Clinical Significance of the Immune Prognostic Index in Patients with Endometrial Carcinoma

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ABSTRACT

The immune prognostic index (IPI) is a new score that combines pretreatment serum lactate dehydrogenase (LDH) levels with a derived neutrophils/(leukocytes minus neutrophils) ratio (dNLR). Our objective was to determine the prognostic value of the IPI in endometrial cancer. This study included 94 patients diagnosed with endometrial cancer after surgical resection between 2000 and 2016. Clinicopathological data including preoperative laboratory results were analyzed retrospectively. The patients were divided into two groups according to the IPI score (good IPI, factor 0; poor IPI, factor 1-2). Of the 94 patients, 70 (74.5%) patients had stage I-II-IIIA-IIIB, and 24 (25.5%) patients had stage IIIC cancer; 68 (72.3%) had endometrioid histologic type. The good IPI group included 38 (40.4%) and the poor IPI group included 56 (59.6%) patients. The median DFS was 105.50 (95% CI: 79.89-131.11) months in the good IPI group and 82.61 (95% CI: 67.16-98.06) months in the poor IPI group (p= 0.791). The median OS was 120.05 (95% CI: 97.28-142.81) months in the good IPI group and 92.53 (95% CI: 79.10-105.96) months in the poor IPI group (p= 0.671). In the poor IPI group, the rate of stage IIIC patients was higher than those in the good IPI group (33.9% and 13.2%, respectively; p= 0.030). In multivariate analysis, a poor IPI score was independently associated with lymph node metastasis (OR: 3.59, 95%CI: 1.06-12.14, p= 0.040). In the endometrial cancer population, a poor IPI score may play a remarkable role in guiding optimal treatment strategies.

Keywords: Endometrial cancer, Immune prognostic index, Lymphatic metastasis, Prognostic value

INTRODUCTION

Endometrial cancer is the most common gynecological cancer in developed countries and the second most common one in developing countries. Worldwide, there are an estimated 417.367 new cases and 97.370 deaths attributed to endometrial cancer in 2020.[1]

Total hysterectomy with bilateral salpingo-oophorectomy is standard treatment for endometrial carcinoma. Endometrial carcinoma is staged surgically according to the International Federation of Gynecology and Obstetrics (FIGO) classification system.[2] In general, the 5-year survival rate is approximately 80-90%, 70-80%, and 20-60% for patients with FIGO stage I, stage II, and stage III-IV, respectively.[3,4] The other prognostic factors that affect survival outcomes in patients with endometrial cancer are age, grade, histologic type, positive peritoneal cytology, and lymphovascular space invasion.[5-8] Most of these prognostic markers are derived from pathology reports after surgery. Any data of reliable prognostic significance can be valuable when planning treatment in the perioperative period.[9]

Inflammation plays a critical role in the development and progression of cancer.[10] Biomarkers of systemic inflammation can be detected in peripheral blood. Therefore, increased plasma markers due to inflammatory response in cancer patients may predict disease recurrence and survival.11 Numerous studies have been conducted on immune-related markers in peripheral blood in endometrial cancer.[9,12] The immune prognostic index (IPI) score is a new score combining pretreatment serum lactate dehydrogenase (LDH) levels with a derived score consisting of white blood cell and neutrophil counts (absolute neutrophil count divided by absolute white blood cell count minus absolute neutrophil count [dNLR]).[13] So far, the prognostic value of the pre-treatment IPI score in various cancers has been investigated.[13-17] In this study, we aimed to investigate the prognostic significance of the IPI score in endometrial cancer.

PATIENTS AND METHODS

Study Population

Patients diagnosed with endometrial cancer were included in the study between January 2000 and October 2016. Patients who were referred to the medical oncology department to be evaluated for chemotherapy by the Gynecologic Oncology Board of our institution after the surgery were included. The exclusion criteria of the study were as follows: (1) Patients with metastases at the time of diagnosis; (2) Patients who did not have surgery in our center; (3) Patients who did not have a regular follow-up in our medical oncology department; (4) patients who received neoadjuvant therapy before the surgery.

Data Collection

Demographic data (age, BMI, smoking history, comorbidities) were obtained from hospital records. The data of complete blood cell counts, LDH, and albumin levels were obtained from the samples taken within 3 days before the operation. Data regarding stage, histologic type, myometrial invasion, lymphovascular invasion, cervical stromal invasion, ovarian involvement, ER/PR expression status, peritoneal cytology, and lymph node metastasis were obtained from the pathology results. A history of chemotherapy or radiotherapy treatments after surgery was recorded. All patients' data on metastasis, recurrence, and mortality were recorded.

Definitions

Endometrial carcinoma was staged surgically according to the FIGO classification system.2 Disease-free survival (DFS) was defined as the time from surgery to the first event of either recurrence or death. Overall survival (OS) was defined as the time from surgery to death from any cause or last follow-up assessment. dNLR was calculated using a formula as follows: absolute neutrophil count/(white blood cell count-absolute neutrophil count). The IPI was calculated based on dNLR (greater than three) and LDH (greater than the upper limit of normal, ULN).13,18 Based on dNLR and LDH, patients were characterized as having one of two possible prognosis groups (good, 0 factors; poor, 1-2 factors).[16]

This retrospective cohort study was conducted in our center after approvals from the local ethics committee (with date 03.03.2016 and number 2016/06-45).

Statistical Analysis

The primary outcomes of the study were DFS and OS. The secondary outcome was the association between clinicopathologic risk factors and the IPI score. Continuous variables were expressed as median and interquartile range (IQR). Continuous variables were compared with Mann–Whitney U-test. Categorical variables were expressed as numbers and percentages. Categorical variables between groups were compared with chi-square or Fisher's exact test. Kaplan-Meier method was used to calculate the DFS, and OS rates and the log-rank test was used to compare the survival rate between two groups. We performed multivariate logistic regression analysis to predict the independent factors for lymph node metastasis (stage IIIC disease). To build the model, a purposeful selection method was used to select a subset of covariates that were considered clinically important, adjusting for confounders and statistical significance. An adjusted

odds ratio (OR) and a 95% confidence interval (CI) were reported for each independent factor. A two-tailed P-value of < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences Version 24, IBM Corp., Armonk, N.Y., USA).

RESULTS

Clinicopathological Characteristics

A total of 94 patients who were diagnosed with endometrial cancer after surgery and followed up in our medical oncology department were included in the study. Median age of the study population was 57.5 (49.0-65.0; Table 1). Of the patients, 84.0% (n= 79) received radiotherapy and 75.5% (n= 71) received chemotherapy. Metastasis or recurrences were detected in 33 (35.1%) patients during follow-up. 28 (29.8%) patients died during the study period. The median LDH level was 210 (182-262) U/L. The median dNLR was 2.04 (1.47-4.04). The good IPI group consisted of 38 patients and the poor IPI group consisted of 56.

Clinicopathological Characteristics According to IPI

In the poor IPI group, the rate of stage IIIC patients was higher than those in the good IPI group (33.9% and 13.2%, respectively; p= 0.030). Lymph node dissection was performed in 69 (73.4%) patients of the entire study group. The number of metastatic lymph nodes was higher in the poor IPI group than in the good IPI group (0.0 [0.0–3.8] vs 0.0 [0.0–0.0] respectively, p= 0.043). The median number of metastatic lymph nodes in patients with stage IIIC was 5.0 (2.0-7.0) in the poor IPI group and 2.0 (1.0-39.0) in the good IPI group (p= 0.450). Cervical stromal invasion rate was higher in the poor IPI group compared to the good IPI group (55.4% and 28.9%, respectively; p= 0.019). The number of patients who received chemotherapy was higher in the poor IPI group compared to the good IPI group (83.9% and 63.2%, respectively; p= 0.028). The mortality rate was similar in the good IPI group and poor IPI group (31.6% vs. 28.6% respectively, p= 0.820)

Prognostic Factors for DFS

Recurrences or metastasis was detected in 33 patients during the follow-up period of the study. The median DFS of the entire study population was 107.12 (95% CI: 90.18-124.06) months. The median DFS was 66.86 (95% CI: 43.69-90.03) months in patients with stage IIIC and 114.69 (95% CI: 95.33-134.04) months in patients with stage I-II-IIIA-IIIB (p= 0.058; Table 2). In this study, no difference was observed in terms of DFS according to serum LDH levels ≥ 220 and dNLR ≥ 3. The median DFS was 105.50 (95% CI: 79.89-131.11) months in the good IPI group and 82.61 (95% CI: 67.16-98.06) months in the poor IPI group (p= 0.791).

Prognostic Factors for OS

28 patients died during the follow-up period of the study. The median OS of the entire study population was 117.10 (95% CI: 101.30-132.89) months. The median OS was 82.99 (95% CI: 62.51-103.47) months in patients with stage IIIC and 121.34 (95% CI: 103.02-139.68) months in patients with stage I-II-IIIA-IIIB (p= 0.165; Table 3). The median OS was 81.52 (95% CI: 66.02-97.03) months in patients with lymphovascular invasion and 109.86 (95% CI: 97.15-122.58) months in patients without lymphovascular invasion (p= 0.014). The median OS was 59.35 (95% CI: 36.35-82.35) months in patients with ovarian involvement and 124.16 (95% CI: 107.51-140.81) months in patients without ovarian involvement (p= 0.006). The median OS was 102.59 (95% CI: 90.60-114.57) months in patients with ER/PR expression and 73.61 (95% CI: 51.34-95.88) months in patients without ER/PR expression (p= 0.020). The median OS was 76.25 (95% CI: 55.15-97.35) months in patients with recurrences or metastasis and 153.60 (95% CI: 140.43-166.77) months in patients without recurrences or metastasis (p< 0.001). The median OS was 120.05 (95% CI: 97.28-142.81) months in the good IPI group and 92.53 (95% CI: 79.10-105.96) months in the poor IPI group (p= 0.671). Additionally, no difference was observed in terms of OS according to serum LDH levels ≥ 220 and dNLR ≥ 3.

Table 1. Demographic and clinical characteristics according to IPI status

Characteristics		All Cases (n= 94)	Good IPI (n= 38)	Poor IPI (n= 56)	p
Age at diagnosis, years		57.5 (49.0-65.0)	54.5 (47.8-62.3)	60.0 (54.3-65.8)	0.066
Body mass index, kg/m^2		30.5 (27.0-35.0)	30.0 (26.8-33.3)	31.0 (27.0-35.9)	0.649
Smoking history		16 (17.0)	9 (23.7)	7 (12.5)	0.237
	Unknown	15 (15.9)	4 (10.5)	11 (19.6)	
Comorbidities	Hypertension	49 (52.1)	17 (44.7)	32 (57.1)	0.294
	Hyperlipidemia	29 (30.9)	12 (31.6)	17 (30.4)	0.476
	Diabetes mellitus	25 (26.6)	12 (31.6)	13 (23.2)	0.645
	Coronary artery disease	4 (4.3)	1 (2.6)	3 (5.4)	1.000
The status of menopause	Premenopausal	15 (16.0)	8 (21.1)	7 (12.5)	0.390
	Postmenopausal	79 (84.0)	30 (78.9)	49 (87.5)	
Histologic type	Endometrioid	68 (72.3)	30 (78.9)	38 (67.9)	0.348
	Non-endometrioid	26 (27.7)	8 (21.1)	18 (32.1)	
Stage	I-II-IIIA-IIIB	70 (74.5)	33 (86.8)	37 (66.1)	0.030
	IIIC	24 (25.5)	5 (13.2)	19 (33.9)	
Number of patients undergoing lymph node dissection		69 (73.4)	25 (65.8)	44 (78.6)	0.234
Number of harvested lymph nodes in all patients		27.0 (16.5-41.0)	33.0 (21.5-46.5)	25.5 (14.5-40.3)	0.160
Number of metastatic lymph nodes in all patients		0.0 (0.0-2.0)	0.0 (0.0-0.0)	0.0 (0.0-3.8)	0.043
Number of metastatic lymph nodes in patients with stage IIIC		4.0 (1.3-6.8)	2.0 (1.0-39.0)	5.0 (2.0-7.0)	0.450
Lymphovascular space invasion	Negative	45 (47.9)	18 (47.4)	27 (48.2)	0.831
	Positive	46 (48.9)	17 (44.7)	29 (51.8)	
	Unknown	3 (3.2)	3 (7.9)	0 (0)	
Myometrial invasion					
Less than 50% of the myometrium		49 (52.1)	17 (44.7)	32 (57.1)	0.522
50% or more of the myometrium		41 (43.6)	17 (44.7)	24 (42.9)	
Unknown		4 (4.3)	4 (10.5)	0 (0)	
Cervical stromal invasion	Negative	52 (55.3)	27 (71.1)	25 (44.6)	0.019
	Positive	42 (44.7)	11 (28.9)	31 (55.4)	
Ovarian involvement	Negative	79 (84.0)	34 (89.5)	45 (80.4)	0.268
	Positive	15 (16.0)	4 (10.5)	11 (19.6)	
ER/PR expression status	Negative	23 (24.5)	8 (21.1)	15 (26.8)	0.804
	Positive	64 (68.1)	26 (68.4)	38 (67.9)	
	Unknown	7 (7.4)	4 (10.5)	3 (5.4)	
Peritoneal cytology	Negative	66 (70.2)	26 (68.4)	40 (71.4)	0.805
	Positive	23 (24.5)	8 (21.1)	15 (26.8)	
	Unknown	5 (5.3)	4 (10.5)	1 (1.8)	

Note: All values are expressed as numbers (percentages) or median (interquartile range).
Abbreviations: ER/PR, estrogen/progesterone receptor; IPI, Immune prognostic index; N/A, not applicable

Logistic Regression Analysis for Predictors of Lymph Node Metastasis

Multivariable analysis (Table 4) showed that a poor IPI score was independently associated with lymph node metastasis (OR: 3.59, 95%CI: 1.06-12.14, p= 0.040). Cervical stromal invasion was not associated with lymph node metastasis (OR: 0.94, 95%CI: 0.33-2.73, p= 0.912).

DISCUSSION

In this study, we assessed the prognostic significance of the IPI score which is based on preoperative dNLR and serum LDH in endometrial cancer. When grouped as good and poor, we could not find a significant correlation between the IPI score and endometrial cancer in terms of DFS and OS. However, we found that patients with at least 1 meta-

Table 2. Analysis of factors associated with disease-free survival (DFS)

Characteristics		Number of patients	Number of events	Median DFS time (months)	95% CI	Log-rank p
Age at diagnosis,years	< 65	68	24	110.90	92.09-129.72	0.275
	≥ 65	26	9	54.14	37.76-70.53	
The status of menopause	Premenopausal	15	5	117.38	79.31-155.44	0.692
	Postmenopausal	79	28	83.70	70.37-97.03	
Histologic type	Endometrioid	68	22	89.71	76.14-103.29	0.111
	Non-endometrioid	26	11	89.99	56.14-123.84	
Stage	I-II-IIIA-IIIB	70	21	114.69	95.33-134.04	0.058
	IIIC	24	12	66.86	43.69-90.03	
Lymph node dissection	Yes	69	27	76.90	63.03-90.78	0.122
	No	25	6	127.49	98.16-156.82	
Lymphovascular space	Yes	46	18	76.05	58.61-93.48	0.165
invasion (n=91)	No	45	13	94.27	78.02-110.51	
Myometrial invasion (n= 90)						
Less than 50% of the myometrium		49	14	94.89	79.32-110.47	0.115
50% or more of the myometrium		41	17	72.32	54.03-90.60	
Cervical stromal invasion	Yes	42	18	68.37	52.23-84.50	0.116
	No	52	15	116.54	94.01-139.06	
Ovarian involvement	Yes	15	5	70.21	43.32-97.09	0.657
	No	79	28	108.50	90.52-126.48	
ER/PR expression status	Yes	64	21	89.04	74.86-103.23	0.138
(n= 87)	No	23	10	68.02	42.04-93.98	
Peritoneal cytology (n=89)	Negative	66	20	91.17	77.22-105.12	0.102
	Positive	23	11	85.25	51.10-119.39	
LDH, U/L	< 220	51	18	104.55	81.20-127.91	0.977
	≥ 220	43	15	82.86	65.64-100.07	
dNLR	< 3	62	23	105.61	85.38-125.83	0.987
	≥ 3	32	10	75.53	58.40-92.65	
IPI score	Good	38	14	105.50	79.89-131.11	0.791
	Poor	56	19	82.61	67.16-98.06	
Adjuvant radiotherapy	Yes	79	28	106.40	87.94-124.86	0.848
	No	15	5	86.48	56.16-116.81	
Adjuvant chemotherapy	Yes	71	22	114.74	95.56-133.92	0.337
	No	23	11	75.06	52.84-97.28	

Abbreviation: dNLR, derived neutrophils/(leukocytes minus neutrophils) ratio

static lymph node (stage IIIC) were more common in poor IPI score group. There was also a positive correlation between the number of metastatic lymph nodes and the poor IPI group.

Inflammatory responses play crucial roles at all stages of the tumor, from its initial appearance to tumor progression and metastatic progression.[10] Neutrophilia, lymphocytopenia, and relative thrombocytosis can be detected in peripheral blood due to systemic inflammatory response.[11] Since there is an inflammatory response at every stage of the tumor, numerous studies have been conducted in endometrial cancer using peripheral biomarkers of the inflammatory response.[9,12] The neutrophil-to-lymphocyte ratio (NLR) as one of the systemic inflammatory markers has been studied in endometrial cancer. A meta-analysis demonstrated that high levels of NLR were associated with decreased OS and DFS in patients with endometrial cancer.[12] Although dNLR gives similar or better values than NLR in predicting prognosis in some other can-

Table 3. Analysis of factors associated with overall survival (OS)

Characteristics		Number of patients	Number of events	Median OS time (months)	95% CI	Log-rank p
Age at diagnosis,years	< 65	68	19	123.87	106.91-140.82	0.050
	≥ 65	26	9	59.82	45.95-73.68	
The status of menopause	Premenopausal	15	2	147.98	118.87-177.08	0.086
	Postmenopausal	79	26	109.53	92.31-126.75	
Histologic type	Endometrioid	68	18	120.64	103.03-138.26	0.130
	Non-endometrioid	26	10	103.03	71.69-134.37	
Stage	I-II-IIIA-IIIB	70	18	121.34	103.02-139.68	0.165
	IIIC	24	10	82.99	62.51-103.47	
Lymph node dissection	Yes	69	23	88.75	76.73-100.77	0.087
	No	25	5	138.08	122.25-163.91	
Lymphovascular space	Yes	46	18	81.52	66.02-97.03	0.014
invasion (n= 91)	No	45	8	109.86	97.15-122.58	
Myometrial invasion (n= 90)						
Less than 50% of the myometrium		49	10	106.57	93.53-119.61	0.052
50% or more of the myometrium		41	16	82.04	65.98-98.09	
Cervical stromal invasion	Yes	42	15	81.75	67.08-96.42	0.125
	No	52	13	126.27	106.22-146.31	
Ovarian involvement	Yes	15	8	59.35	36.35-82.35	0.006
	No	79	20	124.16	107.51-140.81	
ER/PR expression status (n= 87)	Yes	64	15	102.59	90.60-114.57	0.020
	No	23	11	73.61	51.34-95.88	
Peritoneal cytology (n= 89)	Negative	66	17	123.12	105.75-140.49	0.098
	Positive	23	10	89.56	55.10-124.02	
LDH, U/L	< 220	51	14	120.31	98.94-141.68	0.580
	≥ 220	43	14	91.20	76.44-105.96	
dNLR	< 3	62	21	115.49	97.19-133.78	0.717
	≥ 3	32	7	86.87	72.65-101.10	
IPI score	Good	38	12	120.05	97.28-142.81	0.671
	Poor	56	16	92.53	79.10-105.96	
Adjuvant radiotherapy	Yes	79	25	114.02	96.43-131.61	0.329
	No	15	3	142.33	108.19-176.48	
Adjuvant chemotherapy	Yes	71	21	117.26	97.77-136.74	0.547
	No	23	7	124.69	97.24-152.14	
Recurrence or metastasis	Yes	33	22	76.25	55.15-97.35	<0.001
	No	61	6	153.60	140.43-166.77	

Note: Statistically significant values are expressed in bold.
Abbreviations: CI, confidence interval; dNLR, derived neutrophils/(leukocytes minus neutrophils) ratio; ER/PR, estrogen/progesterone receptor; IPI, Immune prognostic index; LDH, lactate dehydrogenase.

cers,[19,20] it has not been clearly evaluated in endometrial cancer.

LDH is one of the other useful and inexpensive prognostic immune-related biomarkers. The association between high serum levels of LDH and poor survival in solid tumors has been demonstrated in meta-analysis.[21]

Mezquita et al. combined the preoperative levels of LDH and dNLR to create the IPI index. They demonstrated that the IPI (combining dNLR greater than 3 and LDH greater than ULN) was significantly associated with treatment outcomes in patients with advanced non-small cell lung cancer.[13] In another study of patients with metastatic non-small cell lung cancer, the IPI score was associ-

Table 4. Logistic regression analysis for predictors of lymph node metastasis

	OR (95% CI)	p
Poor IPI score	3.59 (1.06-12.14)	0.040
Pathological type	0.47 (0.16-1.38)	0.169
Myometrial invasion	3.08 (0.86-11.08)	0.084
Cervical stromal invasion	0.94 (0.33-2.73)	0.912
Ovarian involvement	0.47 (0.11-2.01)	0.308
Lymphovascular space invasion	2.02 (0.55-7.38)	0.287

ated with progression-free survival and OS.[14] The IPI score has also been studied in different cancers. In a study, the IPI score was applied to predict the long-term prognosis in elderly gastric cancer. They found that IPI was a good prognostic indicator for stage II patients.[15] In another study of patients with gallbladder cancer, the IPI was an independent predictor of OS.[16] The IPI was an independent prognostic marker regarding cancer-specific survival in patients with resected esophageal squamous cell carcinoma.[17] We found no association between IPI score and DFS or OS in this study. Although the DFS and OS durations were shorter in the poor IPI group than in the good IPI group, the failure to reach statistical significance may be due to the small sample size of our study.

The standard treatment for endometrial cancer is surgery including total hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment.[22] Lymph node dissection is an important component of comprehensive endometrial cancer staging.[2,23] However, the effect of lymphadenectomy on survival outcomes remains controversial.[23-25] Additionally, comprehensive nodal dissection can cause early and late complications.[23,26,27] Due to possible complications of lymph node dissection in endometrial cancer, nomograms have been developed to predict metastasis in the preoperative period. Many researchers have developed nomograms including risk factors to predict lymph node metastasis in endometrial cancer.[28-30] In a large population-based analysis, a nomogram was developed to predict lymph node metastasis in endometrial cancer patients, using predictors of age, tumor size, histological type, myometrial invasion, cervical stromal invasion, and tumor grade. Nomogram performed well in predicting lymph node metastasis.[31] In our study, patients with at least 1 metastatic lymph node (stage IIIC) were more common in the poor IPI group. Additionally, in the poor IPI group the median number of metastatic lymph nodes was higher than in the good IPI group. In multivariate analysis, we demonstrated that a poor IPI score independently predicted lymph node metastasis.

Cervical stromal invasion is associated with poor outcomes in endometrial cancer, including recurrence and death.[32,33] Therefore, it is important to predict cervical involvement in patients with endometrial cancer. In this study, the rate of patients with cervical stromal invasion was higher in poor IPI group than the good IPI group. However, previous studies have found an association between cervical stromal invasion and lymph node metastasis.[34,35] In multivariate analysis, we found no association between cervical stromal invasion and lymph node metastasis in our population.

A limitation of this study is the use of retrospective data from a small population in a single-center, so bias cannot be excluded.

Conclusion

A poor IPI score was independently associated with lymph node metastasis. In addition to the radiological and intraoperative findings, the IPI score can be used as a simple, inexpensive, and easy method to predict lymph node metastasis. Predicting lymph node metastasis may contribute to accurate staging that guides optimal treatment strategies.

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