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Beyond vascular endothelial growth factor: synergistic diagnostic value of multiple biomarkers in malignant pleural effusion. A cross-sectional analytical study

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Abstract

Malignant pleural effusion (MPE) remains a challenging diagnostic entity within the vast spectrum of pleural effusions. While vascular endothelial growth factor (VEGF) is a widely studied MPE biomarker, its diagnostic performance as a standalone marker is limited. There is growing interest in evaluating whether combined biomarker panels may provide incremental diagnostic information and reduce diagnostic uncertainty. This study aims to explore whether integrating matrix metalloproteinase-9 (MMP-9), tissue inhibitor of metalloproteinase-1 (TIMP-1), and monocyte chemoattractant protein-1 (MCP-1) into VEGF provides incremental diagnostic value in distinguishing malignant from benign pleural effusions. A total of 88 pleural fluid samples were analyzed (33 malignant, 55 benign). Biomarker levels were measured using enzyme-linked immunosorbent assay. Diagnostic performance was assessed via receiver operating characteristic analysis, with optimal cut-off values identified using the Youden Index. Logistic regression models were developed for combined biomarker panels and internally validated using 5-fold cross-validation. VEGF demonstrated moderate individual diagnostic value (area under the curve 0.640; sensitivity 72.7%; specificity 58.2%; and diagnostic odds ratio of 3.71). Other individual markers showed limited accuracy. The four-marker panel (VEGF + MMP-9 + TIMP-1 + MCP-1) showed a modest increase in sensitivity, negative predictive value, and diagnostic odd ratio, although specificity remains limited. These findings suggest that combined pleural fluid biomarkers may provide incremental diagnostic information, but their performance remains modest and requires external validation before clinical application.

Key words: malignant pleural effusion, pleural fluid biomarkers, VEGF, diagnostic accuracy.

Introduction

Pleural effusion, defined by the presence of excess fluid in pleural space, is a common manifestation of many pulmonary and extrapulmonary disorders [1]. Among the potentially diverse causes of pleural effusion, malignant pleural effusion (MPE) has major clinical relevance as it usually indicates a presence of an advanced stage malignancy leading to poor prognosis. MPE is associated with roughly 15% of all cancer patients and is estimated to impact over 150,000 people worldwide each year [2].

MPE is typically diagnosed by cytological examination of pleural fluid or histopathologic confirmation by pleural biopsy. While these techniques are considered gold standard, their limitations are well known. Cytological assessment is only around 60% sensitive, and multiple invasive procedures may lead to adverse events including pneumothorax, hemorrhage, and patient discomfort [3,4].

Molecular biomarkers in pleural fluid have emerged as potent tools to enhance diagnostic accuracy in an as minimally invasive approach as possible. Several novel biomarkers include Matrix Metalloproteinase-9 (MMP-9), Monocyte Chemoattractant Protein-1 (MCP-1), Vascular Endothelial Growth Factor (VEGF), and Tissue Inhibitor of Metalloproteinase-1 (TIMP-1). These biomarkers have been investigated in the context of tumor progression, inflammation, and vascular permeability [5,6].

VEGF is one of key mediators in vascular permeability and angiogenesis, and is therefore an important indicator in the pathophysiology of MPE. It correlates directly with tumor burden and has been shown possess both diagnostic and prognostic utility [7,8]. MCP-1 regulates monocyte recruitment, and is frequently found elevated in malignancy-associated inflammation and drives immune cell infiltration and remodeling of the tumor microenvironment [9]. TIMP-1, a natural inhibitor of MMP-9, has recently been identified as a diagnostic and prognostic biomarker in different cancers. High TIMP-1 levels in pleural fluid are considered as indicators of the host response to tumor invasion and matrix degradation. Overexpression of TIMP-1 has been associated with lung, breast, and gastrointestinal cancer, and may promote tumor growth and apoptosis resistance [5].

Among these markers, VEGF has long been considered a key biomarker for MPE due to its role in vascular permeability and angiogenesis. As a stand-alone marker, however, its

diagnostic performance is suboptimal, with low sensitivities and specificities [10,11]. Although MMP-9, TIMP-1, and MCP-1 are biologically distinct and have individual contributions to tumor pathogenesis [5,6], their diagnostic potential in pleural effusion has not yet been fully established. Previous studies have primarily shown these biomarkers separately, but the accuracy has not been clinically relevant [12].

This study aims to move 'beyond VEGF' and explores whether integrating these markers into diagnostic panels allows for improved distinction of malignant and benign pleural effusions, with the aim of supporting early, accurate and minimally invasive clinical decision-making in real-world settings.

Materials and Methods

This observational analytic study used a cross-sectional design to evaluate the diagnostic performance of pleural fluid biomarkers in distinguishing malignant pleural effusion (MPE) from non-malignant pleural effusion (NPE). The study was conducted at Department of Pulmonology and Respiratory Medicine, Saiful Anwar General Hospital, Malang City, East Java, Indonesia, between January and December 2024. This study was approved by the institutional review board of our hospital, and written informed consent was obtained from all participants. All subjects underwent diagnostic thoracentesis, and pleural fluid samples were collected and analyzed as part of the study protocol. Subjects diagnosed with exudative pleural effusion by Light's Criteria were then further examined through physical examination, pleural fluid cytology, and/or pleural biopsy, and then categorized to MPE group if pleural fluid cytology and/or pleural biopsy were positive for malignant cells.

Inclusion criteria were: (1) patients aged 18 years or older, (2) diagnosed with exudative pleural effusion based on Light's criteria, and (3) underwent thoracentesis with adequate sample volume for biomarker analysis. Exclusion criteria included: (1) concurrent active infection, (2) prior history of thoracic surgery or trauma within the last three months, (3) incomplete clinical data, and (4) contraindications to thoracentesis such as severe thrombocytopenia, coagulopathy, or hemodynamic instability.

Pleural fluid specimens were collected under aseptic conditions using standard thoracentesis techniques. Samples were immediately centrifuged at 3000 rpm for 15

minutes and the supernatants were aliquoted into sterile tubes, then stored at –80°C until analysis. All biomarker measurements were performed within three months of sample collection to ensure stability.

The concentrations of matrix metalloproteinase-9 (MMP-9), tissue inhibitor of metalloproteinase-1 (TIMP-1), vascular endothelial growth factor (VEGF), and monocyte chemoattractant protein-1 (MCP-1) in pleural fluid were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturers' protocols. All assays were performed in duplicate, and laboratory personnel were blinded to the clinical classification of the patients to reduce detection bias. Participants with incomplete clinical data or unavailable biomarker measurements were excluded from the final analysis and no biomarker measurements were missing among the included participants; therefore, no imputation was performed.

Data analysis was conducted using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Normality of data distribution was assessed using the Shapiro–Wilk test. Continuous variables were expressed as mean or median depending on distribution characteristics. Comparative analysis between groups was performed using the independent t-test or Mann–Whitney U test, as appropriate.

Diagnostic performance of each biomarker was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was calculated to assess the accuracy of each marker. Optimal cut-off values were determined based on the Youden index. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated. A p-value < 0.05 was considered statistically significant. To internally validate the logistic regression models and reduce the risk of overfitting, 5-fold stratified cross-validation was applied. AUC values were computed across all folds, and their mean and standard deviation were reported.

Results

A total of 88 patients were enrolled in this study, with an equal distribution between male and female participants. The median age was 57.3 years (23 – 87), with a slight predominance of individuals aged >55 years (n=48; 54.5%). Among the study population,

33 (37.5%) were grouped into MPE group, while 55 (62.5%) were in NPE group. Basic demographics and pleural fluid analysis results from both groups can be seen in Table 1. These baseline characteristics provide a comprehensive overview of the study cohort and serve as a contextual foundation for further clinical and procedural analyses.

The distribution of MCP-1, MMP-9, TIMP-1, and VEGF values was not normal based on Shapiro-Wilk test, hence the comparison between malignant pleural effusion (MPE) and non-malignant pleural effusion (non-MPE) groups was performed using the Mann–Whitney U test.

The median VEGF concentration in the malignant group was 8762.00 (1063.00 – 11128.00) ng/mL, significantly higher than the median level in the non-malignant group which was 2270.00 (1456.00 – 6713.00) ng/mL ($p = 0.029$). This indicates that VEGF levels are significantly elevated in malignant effusions, supporting its role as a tumor-related angiogenic biomarker.

In contrast, no significant differences were observed for MCP-1, MMP-9, or TIMP-1. The median level of MCP-1 was 5884.88 (3378.79 – 6268.83) pg/mL in the non-malignant group and 5857.78 (4065.12 – 6412.6) pg/mL in the malignant group ($p = 0.945$). MMP-9 had a median value of 0.108 (0.075 – 1.584) ug/mL in the non-malignant group and 0.120 (0.057 – 1.820) ug/mL in the malignant group ($p = 0.343$), while TIMP-1 showed median levels of 13804.00 (7320.00 – 14595.00) pg/mL and 13847.00 (10414.00 – 14865.00) pg/mL in non-malignant and malignant groups respectively ($p = 0.584$).

These findings highlight VEGF as the only biomarker among those tested that exhibited a statistically significant difference between malignant and non-malignant effusions (Table 2).

Each biomarker was evaluated for its diagnostic performance using logistic regression and ROC curve analysis. The cut-off value for each biomarker was determined by identifying the threshold that yielded the best balance of sensitivity and specificity (Youden index). Diagnostic parameters including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), diagnostic accuracy, and odds ratio (OR) were subsequently calculated (Figure 1).

Among all biomarkers, VEGF showed the best individual diagnostic performance among the tested biomarkers, with an AUC of 0.640, sensitivity of 72.7%, specificity of 58.2%, PPV of

51.1%, and NPV of 78.0%. The diagnostic odds ratio reached 3.71, with an overall accuracy of 63.6%. MMP-9, TIMP-1 and MCP-1 demonstrated relatively limited diagnostic power (Table 3).

To explore the potential diagnostic value of combined biomarkers, multivariate logistic regression models were constructed using selected combinations. ROC analysis and optimal cut-offs from predicted probabilities were applied to calculate diagnostic performance metrics.

The combination of VEGF + MMP-9 showed a diagnostic odds ratio of 3.71, similar to VEGF alone, without an increase in overall accuracy (63.6%). However, adding TIMP-1 to the model (VEGF + MMP-9 + TIMP-1) resulted in a higher AUC (0.674), improved sensitivity (75.8%), and an OR of 4.35 with diagnostic accuracy of 64.8%. The four-marker model (VEGF + MMP-9 + TIMP-1 + MCP-1) yielded the highest NPV (81.6%) and maintained the same accuracy and OR. Internal validation using 5-fold cross-validation demonstrated consistent AUCs across folds, with average values ranging from 0.615 to 0.652 and standard deviations <0.05 for all models, suggesting acceptable stability despite the limited sample size, although this does not eliminate the risk of overfitting given the small number of malignant cases (Table 4 and Figure 2).

Although the incremental gain in AUC was modest, the increase in NPV may be more clinically relevant in ruling out MPE in ambiguous cases.

Discussion and Conclusions

Among the tested biomarkers, vascular endothelial growth factor (VEGF) had the best diagnostic performance, with an area under the curve (AUC) of 0.640 in this study. This observation is consistent with the prior finding of higher levels of pleural fluid VEGF in patients with malignant pleural effusion (MPE). For example, the study conducted by Fafliora et al. and Psatha et al. reported markedly elevated VEGF levels in MPE than benign effusions, indicating its feasibility in differentiating malignant from non-malignant effusions [13,14].

Although VEGF alone had moderate diagnostic accuracy, its combination with other markers showed an observable trend in improving the NPV. The AUC increased to 0.673

(NPV 81.6%) by combining VEGF, MMP-9, TIMP-1, and MCP-1. This numerical improvement suggests that a multi-biomarker approach may provide incremental information, particularly through a modest increase in sensitivity and negative predictive value. However, the limited specificity and modest AUC indicate that this panel should not be interpreted as a stand-alone diagnostic tool.

The biological rationale behind these findings is supported by the known roles of these biomarkers in tumor microenvironment modulation. VEGF increases vascular permeability and promotes angiogenesis, contributing to malignant dissemination within the pleural cavity [10]. TIMP-1 acts in a regulatory manner to prevent excessive extracellular matrix degradation by MMP-9, but also has been implicated in favoring tumor growth, depending on the condition [15,16]. MCP-1 is an inflammatory mediator and plays a role in recruiting immune cells and mediating tumor-associated inflammation, which can promote metastasis [17].

While VEGF showed the best individual performance, adding MMP-9 and TIMP-1 was associated with a modest numerical increase in sensitivity and negative predictive value (NPV) of the model. This result is consistent with the report by Wang et al., where a multi-marker approach showed better diagnostic performance than individual markers in detecting MPE [18]. Similarly, the combination of pleural biomarkers has been found to increase the probability that a diagnosis of MPE, particularly when cytological examination is negative [19,20]. However, it should be noted that these studies did not utilize the same biomarkers combination used in this study.

It is worth noting that the AUC values of combined biomarker panels in this study (0.674) are in line with the literature reporting similar performance. For instance, Wu et al. reported an AUC of 0.728 for pleural fluid VEGF alone, and showed that combining VEGF with pleural total protein raised sensitivity to 92.6% and NPV to 87.5%, but reduced specificity to 61.7%. This was a sensitivity-specificity trade-off consistent with the pattern observed in the present study [21]. The modest increase in NPV across multi-marker panels may justify further investigation of combined biomarker strategies, particularly if future studies validate these findings in larger and independent cohorts. Although these biomarker panels cannot replace cytology or histopathological confirmation, they may be explored as adjunctive

tools when interpreted together with clinical assessment, imaging findings, and pleural fluid cytology.

Another relevant finding is the numerically higher NPV observed in the four-marker model. From a clinical perspective, a higher NPV may be useful as supportive information when malignancy is considered less likely, particularly in frail patients who are poor candidates for invasive procedures. However, this finding requires external validation before it can be applied in clinical decision-making. Several of these algorithms are currently receiving traction in the management of pleural disease [12,22].

Although TIMP-1 and MCP-1 showed limited standalone diagnostic performance, their inclusion in the combined model was associated with small numerical changes in sensitivity and NPV. AUC for TIMP-1 was 0.535 and MCP-1 was 0.495, which is consistent with prior reports with modest standalone utility for these markers. Their biological relevance may justify further evaluation in multi-marker models, but the present findings do not establish their independent diagnostic utility.

This study has several strengths, including the use of cytology or histopathology-confirmed diagnostic classification, standardized biomarker measurements, and blinded laboratory assessment. The analysis of combinations was also controlled for logistic regression with receiver operating characteristic optimization for statistical rigor. Nevertheless, these strengths should be interpreted in light of several important limitations.

However, some limitations should be addressed. First, the sample size for the entire cohort was relatively small and needs adequate external validation in a larger multicenter population. Second, this study did not assess other promising pleural biomarkers (eg, fibulin-3, galectin-1 or soluble mesothelin-related peptides) that might further add to diagnostic accuracy. In addition, several potential confounders (e.g., systemic inflammation, nutritional status, comorbid infections) were not equally addressed and may influence the levels of these biomarkers.

Ultimately, biomarker panels should not be viewed as replacements for established diagnostic approaches, but as potential adjuncts that require further validation. Future development may involve integrated diagnostic scores or point-of-care biomarker assays as an adjunct to support real-time clinical decision-making.

In this exploratory study, VEGF showed the best individual diagnostic performance among the evaluated biomarkers. Adding MMP-9, TIMP-1, and MCP-1 was associated with modest numerical improvements in sensitivity, NPV, and diagnostic odds ratio, but overall accuracy and specificity remained limited. Internal cross-validation suggested acceptable model stability; However, external validation is required before clinical implementation. These results support the clinical potential of multi-biomarker panels in pleural fluid analysis and provide a compelling rationale for future multicenter studies to validate and operationalize these findings in routine diagnostic workflows.

While the combination of these biomarkers demonstrates an observable trend in improving the negative predictive value (NPV) up to 81.6%, we acknowledge that the incremental gain in the overall AUC remains modest. Statistical comparisons between the diagnostic models were not performed due to the limited sample size and the exploratory nature of this study. Furthermore, from a health economics perspective, measuring four independent biomarkers using separate enzyme-linked immunosorbent assays is not cost-effective for routine clinical practice given the current diagnostic accuracy. Therefore, the findings of this study should be interpreted as a biological proof-of-concept. The clinical utility of this multi-marker panel would only be justified if translated into an affordable, multiplex point-of-care testing platform in the future, specifically utilized as a non-invasive adjunct to rule out malignancy in frail populations who are unfit for invasive procedures.

We emphasize that the proposed multi-biomarker panel is not superior to these established clinical investigations. Instead, it serves as a complementary tool. When interpreted alongside radiological findings and clinical assessment, the higher NPV observed in this study may provide supportive information for ruling out MPE, but should not be used as a stand-alone basis for clinical decisions.

Another important limitation is that this study did not directly compare the biomarker panel with pleural fluid cytology, imaging-based assessment, or other established diagnostic pathways. Because malignant pleural effusion was defined using cytology and/or histopathology, these tests functioned as part of the reference standard rather than independent comparators. Therefore, the added clinical value of the biomarker panel over existing diagnostic approaches could not be determined in this study.

In conclusion, VEGF showed the best individual diagnostic performance among the evaluated biomarkers. Adding MMP-9, TIMP-1, and MCP-1 was associated with modest numerical improvements in sensitivity, NPV, and diagnostic odds ratio, but specificity and overall diagnostic accuracy remained limited. These findings do not support the use of this biomarker panel as a stand-alone diagnostic test, but they provide a rationale for further externally validated studies evaluating combined pleural fluid biomarkers as adjunctive tools in the diagnostic assessment of malignant pleural effusion.

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Table 1. Basic demographics and pleural fluid analysis characteristics.

Parameters	Groups	
	Malignant PE (n=33)	Non-Malignant PE (n=55)
Age		
< 55 yo	19 (57.6%)	29 (52.7%)
≥ 55 yo	14 (42.4%)	26 (47.3%)
Sex		
Male	21 (63.6%)	23 (41.8%)
Female	12 (36.4%)	32 (58.2%)
Smoking History		
Active smoker	11 (33.3%)	32 (58.2%)
Passive smoker	22 (66.67%)	22 (40.0%)
None	0 (0%)	1 (1.8%)
Mean LDH (Pleural) (IU/l)	1280.03 (253.0-5477.0)	799.0 (112.0-4505.0)
Mean Total Protein (Pleural) (g/dl)	4.88 (2.57-10.8)	3.96 (1.61-6.03)
Mean Glucose (Pleural) (mg/dl)	59.27 (11.0-181.0)	96.78 (11.0-292.0)

PE, pleural effusion; LDH, lactate dehydroginase.

Table 2. Median pleural fluid concentrations of MCP-1, MMP-9, TIMP-1, and VEGF in malignant *vs*. non-malignant pleural effusions.

Biomarkers	Medians		*p-value*
	Malignant PE	Non-Malignant PE	
MCP-1 (pg/ml)	5857.78 (4065.12-6412.6)	5884.88 (3378.79-6268.83)	0.945
MMP-9 (ug/ml)	0.12 (0.057-1.820)	0.108 (0.075-1.584)	0.343
TIMP-1 (pg/ml)	13847.00 (10414.00-14865.00)	13804.00 (7320.00-14595.00)	0.584
VEGF (ng/ml)	8762.00 (1063.00-11128.00)	2270.00 (1456.00-6713.00)	0.029

Mann–Whitney U Test. PE, pleural effusion; MCP-1, monocyte chemoattractant protein-1; MMP-9, matrix metalloproteinase-9; TIMP-1, tissue inhibitor of metalloproteinase-1; VEGF, vascular endothelial growth factor.

Table 3. Diagnostic performance of individual pleural fluid biomarkers for malignant pleural effusion.

Biomarkers	AUC	Cutoff	Sensitivity	Specificity	PPV	NPV	PLR	Accuracy	OR
VEGF	0.640	4181.00	72.7%	58.2%	51.1%	78.0%	1.74	63.6%	3.71
MMP-9	0.561	0.11	60.6%	54.5%	44.4%	69.8%	1.33	56.8%	1.85
TIMP-1	0.465	13712.00	63.6%	41.8%	39.6%	65.7%	1.09	50.0%	1.26
MCP-1	0.505	5481.28	75.8%	32.7%	40.3%	69.2%	1.13	48.9%	1.52

AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; OR, odds ratio; MCP-1, monocyte chemoattractant protein-1; MMP-9, matrix metalloproteinase-9; TIMP-1, tissue inhibitor of metalloproteinase-1; VEGF, vascular endothelial growth factor.

Table 4. Diagnostic accuracy metrics of combined biomarker models for malignant pleural effusion.

Biomarker Combinations	AUC	Sensitivity	Specificity	PPV	NPV	PLR	Accuracy	OR
VEGF + MMP-9	0.640	72.7%	58.2%	51.1%	78.0%	1.74	63.6%	3.71
VEGF + MMP-9 + TIMP-1	0.674	75.8%	58.2%	52.1%	80.0%	1.81	64.8%	4.35
VEGF + MMP-9 + TIMP-1 + MCP-1	0.673	78.8%	56.4%	52.0%	81.6%	1.81	64.8%	4.80

AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; OR, odds ratio; MCP-1, monocyte chemoattractant protein-1; MMP-9, matrix metalloproteinase-9; TIMP-1, tissue inhibitor of metalloproteinase-1; VEGF, vascular endothelial growth factor.

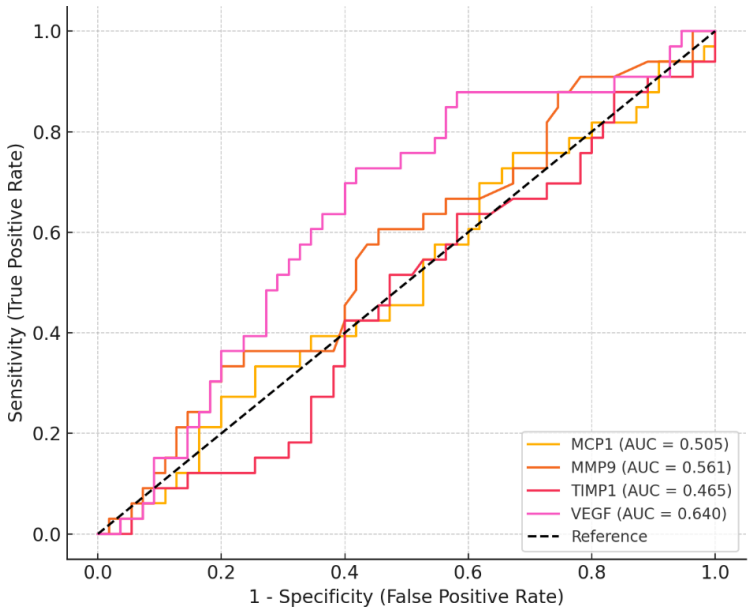

Figure 1. Receiver operating characteristic (ROC) curves of individual pleural biomarkers (VEGF, MMP-9, TIMP-1, MCP-1) in distinguishing malignant from non-malignant effusions. MCP-1, monocyte chemoattractant protein-1; MMP-9, matrix metalloproteinase-9; TIMP-1, tissue inhibitor of metalloproteinase-1; VEGF, vascular endothelial growth factor.

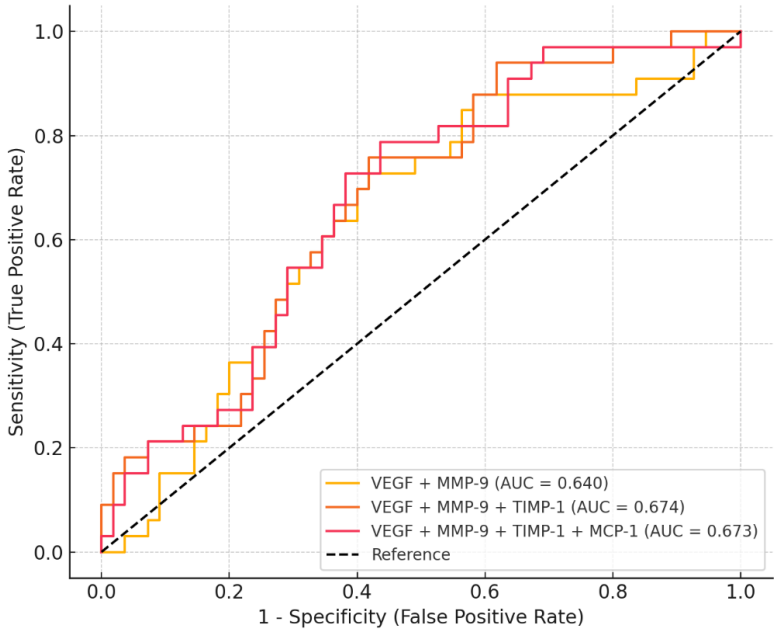

Figure 2. ROC curves of combined biomarker models showing incremental improvements in AUC with addition of MMP-9, TIMP-1 and MCP-1. MCP-1, monocyte chemoattractant protein-1; MMP-9, matrix metalloproteinase-9; TIMP-1, tissue inhibitor of metalloproteinase-1; VEGF, vascular endothelial growth factor.