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Research Article

Histopathological and Bioinformatic Analysis of the IL-6/STAT3 Signaling Pathway in Ovarian Neoplasms

¹Umara Lani Anika, ²Tantri Hellyanti, ³Fachrur Rizal Mahendra and ^{4,5}Ria Kodariah

¹Master's Programme in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, DKI Jakarta, Indonesia

²Department of Anatomical Pathology, Dr. Cipto Mangunkusumo Hospital, DKI Jakarta, Indonesia

³Department of Biochemistry, Faculty of Mathematics and Natural Sciences, Bogor Agricultural University, Bogor, West Java, Indonesia

⁴Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia, DKI Jakarta, Indonesia

⁵Biobank Research, Institute of Medical Research Indonesia, Faculty of Medicine, Universitas Indonesia, DKI Jakarta, Indonesia

Abstract

Background and Objective: Ovarian cancer is a highly lethal gynecologic malignancy, often diagnosed at advanced stages due to nonspecific symptoms. The IL-6/STAT3 pathway promotes tumor progression, chemoresistance and poor prognosis. Therefore, this study aimed to evaluate the histologic patterns of ovarian tumors based on the WHO 2020 classification and investigate the role of the IL-6/STAT3 pathway in ovarian cancer progression. **Materials and Methods:** A retrospective observational study was conducted using 2,309 ovarian biopsy specimens collected between 2016 and 2025 and classified according to the 2020 WHO Classification of Female Genital Tumours. Histopathological data were analyzed using descriptive statistics and the chi-square test ($p < 0.05$). Bioinformatic analyses of TCGA gene expression data were performed using DESeq2 for differential expression analysis and Kaplan-Meier and Cox regression analyses to evaluate the prognostic significance of the IL-6/STAT3 signaling pathway. **Results:** Surface epithelial tumors were the most common ovarian neoplasms (74.08%), followed by germ cell tumors (12.56%). Mucinous ovarian tumors were the predominant epithelial subtype. A significant association between age and malignancy was observed ($p < 0.001$). STAT3 expression was significantly increased in the low-grade group ($p = 0.022$), while IL-6 expression was not statistically significant. **Conclusion:** Ovarian tumors showed diverse histopathological features and STAT3 dysregulation may contribute to ovarian carcinoma prognosis. Integrating histopathological and molecular analysis may improve diagnostic and prognostic assessment.

Key words: Ovarian neoplasms, histological subtypes, IL-6, STAT3, bioinformatics

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Corresponding Author: Ria Kodariah, Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia, DKI Jakarta, Indonesia

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Ovarian cancer is one of the most lethal gynecologic malignancies worldwide, with 324,603 new cases reported in 2022 and causing more than 200,000 deaths annually^{1,2}. The disease is characterized by uncontrolled cellular proliferation, invasive growth and resistance to standard therapy, particularly platinum-based chemotherapy³. The majority of patients are diagnosed at an advanced stage with a markedly poor prognosis. Despite advances in surgery and combination chemotherapy, the five-year overall survival rate for advanced stage is low, only about 29.2% and almost 80% of women with advanced-stage disease who respond to first-line chemotherapy relapse^{3,4}.

Around 80% of benign ovarian tumors are found in younger women between 20-40 years old⁵. Malignant tumors are more frequently observed in women aged 50-60 years and are often associated with poor prognosis⁶. Clinical symptoms are often vague or absent, which leads to delayed diagnosis. This highlights the crucial role of histopathological evaluation in establishing diagnosis and management. That is why the World Health Organization (WHO) 2020 classification provides a standardized framework for categorizing ovarian neoplasms based on histopathological characteristics⁷.

Beyond its morphological characteristics, molecular mechanisms are key determinants of tumor behavior. Among these, the interleukin-6 (IL-6) and Signal Transducer and Activator of Transcription 3 (STAT3) signaling pathway plays a central role in ovarian carcinogenesis. IL-6 activates the JAK/STAT3 pathway through its receptor complex, leading to STAT3 phosphorylation, nuclear translocation and transcriptional gene regulation. Most of these genes are involved in proliferation, inhibition of apoptosis, angiogenesis and immune evasion. Constitutive activation of this pathway has been associated with tumor progression, chemoresistance and poor prognosis in ovarian cancer^{8,9}.

Although histopathological assessment remains the gold standard for the diagnosis of ovarian tumors, morphological evaluation alone cannot explain the molecular mechanisms underlying tumor progression and biological heterogeneity. On the other hand, bioinformatic studies have identified dysregulated genes and signaling pathways associated with tumor behavior but often lack direct pathological context¹⁰. Therefore, integrating histopathological characterization with molecular bioinformatic findings provides a more comprehensive understanding of ovarian tumor biology. This approach connects morphological features with the molecular

mechanisms underlying tumor progression and prognosis. However, despite increasing evidence supporting the role of the IL-6/STAT3 signaling pathway in ovarian cancer, studies integrating comprehensive histopathological characterization with bioinformatic analysis of this pathway remain limited.

Therefore, this study aims to evaluate the histopathological distribution of ovarian tumors based on the WHO 2020 classification⁷ and to integrate these findings with current molecular insights, particularly the role of the IL-6/STAT3 pathway, to provide a comprehensive understanding of ovarian tumor biology.

MATERIALS AND METHODS

Study design and ethical approval: A retrospective observational study was conducted at the Department of Pathology, Faculty of Medicine, Universitas Indonesia. Histopathological records of ovarian specimens collected between January 2016 and December 2025 were retrieved from the departmental database. Ethical approval was obtained from the Health Research Ethics Committee of Universitas Indonesia and Dr. Cipto Mangunkusumo National Hospital (Approval No. ND-62/UN2.F1.MG.35/PDP.00/2026).

Study population: A total of 2,309 ovarian biopsy specimens were included in the study. The inclusion criteria comprised all ovarian biopsy specimens submitted for histopathological examination during the study period. Normal ovarian tissues and cases with incomplete clinicopathological information were excluded from the analysis.

Histopathological evaluation: Histopathological diagnoses were reviewed and classified according to the 2020 World Health Organization (WHO) Classification of Female Genital Tumours⁷. Tumors were categorized based on their histopathological characteristics to determine the distribution of benign, borderline and malignant ovarian neoplasms.

Statistical analysis: Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics version 29.0. Descriptive statistics were expressed as frequencies and percentages. Associations between categorical variables, including patient age and malignancy status of ovarian epithelial tumors, were assessed using the chi-square (χ^2) test. For comparisons of gene expression levels between the study groups, an independent-samples t-test was used. A p-value <0.05 was considered statistically significant.

Bioinformatic data acquisition: Gene expression profiles and corresponding clinical data were obtained from The Cancer Genome Atlas (TCGA) using the TCGAbiolinks package in R. The datasets were downloaded as Summarized Experiment objects containing RNA sequencing data integrated with clinical metadata¹¹.

Data preprocessing: Raw count data were extracted and preprocessed using the dplyr, tidyr and tidyverse packages. Lowly expressed genes were filtered using the genefilter package to minimize background noise and improve the reliability of downstream analyses¹²⁻¹⁴.

Differential gene expression analysis: Differential gene expression analysis was performed using the DESeq2 package. Raw count data were normalized to account for differences in sequencing depth among samples. Gene-wise dispersion estimates were calculated and differential expression was evaluated using a negative binomial generalized linear model. Genes with an adjusted false discovery rate (FDR) <0.05 and an absolute log fold change ($|\log_2 FC| \geq 2$) were considered significantly differentially expressed¹⁵.

Survival analysis: Survival analysis was performed using the survival and survminer packages in R. Kaplan-Meier survival curves were generated to compare overall survival between patient groups and statistical significance was assessed using the log-rank test. Cox proportional hazards regression analysis was subsequently performed to estimate hazard ratios (HRs) and identify prognostic biomarkers associated with clinical outcomes. A p-value <0.05 was considered statistically significant for all analyses^{16,17}.

RESULTS

Histopathological patterns of ovarian neoplasms: A total of 2,309 ovarian mass cases from patients undergoing ovarian biopsy or hysterectomy were evaluated. Specimens included hysterectomy, salpingo-oophorectomy and unilateral or bilateral ovarian cystectomy samples. Among all cases, 1,630 (70.59%) were neoplastic, consisting of 1,220 primary tumors and 77 secondary metastatic tumors. Tumors were classified according to the 2020 WHO Classification as shown in

Supplementary Table 1. The majority of primary ovarian cancers consist of surface epithelial neoplasms, which contributed to 1143 cases or 74.08% of all ovarian cancers (Fig. 1). Non-epithelial ovarian cancers consisted of 410 cases, with most cases being germ cell tumors (290 cases), followed by sex cord stromal tumors (110 cases) and mesenchymal tumors in the ovary (10 cases).

The ovarian epithelial cancer subtypes and malignancy are seen in Fig. 2. Based on its malignancy, these tumors were classified as benign, borderline, low grade carcinoma and high grade carcinoma. Carcinomas (both low-grade and high grade) were the highest number of cases, consisting of 57.6% of all epithelial cancers, followed by benign tumors (cystadenomas) 29.0% and borderline tumors 13.3 %. Regardless of the malignancy, the mucinous subtype was the most common epithelial tumors and Brenner's tumors were the least, with only 2 cases in total (0.2%). Among all epithelial carcinomas, clear cell carcinoma were the highest number of cases (16.1%), followed by high grade serous carcinoma (14.4%), endometrioid carcinoma (12.9%), mucinous carcinoma (8.7%) and low grade serous carcinoma (2.0%). It should be noted that carcinomas previously diagnosed as seromucinous carcinoma (diagnosed before 2020) were reclassified as endometrioid carcinoma according to the 2020 World Health Organization classification.

In this study, the highest number of patients were below 40 years old, with a mean age of 42.7 (SD: 14.02584). The distribution of age groups is as illustrated in Table 1.

Figure 3a shows that benign epithelial ovarian tumors were predominantly diagnosed in patients aged <40 years. Likewise, borderline tumors were most frequently observed in the <40 years age group (Fig. 3b). Low-grade carcinoma occurred most commonly in patients aged 40-49 years (Fig. 3c), whereas high-grade carcinoma was most prevalent among those aged 50-59 years (Fig. 3d). Chi-square analysis demonstrated a significant association between patient age and tumor malignancy ($\chi^2(12) = 142.466$, $p < 0.001$).

Bioinformatic analysis of IL-6/STAT3 gene in ovarian carcinoma: Gene expression and clinical data were obtained from The Cancer Genome Atlas (TCGA) and were analyzed. Ovarian carcinoma cases were filtered and categorized into low grade groups, high grade groups and normal non cancer

Table 1: Age distribution for all cases

Age group	Frequency (n)	Percentage (%)
<40 years	896	38.8
40-49 years	653	28.3
50-59 years	500	21.7
60-69 years	206	8.9
>70 years	54	2.3

Primary ovarian tumors (epithelial vs non epithelial tumors)

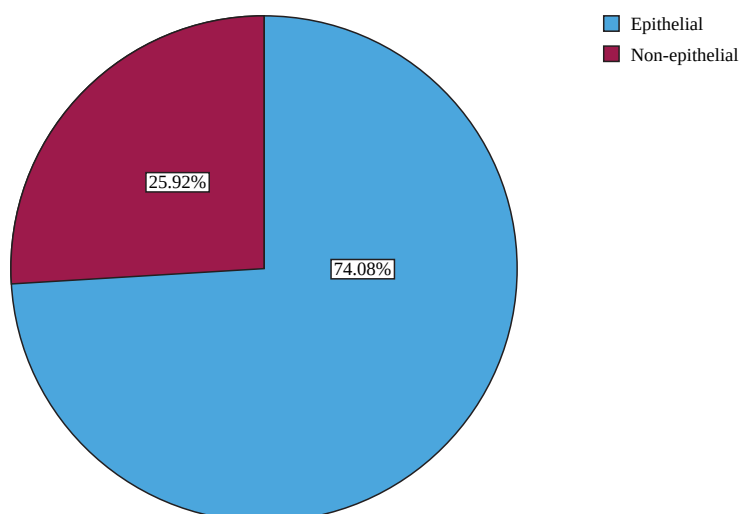


Fig. 1: Ovarian cancer (epithelial vs non-epithelial cancer)

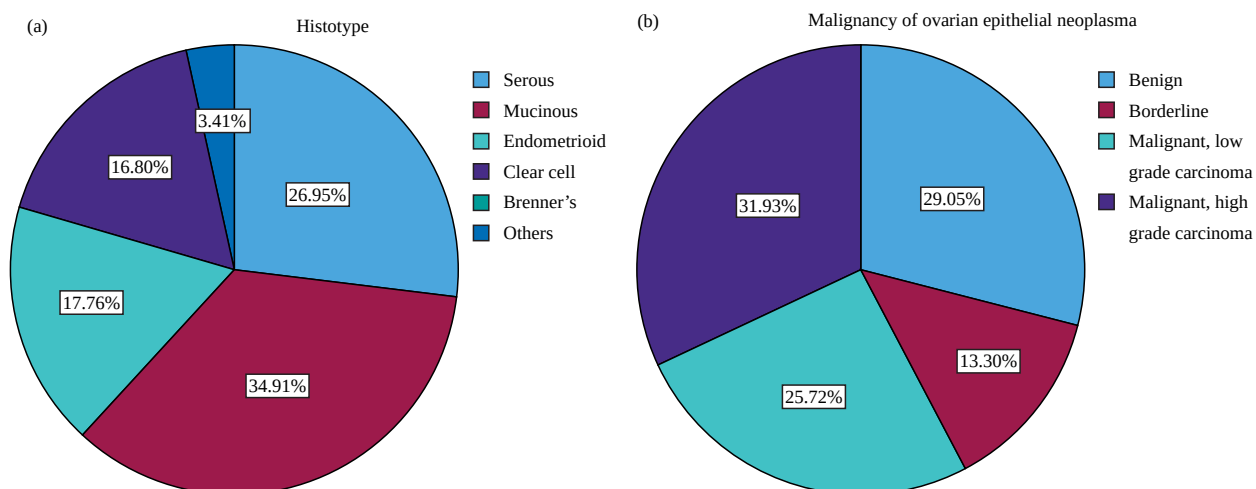


Fig. 2(a-b): Distribution of ovarian epithelial cancer based on (a) Subtypes and (b) Tumor malignancy

groups. Expression of two genes, STAT3 and IL-6, was analyzed within each group. We then compare the expression of these genes on the low grade groups vs non cancer groups and high grade vs. non-cancer groups. Figure 4 illustrates the results of differential expression analysis using a t-test for both STAT3 and IL-6 genes.

As shown in Fig. 4a, STAT3 gene expression was significantly higher in the low-grade cancer group than in the normal group ($p = 0.022$), indicating increased expression in the low-grade cancer group. In contrast, no significant difference in STAT3 expression was observed between the high-grade cancer and normal groups (Fig. 4b; $p = 0.34$), although the data distribution appeared more variable. For the IL-6 gene, neither the low-grade cancer and normal groups (Fig. 4c; $p = 0.079$) nor the high-grade cancer and

normal groups (Fig. 4d; $p = 0.86$) showed statistically significant results. Although a trend toward increased IL-6 expression was observed in the low-grade cancer group (Fig. 4c), it did not reach the threshold for statistical significance ($p < 0.05$). Overall, the t-test results indicate that only STAT3 expression showed a significant change in low-grade cancer, whereas IL-6 expression did not show significant differences.

Figure 5 demonstrates the extensive transcriptional alterations between each group. As shown in Fig. 5a, in the comparison between the low-grade cancer and normal groups, a substantial number of differentially expressed genes were identified, including 4,180 upregulated and 3,495 downregulated genes, whereas the majority of genes did not exhibit significant changes. In contrast, Fig. 5b shows

Distribution of age based on the malignancy of Epithelial ovarian tumors

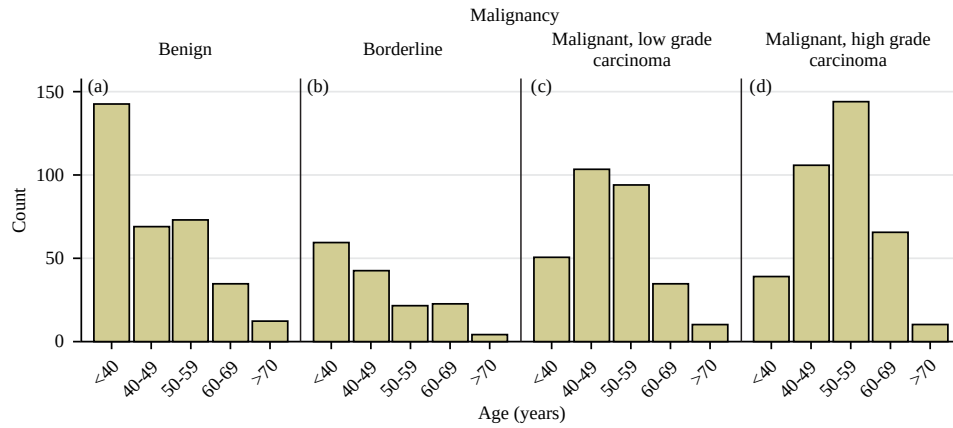


Fig. 3(a-d): Distribution of age based on the malignancy of epithelial ovarian tumors (a) Age distribution of patients with benign epithelial ovarian tumors, (b) Age distribution of patients with borderline epithelial ovarian tumors, (c) Age distribution of patients with low-grade malignant epithelial ovarian carcinoma and (d) Age distribution of patients with high-grade malignant epithelial ovarian carcinoma

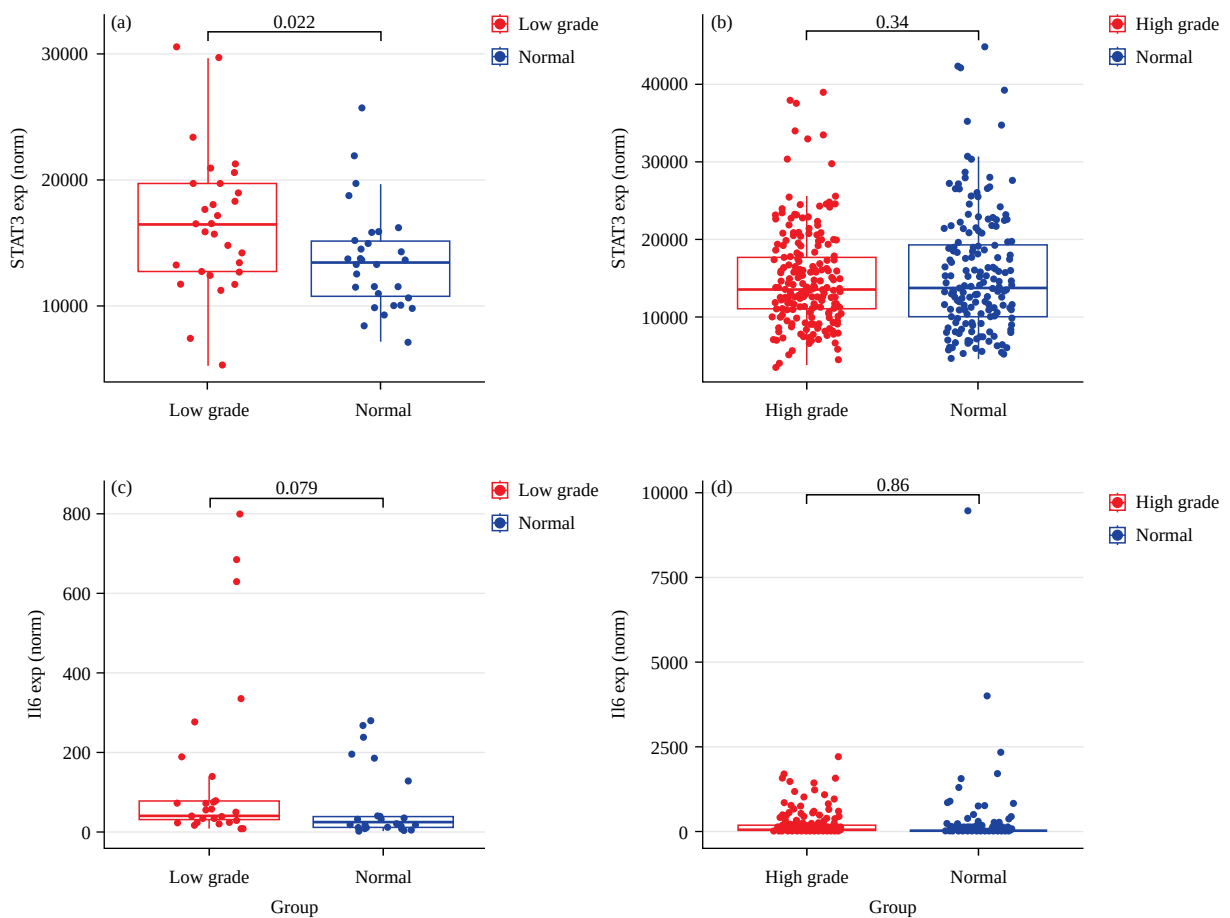


Fig. 4(a-d): Expression of IL-6 and STAT3 genes in low-grade and high-grade vs normal group, (a) Expression of STAT3 in low grade vs normal group, (b) Expression of STAT3 in high grade vs normal group, (c) Expression of IL-6 in low grade vs normal group and (d) Expression of IL-6 in high grade vs normal group
The data are visualized as boxplots with individual points, illustrating the distribution of gene expression within each group

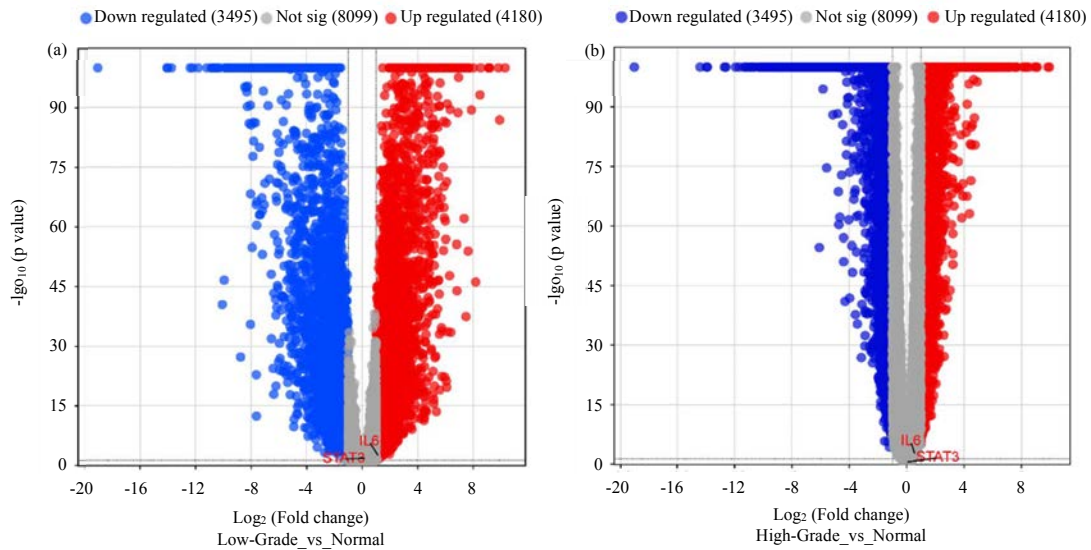


Fig. 5(a-b): A volcano plot illustrating the gene expression between the (a) Low Grade vs Normal group and (b) High Grade vs Normal group (right)
The X-axis represents the magnitude of gene expression changes, while the Y-axis indicates statistical significance. Red dots indicate significantly upregulated genes, blue dots indicate significantly downregulated genes and gray dots represent genes without significant expression

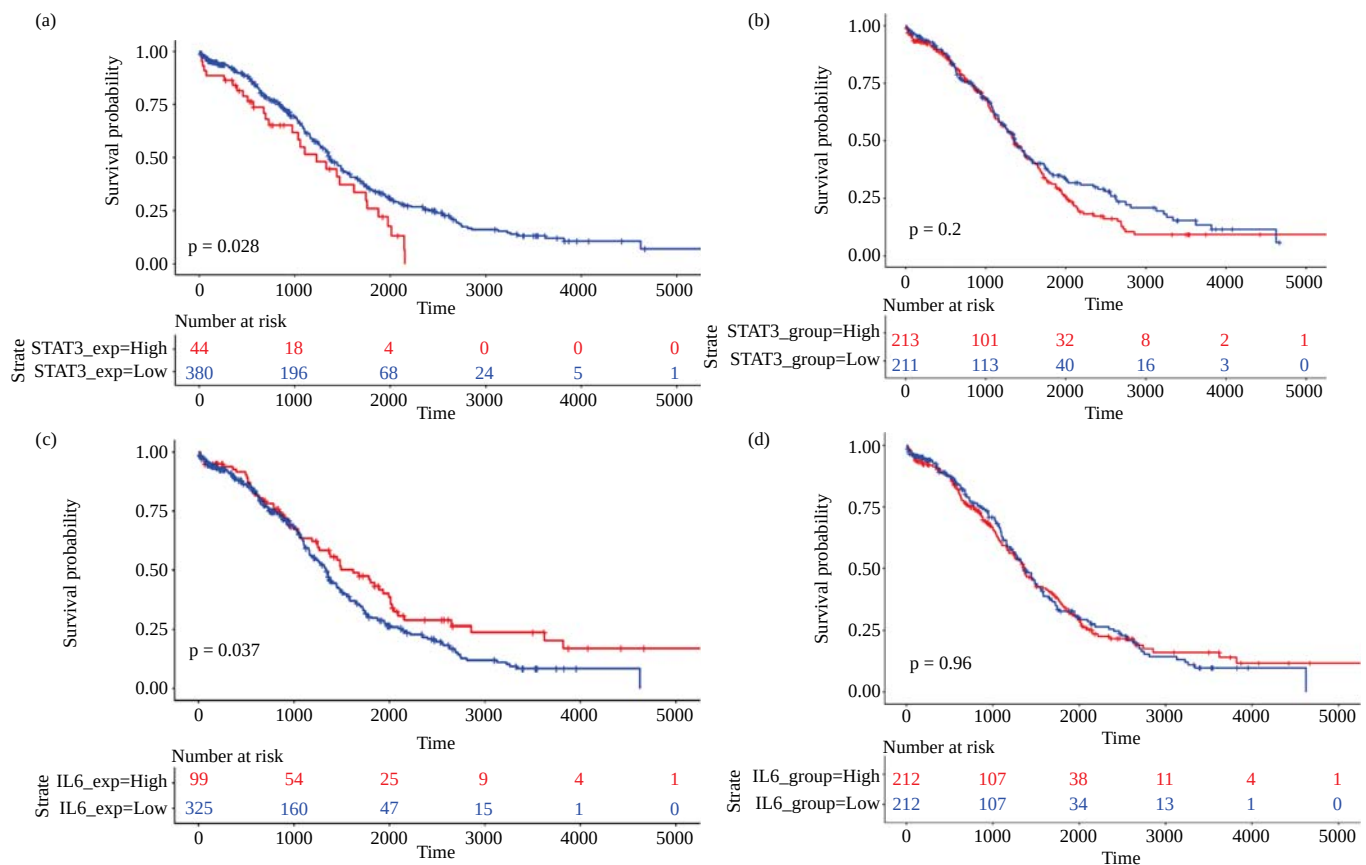


Fig. 6(a-d): Kaplan-Meier survival analysis, (a) STAT3 survival analysis with adjusted optimal cutpoint, (b) STAT3 survival analysis with median cutpoint, (c) IL-6 survival analysis with adjusted optimal cutpoint and (d) IL-6 survival analysis with median cutpoint

that the high-grade cancer and normal groups had a slightly lower number of differentially expressed genes, with 3,768 upregulated and 3,825 downregulated genes.

The Kaplan-Meier survival analysis is shown in Fig. 6. The expression levels of STAT3 and IL6 appear to influence patient survival probability when using the optimal cutpoint instead of using the median as the cutoff. As shown in Fig. 6a, the optimal cutpoint for STAT3 expression resulted in a statistically significant difference in survival between the high- and low-expression groups ($p = 0.028$), with higher expression showing a more rapid decline in the survival curve. In contrast, when the median was used as the cutoff (Fig. 6b), no significant difference in survival was observed ($p = 0.20$). A similar pattern was observed for IL-6. Using the adjusted optimal cutpoint (Fig. 6c), a significant difference in survival was detected between the high and low-expression groups ($p = 0.037$), whereas no significant difference was observed when the median cutoff was applied (Fig. 6d; $p = 0.96$). Overall, our findings indicate that the method used to define the cutpoint influences the results of survival analysis, with the optimal cutpoint demonstrating greater sensitivity in detecting survival differences.

DISCUSSION

Among all neoplastic cases, we found that epithelial ovarian tumors are the most common ovarian neoplasms. This is consistent with previous studies as epithelial ovarian tumors are the most common type of ovarian neoplasm^{3,18}. Similar to prior studies, non-epithelial tumors are less frequent (17.76%), with germ cell tumors being the most frequent subtype^{6,18}. Among all epithelial ovarian tumors, most cases were malignant carcinomas (both low grade carcinoma and high-grade carcinoma). However, there is also a substantial number of benign and borderline tumors. This shows that ovarian mass has a wide pathology spectrum from non-neoplastic lesions to benign, borderline and malignant neoplasms¹⁸.

The 2020 World Health Organization categorizes ovarian epithelial tumors into major histological subtypes including serous, mucinous, endometrioid, clear cell and Brenner tumors⁷. In this study, the mucinous subtype was the most common subtype of epithelial ovarian tumors regardless of their malignancy, followed by serous, clear cell and endometrioid subtypes. Mucinous ovarian cancer is usually rare; our finding is probably due to the high number of benign mucinous cystadenomas, as it is one of the most frequent types of ovarian cystadenomas¹⁹. In malignant neoplasm, clear

cell ovarian carcinoma and high-grade serous ovarian carcinoma were the most frequent epithelial ovarian cancers. High-grade serous ovarian carcinoma is a known prevalent subtype²⁰ and is widely recognized as an aggressive subtype^{3,18}. The relatively high proportion of clear cell carcinoma observed in this study may reflect regional or population-specific variations, as clear cell ovarian carcinoma has been reported to be more prevalent in Asian populations²¹. Brenner tumors were the least frequent, accounting for only 0.2% of epithelial tumors, which is consistent with their rarity in the literature¹⁸. It is also important to note that the reclassification of seromucinous carcinoma may have influenced the observed distribution, emphasizing the importance of standardized histopathological criteria to ensure diagnostic consistency and comparability across studies⁷.

There was a large case of endometriosis cysts in this study, suggesting that the population has a high risk of endometriosis, which is also strongly associated with clear cell ovarian carcinoma. Endometriosis is a known risk factor of certain ovarian malignancies, particularly endometrioid and clear cell carcinomas²². Several studies have demonstrated that chronic inflammation, oxidative stress and hormonal dysregulation in endometriosis may contribute to malignant transformation^{3,22}. However, this study has limited data on hormonal status, previous medical history or medication and related molecular profile so we cannot evaluate these pathogenic mechanisms further. Future studies incorporating medical history and hormonal status can better evaluate the link between endometriosis and ovarian carcinogenesis.

In this study, the overall mean age was 42.7 years old and the highest number of patients were below 40 years old. This suggests that ovarian masses are not exclusively found in older women but also affect younger and reproductive age groups. We found that there is a high number of benign and functional lesions, such as endometrial cysts and germ cell tumors, which are reported to be commonly found in younger individuals²³. However, we also observed a shift in malignancy with increasing age, where malignant tumors were more prevalent in older age groups, particularly high-grade carcinomas. This pattern shows that age is a critical determinant of tumor biology and should be incorporated into clinical risk stratification. Aging contributes to malignant transformation through cumulative genetic alterations, prolonged hormonal exposure and environmental²⁴.

The bioinformatic analysis provides important insights into the biological and clinical relevance of STAT3 and IL-6 expression in ovarian carcinoma. The significant upregulation

of STAT3 observed in the low-grade group suggests that STAT3 activation may be present in the early molecular events of ovarian carcinogenesis. Low-grade ovarian carcinoma is more commonly classified as type 1 carcinoma, which follows the stepwise ladder progression and its initial lesion originates from borderline tumors^{25,26}. Previous evidence demonstrated that the IL-6/JAK/STAT3 signaling axis plays a central role in tumor initiation and progression by promoting proliferation and tumor survival^{27,28}. On the other hand, the absence of significant STAT3 overexpression in high-grade tumors, despite increased variability, may be related to the molecular heterogeneity of high-grade ovarian cancer²⁹.

In contrast, IL-6 expression did not show statistically significant differences. IL-6 is widely recognized as a key cytokine within the tumor microenvironment, acting predominantly through paracrine signaling rather than solely on tumor cell intrinsic expression³⁰. Elevated IL-6 levels have been associated with tumor progression, metastasis and immune modulation, as well as poor clinical outcomes^{8,29}. This suggests that IL6 activity may be regulated beyond transcriptional levels.

Recent evidence demonstrates that IL-6/JAK2/STAT3 signaling promotes malignant phenotypes such as proliferation and invasion in ovarian cancer⁸. Additionally, targeting STAT3 signaling has been shown to suppress tumor growth and metastasis²⁷. So even though IL-6 and STAT3 are not among the most significantly altered genes, they may still act as regulators within a broader oncogenic network. The IL-6/STAT3 pathway is known to interact with several oncogenic cascades, including PI3K/AKT and MAPK pathways, contributing to tumor proliferation and survival^{8,30,31}. Recent findings also show that STAT3 signaling plays a role in tumor progression and resistance mechanisms in multiple cancers, including ovarian cancer³².

The Kaplan-Meier survival analysis highlights the prognostic relevance of both STAT3 and IL-6, with elevated expression levels associated with a more rapid decline in overall survival. Elevated IL-6 levels have been associated with poorer prognosis due to recurrence and therapy resistance^{33,34}. Other than that, IL-6 also mediates chronic inflammation, which promotes an immunosuppressive microenvironment and facilitates tumor progression³⁰. Furthermore, crosstalk between IL-6/STAT3 and other signaling pathways, such as EGFR, has been shown to enhance tumor cell migration and invasion^{28,34}. Similarly, STAT3 activation has been associated with tumor aggressiveness due to its role in promoting anti-apoptotic signaling, epithelial-mesenchymal transition and cancer stemness^{27,28}. Recent evidence also demonstrates that STAT3 activation by IL-6 contributes to chemoresistance in many cancers, including ovarian cancer, which may also contribute to poor prognosis^{33,34}.

CONCLUSION

Ovarian masses demonstrate diverse pathological features, ranging from non-neoplastic lesions to benign, borderline and malignant tumors. Malignant transformation is more commonly observed in the older population, suggesting an association between age and tumor aggressiveness.

Histopathological patterns of ovarian tumors exhibit heterogeneous subtypes with varying malignant potential. Molecular analysis also suggests that dysregulation of the IL-6/STAT3 signaling pathway may contribute to tumor progression, proliferation and survival, indicating its possible role in ovarian carcinogenesis and therapeutic targeting.

Overall, these results highlight the importance of comprehensive histopathological and molecular evaluation in managing ovarian neoplasms. Further studies integrating molecular profiling and clinical outcomes may enhance early detection and improve patient prognosis.

SIGNIFICANCE STATEMENT

This study highlights the histopathological diversity of ovarian neoplasms and demonstrates the potential relevance of the IL-6/STAT3 signaling pathway in ovarian tumor progression and prognosis. Integrating histopathological findings with bioinformatic analysis may improve understanding of ovarian tumor biology and support the identification of potential molecular targets for future diagnostic and therapeutic strategies.

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SUPPLEMENTARY DATA

Supplementary Table 1: Ovarian tumor distribution according to the 2020 WHO⁷ classification

Type	Subtype		No. of case (n)	Percentage (%)
Epithelial tumors	Serous	Serous cystadenoma	86	3.72
		Serous borderline tumor	34	1.47
		Low-grade serous carcinoma	23	1.00
		High-grade serous carcinoma	165	7.15
	Mucinous	Mucinous cystadenoma	189	8.19
		Mucinous borderline tumor	111	4.81
		Mucinous carcinoma	99	4.29
	Endometrioid	Endometrioid cystadenoma	11	0.48
		Endometrioid borderline tumor	4	0.17
		Endometrioid carcinoma	148	6.41
	Clear cell	Clear cell cystadenoma	1	0.04
		Clear cell borderline tumor	0	0.00
		Clear cell carcinoma	191	8.27
	Seromucinous	Seromucinous cystadenoma	40	1.73
	Brenner	Brenner tumors	1	0.04
		Brenner tumors, borderline	1	0.04
		Brenner tumors malignant	0	0.00
	Other	Cystadenoma, adenofibroma (unspecified)	4	0.17
		Borderline epithelial tumors (unspecified)	2	0.09
		Carcinoma (unspecified, low grade)	24	1.04
		High grade Carcinoma (Mixed epithelial mesenchymal, unspecified high grade carcinoma, undifferentiated)	9	0.39
Non epithelial tumors	Germ cell tumor	Teratoma	227	9.83
		Immature teratoma	14	0.61
		Dysgerminoma	27	1.17
		Yolk sac tumor	20	0.87
		Embryonal carcinoma	2	0.09
	Sex cord stromal tumor	Fibroma	38	1.65
		Steroid cell tumors	6	0.26
		Fibrosarcoma	1	0.04
		Adult granulosa cell tumor	53	2.30
		Juvenile granulosa cell tumor	6	0.26
		Sclerosing stromal tumor	3	0.13
		Sertoli-Leydig cell tumor	3	0.13
	Mesenchymal tumors in the ovary	Leiomyoma	5	0.22
		Ovarian myxoma	1	0.04
		Leiomyosarcoma	2	0.09
		Endometrioid stromal sarcoma	2	0.09
Secondary tumor	Metastasis		77	3.33%
Others	Non-neoplastic lesion	Endometriosis cysts	513	22.22%
		Tumor-like lesions in ovary and tubal	108	4.68%
		Inflammation lesion	39	1.69%
		Ectopic Pregnancy	9	0.39%
		Unable to diagnose/specimen incomplete	10	0.43%