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RESEARCH ARTICLE

N-Cadherin Correlates with β-Catenin Expression Across the Spectrum of Mucinous Ovarian Tumors

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Abstract

Background: This study evaluates differences in N-cadherin and β-catenin expression, as well as their correlation across the histopathological spectrum of mucinous ovarian tumors, including cystadenomas, borderline tumors, and carcinomas. **Methods:** A cross-sectional analytical observational study was performed using 60 paraffin-embedded tissue samples from patients diagnosed with mucinous ovarian tumors (MOTs). These comprised mucinous cystadenoma (MC), mucinous borderline tumor (MB), low-grade mucinous ovarian carcinoma (MOC-LG), and high-grade mucinous ovarian carcinoma (MOC-HG). Immunohistochemical staining was then performed to evaluate N-cadherin and β-catenin expression, which was analyzed according to the H-score system. **Results:** The results demonstrated that N-cadherin expression differed significantly across the MOTs spectrum, with significant pairwise differences between MC and MOC-LG, MC and MOC-HG, and MB and MOC-HG. β-catenin expression also varied significantly across tumor types, with significant differences between MC and MOC-LG ($p = 0.001$), MC and MOC-HG, MB and MOC-LG, and MB and MOC-HG. In addition, a positive correlation was observed between N-cadherin expression and the MOTs spectrum ($r = 0.422$) as well as between β-catenin expression and the MOTs spectrum ($r = 0.603$). N-cadherin expression showed a significant positive correlation with β-catenin expression across the MOTs spectrum ($r = 0.487$). **Conclusion:** N-cadherin was significantly correlated with β-catenin across the MOTs spectrum. These results suggested that N-cadherin and β-catenin may serve as potential histopathological diagnostic markers for distinguishing among the benign, borderline, and malignant spectra of MOTs and provide a molecular basis for further investigation into their roles in cancer invasion and metastasis.

Keywords: Cancer- mucinous ovarian carcinoma- diagnostic markers- N-Cadherin, β-Catenin

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Introduction

Globally, ovarian cancer is the seventh most frequently diagnosed malignancy in women and the third leading cause of mortality among gynecological cancers [1]. According to GLOBOCAN 2022, approximately 324,398 new ovarian cancer cases (1.6% of all cancers) and 206,839 related deaths (2.1%) were reported globally [2]. Several studies have shown that the condition is classified based on the origin of the cancer, either epithelial, stromal, or germ cells. In addition, approximately 90% arise from epithelial cells, referred to as epithelial ovarian cancer (EOC). Based on the World Health Organization (WHO) in 2020, EOC is classified into 5 major subtypes, namely low-grade serous carcinoma (LGSC), high-grade serous carcinoma (HGSC), endometrioid carcinoma, clear-cell carcinoma, and mucinous carcinoma [3-5]. Mucinous ovarian carcinoma (MOC) is a relatively rare subtype, accounting for <5% of all EOC cases. However, higher prevalence has been reported in Native Hawaiian/Pacific Islander (13.1%) and Asian (10.8%) populations [6, 7]. Data from Dr. Soetomo Academic General Hospital, Surabaya, Indonesia, showed that among all malignant ovarian carcinomas, MOC was the most prevalent subtype

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(24.8%), followed by endometrioid carcinoma (24.1%) [8]. In addition, recent data collected between 2019 and 2023 showed that mucinous ovarian tumors consisted of 21% benign, 26% borderline, and 53% malignant cases [9].

The diagnosis of mucinous ovarian tumors (MOTs) remains challenging due to overlapping histopathological features across the benign, borderline, and malignant spectrum, gradual transitional changes, and marked intratumoral heterogeneity. MOTs exhibit a broad histopathological spectrum, ranging from benign mucinous cystadenoma (MC), mucinous borderline tumor (MB), to malignant MOC. The transition between these categories is often gradual, and benign, borderline, and malignant components may coexist within the same tumor, thereby further complicating accurate diagnosis and classification [10, 11]. MC is a benign epithelial tumor lined by gastrointestinal- or Müllerian-type epithelium. Meanwhile, MB tumor represents a non-invasive mucinous neoplasm characterized by complex architectural proliferation and predominantly gastrointestinal-type differentiation. MOC is defined as an invasive mucinous neoplasm composed of malignant gastrointestinal-type epithelial cells [5]. Another diagnostic challenge is that a substantial proportion of ovarian mucinous tumors represent metastatic disease, most commonly originating from the lower gastrointestinal tract (colon/appendix; 45%), upper gastrointestinal tract (pancreas/stomach /bile duct; 20%), and the uterus (cervix/endometrium; 18%) [6]. The wide spectrum of morphological features observed in ovarian mucinous tumors further complicates accurate diagnosis and may lead to misclassification [10, 11]. Current diagnostic strategies emphasize immunohistochemical factors, including CK7, CK20, CDX2, SATB2, and PAX8, to distinguish primary ovarian tumors from metastatic disease [12]. Although molecular alterations such as KRAS and TP53 are variably observed across MOTs subtypes [13], their diagnostic utility remains limited and requires further validation.

Diagnostic strategies emphasize the development of robust genomic and proteomic biomarkers to reliably differentiate between MC, MB, and MOC [14]. Proteomic assessment focuses on the evaluation of specific proteins expressed by tumor cells, including β-catenin, which plays a central role within the canonical Wnt/β-catenin signaling pathway. This pathway regulates critical physiological processes, including apoptosis, differentiation, proliferation, invasion, migration, and tissue homeostasis. Alterations in the Wnt/β-catenin pathway contribute to the initiation and progression of various solid tumors, including ovarian neoplasms [15, 16]. Besides β-catenin, cadherin family members such as N-cadherin function as intercellular adhesion molecules broadly distributed in epithelial tissues, where they mediate heterotypic cell–cell adhesion and are essential for maintaining cell polarity and tissue architecture [1, 17]. Overexpression of N-cadherin is associated with enhanced cell migration, angiogenesis, tumor aggressiveness, and metastatic potential across multiple malignancies, including ovarian cancer. However, the clinicopathological implications of N-cadherin expression in MC, MB, and MOC remains unclear [1]. Further studies are required to evaluate the expression of N-cadherin and β-catenin to identify reliable markers for distinguishing the spectrum of MOTs. Therefore, this study aims to evaluate differences in N-cadherin and β-catenin expression and to analyze the correlation between their expression levels across the histopathological spectrum of MOTs, including cystadenomas, borderline tumors, and carcinomas.

Materials and Methods

This study was an observational analytic study with a cross-sectional approach. The study population comprised all patients with a definitive histopathological diagnosis of MOTs, as determined by a pathologist at Dr. Soetomo General Hospital, Surabaya, between 2018 and 2021. Ethical approval for this study was obtained from the Health Research Ethics Committee (No. 0913/KEPK/II/2024).

Sample collection

The sample size was determined according to the calculation formula of Charan and Biswas (2013), namely $n = Z\alpha^2 . p.q/d^2$, with the following explanation: Value n = minimum number of samples required. Value α = 0.05; Value Zα = 1.96; Value p = 0.5; Value q = 1-p = 0.5; Value d = possible error in the study = 0.14 [18]. Based on the sample calculation formula, each group consisted of 14 samples. As a result, the total minimum sample required in this study was 48 samples. A correction factor of 10% brings the total number of samples to 53 samples, rounded up to 56 samples, and then rounded to 60 samples.

A total of 60 formalin-fixed paraffin-embedded (FFPE) blocks from patients with mucinous ovarian tumors were divided into 4 groups, namely MC, MB, MOC-low grade (MOC-LG) for grade 1, and MOC-high grade (MOC-HG) for grade 2 and 3. Each group comprised 15 FFPE blocks.

Histopathology and immunohistochemistry analysis

The diagnosis of MOTs referred to the WHO Classification [5]. Tumors were classified into 3 categories, namely MC, a benign tumor with gastrointestinal or Mullerian-type epithelium; MB tumor, a non-invasive tumor with complex architecture as well as gastrointestinal-type differentiation; and mucinous ovarian carcinoma, an invasive tumor with gastrointestinal-type epithelial cells. The degree of malignancy (grade) in MOC was determined using the Silverberg grading system [19].

N-Cadherin expression was the expression of the N-Cadherin protein examined by immunohistochemistry (IHC) using a polyclonal anti-N-Cadherin ab18203 antibody (Abcam, Cambridge, UK, dilution 1:100). Furthermore, N-Cadherin was positively expressed in the cell membrane and cytoplasm of tumor cells. β-Catenin was the expression of β-Catenin protein examined using immunohistochemistry (IHC) techniques with monoclonal anti-β-Catenin (E-5) antibody: sc-7963 (dilution 1:200, Santa Cruz Biotechnology), and was positively expressed in the cytoplasm and nucleus of tumor cells.

The assessment of N-Cadherin and β-Catenin expression using the H-score system was evaluated by 2 expert anatomical pathologists using a binocular light microscope, Olympus CX41RF, and the average of the assessment results was calculated. Furthermore, the staining intensity (I) was scored as 0 (unstained), 1 (weak), 2 (moderate), or 3 (strong), and the percentage of stained cells was recorded as the total percentage of positive cells (Ptotal=1-100%). Histochemical scoring (H-score; range, 0–300) was calculated using the formula: (0 × percentage of cells scored 0) + (1 × percentage of cells scored 1) + (2 × percentage of cells scored 2) + (3 × percentage of cells scored 3). H-score results were categorized as negative (0–50), weak (51–100), moderate (101–200), or strong (201–300) [20, 21].

Statistical analysis

Differences in N-cadherin and β-catenin expression were analyzed using the Kruskal–Wallis test, and intergroup comparisons were performed using the Mann–Whitney U test. The correlation between N-cadherin and β-catenin expression and the histopathological types of MOTs was analyzed using Spearman's correlation test.

Results

N-Cadherin expression

Immunohistochemical analysis of N-Cadherin expression among mucinous ovarian tumors showed variable staining intensity, categorized as weak, moderate, or strong (Figure 1). The majority of cases exhibited moderate expression in 32 cases (53.3%), followed by weak expression in 25 cases (41.7%) and strong expression in 3 cases (5.0%). No samples showed negative expression.

A statistically significant difference in N-cadherin expression was observed across the MOTs ($p = 0.012$; $p < 0.05$) (Table 1). Furthermore, intergroup analysis revealed a significant difference between the MC and MOC-LG groups ($p = 0.045$), MC and MOC-HG groups ($p = 0.008$), and MB and MOC-HG groups ($p = 0.027$). There were no significant differences in expression between the MC and MB groups ($p = 0.164$), MB and MOC-LG groups ($p = 0.291$), or MOC-LG and MOC-HG groups ($p = 0.122$) (Table 2).

B-Catenin expression

Immunohistochemical analysis of β-Catenin expression across the spectrum of MOTs showed variable staining intensity, in strong, moderate, and negative (Figure 2). Most cases showed strong expression in 33 cases (55.0%), followed by moderate expression in 27 cases (43.3%), while negative expression was found in only 1 case (1.7%). No samples with weak expression were found.

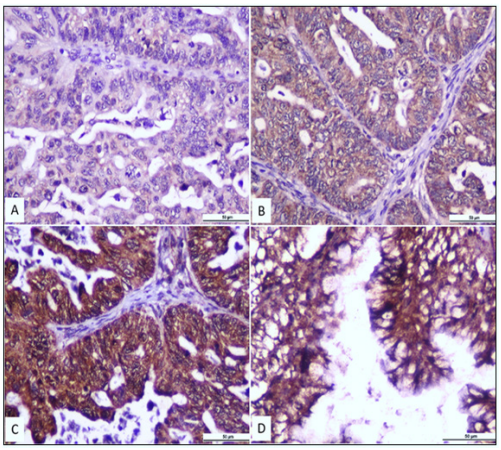

Figure 1. Immunohistochemical Staining of N-cadherin in Mucinous Ovarian Tumors. (A) Weak (A), moderate (B), and strong (C–D) expression observed across the mucinous ovarian tumor spectrum (magnification, 400×).

The results showed a statistically significant difference in β-catenin expression across the MOTs, $p = 0.000$ ($p<0.05$) (Table 1). Further analysis was performed to determine which groups had significant differences in β-Catenin expression across the spectrum of MOTs. Significant differences were observed between the MC and MOC-LG groups ($p = 0.001$), MC and MOC-HG ($p = 0.000$), MB and MOC-LG ($p = 0.011$), and MB and MOC-HG ($p = 0.001$). Meanwhile, no significant differences were found between the MC and MB groups ($p = 0.291$) or the MOC-LG and MOC-HG groups ($p = 0.260$) (Table 2).

Correlation of N-Cadherin and B-Catenin expression

Correlation of N-Cadherin and β-Catenin expression in MOTs was performed by Spearman's test. There was a significant positive correlation between N-Cadherin expression and the spectrum of MOTs ($p = 0.001$; $r = 0.422$). β-Catenin expression had a significant positive correlation with the spectrum of MOTs ($p = 0.000$; $r = 0.603$). A significant positive correlation was observed between N-Cadherin and β-Catenin expression across a wide spectrum of MOTs ($p = 0.000$; $r = 0.487$) (Table 3).

Table 1. The Expression of N-Cadherin and β-Catenin Across the Spectrum of Mucinous Ovarian Tumors

The spectrum of MOTs	N	N-Cadherin		β-Catenin	
		Mean rank	p-value	Mean rank	p-value
MC	15	23.93	0.012*	19.47	0.000*
MB	15	27.4		23.4	
MOC-LG	15	31.2		37.17	
MOC-HG	15	39.47		41.97	

Notes: *p<0.05, Kruskal–Wallis test, mucinous ovarian tumors (MOTs), mucinous cystadenoma (MC), mucinous borderline ovarian tumor (MB), mucinous ovarian carcinoma low grade (MOC-LG), and mucinous ovarian carcinoma high grade (MOC-HG).

Table 2. Mann–Whitney Test Results for N-cadherin and β-catenin Expression Across the Spectrum of Mucinous Ovarian Tumors

The spectrum of MOT	p-value	
	N-Cadherin	β-Catenin
MC and MB	0.164	0.291
MC and MOC-LG	0.045*	0.001*
MC and MOC-HG	0.008*	0.000*
MB and MOC-LG	0.291	0.011*
MB and MOC-HG	0.027*	0.001*
MOC-LG and MOC-HG	0.122	0.26

Notes: *p<0.05, Mann-Whitney test, mucinous ovarian tumors (MOTs), mucinous cystadenoma (MC), mucinous borderline ovarian tumor (MB), mucinous ovarian carcinoma low grade (MOC-LG), and mucinous ovarian carcinoma high grade (MOC-HG).

Discussion

Accurate diagnosis of primary mucinous ovarian tumors was challenging due to their histological similarity to other mucinous carcinomas, particularly those of colorectal origin. Mucinous ovarian tumors exhibited marked histological heterogeneity, with the coexistence of benign, borderline, and malignant components supporting a stepwise model of tumor evolution [7]. Therefore, this study evaluated N-cadherin and β-catenin expression as biomarkers for differentiating mucinous cystadenoma, borderline tumor, and carcinoma.

In this study, N-cadherin expression was considered positive when detected in the cytoplasm and/or membrane. Overall, 53.3% of patients exhibited moderate expression, 41.7% showed weak expression, and 5% showed strong N-cadherin expression. Quattrocchi et al. [22] also reported cytoplasmic N-cadherin expression in 99% of cases, while another study identified membranous N-cadherin expression in 32% of cases [23]. Consistent with these results, a previous study reported a significant association between N-cadherin expression and the mucinous subtype of ovarian carcinoma, in which mucinous carcinoma exhibited high N-cadherin expression, while the serous subtype showed low expression [1]. Furthermore, N-cadherin overexpression was associated with a twofold higher recurrence rate at 5-year follow-up compared with tumors exhibiting low N-cadherin expression. It indicated that high N-cadherin expression is associated with poor prognosis, as reflected by increased recurrence and mortality rates in ovarian cancer. This study was consistent with many studies reporting a significant correlation between N-Cadherin expression in ovarian carcinoma and histological subtype [1, 24].

This study showed a significant difference in N-cadherin expression across the spectrum of MOTs. Significant differences were observed between the MC and MOC-LG groups, the MC and MOC-HG groups, and the MB and MOC-HG groups. Furthermore, N-cadherin expression demonstrated a significant positive correlation with the progressive spectrum of MOTs. Histopathologically, MOC was distinguished from MB by the presence of invasive growth, while MB was characterized by the absence of stromal invasion [25]. MOC exhibited a significantly higher proliferation index than in MB, showing increased cellular proliferation in malignant lesions [25]. N-cadherin regulated cell survival, facilitating epithelial–mesenchymal transition (EMT), migration, and invasion through the recruitment of intracellular signaling molecules [26]. Cadherin switching, characterized by reduced E-cadherin expression accompanied by elevated N-cadherin expression, is a hallmark of epithelial–mesenchymal transition (EMT) and distant metastasis [23, 27]. Furthermore, interaction between N-cadherin with other membrane proteins, such as the fibroblast growth factor receptor (FGFR), activated downstream signaling cascades that regulated cell proliferation, invasion, and cell adhesion [26]. High N-cadherin expression was a marker of the mesenchymal phenotype and promoted enhanced cell motility and invasiveness [22]. Therefore, these results showed that N-cadherin expression functioned as a biomarker of invasiveness and proliferation for distinguishing mucinous ovarian tumors, particularly between MC and MOC-LG, MC and MOC-HG, and MB and MOC-HG.

This study found that strong β-catenin expression was observed in 55% (33/60) of cases, while moderate expression was detected in 43.3% (27/60) of cases. β-catenin expression was considered positive when detected in the nucleus and/or cytoplasm of tumor cells. Cytoplasmic accumulation of β-catenin suggests activation of the Wnt signaling pathway, which is frequently observed in tumors with dysregulated signaling and reflects increased proliferative potential. Nuclear β-catenin functions as a transcriptional co-activator by interacting with TCF/LEF transcription factors, thereby upregulating target genes such as c-MYC, Cyclin D1, and MMPs. These genes are involved in cell proliferation and are strongly associated with oncogenesis and tumor progression [28, 29]. The accumulation of β-catenin in the nucleus is generally a consequence of mutations in CTNNB1 or APC genes, reflecting aberrant activation of the Wnt/β-catenin signaling pathway and serves as marker for distinguishing primary ovarian carcinoma

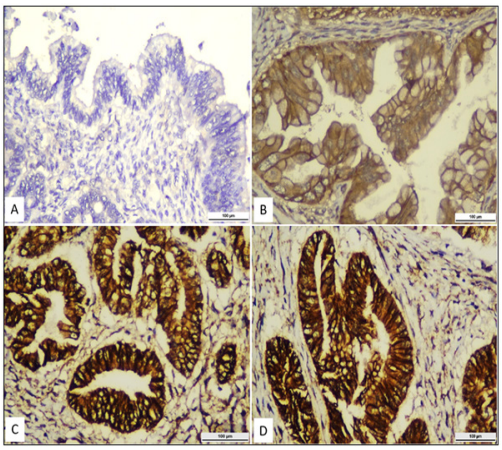

Figure 2. Immunohistochemical Staining of β-catenin in Mucinous Ovarian Tumors. Negative (A), moderate (B), and strong (C–D) expression observed across the spectrum of mucinous ovarian tumors (magnification, 400×).

Table 3. Correlation Analysis between N-cadherin and β-catenin Expression Across the Spectrum of Mucinous Ovarian Tumors

Correlation analysis of variables	p-value	r-value
N-Cadherin expression with the spectrum of MOTs	0.001*	0.422
β-Catenin expression with the spectrum of MOTs	0.000*	0.603
N-Cadherin with β-Catenin across the spectrum of MOTs	0.000*	0.487

Notes: * p<0.05, Spearman's correlation test, mucinous ovarian tumors (MOTs)

from metastatic colorectal cancer [30, 31]. A meta-analysis study reported that immunohistochemical detection of nuclear β-catenin functioned as a reliable surrogate marker for CTNNB1 mutations, with a sensitivity of 88% and a specificity of 85% [32]. Next-generation sequencing (NGS)–based analyses confirmed that nuclear β-catenin expression accurately predicted CTNNB1 exon 3 mutations, showing a sensitivity of 85% and a specificity of 98% [33]. Cytoplasmic and nuclear accumulation of β-catenin indicated dysregulated growth signaling and correlates with increased invasiveness, metastatic behavior, and poor prognosis [28]. In contrast, membranous β-catenin is located at the inner surface of the cell membrane, where it binds to E-cadherin, indicating normal cell regulation in contributing to the maintenance of epithelial integrity, cellular polarity, and tissue architecture [28, 29]. This study increased the β-catenin expression across the spectrum of MOTs, with statistically significant differences observed between MC and MOC-LG and MOC-HG, as well as between MB and MOC-LG and MOC-HG. Therefore, immunohistochemical assessment of nuclear β-catenin represented a practical and cost-effective surrogate for CTNNB1 exon 3 mutation testing [33] and served as a useful additional marker to differentiate MC from MOC-LG and MOC-HG, and MB from MOC-LG and MOC-HG.

A significant positive correlation was observed between β-catenin expression and the histopathological spectrum of MOTs. In ovarian serous carcinoma, β-catenin overexpression occurred more frequently in advanced-stage disease (FIGO stages III–IV) than in early-stage tumors (stages I–II). Patients with β-catenin overexpression exhibited significantly poorer overall survival, suggesting a role for β-catenin dysregulation in the progression of ovarian cancer [34]. Moreover, elevated β-catenin expression correlated with decreased chemotherapy efficacy and significantly reduced progression-free survival (PFS) and overall survival (OS) [35]. The presence of β-catenin at the cell membrane was significantly correlated with chemoresistance, indicating its utility as a predictive marker for therapy response and underscoring its importance as a prognostic factor for PFS and OS in ovarian carcinoma [35].

N-cadherin and β-catenin expression exhibited a significant positive correlation throughout the spectrum of MOTs. Furthermore, both N-cadherin and β-catenin expression individually exhibited a significant positive correlation with the progression of the MOTs spectrum. The underlying mechanism required the interaction of N-cadherin with the actin cytoskeleton through β-catenin, forming the N-cadherin–catenin complex, which played role in maintaining cell–cell adhesion and intracellular signaling [16]. In tumor cells, disruption or degradation of the N-cadherin and β-catenin complex led to releasing β-catenin and then translocate into the nucleus. Furthermore, it activated T-cell factor or lymphoid enhancer factor (TCF/LEF)-mediated transcription and induced the expression of metastasis-related genes, including CD44 and matrix metalloproteinases (MMPs) [16]. The cytoplasmic domain of N-cadherin played a major role in regulating MMP-9 expression, and the subsequent increase in MMP-9 induced by N-cadherin represented a crucial step in tumor invasion and metastatic progression [16]. Consistent with this mechanism, these results showed N-cadherin expression predominantly in the cytoplasm and membrane, while β-catenin was observed in both the cytoplasm and nucleus. Collectively, these results supported the utility of this invasion-associated marker panel as a molecular basis for distinguishing subtypes of mucinous ovarian carcinoma.

However, this study has limitations, including its cross-sectional design, which precludes determination of causal relationships between biomarker expression and tumor progression, and its single-center setting with a relatively small sample size, which may limit statistical power and generalizability to broader populations. In addition, this study focused on the immunohistochemical assessment of N-cadherin and β-catenin protein expression without evaluating genomic alterations or transcriptional changes in the CDH2 (Cadherin 2) and CTNNB1 (Catenin Beta 1) genes, which encode N-cadherin and β-catenin, respectively. Therefore, future prospective longitudinal multi-center studies with larger cohorts, incorporating molecular validation (e.g., CDH2 and CTNNB1 mutation analysis) and correlation with clinical outcomes, are warranted to confirm these findings and to further elucidate the causal and prognostic significance of these biomarkers in tumor progression.

Despite these limitations, the significant association of N-cadherin and β-catenin with tumor progression suggests important clinical implications. Their expression patterns may assist pathologists in distinguishing benign, borderline, and malignant mucinous ovarian tumors, particularly in cases with overlapping histological features. Thus, incorporating N-cadherin and β-catenin into routine immunohistochemical panels may improve diagnostic accuracy and support more appropriate clinical management decisions.

In conclusion, N-cadherin expression is significantly correlated with β-catenin across the spectrum of MOTs, and both markers individually show a significant positive association with tumor progression. These results show

that N-cadherin and β-catenin have discriminatory utility for differentiating MC from MOC-LG and MOC-HG, as well as distinguishing MB from MOC-HG. Furthermore, β-catenin expression shows discriminatory utility in distinguishing MB from MOC-LG. Collectively, these results support the potential of N-cadherin and β-catenin as complementary histopathological diagnostic markers across the benign–borderline–malignant spectrum of MOTs and provide a molecular basis for further investigation into their roles in tumor invasion and metastasis.

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General

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Conflict of Interest

There is no conflict of interest

Ethical Declaration

This study was approved by the Health Research Ethics Committee of Dr. Soetomo General Hospital, Surabaya (Approval No. 0913/KEPK/II/2024).

Authors Contribution

All authors are responsible for the content, critical review, and approve the final manuscript. GM: the main idea, conceptual framework, writing manuscript and revisions. AR: histopathological analysis and revision final manuscript. ASR: histopathological analysis and revision final manuscript. ASS: sampel diagnosis and histopathological analysis. LNR: statistical analysis and revision manucript. HFT: histopathological and statistical analysis. RCWO: sample collecting.

Originality Declaration for Figures

All figures included in this manuscript are original and have been created by the authors specifically for the purposes of this study. No previously published or copyrighted images have been used. The authors confirm that all graphical elements, illustrations, and visual materials were generated from the data obtained in the course of this research or designed uniquely for this manuscript.

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