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A New Model to Improve the Prediction of Prognosis of Endometrial Carcinoma by Combining Traditional Classification With the Presence of Tumor-infiltrating Lymphocytes

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Abstract. *Background/Aim: We aimed to predict the prognosis of endometrial carcinoma by combining traditional histological classification with the status of tumor-infiltrating lymphocytes (TILs). Patients and Methods: All patients with endometrial carcinoma, treated at our hospital, were classified into four categories—Category I: Type I positive for TILs; category II: type I negative for TILs; category III: type II positive for TILs; and category IV: type II negative for TILs. Prognoses were compared across all the categories. Positivity for TILs was defined as a continuously formed thick zone of TILs at the invasive front. Results: Multivariate analyses of progression-free and overall survival indicated that category classification was an independent prognostic factor, with hazard ratios of 3.127, 3.483, and 8.459 for progression-free survival, and 3.444, 4.374, and 11.058 for OS for patients in categories II, III, and IV, respectively. Conclusion: Combining traditional histological classification with TIL status might better predict prognosis of endometrial carcinoma.*

Endometrial carcinoma is the sixth most common cancer in women worldwide (1). The basic treatment for endometrial carcinoma is primary surgery, followed by adjuvant treatment, including radiotherapy or chemotherapy, according to the classification of the risk of recurrence using pathology of surgical specimens (2). The classification is based on histology, myometrial invasion, and invasion of cervical stroma, as well as the presence of lymph node metastasis and distant metastasis (2).

Histological subtypes are classified into two groups: Estrogen-dependent moderately or highly differentiated type I carcinoma and estrogen-independent poorly differentiated type II carcinoma (3). Although mutations of phosphatase and tensine homolog (*PTEN*) and *Homo sapiens* catenin beta 1 (*CTNNB1*) are representative genetic differences between these two types of carcinoma, they are more frequently observed in type I endometrial carcinoma. However, tumor protein p53 (*TP53*) mutation and human epidermal growth factor receptor 2 (*HER2*) amplification are more often observed in type II (4).

Recently, tumor-infiltrating lymphocytes (TILs) have been found to be associated with clinical outcomes in several carcinoma types, as well as with tumor malignancy and prognosis (5-7). TILs present in the tumor stroma and at the invasive front are important factors in endometrial carcinoma, and have been associated with the International Federation of Gynecology and Obstetrics (FIGO) staging of endometrial carcinoma, along with histological subtype, lymphovascular invasion, and prognosis (8-11). TILs are also associated with DNA polymerase epsilon (*POLE*) mutations and microsatellite instability (MSI) in tumor cells (12).

Thus, both traditional classification and TIL status are related not only to prognosis but also to several other factors associated with endometrial carcinoma. The present study, therefore, aimed to combine traditional classification with the presence of TILs, to establish a new model capable of providing an accurate prognosis of endometrial carcinoma.

Patients and Methods

Patients with endometrial carcinoma who underwent surgery at the National Defense Medical College in Japan between 1989 and 2017 were identified. Cases with other carcinoma types, or prior history of chemotherapy before surgery, as well as those without medical records and surgical specimens were excluded.

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Key Words: Endometrial carcinoma, tumor-infiltrating lymphocyte, traditional classification, prognosis.

Table I. *Characteristics of patients according to criteria that combine traditional classification with tumor-infiltrating lymphocytes.*

Characteristic	Subgroup	Category I n=94	Category II n=305	Category III n=70	Category IV n=115	*p*-Value
Age	<65 Years	77 (82%)	219 (72%)	48 (69%)	51 (44%)	<0.0001
	≥65 Years	17 (18%)	86 (28%)	22 (31%)	64 (56%)	
FIGO stage	I	79 (84%)	243 (80%)	43 (62%)	50 (43%)	<0.0001
	II	5 (5%)	23 (7%)	3 (4%)	7 (6%)	
	III	10 (11%)	31 (10%)	15 (21%)	34 (30%)	
	IV	0 (0%)	8 (3%)	9 (13%)	24 (21%)	
Histology	Grade 1 endometrioid carcinoma	62 (66%)	235 (77%)	-	-	
	Grade 2 endometrioid carcinoma	31 (33%)	66 (22%)	-	-	0.0628*
	Mucinous carcinoma	1 (1%)	4 (1%)	-	-	
	Grade 3 endometrioid carcinoma	-	-	38 (54%)	27 (24%)	
	Serous carcinoma	-	-	11 (16%)	35 (24%)	<0.0001**
	Clear-cell carcinoma	-	-	2 (3%)	9 (8%)	
	Carcinosarcoma	-	-	4 (6%)	24 (21%)	
	Mixed carcinoma	-	-	13 (18%)	20 (17%)	
	Undifferentiated carcinoma	-	-	2 (3%)	0 (0%)	
Myometrial invasion of corpus	<1/2	71 (75%)	218 (71%)	46 (66%)	55 (48%)	<0.0001
	≥1/2	23 (25%)	87 (29%)	24 (34%)	60 (52%)	
Cervical involvement	Positive	8 (9%)	36 (12%)	10 (14%)	26 (23%)	0.0180
	Negative	86 (91%)	269 (88%)	60 (86%)	89 (77%)	
Ovarian metastasis	Positive	0 (0%)	15 (5%)	4 (6%)	15 (13%)	0.0002
	Negative	94 (100%)	290 (95%)	66 (94%)	100 (87%)	
Lymph node metastasis	Positive	8 (9%)	25 (8%)	15 (21%)	26 (23%)	<0.0001
	Negative	76 (81%)	229 (75%)	44 (63%)	58 (50%)	
	Unknown	10 (10%)	51 (17%)	11 (16%)	31 (27%)	
Distant metastasis	Positive	0 (0%)	8 (3%)	9 (13%)	23 (20%)	<0.0001
	Negative	94 (100%)	297 (97%)	61 (87%)	92 (80%)	
Lymphovascular invasion	Positive	31 (33%)	92 (30%)	38 (54%)	69 (60%)	<0.0001
	Negative	63 (67%)	213 (70%)	32 (46%)	46 (40%)	
Ascites or lavage cytology	Positive	7 (7%)	41 (13%)	15 (21%)	44 (38%)	<0.0001
	Negative	87 (93%)	264 (87%)	55 (79%)	71 (62%)	
Adjuvant therapy	Yes	41 (44%)	121 (40%)	50 (71%)	92 (80%)	<0.0001
	No	53 (56%)	184 (60%)	20 (29%)	23 (20%)	
Five-year survival	Progression-free (%)	95.5	84.9	75.6	41.3	<0.0001
	Overall survival (%)	97.7	93.4	88.5	65.8	<0.0001

FIGO: International Federation of Gynecology and Obstetrics (14); category I: type I tumor positive for tumor-infiltrating lymphocytes (TILs); category II: type I tumor negative for TILs; category III: type II tumor positive for TILs; category VI: type II tumor negative for TILs. *Category I *vs*. II. **Category III *vs*. VI.

Pathological reviews of 584 patient specimens were performed using hematoxylin and eosin staining, followed by classification according to the 2014 World Health Organization criteria (13). Histological subtypes were classified as type I, which includes grade 1 and 2 endometrioid carcinoma and mucinous carcinoma; and type II, comprising serous carcinoma, clear-cell carcinoma, mixed carcinoma, and carcinosarcoma. TILs in the slides were simultaneously evaluated at the time of pathological review, based on our previous report (10). Positivity for TILs was defined as the presence of a continuously formed thick zone of TILs at the invasive front, with allowance for minor inconsistencies (Figure 1A). Negativity for TILs was defined as the absence of TILs at the invasive front and a lack of a continuous thick zone of TILs; in some cases with TILs, a discontinuous agglomeration was formed (Figure 1B). After review, all endometrial carcinoma cases were classified into four categories: Category I: Type I positive for TILs; category II: type I negative for TILs; category III: type II positive for TILs; and category IV: type II negative for TILs.

Clinical information was obtained from past medical records. Staging of carcinomas was re-evaluated using the 2014 FIGO criteria (14). Progression-free survival (PFS) was defined as the period from the day of primary surgery to the day of death or recurrence/progression of the disease. Overall survival (OS) was defined as the period from the day of primary surgery to the day of death or last contact.

Statistical analysis was performed using JMP Pro 14 software (SAS Institute Inc., Cary, NC, USA). The chi-squared test and Fisher's exact test were used to evaluate the clinical significance of the clinicopathological factors. PFS and OS curves were generated using the Kaplan–Meier method. Subsequently, comparisons of the survival distributions were made using the log-rank test. Cox proportional hazards regression was used for further univariate and multivariate analyses of PFS and OS. Statistical significance was defined as a value of $p<0.05$.

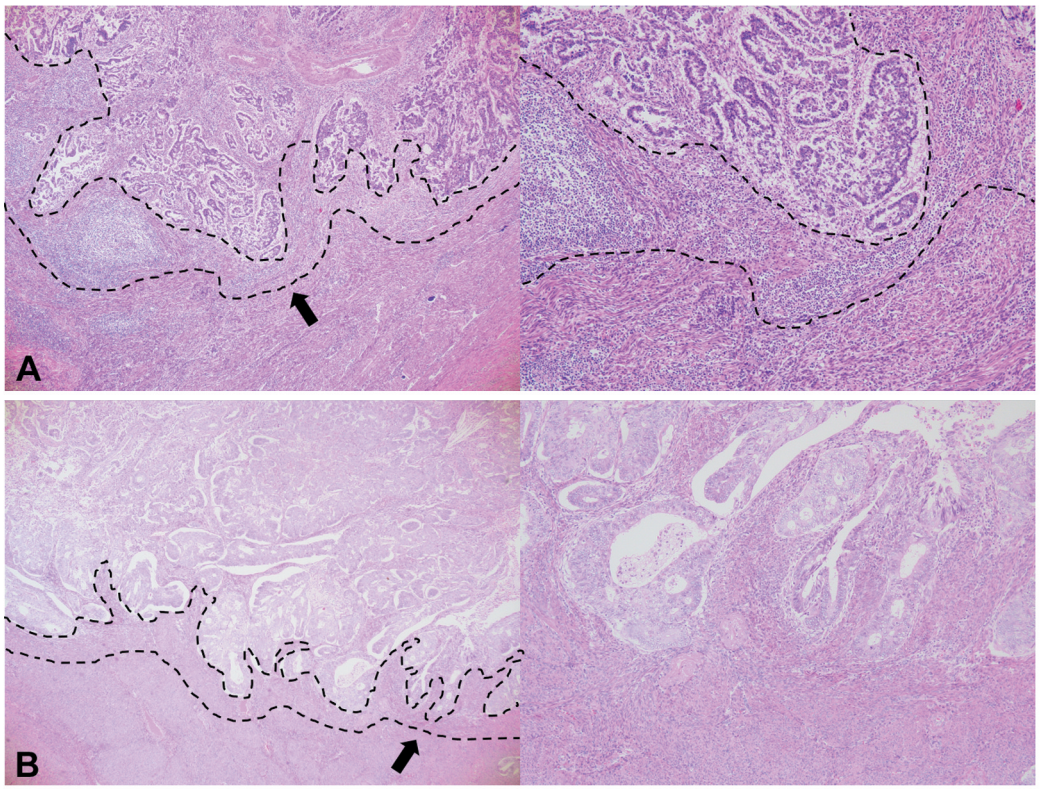

Figure 1. *Representative images of tumor-infiltrating lymphocytes (TILs) in cases defined as being positive (A) or negative (B) for TILs under hematoxylin and eosin staining. The areas demarcated by dotted lines are the regions evaluated for TILs at the invasive front. The arrows in the left panel (×10) indicates the region shown at higher magnification (×20) in the right panel. A thick zone of TILs was formed at the invasive front in A, while there were no TILs at the invasive front in B.*

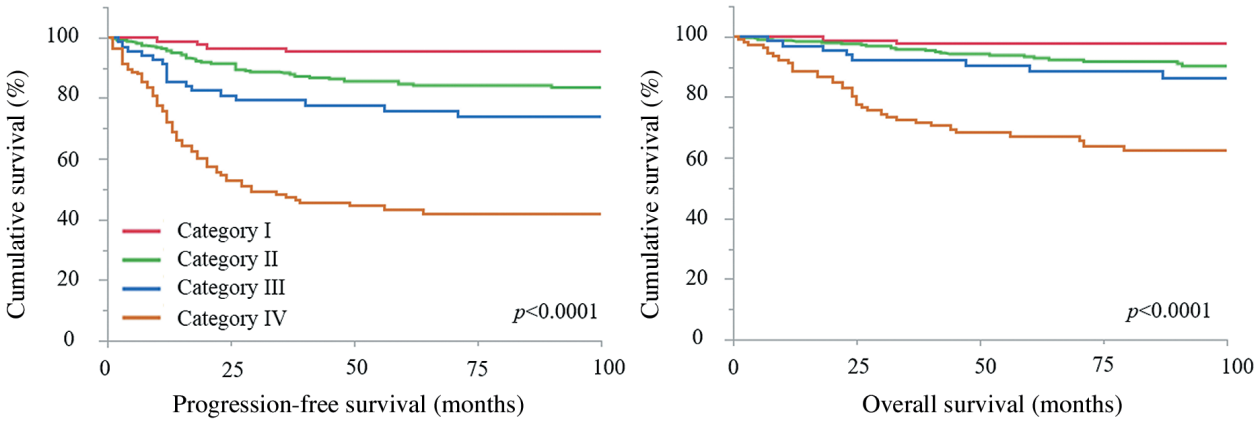

Figure 2. *Progression-free (A) and overall (B) survival of patients with endometrial carcinoma, according to the two-factor categorization. Category I: Type I tumor positive for tumor-infiltrating lymphocytes (TILs); category II: type I tumor negative for TILs; category III: type II tumor positive for TILs; category VI: type II tumor negative for TILs.*

All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee, as well as the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Since this was a retrospective study, informed consent was not obtained. This study was approved by the Ethics Committee of the National Defense Medical College, Tokorozawa, Japan (no. 3084).

Results

A total of 584 cases, comprising 94 cases in category I, 305 in category II, 70 in category III, and 115 in category IV, were included in our study. The median observational period was 73.5 months.

Table I presents the characteristics of patients. Among patients with type I and type II cancer, the number of cases positive for TILs was 94/399 (23%) and 70/185 (38%), respectively. A higher proportion of patients in category IV were more than 65 years of age ($p<0.0001$) and had stage III and IV disease ($p<0.0001$), more than half myometrial invasion of the corpus ($p<0.0001$), cervical involvement ($p=0.0180$), ovarian metastasis ($p=0.0002$), distant metastasis ($p<0.0001$), lymphovascular invasion ($p<0.0001$), positive ascites cytology or lavage cytology ($p<0.0001$), and also received adjuvant therapy ($p<0.0001$). The proportion of lymph node metastasis in category IV was almost equivalent to that in category III, but was higher than that in categories I and II ($p<0.0001$). There was no significant difference between the histological subtypes in categories I and II ($p=0.0628$). Furthermore, there were more cases with grade 3 endometrioid carcinoma in category III ($p<0.0001$) than in category IV. Additionally, the number of cases positive for TILs was higher in grade 3 endometrioid carcinoma than in grades 1 and 2 [38/65 (58.4%) *vs*. 93/394 (23.6%); $p<0.0001$].

The resultant PFS and OS were inversely correlated with category number (Figure 2; $p<0.0001$). Multivariate analysis of PFS revealed that the two-factor category was a significantly independent prognostic factor, with hazard ratios of 3.127, 3.483, and 8.459, respectively, for categories II, III, and IV *versus* category I, in addition to age, FIGO stage, lymphovascular invasion, and adjuvant therapy (Table II). However, there were no statistically significant differences in PFS between category II and III cases. Similarly, multivariate analysis of OS revealed that our novel histological categorization was an independent prognostic factor, with hazard ratios of 3.444, 4.374, and 11.058 for categories II, III, and IV *versus* category I, respectively, along with FIGO stage, lymphovascular invasion, and adjuvant therapy (Table III). There were no statistically significant differences in OS between category II and III cases.

Discussion

In our study, the novel two-factor histological categorization of endometrial carcinoma was found to be associated with several clinicopathological features. Multivariate analysis revealed that the histological category was an independent prognostic factor of PFS and OS. This study combined the traditional classification with the status of TILs, in order to accurately predict the prognosis of patients with endometrial carcinoma, using only hematoxylin and eosin-stained slides.

The Cancer Genome Atlas project classified endometrial carcinomas into four groups: An ultramutated group with mutations of *POLE,* a hypermutated group with MSI, an endometrioid group with low copy-number aberrations, and a serous-like group with high copy-number aberrations (15). Since *POLE* mutations as well as MSI in endometrial carcinoma accumulate high neoantigen loads, which results in tumors being exposed to a number of TILs, the ultramutated group with mutations of *POLE* and the hypermutated group with MSI are strongly associated with TILs (12). According to a systematic review and meta-analysis of endometrial endometrioid carcinoma, grade 3 endometrioid carcinomas were more frequently observed in the *POLE*-mutated subgroup (12.1% *vs*. 6.2%) and the MSI subgroup (39.7% *vs*. 24.7%), than grade 1 and 2 endometrioid carcinomas (16). Hence, the incidences of *POLE* mutations and MSI in serous and clear-cell carcinoma were found to be lower than those in endometrioid carcinoma (4, 17-19). Moreover, in another systematic review and meta-analysis of endometrial carcinosarcoma, 5.3% cases had *POLE* mutations, while 7.3% had MSI (20). Furthermore, *POLE* mutations have been detected in mixed carcinomas (21). In our study, more cases with grade 3 endometrioid carcinoma were TIL-positive than those with grade 1 and 2 endometrioid carcinomas, and the prevalence of TIL-positive grade 3 endometrioid carcinoma was the highest among type II tumors. These results might reflect an association between TILs and the status of *POLE* mutations and MSI.

Several reports have revealed an important association between TILs and the prognosis of endometrioid carcinoma (8-12, 22-24). These studies demonstrated that cluster of differentiation (CD)3^+ T-lymphocytes, $CD8^+$ T-lymphocytes, $CD45R0^+$ T-lymphocytes, and $CD8^+$/forkhead box protein (FOXP)3^+ ratios were associated with prognosis. Moreover, Chen *et al*. demonstrated a cancer-immunity cycle consisting of seven steps: The release of cancer antigen, cancer antigen presentation, priming and activation, trafficking of T-cells to tumors, infiltration of T-cells into tumors, recognition of cancer cells by T-cells, and killing of cancer cells (25). Several cell types, such as $CD4^+$ T-lymphocytes, $CD8^+$ T-lymphocytes, and antigen-presenting cells, rather than any single kind of lymphocyte, have been implicated in these steps. Therefore, immune reactions are based on several kinds of TILs, and not just a single type that emerges against tumor. For this reason, our study did not perform subset analysis of lymphocytes, but did clearly demonstrate that TILs were overall an important factor related to prognosis. However, subset analysis of TILs does hold its own significance; a recent study demonstrated $CD8^+$ T-lymphocytes to be a key biomarker in immunotherapy (26).

Several previous studies evaluated TILs in the tumor

Table II. *Univariate and multivariate analysis of progression-free survival of patients with endometrial carcinoma.*

		Univariate analysis		Multivariate analysis	
Characteristic	Subgroup	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	≥65 *vs*. <65 Years	2.447 (1.732-3.448)	<0.0001	1.583 (1.102-2.272)	0.0130
FIGO stage	II *vs*. I	1.871 (0.769-3.904)	0.1544	2.550 (1.006-5.642)	0.0487
	III *vs*. I	7.490 (4.956-11.372)	<0.0001	5.024 (2.870-8.917)	<0.0001
	IV *vs*. I	24.416 (15.217-38.915)	<0.0001	17.938 (9.679-33.721)	<0.0001
Lymphovascular invasion	Positive *vs*. Negative	3.587 (2.517-5.184)	<0.0001	2.026 (1.325-3.1069)	0.0011
Ascites cytology	Positive *vs*. Negative	4.479 (3.146-6.331)	<0.0001	1.401 (0.929-2.114)	0.1076
Adjuvant therapy	Yes *vs*. no	2.878 (1.970-4.310)	<0.0001	0.442 (0.253-0.775)	0.0044
Histological category	II *vs*. I	3.719 (1.150-12.341)	0.0025	3.127 (1.262-10.416)	0.0111
	III *vs*. I	66.75 (2.470-23.198)	<0.0001	3.483 (1.255-12.310)	0.0150
	IV *vs*. I	21.015 (8.679-69.161)	<0.0001	8.459 (3.301-28.755)	<0.0001
	III *vs*. II	1.795 (0.999-3.075)	0.0502	1.114 (0.606-1.598)	0.7189
	IV *vs*. II	5.652 (3.873-8.321)	<0.0001	2.705 (1.731-4.274)	<0.0001
	IV *vs*. III	3.148 (1.890-5.545)	<0.0001	2.429 (1.443-4.317)	0.0006

FIGO: International Federation of Gynecology and Obstetrics (14); category I: type I tumor positive for tumor-infiltrating lymphocytes (TILs); category II: type I tumor negative for TILs; category III: type II tumor positive for TILs; category VI: type II tumor negative for TILs; CI: confidence intervaI; HR: hazard ratio.

Table III. *Univariate and multivariate analysis of overall survival of patients with endometrial carcinoma.*

		Univariate analysis		Multivariate analysis	
Characteristic	Subgroup	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	≥65 *vs*. <65 Years	2.208 (1.380-3.485)	0.0011	1.537 (0.941-2.493)	0.0855
FIGO stage	II *vs*. I	3.221 (1.835-7.496)	0.0244	6.057 (2.043-15.858)	0.0021
	III *vs*. I	6.475 (3.668-11.531)	<0.0001	4.902 (2.253-10.945)	<0.0001
	IV *vs*. I	25.521 (13.940-46.900)	<0.0001	21.606 (9.185-52.874)	<0.0001
Lymphovascular invasion	Positive *vs*. Negative	4.003 (2.491-6.645)	<0.0001	2.492 (1.428-4.378)	0.0013
Ascites cytology	Positive *vs*. Negative	5.205 (3.309-8.154)	<0.0001	1.720 (0.996-2.983)	0.0516
Adjuvant therapy	Yes *vs*. no	2.465 (1.519-4.189)	0.0002	0.247 (0.116-0.526)	0.0003
Histological category	II *vs*. I	4.173 (1.244-25.931)	0.0171	3.444 (1.013-21.522)	0.0472
	III *vs*. I	7.935 (2.086-51.704)	0.0015	4.374 (1.106-29.067)	0.0342
	IV *vs*. I	26.093 (7.984-160.541)	<0.0001	11.058 (3.116-70.639)	<0.0001
	III *vs*. II	1.901 (0.868-3.863)	0.1042	1.270 (0.534-2.663)	0.5482
	IV *vs*. II	6.252 (3.797-10.523)	<0.0001	3.210 (1.790-5.884)	<0.0001
	IV *vs*. III	3.288(1.713-6.960)	0.0002	2.528(1.299-5.412)	0.0054

FIGO: International Federation of Gynecology and Obstetrics (14); category I: type I tumor positive for tumor-infiltrating lymphocytes (TILs); category II: type I tumor negative for TILs; category III: type II tumor positive for TILs; category VI: type II tumor negative for TILs; CI: confidence intervaI; HR: hazard ratio.

stroma (8, 9, 22-24). However, our earlier reports focused on TILs at the invasive front and indicated their importance in prognosis (10, 11). Recently, Pagès *et al*. suggested that the presence of $CD3^+$ as well as cytotoxic $CD8^+$ T-cells in the tumor and in the invasive margin constitute prognostic factors for patients with colon cancer (27). Therefore, the total population of TILs in tumors and invasive margins might be significant in prognosis. Furthermore, the digital pathology method used by Pages *et al*. to quantify TILs has a high level of reproducibility. The choice of locations to be evaluated and the quantification of TILs, however, remain challenges for future studies.

Category IV as defined in our study had the highest proportion of cases with locally and systemically advanced disease, along with poor prognosis. Hence, although the 5-year OS rate of patients in category III was worse than that in category I, it was not statistically different from that in category II. Therefore, even if the histology shows a type II tumor, the presence of TILs might improve prognosis up to a level close to that of type I; accordingly, category IV (type

II negative for TILs) should be the primary focus group for the development of new treatment modalities.

One of the limitations of this study is that it was a retrospective and single-institutional analysis. Moreover, it is unknown whether the classification we have proposed is associated with genetic alterations, and quantification of TILs was not performed. However, our two-factor category model suggests a strong association with prognosis and several clinical and pathological features. Further research must be conducted to examine the relationship between our classification and the genetic background, as well as to establish the quantification of TILs with high reproducibility, in order to increase its usefulness in clinical settings.

In conclusion, our study demonstrated that combining traditional classification with the presence of TILs might improve the prediction of prognosis of patients with endometrial carcinoma.

Conflicts of Interest

All Authors declare no conflicts of interest.

Authors' Contributions

Protocol/project development: MM, TH, HT, and MT. Data collection and/or management: HI, HI, SK, RS, TS, and HM. Data analysis: MM, TH, and HT. Article writing/editing: MM and MT.

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