



## Integration of immunological and hormonal biomarkers for risk stratification in ovarian carcinoma

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### Article info

Received 15.01.2026

Received in revised form 25.02.2026

Accepted 16.03.2026

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*Al-Nuaimi, Z. J. A., Alkaissy, S. N. J., Fadhil, Z. J., & Mohsein, O. A. (2026). Integration of immunological and hormonal biomarkers for risk stratification in ovarian carcinoma. Regulatory Mechanisms in Biosystems, 17(2), e26047. doi:10.15421/0226047*

Ovarian carcinoma is a biologically complicated cancer which is associated with immune dysregulation and hormonal imbalance, both of which play a role in tumor development, progression and poor clinical outcomes. Our research aimed to assess how immunological and hormonal biomarkers can be integrated together and how they can be used in combination in risk stratification and prognosis of disease progression in patients with ovarian carcinoma. In this case control study (April 2025 to February 2026), 100 newly diagnosed patients with epithelial ovarian carcinoma were utilized and 50 age-matched normal controls. Diagnosis was done histopathologically using WHO criteria. Women aged from 30 to 75 years and who had never undergone any therapy before were considered; autoimmune, inflammatory, endocrine or other malignant conditions were exclusion criteria. Blood samples were collected on fasting and stored at -80 °C. ELISA was used to measure IL-6, TNF- $\alpha$ , IL-10 and CRP, whereas CLIA was used to measure estradiol, progesterone, FSH and LH. There were no noteworthy differences between patients and control in age, BMI, and menopausal status, yet a positive family history of ovarian carcinoma was more frequent in the patient group. The majority of the cases showed up at advanced stages. There was significant increase in IL-6, TNF- $\alpha$ , IL-10 and CRP and also estradiol, FSH and LH and low progesterone. The inflammatory and hormonal levels were elevated in the advanced stages. There were very significant positive correlations between biomarkers. Risk factors that were independent included IL-6, TNF- $\alpha$ , estradiol and family history, with progesterone being protective. Systemic inflammation and hormonal imbalance are closely related to ovarian carcinoma. Inflammatory signaling and proliferative pathways contribute to tumor progression via high levels of IL-6, TNF- $\alpha$  and estradiol, whereas low levels of progesterone minimize the protective action. Combining biological markers of immunology and hormones enhances prognostics and risk stratification.

**Keywords:** ovarian carcinoma; inflammatory cytokines; hormonal imbalance; risk stratification; biomarkers.

### Introduction

Ovarian carcinoma is one of the deadliest gynecologic tumors in the world, and the primary causes of such a situation include the late stage at which the disease is detected, the absence of viable screening measures, and the lack of symptoms in the early tumor development. Despite the increased success of surgical practices and platinum-based chemotherapy, survival over time remains poor, particularly in those patients who find themselves at the stage III–IV of the disease (Liberto et al., 2022). Oncogenetic diversity of ovarian carcinoma, both at the molecular level and at the clinical level, poses significant difficulties in the matter of early diagnosis, prognostic evaluation and treatment choice. This has created an urgent need to identify good biomarkers that not only improve the diagnostic accuracy but also and more importantly the risk stratification and prognostic forecast (Mathieu et al., 2018; Sideris et al., 2024).

The conventional examples of biomarkers that are utilized in clinical practice to help in diagnosis and treatment response monitoring are CA-125 and HE4. However, the indicators are not sensitive and specific, particularly in the initial stages of disease, and poorly distinguish between malignant and benign masses in the ovaries (Ghose et al., 2024). It is increasingly emerging that ovarian carcinoma cannot simply be called a localized epithelial malignancy but is a systemic disease and there exist complex interactions between tumor cells, immune system and endocrine signal pathways. Therefore, the utilization of immunological and hormonal biomarkers can be used to develop a more elaborate image of tumor biology and a more effective stratification of patients (Dochez et al., 2019; Mohammed et al., 2026).

Chronic inflammation has already become a characteristic feature of cancer and one of the key determinants of ovarian carcinogenesis.

The ovarian carcinoma tumor microenvironment is also abundant in inflammatory and chemokines and immune cells that in combination with each other trigger tumor growth, angiogenesis, invasion and immune evasion (Savant et al., 2018). Of these mediators, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6) are of special importance. The JAK/STAT3 signaling pathway by IL-6 increases the survival, proliferation and resistance to apoptosis of cancer cells, whereas the NF- $\kappa$ B activity through TNF- $\alpha$  promotes a pro-tumorigenic inflammatory environment (Abdullhussien et al., 2026). High blood concentrations of such cytokines have been linked to high stage, unfavorable prognosis and decreased overall survival. Also, C-reactive protein (CRP), an acute-phase respondent provoked by IL-6, indicates general inflammation and is associated with higher risk of cancer and disease progression (Dinca et al., 2023; Muhammed et al., 2026).

Besides the pro-inflammatory mediators, there are immune regulatory cytokines like interleukin-10 (IL-10) that have a dual role in ovarian carcinoma. In spite of its traditional anti-inflammatory effect, IL-10 can mediate immune escape by the tumor, by inhibiting successful cytotoxic T-cells and antigen presentation. This anti-immune setting facilitates the existence and spread of tumors. Therefore, the profiling of inflammatory and immunomodulatory cytokines could provide beneficial information on the severity of the disease and biological behavior (Abakumova et al., 2022; Pankowska et al., 2023).

Hormonal imbalance is parallel to immunodysregulation, and is also another critical element in ovarian carcinogenesis. Ovarian epithelium is very sensitive to steroid hormones especially estrogen and progesterone. Chronic exposure to estrogen has been involved in the proliferation of the epithelia, genomic instability, and malignant transformation. Estradiol may have a direct effect on tumor growth through the estrogen receptor mediated transcriptional activation and the indirect

effects through the regulation of inflammatory signaling pathways (Bartkowiak-Wieczorek et al., 2024). On the other hand, progesterone has also been suggested to produce a protective effect by induction of apoptosis and prevention of estrogen-induced proliferation. The association between lower incidences of ovarian cancer in women using contraceptives that contain progesterone or even in pregnancy further underlines the significance of the hormonal manipulation (Kozielec et al., 2023).

FSH and LH are gonadotropins that can have an effect on the biology of ovarian tumors. High levels of gonadotropins, especially in postmenopausal women, have been conjectured to induce development of the surface epithelium of the ovary and encourage the development of malignancy. According to the theory of gonadotropins, persistent hormonal stimulation is one of the factors that lead to epithelial damage and predisposition to oncogenic mutations (Devesa et al., 2019). So, the simultaneous analysis of the interaction of steroid hormones and gonadotropins with inflammatory markers could provide a multidimensional profile of biomarkers (Lambertini et al., 2029).

Notably, there is also emerging evidence that there exists substantial cross-talk between inflammatory and hormonal pathways. The production of cytokines can be modified by estrogen signaling, whereas the inflammatory mediators can stimulate and optimize the local aromatase activity and steroid metabolism in the tumor microenvironment. This two-way interdependence forms a feedback mechanism, which perpetuates the tumor development. Therefore, individual biomarker strategies can overcome the complexity of the biology of ovarian carcinoma (Vella et al., 2020).

In this regard, a combination of immunological and hormonal biomarkers should be a promising approach to finer risk stratification in ovarian cancer. An integrated biomarker panel can enhance the ability to distinguish among malignant and benign disease, also to enrich information on patients at increased risk of progressive disease as well as assist in providing prognostic data not given by traditional clinical parameters. Furthermore, the dynamic interplay between immune activation and endocrine disequilibrium could be a great opportunity to explore new research avenues in the field of individual therapeutic intervention, involving the pathways of inflammatory and hormonal processes.

## Materials and methods

The Human Research Ethics Committee of Al-Habboubi Teaching Hospital approved the study. The study objectives and procedures were explained to all the participants and informed consent was signed in writing before the study was conducted. All of the patient information was kept confidential and private during the study.

The study was a case-control study that was carried out from 10 April 2025 to 5 February 2026 to examine how immunological and hormonal biomarkers can be integrated to risk stratify ovarian carcinoma. 150 patients were recruited into the study, 100 of them recently diagnosed with ovarian carcinoma and 50 healthy controls who matched the age of the patients. The patients were enrolled in the Gynecology Oncology Unit where the diagnosis was made by clinical examination, transvaginal ultrasonography, serum CA-125, radiological examination (CT/MRI), and the confirmation of the diagnosis was made by histopathological examination upon surgical biopsy according to the WHO classification criteria. Inclusion criteria were women, aged 30–75 years with newly detected epithelial ovarian carcinoma, who had never undergone chemotherapy, radiotherapy or hormonal therapy before sampling. Both autoimmune disorders and chronic inflammatory diseases as well as other malignancies, infectious diseases, endocrine disorders, and using immunomodulatory or hormonal drugs were exclusion criteria. Controls were clinically healthy women without malignancy or chronic inflammatory diseases. Under aseptic conditions venous blood samples (57mL) were collected from fasting participants and were separated into EDTA tubes and plain tubes. The obtained serum was clotted and centrifuged at 3000 rpm for 10 minutes before aliquot and stored in ice at minimum temperature of  $-80^{\circ}\text{C}$  till analysis. Immunological biomarkers (IL-6, TNF- $\alpha$ , IL-10) and CRP were determined by using an enzyme-linked immunosorbent as-

say (ELISA) kit which is based on the sandwich immunoassay technology. According to the protocols of the manufacturer, hormonal biomarkers (estradiol, progesterone, FSH, and LH) were detected in chemiluminescent immunoassay (CLIA) on an automated analyzer. Each assay was performed in triplicate and quality control samples were also taken to guarantee reproducibility and quality of analysis.

Data were analyzed using SPSS version 26. Continuous variables were expressed as mean  $\pm$  SD and categorical variables as frequencies and percentages. Normality was assessed using the Shapiro–Wilk test. Independent t-test or Mann–Whitney U test was used for group comparisons as appropriate. Chi-square test evaluated categorical variables. Correlations were assessed using Pearson or Spearman tests, and multivariate logistic regression identified independent predictors. A P-value  $< 0.05$  was considered statistically significant.

## Results

The findings in Table 1, showed no significant differences between ovarian carcinoma patients and controls regarding age, BMI, or postmenopausal status ( $P > 0.05$ ). However, a significantly higher proportion of patients reported a positive family history of cancer compared to controls (29% vs. 12%,  $P = 0.018$ ). Regarding tumor staging, 42% of the patients were diagnosed at early stages (I–II), whereas the majority (58%) presented with advanced stages (III–IV).

**Table 1**

Baseline comparison of age, BMI, menopausal status, family history, and tumor stage distribution

Variable	Ovarian carcinoma (n = 100)	Controls (n = 50)	P-value
Age, years (mean $\pm$ SD)	54.8 $\pm$ 9.6	52.3 $\pm$ 8.9	0.118
BMI, kg/m <sup>2</sup>	29.1 $\pm$ 4.3	27.8 $\pm$ 3.9	0.062
Postmenopausal (%)	68 (68%)	30 (60%)	0.324
Family history of cancer (%)	29 (29%)	6 (12%)	0.018
Stage I–II (%)	42 (42%)	–	–
Stage III–IV (%)	58 (58%)	–	–

Inflammatory biomarkers in serum were highly increased in ovarian carcinoma patients more than in controls ( $P < 0.001$ ). The levels of IL-6, TNF- $\alpha$ , IL-10, and CRP were significantly elevated in patients, which means that the systemic inflammatory and immunomodulatory response was rather strong. Such results indicate that the role of chronic inflammation and dysregulation of cytokines could prove to be essential in tumor development and be useful as biomarkers to risk stratify and monitor disease as indicated in Table 2.

**Table 2**

Serum levels of IL-6, TNF- $\alpha$ , IL-10, and CRP between study groups (mean  $\pm$  SD)

Biomarker	Patients (n = 100)	Controls (n = 50)	P-value
IL-6, pg/mL	14.2 $\pm$ 5.1	4.6 $\pm$ 1.8	$< 0.001$
TNF- $\alpha$ , pg/mL	22.8 $\pm$ 6.7	9.4 $\pm$ 3.2	$< 0.001$
IL-10, pg/mL	6.1 $\pm$ 2.4	3.2 $\pm$ 1.1	$< 0.001$
CRP, mg/L	11.5 $\pm$ 4.3	2.8 $\pm$ 1.2	$< 0.001$

In Table 3, significant hormonal alterations were observed in ovarian carcinoma patients compared to controls ( $P \leq 0.003$ ). Estradiol, FSH, and LH levels were markedly elevated in patients, while progesterone levels were significantly reduced. These findings suggest endocrine imbalance characterized by increased estrogenic activity and gonadotropin stimulation, which may contribute to tumor growth, hormonal dysregulation, and disease progression.

**Table 3**

Serum levels of estradiol, progesterone, FSH, and LH between study groups (mean  $\pm$  SD)

Hormone	Patients (n = 100)	Controls (n = 50)	P-value
Estradiol, pg/mL	68.4 $\pm$ 21.5	42.7 $\pm$ 16.3	$< 0.001$
Progesterone, ng/mL	0.92 $\pm$ 0.41	1.35 $\pm$ 0.52	0.003
FSH, mIU/mL	49.6 $\pm$ 18.4	39.2 $\pm$ 15.7	0.002
LH, mIU/mL	31.5 $\pm$ 12.3	24.8 $\pm$ 9.4	0.001

There was a significant increase in IL-6, TNF- $\alpha$ , estradiol, and CRP levels of patients at advanced stages (III-IV) of ovarian cancer compared to the early stages (I-II) (pSchemata: 0.004). These results show that tumor progression can be related to increased systemic inflammation and hormonal changes, which may suggest that the combination of inflammatory and endocrine dysregulation can cause disease progression and can be used as signs of tumor severity as illustrated in Table 4.

**Table 4**  
Comparison of IL-6, TNF- $\alpha$ , estradiol, and CRP levels between early and advanced stages (mean  $\pm$  SD)

Marker	Stage I-II (n = 42)	Stage III-IV (n = 58)	P-value
IL-6	10.8 $\pm$ 3.4	16.7 $\pm$ 4.8	<0.001
TNF- $\alpha$	18.5 $\pm$ 4.6	25.9 $\pm$ 6.2	<0.001
Estradiol	59.2 $\pm$ 18.1	75.3 $\pm$ 22.7	0.004
CRP	8.4 $\pm$ 3.1	13.6 $\pm$ 4.2	<0.001

Considerable positive associations in Table 5, were established between all the examined biomarkers. There were strong correlations of IL-6 with TNF- $\alpha$  ( $r = 0.71$ ,  $P < 0.001$ ) and CRP ( $r = 0.68$ ,  $P < 0.001$ ) and a moderate correlation with estradiol ( $r = 0.52$ ,  $P < 0.001$ ). CRP ( $r = 0.61$ ,  $P < 0.001$ ) and estradiol ( $r = 0.47$ ,  $P < 0.001$ ) also had a strong correlation with TNF- $\alpha$ . This result suggests that the interplay between inflammatory and hormonal processes in ovarian carcinoma development is coordinated.

**Table 5**  
Interrelationships between IL-6, TNF- $\alpha$ , estradiol, and CRP levels

Variable	IL-6	TNF- $\alpha$	Estradiol	CRP
IL-6	1	–	–	–
TNF- $\alpha$	0.71***	1	–	–
Estradiol	0.52***	0.47**	1	–
CRP	0.68***	0.61***	0.44**	1

The multivariate analysis has shown that IL-6 (OR = 1.42), TNF- $\alpha$  (OR = 1.35), and estradiol (OR = 1.18) are important independent risk factors in ovarian carcinoma ( $P = 0.002$  or less). Positive family history was another risk factor (OR = 2.41,  $P = 0.021$ ). Conversely, the progesterone was protective (OR = 0.72,  $P = 0.011$ ). These results indicate the compounded effect of inflammatory activation, hormonal imbalance and genetic predisposition in disease development as indicated in Table 6.

**Table 6**  
Odds ratios of inflammatory, hormonal markers, and family history

Variable	OR	95% CI	P-value
IL-6	1.42	1.21–1.67	<0.001
TNF- $\alpha$	1.35	1.14–1.59	<0.001
Estradiol	1.18	1.06–1.32	0.002
Progesterone	0.72	0.55–0.93	0.011
Family history	2.41	1.14–5.09	0.021

## Discussion

The existing study has presented integrated results indicating that the ovarian carcinoma is characterized by a complex interdependence of genetic vulnerability, systemic inflammation and endocrine disruption. Considering the sociodemographic and baseline clinical characteristics (Table 1), there were no statistically significant differences between the patients and the controls in terms of age, BMI or postmenopausal status. Such comparability reinforces the internal validity of the study as such variables reduce the confounding variables on the inflammatory and hormonal markers. Even though BMI was marginally greater in the patients, it was not statistically significant ( $P = 0.062$ ), possibly, due to the sample size limitations or difference within a group. Past epidemiological studies have shown inconsistent results on the links between BMI and ovarian cancer with some studies indicating that they have weak associations but others showing no results, more so when they examine the links with menopausal status and hormonal influences (Momenimovahed et al., 2019; Ali et al.,

2023). However, the percentage of patients who reported a positive family history of cancer was much higher (29% vs. 12%,  $P = 0.018$ ). This observation is biologically reasonable and conforms to the long-established role of hereditary disposition, specifically BRCA1 and BRCA2 mutations in ovarian carcinogenesis (Mann et al., 2019; Liu et al., 2021). There is family clustering that increases the lifetime risks due to impaired DNA repair and genomic instability that facilitates malignant transformation. The higher-stage disease (58% of III–IV) preeminence is also evidence in support of a silent clinical course of ovarian carcinoma that often results in late diagnosis and presentation of a late-stage disease (Chen et al., 2019).

Table 2 shows that there were significant increases of IL-6, TNF- $\alpha$ , IL-10, and CRP in patients relative to controls ( $p < 0.001$ ). These results can be used to justify the idea that chronic inflammation is a symptom of ovarian cancer. IL-6 is a key mediator, which triggers the JAK/STAT3 signal pathway, facilitating tumor growth, angiogenesis and anti-apoptotic resistance (Johnson et al., 2018). It has been repeatedly demonstrated that high IL-6 circulating levels are indicative of ovarian carcinoma and are correlated with poor prognosis and advanced disease (Huang et al., 2021). On the same note, NF- $\kappa$ B is activated by TNF- $\alpha$ , which promotes tumor progression, cell survival, invasion, and metastasis (Manore et al., 2022). CRP increase is an overall acute-phase reaction of the system dominated by IL-6, which also speaks in favor of a pro-inflammatory tumor microenvironment (Manore et al., 2022).

Interestingly, there was also a serious increase in IL-10. As anti-inflammatory, IL-10, however, can facilitate the evasion of the immune system in cancer by dampening the effective anti-tumor immune reaction and blocking the antigen-presenting cells in the context of cancer (Chang et al., 2021). In other studies, it has been found that IL-10 levels are high in ovarian cancer patients, which is associated with tumor burden (Rallis et al., 2022), but in other studies the levels are lower or do not differ, which could be explained by the tumor histology, disease stage, assays methodology, or even time of samples. These differences point to the variability of immune responses in different populations of patients (Rallis et al., 2022).

The hormone levels (Table 3) showed a significant increase of estradiol, FSH, and LH and a decrease of progesterone levels in patients. The increase in estradiol could lead to tumorigenesis via proliferative signaling via estrogen receptor and subsequent amplification of local inflammatory mechanisms (Bonkhoff, 2018). Prolonged exposure to estrogens has been suspected of rearranging the epithelial transformations, especially in postmenopausal patients. On the other hand, progesterone can have a protective effect by triggering antiproliferative effects of apoptosis and reversing estrogen-induced proliferation (Teresinski et al., 2019). This biological process is supported by the protective association of logistic regression (OR = 0.72). The increased gonadotropins (FSH and LH) could indicate postmenopausal endocrine processes and has been suggested to cause stimulation of ovarian surface epithelium or fallopian tube epithelium and ovarian cysts to undergo malignant transformation (Kawakita et al., 2023).

As seen in Table 4, comparisons based on the stage further showed that patients at advanced stages had significantly higher IL-6, TNF- $\alpha$ , estradiol, and CRP levels. This implies that inflammation and hormonal imbalance aggravates as the tumor develops. The late-stage disease is normally associated with increased tumor burden, necrosis, and stromal remodeling, which increases the production of cytokines. Past researches have also demonstrated an increased level of IL-6 and CRP in FIGO stage III–IV than in the early stages, which can confirm their possible usefulness as indicators of the disease severity (Kampan et al., 2020; Hou et al., 2022).

The correlation analysis (Table 5) showed that there were close positive correlations between IL-6, TNF- $\alpha$ , and CRP and these were a reflection of coordinated inflammatory route activation. The strong association of these two is because the IL-6 promotes the production of hepatic CRP. The mediocre associations between estradiol and inflammatory markers report two-way relations between the endocrine and immune systems. The modulatory capacity of estrogen to cytokine production, inflammatory mediators to aromatase activity and local estrogen production in the tumor microenvironment are possible.

This interaction has the potential to establish a vicious cycle that favors the growth of tumors (Olsthoorn et al., 2021).

The independent risk factors were confirmed by multivariate logistic regression (Table 6) as IL-6, TNF- $\alpha$ , estradiol, and family history, but progesterone had a protective effect. These conclusions support the idea that ovarian carcinoma is a multifactorial disease which combines genetic predisposition, chronic inflammation and hormonal imbalance. Similar research reports that IL-6 and CRP are independent predictors of the risk of ovarian cancer (Pawlik et al., 2021), and hereditary background belongs to the category of risks that have been identified to be strong. The discrepancies between supportive and conflicting studies can be explained by sample, ethnic, tumor histological subtype, and stage distribution and methodological variability in the cytokine quantification methods (Yang et al., 2021).

## Conclusion

Altogether, current results support the idea that ovarian carcinoma is a result of a dynamic interaction of the inflammatory signaling and hormonal imbalance, overlaid on genetic vulnerability. The joint analysis of immunological and endocrine biomarkers could thus improve risk stratification, prognostic analysis and individual therapeutic approaches.

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