RESEARCH ARTICLE

**Editorial Process:** Submission:10/08/2025 Acceptance:03/16/2026 Published:04/07/2026

# Bioinformatics Analysis Reveals Distinct Oncogenic Profiles of HPV-16 and HPT-18 to Other Subtypes in Cervical Cancer

**I Gde Sastra Winata[1]*, Stephen Dario Syofyan[2], Joshua Francisco Syofyan[3], Regina Caeli Santoso[2], Nakeisha Jovita Purnomo[2], Evannelson Enggar Pradipta Wardhana[2], Elia Setiawan[2], Haryo Purwodiningrat[2], Felisha Yuwono[2], Natasya Aya Pusparani[3], I Made Krishna Putra Pramanda[3], Jessica Nathalia[4]**

## Abstract

**Background:** HPV types 16 and 18 are associated with 70% of invasive cervical cancers. Between these two types of HPV, HPV type 16 is more commonly found in cervical cancer patients, whereas HPV type 18 is less frequently reported. Currently, the molecular mechanism underlying the increased cancer risk in HPV type 16, compared to HPV type 18, has not yet been fully elucidated. **Objective:** This paper aims to identify the factors that make HPV type 16 the primary contributor to cervical cancer by comparing gene expression profiles with those of HPV type 18. **Method:** The examination began after obtaining the RNA sequencing dataset (GSE192897). The dataset's genes were then analyzed to identify differentially expressed genes (DEGs) using the GEO2R tool. With the help of Enrichr and SRplot tools, the DEGs were first enriched and analyzed through Gene Ontology (GO), GeDiPNet, and the Kyoto Encyclopedia of Genes and Genomes (KEGG). Finally, a protein–protein interaction (PPI) network was constructed using Cytoscape, and the top ten hub genes were ranked with the help of CytoHubba. **Result:** DEG analysis revealed 128 differentially expressed genes (DEGs), including 14 upregulated and 114 downregulated genes. The upregulated genes were associated with positive regulation of interferon-beta production, vesicle-related processes, endopeptidase inhibitor activity, and interferon-gamma signaling. The downregulated genes were linked to positive regulation of cell motility, the endoplasmic reticulum lumen, cytokine activity, and signal transduction. **Discussion:** There are several differentially expressed genes (DEGs) in HPV type 16 compared to type 18; these upregulated genes may potentially play a role in promoting cervical cancer development more significantly than HPV type 18. These DEGs underscore the urgency of implementing HPV genotyping tests to identify HPV types with higher cervical cancer prevalence. **Conclusion:** This analysis identified BUB1, DLGAP5, and ASPM as key genes specifically expressed in HPV-16/18–related cervical cancer, suggesting their potential as biomarkers for prognosis and disease progression.

**Keywords:** Bioinformatics- HPV 16- HPV 18- Cervical Cancer- Gene Expression

*Asian Pac J Cancer Prev,* **27 (4)**, 1505-1513

## Introduction

In 2022, cervical cancer ranked as the fourth most common type of cancer among women globally with 660.000 new cases [1]. A significant number of deaths is about 350.000 cases and 94% of them are concentrated in low and middle income countries [1, 2]. Persistent infection of high-risk human papillomavirus (HR-HPV) is the primary etiological factor in the pathogenesis of cervical cancer with 99% of total cases [2, 3]. Around 30 types of HPV are transmitted through sexual contact [4]. HPV is a non-enveloped pathogen with a nano-sized (55 nm) icosahedral capsid. Within the HPV genome, the Long Control Region (LCR) serves as the main regulator of genetic material replication and gene transcription, including early gene (E1-E7) and late structural genes (L1 and L2) [5]. Premalignant cervical lesions and cancer preferentially arise in the HPV-targeted transformation zone of the cervix due to its inherent susceptibility. Micro-wounds serve as entry points for HPV infection of basal epithelial cells in the stratified cervical tissue (Figure 1).

HPV drives cervical carcinogenesis through the oncogenic potential of its E5, E6, and E7 proteins, which subvert critical cellular processes by interacting with host cell proteins, thereby disrupting regulatory pathways

*[1]Division of Oncogynecology, Department of Obstetrics and Gynecology, Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali, Indonesia. [2]Faculty of Medicine, University of Indonesia, Jakarta, Indonesia. [3]Faculty of Medicine, Udayana University, Bali, Indonesia. [4]Department of Obstetrics and Gynecology, Faculty of Medicine, Udayana University, Bali, Indonesia. *For Correspondence: sastra@unud.ac.id*

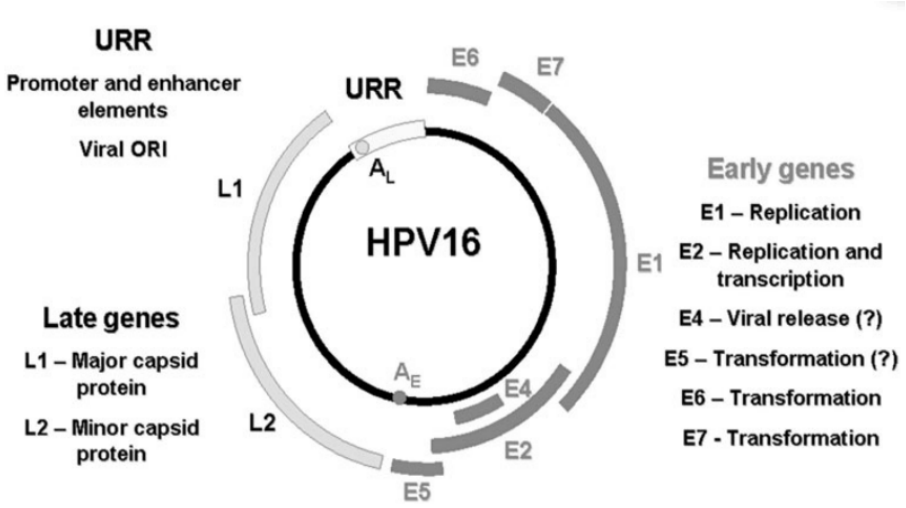


Figure 1. Genome Organization of HPV16 [6]

governing proliferation, DNA repair, immune response, apoptosis, and metabolism. Cervical carcinogenesis frequently involves HPV genomic instability manifesting as gene loss, duplication, or overexpression driven by deletions, replicative errors, or mutations that amplify viral oncoprotein production [4, 5]. From all HPV types, about 71% of cervical cancer cases globally are caused by HPV type 16 and 18 [3]. While HPV16 and HPV18 are known to be the most oncogenic, the detailed molecular mechanisms (oncogenic profiles) distinguishing them from each other and, crucially, from other high-risk HPV subtypes are not well characterized or systematically compared using modern bioinformatics. Therefore, this study aims to analyze the underlying factors that make HPV type 16 the primary cause of cervical cancer by comparing the gene expression with HPV type 18. By integrating transcriptomics data from HPV-positive cervical cancer samples, the researchers examined differences in viral and host gene expression, signaling pathways, and immune landscape characteristics. Machine learning techniques were also used to classify molecular patterns associated with specific HPV subtypes. This approach provides new insight into the diverse oncogenic processes driven by different HPV types, highlighting biologically meaningful differences that extend beyond their relative prevalence.

## Materials and Methods

*Identification of common upregulated and downregulated DEGs*

Gene expression datasets related to HPV and cervical cancer were retrieved from the GEO database (https://www.ncbi.nlm.nih.gov/geo/) [6]. Datasets regarding HPV-positive cervical cancer were found with the following search terms: "HPV" AND "Cervical cancer" AND "geo2r"[filter]. In the search process, there were several inclusion criteria used: (1) Studies with HPV-positive cervical cancer samples; (2) Studies that provided RNA-seq data; (3) Studies that could be analyzed with the GEO2R tool. After the search was conducted, five datasets were found (GSE39001, GSE228568, GSE9750, GSE147009, and GSE67522). Following that, these datasets were analyzed with the GEO2R tool, revealing the DEG. Then, the results of the GEO2R analysis were filtered further with Microsoft Excel, where the DEGs were filtered with a cutoff value of an adjacent p value < 0.05 and |log fold change| > 1 to identify the significant upregulated and downregulated genes. Following that, the InteractiVenn tool (http://www.interactivenn.net/) was used to analyze the overlapping upregulated and downregulated DEGs to identify the specific DEGs for cervical cancer caused by HPV [7].

*Functional and Pathway Enrichment*

DEGs specific to advanced GBC were analyzed further with the GO and KEGG pathway enrichment analysis using Enrichr [8-10]. GO analysis of biological process (BP), molecular function (MF), and cellular component (CC) of the upregulated and downregulated genes was conducted and ranked based on their p-values.

*Network construction and hub genes analysis*

PPI of the DEGs specific to advanced GBC was created with the Cytoscape software and the STRING plugin [11,12]. The interactions between the DEGs were filtered with a confidence score > 0.9. Following that, the PPI network was divided into several clusters with the MCODE plugin and ranked with the Cytohubba plugin based on the maximal clique centrality (MCC).

*Gene Survival Analysis and Expression Tendency*

The 10 hub genes found were then analyzed further for their survival analysis and expression tendency with the GSCA tool [13, 14]. The genes with a significant effect on the survival of cervical cancer patients and constant expression during the progression of the disease were analyzed further with the GEPIA2 tool [15].

## Results

Table 1 Characteristics of included studies.

*DEG identification*

An in silico analysis was conducted using five RNA-

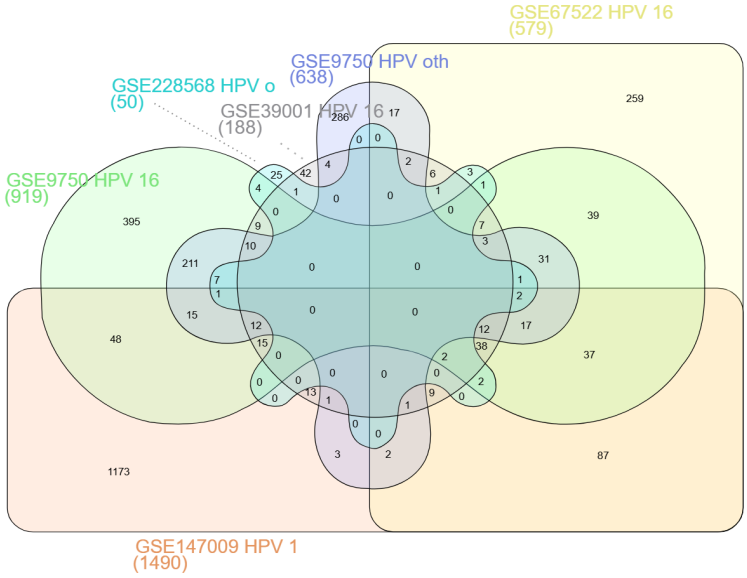


Figure 2. Upregulated Common DEGs in HPV 16 and HPV 18 vs Other Subtypes of HPV

Seq datasets of normal and cancerous cervical tissues obtained from the Gene Expression Omnibus (GEO): (GSE39001), (GSE228568), (GSE9750), (GSE147009), and (GSE67522). Following that, the GEO2R tool was used to identify the upregulated and downregulated differentially expressed genes (DEG) and screened based on (|log2-fold change|≥1 and adj. P<0.05) as a cutoff value. Analysis of DEGs with the venn diagram (Figure 2)

Table 1. Characteristics of included studies

| Study | Dataset | Samples (n) | | | Tissue | Protocol design |
|---|---|---|---|---|---|---|
| | | Healthy | HPV-16 positive cervical cancer | HPV-18 positive cervical cancer | | |
| Espinosa, 2013 | GSE39001 | 17 | 62 | - | Endocervix, exocervix | Expression profiling by array |
| Zhou, 2023 | GSE228568 | 3 | 3 | 3 | Cervix tissue (unspecified) | Expression and non-coding RNA profiling by array |
| Scotto, 2008 | GSE9750 | 24 | 19 | 3 | Cervix epithelium | Expression profiling by array |
| Zhang, 2020 | GSE147009 | 6 | 6 | - | Cervix epithelium | Non-coding RNA profiling by high throughput sequencing |
| Sharma, 2015 | GSE67522 | 11 | 20 | - | Cervix tissue (unspecified) | Expression profiling by array |

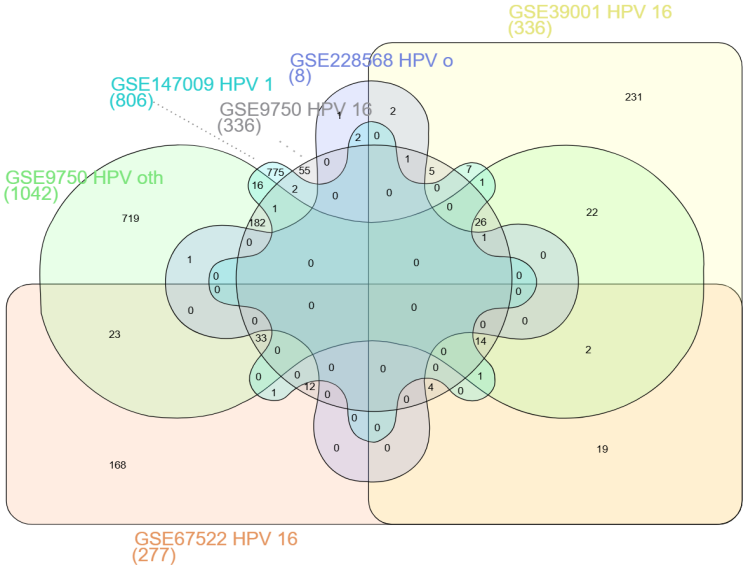


Figure 3. Downregulated DEGs in HPV 16 and HPV 18 vs Other Subtypes of HPV

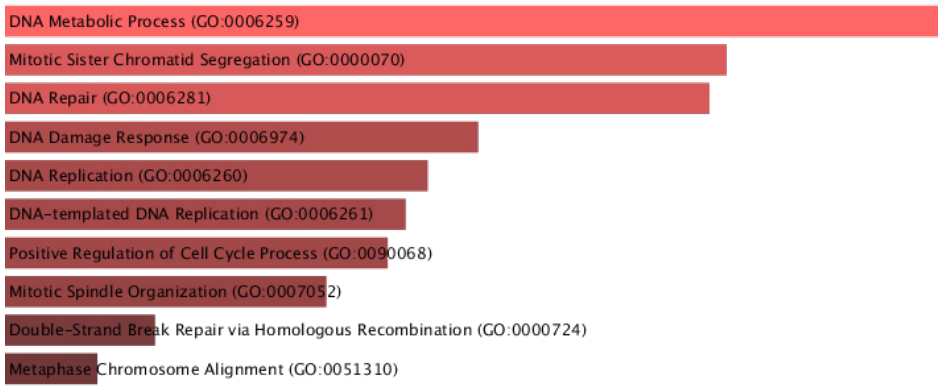


Figure 4. GO of Upregulated Biological Process

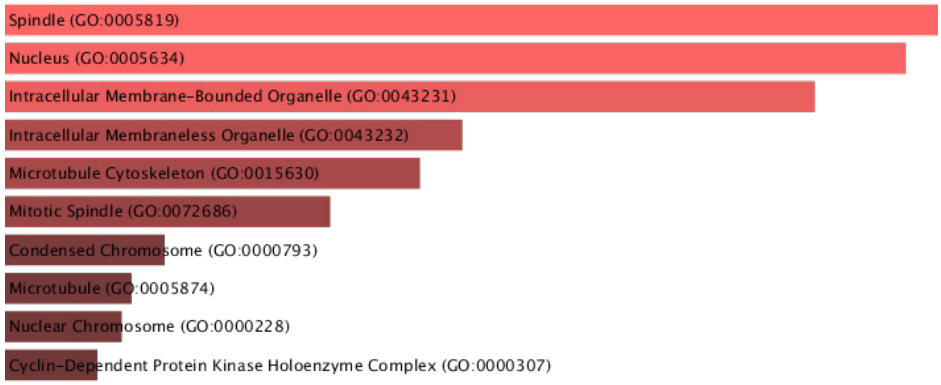


Figure 5. GO of Upregulated Cellular Component

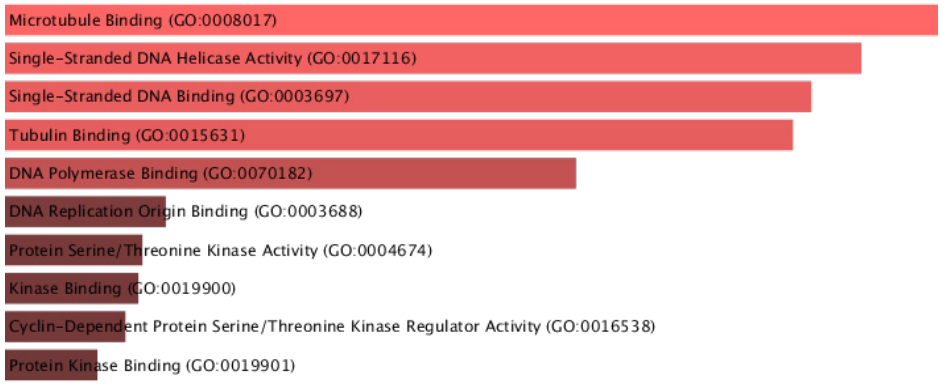


Figure 6. GO of Molecular Function

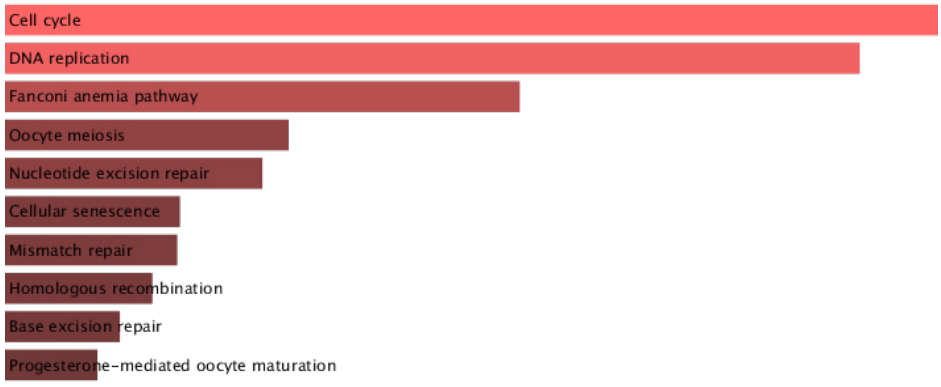


Figure 7. Upregulated KEGG

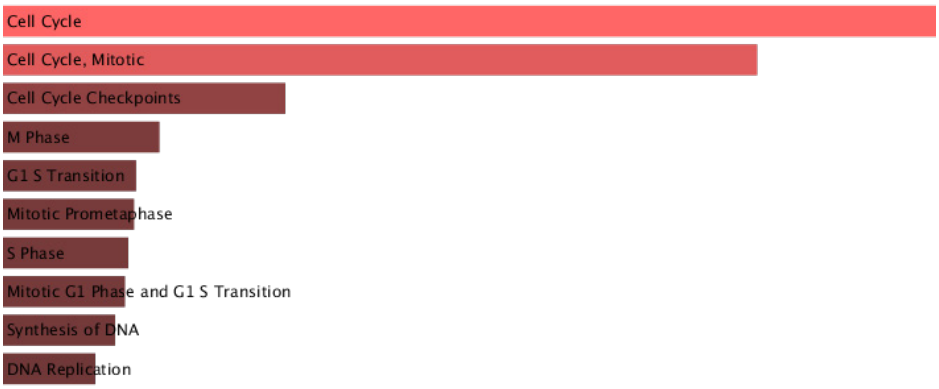


Figure 8. Upregulated Reactome

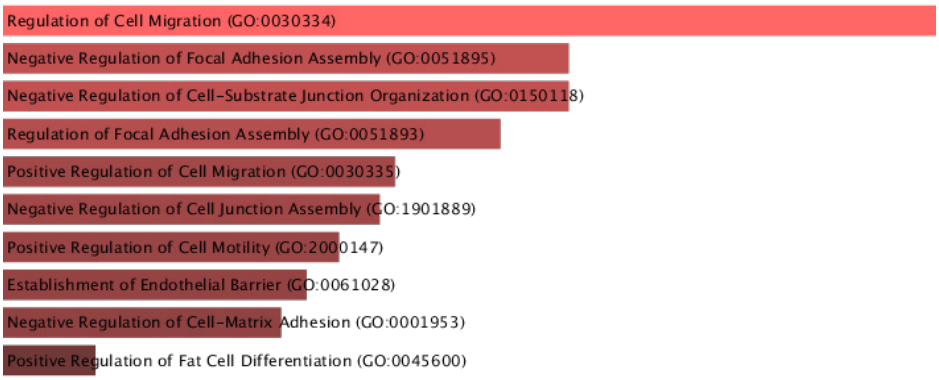


Figure 9. Downregulated Biological Process

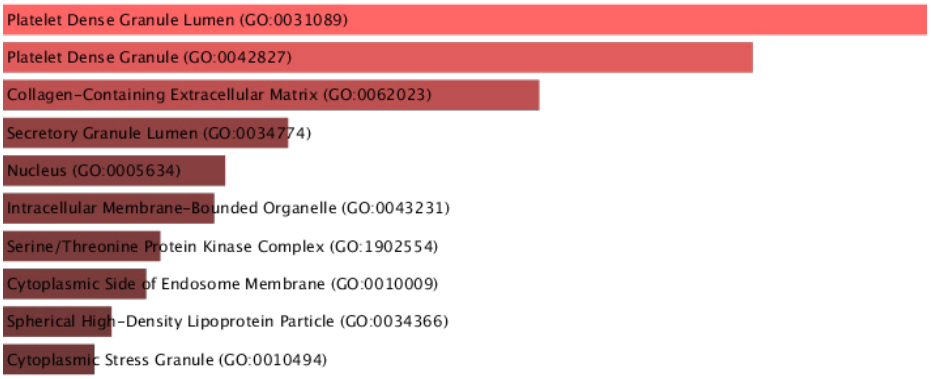


Figure 10. Downregulated Cellular Component

of the upregulated genes between HPV 16 and HPV 18 vs other subtypes of HPV showed 2,854 genes, while the venn diagram (Figure 3) of the downregulated genes showed 2,343 genes.

*GO/KEGG enrichment analysis*

2,854 upregulated genes were uploaded to Enrichr for GO, KEGG, and Reactome pathway analysis. The results revealed that the upregulated genes' biological processes (Figure 4) were related to DNA metabolic process, mitotic sister chromatid segregation, and DNA repair. The upregulated genes' cellular components (Figure 5) were associated with the spindle, nucleus, and intracellular membrane-bounded organelle. The molecular function of the upregulated genes (Figure 6) was linked with microtubule binding, single-stranded DNA helicase activity, single-stranded DNA binding, tubulin binding, and DNA polymerase binding. KEGG pathway analysis of the upregulated genes (Figure 7) was mostly associated with cell cycle and DNA replication. Reactome pathway enrichment analysis (Figure 8) showed that the upregulated genes were mostly linked with cell cycle and specifically to the mitotic phase of cell cycle.

2,343 downregulated genes were uploaded to Enrichr for GO, KEGG, and Reactome pathway analysis. The results revealed that the downregulated genes' biological processes (Figure 9) were linked to regulation of cell migration. The downregulated genes'

cellular components (Figure 10) were associated with platelet dense granule lumen and platelet dense granule. The molecular function of the downregulated genes (Supplementary Figure 1) was linked with histone acetyltransferase binding. KEGG pathway analysis of the downregulated genes (Supplementary Figure 2) was mostly associated with fluid shear stress, atherosclerosis and amphetamine addiction. Reactome pathway enrichment analysis (Supplementary Figure 3) showed that the downregulated genes were mostly associated with platelet activation, signaling and aggregation.

PPI Network analysis was constructed with the STRING tool, containing the upregulated and downregulated genes in the dataset. The cutoff value for the interaction score was 0.9 to ascertain the level of interaction. The interaction network produced had 190 nodes and 914 edges as seen in Supplementary Figure 4. The molecular complex detection plug-in was used in cytoscape, which then revealed the top module that is identified by Mcode (Supplementary Figure 4b) comprised of 26 genes and 45 connections, The Cytohubba analysis of the top module showed the top 10 hub genes: *KIF11, DLGAP5, TOP2A, KIF2C, BUB1B, KIF20A, CCNB1, BUB1, CDK1,* and *ASPM*. (Supplementary Figure 4c & 4d).

*Gene Set Cancer Analysis (GSCA) of Survival and Expression Tendency*

Among the top 10 hub genes, survival analysis (Supplementary Figure 5) indicates that their expression had the most apparent impact on disease-free interval (DFI), although the associations were not statistically significant. Similar non-significant patterns were observed in relation to disease-specific survival (DSS) and overall survival (OS) for several genes. Notably, BUB1 was the only gene that demonstrated a marked effect on progression-free survival (PFS), where higher expression was associated with an increased risk of death. In the stage-wise mRNA expression analysis (Supplementary Figure 6), ASPM exhibited an upward trend in expression from clinical stage I to stage IV in cervical cancer (CESC), showing nominal significance. However, this finding did not remain significant after false discovery rate (FDR) correction (FDR = 0.415), indicating the need for cautious interpretation and further validation. Additionally, pathway activity analysis (Supplementary Figure 7) revealed distinct associations between several genes and specific signaling pathways, including KIF2C, DLGAP5, CCNB1, and BUB1, which were linked to cell cycle activation, while DLGAP5 was also associated with activation of the TSC-mTOR pathway.

Gene set–level analysis was performed to assess associations with survival outcomes, clinical stage, and pathway activity. In cervical cancer (CESC), higher GSVA scores were linked to increased hazard ratios across all survival endpoints, including overall survival (OS), progression-free survival (PFS), disease-specific survival (DSS), and disease-free interval (DFI), as shown in Supplementary Figure 8. However, none of these associations reached statistical significance. Notably, continuous survival analysis revealed a markedly elevated hazard ratio for DFI (HR = 26.96), indicating a possible link between elevated pathway activity and increased risk of disease recurrence. Still, the result was not statistically significant (p = 0.186) and should be interpreted with caution.

GSVA scores across clinical stages were visualized using both box plots and trend plots (Supplementary Figure 9 and Supplementary Figure 10). As shown in Supplementary Figure 9, the GSVA scores display a slight upward shift in later stages, with Stage IV having a marginally higher median score compared to Stage I. However, the overall difference among stages is not statistically significant (diff_p = 0.0649), though it borders conventional significance thresholds. Supplementary Figure 10 depicts the trend of GSVA scores, showing a minor rise from Stage I to II, a dip at Stage III, and a sharp increase at Stage IV. This progression is numerically supported by a trend score of 1.019, indicating a weak upward tendency. Nevertheless, the Mann-Kendall trend test yields a non-significant result (p = 0.308).

Furthermore, among the pathways assessed through the GSVA-pathway correlation analysis (Supplementary Figure 11), only the cell cycle pathway demonstrated a significant positive correlation between gene expression–derived GSVA scores and RPPA-based protein activity (Spearman ρ = 0.32, FDR = 0.000176). In contrast, other pathways such as apoptosis, epithelial-mesenchymal transition (EMT), and hormone signaling did not show significant relevance.

*GEPIA2 Pathological Stage Expression Analysis*

The genes that significantly affected the GSCA survival and expression tendency analysis are found to be BUB1, ASPM, and DLGAP5. Following that, the 3 genes were analyzed further with the pathological stage expression Analysis with GEPIA2 tool (Supplementary Figure 12, Supplementary Figure 13, and Supplementary Figure 14). Out of the 3 genes, ASPM (Supplementary Figure 13) showed the highest variance between stages (F = 2.15, Pr(>F) = 0.0937). ASPM showed a marginal trend toward differential expression across clinical stages (F = 2.15, Pr(>F) = 0.0937), suggesting a moderate degree of variation in expression levels that may reflect stage-associated regulatory changes. In contrast, BUB1 (F = 1.44, Pr(>F) = 0.231) and DLGAP5 (F = 0.717, Pr(>F) = 0.542) in Supplementary Figure 12 and Supplementary Figure 14 respectively did not exhibit statistically significant variation, with relatively low F values indicating that the expression differences across stages were minor compared to within-group variability. These findings suggest that ASPM may have some stage-associated regulation, although not conclusively, while BUB1 and DLGAP5 appear to be stage-independent in their expression profiles.

*Overall Survival Analysis using Kaplan-Meier*

To further evaluate the clinical significance of BUB1 (Supplementary Figure 15), ASPM (Supplementary Figure 16), and DLGAP5 (Supplementary Figure 17), a Kaplan-Meier survival

analysis was conducted. The outcome showed that both BUB1 and DLGAP5 had non-significant trends toward poorer overall survival in patients with high gene expression (HR = 1.4; p = 0.15 and 0.16, respectively). These results suggest a possible association with worse prognosis, although the differences were not statistically significant. In contrast, ASPM expression showed no association with survival (HR = 1.0; p = 0.97), indicating nearly identical survival outcomes between high and low expression groups. These findings suggest that all gene expression may not play as prominent role in survival outcomes for CESC patients.

## Discussion

Cervical cancer is a serious global health problem with increasing incidence rates, where HPV16 and HPV18 are recognized as the main oncogenic subtypes that drive its development through disruption of key cellular processes [2, 16]. In this study, bioinformatics analysis revealed ten top hub genes from the Cytohubba ranking, which are *KIF11, DLGAP5, TOP2A, KIF2C, BUB1, KIF20A, CCNB1, BUB1, CDK1*, and *ASPM*. Among these genes, *BUB1, ASPM*, and *DLGAP5* were observed to be clinically related to the DSS and OS.

BUB1 was the only gene that demonstrated a marked effect on progression-free survival (PFS), where higher expression was associated with an increased risk of death. This relationship suggests that BUB1 activity may influence early tumor recurrence or rapid progression despite treatment. As a mitotic checkpoint kinase, BUB1 regulates proper chromosome alignment and segregation and its dysregulation leads to chromosomal instability (CIN) which is a hallmark of aggressive tumor biology. Studies have shown that cancers with elevated CIN tend to recur earlier, respond poorly to therapy, and display greater genomic heterogeneity, which can drive treatment resistance [17]. The fact that BUB1 expression correlates with poorer PFS in our dataset mirrors these mechanisms. A previous study had found that BUB1, as one of the key components during mitosis, if expressed abnormally can cause mutation leading to various human malignancies, such as hepatocellular carcinoma [18]. Together, these clinical and molecular findings indicate that BUB1 overexpression in cervical cancer may mark tumors with highly proliferative and genomically unstable phenotypes, making it a potential biomarker for early relapse.

Similarly, DLGAP5 showed a similar trend in survival outcomes indicating a poorer prognosis. The clinical relevance of DLGAP5 may stem from its dual involvement in cell cycle progression and mTOR pathway activation. DLGAP5 works as activation of mTOR pathways that plays a major role in cervical cancer as a regulator for cell proliferation and growth. Activation of this pathway has already proven to be involved in many cancers such as ovarium, lung, and prostate cancer [19]. In cervical cancer, mTOR activation is associated with radioresistance, chemoresistance, and enhanced metastatic potential [20]. Thus, elevated DLGAP5 expression in patients with poorer DSS and OS may reflect heightened anabolic and proliferative activity within the tumor, leading to more aggressive clinical behavior. Furthermore, the strong association between DLGAP5 expression and cell cycle pathway activation shown in our GSCA pathway analysis supports the hypothesis that DLGAP5 contributes to an accelerated mitotic state, which is often correlated with worse treatment response and reduced survival.

Meanwhile, the ASPM gene is involved in staged-associated regulatory changes in cancer showing that ASPM expression tends to increase as cervical cancer becomes more advanced. Although the association did not remain statistically significant after FDR correction, this upward trend suggests that ASPM may contribute to tumor evolution across stages, potentially through its role in spindle formation and genomic maintenance. Although ASPM expression had no association with overall survival, a previous study indicates that ASPM is involved in developmental and stemness of cancer cells and can be a therapeutic target across different cancer types [21]. Cancers with higher stemness features typically exhibit greater plasticity, resistance to therapy, and the ability to drive recurrence [21]. Therefore, the stage-associated increase in ASPM expression may indicate a shift toward a more stem-like, treatment-tolerant phenotype in later-stage cervical cancers, which could explain the clinical trend despite non-significant survival findings.

Taken together, these findings suggest that the hub genes identified are tightly connected to core cell-cycle machinery, genomic stability, and proliferative signaling, all of which have known implications for clinical outcomes. The weak but consistent trends observed across PFS, DSS, OS, and stage analyses point to potential biological relevance even when statistical significance was not reached, likely due to limited sample sizes or the inherent heterogeneity of cervical cancer. Although their prognostic value showed non-significant patterns in survival analysis, the biological relevance of these genes remains compelling and consistent with known mechanisms of HPV-driven cervical carcinogenesis. Further research involving larger patient cohorts and comprehensive molecular profiling is necessary to clarify the prognostic potential of these genes and better understand their roles in cervical cancer progression.

BUB1 was the only gene that demonstrated a marked effect on progression-free survival (PFS), where higher expression was associated with an increased risk of death. A previous study had found that BUB1, as one of the key components during mitosis, if expressed abnormally can cause mutation leading to various human malignancies, such as hepatocellular carcinoma [17]. Similarly, DLGAP5 showed a similar trend in survival outcomes indicating a poorer prognosis. DLGAP5 works as activation of mTOR pathways that plays a major role in cervical cancer as a regulator for cell proliferation and growth. Activation of this pathway has already proven to be involved in many cancers such as ovarium, lung, and prostate cancer [18]. Meanwhile, the ASPM gene is involved in staged-associated regulatory changes in cancer showing that ASPM expression tends to increase as cervical cancer becomes more advanced. Although ASPM expression had no association with overall survival, a previous study indicates that ASPM is involved in developmental and

stemness of cancer cells and can be a therapeutic target across different cancer types [19].

Further research involving larger patient cohorts and comprehensive molecular profiling is necessary to clarify the prognostic potential of these genes and better understand their roles in cervical cancer progression.

In conclusion, the results of this analysis revealed several key gene expressions specific to HPV 16 and 18 not expressed in other subtypes of HPV causing cervical cancer. The genes whose expression is significant and is related to the prognosis of HPV type 16 and 18 cervical cancer are BUB1, DLGAP5, and ASPM. It is recommended that these genes be studied further for their potential as prognosis and progression biomarkers for cervical cancer caused by HPV type 16 and 18.

## Author Contribution Statement

Conceptualization: IGSW, SDS, JFS; Data curation: RCS, NJP, EEPW, ESHP, FY, NAP, IMKPP, JN; Supervision: IGSW; Writing - original draft: NAP, IMKPP; Funding acquisition: IGSW; Writing - review and editing: NAP, IMKPP, JN. All authors have read and agreed to the final version of the manuscript.

## Acknowledgements

The authors would like to thank all participants in this study and the research council of Departement Obstetrics and Gynecology, Udayana University and Faculty of Medicine, University of Indonesia for their assistance. All supporting data have been shown in the manuscript.

*Ethical Issue and Availability of Data*

This study is a bioinformatics study done with data available publicly in the GEO DataSets (https://www.ncbi.nlm.nih.gov/geo/) which does not need an ethical approval from any institution.

*Study Registration*

As a narrative review, this study does not involve primary data collection, clinical trials, or meta-analyses, and thus does not require formal registration in a research database.

*Conflict of Interest*

The authors declare that there are no conflicts of interest.

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