Expression levels of STAT3, and protein levels of IL-6 and sPD-L1 in different pathological characteristics of endometrial adenocarcinomas

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Received August 5, 2024; Accepted December 13, 2024

DOI: 10.3892/ol.2025.14901

Abstract. Endometrial cancer is a common type of cancer in women, with endometrial adenocarcinoma (EA) being the most common type. Monitoring the expression levels of signal transducer and activator of transcription 3 (STAT3), the protein levels of interleukin 6 (IL-6) and soluble programmed death ligand 1 (sPD-L1), and their differences in patients with various pathological characteristics is beneficial for accurately evaluating the disease stage and differentiation degree of patients in clinical practice. The aim of the present study was to assess the expression levels of STAT3, and the protein levels of IL-6 and sPD-L1 in EA. In the present retrospective study, data were retrieved from the medical records of 137 patients with EA who received surgical treatment at The First Affiliated Hospital of Hebei North University from January 2017 to December 2022. Of the 137 cases, 90 met the inclusion criteria. The patients with EA were matched with a cohort of 30 patients with atypical endometrial hyperplasia in a ratio of 3:1. Among the 90 patients with EA, 30 patients with well-differentiated EA were matched with 30 patients with moderately differentiated EA and 30 patients with poorly differentiated EA in a 1:1:1 ratio. Expression level of STAT3, and protein levels of IL-6 and sPD-L1 were recorded preoperatively and compared between patients with different pathological characteristics [such as differentiation degree, disease stage, depth of myometrial invasion and lymph node metastasis (LNM)] and prognosis. Levels of IL-6, STAT3 and sPD-L1 in the observation group were significantly higher compared with the control group (P<0.001). Additionally, there were significant differences in IL-6, STAT3 and sPD-L1 levels between patients with different differentiation degrees, disease stages, myometrial invasion and LNM (P<0.001). The increase in IL-6, STAT3 and sPD-L1 levels were significantly associated with the decrease in the differentiation degree and the increase in the disease stage, depth of myometrial invasion and LNM (P<0.001). IL-6, STAT3 and sPD-L1 levels in patients with a poor prognosis were significantly higher compared with patients with good prognoses (P<0.001). Overall, the expression levels of STAT3, and the protein levels of IL-6 and sPD-L1 were increased in patients with EA compared with in those without EA, and their increase is associated with the pathological characteristics of the disease. The levels of these indices may be detected in clinical practices to evaluate the disease and predict the prognosis.

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Key words: endometrial adenocarcinoma, interleukin 6, signal transducer and activator of transcription 3, programmed death ligand 1

Introduction

Endometrial cancer is the 6th most common cancer in women worldwide; the age-standardized global incidence and age-standardized global mortality rates for 2022 were 8.4 and 1.7 per 100,000 population, respectively (1). There are several types of endometrial cancer, with endometrial adenocarcinoma (EA) being the most common type, accounting for 70-80% of all endometrial cancer cases (2). At present, the pathogenesis of EA remains unclear, and it is generally considered that the onset and the progression of the disease are the result of a synergistic effect of several factors, such as activation of oncogenes and inactivation of tumor suppressor genes (3). Previous studies have demonstrated that the inflammatory response is associated with EA, and promotes the development and progression of malignant tumors (4,5).

As an inflammatory factor, IL-6 serves an important role in the pathogenesis, progression, invasion and metastasis of EA (6). Therefore, evaluating the expression characteristics of IL-6 in patients with EA is notable in the assessment of the disease condition (7). IL-6 is also an important classical activator of STAT3. Under normal physiological conditions, the duration of STAT3 activation is relatively short. However, it can still affect the normal physiological functions of cells, including inducing target gene transcription and transmitting extracellular signals (8). However, when STAT3 expression is abnormal, it can modulate the inflammatory signaling pathway

Table I. Baseline characteristics of the patients in the present study.

Characteristic	Observation group (n=90)	Control group (n=30)	t/χ^2	P-value
Age, years	52.47±9.55	53.22±8.28	0.384	0.701
Menopausal status			0.013	0.909
Yes	56 (62.22)	19 (63.33)		
No	34 (37.78)	11 (36.67)		
BMI, kg/m^2	22.09±3.14	21.78±3.32	0.462	0.645
Disease stage			-	-
I/II	71 (78.89)	-		
III/IV	19 (21.11)	-		
Depth of myometrial invasion			-	-
≥50% of the myometrium	54 (60.00)	-		
<50% of the myometrium	36 (40.00)	-		
Lymph node metastasis			-	-
Yes	33 (36.67)	-		
No	57 (63.33)	-		
Poor prognosis			-	-
Mortality	11 (12.22)	-		
Relapsed	18 (20.00)	-		

Data are presented as mean ± standard deviation or n (%). IL-6, interleukin 6; STAT3, signal transducer and activator of transcription 3; sPD-L1, soluble programmed death ligand 1.

Table II. Comparison of interleukin 6, signal transducer and activator of transcription 3 and programmed death ligand 1 levels between the observation and the control groups.

Index	Observation group (n=90)	Control group (n=30)	Z/t	P-value
IL-6, pg/ml	79.00 (56.25, 95.00)	31.00 (28.00, 38.25)	-7.911	<0.001
STAT3	0.99 (0.81, 1.21)	0.32 (0.27, 0.41)	-8.183	<0.001
sPD-L1, pg/ml	224.36±60.30	55.07±14.41	15.192	<0.001

IL-6, interleukin 6; STAT3, signal transducer and activator of transcription 3; sPD-L1, soluble programmed death ligand 1. Normally distributed continuous data are presented as the mean ± standard deviation and the non-normally distributed continuous data are presented as the median (interquartile range).

as an inflammatory response regulator, serving a role in cell proliferation, differentiation, invasion and apoptosis (9,10). Therefore, evaluating the STAT3 expression levels in patients with EA may assess the condition of the patient as well as the lesion invasion status, guiding the clinical implementation of targeted treatments.

Soluble programmed death ligand 1 (sPD-L1), an important member of the immunoglobulin superfamily, can attenuate the host immune response to tumor cells (11). Its expression level is markedly increased in malignant tumors compared with in non-malignant tumors and is associated with the prognosis of tumors (11). Clinically, monitoring sPD-L1 is considered a tool to assess disease stage, lymph node metastasis (LNM) and depth of myometrial invasion in patients with EA (12). It can serve as an important basis for implementing precise treatments in clinical practice and is important for ensuring disease prognosis.

Recent research suggests that monitoring the expression levels of STAT3, the protein levels of IL-6, and sPD-L1, and their differences in patients with various pathological characteristics is beneficial for accurately evaluating the disease stage, differentiation degree and other diseases of the patient in clinical practice (6-12). Furthermore, it may allow clinicians to choose comprehensive treatment measures such as surgery, radiotherapy or chemotherapy based on the specific condition of the patient to avoid improper or excessive treatment. The present study aimed to assess the expression characteristics and detection values of IL-6, STAT3 and sPD-L1 in patients with EA.

Patients and methods

Study cohort. The present retrospective study selected data from the medical records of 137 patients with EA who received

surgical treatment in The First Affiliated Hospital of Hebei North University (Zhangjiakou, China) from January 2017 to December 2022. Of the cases selected, 90 met the eligibility criteria and were included in the analysis. The female patients were aged 35-69 years (mean, 53.03±8.58 years). The 90 patients with EA (observation group) were retrospectively matched with a cohort of 30 patients with atypical endometrial hyperplasia (AEH; control group) in a ratio of 3:1. Among the 90 patients with EA, 30 patients with well-differentiated EA were matched with 30 patients with moderately-differentiated EA and 30 patients with poorly-differentiated EA in a 1:1:1 ratio. The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Hebei North University (approval no. 2023925).

The inclusion criteria were as follows: i) EA diagnostic criteria met (observation group only) (13); ii) diagnostic criteria for AEH met (control group only) (14); iii) confirmed EA through pathological examination; and iv) the clinical data was complete. The exclusion criteria were as follows: i) Diagnosis with other types of endometrial cancer; ii) diagnosis with other benign and malignant tumors; iii) diagnosis with other infectious diseases; iv) diagnosis with autoimmune diseases; v) diagnosis with vital organ dysfunction, such as kidney, liver, heart or lung dysfunction; vi) history of using any type of drugs for EC, such as sex hormones; and vii) diagnosis with immune system deficiencies. All patients underwent an assessment of their IL-6, STAT3 and sPD-L1 levels after fasting on the morning of the second day after admission.

Enzyme-linked immunosorbent assay (ELISA). A total of 4 ml venous blood was collected from each patient. The samples were subsequently placed at room temperature for two hours and centrifuged at 1,000 x g for 20 min at 4˚C to obtain the supernatant. Levels of IL-6 and sPD-L1 were then detected in the supernatant using ELISA. The IL-6 ELISA kit (cat. no. JN18468) and the sPD-L1 ELISA kit (cat. no. JN6121) were purchased from Shanghai Jining Biotechnology Co., Ltd.

Reverse transcription (RT)-quantitative (q)PCR. STAT3 expression levels were detected using RT-qPCR. From each patient, 4 ml peripheral blood was collected, transferred to heparin-containing test tubes and mixed with an equal amount of Hanks' balanced salt solution. The blood samples were added to a centrifuge tube containing 2 ml Ficoll (Thermo Fisher Scientific, Inc.) with a dilution ratio of 2:1 and centrifuged at 1,000 x g for 20 min at 4˚C. After centrifugation, the second cell layer from the top [the peripheral blood mononuclear cell (PBMC) layer] was aspirated using a pipette to extract PBMCs. Total RNA was extracted using RNA extraction reagent (cat. no. R0018S; Beyotime Institute of Biotechnology) and was reverse transcribed into cDNA using the BeyRT™ II cDNA First Chain Synthesis kit (RNase H; Beyotime Institute of Biotechnology), according to the manufacturer's protocol. cDNA was amplified using 2xQ3 SYBR qPCR Master Mix (Beyotime Institute of Biotechnology) and the following primers: STAT3 forward, 5'-CTGGCCGACAATACTTTCCG-3' and reverse, 5'-AAAGCAGCAAAGAAG-GAGGC-3'; GAPDH forward, 5'-AGCCACATCGCTCAGACAC-3' and reverse, 5'-GCCCAA TACGACCAAATCC-3'. qPCR thermocycling conditions were as follows: Pre-denaturation at 95˚C for 10 min, followed by

Table III. Comparison of interleukin 6, signal transducer and activator of transcription 3 and programmed death ligand 1 levels among individuals with different pathological characteristics in the observation group.

		Differentiation degree				Tumor stage			Depth of myometrial invasion				Lymph node metastasis			
Index	Good (n=30)	Moderate (n=30)	Poor (n=30)	F/H	P-value	I/II (n=51)	III/IV (n=39)	Z	P-value	<50% of myometrium (n=36)	≥50% of myometrium (n=54)	Z/t	P-value	No (n=57)	Yes (n=33)	Z	P-value
IL-6, pg/ml	50.57±8.56	83.00±14.81[a]	97.40±15.63[a,b]	127.423[c]	<0.001	58.00 (47.00, 75.00)	96.00 (85.00, 106.00)	-7.086[e]	<0.001	51.50 (45.00, 61.00)	92.50 (79.00, 102.75)	-7.225[e]	<0.001	48.00 (36.00, 69.00)	95.00 (84.50, 110.00)	-7.148[e]	<0.001
STAT3	0.74 (0.63, 0.82)	0.95 (0.89, 1.08)[a]	1.43 (1.12, 1.55)[a,b]	65.752[d]	<0.001	0.824 (0.71, 0.95)	1.28 (1.06, 1.52)	-6.967[e]	<0.001	0.77 (0.66, 0.87)	1.14 (0.98, 1.46)	-6.912[e]	<0.001	0.71 (0.39, 0.93)	1.35 (1.11, 1.54)	-8.006[e]	<0.001
sPD-L1, pg/ml	154.63±24.48	230.80±18.29[a]	287.63±31.82[a,b]	205.961[c]	<0.001	185 (154, 231)	276 (251, 296)	-6.939[e]	<0.001	167.31±36.44	262.39±39.30	-11.571[e]	<0.001	154 (68, 209)	276 (261, 296)	-8.215[e]	<0.001

[a]Compared with good degree of differentiation; [b]Compared with moderate degree of differentiation; [c]Welch's ANOVA test; [d]Kruskal-Wallis test. [e]Mann-Whitney U test. IL-6, interleukin 6; STAT3, signal transducer and activator of transcription 3; sPD-L1, soluble programmed death ligand 1. Normally distributed continuous data are presented as the mean ± standard deviation and the non-normally distributed continuous data are presented as the median (interquartile range).

Table IV. Comparison of interleukin 6, signal transducer and activator of transcription 3 and programmed death ligand 1 levels in patients with different prognoses.

Index	Poor prognosis (n=29)	Good prognosis (n=61)	Z	P-value
IL-6, pg/ml	95.00 (84.50, 113.00)	66.00 (48.50, 87.50)	-5.471	<0.001
STAT3, ng/ml	1.42 (1.12, 1.56)	0.86 (0.74, 1.01)	-6.814	<0.001
sPD-L1, pg/ml	291 (267, 303)	198(158, 231)	-7.133	<0.001

IL-6, interleukin 6; STAT3, signal transducer and activator of transcription 3; sPD-L1, programmed death ligand 1. Data are presented as the median (interquartile range). Mortality and relapse were considered a poor prognosis, whereas survival without disease relapse was considered a good prognosis.

40 cycles of denaturation at 95˚C for 10 sec and annealing at 60˚C for 60 sec, and a final extension step at 95˚C for 15 sec. The relative expression level of STAT3 was assessed using the $2^{-\Delta\Delta Cq}$ method (15). GAPDH was used as a reference gene control.

Observation indicators. The observation indicators were as follows: i) Different pathological features, including differentiation degree, disease staging, depth of myometrial invasion and LNM; ii) serum levels of IL-6, STAT3 and sPD-L1; and iii) prognosis recorded 3 years after treatment. Mortality and relapse were considered a poor prognosis and survival without disease relapse was considered a good prognosis.

Statistical analysis. SPSS 26.0 (IBM Corp.) was used for analysis. Normally distributed continuous data were presented as the mean ± standard deviation and non-normally distributed continuous data were presented as the median and interquartile range. For comparisons between two groups of normally-distributed data, the unpaired Student's t-test was used; for comparisons between two group of non-normally distributed data, the Mann-Whitney U test was used. For comparisons between different differentiation degrees, Welch's ANOVA test and the Games-Howell post hoc test was used for normally distributed data with unequal variances; and the Kruskal-Wallis test and Dunn's post hoc test was used for non-normally distributed data with unequal variances. Categorical data are presented as n (%), and the χ^2 test was used for comparison between groups. P<0.05 was considered to indicate a statistically significant difference.

Results

There were no statistically significant differences in baseline characteristics between the observation and control groups (P>0.05). The mean age of the patients was 53.22±8.28 years in the control group and 52.47±9.55 years in the observation group. Furthermore, the menopausal status was positive in 19 cases and negative in 11 cases in the control group, whereas it was positive in 56 cases and negative in 34 cases in the observation group. Moreover, in the observation group, 71 patients with EA were characterized as being at disease stage I or II, and 19 patients with EA were at stage III or IV. The depth of myometrial invasion was ≥50% of the myometrium in 54 patients with EA and <50% of the myometrium in 36 cases. There were 33 patients with EA and LNM, whilst 57 patients with EA did not have LNM. There were 29 patients with a poor prognosis in the observation group with 11 cases of mortality and 18 cases of relapse (Table I).

The levels of IL-6, STAT3 and sPD-L1 in the observation group were significantly higher compared with those in the control group (P<0.001; Table II). Furthermore, there were significant differences in the IL-6, STAT3 and sPD-L1 levels in patients with different differentiation degrees, disease stages, myometrial invasion and LNM (P<0.001). Changes in the levels of IL-6, STAT3 and PD-1 were negatively associated with the changes in the differentiation degree, and positively associated with the changes in the disease stage, depth of myometrial invasion and LNM (P<0.001; Table III).

During the follow-up period of the observation group, there were 29 cases of poor prognoses (11 mortalities and 18 relapses) and 61 cases of good prognoses. Levels of IL-6, STAT3 and sPD-L1 in patients with a poor prognosis were significantly higher compared with those in patients with a good prognosis (P<0.001; Table IV).

Discussion

The present study demonstrated that IL-6, STAT3 and sPD-L1 have different expression levels in patients with EA compared with patients with AEH, suggesting that they may be involved in the pathogenesis of EA.

IL-6 is involved in regulating the body's immune response and hematopoiesis and serves an important role in the differentiation and proliferation of many cell types (16). Lu *et al* (17) reported a close association between the levels of inflammatory factors including IL-6 and EA, and reported that IL-6 is associated with many biological processes, such as tumor onset, progression, invasion and metastasis. STAT3 is a signal transduction molecule distributed in the cytoplasm, which can bind to DNA after activation and couple with the tyrosine phosphorylation signaling pathway to regulate cell apoptosis, proliferation, differentiation and immune regulation (18). Dong *et al* (19) reported that the levels of STAT3 in patients with EA were abnormally elevated, which is consistent with the results of the present study. STAT3 is a highly homologous signal transduction molecule that can mediate the signaling of several cytokines and growth factors, promote target gene transcription and regulate cellular functions. STAT3 expression can be activated by cytokine receptors, resulting in abnormally high expression in the inflammatory

microenvironment of patients with EA (20), and its levels are closely associated with tumor cell apoptosis, pathogenesis and progression (6,21,22).

Studies have reported that the expression of PD-1 can serve as a good prognostic marker in several cancers (23,24). sPD-L1 expression can inhibit T lymphocyte activity, which, in turn, leads to the formation of a tumor microenvironment (25). Furthermore, sPD-L1 expression affects several pathways of tumor cells, such as adhesion, apoptosis, growth, proliferation, immune regulation and inflammatory response (26). The findings of Post *et al* (27) are consistent with the observations in the present study and also demonstrate that sPD-L1 is an important immune checkpoint. It is mainly expressed on activated natural killer cells, B and T lymphocytes and has immunosuppressive effects. EA cells with high expression of sPD-L1 binding to PD-1 on the surface of T cells can produce negative immune regulatory effects, leading to loss of T cell function and tumor immune escape (26,27).

The present study also compared and analyzed the expression of IL-6, STAT3 and sPD-L1 in patients with EA with different pathological characteristics. The results demonstrated significant differences in IL-6, STAT3 and sPD-L1 levels among patients with varying degrees of differentiation, disease stages, myometrial invasion and LNM. The results demonstrated that the levels of IL-6, STAT3 and sPD-L1 in patients with a poor prognosis were significantly higher than in patients with a good prognosis. This indicates that IL-6, STAT3 and sPD-L1 may have applications in evaluating the pathological features and predicting the prognosis of EA. IL-6 participates in the differentiation and proliferation of EA cells through the ERK-NF-κB pathway and mediates regulation of tumor metabolism via pyruvate kinase M2 type, which is associated with tumor pathological characteristics (28). STAT3 participates in the early development process of cells and has oncogene functions. After activation, it can promote the migration, proliferation and invasion of EA tumor cells, inhibit tumor cell apoptosis and accelerate tumor cell immune escape (29). In EA, activated STAT3 is associated with increased expression of the antiapoptotic genes Bcl-xL, survivin and Mcl-1 in endometrial tissues (21). sPD-L1 is a negative T cell stimulatory ligand that serves an important role in the proliferation and activation of T cells such as CD4 and CD8 and is highly expressed in tumor cells. As the pathological staging increases and the differentiation degree decreases (the condition of the patient worsens), the expression of sPD-L1 decreases (30). Therefore, IL-6, STAT3 and sPD-L1 are associated with one another and can be used for prognostic evaluation (31). Future studies should further investigate the potential value of IL-6, STAT3 and sPD-L1 in clinical applications and evaluate their diagnostic efficiency compared with pathological diagnoses.

The present study had a number of limitations. For example, it was a retrospective, single-center study with a relatively small sample size. In addition, the follow-up period was only 3-years. Finally, the present study was not performed in conjunction with online databases. Further prospective, large, multi-center studies with longer follow-up periods in conjunction with online databases are needed to validate the results of the present study.

In conclusion, IL-6, STAT3 and sPD-L1 were expressed at increased levels in patients with EA compared with patients with AEH, and their increase was associated with the disease stage, LNM and degree of myometrial infiltration. The levels of IL-6, STAT3 and sPD-L1 may be detected in the clinic for disease assessment and prognosis prediction.

Acknowledgements

Not applicable.

Funding

The present study received funding from the Hebei Province Medical Research Project Plan (grant no. 20231404) and the Zhangjiakou City Science and Technology Plan Self-funded Project (grant no. 1921027D).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CM conceived and designed the study. YH, JW, JZ, XH, SW, LC and LS collected the data and performed the analysis. CM was involved in the writing of the manuscript. CM and LS confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Medical Ethics Committee of First Affiliated Hospital of Hebei North University (Zhangjiakou, China; approval no. 2023925). The ethics committee waived the informed consent due to the observational and retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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