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Exosomal extracellular RNAs in HPV-associated cervical carcinoma and oropharyngeal squamous cell carcinoma: biomarker, mechanistic, and therapeutic perspectives

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Highlights:

- Tumor-derived exosomal miRNAs, lncRNAs, and circRNAs constitute non-invasive biomarkers in HPV-associated cancers.
- HPV oncoproteins E6 and E7 remodel exosomal RNA cargo to sustain oncogenic intercellular signaling.
- Exosomal RNAs facilitate immune evasion by suppressing NK-cell and cytotoxic T-lymphocyte activity.
- Engineered exosomes carrying tumor-suppressive RNAs represent a promising therapeutic platform in HPV-driven malignancies.

Abstract: Extracellular RNAs (exRNAs) packaged within tumor-derived exosomes have emerged as compelling candidates for non-invasive cancer biomarkers and active mediators of oncogenic intercellular communication. Human papillomavirus (HPV)-associated malignancies, principally cervical carcinoma and oropharyngeal squamous cell carcinoma, impose a significant global burden for which early molecular detection remains an unmet clinical need. Exosomes released by HPV-positive tumor cells carry diverse RNA species, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and PIWI-interacting RNAs (piRNAs), whose composition faithfully mirrors the molecular landscape of the originating malignant cell. Protected from extracellular nuclease degradation by their lipid bilayer membrane, these RNA species are detectable in peripheral blood, saliva, and urine, conferring amenability to liquid biopsy strategies. This review provides a comprehensive synthesis of the biogenesis and cargo composition of exosomal extracellular RNAs, their diagnostic and prognostic utility in HPV-associated cancers, their mechanistic contributions to tumor progression and immune evasion, and their emerging potential as therapeutic targets and drug delivery vehicles. Integration of exosomal RNA profiling into clinical oncology holds significant potential; however, rigorous prospective validation and methodological standardization are required before clinical translation can be realized.

Keywords: extracellular RNA; exosomes; human papillomavirus; cervical cancer; oropharyngeal squamous cell carcinoma; microRNA; long non-coding RNA; circular RNA; liquid biopsy; tumor immunity

1. Introduction

Cancer remains the foremost cause of mortality worldwide, with approximately 19.3 million new diagnoses estimated globally in 2022 [1]. Among infectious-agent-attributable malignancies, those driven by persistent infection with high-risk human papillomavirus (HPV) genotypes occupy a position of exceptional epidemiological significance. HPV is a small, non-enveloped, double-stranded DNA virus whose integration into the host genome drives malignant transformation through the constitutive expression of viral oncoproteins E6 and E7, and is causally implicated in virtually all cervical cancers as well as substantial proportions of oropharyngeal, anal, vulvar, vaginal, and penile carcinomas [2]. While HPV contributes to the pathogenesis of anal, vulvar, vaginal, and penile carcinomas, the present review focuses on cervical carcinoma and oropharyngeal squamous cell carcinoma, for which exosomal extracellular RNA (exRNA) evidence is most extensively characterized in the published literature.

Globally, HPV is responsible for an estimated 690,000 cancer cases per year, establishing it as the second most oncogenic pathogen after the hepatitis B and C viruses [3]. Despite prophylactic vaccination programs and cytology-based screening, a substantial proportion of HPV-associated cancers continue to be diagnosed at advanced stages, where curative therapeutic options are limited. This diagnostic gap has galvanized investigation into molecularly precise, minimally invasive liquid biopsy strategies capable of detecting malignancy earlier and monitoring disease progression with greater fidelity [4].

Extracellular vesicles (EVs), and exosomes in particular, are nanoscale (30 to 150 nm) lipid-bilayer-enclosed particles constitutively secreted by virtually all mammalian cell types. A landmark discovery demonstrated that exosomes transfer functional messenger RNA (mRNA) and microRNA (miRNAs) between cells in a biologically active form, establishing a novel mechanism of horizontal genetic information exchange [5]. Circulating miRNAs present in plasma exhibit remarkable stability and serve as informative non-invasive biomarkers for cancer detection [6]. Beyond miRNAs, the exosomal cargo encompasses long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and PIWI-interacting RNAs (piRNAs), and small nucleolar RNAs, each reflecting the molecular identity of the originating tumor cell [7].

Dysregulation of non-coding RNA networks is a conserved hallmark of malignant transformation. Aberrant miRNA expression profiles have been exploited to classify human cancers with high accuracy [8,9]. In the specific context of HPV-driven carcinogenesis, the oncoproteins E6 and E7 not only reprogram the host transcriptome but also alter exosomal RNA cargo composition and secretion dynamics, enabling tumor cells to propagate pro-oncogenic signals to stromal, endothelial, and immune cells within the tumor microenvironment [10]. The present review comprehensively synthesizes current evidence on the biogenesis and cargo of exosomal extracellular RNAs in HPV-associated cancers, their diagnostic and prognostic value, their mechanistic roles in tumor biology, and their therapeutic potential.

2. Classification and biogenesis of extracellular RNAs

EVs are broadly classified into three principal subtypes by size, biogenesis, and surface markers: exosomes (30 to 150 nm), microvesicles (100 to 1,000 nm), and apoptotic bodies (1000 to 5000 nm) [11].

The MISEV2018 guidelines standardized EV nomenclature and methodological requirements, emphasizing orthogonal characterization using nanoparticle tracking analysis, electron microscopy, and tetraspanin immunophenotyping [4]. The subsequent MISEV2023 consensus document, developed with contributions from more than 1000 scientists under the auspices of the International Society for Extracellular Vesicles, further refined nomenclature, expanded guidance on EV release and uptake assays, and introduced recommendations for *in vivo* methodologies and advanced single-vesicle characterization approaches [12]. Exosomes originate via the endosomal pathway, whereby early endosomes mature into multivesicular bodies (MVBs) through inward budding of their limiting membrane, generating intraluminal vesicles (ILVs). Subsequent MVB fusion with the plasma membrane releases ILVs as exosomes into the extracellular space [13].

The discovery that sheep reticulocytes externalize transferrin receptors via exosome release established the foundational concept of exosomal biogenesis [14]. Canonical ILV formation relies on the endosomal sorting complexes required for transport (ESCRT-0, -I, -II, and -III), which sequentially recognize ubiquitinated cargo and facilitate membrane invagination. ESCRT-independent pathways involving ceramide biosynthesis, tetraspanins (CD63, CD9, CD81), and the GTPase RAB31 contribute additional selectivity to cargo sorting [15].

MicroRNAs are endogenous non-coding single-stranded RNA molecules of approximately 22 nucleotides processed from longer primary transcripts by the sequential enzymatic activity of Drosha-DGCR8 in the nucleus and Dicer in the cytoplasm [16]. Mature miRNAs associate with Argonaute-2 within the RNA-induced silencing complex to mediate post-transcriptional gene silencing via 3-prime UTR base-pairing [17]. Selective miRNA loading into exosomes is directed by hnRNPA2B1 recognition of GGAG or ACCAGCCU tetramer sequence motifs and is regulated by sumoylation-dependent hnRNPA2B1 activity and by nSMase2-dependent ceramide production [18].

Long non-coding RNAs are transcripts exceeding 200 nucleotides that function through chromatin remodeling, transcriptional regulation, competing endogenous RNA (ceRNA) network participation, and protein scaffolding [19]. Circular RNAs, produced by pre-mRNA back-splicing, are covalently closed and therefore resistant to exonucleolytic degradation, conferring exceptional stability in biological fluids [20]. PIWI-interacting RNAs (26 to 31 nucleotides), generated independently of Dicer, primarily suppress transposable elements through epigenetic silencing and exhibit aberrant expression across multiple somatic cancer types [21].

Proteomic and transcriptomic characterization of EV subpopulations supports a tightly regulated, non-stochastic cargo loading model [22]. Extracellular miRNAs also circulate in non-vesicular forms associated with Argonaute-2 complexes, representing an additional analyte pool accessible via liquid biopsy [23]. The functional diversity of non-coding RNA classes in disease contexts positions exosomal exRNAs as tractable targets for both biomarker discovery and therapeutic intervention [24,25]. Advances in multi-omics integration - encompassing EV proteomics, transcriptomics, lipidomics, and metabolomics - have enabled comprehensive cargo profiling that captures the full molecular identity of tumor-derived vesicles [26]. Curated repositories including Vesiclepedia 2024, which catalogs more than 566,000 protein entries and 50,000 RNA entries from 3533 EV studies, and EVmiRNA2.0, which integrates over 7200 human EV small RNA sequencing datasets spanning 143 disease types, provide indispensable reference frameworks for biomarker discovery in HPV-associated cancers [27,28].

RNA species depicted schematically; for molecule-specific annotations, refer to Tables 1 and 2.

Figure 1 illustrates the biogenesis of tumor-derived exosomes in HPV-positive cancer cells and their intercellular communication with recipient cells. Three sequential steps are depicted: (1) the endosomal pathway, in which early endosomes mature under the influence of HPV oncoproteins E6 and E7; (2) MVB and ILV formation via ESCRT-0/I/II/III-, ceramide (nSMase2)-, and RAB31-dependent mechanisms, with selective RNA cargo loading directed by hnRNPA2B1 (GGAG motif recognition) and sumoylation; and (3) secretion of exosomes (30-150 nm) through MVB fusion with the plasma membrane. Released exosomes carrying miRNA, lncRNA, circRNA, and piRNA cargo are taken up by stromal fibroblasts (inducing CAF activation and VEGF/FGF2 upregulation), endothelial cells (promoting angiogenesis), and dendritic cells (suppressing MHC II expression and IL-12 secretion). An electron micrograph (scale bar: 100 nm) illustrates the morphology of secreted exosomes.

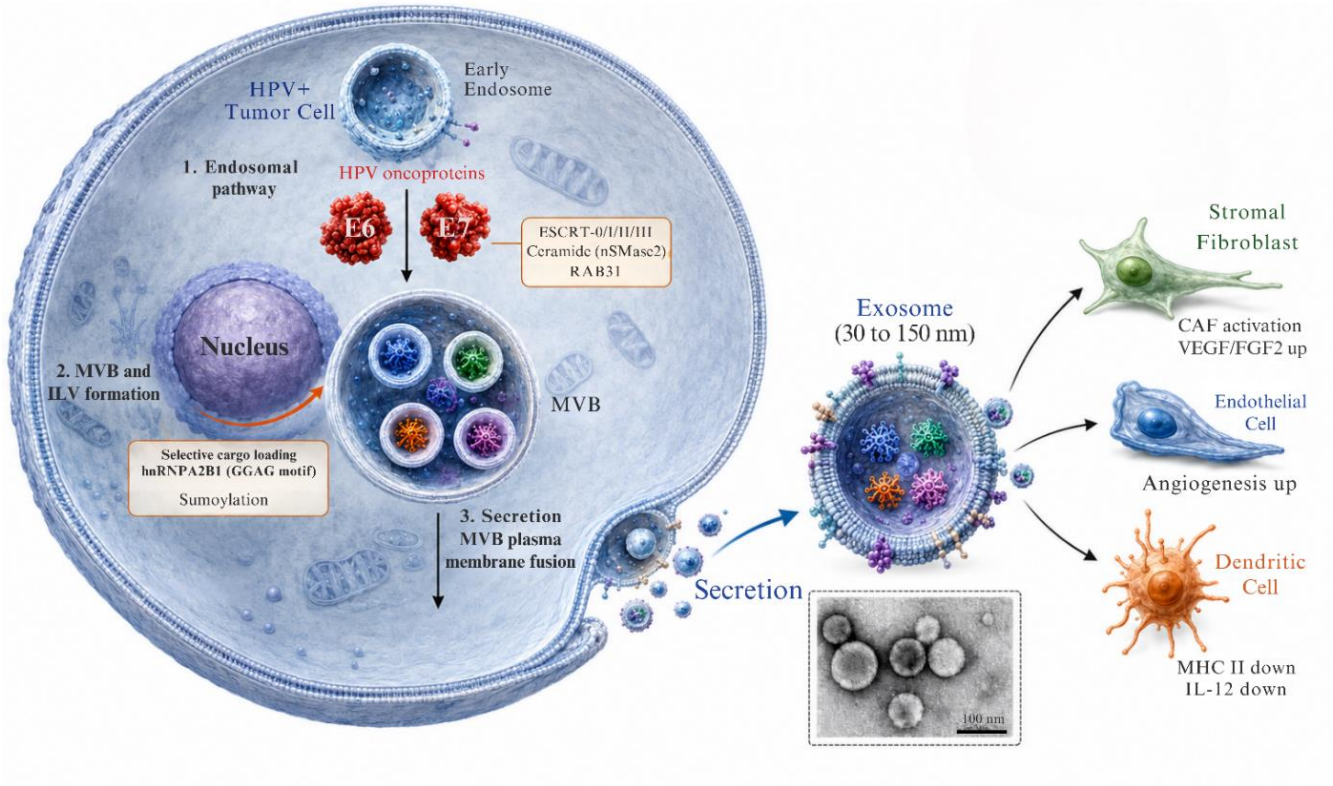

Figure 1. Biogenesis of tumor-derived exosomes and selective RNA cargo loading. Illustrates the endosomal pathway (early endosome to multivesicular body formation), ESCRT-dependent and ESCRT-independent intraluminal vesicle formation, and selective packaging of diverse exRNA species into nascent exosomes. RNA cargo categories represented in the figure include miRNA, lncRNA, circRNA, and piRNA; individual species are depicted schematically and are further detailed in Table 1 and Table 2. This figure was created with the assistance of artificial intelligence tools. Figures in this manuscript were generated with the assistance of AI-based visualization tools. The authors take full responsibility for the accuracy and scientific integrity of all visual content.

Table 1. Classification, biogenesis, and key properties of extracellular RNA species detected in HPV-associated cancer exosomes.

RNA Class	Length	Biogenesis	Exosomal Stability	Key Function in Cancer	Ref.
miRNA	~22 nt	Drosha-DGCR8/Dicer	High (protein-protected)	Post-transcriptional gene silencing; oncomiR activity	[15]
lncRNA	> 200 nt	RNA Pol II transcription	Moderate (membrane-protected)	Epigenetic regulation; ceRNA network; protein scaffolding	[18]
circRNA	Variable	Pre-mRNA back-splicing	Very high (covalently closed)	miRNA sponge; competing endogenous RNA; RIG-I activation	[19]
piRNA	26–31 nt	Dicer-independent	Moderate	Transposon silencing; DNMT3A-mediated epigenetic control	[21]
mRNA	Variable	RNA Pol II transcription	Moderate	Functional protein production in recipient cells	[5]
snRNA	~150 nt	RNA Pol II/III	Moderate	Splicing regulation; stress response in recipient cells	[21]

Abbreviations: nt, nucleotide; miRNA, microRNA; lncRNA, long non-coding RNA; circRNA, circular RNA; piRNA, PIWI-interacting RNA; mRNA, messenger RNA; snRNA, small nuclear RNA; RNA Pol II, RNA polymerase II; RNA Pol III, RNA polymerase III; ceRNA, competing endogenous RNA; RIG-I, retinoic acid-inducible gene I; DNMT3A, DNA methyltransferase 3 alpha; ESCRT, endosomal sorting complexes required for transport. Ref., reference.

3. Exosomes in HPV-associated cancers: cargo, composition, and oncogenic communication

3.1. Cervical cancer

Cervical cancer is the fourth most common malignancy in women worldwide, attributable to persistent high-risk HPV infection in more than 99 percent of cases [1]. The HPV oncoproteins E6 and E7 drive malignant transformation through proteasomal degradation of p53 and inactivation of the retinoblastoma protein (pRb), respectively, disrupting cell cycle checkpoints and apoptotic programs [2]. Critically, E6 and E7 expression alters not only the transcriptome of infected cells but also the biogenesis, secretion rate, and RNA cargo composition of tumor-derived exosomes [10].

Taylor and Gercel-Taylor established that tumor-derived exosomes harbor disease-specific miRNA signatures, providing the conceptual framework for HPV-associated cancer liquid biopsy in gynecological malignancies [29]. In cervical carcinoma, exosomal miR-21, which targets the tumor suppressor PTEN, is consistently overexpressed and detectable in patient serum [30]. miR-155 and miR-141, governing inflammatory signaling and epithelial–mesenchymal transition (EMT) via zinc finger E-box-binding homeobox 1/2 (ZEB1/ZEB2) suppression, are similarly elevated in the circulating exosomal fraction of cervical cancer patients [30]. The HPV E6 oncoprotein suppresses transcription of miR-34a, a p53-regulated tumor suppressor that ordinarily induces apoptosis and restrains Notch and Wnt pathway activation [31].

The intercellular transfer of oncogenic microRNAs (oncomiRs) from HPV-positive tumor cells to stromal fibroblasts, endothelial cells, and immune effectors propagates pro-tumorigenic signals across

the tumor microenvironment, contributing to angiogenic switching, stromal reprogramming, and immune exclusion [10]. This non-cell-autonomous dimension of viral oncogenesis has profound implications for both biomarker development and therapeutic targeting.

3.2. Head and neck squamous cell carcinoma

The incidence of HPV-associated head and neck squamous cell carcinoma (HNSCC), particularly oropharyngeal carcinoma, has risen dramatically over three decades in high-income countries, driven primarily by HPV-16 [3]. HPV-positive oropharyngeal tumors display improved chemoradiation responsiveness and a markedly better prognosis than HPV-negative counterparts, establishing HPV status as a critical determinant of treatment intensity and prognosis [3]. Saliva-based liquid biopsy is particularly attractive for oropharyngeal carcinoma given anatomical proximity of the primary lesion to the oral cavity [32].

Lajer *et al.* demonstrated that HPV-positive oropharyngeal squamous cell carcinomas harbor a distinct salivary exosomal miRNA signature compared to HPV-negative tumors, with differential expression of miR-9, let-7 family members, and miR-100 family members [32]. Whiteside subsequently documented that HNSCC-derived exosomes carry functional miRNA cargo capable of suppressing natural killer (NK) cell cytotoxicity and inducing regulatory T-cell expansion, mechanistically linking exosomal RNA to immune evasion in HPV-positive oropharyngeal disease [33].

3.3. Other HPV-associated malignancies

Beyond cervical and oropharyngeal carcinomas, high-risk HPV contributes to anal, vulvar, vaginal, and penile cancers [3]. Although exosomal RNA profiling in these less-studied tumor types remains nascent and falls outside the primary scope of this review, the shared HPV-driven transcriptional reprogramming mechanisms identified in cervical and oropharyngeal malignancies provide a rational biological foundation for future exosomal RNA biomarker investigations across the full spectrum of HPV-associated cancers [10,34,35].

Figure 2 depicts the exosomal RNA-mediated intercellular communication network established by HPV-positive tumor cells within the tumor microenvironment. Central to the diagram is the HPV-positive tumor cell expressing E6 and E7 oncoproteins, which releases exosomes carrying diverse RNA cargo and surface-bound ligands to multiple recipient cell types. Exosomal miR-9 and surface PD-L1 suppress NK cell cytotoxicity and BLIMP1 expression; exosomal miR-210 and miR-21 promote angiogenesis and vascular permeability in endothelial cells; exosomal miR-21 and miR-155 impair dendritic cell antigen presentation by downregulating MHC II and IL-12, reducing T-cell priming; exosomal TGF-β and miR-155 induce regulatory T-cell expansion and immune suppression; and exosomal lncRNA HOTAIR and miR-155 activate stromal fibroblasts toward a cancer-associated fibroblast (CAF) phenotype, upregulating VEGF and FGF2. Surface PD-L1 on released exosomes additionally suppresses T-cell activation in draining lymph nodes independently of the primary tumor microenvironment.

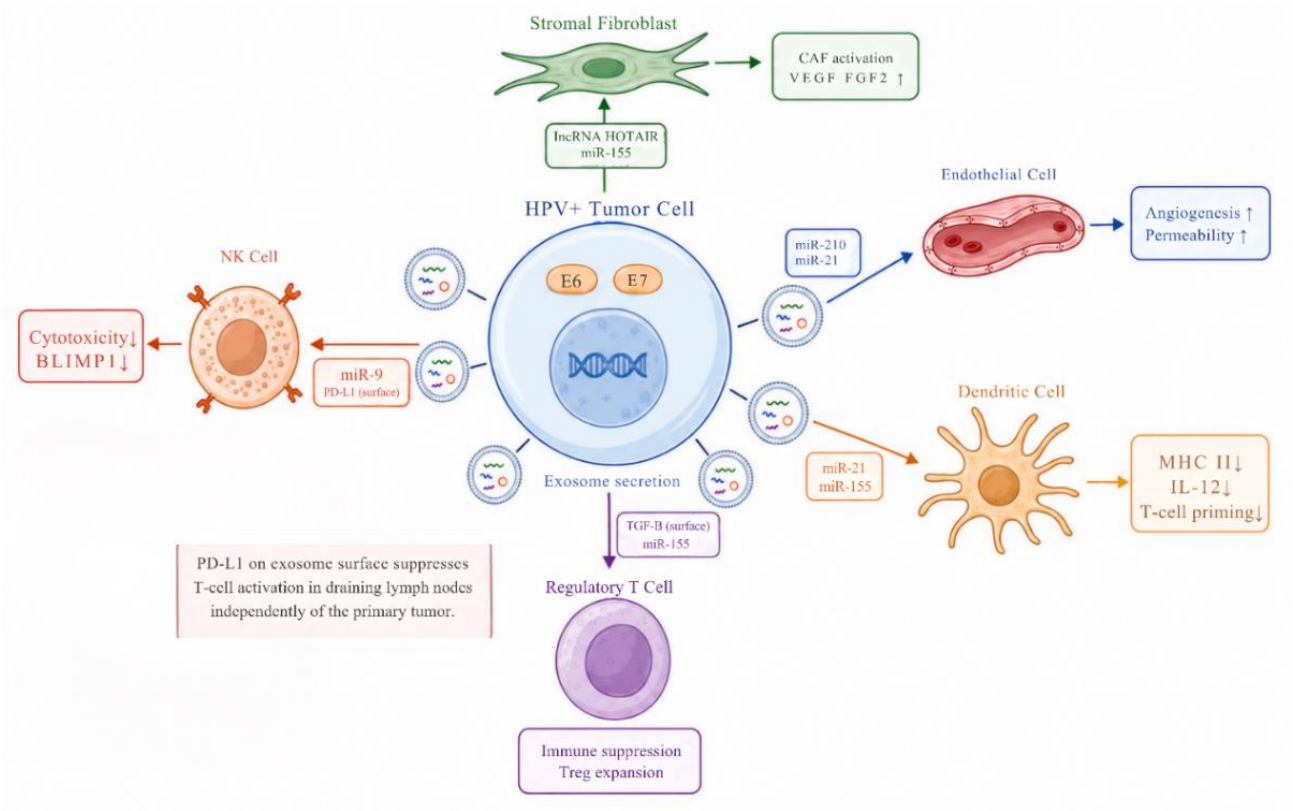

Figure 2. Exosomal RNA-mediated intercellular communication in the HPV-associated tumor microenvironment. Depicts HPV-positive tumor cells releasing exosomes bearing miR-21, miR-155, miR-141, lncRNA HOX transcript antisense intergenic RNA (HOTAIR), and circRNA-101996, taken up by stromal fibroblasts, endothelial cells, dendritic cells, NK cells, and regulatory T cells, illustrating downstream pro-tumorigenic and immunosuppressive effects.

4. Extracellular RNAs as non-invasive biomarkers

4.1. MicroRNAs as diagnostic and prognostic biomarkers

The stability of miRNAs in biological fluids, attributable to encapsulation within lipid bilayer membranes or association with Argonaute-2 complexes, makes them exceptionally suitable circulating biomarkers [23]. Extracellular miRNAs also circulate in association with high-density lipoproteins, expanding the diversity of accessible analyte pools [36]. Chen *et al.* demonstrated that serum miRNAs are highly stable and reproducibly quantifiable across individuals [37]. Schwarzenbach *et al.* subsequently articulated the diagnostic and prognostic relevance of circulating cell-free miRNAs across multiple cancer types [38].

In HPV-associated cervical cancer, an exosomal panel comprising miR-21, miR-155, and miR-141 has demonstrated diagnostic area-under-the-curve values superior to conventional cytology for early-stage disease [30]. A prospective clinical study demonstrated that an exosomal miRNA expression signature in cervical cancer patients undergoing concurrent chemoradiotherapy significantly predicts treatment response and disease-free survival, supporting clinical translation of exosomal RNA profiling as a pharmacodynamic and prognostic tool [30]. For HPV-positive HNSCC, plasma exosomal miR-9 and miR-200c correlate significantly with tumor stage, lymph node metastasis status, and disease-free

survival [32]. The clinical utility of EV-derived RNA analytes as next-generation oncological biomarkers has been comprehensively documented across multiple cancer types [39].

4.2. Long non-coding RNAs and circular RNAs as prognostic indicators

Exosomal lncRNAs have attracted growing attention as prognostic biomarkers owing to their functional versatility and high cell-type specificity [18]. HOTAIR is among the most studied lncRNAs in cervical malignancy; elevated circulating HOTAIR is significantly associated with tumor size, lymphovascular space invasion, lymph node metastasis, and reduced disease-free and overall survival in cervical cancer patients, while exosomal HOTAIR and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) are differentially enriched in cervicovaginal lavage samples from cervical cancer patients compared to cancer-free controls [40,41]. lncRNA MALAT1, whose transcription is upregulated in HPV-positive cervical cancer cells by the E7 oncoprotein through direct MALAT1 promoter binding, is detectable in the exosomal fraction and promotes cisplatin resistance via the MALAT1/miR-370-3p/signal transducer and activator of transcription 3 (STAT3)/phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) positive feedback loop [42,43]. Circular RNAs are especially well-suited as stable liquid biopsy analytes given their covalently closed structure [19]. In cervical squamous cell carcinoma, exosomal circRNA-101996 promotes proliferation and invasion by functioning as a sponge for miR-8075, derepressing downstream oncogenic targets [44]. The piRNA class represents an emerging biomarker category in HPV-associated malignancies; piRNA-14633 is overexpressed in cervical cancer tissues and promotes proliferation, migration, and invasion through the methyltransferase-like 14 (METTL14)/cytochrome P450 family 1 subfamily B member 1 (CYP1B1) signaling axis, while systematic piRNA profiling of cervical cancer plasma exosomes has identified multiple differentially expressed piRNAs with diagnostic potential [45].

Table 2 summarizes the exosomal RNA species with reported diagnostic and prognostic utility in HPV-associated cancers, detailing their expression status, proposed molecular mechanisms, and clinical utility across cervical carcinoma and HPV-positive head and neck squamous cell carcinoma.

Table 2. Exosomal extracellular RNA biomarkers in HPV-associated cancers with reported diagnostic and prognostic roles.

RNA Species	Cancer Type	Expression	Proposed Mechanism	Clinical Utility	Ref.
miR-21	Cervical carcinoma	Upregulated	PTEN suppression; PI3K/AKT activation	Early diagnosis; stage correlation	[30]
miR-155	Cervical carcinoma	Upregulated	NF-kB activation; immune modulation	Diagnosis; promotes EMT	[30]
miR-141	Cervical carcinoma	Upregulated	ZEB1/ZEB2 suppression; EMT regulation	Diagnosis and prognosis	[30]
miR-34a	Cervical carcinoma	Downregulated	E6-mediated loss; p53/apoptosis disruption	Therapeutic target; cell cycle marker	[31]
miR-9	HPV+HNSCC/ Oropharyngeal	Upregulated	BLIMP1 suppression; immune evasion	Prognostic; nodal metastasis correlate	[32]

Table 2. *Cont.*

RNA Species	Cancer Type	Expression	Proposed Mechanism	Clinical Utility	Ref.
miR-200c	HPV+HNSCC/ Oropharyngeal	Upregulated	ZEB-axis EMT regulation	Disease-free survival predictor	[32]
let-7 family	HPV+Oropharyngeal	Downregulated	HMGA2 suppression; oncogene restraint loss	HPV status discrimination in saliva	[32]
lncRNA HOTAIR	Cervical carcinoma	Upregulated	PRC2 recruitment; epigenetic silencing	Advanced FIGO stage; poor prognosis	[40,41]
lncRNA MALAT1	Cervical carcinoma	Upregulated	Alternative splicing; metastatic colonization	Distant metastasis biomarker	[42,43]
circRNA-101996	Cervical carcinoma	Upregulated	miR-8075 sponge; oncogenic derepression	Proliferation and invasion marker	[44]
piRNA-14633	Cervical carcinoma	Upregulated	METTL14/CYP1B1 axis, m6A methylation	Proliferation and invasion marker	[45]

Abbreviations: miR, microRNA; lncRNA, long non-coding RNA; circRNA, circular RNA; piRNA, PIWI-interacting RNA; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; EMT, epithelial-to-mesenchymal transition; FIGO, International Federation of Gynecology and Obstetrics; PRC2, polycomb repressive complex 2; ZEB, zinc finger E-box-binding homeobox; NF-kB, nuclear factor kappa B; PI3K/AKT, phosphoinositide 3-kinase/protein kinase B; PTEN, phosphatase and tensin homolog; DNMT3A, DNA methyltransferase 3 alpha; HMGA2, high mobility group AT-hook 2. Ref., reference.

5. Mechanisms of extracellular RNAs in tumor progression

The oncogenic potential of exosomal extracellular RNAs extends beyond their utility as passive biomarkers; they are active effectors of the intercellular communication networks that sustain and amplify malignant growth. Fabbri *et al.* demonstrated that tumor-secreted miRNAs engage Toll-like receptors on immune cells, triggering pro-inflammatory and pro-metastatic cytokine secretion in a feed-forward loop [39]. In HPV-driven carcinogenesis, oncomiRs exported from E6/E7-expressing tumor cells convert neighboring stromal fibroblasts and macrophages into tumor-supportive accomplices via exosomal RNA transfer [46].

Selective packaging of miRNAs into exosomes is regulated by ceramide biosynthesis via nSMase2-dependent lipid remodeling of the endosomal membrane; nSMase2 inhibition significantly reduces exosomal miRNA secretion [47]. In HPV-positive cancer cells, E6-mediated p53 degradation and E7-mediated pRb inactivation upregulate the PI3K/AKT/mechanistic target of rapamycin (mTOR) axis, which promotes ceramide biosynthesis and amplifies exosome secretion rates [2].

Pre-metastatic niche formation is a key process through which tumor-derived exosomes orchestrate the distant microenvironment in advance of cancer cell arrival [48]. Exosomal integrins encode organotropic metastatic preferences by engaging tissue-specific extracellular matrix ligands at predetermined metastatic sites [49]. The RNA cargo within these organotropic exosomes promotes vascular permeability, suppresses innate immune surveillance, and induces a permissive extracellular matrix scaffold [48].

The hallmarks of cancer encompass sustained proliferative signaling, resistance to apoptosis, replicative immortality, angiogenesis, invasion, and immune evasion [47]. Exosomal extracellular RNAs contribute mechanistically to each hallmark in HPV-associated carcinogenesis. The 2022 updated hallmarks framework further incorporated nonmutational epigenetic reprogramming, polymorphic microbiomes, senescent cells, and unlocking phenotypic plasticity as emerging hallmarks - dimensions increasingly relevant to exosome-mediated oncogenic programming in HPV-associated tumors [50]. MicroRNA dysregulation, a conserved feature across virtually all human malignancies [51,52], is amplified by exosomal dissemination, converting a cell-intrinsic molecular lesion into a field-wide oncogenic perturbation.

Table 3 summarizes the key signaling pathways dysregulated by exosomal RNAs in HPV-associated cancers, identifying the specific RNA mediator responsible, the directional effect on pathway activity, and the resultant biological consequence. Pathways represented include PI3K/AKT/mTOR, p53/apoptosis, Wnt/β-catenin, NF-κB, TGF-β/Smad, VEGF/angiogenesis, RIG-I/interferon, and the ceramide/nSMase2 axis, collectively illustrating the breadth of oncogenic reprogramming mediated by tumor-derived exosomal cargo in HPV-driven malignancies.

Table 3. Key signaling pathways dysregulated by exosomal RNAs in HPV-associated cancers.

Pathway	Exosomal RNA Mediator	Effect	Biological Consequence	Ref.
PI3K/AKT/mTOR	miR-21 (targets PTEN)	Activation	Enhanced proliferation; therapy resistance	[30]
p53/apoptosis	miR-34a (suppressed by E6)	Inhibition	Apoptotic evasion; sustained cell survival	[31]
Wnt/beta-catenin	miR-34a loss; lncRNA HOTAIR	Activation	EMT induction; cancer stem cell expansion	[40]
NF-kB/inflammation	miR-155 (TLR axis engagement)	Activation	Pro-metastatic cytokine milieu	[46]
TGF-beta/Smad	Exosomal surface TGF-beta	Activation	Regulatory T-cell induction; Th17 skewing	[33]
VEGF/angiogenesis	lncRNA HOTAIR; miR-210	Activation	Tumor vascularization; hypoxic adaptation	[40]
RIG-I/IFN axis	circRNA (HPV-E6 suppresses IRF3)	Inhibition	Attenuated innate immune sensing	[20]
Ceramide/nSMase2	All exosomal cargo (amplified)	Activation	Increased exosome secretion; oncomiR spread	[47]

Abbreviations: PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; NF-kB, nuclear factor kappa B; TGF-beta, transforming growth factor beta; VEGF, vascular endothelial growth factor; RIG-I, retinoic acid-inducible gene I; IFN, interferon; IRF3, interferon regulatory factor 3; nSMase2, neutral sphingomyelinase 2; TLR, Toll-like receptor; EMT, epithelial-to-mesenchymal transition; Th17, T helper 17 cell; Ref., reference.

6. Extracellular RNAs in tumor immunity

Tumor-derived exosomes constitute a sophisticated mechanism through which malignant cells actively subvert immune surveillance. Exosomal miR-21 and miR-155, transferred from HPV-positive tumor cells to dendritic cells, impair antigen presentation by downregulating MHC class II expression and reducing IL-12 secretion, diminishing cytotoxic T-lymphocyte priming [33]. Exosomal PD-L1 on tumor-derived vesicles engages programmed death 1 (PD-1) receptors on T cells in draining lymph nodes, suppressing effector T-cell activation independently of the primary tumor microenvironment [33].

In HPV-driven immune evasion, E7-upregulated exosomal miR-9 is transferred to cytotoxic T lymphocytes and NK cells, suppressing PRDM1 (BLIMP1) expression and impairing effector differentiation and cytokine production [32]. HPV-positive exosomes additionally carry surface-bound TGF-beta that

synergizes with exosomal miRNA cargo to induce regulatory T-cell expansion and T helper 17 (Th17) cell polarization [33]. Melanoma-derived exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype, illustrating the systemic reach of tumor-derived exosomal programming applicable to HPV-associated cancers [53].

Exosomal circRNAs act as modulators of innate immune sensing by activating the RNA-sensing receptor RIG-I in adjacent immune cells, triggering interferon signaling. However, HPV E6 mediates IRF3 degradation, attenuating interferon signaling and insulating the tumor microenvironment from immune clearance [31,34]. The co-administration of immune checkpoint inhibitors with exosomal RNA-targeting interventions may provide synergistic benefit by simultaneously relieving checkpoint suppression and abrogating exosome-mediated immunosuppressive signaling [33].

7. Extracellular RNAs as potential therapeutic targets in HPV-associated cancers

Two complementary therapeutic strategies have emerged: inhibitory approaches neutralizing pathogenic oncomiRs and oncogenic lncRNAs, and reconstructive approaches leveraging exosomes as biocompatible RNA delivery platforms [54]. Anti-miRNA oligonucleotides (antagomiRs) and locked nucleic acid (LNA) inhibitors targeting miR-21 and miR-155 reduce HPV-positive tumor cell proliferation and restore apoptotic sensitivity *in vitro* and in xenograft models [55]. Encapsulation within engineered nanoparticles or exosomes substantially improves pharmacokinetic stability and intracellular delivery efficiency [56].

El-Andaloussi *et al.* pioneered targeted exosome-mediated small interfering RNA (siRNA) delivery by decorating dendritic cell-derived exosomes with rabies virus glycoprotein (RVG) peptides, establishing proof of concept for engineered exosome therapeutics [54]. In HPV-associated cancers, exosomes carrying siRNAs targeting E6 and E7 mRNA restore p53 and pRb activity, induce G1 cell cycle arrest, and sensitize tumor cells to cisplatin-based chemotherapy [10]. Dendritic cell-derived exosomes loaded with tumor-associated antigens have entered clinical evaluation as cancer vaccines, establishing precedent for exosome-based immunotherapy in HPV-driven malignancies [57].

Exosome-based delivery of tumor-suppressive miRNAs, including miR-34a and miR-143, inhibits cervical carcinoma cell growth and migration in preclinical models [31,56]. Exosomal mechanisms of therapy resistance, including redistribution of chemotherapeutic drugs and propagation of resistance-conferring miRNAs to sensitive neighboring cells, represent a parallel challenge [58]. Pharmacological nSMase2 inhibition disrupts this resistance propagation and re-sensitizes HPV-positive tumor cells to standard-of-care agents [47]. Hybrid EV-liposome platforms have demonstrated improved loading efficiency in early experimental settings; however, these systems remain at preclinical stages and their clinical translatability has not yet been established. Exosome-mediated RNA delivery confers advantages over synthetic nanoparticles, including natural cell tropism, reduced immunogenicity, and superior endosomal escape, however, scalable manufacturing, cargo loading efficiency, and *in vivo* targeting specificity represent substantial translational barriers that must be overcome before clinical application can be considered [59].

Table 4 summarizes the principal therapeutic strategies targeting exosomal RNA in HPV-associated cancers, encompassing antagomiR-based silencing, exosome-mediated siRNA and miRNA mimic delivery, nSMase2 pharmacological inhibition, dendritic cell-derived exosome vaccination, combination immunotherapy, and hybrid EV-liposome platforms. For each strategy, the specific agent or approach, RNA target, cancer type, and current developmental stage are indicated.

Table 4. Therapeutic strategies targeting exosomal RNA in HPV-associated cancers.

Strategy	Agent/Approach	RNA Target	Cancer Type	Stage	Ref.
antagomiR silencing	LNA anti-miR-21	miR-21 (PTEN pathway)	Cervical carcinoma	Preclinical	[44]
antagomiR silencing	LNA anti-miR-155	miR-155 (NF-kB pathway)	HPV+HNSCC	Preclinical	[55]
Exosomal siRNA delivery	E6/E7 siRNA-loaded exosomes	HPV E6/E7 mRNA	HPV+cervical carcinoma	Preclinical	[10]
miRNA mimic delivery	miR-34a mimic in exosomes	Oncogenic targets	Cervical carcinoma	Preclinical	[31]
miRNA mimic delivery	miR-143 mimic in exosomes	KRAS; ERK5 targets	HPV+carcinoma	Preclinical	[56]
nSMase2 inhibition	GW4869	All exosomal cargo	HPV+tumors (broad)	Preclinical	[47]
DC-exosome vaccine	DEX+tumor antigen RNA payload	Immune activation	Multiple solid tumors	Phase I/II clinical trials	[57]
Combination immunotherapy	anti-PD-1+exosome blockade	PD-L1/immune extracellular RNA	HPV+oropharyngeal SCC	Investigational	[33]
EV-liposome hybrid	Synthetic EV mimetic+RNA	Configurable cargo	HPV-associated (proposed)	Investigational	[59]

Abbreviations: LNA, locked nucleic acid; siRNA, small interfering RNA; miRNA, microRNA; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; DC, dendritic cell; DEX, dendritic cell-derived exosomes; EV, extracellular vesicle; nSMase2, neutral sphingomyelinase 2; GW4869, nSMase2 pharmacological inhibitor; SCC, squamous cell carcinoma; PD-1, programmed death 1; PD-L1, programmed death ligand 1; NF-kB, nuclear factor kappa B; KRAS, Kirsten rat sarcoma viral proto-oncogene. Ref., reference.

Figure 3 illustrates four complementary therapeutic strategies employing engineered exosomes to target HPV-associated cancers. Panel A depicts antagomiR silencing, in which engineered exosomes loaded with LNA anti-miR-21 and anti-miR-155 are taken up by HPV-positive cells, suppressing oncogenic miRNA activity and resulting in PTEN upregulation, increased apoptosis, and reduced proliferation. Panel B shows E6/E7 siRNA delivery via RVG surface-decorated engineered exosomes, which achieve endosomal escape and silence HPV oncoprotein expression, restoring p53 and pRb activity and sensitizing tumor cells to cisplatin. Panel C illustrates tumor-suppressive miR-34a mimic delivery into HPV-positive cervical carcinoma cells, which downregulates NOTCH1, CDK6, and MYC, inducing apoptosis and reducing migration and invasion. Panel D demonstrates pharmacological nSMase2 inhibition by GW4869, which disrupts ceramide-dependent exosome packaging, blocks oncomiR secretion and dissemination, restores NK cell cytotoxicity, and re-sensitizes tumor cells to chemotherapy.

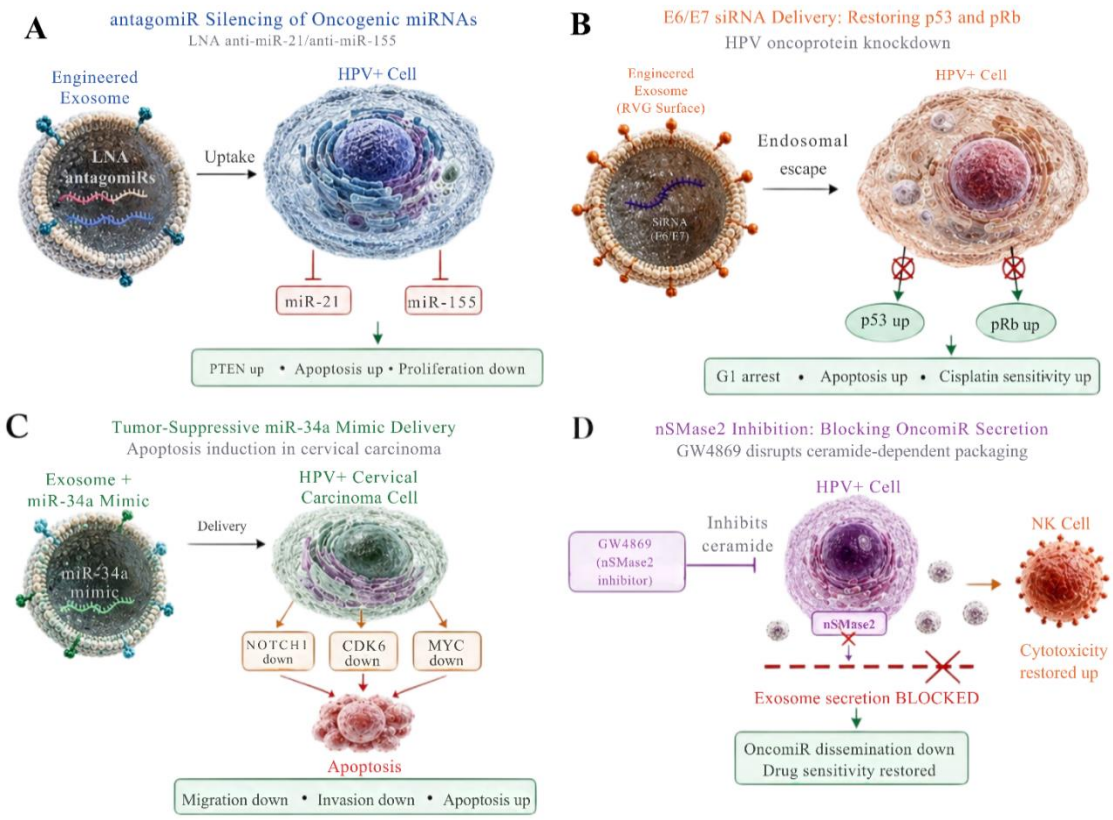

Figure 3. Engineered exosome platforms for therapeutic RNA delivery in HPV-associated cancers. Panels: **(A)** antagomiR-loaded exosomes silencing miR-21/miR-155; **(B)** E6/E7 siRNA-loaded exosomes restoring p53/pRb activity; **(C)** miR-34a mimic delivery inducing apoptosis; **(D)** nSMase2 inhibitor blockade of oncomiR secretion.

8. Discussion

The body of evidence reviewed herein positions exosomal extracellular RNAs as a scientifically compelling and clinically actionable dimension of HPV-associated cancer biology. The capacity of tumor-derived exosomes to mirror the molecular identity of originating malignant cells, combined with the accessibility of biofluids for minimally invasive sampling, creates a uniquely favorable context for exRNA-based liquid biopsy.

A conceptually important insight is the mechanistic duality of exosomal RNAs as both effectors of oncogenic signaling and reflectors of tumor molecular state. Unlike traditional biomarkers that passively correlate with disease, exosomal RNAs are active propagators of malignant programs. This mechanistic relevance strengthens the rationale for clinical targeting, since inhibiting pathogenic exosomal RNA species may simultaneously yield therapeutic benefit and a measurable pharmacodynamic readout.

The HPV-specific alteration of exosomal RNA cargo, mediated primarily by E6 and E7 oncoproteins, generates disease-specific signatures with potential to complement established diagnostic algorithms, including HPV DNA testing and p16 immunohistochemistry. The ability to discriminate HPV-positive from HPV-negative cancers at the exosomal RNA level has direct implications for determining treatment intensity, predicting immunotherapy response, and guiding post-treatment surveillance.

The immunomodulatory dimension of exosomal RNAs presents both a mechanistic challenge and a therapeutic opportunity. Systematic suppression of innate and adaptive antitumor immunity by tumor-derived exosomal miRNAs and surface-associated PD-L1 suggests that these vesicles constitute a mobile immune checkpoint operating locally and systemically. Strategies to intercept exosome secretion or neutralize immunosuppressive cargo warrant rigorous investigation in combination with approved checkpoint inhibitors.

Current limitations include the predominance of cell line and xenograft model data, sparse prospective clinical validation, and absence of standardized EV isolation and RNA quantification protocols across institutions. Adoption of the MISEV2023 consensus framework and harmonized reporting through community repositories such as Vesiclepedia 2024 and EVmiRNA2.0 represent critical steps toward methodological standardization [12,27,28]. The emergence of single-vesicle characterization platforms including nano-flow cytometry, and the integration of spatial transcriptomics with EV tracking, will further resolve population-level heterogeneity and contextualize exosomal RNA signaling within intact tumor microenvironment architecture [60,61]. A critical and underappreciated challenge in the exosomal RNA biomarker field is the lack of methodological standardization across pre-analytical and analytical steps. Variables including biofluid collection tubes, centrifugation protocols, EV isolation method (ultracentrifugation, size-exclusion chromatography, precipitation-based kits), RNA extraction platform, and normalization strategy each independently introduce systematic bias that precludes direct inter-study comparison. The MISEV2023 guidelines provide an updated and expanded framework to address these issues, yet compliance in published HPV-related EV studies remains inconsistent [12]. Adoption of EV-TRACK transparent reporting standards and deposition of raw datasets into community repositories such as Vesiclepedia 2024 and EVmiRNA2.0 are urgently needed to enable meta-analytic synthesis and accelerate clinical translation [27,28]. These gaps must be addressed to generate reproducible, clinically deployable evidence.

9. Conclusion

Exosomal extracellular RNAs represent a rich and functionally significant dimension of HPV-associated cancer biology with compelling translational implications. The convergence of exosome biology, non-coding RNA science, and HPV oncology has illuminated vesicle-mediated communication networks that sustain tumor growth, subvert immune clearance, and prepare distant metastatic niches.

The dual potential of exosomal RNAs as pharmacological targets amenable to antagomiR-based silencing and as carriers for precision RNA therapeutics positions exosome-centric approaches as a frontier of sustained scientific and clinical investment. Future research should prioritize prospective biomarker validation in HPV-specific cohorts, mechanistic dissection of oncoprotein-exosome interactions, and rational design of combination strategies integrating exosomal RNA targeting with immune checkpoint blockade and standard-of-care chemoradiation. Nonetheless, the majority of therapeutic findings reviewed herein derive from preclinical models, and the translational barriers of scalable production, targeted delivery, and long-term safety must be systematically addressed before clinical deployment.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, AI-assisted tools were used for language editing and readability enhancement. During the preparation of this manuscript, the authors used generative AI tools only to improve language and readability. Specifically, the authors used Claude and ChatGPT for language polishing, structural editing, and improving the narrative flow of the manuscript, and AI-assisted tools for figure preparation. The authors take full responsibility for the content of the manuscript. The authors take full responsibility for the integrity, originality, and accuracy of all scientific content.

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Authors' contribution

Conceptualization, M.O.C and M.O; methodology, M.O.C; software, M.O.C; validation, M.O.C, B.K.Y and M.O; formal analysis, M.O.C; investigation, M.O.C; resources, M.O; data curation, M.O.C; writing—original draft preparation, M.O.C; writing—review and editing, B.K; visualization, B.K; supervision, B.K.Y and M.O; project administration, M.O.C; funding acquisition, M.O. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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