RESEARCH ARTICLE

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MUC5AC Protein Expression as a Potential Predictor of Metastasis in Mucinous Ovarian Carcinoma: Unveiling a New Biomarker in a Rare Cancer Subtype

Rina Masadah[1,2]*, Syahrul Rauf[2,3], Desy Ekadamadayani Ahmad[1], Muhammad Faruk[2,4]

Abstract

Background: Mucinous ovarian carcinoma (MOC) is a distinct and lethal histological subtype of ovarian cancer, frequently characterized by late-stage diagnosis and chemoresistance. The role of MUC5AC a gel-forming mucin associated with aggressive behavior in various epithelial malignancies remains under-investigated in the context of MOC metastasis, particularly within Indonesian populations. This study aimed to evaluate the correlation between MUC5AC expression and metastatic occurrence in MOC to determine its utility as a predictive biomarker. **Methods:** A retrospective analysis was conducted on 63 MOC tissue samples, collected between 2021 and 2024. MUC5AC expression was evaluated via immunohistochemistry (IHC) using a semi-quantitative scoring system. Statistical associations were determined using the Chi-square test, with an emphasis on calculating the odds ratio (OR) for metastatic risk. **Results:** Among the 63 cases, metastatic involvement (omental or extra-ovarian) was identified in 37 samples (58.7%). A significant correlation was noted between high MUC5AC expression and the occurrence of metastasis in MOC (p=0.002). Furthermore, tumors exhibiting high MUC5AC expression demonstrated a 6.4-fold increased probability of metastasis compared to those with low expression (OR = 6.40; 95% CI: 1.89–21.5). **Conclusion:** Elevated MUC5AC expression is significantly correlated with metastatic involvement in primary MOC. These findings suggest that MUC5AC has the potential to serve as a predictive biomarker for metastasis in this rare cancer subtype, potentially assisting in the identification of patients who require more intensive staging and surveillance.

Keywords: MUC5AC- Mucinous Ovarian Carcinoma- Metastasis- Biomarker

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Introduction

Ovarian cancer continues to pose a significant challenge in gynaecologic oncology, as the primary cause of mortality among malignant tumours of the female reproductive system. The unfavourable survival outcomes are mostly attributed to the diagnosis of many patients at an advanced stage, when metastatic illness has already developed [1, 2]. Most cases are of the serous subtype, whereas a minority exhibit mucinous differentiation. Mucinous ovarian carcinoma (MOC) is relatively rare and clinically significant due to its unique histological features, divergent biological progression, and diminished responsiveness to conventional platinum-based chemotherapy protocols [2, 3]. These data underscore the necessity for dependable biomarkers capable of forecasting aggressive behaviour and metastatic potential in this subtype, thus facilitating earlier detection and more customised management options.

MUC5AC is a high-molecular-weight, gel-forming mucin typically synthesized by epithelial cells in the stomach and respiratory tract. Aberrant expression of this protein has been documented in various epithelial malignancies and is increasingly linked to tumor progression and invasive processes [4, 5]. Experimental findings indicate that the overexpression of MUC5AC may induce epithelial-mesenchymal transition (EMT)-like changes, enhance cellular motility, and promote the spread of cancer cells [6, 7]. Consequently, these observations provide a compelling biological rationale for exploring the potential role of this marker in the metastatic behavior of MOC.

Although substantial evidence has emerged from gastrointestinal and pancreatic cancers, the prognostic relevance of MUC5AC in mucinous ovarian tumors remains poorly defined. Current evidence linking MUC5AC specifically to omental or extra-ovarian dissemination remains limited, despite the critical

*[1]Department of Pathology Anatomy, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia. [2]Hasanuddin University Hospital, Makassar, Indonesia. [3]Department of Obstetrics & Gynecology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia. [4]Faculty of Medicine, Hasanuddin University, Makassar, Indonesia. *For Correspondence: r.masadah@med.unhas.ac.id*

importance of such findings in determining clinical stage and prognosis. The prognostic value of MUC5AC in MOC remains undefined, particularly regarding its utility as a predictive tool for advanced disease. Clarifying this relationship is essential, as immunohistochemistry (IHC) for MUC5AC is readily accessible, cost-effective, and highly suitable for integration into routine pathology practice.

The present study was conducted to evaluate the association between high MUC5AC expression and metastasis in primary MOC. This study addresses the existing knowledge gap by determining if this biomarker can function as an effective predictor of metastatic risk, thereby informing risk stratification, surveillance methodologies, and the optimization of multimodal treatment regimens.

Materials and Methods

Study Design and Samples

A retrospective cross-sectional analytic investigation was performed on 63 tissue specimens of primary MOC at the Department of Anatomical Pathology, Hasanuddin University, from 2021 to 2024. Formalin-fixed paraffin-embedded (FFPE) tissue specimens and associated clinical records were examined. The variables analysed comprised patient age, parity, histological grade (categorized according to the 2020 WHO criteria [8], and clinical stage (based on the FIGO system [9, 10]. In this study, metastatic status was specifically defined as histologically verified omental or extra-ovarian dissemination (equivalent to FIGO Stage III or higher). Cases with insufficient data, secondary mucinous tumors (metastatic from the GI tract), or substandard tissue preservation were eliminated.

Research Procedure

The diagnosis of MOC was confirmed using haematoxylin and eosin (HE) stained slides in accordance with the 2020 World Health Organization (WHO) classification. Immunohistochemical staining for MUC5AC was conducted on 4 µm-thick FFPE sections utilizing a rabbit polyclonal antibody (D-AB-10374L; Elabscience) at a dilution of 1:1200. Each staining series had both positive and negative controls to verify authenticity.

Evaluation of MUC5AC Expression

The IHC slides were evaluated independently by two anatomical pathologists blinded to the clinical and metastatic status of the patients. In cases of divergent scores, the final results were determined through consensus using a multi-headed microscope to ensure diagnostic consistency.

The degree of MUC5AC expression was evaluated using a semi-quantitative scoring system based on both staining intensity and the percentage of positive tumor cells, as previously described by Chelariu-Raicu et al. [11]. Staining intensity was graded as 0 (absent), 1+ (weak), 2+ (moderate), and 3+ (strong). The distribution was assessed based on the percentage of immunoreactive neoplastic cells.

The dichotomization of MUC5AC expression into low expression (0 and 1+) and high expression (2+ and 3+) was performed to differentiate clinically significant protein overexpression from baseline or weak immunoreactivity. This thresholding approach is consistent with established protocols for mucinous biomarkers in ovarian and gastrointestinal neoplasms, as it emphasizes moderate-to-strong intensity as the driver of aggressive biological behavior [5, 11]. This categorization also facilitates robust statistical analysis for risk stratification, a common practice in clinical biomarker studies.

Statistical Analysis

Associations between MUC5AC expression and clinicopathological variables were analyzed using Pearson's chi-square test. The magnitude of association was expressed as Odds Ratio (OR) with 95% confidence intervals (CI). Statistical significance was set at a two-sided p-value of <0.05. Data were processed and analyzed using IBM SPSS Statistics version 26.

Results

Clinicopathological Characteristics

A total of 63 tissue specimens of primary MOC were examined. Table 1 shows the clinicopathological characteristics of the samples. The mean patient age was 43.02±14.22 years, with 42 cases (66.7%) involving women under 50 years. In terms of parity, the majority of

Table 1. Clinicopathological Characteristics of the Study (n=63)

Characteristic	n (%)
Age (years)	
< 50	42 (66.7)
≥ 50	21 (33.3)
Mean ± SD	43.02 ± 14.22
Parity	
Nulliparous	16 (25.4)
Multiparous	39 (61.9)
Grand multiparous	8 (12.7)
Histological Grade	
Grade 1 (Well)	35 (55.6)
Grade 2 (Moderate)	23 (36.5)
Grade 3 (Poor)	5 (7.9)
FIGO stage	
Early (Stage I-II)	26 (41.3)
Advanced (Stage III-IV)	37 (58.7)
Metastasis	
Non-metastatic	26 (41.3)
Metastatic	37 (58.7)
MUC5AC expression	
Negative	2 (3.2)
Weak	16 (25.4)
Moderate	20 (31.7)
Strong	25 (39.7)

Table 2. MUC5AC expression versus metastasis status (n = 63)

MUC5AC Expression	Metastasis Status		OR (CI 95%)	p-value
	With metastasis (%)	Without metastasis (%)		
High (n=45)	32 (86.5)	13 (50.0)	6.40 (1.89-21.5)	0.002*
Low (n=18)	5 (13.5)	13 (50.0)		

Note: *Chi-square test, Significant p-value if p<0.05

patients were multiparous (61.9%).

Regarding the histological features, the majority of the cases were classified as well-differentiated tumors, with 35 cases (55.6%) classified as Grade 1, 23 cases (36.5%) as Grade 2, and 5 cases (7.9%) as Grade 3. Metastatic involvement, characterized by histologically verified omental or extra-ovarian dissemination (corresponding to advanced FIGO stages), was observed in 37 cases (58.7%), while the remaining 26 cases (41.3%) were non-metastatic.

Immunohistochemical staining for MUC5AC revealed a distribution of 2 cases (3.2%) negative, 16 cases (25.4%) weak, 20 cases (31.7%) moderate, and 25 cases (39.7%) strong, as shown in Figure 1. For analytical purposes, cases were categorized into low expression (n=18; 28.6%) and high expression (n=45; 71.4%).

Association Between MUC5AC Expression and Metastasis

It was noted that high MUC5AC expression was significantly more prevalent in the metastatic cohort compared to the non-metastatic group. Specifically, 32 of 37 metastatic cases (86.5%) exhibited high MUC5AC expression, whereas only 13 of 26 non-metastatic cases (50.0%) showed similar levels.

As detailed in Table 2, a significant correlation was observed between high MUC5AC expression and the occurrence of metastasis (p=0.002). Tumours with high expression demonstrated an approximately six-fold increased probability of metastasis (OR = 6.40; 95% CI: 1.89–21.5; p=0.002).

Subgroup Analysis of Confounding Factors

To rule out potential confounding factors, MUC5AC expression was analyzed against other clinicopathological variables. As shown in Table 3, no significant associations were found between MUC5AC expression and patient age

Table 3. Association between MUC5AC Expression and Clinicopathological Features

Variable	MUC5AC Low (n = 18)	MUC5AC High (n = 45)	p-value
Age (years)			
< 50	11	31	0.542*
≥ 50	7	14	
Parity			
Nulliparous	5	11	0.724*
Parous (≥ 1)	13	34	

Note: * Chi-square test

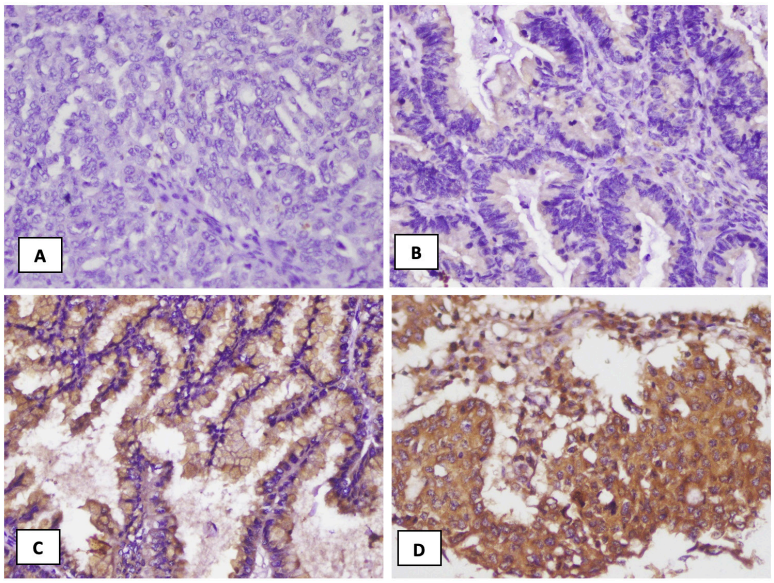

Figure 1. Representative Images of MUC5AC Immunohistochemical Staining in Primary Mucinous Ovarian Carcinoma. (A) Negative expression (Score 0); (B) Weak cytoplasmic staining (Score 1+); (C) Moderate cytoplasmic staining (Score 2+); and (D) Strong cytoplasmic staining (Score 3+). All images are shown at 200× total magnification. Sections were incubated with rabbit polyclonal antibody against MUC5AC (Catalog No. D-AB-10374L; Elabscience, USA) at a dilution of 1:1200, followed by 3,3'-Diaminobenzidine (DAB) chromogen and hematoxylin counterstaining.

(p=0.542) or parity (p=0.724). These findings suggest that MUC5AC is an independent predictor of metastatic potential, regardless of the patients' demographic background.

Discussion

MOC remains a relatively uncommon entity compared to serous carcinoma, yet when diagnosed at advanced stages, it carries a high risk of mortality. This gap between incidence and lethality underscores the importance of further exploring its underlying biology and molecular determinants [2, 12–14]. This investigation confirms a robust association between high MUC5AC expression and metastasis, with high expression yielding a six-fold increase in the probability of omental or extra-ovarian dissemination (OR 6.40; 95% CI: 1.89–21.5). These findings suggest that MUC5AC is a pivotal molecular determinant of MOC progression rather than a mere marker of mucinous differentiation.

The metastatic potential of MUC5AC likely stems from its ability to modulate the tumor microenvironment. As a gel-forming mucin, MUC5AC creates a viscoelastic barrier that reduces cell–cell and cell–matrix adhesion, facilitating the detachment of malignant cells [11, 15]. At the signaling level, MUC5AC-rich membranes activate focal adhesion kinase (FAK)-dependent pathways, triggering cytoskeletal reconfiguration and EMT-like phenotypic shifts. These alterationsmarked by E-cadherin downregulationenhance cellular motility and survival within ascitic fluid, ultimately promoting peritoneal implantation [6, 16–19].

Evidence from other malignancies corroborates this model. In colorectal and pancreatic carcinomas, MUC5AC drives invasion and metastatic activity via β-catenin/CD44 and KLF4–Src–STAT3 signaling cascades [6, 7, 15]. While MUC5AC and MUC6 are traditionally utilized as diagnostic adjuncts to differentiate primary MOC from metastatic gastrointestinal cancers [2, 5, 9, 11, 15, 16, 19–21], our results provide a novel prognostic dimension. We demonstrate that while MUC5AC presence confirms a mucinous phenotype (diagnostic), its high expression serves as a quantitative indicator of tumor aggressiveness (prognostic). This biological transition from a localized to a metastatic phenotype is characterized by massive MUC5AC secretion, which facilitates the "seeds" of metastasis by increasing microenvironmental viscoelasticity and promoting EMT.

Building upon its established biological role in other epithelial malignancies, our study highlights a critical shift in the clinical application of this marker within the context of ovarian oncology. Historically, MUC5AC has been predominantly utilized as a diagnostic adjunct, specifically to differentiate primary mucinous ovarian tumors from metastatic gastrointestinal carcinomas [2, 15]. However, our findings suggest a transition toward its utility as a prognostic biomarker. The distinction lies in the functional involvement of MUC5AC in the metastatic cascade. While its presence confirms a mucinous phenotype (diagnostic), its high expression serves as a quantitative indicator of tumor aggressiveness (prognostic).

The biological transition from a localized to a metastatic phenotype in MOC is characterized by the massive secretion of MUC5AC, which provides more than just a histological clue; it actively facilitates the "seeds" of metastasis. By increasing the viscoelasticity of the tumor microenvironment and promoting EMT, high MUC5AC levels represent a functional shift toward a more invasive state. Therefore, measuring MUC5AC intensity allows clinicians to move beyond identifying the tumor's origin and toward forecasting its clinical trajectoryspecifically the risk of omental and extra-ovarian dissemination.

From a clinical standpoint, integrating MUC5AC IHC into routine pathology practice offers a cost-effective strategy for risk stratification. High MUC5AC expression at diagnosis could serve as an early indicator of occult advanced disease, prompting clinicians toward more rigorous surgical staging evaluation and intensified surveillance [9, 22, 23]. Given that MUC5AC IHC is technically uncomplicated and widely accessible, it is particularly suitable for implementation in resource-constrained environments to optimize patient management.

In evaluating these findings, it is imperative to address potential confounding factors. Our subgroup analysis demonstrated that MUC5AC expression was not significantly associated with patient age or parity, reinforcing its independence from demographic variables. However, we acknowledge that histological grade and FIGO stage were not included in a multivariable statistical model. The predominant presentation of Grade 1 and 2 tumors in our cohorttypical for primary MOClimited the power for multivariate grading analysis. Furthermore, because omental metastasis is a defining criterion for advanced FIGO stage, these variables exhibit inherent collinearity.

This study has several limitations. It was retrospective and single-centre, with a relatively small sample size, which restricts generalizability and precludes survival analysis. Moreover, the investigation relied solely on a single biomarker, MUC5AC, as the variable of interest. Although MUC5AC expression was evaluated by two independent pathologists and discrepancies were resolved by consensus, a formal statistical assessment of interobserver agreement, such as Cohen's kappa coefficient, was not performed. Future studies should include such metrics to further validate the reproducibility of the scoring system. Prospective multi-centre studies are warranted to validate reproducibility across laboratories, evaluate survival outcomes, and clarify whether the addition of MUC5AC improves risk prediction when combined with other clinicopathological or molecular markers. Parallel mechanistic studies addressing epithelial–mesenchymal transition, adhesion/FAK signalling, and tumour–microenvironment crosstalk will also be important to support causal interpretation and therapeutic exploration.

In conclusion, our findings demonstrate that high MUC5AC expression is significantly correlated with metastatic involvement in primary MOC. These preliminary results suggest that MUC5AC has the

potential to serve as a predictive biomarker for omental and extra-ovarian dissemination. Integrating MUC5AC immunohistochemistry into standard diagnostic protocols may serve as a cost-efficient adjunct to assist in identifying patients who require enhanced monitoring and more rigorous staging evaluation. However, further validation through extensive, multi-center prospective research is essential to confirm its clinical utility and facilitate its formal incorporation into oncological decision-making.

Author Contribution Statement

Contributors: RM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. SR: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Software, Validation, Visualization, Writing – original draft. DEA: Conceptualization, Data curation, Formal analysis, Investigation, Validation, Writing – original draft. MF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing.

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Ethics approval

mittee of the Faculty of Medicine Universitas Hasanuddin, Makassar, Indonesia, with protocol number: UH24090816 on October 12, 2024. We promised that the participants' data were anonymized or maintained with confidentiality, the rights or interests of participants were not invaded, and informed consent was taken from all individual participants.

Data availability statement:

Data is accessible upon justifiable request.

Competing interests

No competing interests were reported.

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