NGAL/MMP-9 as a Biomarker for Epithelial Ovarian Cancer: A Case–Control Diagnostic Accuracy Study

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Abstract

Background: Epithelial ovarian cancer (EOC) are often diagnosed late due to lack of specific symptoms and efficient tumor markers. Neutrophil gelatinase-associated lipocalin/matrix metallopeptidase-9 (NGAL/MMP-9) complex are involved in the development and progression of various cancers and have potential as a biomarker for diagnosing ovarian cancer.

Objectives: To compare the serum NGAL/MMP-9 complex levels in patients with EOC, benign ovarian tumor, and healthy controls, and determine the potential cut-off values of NGAL/MMP-9 complex for diagnosing EOC.

Materials and Methods: The study included 50 patients each with EOC and benign ovarian tumor, along with 50 age-matched healthy controls (N = 150). The level of serum NGAL/MMP-9 complex was estimated based on sandwich ELISA. The mean and median of the three groups were compared, and the ROC curve was used to determine the optimum cut-off, sensitivity, and specificity of serum NGAL/MMP-9 complex levels in the diagnosis of EOC.

Results: A significant difference was found in the median values of the NGAL/MMP-9 complex (malignant EOC: 67.5 ng/ml, benign ovarian tumor: 53.7 ng/ml, controls: 29.2 ng/ml; P < 0.01). NGAL/MMP-9 complex level was also significantly associated with the FIGO staging (Stages I and II: 42.9 ng/ml; Stages III and IV: 70.5 ng/ml; P < 0.003). At a 55.0 ng/ml cut-off value, the NGAL/MMP-9 complex had 82.0% sensitivity and 78.0% specificity in diagnosing EOC.

Conclusion: The NGAL/MMP-9 complex may be a promising biomarker for determining the progression of EOC as well as in detecting advanced-stage ovarian cancer.

Keywords: Biomarker, diagnosis, epithelial ovarian cancer, FIGO staging, matrix metalloproteinase, neutrophil gelatinase-associated lipocalin

INTRODUCTION

Epithelial ovarian cancer (EOC) is the second most common cancer among women after cervical cancer and is the most lethal gynecological malignancy.[1] In the advanced stages of EOC, the recurrence rate is high and the overall 5-year mean survival rate is only around 45–50%, despite aggressive treatment modalities.[2,3] EOC often does not present with specific symptoms or remains asymptomatic,

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Cancer antigen 125 (CA-125) and radiological tools are currently used for the diagnosis and prognosis of EOC, but have low efficiency in making an early-stage diagnosis.\[5\] Therefore, there is a need to identify new biomarkers that identify EOC early, and in turn, potentially improve clinical outcomes. Neutrophil gelatinase-associated lipocalin (NGAL) has emerged as a promising new biomarker for diagnosing various types of cancer.\[10\]-\[16\] NGAL, also known as lipocalin 2, is a small protein of 178 amino acid residues encoded by the LCN2 gene. It is highly expressed in the presence of bacterial infections in granules of the neutrophils. It binds with gelatinase B and specific receptors at the cell surface\[17\]-\[19\] and covalently with matrix metalloproteinase-9 (MMP-9) protein to form the NGAL/MMP-9 complex. The NGAL/MMP-9 complex is involved in the development and progression of cancer.\[20\] Normal ovarian cells do not express or have a low expression of NGAL protein, but this expression is high in ovarian cancer cells.\[21\] Highly expressed NGAL from ovarian cancer cells may enter circulation and could be measured in the blood by a simple test. Furthermore, it has been found that urine MMP-9 could be used to distinguish ovarian cancer patients with a normal level of CA-125 from healthy controls; therefore, urinary MMP-9 can be clinically valuable in identifying advanced or recurring ovarian cancer.\[22\] High expression of NGAL has also been found in breast, colon, rectal, lung, and pancreatic cancers.\[23\]

Despite its promise, there is currently insufficient evidence regarding the use of NGAL/MMP-9 complex as a biomarker for diagnosing ovarian cancer. Therefore, the current study analyzed the serum NGAL/MMP-9 complex in patients with benign and malignant ovarian cancer and assessed its accuracy as a diagnostic cancer biomarker. Based on the literature, the authors hypothesize that the NGAL/MMP-9 complex levels may increase in EOC, making it useful for diagnosing EOC and differentiating between benign and malignant EOC.

**MATERIALS AND METHODS**

**Study design and setting**

This is a hospital-based, prospective, case–control diagnostic accuracy study conducted in the Biochemistry and the Obstetrics & Gynecology departments of Maulana Azad Medical College and Lok Nayak Hospital, New Delhi, India, between 2012 and 2015. The study was approved by the Ethics Committee of Maulana Azad Medical College, New Delhi, India, and was performed in accordance with the Declaration of Helsinki, 2013. This manuscript was prepared following the STARD guideline.

**Study population**

The study included a total of 150 participants who were selected conveniently and divided into the following three groups: Group I (50 histopathologically diagnosed patients of ovarian cancer), group II (50 patients with benign ovarian conditions), and group III (50 age-matched healthy controls with no indication of benign or malignant ovarian pathology), as determined by clinical examination and relevant investigations [Figure 1].

On histopathological examination of the biopsy samples, patients diagnosed with non-malignant ovarian conditions were included in group II. Patients of malignant ovarian tumors were categorized according to the International Federation of Gynecology and Obstetrics (FIGO) staging, and any FIGO stage of EOC was considered eligible for inclusion in this study. Healthy controls were randomly enrolled from the outpatient department of Lok Nayak Hospital, and were neither on any medications nor diagnosed with any acute or chronic disease. Those presenting with any other malignancy, on steroid therapy, with kidney disease, and chronic inflammation were excluded from the study.

![Figure 1: Flow of participants included in the study](image-url)
**Sample size calculation**

The authors first assessed the NGAL/MMP-9 complex levels in 10 EOC patients, of which 2 patients were found to have had increased NGAL/MMP-9 complex (i.e., prevalence = 20.0%). Based on this and using the formula \( N = \frac{(Z^2)(pq)}{L^2} \) (\( Z = \) Confidence interval, \( P = \) prevalence, \( q = 1 - \text{prevalence} \) and \( L = \) absolute error of 10%), the sample size was calculated as 64. For increased statistical power, the authors included 150 participants across the three groups.

**Neutrophil gelatinase-associated lipocalin/matrix metallopeptidase-9 complex estimation**

About 4 ml blood was collected before surgery from patients of EOC and benign ovarian tumors and healthy controls in plain vacutainer to estimate the NGAL/MMP-9 complex. Serum NGAL/MMP-9 complex was estimated by commercially available enzyme-linked immunosorbent assay (ELISA) kit of R & D Systems (Minneapolis, MN, USA) based on the principle of sandwich ELISA.

**Statistical analysis**

All data were evaluated using SPSS PC version 17 (SPSS Inc., Chicago, IL, USA). Non-skewed data were expressed as mean and standard deviation (SD), and skewed data were expressed as median and range. Significant differences of mean and median in different groups were calculated by the ANOVA and the Kruskal–Wallis tests, respectively. The receiver operating characteristic (ROC) curve was used to detect the optimum cut-off of the parameters, their sensitivity, and specificity in predicting the diagnosis of ovarian cancer. \( P < 0.05 \) was considered statistically significant.

**RESULTS**

The mean (±SD) ages of patients with malignant EOC, benign ovarian tumors, and healthy controls were 50.1 (±10.7), 43.6 (±15.9), and 48.5 (±9.2) years, respectively; there was no significant difference in the age across the three groups (\( P = 0.274 \)). Baseline characteristics of benign and malignant ovarian tumors are described in Table 1. The incidence was high in the age group 30–50 years (54%) and 50+ years (66%) ovarian tumors. In terms of the FIGO staging, most patients were stage III (40%), followed by stage IV (24%), stage II (20%), and stage I (16%). The incidence of serous-type histopathology (52%) was high in benign ovarian tumors, while mucinous-type histopathology (44%) was high in malignant ovarian tumors.

The median values of NGAL/MMP-9 complex were 42.9 ng/ml and 70.3 ng/ml in the early and late stages, respectively [Table 4]. The area under of curve for NGAL was 0.827 [Figure 3]. The cut-off value of NGAL/MMP-9 complex was 55.0 ng/ml, at which the complex had 82.0% sensitivity and 78.0% specificity to detect EOC [Table 5].

The median values of NGAL/MMP-9 complex were 67.5 ng/ml, 53.7 ng/ml, and 29.2 ng/ml, respectively. Data were found to be non-parametric by the Kolmogorov–Smirnov analysis. The median values between the three groups differed significantly (\( P < 0.001 \)) [Table 2]. In addition, the NGAL/MMP-9 complex levels were significantly high in malignant ovarian conditions compared with benign ovarian conditions and healthy controls [Table 3 and Figure 2].

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**Table 1: Baseline characteristic of benign and malignant ovarian tumor**

| Variables                  | Benign ovarian tumor, n (%) | Malignant ovarian tumor, n (%) |
|----------------------------|-----------------------------|--------------------------------|
| Age (years)                |                             |                                |
| <30                        | 9 (18)                      | 5 (10)                         |
| 30-50                      | 27 (54)                     | 33 (66)                        |
| >50                        | 14 (28)                     | 12 (24)                        |
| FIGO staging               |                             |                                |
| Stage I                    | -                           | 8 (16)                         |
| Stage II                   | -                           | 10 (20)                        |
| Stage III                  | -                           | 20 (40)                        |
| Stage IV                   | -                           | 12 (24)                        |
| Histopathology type        |                             |                                |
| Mucinous                   | 11 (22)                     | 22 (44)                        |
| Serous                     | 26 (52)                     | 20 (40)                        |
| Endometroid/cyst           | 13 (26)                     | 3 (6)                          |
| Clear cell                 | -                           | 5 (10)                         |

FIGO = International federation of gynecology and obstetrics staging

**Table 2: Serum level of NGAL/MMP-9 complex in study participants**

| Study groups                      | NGAL/MMP-9 complex (ng/ml) |          |          |
|-----------------------------------|---------------------------|----------|----------|
|                                   | Median                    | Range    |          |
| Healthy controls                  | 29.2                      | 20.7-41.8|          |
| Benign ovarian tumor              | 53.7                      | 25.6-77.8|          |
| Malignant ovarian tumor           | 67.5                      | 35.2-99.2|          |
| \( P^* \)                         |                           | <0.001   |          |

* \( P^* \) value calculated by Kruskal–Wallis test. NGAL = Neutrophil gelatinase-associated lipocalin; MMP-9 = Matrix metallopeptidase-9

**Table 3: Result of post hoc Dunn test for NGAL/MMP-9 complex in study participants**

| Study groups                      | Median (ng/ml) |          |          |
|-----------------------------------|----------------|----------|----------|
| Healthy controls                  | 29.2           |          | <0.01    |
| Benign ovarian tumor              | 53.7           |          | <0.01    |
| Healthy controls                  | 29.2           |          | <0.01    |
| Malignant ovarian tumor           | 67.5           |          | <0.01    |
| Benign ovarian tumor              | 53.7           |          | <0.01    |
| Malignant ovarian tumor           | 67.5           |          |          |

* \( P^* \) value calculated by post hoc Dunn test
DISCUSSION

This study found that the NGAL/MMP-9 was significantly higher in those with malignant EOC and benign ovarian tumors than the healthy controls. In addition, the serum levels of the NGAL/MMP-9 complex was significantly lower in those with benign ovarian tumors than EOC cases. At a 55.0 ng/ml cut-off value, NGAL has 82.0% sensitivity and 78.0% specificity in detecting EOC. These findings suggest that estimating the serum levels of NGAL/MMP-9 has potential as a biomarker to diagnose EOC and differentiate between the malignant EOC and benign ovarian tumor cases.

NGAL/MMP-9 complex was also significantly associated with the FIGO staging: the higher the stage, the higher the level of the NGAL/MMP-9 complex. This suggests that the complex may have a direct role in the progression of ovarian cancer. NGAL plays a key role in cell adhesion and cell growth in the cell of malignancy. It has been associated with increased invasiveness of cancer cells.[21] Some researchers observed that NGAL has an important role as a tumor oncogene and tumor suppressor gene.[22] Matrix metalloproteinases are groups of proteinases that require zinc as a cofactor. It degrades the extracellular matrix and plays a key role in the invasion and metastasis of cancers.[23] NGAL forms a homodimer with MMP-9 and prevents degradation of MMP-9. MMP-9 further degrades collagen type I, IV, and gelatin type I in the basement membrane. Basement degradation is also found during the development of ovarian carcinogenesis.[24] Therefore, the increased NGAL/MMP-9 complex may be one of the reasons for the development of EOC.

Similar to our study, Lim et al.[25] reported that NGAL concentration was higher in those with benign ovarian tumours and malignant EOC compared with healthy controls. Cho et al.[26] have also reported significantly higher level of lipocalin 2 and its correlation with tumor differentiation in EOC. Manenti et al.[27] have also found an increased serum level of MMP-9 in EOC compared with benign ovarian cases and healthy controls. MMP-9 overexpression has also been found in ovarian cancer cell lines and ascitic fluid of patients diagnosed with advanced ovarian cancer. Furthermore, expression of MMP-9 has been shown to have significant correlation with the severity of invasiveness in ovarian cancer lines.[28]

NGAL expression was found to be low in benign ovarian tissue and high with moderate staining in borderline ovarian tumors. NGAL could be a valuable marker for monitoring the transition of benign lesions to malignant ovarian cancer, and it may be involved in the progression of EOCs.[22] The incidence of serous type histopathology (52%) was high in benign ovarian tumors, and mucinous type histopathology (44%) was high in malignant ovarian tumors. High incidence of mucinous histopathology may influence study results, and it remains to be investigated.
whether these findings can be generalized to other patient populations, including higher rates of patients with low-grade or high-grade serous ovarian carcinoma.

NGAL/MMP-9 complex has been found to be elevated in various cancer. For example, Tsakogiannis et al. reported that the NGAL/MMP-9 complex might be a promising biomarker for detecting breast cancer in premenopausal obese women. In addition, MMP-9 and NGAL has been found to be expressed significantly higher in gastric cancer tissues than in normal tissues in immunohistochemistry analysis \((P < 0.001)\), based on which the NGAL/MMP-9 complex was considered a novel biomarker to diagnose gastric cancer at an early stage. Similarly, based on the results of the current study, NGAL/MMP-9 complex can be considered a viable biomarker for determining the development and progression of EOC.

**Limitations**

The limitations of our study are the small sample size, lack of follow-up or survival, no follow-up data from the control patients to determine if they developed EOC in the future, and no comparison with CA-125 serum levels. Therefore, a multicenter, large-scale, follow-up study that measures the NGAL/MMP-9 complex levels in the blood and serum of patients of EOC and healthy controls should be conducted to substantiate the findings of this study. Furthermore, along with NGAL/MMP-9 complex measurement, real-time polymerase chain reaction (RT-PCR) and immunohistochemistry can be performed to detect the correlation between blood level and tissue expression.

**CONCLUSION**

The serum level of NGAL/MMP-9 complex was significantly higher in EOC patients than benign and healthy controls. In addition, the level of NGAL/MMP-9 complex was significantly associated with the staging of EOC. Therefore, the NGAL/MMP-9 complex may be a promising biomarker for determining the progression of EOC and detecting advanced-stage ovarian cancer.

**Ethical considerations**

The protocol for the study was approved by the Ethics Committee of Maulana Azad Medical College, New Delhi (Ref No: 11; Date: October 10, 2012). All subjects volunteered to participate in the study and provided signed informed consent before inclusion in the study. The study was conducted in accordance with the Declaration of Helsinki, 2013.

**Data availability statement**

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

**Peer review**

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**Conflict of interest**

There are no conflicts of interest.

**REFERENCES**

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.
3. Coleman RL, Monk BJ, Sood AK, Herzog TJ. Latest research and treatment of advanced-stage epithelial ovarian cancer. Nat Rev Clin Oncol 2013;10:211-24.
4. Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. CA Cancer J Clin 2011;61:183-203.
5. Das PM, Bast RC Jr. Early detection of ovarian cancer: From traditional methods to proteomics. Can we really do better than serum CA-125? Am J Obstet Gynecol 2008;199:215-23.
6. Nossow V, Amneus M, Su F, Lang J, Janco JM, Reddy ST, et al. The early detection of ovarian cancer: From traditional methods to proteomics. Can we really do better than serum CA-125? Am J Obstet Gynecol 2008;199:215-23.
7. Rauh-Hain JA, Krivak TC, Del Carmen MG, Olawaiye AB. Ovarian cancer screening and early detection in the general population. Rev Obstet Gynecol 2011;4:15-21.
8. Ren X, Zhang H, Cong H, Wang X, Ni H, Shen X, et al. Diagnostic model of serum miR-193a-5p, HE4 and CA125 improves the diagnostic efficacy of epithelium ovarian cancer. Pathol Oncol Res 2018;24:739-44.
9. van Nagell JR Jr., DePriest PD, Ueland FR, DeSimone CP, Cooper AL, McDonald JM, et al. Ovarian cancer screening with annual transvaginal sonography: Findings of 25,000 women screened. Cancer 2007;109:1887-96.
10. Cowland JB, Borregaard N. Molecular characterization and pattern of tissue expression of the gene for neutrophil gelatinase-associated lipocalin from humans. Genomics 1997;45:17-23.
11. Coticchia CM, Curatolo AS, Zurakowski D, Yang J, Daniels KE,
Matulonis UA, et al. Urinary MMP-2 and MMP-9 predict the presence of ovarian cancer in women with normal CA125 levels. Gynecol Oncol 2011;123:295-300.

12. Bauer M, Eickhoff JC, Gould MN, Mundhenke C, Maass N, Friedl A. Neutrophil gelatinase-associated lipocalin (NGAL) is a predictor of poor prognosis in human primary breast cancer. Breast Cancer Res Treat 2008;108:389-97.

13. Wang Y, Zeng TT. Clinical significance of neutrophil gelatinase-associated lipocalin (NGAL) in colorectal cancer: A meta-analysis. Genet Mol Res 2014;13:7102-12.

14. Barresi V, Lucianò R, Vitarelli E, Labate A, Tuccari G, Barresi G. Neutrophil gelatinase-associated lipocalin immunoexpression in colorectal carcinoma: A stage-specific prognostic factor? Oncof Lett 2010;1:1089-96.

15. Mir SU, Jin L, Craven RJ. Neutrophil gelatinase-associated lipocalin (NGAL) expression is dependent on the tumor-associated sigma-2 receptor S2Rgrmc1. J Biol Chem 2012;287:14494-501.

16. Moniaux N, Chakraborty S, Yalniz M, Gonzalez J, Shostrom VK, Standop J, et al. Early diagnosis of pancreatic cancer: Neutrophil gelatinase-associated lipocalin as a marker of pancreatic intraepithelial neoplasia. Br J Cancer 2008;98:1540-7.

17. Flower DR. The lipocalin protein family: Structure and function. Biochem J 1996;318:1-14.

18. Flo TH, Smith KD, Sato S, Rodriguez DJ, Holmes MA, Strong RK, et al. Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron. Nature 2004;432:917-21.

19. Kjeldsen L, Johnsen AH, Sengelov H, Borregaard N. Isolation and primary structure of NGAL, a novel protein associated with human neutrophil gelatinase. J Biol Chem 1993;268:10425-32.

20. Chakraborty S, Kaur S, Guha S, Batra SK. The multifaceted roles of neutrophil gelatinase associated lipocalin (NGAL) in inflammation and cancer. Biochim Biophys Acta 2012;1826:129-69.

21. Candido S, Abrams SL, Steelman IS, Lertpiiyapong K, Fitzgerald TL, Martelli AM, et al. Roles of NGAL and MMP-9 in the tumor microenvironment and sensitivity to targeted therapy. Biochim Biophys Acta 2016;1863:438-48.

22. Candido S, Maestro R, Polese J, Catania A, Maira F, Signorelli SS, et al. Roles of neutrophil gelatinase-associated lipocalin (NGAL) in human cancer. Oncotarget 2014;5:1576-94.

23. Kessenbrock K, Plaks V, Werb Z. Matrix metalloproteinases: Regulators of the tumor microenvironment. Cell 2010;141:52-67.

24. Saad AF, Hu W, Sood AK. Microenvironment and pathogenesis of epithelial ovarian cancer. Horm Cancer 2010;1:277-90.

25. Lim R, Ahmed N, Borregaard N, Riley C, Wafai R, Thompson EW, et al. Neutrophil gelatinase-associated lipocalin (NGAL) an early-screening biomarker for ovarian cancer: NGAL is associated with epidermal growth factor-induced epithelio-mesenchymal transition. Int J Cancer 2007;120:2426-34.

26. Cho H, Kim JH. Lipocalin2 expressions correlate significantly with tumor differentiation in epithelial ovarian cancer. J Histochem Cytochem 2009;57:513-21.

27. Manenti L, Paganoni P, Florian I, Landoni F, Torri V, Buda A, et al. Expression levels of vascular endothelial growth factor, matrix metalloproteinases 2 and 9 and tissue inhibitor of metalloproteinases 1 and 2 in the plasma of patients with ovarian carcinoma. Eur J Cancer 2003;39:1948-56.

28. Schmalfeldt B, Prechtel D, Häring K, Späthe K, Ruthe S, Konik E, et al. Increased expression of matrix metalloproteinases (MMP)-2, MMP-9, and the urokinase-type plasminogen activator is associated with progression from benign to advanced ovarian cancer. Clin Cancer Res 2001;7:2396-404.

29. Tsakogiannis D, Kalogera E, Zagouri F, Zografos E, Balalis D, Bletsa G. Determination of FABP4, RBP4 and the MMP-9/NGAL complex in the serum of women with breast cancer. Oncol Lett 2021;21:85.

30. Shimura T, Dagher A, Sachdev M, Ebi M, Yamada T, Yamada T, et al. Urinary ADAM12 and MMP-9/NGAL complex detect the presence of gastric cancer. Cancer Prev Res (Phila) 2015;8:240-8.