Original Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.9702468135-792

CD163 Tumor-Associated Macrophage Expression as a Predictor of Distant Metastasis in Invasive Breast Cancer: A Cross-Sectional Study

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ARTICLE INFO

Received:
28 July 2025
Revised:
16 October 2025
Accepted:
26 October 2025

Keywords:
breast neoplasms, neoplasm metastasis, tumor-associated macrophages, CD163 protein

ABSTRACT

Background: Breast cancer is the most common malignancy among women globally, with distant metastasis being the primary cause of mortality. The tumor microenvironment, particularly Tumor-Associated Macrophages (TAMs), plays a crucial role in cancer progression. This study aimed to evaluate the association between CD163 expression in TAMs and the presence of distant metastasis in patients with breast cancer.

Methods: A cross-sectional study was conducted on 71 patients with invasive breast cancer at Hasanuddin University Hospital in Makassar. CD163 expression in TAMs was analyzed using immunohistochemistry in formalin-fixed paraffin-embedded tissues. Clinical and pathological data were collected from the medical records. Statistical analyses were performed using the Chi-square test for categorical data and the Mann-Whitney U test for continuous data, with significance defined as $p < 0.05$. Associations are presented as odds ratios (ORs).

Results: Of the 71 patients, 59.2% showed a high level of CD163 expression in TAMs. A significant association was observed between high CD163 expression and advanced cancer stage ($p < 0.001$), high histopathological grading ($p < 0.001$), and distant metastasis status ($p < 0.001$). After adjusting for key confounders, high CD163 expression was associated with an 11.2-fold increase in the odds of distant metastasis (adjusted OR = 11.2; 95% CI: 3.5–35.8; $p < 0.001$).

Conclusion: High CD163 expression in TAMs is significantly associated with an increased risk of distant metastasis in breast cancer and correlates with more aggressive tumor characteristics. These findings indicate that CD163-positive TAMs represent a potential prognostic biomarker for risk stratification in patients with breast cancer.

INTRODUCTION

Breast cancer is the most diagnosed malignancy in women globally[1] and a leading cause of cancer-related mortality[2], primarily due to the development of distant metastasis. In many regions, including Indonesia, a significant proportion of patients are diagnosed at advanced stages[3], underscoring the urgent need for robust biomarkers that can predict

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metastatic risk and inform clinical management. Progression to metastatic disease is heavily influenced by intricate crosstalk within the tumor microenvironment (TME). [4] Therefore, it is critical to understand the biological mechanisms that drive metastasis.

Tumor-associated macrophages (TAMs) are critical regulators of cancer progression. [5] TAMs exhibit remarkable plasticity and can be broadly categorized into a classical M1 (pro-inflammatory and anti-tumor immunity) phenotype and an alternative M2 (anti-inflammatory and pro-tumoral) phenotype. [6,7] The M2-polarized TAMs, specifically identified by the scavenger receptor CD163, orchestrate multiple steps in the metastatic cascade. [8] These macrophages facilitate tumor cell invasion by remodelling the extracellular matrix [8], promoting angiogenesis by secreting factors such as VEGF [8,9], and creating an immunosuppressive niche that allows cancer cells to evade immune destruction [10], thereby promoting their survival and dissemination to distant organs. [8,9] To identify this clinically relevant macrophage subset, we focused on CD163, a hemoglobin scavenger receptor that serves as a highly specific and widely validated immunohistochemical marker for M2-like TAMs in clinical tissues. Crucially, high densities of CD163+ TAMs have been consistently linked in previous studies to aggressive tumor features, including increased angiogenesis [8,9], immune suppression [10], and enhanced metastatic potential in breast cancer, making CD163 a prime candidate for investigation as a prognostic biomarker.

Given the established role of TAMs in promoting tumor progression and metastasis, evaluating the expression of specific TAM markers, such as CD163, in breast cancer may yield valuable insights into disease prognosis and the risk of distant metastasis. Although the pro-metastatic function of M2-like TAMs has been well-documented globally, there is a lack of comprehensive understanding of this association in Indonesian patients. In particular, direct correlation studies assessing CD163 expression in relation to clinicopathological parameters and distant metastasis in an Indonesian cohort are scarce. Therefore, this study aimed to investigate the relationship between CD163 expression in TAMs and the incidence of distant metastasis in patients with breast cancer.

METHODS

Study Design and Location

This was an observational, analytical study with a cross-sectional design, conducted at Hasanuddin University Hospital Makassar from December 2024 to February 2025.

Population and Research Participants

The study population comprised all female patients with breast cancer diagnosed via histopathological examination of *carcinoma mammae* and treated at our institution. The study sample was recruited using consecutive sampling. All patients who were diagnosed with invasive breast cancer at our institution during the study period and met the inclusion criteria were included in the analysis. This approach minimized selection bias by including all available eligible cases from the defined timeframe.

The inclusion criteria were as follows: (1) women with a histopathological diagnosis of invasive breast cancer; (2) women with breast cancer with *de novo* metastasis (at initial diagnosis) or without metastasis; (3) complete data available regarding distant metastasis status (based on imaging and/or clinical results); and (4) availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue blocks from biopsy. Exclusion criteria were as follows: (1) a history of other malignancies, (2) receipt of neoadjuvant therapy prior to biopsy, and (3) inadequate tissue samples for immunohistochemical examination.

The a priori sample size was estimated using the formula to compare two independent proportions. The calculation was based on the ability to detect a significant difference in the presence of distant metastasis between the high and low CD163 expression groups, with a statistical power of 80% and the two-sided significance level (α) of 0.05. Based on data from previous studies, which indicated an approximate metastasis rate of 50% in patients with high M2 TAM infiltration compared to 20% in those with low infiltration, the minimum required sample size was estimated to be 100 participants (50 per group). After applying all the criteria, the final study population consisted of 71 eligible patients who were available during the recruitment period.

Research Procedures

Tissue specimen examination by immunohistochemistry was performed at the Anatomic Pathology Laboratory of our institution. After identifying the participants who met the criteria, FFPE tissue blocks were retrieved from the Anatomic Pathology Laboratory. CD163 expression in tumor-associated macrophages (TAMs) was examined by immunohistochemistry. This procedure involved cutting FFPE tissue sections, deparaffinization, rehydration, antigen retrieval, incubation with anti-CD163 primary antibody, incubation with secondary antibody, and detection using an appropriate staining system. Interpretation of CD163 expression was

performed independently by two anatomical pathologists who were blinded to clinical outcomes.

A semi-quantitative H-score was calculated by multiplying the staining intensity (graded as 0 [none], 1 [weak], 2 [moderate], or 3 [strong]) by the percentage of positively stained macrophages at each intensity level, using the formula: H-score = [1 × (% cells 1+) + 2 × (% cells 2+) + 3 × (% cells 3+)]. [11] The final scores ranged from 0 to 300. For statistical analysis, expression was dichotomized into 'low' and 'high' categories, using the median H-score of the entire cohort as the cut-off value.

To assess inter-observer reliability, Cohen's kappa (κ) statistic was calculated for the final dichotomized scores, which demonstrated excellent agreement ($\kappa = 0.88$; $p < 0.001$). Any discordant cases were resolved by a joint review to reach a final consensus score before data analysis.

Data Collection

Data were collected from the patients' medical records and relevant laboratory test results. These variables included age, menopausal status, cancer stage (based on the TNM system), metastasis status (present/absent), metastasis location (if any), histopathological type, histopathological grading, and hormone receptor status (ER, PR, and HER2).

Histopathological grading was performed using the modified Scarff-Bloom-Richardson method. For the purpose of analysis, the patients were divided into two groups: low-to-moderate grade (I–II) and high grade (III). Cancer staging followed the American Joint Committee on Cancer (AJCC) 2017 classification, and patients were similarly categorized into two groups: stages I–II and stages III–IV. Metastatic breast cancer (stage IV) was defined as the presence of metastasis in one or more distant organs (e.g., lungs, bones, liver, or brain) at initial diagnosis, as confirmed by imaging (ultrasound, X-ray, and/or CT scan).

Data Analysis

All statistical analyses were performed using IBM SPSS version 26.0. Descriptive statistics were used to summarize patient characteristics, presented as frequencies and percentages for categorical variables, and as means ± standard deviations (SD) for continuous variables. The association between CD163 expression and clinicopathological characteristics including age, menopausal status, cancer stage, histopathological grade, hormonal receptor status, HER2 status, and molecular subtype was initially assessed using the Pearson's chi-squared test or Fisher's Exact Test, as appropriate.

To identify independent predictors of distant metastasis, a two-step logistic regression approach was employed. First, univariate logistic regression was conducted to evaluate the effect of each explanatory variable on metastasis status. Variables with a p-value < 0.20 in the univariate analysis were considered eligible for inclusion in the multivariate logistic regression model. This threshold was used to ensure that potential confounders were not excluded prematurely.

In the multivariate analysis, distant metastasis (yes/no) served as the dependent variable, while variables meeting the selection criteria specifically cancer stage, histopathological grade, hormonal receptor status, and CD163 expression were included as independent predictors. The final model was adjusted for these covariates following the "≥10 events per predictor variable" rule of thumb to prevent model overfitting and ensure model stability. The strength of association was expressed as odds ratios (OR) and adjusted odds ratios (aOR) with 95% confidence intervals (CI). A two-tailed p-value < 0.05 was considered statistically significant.

RESULTS

A total of 71 patients with invasive breast cancer were included in this study. The mean age was 52.0 ± 10.8 years (range: 30–73 years), with most participants belonging to the 50–69-year age group (52.1%). Slightly more than half of the patients (50.7%) were postmenopausal. The majority of cases were diagnosed at advanced stages (Stage III: 31.0%; Stage IV: 42.3%). The predominant histopathological type was invasive carcinoma of no special type (NST) (81.7%), and most tumors were of low to intermediate histopathological grade (63.4%).

Regarding molecular subtypes, luminal breast cancer was the most common (62.0%). High CD163 expression in tumor-associated macrophages (TAMs) was observed in 59.2% of the patients. The clinicopathological characteristics of the study population and their relationship with CD163 expression are summarized in Table 1.

High CD163 expression was significantly correlated with advanced cancer stage, higher histopathological grade, and negative hormonal receptor status.

Association of CD163 Expression with Clinicopathological Parameters

As shown in Table 1, high CD163 expression was significantly associated with advanced cancer stage ($p < 0.001$), high histopathological grade ($p < 0.001$), and negative hormonal receptor status ($p < 0.001$). Additionally, a significant difference was observed across molecular subtypes ($p = 0.001$), with higher CD163 expression more frequently seen in HER2 and TNBC subtypes compared to luminal types.

No significant associations were found between CD163 expression and patient age, menopausal status, histopathological type, or HER2 status (all $p > 0.05$). These findings indicate that elevated CD163 expression is associated with more aggressive tumor characteristics.

Table 1. Association of CD163 Expression in Tumor-Associated Macrophages (TAMs) with Clinicopathological Characteristics (n = 71)

Variable	n (%)	CD163 Expression		p-value
		High (n = 42, 59.2%)	Low (n = 29, 40.8%)	
Age (years)				0.289[c]
< 40	9 (12.7)	4 (9.5)	5 (17.2)	
40–49	19 (26.8)	15 (35.7)	4 (13.8)	
50–69	37 (52.1)	21 (50.0)	16 (55.2)	
> 69	6 (8.5)	2 (4.8)	4 (13.8)	
Menopausal status				0.701[b]
Premenopausal	35 (49.3)	22 (52.4)	13 (44.8)	
Postmenopausal	36 (50.7)	20 (47.6)	16 (55.2)	
Cancer stage				<0.001[c]
I–II	19 (26.8)	5 (11.9)	14 (48.3)	
III	22 (31.0)	10 (23.8)	12 (41.4)	
IV	30 (42.3)	27 (64.3)	3 (10.3)	
Metastasis status				<0.001[c]
Present	30 (42.3)	27 (64.3)	3 (10.3)	
Absent	41 (57.7)	15 (35.7)	26 (89.7)	
Histopathological grade				<0.001[c]
I–II	45 (63.4)	19 (45.2)	26 (89.7)	
III	26 (36.6)	23 (54.8)	3 (10.3)	
Hormonal receptor status				<0.001[c]
Positive (ER/PR+)	44 (62.0)	19 (45.2)	25 (86.2)	
Negative	27 (38.0)	23 (54.8)	4 (13.8)	
Molecular subtype				0.001[c]
Luminal	44 (62.0)	19 (45.2)	25 (86.2)	
HER2-enriched	19 (26.8)	16 (38.1)	3 (10.3)	
Triple Negative (TNBC)	8 (11.3)	7 (16.7)	1 (3.4)	
Histopathological type				0.815[c]
Invasive carcinoma NST	58 (81.7)	34 (81.0)	24 (82.8)	
Invasive lobular	5 (7.0)	3 (7.1)	2 (6.9)	
Mucinous	4 (5.6)	2 (4.8)	2 (6.9)	
Papillary	4 (5.6)	3 (7.1)	1 (3.4)	
HER2 Neu status				0.249[b]
Positive	42 (59.2)	23 (54.8)	19 (65.5)	
Negative	29 (40.8)	19 (45.2)	10 (34.5)	

[b]Pearson's Chi-square test; [c]Fisher's Exact Test. $p < 0.05$ considered statistically significant.

Univariate and Multivariate Logistic Regression Analysis for Predictors of Distant Metastasis

To determine the independent predictors of distant metastasis, logistic regression analyses were performed (Table 2). In the univariate logistic regression, four variables of cancer stage, histopathological grade, hormonal receptor status, and CD163 expression demonstrated statistically significant associations with distant metastasis ($p < 0.20$). These variables were subsequently included in the multivariate logistic regression model.

After adjustment, high CD163 expression remained a strong and independent predictor of distant metastasis (adjusted OR = 11.20, 95% CI: 3.50–35.80, $p < 0.001$). Cancer stage also retained a statistically significant association (aOR = 3.42, 95% CI: 1.11–10.56, $p = 0.032$). Although histopathological grade and hormonal receptor status were initially significant in the univariate analysis, their effects became non-significant after adjustment, suggesting that their influence on metastasis may be mediated through other covariates. These results indicate that CD163 expression in TAMs is an independent and robust biomarker of distant metastasis risk in invasive breast cancer, even after controlling for conventional prognostic factors.

Table 2. Univariate and Multivariate Logistic Regression Analysis for Predictors of Distant Metastasis in Invasive Breast Cancer

Variable	Univariable OR (95% CI)	p-value	Multivariable aOR (95% CI)	p-value
Age (≥50 years)	1.42 (0.61–3.32)	0.412	—	—
Menopausal status (Post vs. Pre)	1.25 (0.55–2.84)	0.593	—	—
Cancer stage (III–IV vs. I–II)	6.80 (2.34–19.74)	0.001	3.42 (1.11–10.56)	0.032
Histopathological grade (III vs. I–II)	4.92 (1.72–14.06)	0.003	2.31 (0.84–6.38)	0.104
Hormonal receptor status (Negative vs. Positive)	3.68 (1.31–10.34)	0.013	1.82 (0.67–4.93)	0.241
CD163 expression (High vs. Low)	15.60 (4.04–60.27)	<0.001	11.20 (3.50–35.80)	<0.001

Variables with $p < 0.20$ in univariate analysis were entered into the multivariate logistic regression model. Adjusted odds ratios (aOR) were calculated while controlling for cancer stage, histopathological grade, and hormonal receptor status. Statistical significance was set at $p < 0.05$.

DISCUSSION

This study provides compelling evidence that high CD163 expression in TAMs is a strong and independent predictor of distant metastasis in patients with invasive breast cancer. The results demonstrated that patients with high CD163$^+$ TAM density had an approximately eleven-fold increased risk of metastasis compared to those with low expression, even after adjusting for major clinicopathological variables such as cancer stage, histopathological grade, and hormonal receptor status. These findings reinforce the pivotal role of TAM-mediated immunomodulation in the metastatic cascade and highlight CD163 as a clinically relevant biomarker for prognostic stratification.

The present findings align with multiple previous studies and meta-analyses that identified high CD163$^+$ TAM infiltration as a hallmark of aggressive tumor behavior and poor prognosis in breast cancer. Stavrou *et al.*[12] and Mwafy and El-Guindy[13] both reported a strong association between CD163$^+$ macrophage density and advanced stage, lymph node metastasis, and shortened survival. Similarly, the meta-analysis by Ni *et al.* demonstrated that high CD163 expression was significantly correlated with higher tumor grade, larger tumor size, and decreased overall survival.[14] The consistency between our results and those of international studies underscores the biological universality of CD163$^+$ TAMs as promoters of metastasis across different populations, including Indonesian patients who are often diagnosed at advanced stages.

Theoretically, several mechanisms explain the role of TAMs in the promotion of distant metastasis. First, TAMs promote tumor invasion and migration by secreting proteolytic enzymes such as matrix metalloproteinase-9 (MMP-9) and cathepsins, which degrade the extracellular matrix and enable tumor cell intravasation.[12] Additionally, TAM-derived chemokines such as CCL18 interact with the PITPNM3 receptor on breast cancer cells, inducing epithelial–mesenchymal transition (EMT) and enhancing motility.

Second, TAMs promote angiogenesis by releasing vascular endothelial growth factor (VEGF) and other pro-angiogenic mediators, increasing microvessel density and providing conduits for tumor cell dissemination.[4,9,15] The formation of the "tumor microenvironment of metastasis" (TMEM) triad comprising perivascular TAMs, tumor cells, and endothelial cells represents a critical interface for intravasation.[4] Third, TAMs create an immunosuppressive microenvironment by secreting IL-10 and TGF-β and expressing immune checkpoint ligands such as PD-L1.[16] These molecules inhibit cytotoxic T-cell activity and support tumor immune evasion. Finally, at metastatic sites, TAMs contribute to colonization and outgrowth of secondary tumors by promoting angiogenesis, matrix remodelling, and the maintenance of stem-like phenotypes in disseminated tumor cells.[17] Collectively, these mechanisms suggest that CD163$^+$ TAMs not only initiate but also sustain metastatic progression.

This study also demonstrated a significant correlation between high CD163 expression and higher histopathological grade, consistent with previous reports.[18,19] The hypoxic and necrotic microenvironment of high-grade tumors stimulates macrophage recruitment via chemokines such as CCL2, CSF-1, and VEGF, leading to M2-polarized differentiation.[18,20,21] These macrophages, in turn, enhance tumor aggressiveness through IL-10- and TGF-β-mediated immunosuppression and by promoting angiogenesis and extracellular matrix remodelling.[22,23]

Moreover, CD163 expression was inversely associated with hormonal receptor positivity. Tumors that are ER/PR-negative often exhibit increased TAM

infiltration and heightened inflammatory signalling. This observation is consistent with reports indicating that hormone receptor–negative subtypes, particularly HER2-enriched and triple-negative breast cancer (TNBC), harbor a more immunologically active but tumor-promoting macrophage population. Interestingly, a subset of studies[24] found that CD163$^+$ macrophages might paradoxically confer better outcomes in certain TNBC contexts, possibly due to unique macrophage activation states. However, in most molecular subtypes, including HER2-positive and luminal tumors, CD163$^+$ TAM density remains a reliable indicator of aggressiveness and metastatic potential.

The results of this study have important clinical implications. CD163$^+$ TAM density can serve as a prognostic biomarker to stratify patients into distinct risk categories at diagnosis. Patients exhibiting high CD163 expression may benefit from more intensive adjuvant therapy, closer follow-up, or inclusion in clinical trials exploring macrophage-targeted therapies. Furthermore, the emerging field of TAM-directed therapeutics including CSF-1R inhibitors, CCL2 blockade, and CD47–SIRPα checkpoint modulation represents a promising avenue for future interventions. By selectively reprogramming M2-like macrophages toward an anti-tumoral phenotype, such therapies may disrupt the pro-metastatic tumor microenvironment. Integration of CD163 assessment into routine histopathology could therefore provide both prognostic and predictive value in personalized breast cancer management.

The strengths of this study include the use of CD163 as a specific marker for M2 macrophages, which enhances the specificity of pro-tumor TAM identification. The IHC method with semiquantitative scoring allows for a comprehensive and reproducible assessment. This study also fills a gap in local data in Makassar by involving 71 samples and demonstrates a strong association between TAM expression and metastasis (OR = 11.20). Furthermore, analysis of various clinicopathological factors provides a more comprehensive overview.

Our findings highlight the potential of CD163$^+$ TAMs as therapeutic targets. However, translating TAM-targeted therapies into clinical practice remains a considerable challenge. A major obstacle lies in the profound plasticity and heterogeneity of the TAM populations. Therapeutic approaches designed to deplete or repolarize M2-like macrophages may be limited by compensatory mechanisms or by the emergence of resistant macrophage subsets. Moreover, because macrophages play indispensable roles in tissue repair and host defence, the systemic inhibition of their functions carries a substantial risk of toxicity and immunosuppression. Therefore, future strategies must focus on selectively modulating the pro-tumoral activities of TAMs within the tumor microenvironment while preserving their essential homeostatic roles. The development of robust predictive biomarkers to identify patients most likely to benefit from such therapies, along with innovations in drug delivery to overcome barriers posed by the dense tumor stroma, represents a critical priority for advancing this therapeutic approach.

The limitations of this study include the lack of a standardized scoring system for TAM assessment, which may introduce an interpretation bias. Furthermore, it is critical to acknowledge the inherent limitations of using CD163 as a standalone biomarker and the heterogeneity of the TAM population. The M1/M2 classification, while a useful framework, is a simplification of the continuous spectrum of macrophage activation states. TAMs in situ are highly plastic and can exhibit mixed phenotypes, co-expressing both proinflammatory (M1-like) and anti-inflammatory (M2-like) markers. Our study focused on the well-established M2 marker CD163 to capture a dominant pro-tumoral signature, but this approach may not reflect the full functional complexity of all macrophage subsets within the tumor microenvironment.

Metastasis was determined based on clinical examination (chest radiography, abdominal ultrasonography, and radiological supporting examinations according to symptoms). Detecting metastasis using these modalities might miss small or asymptomatic lesions; ideally, a PET Scan or whole-body MRI would be more accurate. The cross-sectional study design limits causal inferences. This study shows a strong correlation, but cannot confirm that high TAM expression precedes and causes metastasis; thus, prospective longitudinal studies are needed to prove the prognostic role of TAMs. Finally, the single-center nature of the study may limit the generalizability of our findings.

Furthermore, although CD163 is a robust and widely used marker for M2-polarized macrophages, it is important to acknowledge its limitations as a standalone biomarker. The M1/M2 classification represents a simplified paradigm involving a complex and continuous spectrum of macrophage activation states. TAMs exhibit remarkable plasticity and can co-express various markers, indicating that relying solely on CD163 may not capture the full functional heterogeneity of the macrophage population within the tumor microenvironment. Additionally, potential intratumoral heterogeneity in CD163 expression could lead to sampling bias, where a single biopsy may not be fully representative of the immune landscape of the entire tumor. Therefore, while our study demonstrates a strong prognostic association,

future research incorporating multiplex immunohistochemistry or spatial transcriptomics could offer a more comprehensive profile of diverse macrophage subsets and their precise functional roles in mediating metastasis.

CONCLUSION

This study demonstrated that high CD163 TAM expression is a significant and independent predictor of distant metastasis in breast cancer (aOR = 11.20; 95% CI: 3.50–35.80). These findings have direct implications in personalized medicine. Assessment of CD163 expression at diagnosis could serve as a valuable prognostic biomarker for stratifying patients into distinct risk categories. For instance, patients with high CD163+ TAM infiltration may be candidates for more intensive adjuvant therapy or heightened surveillance protocols. Furthermore, our results provided a strong rationale for the clinical development of TAM-targeted therapies. High CD163 density could function as a predictive biomarker to select patients most likely to respond to agents designed to deplete or repolarize M2 macrophages. As the therapeutic landscape evolves, integrating biomarkers, such as CD163, is crucial for guiding treatment decisions.

However, the findings of this single-center cross-sectional study should be considered exploratory. Validation in larger prospective multi-center cohorts is essential to confirming the prognostic and predictive value of CD163+ TAMs before this biomarker can be integrated into routine clinical practice.

CONFLICTS OF INTEREST

No competing interests were reported.

ETHICAL CONSIDERATIONS

The study was approved by the Research Ethics Committee of the Faculty of Medicine Universitas Hasanuddin, Makassar, Indonesia, number: (No: 1045/UN4.6.4.5.31/PP36/2024 on November 28, 2024. Informed consent was obtained from all participants. Data were anonymized to protect confidentiality, and the rights and interests of all individuals were safeguarded.

FUNDING

This research received no external funding and was self-funded by the authors.

DATA AVAILABILITY

Data is available upon justifiable request.

ACKNOWLEDGMENT

The authors would like to thank the dedicated staff of the Anatomic Pathology Laboratory at Hasanuddin University Hospital for their invaluable technical assistance with the immunohistochemistry procedures.

AI DISCLOSURE

Artificial intelligence tools were used to assist with language editing and improve clarity of the manuscript. These tools were not involved in study design, data analysis, interpretation of results, or generation of scientific content. All authors reviewed and approved the final version and take full responsibility for the content. .

AUTHOR CONTRIBUTIONS

MTJ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing.

JP: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Software, Validation, Visualization, Writing – original draft.

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How to Cite This Article

Jauhari MT, Pieter Jr. J, Smaradhania N, Zainuddin AA, Nelwan BJ, Indra, et al. CD163 Tumor-Associated Macrophage Expression as a Predictor of Distant Metastasis in Invasive Breast Cancer: A Cross-Sectional Study. Arch Breast Cancer. 2025; 13(1):42-9.
Available from: https://www.archbreastcancer.com/index.php/abc/article/view/1172