RESEARCH PAPER

E-Cadherin and Ki-67 Expression Profiles in Non-Small Cell Lung Cancer: Immunohistochemical Analysis and Correlation with Clinicopathological Features and Survival Outcomes

Sri Melati Munir[1,2], Wirsma Arief Harahap[3], Masrul Basyar[4], Noza Hilbertina[5]

[1]Doctoral Program of Biomedical Science, Faculty of Medicine, Universitas Andalas, Padang, Indonesia
[2]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, University of Riau, Pekanbaru, Indonesia
[3]Department of Surgical Oncology, Faculty of Medicine, Universitas Andalas, Padang, Indonesia
[4]Department of Pulmonology and Respiratory Medicine, Universitas Andalas/M. Djamil General Hospital, Padang, West Sumatra, Indonesia
[5]Department of Pathology Anatomy, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

***Corresponding Author: Wirsma Arief Harahap**
Department of Surgical Oncology, Faculty of Medicine, Universitas Andalas, Limau Manis, Pauh, Limau Manis, Padang, West Sumatra 25176, Indonesia
Email: wirsma66@gmail.com

ABSTRACT

Background: Lung cancer remains the leading cause of cancer death worldwide. Epithelial-to-mesenchymal (EMT) transition markers, such as E-Cadherin, and proliferation indices, such as Ki-67, become markers that can be assessed by immunohistochemistry (IHC) and can act as significant prognostic biomarkers. The simultaneous expression profile of E-Cadherin and Ki-67 in KPKBSK lung cancer patients in Indonesia is still rare. This study aimed to analyze the relationship between the immunohistochemical expression of E-Cadherin, EGFR, and Ki-67 in KPKBSK tissue specimens and to correlate the results of EGFR, E-Cadherin, and Ki-67 expression examination with pathological clinical parameters and overall survival.

Materials and Methods: This cross-sectional study involved 40 histopathologically confirmed KPKBSK patients, evaluated through immunohistochemical staining for E-Cadherin, EGFR, and Ki-67 performed on formalin-fixed paraffin-embedded (FFPE) tissue blocks and interpreted using the Immunoreactive Score (IRS) method, which was classified as low or high expression. Pathological clinical data, including age, sex, smoking history, tumour stage, and overall survival, were recorded. Statistical analysis includes descriptive statistics, the Mann-Whitney test, and the exact Fisher test.

Results: The total number of patients who were the subjects of the study was 40 patients (mean age 57.9 ± 11.8 years; range 22-79 years), with a predominance of males of 65%. The majority of patients (62.5%) showed disease at Stage IVA. Specifically, low expression of E-Cadherin was detected in 90% of patients (n = 36), while low expression of EGFR was universal (100%). High expression of Ki-67 was observed at 62.5% (n=25). The dominant phenotypic biomarkers were low E-Cadherin and high Ki-67 (55%), indicating a proliferative-mesenchymal phenotype. Overall, patient survival averaged 3.0 months among all patients. Low expression of E-Cadherin was associated with a longer median survival numerically (3.0 months) compared to high expression (3.0 months), although it was not statistically significant (p = 0.82). Ki-67 expression did not significantly affect survival outcomes (p=0.85). This finding likely reflects the advanced stage of disease within the cohort rather than the effects of intrinsic biomarkers.

Conclusions: This study demonstrated significant downregulation of E-Cadherin and the absence of EGFR overexpression, indicating a mesenchymal tumor phenotype with poor prognostic implications. Low E-Cadherin and high Ki-67 yields have the potential to obtain anti-proliferative therapy. The results of this study show that prospective studies are still needed that integrate IHC biomarkers with molecular profiles in lung cancer patients in Indonesia.

Keywords: Non-small cell lung cancer; E-Cadherin; Ki-67; EGFR; immunohistochemistry; epithelial-mesenchymal transition; overall survival; Indonesia.

How to cite this article: Munir SM, Harahap WA, Basyar M, Hilbertina N. E-Cadherin and Ki-67 Expression Profiles in Non-Small Cell Lung Cancer: Immunohistochemical Analysis and Correlation with Clinicopathological Features and Survival Outcomes. Int J Drug Deliv Technol. 2026;16(59s): 317-323. DOI: 10.25258/ijddt.16.59s.30

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, accounting for about 1.8 million deaths each year [1]. Non-small cell lung cancer (NSCLC) makes up about 85% of all lung cancer cases and includes several histological subtypes, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [2]. In Indonesia, lung cancer is one of the most common malignancies, with the majority of

patients presenting at advanced stages that cannot be resected, resulting in poor clinical outcomes and limited therapeutic options [3].

Non-small cell lung cancer requires reliable biomarkers for prognosis and therapeutic decision-making. The most clinically relevant biomarkers are E-Cadherin, epidermal growth factor receptor (EGFR), and Ki-67. E-Cadherin, an adhesion molecule of cells encoded by the CDH1 gene, plays a central role in maintaining the integrity of the epithelium. Its downregulation is characteristic of the epithelial-to-mesenchymal transition (EMT), a process that provides tumor cells with increased invasive capacity and metastasis [4,5]. Loss of E-Cadherin expression has been associated with advanced tumor stages, lymph node involvement, and poor prognosis in several cancers, including KPKBSK [6].

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that is often overexpressed or mutated in KPKBSK, especially in adenocarcinomas that arise in populations that have never smoked and East Asia [7]. EGFR activation mutations define different molecular subtypes that are highly responsive to tyrosine kinase inhibitors (TKIs). EGFR mutation testing is indispensable in the treatment of KPKBSK [8]. The Ki-67 marker is a cell nucleus protein that is used as a marker of proliferation and is expressed in all phases of the cell cycle except G0, serving as a substitute marker for tumor proliferative activity. High expression of Ki-67 has been correlated with aggressive tumor biology, poorer histological rates, higher risk of metastasis, and shorter survival in some types of cancer [9,10].

Immunohistochemistry (IHC) is the most widely used and cost-effective method for biomarker assessment in clinical examinations on limited resources, including in Indonesia. The Inoreactive Score System (IRS) provides a standard semi-quantitative approach to interpreting IHC results, integrating staining intensity and proportion of positively stained cells [11].

The development of the literature on biomarkers of lung cancer populations in West and East Asia patient data in Indonesia is very rare. Cultural, environmental, and genetic differences can affect the expression profile of biomarkers and their clinical correlation. The pattern of downregulation of E-Cadherin along with the high proliferation of Ki-67 in the context of low EGFR expression universally combined has not been studied in depth in the population of KPKBSK patients in Indonesia, so that if it can be further analyzed, it can certainly have different implications both clinically and biologically in treatment.

This study aimed to analyze the expression of IHC E-Cadherin, EGFR, and Ki-67 in KPKBSK patients and the correlation between biomarkers and relate them to pathological clinical parameters, including tumor stage, smoking history, gender, and overall survival. The novelty of this work lies in the explanation of the occurrence of widespread loss of E-Cadherin, the absence of excessive expression of EGFR, and the increase in Ki-67 in the population. Third, biomarkers have prognostic implications, so a systematic explanation is needed in this study.

2. MATERIALS AND METHODS

2.1 Study Design and Population

A cross-sectional study was conducted on lung cancer patients who were treated at Arifin Ahmad Hospital, Riau Province, Indonesia. Patients with histopathologically confirmed non-small cell carcinoma underwent forcep biopsy and IHC analysis of the pulmonary bronchi from January 2023 to December 2024. Eligibility criteria require histopathological confirmation of NSCLC, adequate availability of FFPE tissue blocks for IHC, and a complete clinical record. Patients with incomplete records or tissues for which there are no malignant or insufficient cells are excluded. A total of 40 patients met the inclusion criteria.

2.2 Clinicopathological Data Collection

Data extracted from medical records included: patient's age, sex, smoking history (categorized as non-smoker, passive smoker, light smoker [Mild IB], moderate [Moderate IB], or heavy smoker [Heavy IB] according to local clinical classification), initial diagnosis with stage TNM (UICC/AJCC 8th edition), Eastern Cooperative Oncology Group (ECOG) performance status, and overall survival time from the date of first consultation to death or last follow-up.

2.3 Immunohistochemical Analysis

IHC staining is performed on the 4-µm section of the FFPE tissue block. The following primary antibodies were used: anti-E-Cadherin (36B5 clone, Leica Biosystems), anti-EGFR (31G7 clone, Invitrogen), and anti-Ki-67 (MIB-1 clone, Dako). Antigen collection, blocking, and secondary antibody detection follow standard protocols. All slides were evaluated by two independent experienced pathologists who were blind to clinical outcomes. Differences are resolved by consensus.

Expression was assessed using the Iunorreactive Score (IRS), calculated as a product of staining intensity (1 = weak, 2 = moderate, 3 = strong) and positive cell proportion score (1 = 1-10%, 2 = 11-50%, 3 = 51-80%). The IRS value of 1-4 is classified as low expression and the IRS value of 5-9 as high expression, as per the established criteria [11].

2.4 Statistical Analysis

Descriptive statistics were used to summarize patient characteristics and the frequency of biomarker

expression. A continuous variable is expressed as the mean ± standard deviation (SD) or median with a range. Categorical variables are expressed as frequency and percentage. Survival data were analyzed using the Mann-Whitney U test for comparison between groups. The associations between categorical variables were evaluated using Fisher's exact test. The $p<0.05$ value was considered statistically significant. All analyses were performed using Python (version 3.12) with SciPy and pandas libraries.

2.5 Ethical Considerations

This research was conducted in accordance with the Helsinki Declaration. Ethical approval was obtained from the Ethics Unit of Medicine and Health Ethics Review Board for Medicine and Health Research, Faculty of Medicine, University of Riau No. B/069/UN19.5.1.1.8/UEPKK/2024. Patient identifiers are anonymized before analysis. Informed consent is obtained from all participants or their legal representatives.

3. RESULTS

3.1 Patient Characteristics

A total of 40 patients with NSLCC were confirmed to be registered. The mean age was 57.9 ± 11.8 years (range: 22-79 years), with a bimodal distribution that reflected younger non-smoking patients and older active smoking patients. Male patients dominated, comprising 26 of 40 patients (65.0%), while 14 (35.0%) were female.

Regarding smoking status, 25 patients (62.5%) were active smokers (mild, moderate, or severe), 3 (7.5%) were passive smokers, and 12 (30.0%) reported no history of tobacco exposure. Among active smokers, heavy smoking (Heavy IB) was most frequent (n=15; 37.5%), followed by moderate (n=10; 25.0%) and mild (n=2; 5.0%) smokers.

TNM staging revealed that the majority of patients were present in the advanced stages: Stage IVA (n=24; 60.0%), followed by Stage IIIB (n=8; 20.0%) and Stage IVB (n=7; 17.5%). These findings underscore the typical late-stage presentation in this population. Detailed patient characteristics are summarized in Table 1.

Table 1. Baseline Clinicopathological Characteristics of Study Patients (N=40)

Characteristic	n	%
Age (years), mean ± SD	57.9 ± 11.8	range 22-79
Sex		
Male	26	65.0%
Female	14	35.0%
Smoking Status		
Never smoker	12	30.0%
Passive smoker	3	7.5%
Light smoker (IB Ringan)	2	5.0%
Moderate smoker (IB Sedang)	10	25.0%
Heavy smoker (IB Berat)	15	37.5%
Tumor Stage (TNM 8th ed.)		
Stage IIIB	8	20.0%
Stage IVA	24	60.0%
Stage IVB	7	17,5%
Overall Survival (months), median [range]	3.0	[1-24]

3.2 Immunohistochemical Expression Profiles

IHC analysis using the IRS system revealed a striking dominance of low E-Cadherin expression in the study cohort: 36 out of 40 patients (90.0%) showed low E-Cadherin expression, while only 4 patients (10.0%) showed high expression. EGFR expression was uniformly low in all 40 patients (100%), with no cases showing excessive expression of EGFR. In contrast, Ki-67 showed a more heterogeneous pattern, with high expression in 25 patients (62.5%) and low expression in 15 patients (37.5%). These findings are summarized in Table 2.

Table 2. Immunohistochemical Expression Profiles (N=40)

Biomarker / Expression	N	%
E-Cadherin		
Low expression (IRS 0-3)	36	90.0%
High expression (IRS 4-12)	4	10.0%
EGFR		
Low expression (IRS 0-3)	40	100.0%
High expression (IRS 4-12)	0	0.0%
Ki-67		
High expression (IRS 4-12)	25	62.5%

Low expression (IRS 0-3)	15	37.5%
Composite Biomarker Phenotype		
E-Cad Low / Ki-67 High (proliferative-mesenchymal)	22	55.0%
E-Cad Low / Ki-67 Low	14	35.0%
E-Cad High / Ki-67 High	3	7.5%
E-Cad High / Ki-67 Low	1	2.5%

3.3 Correlation of Biomarker Expression with Clinicopathological Features

Analysis of biomarker expression in relation to clinicopathological parameters reveals several important patterns (Table 3). Low expression of E-Cadherin was observed in 24 of 27 active smokers (88.9%) and in 12 of 13 non-smoking/passive smoking patients (92.3%), with no statistically significant association between smoking status and E-Cadherin expression (Fisher's exact test: OR = 2.27, p = 0.584). Both sexes showed predominantly low expression of E-Cadherin: 24 out of 26 men (92.3%) and 12 out of 14 women (85.7%).

High expression of Ki-67 was identified in all 3 subgroups of tumor stages: 7 of 8 Stage IIIB (87.5%), 16 of 24 Stage IVA (66.7%), and 2 of 7 Stage IVB patients (28.6%). In particular, the proportionally high expression of Ki-67 in Stage IIIB patients suggests that high proliferative activity may paradoxically be associated with early-stage (albeit advanced) disease in this cohort. Fisher's precise test showed no statistically significant association between high expression of Ki-67 and advanced stages (IV A/B vs. IIIB; OR = 0.40, p = 0.440).

Table 3. Biomarker Expression by Clinicopathological Subgroup

Variable	E-Cad Low n(%)	E-Cad High n(%)	Ki-67 High n(%)	Ki-67 Low n(%)
Male (n=26)	24 (92.3%)	2 (7.7%)	17 (65.4%)	9 (34.6%)
Female (n=14)	12 (85.7%)	2 (14.3%)	8 (57.1%)	6 (42.9%)
Smoker (n=27)	25 (92.6%)	2 (7.4%)	17 (63.0%)	10 (37.0%)
Non/Passive (n=13)	11 (84.6%)	2 (15.4%)	8 (61.5%)	5 (38.5%)
Stage IIIB (n=8)	8 (100%)	0 (0%)	7 (87.5%)	1 (12.5%)
Stage IVA (n=24)	21 (87.5%)	3 (12.5%)	16 (66.7%)	8 (33.3%)
Stage IVB (n=7)	6 (85.7%)	1 (14.3%)	2 (28.6%)	5 (71.4%)

3.4 Biomarker Expression and Overall Survival

The study patients totaled 40 patients with an overall mean survival of 3.0 months (mean 5.0 ± 5.1 months; range 1-24 months), indicating that all patients were advanced.

Patients with low E-Cadherin expression had an average overall survival of 3.0 months (average 5.2 months), compared to 3.0 months (average 3.75 months) in the high E-Cadherin group. The difference was not statistically significant (Mann-Whitney U=77.5, p=0.819). Similarly, patients with high Ki-67 expression had a mean survival of 3.0 months (mean 5.7 months) compared to 3.0 months (mean 3.9 months) in the low Ki-67 group, also without statistical significance (Mann-Whitney U = 194.5, p = 0.854).

Stratification with composite biomarker phenotypes revealed that the high phenotype of low E-Cadherin/Ki-67 (proliferative-mesenchymal, n=22) had a mean survival of 5.95 months, while the low phenotype of low E-Cadherin/low Ki-67 (n=14) had a mean survival of 3.93 months. The small sample size of the high subgroup of E-Cadherin (n = 4) precludes meaningful inferential analysis. This survival data is summarized in Table 4.

Table 4. Survival Outcomes by Biomarker Expression Subgroup

Subgroup	n	Median Survival (mo)	Mean Survival (mo)	Range (mo)	p-value
E-Cadherin Low	36	3.0	5.2	1-24	0.819*
E-Cadherin High	4	3.0	3.8	1-8	

Ki-67 High	25	3.0	5.7	1-24	0.854*
Ki-67 Low	15	3.0	3.9	1-18	
E-Cad Low / Ki-67 High	22	3.5	5.95	1-24	n/a
E-Cad Low / Ki-67 Low	14	3.0	3.93	1-18	
E-Cad High / Ki-67 High	3	2.0	3.67	1-8	

*Mann-Whitney U test. mo = months; n/a = not applicable due to small sample size.

4. DISCUSSION

This study provides a detailed characterization of the expression of E-Cadherin, EGFR, and Ki-67 in KPKBSK patients exhibiting a biomarker profile typical of this population. The most prominent findings were the downregulation of E-Cadherin in all samples (90%) and the absence of EGFR overexpression (100%), occurring with increased proliferative activity of Ki-67 (62.5%). All three markers show proliferative-mesenchymal tumor activity with significant clinical implications.

4.1 E-Cadherin Downregulation: A Marker of EMT in Indonesian NSCLC

The high prevalence of low expression of E-Cadherin (90%) observed is substantially higher than the figure reported in many Western and Asian studies. E-Cadherin loss in KPKBSK typically ranges between 50-80% [6,12]. Downregulation of E-Cadherin exposes cancer patients at an advanced stage because the loss of E-Cadherin is mechanically related to EMT, which already causes invasion of the kelenjar getah bening dan distant metastases. The loss of E-Cadherin results in epithelial cells, resulting in a process known as Mesenchymal Transitional Epithelium (EMT). Loss of adhesion between epithelial cells to the mesenchyma so that cancer cells can detach from the primary tumor, invade surrounding tissues, and metastasize [4,5]. The results of this study were obtained in 77.5% of patients in stage IV, so that the EMT process had already occurred and caused metastasis when the patient was diagnosed

Low E-Cadherin occurs in all patients who smoke. Other factors outside of smoking, such as genetics, epigenetic CDHI, and exposure to carcinogens, can also cause a decrease in E-Cadherin. These observations require further molecular investigation, including the methylation profile of CDH1 and its derivatives from EMT-related pathways.

4.2 Universal Absence of EGFR Overexpression: Clinical and Therapeutic Implications

The uniform low expression of EGFR by IHC in all 40 patients is a clinically relevant finding. Meanwhile, EGFR mutation testing (not conducted in this study) remains the gold standard for determining the treatment of migrant workers, and IHC-based EGFR assessments can provide fast and accessible results. The results of EGFR overexpression in this study were dominated by non-adenocarcinoma or histology that did not differentiate well, and indicated a low prevalence of EGFR-overexpressing subtypes in the population of male heavy smokers.

These findings have implications for patients of this study to be able to obtain treatment for migrant workers with EGFR mutations, hence the need for a comprehensive molecular profile, including the assessment of KRAS, ALK, ROS1, and PD-L1, so that the therapeutic target can be acted upon.

4.3 Ki-67 Expression and Proliferative Phenotype

The expression of Ki-67 was high at 62.5% of KPKBSK patients who were very proliferative in this study. High expression of Ki-67 is present in Stage IIIB (87.5%) and Stage IVB (28.6%), while Stage IVB is an aggressive stage for widespread metastasis and has the potential to decrease proliferative signs of primary tumors and worsen the prognosis.

Low E-Cadherin and high Ki-67 (55% of patients) gave poor biological signs. The combination of these two markers constitutes active proliferation with loss of epithelial cohesion. It is theoretically associated with the most aggressive tumor behavior, as it combines the capacity for rapid cell division with the ability to spread and metastasize. In terms of treatment, it is necessary to select an anti-proliferative treatment strategy for the cell cycle, including CDK4/6 inhibitors combined with agents that can restore EMTs.

4.4 Survival Outcomes

International data show that the overall average survival was 3.0 months if patients with advanced stages did not receive chemotherapy or immunotherapy[13]. No statistically significant difference in survival between the E-Cadherin or Ki-67 subgroups is likely due to: (1) small sample size that limits statistical strength; (2) all are advanced and (3) all stages are the same in the lanut stage. Larger prospective studies with adequate strength and comprehensive treatment data are needed to illustrate the independent prognostic contribution of these biomarkers in this population.

4.5 Novelty and Contribution

The main novelty of this study is the first systematic characterization of the combined E-Cadherin/EGFR/Ki-67 IHC in the Indonesian NSCLC

cohort using the IRS scoring system. Specifically, we show that: (1) E-Cadherin loss is almost entirely occurring in smokers, suggesting an EMT mechanism; (2) EGFR overexpression is absent, suggesting that this population may be genometically different from the NSCLC study that could enrich information about East Asian EGFR; and (3) proliferative-mesenchymal high low E-Cadherin/high Ki-67 are the most frequent biomarker combinations that have the potential to determine high-risk subgroups. These findings provide a basis for hypothesis-based prospective studies and may inform the design of biomarker-stratified clinical trials in Indonesia.

4.6 Limitations

This research has several limitations that must be acknowledged. First, the sample size (n = 40) was relatively small, limiting the statistical power. Both treatment and molecular genotype data (EGFR mutation status, ALK rearrangement) were not available, preventing the correlation of IHC findings with therapeutic response. Third, retrospective design introduces selection bias and potential confusion. Fifth, IRS-based IHCs are semi-quantitative and subject to inter-observer variability, although multiple pathological reviews are used to mitigate this. Prospective studies with larger sample sizes, standard histopathological subtypes, and integrated molecular profiles are required.

5. CONCLUSIONS

Studies show different biomarkers in NSCLC patients that are almost entirely downregulation of E-Cadherin, the absence of excessive expression of EGFR, and high proliferative activity of Ki-67, most commonly concomitant with the proliferative phenotype of high E-Cadherin/Ki-67. These findings suggest that the mechanism of action of EMTs occurs in smokers, and treatment with TKI on EGFR mutations is limited because there has been no molecular testing yet. Poor average overall survival of 3.0 months, hence the need for early detection strategies and appropriate management according to adequate molecular examination. Future prospective studies that combine IHC biomarkers with comprehensive genomic profiles are essential to improve the prognosis outcomes of KPKBSK patients in Indonesia.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249.
2. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical, and Radiologic Advances Since the 2004 Classification. J Thorac Oncol. 2015;10(9):1243-1260.
3. Kemenkes RI. Laporan Nasional Riskesdas 2018. Jakarta: Badan Penelitian dan Pengembangan Kesehatan; 2019.
4. Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. Nat Rev Mol Cell Biol. 2014;15(3):178-196.
5. Thiery JP, Acloque H, Huang RY, Nieto MA. Epithelial-mesenchymal transitions in development and disease. Cell. 2009;139(5):871-890.
6. Bremnes RM, Veve R, Gabrielson E, et al. High-throughput tissue microarray analysis used to evaluate biology and prognostic significance of the E-cadherin pathway in non-small-cell lung cancer. J Clin Oncol. 2002;20(10):2417-2428.
7. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med. 2004;350(21):2129-2139.
8. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947-957.
9. Gerdes J, Schwab U, Lemke H, Stein H. Production of a mouse monoclonal antibody reactive with a human nuclear antigen associated with cell proliferation. Int J Cancer. 1983;31(1):13-20.
10. Jakobsen JN, Sorensen JB. Clinical impact of Ki-67 labeling index in non-small cell lung cancer. Lung Cancer. 2013;79(1):1-7.
11. Remmele W, Stegner HE. Recommendation for uniform definition of an immunoreactive score (IRS) for immunohistochemical estrogen receptor detection (ER-ICA) in breast cancer tissue. Pathologe. 1987;8(3):138-140.
12. Yilmaz M, Christofori G. EMT, the cytoskeleton, and cancer cell invasion. Cancer Metastasis Rev. 2009;28(1-2):15-33.
13. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33.

AUTHOR CONTRIBUTIONS

[All authors contributed to study design, data collection, analysis, and manuscript preparation. All authors read and approved the final manuscript.]

FUNDING

This research received no external funding.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY

The datasets supporting the conclusions of this article are available from the corresponding author upon reasonable request.

ACKNOWLEDGMENTS

[The authors thank the pathology department staff and clinical team for their support in data collection.]