipoRon • Luciferase	• Luminex assay • Relative migration rates (wound healing assay) • Transwell inserts • Ibo-FECT CP transfection reagent • RT-qPCR • Immunoblotting • Dual-Luciferase Reporter Assay	• Prognostic indicators • Interaction with other biomarker • Molecular mechanism • NPC biomarker expression • NPC risk biomarker	Absent
20.	Li *et al.* (35)	• Apolipoprotein AI (Apo AI) • HDLC • NAR • MAR	• Automated blood analyzer • Automatic biochemical analyzer	• Prognostic indicator	Absent

(cont.) **Table 3. Summary of study outcome.** (cont.)

No.	References	Biomarkers	Detection Methods	Proposed Roles	Present/Absent of LMP-1 Measurement
		• LAR • PAR • NHR • MHR • LHR • PHR • EBV DNA			
21.	Li *et al.* (36)	• EGFR blockers • CDK4/6 inhibitors • 102 cytokines • EGFR • EGFRp • ERK1/2p • Tubulin • RB1 • RBp • E2F1 • CDK4	• Cytokine array • High throughput sequencing • RT-PCR • WB	• Prognostic indicator • Treatment response • Interaction with other biomarker • Molecular mechanism • NPC biomarker expression	Absent
22.	Muraro *et al.* (37)	• BARF-1 • CD8 • IFN-γ • IDO • PDL-1 • PD-1 • FoxP3 intron 1 methylation	• RT-qPCR • Methylation specific PCR • IFN-γ ELISPOT assay	• Prognostic indicator • NPC biomarker expression	Absent
23.	Niu *et al.* (38)	• rs1024611 • MCP-1	• PCR RFLP • RT-qPCR • GTEx (v7) official website	• Interaction with other biomarker • Molecular mechanism • NPC biomarker expression • NPC risk biomarker	Absent
24.	Li *et al.* (39)	• SDF-1 • CXCR4	• IHC • RT-qPCR • WB	• NPC biomarker expression • Prognostic value	Absent
25.	Li *et al.* (40)	• EBV-encoded RNAs (EBERs) • TLR-3 • **LMP-1** • TNF-α • IL-6 • IL-1α • CXCL8 • MCP-1 • MCSF	• Immunoblotting • Luciferase assay • Chromatin • Anchorage Independent Growth Assay • IHC • *In situ* Hybridization (ISH) • Tissue array • Transmission electron microscopy (TEM)	• Interaction with other biomarker • Molecular mechanism • Prognostic indicators	Present
26.	Zhang *et al.* (41)	• IL-35 • EBI3 • p53	• IHC	• NPC biomarker expression • Prognostic predictor	Absent
27.	Fang *et al.* (42)	• PDL-1 • **LMP-1** • IFN-γ	• qPCR • WB • IF • Flowcytometry • ELISA • IHC	• Interaction with other biomarker • Molecular mechanism • Prognostic indicators	Present

(cont.) **Table 3. Summary of study outcome.**

No.	References	Biomarkers	Detection Methods	Proposed Roles	Present/Absent of LMP-1 Measurement
28.	Liu *et al.* (43)	• Leukemia inhibitory factors (LIF) • 20 cytokines • **LMP-1** • mTOR • p70S6K • GSK3α/β • ERK1/2 • STAT3 • DDR proteins (ATM, p53, γH2AX, NBS1, CDC25C)	• Cytokine array • IHC • xCelligence realtime analyzer • EdU incorporation assays • WB • *In vivo* imaging system	• Predictive indicator • Treatment response • Prognostic indicators	Present

load showed a positive correlation with pre-treatment serum levels of IL-6, and negatively correlated with 2-years survival rate.(29) The regression analysis defined high pre-treatment IL-6 as a specific predictor for mortality (β=-0.529, t=3.584, p=0.001). Chemotherapy treatment significantly decreased the serum levels of IL-6 (p=0.0001). Similarly, a significant change of IL-6 plasma after treatment provision using Intensity-modulated radiotherapy (IMRT) ($p\leq$0.001).(20) In addition, a pre-clinical study stated that EBERs causing upregulation of IL-6 *in vitro*. The IL-6 is then activated by the NF-κB pathway via Toll-like Receptor-3 (TLR-3).(40)

IL-10, IL-8, IL-17A, IL-1α, and IL-1β were observed in two studies. All the ILs, excluding IL-1-α and IL-1β, showed high levels in NPC.(20,21,26,27,28,31,40). Most studies used blood plasma (n=6), followed by tissues (n=4), and serum (n=2). A previous study found that IL-8 and IL-10 had a positive correlation with viral load in NPC plasma.(28) A ratio of IL-8:IL-10 in pretreatment of NPC plasma greater than 1 suggested a poor prognosis and indicated disease progression. The higher levels of IL-8 in plasma also had worse prognosis for overall survival.(31) The 4-year overall survival rates for patient subgroups with lower levels of these markers were significantly better than those with higher levels. The IL-17A was other types of ILs showed poor prognosis as indicated by significantly shorter median survival in NPC patients (13.0 months) compared to IL-17A in negative NPC patients (21.0 months). Using tissue samples, higher IL-17A levels were associated with stage III + IV NPC, tumor volume ≥50 mm, hepatic envelope invasion, and cervical lymph node metastasis.

IL-1α and IL-1β are part of IL-1 family and bind to the same receptor, IL-1R1, which is expressed in many cell types. These two have been involved in various cancer development stages (tumorigenesis, cancer progression, metastasis), also in response against treatment.(44) IL-1α and IL-1β also present in the TME of NPC, together with other immune cells and cytokines to protect the cancer from host immune exposure.(45) A 33 inflammatory cytokines had been analyzed and showed level of IL-1α with NPCs (p<0.05) than control patients in case-control study, and this was associated with increasing NPC risk.(27,31) On the other hand, an increasing of IL-1α was obtained using *in vitro* transcribed EBER.(40) IL-1α frequently had an elevated expression in NPC causing tumor growth, $CD4^+$ T cells infiltration, and metastasis.(46) IL-1α and IL-1β can be synthesized spontaneously induced by EBV LMP-1 via NF-κB pathway, thus enhancing growth of epithelial cell line.(47) This result was aligned with previous study, indicating a positive regulatory loop between EBERs and LMP-1, with NF-κB acting as a key node, which amplifies inflammatory signals in EBV-infected epithelial cells.(40) However, IL-1A gene polymorphism is affected in reducing the secretion of serum IL-1α and gives an increased risk of NPC.(47) These diametrically opposed differences suggested why the IL-1α showed mixed results, hence required further study.

In other NPC treatment modalities, the serum IL-1β level was increased in post chemotherapy compared with pre-treatment of IL-1β (p=0.001).(27) Although the serum level of IL-1β is reported to have a positive correlation with survival rate, it had negative correlation with clinical staging and plasma EBV DNA viral load. Conversely, a reduced plasma IL-1β was observed post IMRT treatment (20), similar to previous study that further explained the anti-cancer action capacity of IL-1β in pro inflammatory reaction.(26) The use of IL-12p70, IL-22, and IL-5, IL-4, IL-18, and IL-7, were also reported.(17,20,21,33) Plasma IL12p70, IL-22, and IL-5 was higher in NPC patients compared to healthy controls ($p\leq$0.001). NPC Post IMRT

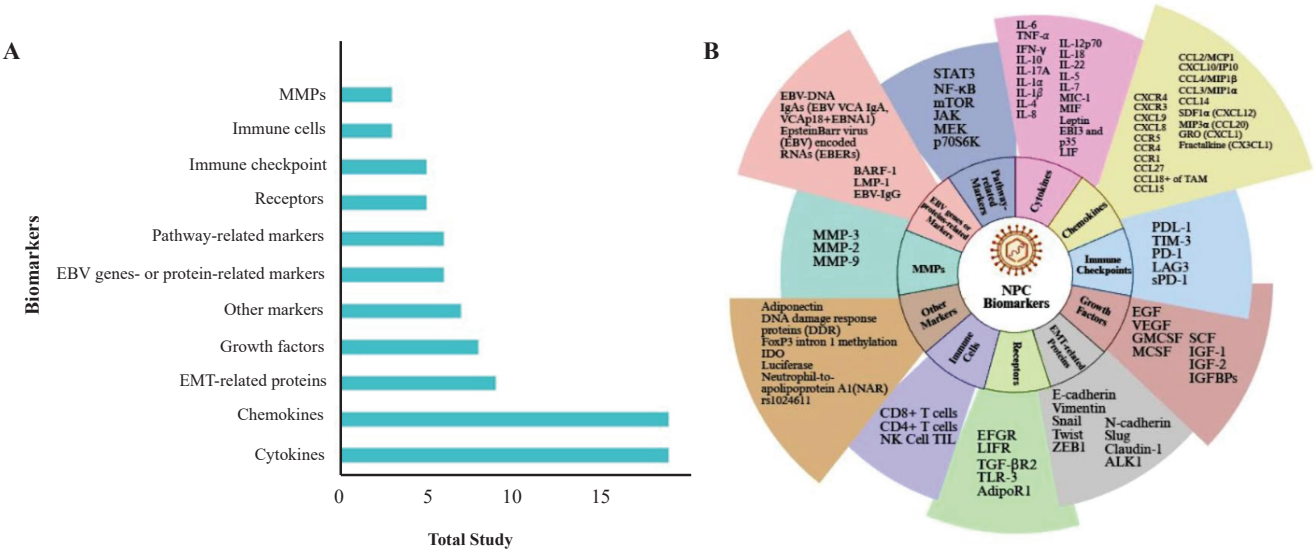

Figure 2. The biomarkers identified in 28 full articles reviewed in this study. A: categorized by biomarkers; B: details of biomarkers based on the assigned categories. (Image created using Biorender.com).

blood plasma of IL12p70, IL-22, and IL-5 showed decreased compared with pre-IMRT ($p \leq 0.001$). While expression of IL-8 in NPC tissue was higher compared to healthy nasopharynx, with no difference of serum IL-8 between the two groups.(17) The IL-8 induced expression of PD-1 on NK TIL cells in dose dependent manner. Higher serum and PBMC IL-4 showed to differentiate EBV positive NPC and infectious mononucleosis (IM) compared to EBV-negative controls ($p<0.05$).(17) Additionally, higher serum IL-7 was associated with decreased risk of NPC.(18) As IL-7 role in B-cell and T-cell development, it is suggested that IL-7 has anti-tumor effect.(48)

Beyond the interleukin group, TNF-α played a prominent role in the progression of NPC. Five studies had examined the TNF-α in NPC in serum, plasma, tissue and NPC cell line.(20,26,29,34,40) TNF-α can induce cellular invasion and migration of NPC cells and is involved in metastatic progression via NF-κB and STAT pathway.(34) Using *in vitro* and *in vivo*, the expression of EBERs led to upregulate the TNF-α through NF-κB pathway via TLR-3 activation, further activated macrophages, and creating a pro-tumorigenic microenvironment for tumor growth.(40)

Previous study demonstrated significantly elevated plasma TNF-α in NPC compared to healthy controls.(31) Additionally, clinical staging and EBV DNA plasma load showed positively correlated with pretreatment of serum TNF-α, and negatively correlated with 2-year survival rate, similar to IL-6.(26) Therapy administration such as chemotherapy and IMRT could decrease the TNF-α plasma and serum levels. (20,26) While EBER and TNF-α were higher in NPC tumor compared to non-tumor specimens ($p<0.0001$), a strongly positive correlation was found between EBERs and TNF-α levels in tumor tissue ($p<0.0001$, r=0.647). Further, combination of EBERs and TNF-α expression was proposed as a predictor of poor survival for NPC patients ($p=0.011$).(40)

Serum IFN-γ levels were higher in NPC patients compared to IM and control groups ($p<0.05$).(32) The upregulation of IFN-γ affected the downregulation of IL-4 during NPC-EBV infection, thus becoming a reason for the lower serum of IL-4 detection in NPC patients. Other study showed serum IFN-γ levels in NPC patients had a positive correlation with EBV burden (plasmid EBV DNA copy numbers), with statistically significant differences between groups with varying EBV DNA loads ($p>0.05$). (42) Using a different patient group, the expression of tissue IFN-γ was also higher in undifferentiated nasopharyngeal carcinoma (UNPC) compared to controls.(37) Several types of treatment against NPCs reduced IFN-γ expression. For example, the IMRT treatment significantly lowered the plasma levels of IFN-γ compared pre-IMRT ($p \leq 0.001$).(20) IFN-γ also significantly found decreased in UNPC relapsed patients within 2 years after radiotherapy treatment.(37)

Other types of cytokines were reported in several studies, such as macrophage inhibitory cytokine 1 (MIC1), macrophage migration inhibitory factor (MIF), leptin, Epstein-Barr virus-induced gene 3 (EBI3) and p35 (subunit IL-35), and Leukemia Inhibitory Factor (LIF). (18,22,34,41,43) Overall, these cytokines had higher expression in NPC compared to control group. A 174

soluble cytokines were examined and obtained MIF plasma level was significantly higher than EBV VCA-IgA positive and EBV VCA-IgA negative healthy control (p<0.001).(22) similarly to plasma MIC-1 (p<0.001).(18) Plasma MIC-1 concentrations significantly dropped after radiotherapy (from 778.75pg/mL, to 511.26pg/mL, p=0.027), indicating its potential for monitoring treatment response. The plasma MIF levels correlated with sex and tumor staging classification, similarly to the expression of EBI3 and P35 (subunit of IL-35) in tissue samples, EBI3 expression was independently associated with patient outcome. On the other hand, P35 positive expression was associated with worse overall survival, but was not an independent prognostic predictor in multivariate analysis.(22,41) In the same sample types, the LIF levels were significantly higher in NPC tumor samples compared with normal samples. This result was supported with higher serum levels of LIF in NPC patients who developed local recurrence compared to those with complete tumor remission. This result also showed significant poorer local recurrence-free survival and progression-free survival.

LIF as the most pleiotropic member of IL-6 superfamily, in preclinical setting play major contribution to NPC tumor growth and radio-resistance. NPC treated with LIF activated the mechanistic target of rapamycin complex 1/70 kDa ribosomal protein S6 kinase mTORC1/p70S6K signaling pathway, enhancing tumor growth and inhibiting DNA damage responses. This evidenced by LIF treatment decreases the phosphorylation levels of DNA damage response proteins (*e.g.*, Ataxia-Telangiectasia mutated (ATM), P53, gamma H2AX (γH2AX), Nijmegen breakage syndrome 1 (NBS1), cell division cycle 25C (CDC25C)) in irradiated NPC cells, suggesting a suppression of DNA damage signaling and apoptosis. Treatment with soluble leukemia inhibitory factor receptor (sLIFR) significantly reduced tumor growth by blocking DNA synthesis in NPC cell proliferation. Rapamycin also significantly reduced LIF-mediated tumor growth. LIF-stimulated cells showed better survival after irradiation compared to phosphate-buffered saline (PBS)-treated cells. Treatment with sLIFR dramatically decreased cell survival following ionizing radiation (IR). Suppression of p70S6K by rapamycin sensitized LIF-treated tumors to IR. Modulating LIF-mediated signaling, for example, by using LIF antagonists or mTOR inhibitors, could be a viable treatment strategy to sensitize radioresistant NPC tumors.(43)

b) Chemokines

Nine β-chemokines (CC)-groups have been examined related with NPC, consisting of C-C motif chemokine ligand-2/monocyte chemoattractant protein-1 (CCL2/MCP1) in four studies, CCL3/macrophage inflammatory protein-1 alpha (MIP-1α) and CCL4/macrophage inflammatory protein-1 beta (MIP-1β) in two studies, and CCL14, CCL15, $CCL18^{+}$ of tumor associated macrophage (TAM), CCL20/macrophage inflammatory protein-3α (MIP-3α), CCL27, chemokine receptors (CCR) 1, CCR4, and CC5R5. In general, the CC-group with had a high expression in NPCs were CCL2/MCP1, MIP3α (CCL20), CCL27, and $CCL18^{+}$ of TAM.(21,23,24,27,31,38,40) While CCL14, CCL15, CCR1, CCR4, and CCR5 had low expression.(33) These were detected in various sample types, including plasma, serum, and tissue. Inconsistent results were found in CCL3/MIP-1α and CCL4/MIP-1β which showed the low serum MIP-1α and MIP-1β that associated with an increasing risk of NPC, even when considering only cases diagnosed more than one year after blood collection, suggesting a preclinical association.(21) In contrast, a high expression of CCL3 in plasma levels of NPC patients was found compared with VP and VN groups.(22) A combination of CCL3 and MIF demonstrated high diagnostic accuracy for distinguishing NPC from the VN cohort. This contrast result could be linked with the duality role of CCL3 as pro-tumor and anti-tumor behavior.(49) Previous study also found similar observation in CCL4 plasma concentration of NPC and control groups.(31)

The prognostic role of CC-chemokine detection varied among different specific CC types and studies. As level of macrophage infiltration is associated with poor prognosis, the level of CCL2/MCP1, a macrophage chemoattractant was often used for prognosis. The plasma expression level of CCL2/MPC1 was performed a higher result in NPC (254.0 pg/mL) than normal control (137.3 pg/mL).(24) Additionally, among NPC, correlation between level of this type of chemoattractant was correlated with differential organ metastasis. The lung metastasis group had significantly lower mean values of MCP1 (160.7±16.0) compared to the bone (270.6±46.8) and liver (378.8±91.2) groups. Liver metastatic tissue exhibited a higher density of infiltrating macrophages compared to the lung metastatic group.(27) The high plasma MIP3α (CCL20) also showed worse prognosis for overall survival (p=0.005). MIP3α significantly elevated in advanced stage disease and higher N classification.(31) In NPC tumor TAM and the CCL18 were found to be expressed in NPC progression. Patients with higher TAM counts or $CCL18^{+}$ TAM counts had shorter disease-free survival (DFS), overall survival (OS), and disease-specific survival (DSS) compared to those with lower count. A higher count was significantly associated

with a higher histological grade, regional and distant metastases, as well as more advanced cancer stage.(24) In addition, after adjusted with with Union for International Cancer Control (UICC) stage, tumor size, and node status, $CCL18^+$ TAM counts showed as an independent prognostic factor for survival. While the upregulation of CCL3 tissues and cell line was associated with overall stage.(22)

Other subgroups of chemokine, known as α-chemokines or CXC-group were observed in NPCs. Two studies examined CXCL10/interferon-gamma-induced protein 10 kDa (IP10) (27,31) and CXCR4 (33, 39), CXCL1/growth-regulated oncogene-alpha (GRO-α), CXCL8, CXCL9, CXCL12/stromal cell-derived factor-1alpha (SDF-1α), and Fractalkine (CX3CL1) was presented each in one study.(21,23,29,40) Using various sample types (plasma, serum, tissues) all these chemokines generally had a high expression or upregulated in NPC cases. The majority also correlated with prognosis, tumor staging and metastasis. Along with MCP1, the plasma levels of CXCL10/IP10 also correlated with single organ metastasis, with liver metastasis group had a highest mean value.(27) Elevating plasma levels of IP10 had an impact in patients with advanced staging diseases and N (nodus) classification, along with IL6, IL8, IP10, and MIP3α.(31) In CXCL9, higher serum of NPC patients was significantly associated with advanced tumor stages, nodal stages, and overall stages. A worse prognosis of overall survival and disease-free survival also presented. (29) Other study demonstrated the positive expression of SDF-1 and CXCR4 in tissue patients were significantly associated with advanced T staging, N staging, tumor node metastasis (TNM) staging, skull base invasion, and cervical node metastasis. Patients with positive expression of SDF1α and CXCR4 had a significantly shorter survival time compared to those with negative expression. The 5-year survival rate for patients with positive SDF-1α was 39.1% versus 75.0% for negative expression. For CXCR4, the 5-year survival rate was 52.0% for positive expression versus 77.8% for negative expression.(39)

c) Growth factors

Seven growth factors included in six studies. (21,25,26,31,35,40) Among the growth factor groups, the epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), granulocyte-macrophage colony-stimulating factor (GMCSF), macrophage colony-stimulating factor (MCSF), and insulin-like growth factor-binding protein-1 (IGFBP-1) had a high expression in NPCs. In contrast, the other groups such as stem cell factor (SCF), insulin-like growth factor (IGF)-1 and -2 had a low expression. Younger patients (≤30 years) with recurrent/metastatic NPC showed significantly higher plasma EGF levels compared to older patients (≥70 years).(35) On the other hand, higher VEGF plasma levels obtained in advanced T classification of NPC patients; hence a worse prognosis for overall survival.(31) This result explained in pre-clinical studies, showing an increase of VEGF and GMCSF production, on humanized mice that was injected subcutaneously with EBV^+ cells, leading to macrophage infiltration in the xenografts, and causing EMT phenotype.(24)

NPC patients with higher IGFBP-1 serum levels and the IGFBP-1/IGF-1 ratio had adverse relapse-free survival (RFS) (p=0.046 and p=0.038, respectively) and overall survival (OS) (p=0.037 and p=0.009, respectively). Multivariate analysis further confirmed IGFBP-1/IGF-1 ratio as an independent risk factor for poor recurrence-free survival (RFS) and OS (p=0.035 and p=0.044). Higher IGFBP-1 serum levels and the IGFBP1/IGF1 ratio significantly correlated with age, WHO histological classification, and EBV early antigen-IgA (EA) titre. The group with lower IGFBP-1 levels displayed a significantly better 5-year survival rate (87.6%) compared to the group with higher IGFBP-1 levels (71.4%).(25)

d) Immune checkpoint

The PDL-1 and lymphocyte-activation gene 3 (LAG-3) was obtained a high plasma levels, but lower sPD-1 and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) in pre-treatment of IMRT compared post-IMRT of NPC patients.(20) Among these immune checkpoints, only sPD-1 expression was significantly higher in TNM I/II patients compared to tumor node metastasis (TNM) III/IV patients (16.0±5.9 *vs.* 9.7±8.1 pg/mL, p=0.012). High sPD-1 had longer survival than those with low sPD-1 (≤10.19 pg/mL); p=0.021). Higher expression of PDL-1 also obtained in NPC tissue sample, serum, and cell line. (37) Higher PDL-1 expression was associated with poorer DFS and became an independent prognostic factor in NPC patients.(25) High expression levels of PD-1 also detected in NPC patients.(17,37) However, in specific region such as Indonesia obtained a low PD-1 mRNA expression but high expression of PDL-1 in NPC patients. The PD-1 expression was correlated with TNM status.(50)

e) Immune cells

Previous study demonstrated cluster of differentiation 8 positive ($CD8^+$) molecule expression was low in tumor and healthy tissues of undifferentiated type of NPC patients who relapsed within two years post-chemotherapy.(37) In similar note, a lower counts of $CD8^+PD1^+$ and $CD8^+LAG\text{-}3^+$ in EBV-clearers of post radiotherapy (RT) NPC was obtained compared to non EBV clearers.(33) Those were

associated with low frequency of CXCR3. Conversely, there was an acutely increased frequencies of $CD8^+$ T cells expressing CCR1, CCR4, and/or CCR5, including those co-expressing these CCRs with CXCR4. These results suggested an increased in the presence of matured $CD8^+$ T cells (CCR7CD45RA) and $0X40^+CD8^+$ T cells, which shown abundant in the post RT patients. When patients were stratified further by their clinical response, nonrecurrent NPC patients showed an RT-mediated increase in CCR1, CCR4, and/or CCR5 expressing $CD8^+$ T cells, as well as in $CD4^+$ T cell, which was not observed in recurrent patients. Besides $CD8^+$ and $CD4^+$, natural killer tumor-infiltrating lymphocytes (NK TIL) was categorized as immune cells with high expression in NPC tissue sample corelated with poorer 2-year survival. NK-high cohort group had a NK TIL co-expressed PD-1 and TIM-3. The expression of PD-1 was induced by IL-18. When the presence of $NK^+PD\text{-}1^+$/ $NK^+TIM\text{-}3^+$ was high, it is suggested that large proportion NK cells were exhausted or compromised.(17)

f) Receptors

Several studies performed epidermal growth factor receptor (EGFR), LIFR, and TLR-3, had a high expression in NPC,(34,35,40,43) besides of transforming growth factor beta receptor 2 (TGF-βR2) and adiponectin receptor 1 (AdipoR1) performed low expression.(30,34) In patients with metastatic NPC, high EGFR expression (IHC score >grade 3) was significantly associated with poor survival, while low level of TGF-βR2 expression was as negatively correlated with poor survival.(30) Treatment of EGFR using EGFR inhibitors (EGFRi) and the cell cycle blocker palbociclib (PAL) significantly inhibited tumor growth. Combination treatment with EGFRi and palbociclib demonstrated an additive suppressive effect, achieving approximately 90% repression of patient-derived xenograft (PDX) tumor growth.(35) In cell line sample, knockdown of TLR-3 in NPC cells significantly reducing TNF-α and IL-6 transcripts and release, in contrast with knockdown of AdipoR1 inducing cell migration.(34,40)

f) MMPs

Elevated serum MMP-3 levels and concentration were significantly found and associated with NPC progression and EBV infection in NPC patients.(17) Serum MMP-3 enzymatic activity demonstrated better diagnostic performance than MMP-3 concentration alone.(17) Increasing of other MMPs, such as MMP-2 and MMP-2 impacted in EMT development.(34)

B. Other Biomarkers

Other biomarkers excluding the immune component in our review consisting of adiponectin, DNA damage response proteins (DDR), Forkhead box P3 (FoxP3) intron 1 methylation, IDO, luciferase, Neutrophil-to-apolipoprotein A1 (NAR), and rs1024611.(34,35,37,38) In UNPC patients showed high level of indoleamine 2,3-dioxygenase-1 (IDO-1) and hypomethylated of FoxP3 intron 1.(37) This hypomethylation in tumor tissues of relapsed UNPC patients was significant compared to patients free from relapse.(37) In several high-density lipoprotein-cholesterol ratios obtained optimal cut-off values of NAR.(35) A higher NAR was significantly associated with both poor 5-year OS, and poor RFS, while the NAR index showed a high correlation with OS and regional control rate.(35) The G allele of rs1024611 was found significantly associated with an increased risk of NPC, as this associated with increased of mRNA expression levels of MCP1 in EBV-transformed lymphocytes.(37) Thus concludes that the rs1024611 may regulate MCP1 gene expression in NPC.(37)

The damage response proteins (DDR) (*e.g.*, ATM, p53, γH2AX, NBS1, CDC25C) had a lower level of phosphorylation affected by LIF among NPC samples. This suggests that NPC related LIF could be suppressed of DNA damage signaling and apoptosis.(43) Previous study showed serum adiponectin levels were found to be inversely correlated with the risk of nasopharyngeal carcinoma (NPC) and associated with higher tumor stages, recurrence, and metastasis in NPC patients.(34) *In vitro* study showed that adiponectin was able to reduce migration and invasion of NPC cells (S18 and 58F cells), inhibited EMT, and blocked the migration and invasion that enabled by pro-inflammatory cytokines works, such as leptin-induced NPC cell migration, IL-6, and TNF-α. They also inhibited NPC tumor metastasis *in vivo*, as evidenced by weaker luciferase signals, reduced lung wet weight, and fewer metastatic nodules.(34)

C. EMT-related Markers

Groups of proteins increased in EMT-related NPC aggressiveness and metastasis were vimentin, snail, twist, zinc finger E-box-binding homeobox 1 (ZEB-1), N-cadherin, and slug. In contrast, the E-cadherin, claudin-1, and ALK-1 had decreased.(24,30,34) Increasing of vimentin, decreased E-cadherin, and upregulation of EMT-transcription factors (snail, twist, ZEB1) affected by CCL18+ TAMs and promotes EMT in NPC.(24) Adiponectin and AdipoRon, the agonist of Adiponectin, could inhibit EMT by elevating E-cadherin and Claudin-1 expression and decreasing N-cadherin, vimentin, Snail, and Slug levels, besides of MMP-2 and MMP-9. Inhibited EMT, a process crucial for metastasis, by elevating E-cadherin and Claudin-1 expression while decreasing N-cadherin, vimentin, MMP-2, MMP-9, Snail, and Slug levels.(30,34)

D. Pathway-related Markers

NF-κB is activated by NPC cells and/or key marker related with NPC such as LMP-1 and EBER. It has diverse roles, including activated pro-inflammatory cytokine (such as TNF-α), increasing production of several growth factors (for example, GMCSF and VEGF), activated PD-L1, and exhibited EMT phenotype associated with metastasis. (23,40,42) Adiponectin is able to decrease the transcriptional activity of NF-κB, and reduced the phosphorylation of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (pIκBα), a key mediator of NF-κB signaling. Adiponectin also inhibited STAT3 pathway and phosphorylation on NPC tumor metastasis. The STAT3 also induced PDL-1 expression, along with NFκB, Janus kinase 3 (JAK3), and mitogen-activated protein kinase kinase (MEK) pathway.(42) The mTOR/p70S6K is another pathway contributed to enhancing tumor growth and inhibiting DNA damage responses. Suppression of p70S6K by rapamycin sensitized LIF-treated tumors to IR. Modulating LIF-mediated signaling, for example, by using LIF antagonists or mTOR inhibitors, could be a viable treatment strategy to sensitize radioresistant NPC tumors.(43)

E. EBV-based Molecular Biomarkers

The EBV-DNA (n=9), IgaAs (EBV VCA IgA and VCAp18+EBNA1) (n=8), LMP-1 (n=4), EBERs (n=2), BARF-1 (n=1), and EBV-IgG are group of crucial EBV markers found in this review. Those associated with several outcomes, including expression and correlation with other markers, prognostic indicator, diagnostic/screening value, and treatment responses, summarized in Table 4.

Discussion

The current scoping review was primarily targeted at the role of LMP-1 as biomarker in clinical setting of EBV-NPC cases, along with pro- and/or anti-inflammatory cytokine related with LMP-1. However, only three cytokines were correlated with LMP-1, *i.e.*, IFN-γ, LIF, and a positive association with other EBV biomarker (EBERs). No studies assessed LMP-1 in clinical settings, including screening, diagnosis, prognosis, or treatment response. This finding highlights a clear gap compared with other EBV molecules measurements, such as EBV DNA or EBV-IgA (Table 3). The use of plasma or serum EBV DNA, followed by EBV IgA serology assay is widely used to clinical assessment of NPC, such as screening, determining the prognostication, and detection of early cancer relapses; other than studies for EBV NPC detection method itself.(51) This because the plasma EBV DNA showed the highest sensitivity and specificity (approximately 91.4% and 93.2%) compared with EBV DNA in serum sample (84.4% and 76.0%). (51,52) Although IgA is also frequently used, it has lower sensitivity and specificity than EBV DNA, and no single marker had optimal result.(51) IgA-EBV was undetectable in approximately 4-24% patients with NPC.(51,53,54) The detection rate of LMP-1 in tissues using conventional IHC methods is relatively low, at approximately 20-60%. This low percentage is likely due to low LMP-1 expression, which result in detection failure by IHC.(13,56) In contrast, the tissue samples- primarily obtained from tissue biopsy-can be assessed using EBERs in situ hybridization (ISH). EBERs-ISH is the gold standard for detecting EBV infection. (56) However, EBER has lack of functional insight, therefore does not describe tumor activity, hence can not be used to measure prognosis of predictive status of NPC.(13) This leaves gap on in-situ NPC clinical biomarker.

Although liquid biopsy approaches using EBV DNA and EBV IgA, as well as histological assessment with EBERs-ISH is widely used to detect NPC, a globally "gold standard" detection methods has not been established in all clinical settings. Several factors contribute to this limitations are: 1) The optimal specimens for viral loads measurement remain uncertain due to different form of EBV-DNA in peripheral blood and different varying pathologies associated with EBV diverse states, 2) Difficulty in obtaining the uniform cut-off value to determine the positive result, 3) The EBV gene heterogeneity, along with the use of multiple commercial kits, antibody assays, and sample types.(51,56-59) Figure 3 outlines the result of our scoping review, including sample types, biomarkers, pathways, EBV-markers (including the LMP-1), and clinical outcomes. Among these, numerous biomarkers have not yet been explored for their correlation with EBV-markers, including LMP-1 as main EBV oncoprotein. As many studies propose biomarkers based on oncogenic pathways, as discussed in this review, a recent study used a mega-data bioinformatics analysis to screen available public databases. This approach was further confirmed by in-situ analysis confirming that increased expression of ras guanyl nucleotide releasing protein 2 (RASGRP2) and decreased expression of tetratricopeptide repeat domain 9 (TTC9), CD37, dolichyl-phosphate mannosyltransferase subunit 3 (DPM3) and Rho GTPase-activating protein 4 (ARHGAP4) suggesting potential for prognostic biomarkers for NPC. (60) These proposed biomarkers may directly and indirectly correlate with immune work, adding the pool for potential biomarkers for NPC. As a scoping review, this study has

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Table 4. EBV-related biomarkers for NPC and proposed clinical correlation.

	Types of EBV Biomarkers					
Outcome	**EBV DNA**	**EBV-IgAs**	**LMP-1**	**EBERs**	**BARF-1**	**EBV-IgG**
Expression and/or correlation with another marker	• Positively correlated with serum of IL-6 and TNF-α before therapy; and negatively correlated with IL-1β.(26) • Correlated with IP10 and MCP-1 in metastasis.(27) • Correlated with CXCL9.(29)	• EBV early antigen-IgA (EA) titre correlated with higher IGFBP1 serum levels and the IGFBP1/IGF1 ratio.(25)	• Significant correlation of the IHC scores with CXCL9.(29) • Increasing of LMP-1 promotes EBER-1 and EBER-2 transcript.(40) • LMP-1 upregulates PDL-1 expression through various pathways (NF-κB, STAT3, JAK, MEK, API-1). LMP1-positive NPC cell lines treated with IFNγ exhibited even higher PDL1 levels.(42) • LMP-1 significantly upregulated LIF mRNA expression and enhances LIF production in NPC cells.(43)	• Upregulated TNF-α, IL-6, positive correlation with TNF-α, activated NF-κB pathway via TLR-3, increased LMP-1 expression.(40) • Significant association with ALK-1 and TGFβR2) (p =0.000 and 0.003).(30)	• High levels in UNPC patients.(37)	
Correlation with others	• Correlated with tumor weight.(35) • Positive correlation with higher T and N classification patient.(31)	• EBV VCA IgA serum concentration increased in smokers.(24)		• In combination with TNF-α expression became poor predictor of NPC survival.(40)		
Prognostic indicator	• 2-year survival rate had negative correlated with EBV DNA.(26) • Lower EBV DNA contribute to the favorable overall survival in NPC patients with lung metastasis.(27) • High EBV DNA had worse prognosis in 4-year overall survival.(31)					• EBV-IgG status performed as independent risk factor for NPC prognosis.(36)
Diagnostic/screening value	• With MIC-1 improved the identification of EBV DNA- negative NPC patients.(18) • MIP3α and SCF increased the screening efficacy of EBV DNA, but not the accuracy of the diagnostic panel.(31)	• Besides EBV DNA, MIP3α and SCF could increase screening efficacy ofVCA IgA.(31) • Combination with MMP-3 activity and EA-IgA improved the diagnostic performance.(16) • MIC-1 could be distinguished the NPC from VCA-IgA positive healthy controls and EBV DNA-negative NPC patients.(18) • MIF, CCL3, and VCA-IgA combinations had diagnostic accuracy to differentiate NPC from the VP cohort and distinguishing NPC from the combined VN+VP cohort.(22) • Plasma CCL27 could be used for distinguishing between NPC patients, early stage of NPC patients and VCA-IgA positive healthy donors.(23)				
Treatment response	• Low plasma levels after IMRT (17), and chemotherapy.(26) • "EBV DNA clearers" had a lower expression of $CD8^{+}PD\text{-}1^{+}$ T cells and increased mature $CD8^{+}$ T cells.(33)					

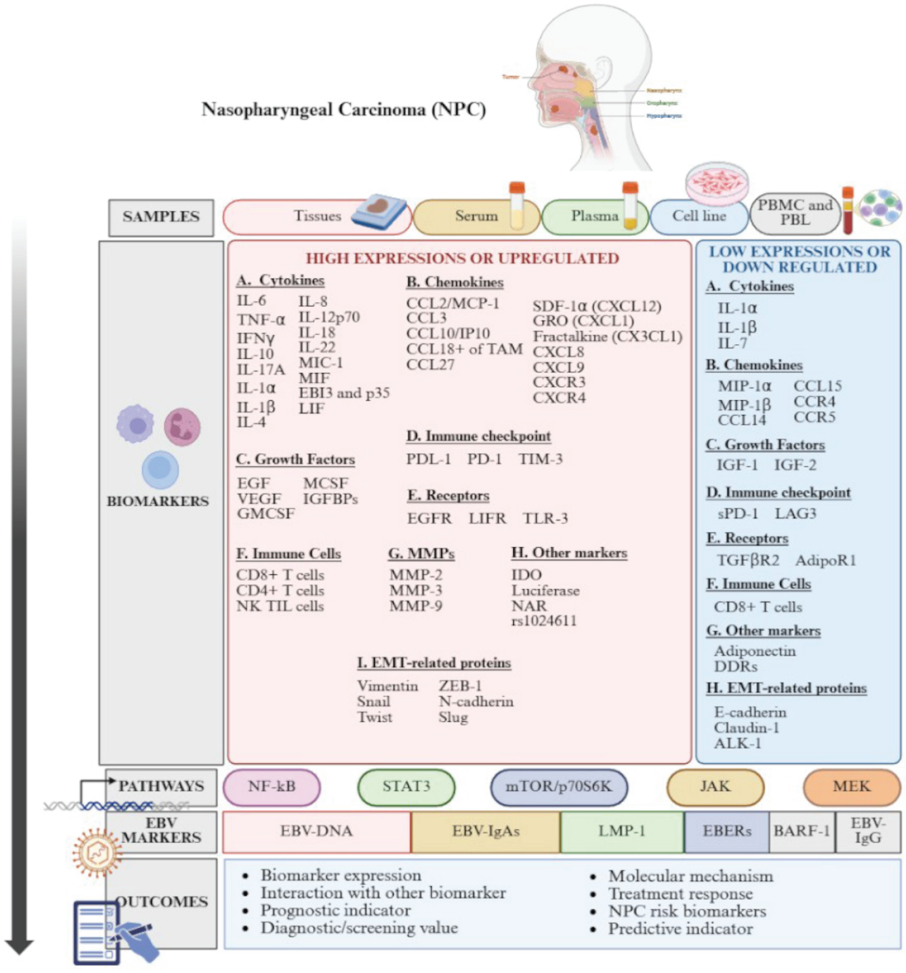

Figure 3. The outline of NPC scoping reviews. The different big-to small of shape and red-to black color in samples and EBV markers indicated the high-to low amount of those obtained from 28 articles. (Image created using Biorender.com).

several limitations. First, only two databases were searched. Although LMP-1 was included as a search criterion, many of the screened abstracts did not investigate LMP-1 as a biomarker, which reduced the number of eligible full-text articles, hence led to a scoping review. Furthermore, during full-text analysis, we did not further evaluate patient selection criteria or population characteristics, sample collection procedures, the specific assays or kits used, biomarker cut-off values, or the clinical timing of biomarker application. These factors may have contributed to heterogeneity and may influence the interpretation of the findings

Conclusion

In summary, the LMP-1 in our scoping review only pointing in expression and/or correlates with minimal cytokine markers, consist of IFN-γ, LIF, and CXCL9, an immune checkpoint (PDL-1) and a positive loop with other EBV biomarker (EBERs). However, numerous potential biomarkers from various types of samples could be explored with their correlation or impact in LMP-1 roles, and the clinical outcomes.

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Authors Contribution

JF and DKP were involved in concepting, planning the research, and grant finding, with JF playing role as the principal investigator. NBWAH developed search term and running data acquisition. JF and NBWAH did primary

screening, with DKP and FR confirmed discrepancy. JF, FR, NBWAH, and DKP together draft the manuscript, while FR solely drafted tables and figures. All authors took part in giving critical revision of the manuscript and agree upon the final format of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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