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Artikel Penelitian

# EKSPRESI HSP70 DAN KLASIFIKASI BETHESDA PADA SEL MUKOSA BUKAL PENDUDUK SEKITAR TPA MEDAN

## *HSP70 EXPRESSION AND BETHESDA CLASSIFICATION IN BUCCAL MUCOSAL CELLS OF RESIDENTS NEAR MEDAN LANDFILL*

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**A B S T R A K**

Pajanan kronis terhadap polutan dari lingkungan tempat pembuangan akhir (TPA) berpotensi menimbulkan stres oksidatif dan genotoksik pada sel epitel rongga mulut, sementara *Heat Shock Protein 70* (HSP70) berperan dalam mekanisme protektif seluler dan dapat berfungsi sebagai penanda awal perubahan epitel. Tujuan penelitian ini adalah mengevaluasi hubungan antara ekspresi HSP70 dan klasifikasi sitologi Bethesda 2014 pada sel mukosa bukal penduduk yang tinggal di sekitar TPA Terjun, Medan. Metode penelitian menggunakan desain analitik potong lintang pada 100 peserta, terdiri dari 24 penduduk yang tinggal dalam radius ≤1–3 km dan 76 penduduk ≥3 km. Sampel mukosa bukal dikumpulkan dengan cytobrush, diperiksa menggunakan pewarnaan Papanicolaou, dan dinilai ekspresi HSP70 secara imunositokimia menggunakan *Immunoreactive Score* (IRS) yang dikategorikan sebagai rendah (≤4) atau tinggi (>4). Analisis statistik dilakukan menggunakan *Fisher's Exact Test* dengan batas signifikansi p<0,05. Hasil penelitian menunjukkan bahwa 98% sampel diklasifikasikan sebagai NILM dan 2% sebagai ASC-US, dengan ekspresi sitoplasmik HSP70 tinggi pada 5% sampel, terutama pada kelompok terpajan, dan menunjukkan hubungan bermakna secara statistik. Kesimpulannya, pola ekspresi HSP70 yang rendah dengan sedikit peningkatan pada kelompok terpapar mengindikasikan kemungkinan respons adaptif awal terhadap pajanan polutan, sehingga HSP70 berpotensi digunakan sebagai biomarker noninvasif untuk memantau stres epitel akibat lingkungan.

**Keywords**

*HSP70, buccal mucosa, landfill, Bethesda classification, immunocytochemistry*

***A B S T R A C T***

*Chronic exposure to pollutants generated from landfill environments may induce oxidative and genotoxic stress in oral epithelial cells, while Heat Shock Protein 70 (HSP70) functions as a key cellular chaperone involved in maintaining proteostasis and mediating adaptive responses to environmental stressors. This study aimed to evaluate the association between HSP70 expression and the Bethesda 2014 cytological classification in buccal mucosal cells of residents living in proximity to the Terjun landfill in Medan, Indonesia. A cross-sectional analytical design was employed involving 100 adult participants, comprising 24 individuals residing within ≤1–3 km of the landfill and 76 residing ≥3 km away. Buccal epithelial samples were collected using sterile cytobrushes, examined using Papanicolaou staining, and assessed immunocytochemically for HSP70 expression using the Immunoreactive Score (IRS), categorized as low (≤4) or high (>4). Statistical analysis was performed with Fisher's Exact Test at a significance level of p<0.05. The results demonstrated that 98% of samples were classified as NILM and 2% as ASC-US, with high cytoplasmic HSP70 expression identified in 5% of samples, predominantly among the exposed group; however, a statistically significant association was observed between HSP70 expression and Bethesda classification. In conclusion, the overall low HSP70 expression with slight elevation among exposed individuals suggests early adaptive epithelial responses to chronic pollutant exposure, supporting the potential role of HSP70 as a noninvasive biomarker for monitoring environmentally induced epithelial stress.*

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## INTRODUCTION

Landfills emit complex pollutants, including particulate matter (PM2.5 and PM10), volatile organic compounds, polycyclic aromatic hydrocarbons, and heavy metals, contributing to oxidative damage and genotoxic stress.[1,2, 3,4 ,5] The oral mucosa, as a primary barrier, reflects early biological responses to environmental exposure and is widely used as a biomonitoring tissue.[6,7,8] Buccal epithelial cells demonstrate susceptibility to airborne pollutants and frequently serve as indicators of cytological and molecular alterations in exposed populations.[7,8]

Heat Shock Protein 70 (HSP70) functions as a molecular chaperone, assisting protein folding, regulating stress responses, and maintaining proteostasis during oxidative or toxic cellular injury.[9,10,11] Overexpression of HSP70 has been documented in oral precancerous and cancerous lesions, including leukoplakia, epithelial dysplasia, and oral squamous cell carcinoma, highlighting its potential role as an early biomarker of epithelial stress and carcinogenic transformation.[12,13,14,15,16,17]

Given the chronic pollutant exposure among residents living near the Terjun landfill in Medan, Indonesia, evaluating HSP70 expression in buccal epithelial cells may provide insights into early stress responses that precede morphological changes. This study aimed to assess the association between HSP70 expression and the Bethesda 2014 cytological classification in buccal mucosal cells of residents living near the Terjun landfill.

## METHODS

A cross-sectional analytical study was conducted from October 2024 to October 2025 at the Department of Anatomical Pathology, Universitas Sumatera Utara. A total of 100 participants aged ≥18 years were enrolled, consisting of 24 residents living within ≤1–3 km of the Terjun landfill in the Medan Marelan District (exposed group), categorized as *landfill residents*, and 76 individuals residing ≥3 km away (non-exposed group), categorized as *non-landfill residents*. These terms and distance criteria are used consistently throughout the manuscript to indicate levels of environmental exposure.[18,19,20,21] Buccal epithelial samples were collected using sterile cytobrushes following standardized exfoliative cytology procedures.[21,22,23] Cytological evaluation was performed using Papanicolaou staining and classified according to the Bethesda 2014 system, including NILM (*Negative for Intraepithelial Lesion or Malignancy)*, ASC-US (*Atypical Squamous Cells of Undetermined Significance*), LSIL (*Low-grade Squamous Intraepithelial Lesion*), HSIL (*High-grade Squamous Intraepithelial Lesion*), and SCC (*Squamous Cell Carcinoma*) .[24,25]

Immunocytochemical staining for HSP70 expression was conducted using a monoclonal HSP70 antibody (Dako, Denmark) at a 1:200 dilution. Antigen retrieval was performed using citrate buffer (pH 6.0), and DAB was used as the chromogen, following established immunocytochemistry and immunohistochemistry guidelines.[26,27,28] The Immunoreactive Score (IRS) was calculated by multiplying staining intensity (0–3) by the

percentage of positive cells (0–4), based on validated scoring methods for HSP70 assessment.[13,29] IRS values ≤4 were categorized as low expression, whereas values >4 were categorized as high expression. Data were analyzed using Fisher's Exact Test with SPSS version 26, and a p-value <0.05 was considered statistically significant.[30]

Ethical approval for this study was obtained from the Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara (No. 395/KEPK/USU/2025). Written informed consent was obtained from all participants before sample collection.

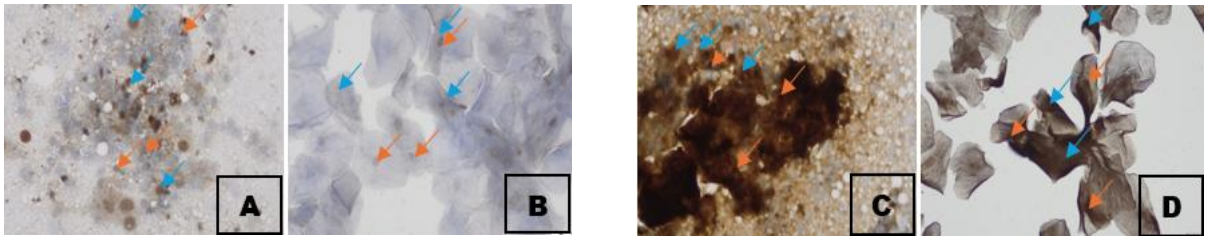


**Figure 1. Representative immunocytochemistry images showing cytoplasmic HSP70 expression in buccal epithelial cells A and C (100x), B and D (400x) . (A, B) Low (+1) cytoplasmic HSP70 expression in normal (NILM) buccal epithelial cells, showing faint brown DAB staining in the cytoplasm and nuclei. (C, D) High (+3) cytoplasmic HSP70 expression with intense, diffuse brown staining (A: 100×, B: 400×, C: 100×, D: 400×).**

## RESULTS

A total of 100 participants were included, consisting of 66 females and 34 males. Most participants were aged 36–45 years and had lived in their respective areas for more than five years. Based on the Bethesda 2014 classification, 98% (98/100) of buccal epithelial samples demonstrated NILM, while 2% (2/100) were categorized as ASC-US, all from individuals residing ≤3 km from the landfill.

High cytoplasmic HSP70 expression was identified in 5% (5/100) of samples, and all cases occurred among landfill residents. A statistically significant association was observed between residential proximity to the landfill and high cytoplasmic HSP70 expression (p = 0.001). Additionally, cytoplasmic HSP70 expression demonstrated a significant correlation with Bethesda classification (p = 0.002), where all ASC-US cases showed high HSP70 expression.

Meanwhile, there was no statistically significant association between residential proximity and Bethesda classification alone (p = 0.056). Nuclear HSP70 expression remained uniformly low in all samples. Tables 1–3 present the demographic characteristics, HSP70 expression patterns, and statistical correlations with Bethesda classification.

Based on the Bethesda 2014 classification, 98% of samples were NILM and 2% were ASC-US. High cytoplasmic HSP70 expression was observed in 5% of cases, predominantly in the exposed group, and this difference was statistically significant. This pattern aligns with reports indicating that early molecular alterations may occur despite normal cytomorphology in pollution-exposed

populations.[21,22,23] Tables 1–3 summarize demographic characteristics, HSP70 expression distribution, and its association with Bethesda classification.

**Table 1. Demographic characteristics of study participants.**

| Variable | Landfill Resident (n=24) | Non-Landfill Resident (n=76) | Total (n=100) |
|---|---|---|---|
| Sex | Male: 15 (62.5%)<br>Female: 9 (37.5%) | Male: 19 (25.%)<br>Female: 57 (75%) | 34 (34%)<br>66 (66%) |
| Age group (years) | 18-25: 3 (12.5%)<br>26-35: 4 (16.7%)<br>36-45: 8 (33.3%)<br>46-55: 7 (29.2%)<br>>55: 2 (8.3%) | 18-25: 7 (9.2%)<br>26-35: 23 (30.3%)<br>36-45: 28 (36.8%)<br>46-55: 11 (14.5%)<br>>55: 7 (9.2%) | 18-25: 10 (10.0%)<br>26-35: 27 (27%)<br>36-45: 36 (36%)<br>46-55: 18 (18%)<br>>55: 9 (9%) |
| Duration of residence | ≥5 years: 24 (100%) | ≥5 years: 76 (100%) | 100 (100%) |
| Bethesda classification | NILM: 22 (91.7%)<br>ASCUS: 2 (8.3%) | NILM: 76 (100%)<br>ASCUS: 0 (0%) | NILM: 98 (98%)<br>ASCUS: 2 (2%) |

**Table 2. Distribution of HSP70 expression in buccal mucosal cells (cytoplasmic and nuclear).**

| Location | Expression | Landfill Resident (n=24) | Non-Landfill Resident (n=76) | Total (%) | p-value* |
|---|---|---|---|---|---|
| Cytoplasmic | High | 5 (20.8%) | 0 (0%) | 5 (5%) | 0.001 |
| | Low | 19 (79.2%) | 76 (100%) | 95 (95%) | |
| Nuclear | High | 0 (0%) | 0 (0%) | 0 (0%) | N.A* |
| | Low | 24 (100%) | 76 (100%) | 100 (100%) | |

*Fisher's Exact Test. N.A. = Not Applicable (no variation in nuclear expression)

**Table 3. Correlation between HSP70 expression and Bethesda 2014 classification.**

| Bethesda classification | High HSP70 expression(n, %) | Low HSP70 expression (n, %) | p-value* |
|---|---|---|---|
| Cytoplasmic | NILM: 3 (3.1%) | NILM: 95 (96.9%) | 0.002 |
| | ASCUS: 2 (100%) | ASCUS: 0 (0%) | |
| Nuclear | NILM: 0 (0%) | NILM: 98 (100%) | N.A* |
| | ASCUS: 0 (0%) | ASCUS: 2 (100%) | |

*Fisher's Exact Test. N.A. = Not Applicable (no variation observed)

## DISCUSSION

The findings of this study demonstrate that most buccal epithelial samples exhibited normal cytological features, with minimal atypia (ASC-US) observed only among residents living ≤3 km from the landfill, . ,while all residents living ≥3 km remained NILM (Table 1). This is consistent with previous research showing that early epithelial exposure to environmental pollutants may not immediately manifest as overt cytomorphological abnormalities.[22,23] Buccal mucosa often displays subtle cellular adaptations under chronic pollutant exposure, especially in environments containing particulate matter, combustion residues, and volatile hydrocarbons.[7,8]

The significantly higher cytoplasmic HSP70 expression in landfill residents (p=0.001; Table 2) suggests the presence of early stress responses. This aligns with well-established evidence that airborne pollutants induce redox imbalance, oxidative stress, and activation of

cytoprotective pathways, including HSP70 upregulation.[1,2,3,4,5,9,10] HSP70 is known to protect epithelial cells against oxidative injury, maintain protein homeostasis, and modulate stress-induced signaling pathways.[9,10,11]

Furthermore, increased HSP70 expression has been documented in oral leukoplakia, epithelial dysplasia, and oral squamous cell carcinoma, supporting its involvement in early epithelial stress and carcinogenic progression.[12–17] In our study, although high cytoplasmic HSP70 expression was more frequently observed in residents living ≤3 km from the landfill, its association with Bethesda classification was statistically significant (Table 3). This suggests that molecular stress responses may already be activated while morphological features remain cytologically normal.

Chronic exposure to landfill-derived pollutants may induce sustained oxidative stress, mitochondrial dysfunction, and DNA damage, thereby activating adaptive molecular pathways such as heat shock responses.[1,2,3,4,5] Molecular and epigenetic studies have shown that particulate pollutants can cause oxidative DNA damage, genomic instability, and DNA methylation changes that precede visible cytological abnormalities.[31,32,33] This slow or absent cytological transformation may be explained by the high regenerative capacity of the buccal epithelium and the protective role of HSP70, which allows cells to maintain normal morphology by counteracting oxidative injury and delaying progression to dysplasia despite chronic pollutant exposure .

Overall, the results indicate that HSP70 upregulation represents an early adaptive response to pollutant exposure, occurring prior to cytomorphological alteration. Although the majority of samples in our study were NILM (98%), the higher frequency of cytoplasmic HSP70 expression in residents living ≤3 km from the landfill suggests that molecular epithelial stress may already be present while morphological features are still preserved. Therefore, HSP70 may serve as a sensitive early biomarker for monitoring environmentally induced epithelial stress. Larger studies incorporating molecular assays, environmental exposure quantification, and longitudinal follow-up are recommended to further validate the diagnostic and prognostic value of HSP70 in populations residing near landfill environments.

This study has limitations, including the absence of direct environmental measurements (e.g., PM10, heavy metals) and the homogeneity of cytological findings, which restricted analysis of the association between biomarker expression and morphological changes. Potential confounders such as traffic and indoor pollution also could not be fully controlled. Future studies should include quantitative exposure assessment, additional molecular biomarkers, and longitudinal follow-up to observe progression from molecular stress to epithelial alteration. Despite these limitations, the elevation of HSP70 expression in residents living closer to the landfill highlights the need for early biological monitoring and strengthened public health measures for communities surrounding landfill environments.

## CONCLUSION

Most buccal mucosal samples in this study demonstrated normal cytological features (98% NILM), with only 2% categorized as ASC-US. No high-grade intraepithelial lesion or malignant cytological changes were identified in either comparison group. However, the higher frequency of cytoplasmic HSP70 expression observed among residents living within ≤3 km of the landfill suggests the presence of early molecular epithelial stress responses prior to cytological transformation. These findings support the potential role of HSP70 as a sensitive noninvasive biomarker for detecting pollutant-related cellular stress. Further research incorporating quantitative exposure measurements, additional molecular biomarkers, and longitudinal monitoring is recommended to confirm the progression from molecular adaptation to epithelial alteration in landfill-exposed populations.

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