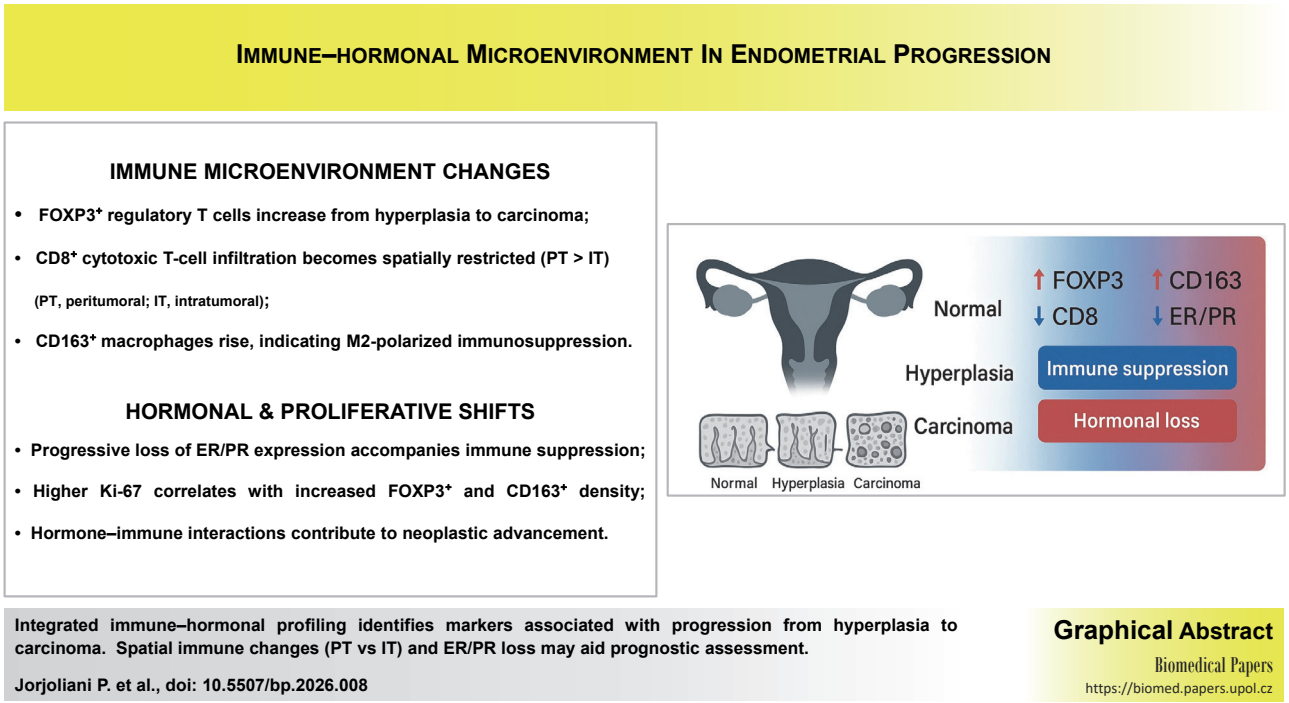
Comparative study of the endometrial microenvironment's immunohistochemical profile in pre-tumour and tumour conditions: endometrial hyperplasia, endometrioid carcinoma, and serous carcinoma

Paata Jorjoliani, Zaza Bokhua, George Burkadze, Shota Kepuladze

Background. Endometrial carcinogenesis involves complex interactions between hormonal signaling and the local immune microenvironment. While atypical endometrial hyperplasia is a recognized precursor to carcinoma, the spatial and phenotypic evolution of immune and hormonal markers during progression remains incompletely characterized.
Methods. A retrospective cohort of 150 endometrial specimens, including hyperplasia without atypia (n=40), hyperplasia with atypia (n=40), endometrioid carcinoma (n=40), and serous carcinoma (n=30), was analyzed using immunohistochemistry for CD3, CD4, CD8, FOXP3, CD68, CD163, estrogen receptor (ER), and progesterone receptor (PR). Digital whole-slide imaging and QuPath were applied to quantify immune cell densities in intratumoral and peritumoral compartments. Correlations between immune markers and hormonal receptors were evaluated, and a subgroup of 27 paired hyperplasia–carcinoma cases was analyzed separately.
Results. $CD3^+$ and $CD8^+$ T-cell densities increased progressively from hyperplasia to carcinoma ($P<0.001$), with hyperplastic lesions demonstrating predominant peritumoral localization consistent with immune exclusion. $FOXP3^+$ regulatory T cells were enriched in neoplastic lesions, particularly in ER/PR-positive tumors. $CD8^+$ intratumoral and peritumoral densities showed significant inverse correlations with ER and PR expression (both $r=-0.76$, $P<0.001$), whereas $FOXP3^+$ infiltration correlated positively with ER and PR ($r=0.64$, $P<0.001$). M2 $CD163^+$ macrophages demonstrated an inverse association with ER ($r=-0.49$, $P<0.01$), while M1 $CD68^+$/iNOS macrophages showed no statistically significant correlations. In the paired subgroup, higher peritumoral than intratumoral $CD8^+$ densities persisted, indicating residual immune exclusion despite malignant transformation.
Conclusions. Endometrial neoplastic progression is characterized by a transition from peritumoral immune exclusion in hyperplasia to increased intratumoral immune infiltration in carcinoma, although this shift is not universal. Hormone receptor–positive tumors exhibit enrichment of $FOXP3^+$ regulatory T cells and $CD163^+$ macrophages, suggesting hormone-linked immune suppression. These findings highlight combined immune–hormonal biomarkers as potential indicators of progression risk and support further investigation of integrated immunomodulatory and hormone-targeted therapeutic strategies.



Key words: endometrial hyperplasia, endometrioid carcinoma, serous carcinoma, tumor microenvironment, FOXP3, CD8, CD163

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INTRODUCTION

Endometrial carcinogenesis arises from a complex interaction between hormonal signaling, epithelial proliferation, and immune microenvironment dynamics[1]. The tumor immune milieu in endometrial cancer shows distinct patterns of immunosuppression influenced by molecular subtype and microenvironmental context[1]. Accurate pathological staging further guides risk stratification and management, as reflected in the updated FIGO classification[2].

Atypical endometrial hyperplasia represents a well-established precursor lesion with a significant risk of progression to carcinoma, particularly when inadequately managed[3]. During this transition, progressive alterations in the immune microenvironment – including reduced cytotoxic activity, increased regulatory T-cell function, and macrophage polarization – may contribute to neoplastic advancement[4,5].

Immune modulation is further influenced by hormonal receptor expression. High estrogen and progesterone receptor activity has been associated with reduced T-cell infiltration in several hormone-related malignancies, suggesting a potential immunosuppressive interplay[6]. Immunohistochemical studies also show that ER and PR expression patterns vary across endometrial cancer subtypes and correlate with tumor histology and behavior[7].

Beyond hormonal regulation, the endometrial immune environment itself plays a pivotal role in shaping tumor evolution. Local immune cell composition, cytokine profiles, and microenvironmental architecture influence both disease progression and therapeutic responsiveness[8]. Notably, immune infiltration patterns have been linked to clinical outcomes in early-stage endometrial cancer, with specific immune signatures predicting prognosis[9].

Macrophages represent another key component of the tumor microenvironment. M2-polarized $CD163^+$ macrophages contribute to immunosuppression, tissue remodeling, and tumor progression[10], and their density has been associated with patient outcomes across multiple tumor types, including endometrial carcinoma. Cytotoxic $CD8^+$ lymphocyte infiltration also has prognostic value; increased intratumoral $CD8^+$ density correlates with improved survival in endometrial cancer[11].

Furthermore, hormonal–immune interactions extend to the regulation of regulatory T cells. Estrogen receptor binding to the FOXP3 promoter has been shown to modulate T-regulatory function, indicating a mechanistic link between hormonal status and local immune suppression[12]. This suggests that immune–hormonal crosstalk contributes meaningfully to disease biology.

Despite growing evidence, integrated characterization of proliferative, hormonal, and immune markers across the full continuum from hyperplasia to carcinoma remains limited[4]. Understanding how these pathways evolve spatially and phenotypically may improve risk prediction, refine diagnostic thresholds, and support the development of targeted therapeutic strategies.

MATERIALS AND METHODS

This retrospective study analysed 150 endometrial tissue specimens obtained from patients diagnosed with endometrial hyperplasia without atypia, endometrial hyperplasia with atypia, endometrioid carcinoma, and serous carcinoma. The specimens were collected from hysterectomy and curettage samples archived at the Tbilisi State Medical University Laboratory (2015–2025). Clinical and histopathological data were retrieved from institutional records.

All specimens were formalin-fixed and paraffin-embedded (FFPE) and stained with hematoxylin and eosin (H&E) for histopathological evaluation. The classification was performed according to the World Health Organization (WHO 2020) criteria for endometrial neoplasia. Tumor grading (Grade 1, Grade 2, Grade 3) and pT staging (pT1–pT4) were assigned following the

Table 1. Immunohistochemical antibodies used in the research with specific antibody clones and dilution.

Marker	Target Cell Type	Clone	Dilution	Supplier
CD3	Pan-T cells	SP7	1:100	Leica
CD4	Helper T cells	4B12	1:100	Leica
CD8	Cytotoxic T cells	C8/144B	1:100	Leica
FOXP3	Regulatory T cells	236A/E7	1:100	Leica
CD68	M1 macrophages	KP1	1:100	Leica
CD163	M2 macrophages	MRQ-26	1:100	Leica
ER	Estrogen receptor	1D5	1:50	Leica
PR	Progesterone receptor	636	1:50	Leica

Table 2. Patient clinical and pathological characteristics. Percentages were calculated within each diagnostic group relative to the total number of cases in that category.

Variable	Hyperplasia without atypia (n=40)	Hyperplasia with atypia (n=40)	Endometrioid carcinoma (n=40)	Serous carcinoma (n=30)
Age (years), mean ± SD	51.4 ± 7.8	53.1 ± 8.2	59.3 ± 9.1	68.4 ± 6.7
Postmenopausal	15 (38%)	18 (45%)	25 (62%)	25 (83%)
Comorbidities				
Obesity (BMI ≥30)	17 (42%)	19 (48%)	22 (55%)	10 (33%)
Hypertension	14 (36%)	18 (44%)	23 (58%)	19 (63%)
Diabetes mellitus	7 (18%)	9 (23%)	12 (30%)	8 (27%)
Specimen type				
Curettage	26 (65%)	24 (60%)	10 (25%)	3 (10%)
Hysterectomy	14 (35%)	16 (40%)	30 (75%)	27 (90%)
Tumour grade	NA	NA	G1: 18 (45%), G2: 14 (35%), G3: 8 (20%),	All high-grade
pT stage	NA	NA	pT1: 18 (45%), pT2: 14 (35%), pT3: 8 (20%)	pT1: 3 (10%), pT2: 12 (40%), pT3: 15 (50%)

International Federation of Gynecology and Obstetrics (FIGO) guidelines. Tumor-infiltrating lymphocytes (TILs) were assessed using the International TILs Working Group recommendations. Clinical variables extracted for each patient included age, menopausal status, comorbidities (hypertension, diabetes, obesity), and specimen type (hysterectomy or curettage). Tumours were not assessed for MSI/neoantigen burden because MSI testing was not available in all archival cases; this limitation is acknowledged in the Discussion.

Immunohistochemistry (IHC) was performed to evaluate the immune microenvironment using Leica Bond-Max automated staining system on 4-µm thick FFPE sections. The following primary antibodies were used (see Table 1).

Antigen retrieval was performed for all antibodies using citrate buffer (pH 6.0) at 95 °C for 20 min. Detection was achieved using the DAB chromogen (3,3′-diaminobenzidine) system, and counterstaining was performed with hematoxylin. Negative controls (without primary antibody) were included in each batch.

Whole slide imaging (WSI) was done using a Motic scanner at 40× magnification. Immune cell quantification was performed in QuPath (v0.4.0), an open-source digital pathology tool. The analysis included: 1. Tumor-stroma segmentation using QuPath's AI classifier; 2. Region annotation, with the peritumoral (PT) area defined as 500 µm around the tumor; 3. Automated immune cell detection based on colour deconvolution and cell morphology; 4. Immune cell density calculation (cells/mm^2) in intratumoral (IT) and PT regions; 5. IT/PT ratio analysis to evaluate immune exclusion or enrichment (Fig. 1). IT – intratumoral; PT – peritumoral.

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Tbilisi State Medical University. Because it was retrospective, informed consent was waived.

RESULTS

The study cohort comprised 150 endometrial tissue specimens, stratified into four histopathological categories: Endometrial Hyperplasia without Atypia (n=40), Endometrial Hyperplasia with Atypia (n=40), Endometrioid Carcinoma (n=40), and Serous Carcinoma (n=30). Specimens were obtained from hysterectomy and curettage samples archived at the Tbilisi State Medical University Scientific and Research Laboratory from 2015 to 2025.

Immune microenvironment analysis across histological groups: Quantitative assessment of immune markers (CD3, CD4, CD8+ Intra-Tumoral, CD8+ Peri-Tumoral, FOXP3, M1 CD68+/iNOS, and M2 CD163+) revealed distinct immunophenotypic profiles among endometrial lesions. CD3+ and CD8+ T cell densities exhibited a stepwise increase from hyperplasia without atypia to invasive carcinoma, whereas FOXP3+ regulatory T cells were enriched in neoplastic conditions, particularly hormone receptor-positive cases (Fig.4A–D).

CD8+ T cell distribution in intratumoral vs. peritumoral compartments: The mean intratumoral (IT) and peritumoral (PT) CD8+ T cell densities (cells/mm^2) were as follows: Endometrial Hyperplasia without Atypia: IT = 0.00, PT = 0.63; Endometrial Hyperplasia with Atypia: IT = 1.75, PT = 2.50; Endometrioid Carcinoma: IT = 15.30, PT = 18.33; Serous Carcinoma: IT = 8.63, PT = 10.87

A statistically significant increase in CD8+ IT and PT densities was detected in malignant lesions compared to hyperplastic conditions (P<0.001). Notably, in hyperplastic lesions, CD8+ T cells are preferentially localised within the peritumoral compartment, suggesting a pattern of immune exclusion. In contrast, endometrial carcinoma cases demonstrated higher IT/CD8+ densities, reflecting a shift toward a more immunologically active tumour microenvironment (Fig. 3).

Due to low case numbers in some subgroups, several

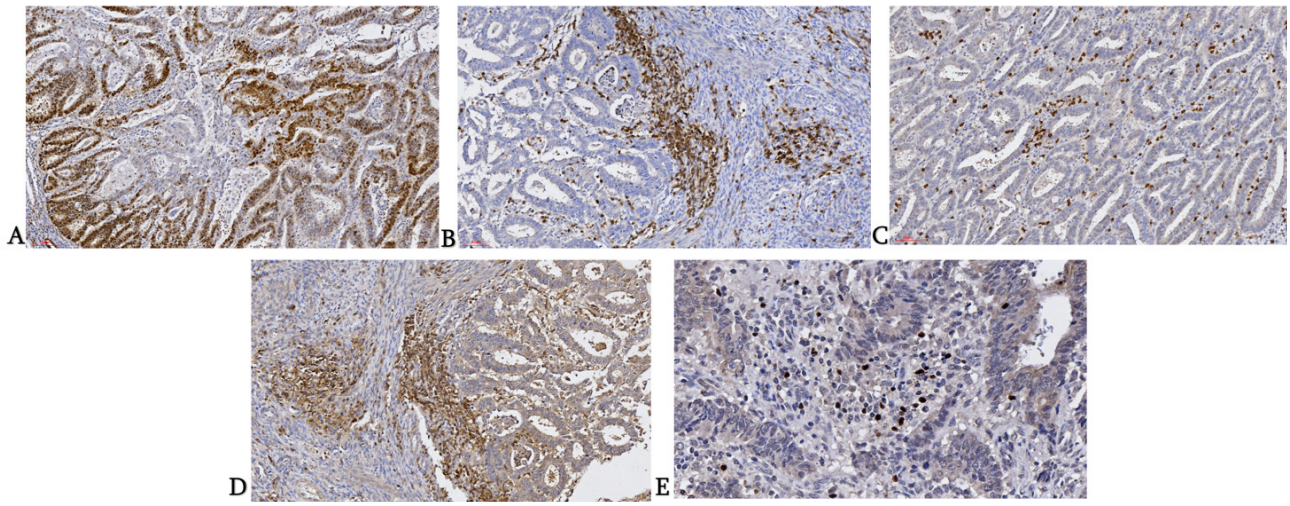


Fig. 1. Immunohistochemical characterization of hormonal receptor expression and immune cell infiltration in endometrial carcinoma. **A.** Diffuse strong nuclear expression of progesterone receptor (PR) in neoplastic glandular epithelium; **B.** $CD3^+$ T-lymphocyte infiltration within the peritumoral stroma and tumor nests; **C.** $CD8^+$ cytotoxic T-cell infiltration within the tumor microenvironment; **D.** $CD4^+$ T-helper lymphocytes distributed in stromal and invasive front compartments; **E.** $FOXP3^+$ regulatory T cells identified within the tumor microenvironment at higher magnification. Magnification: ×200 for panels A–D; ×400 for panel E.

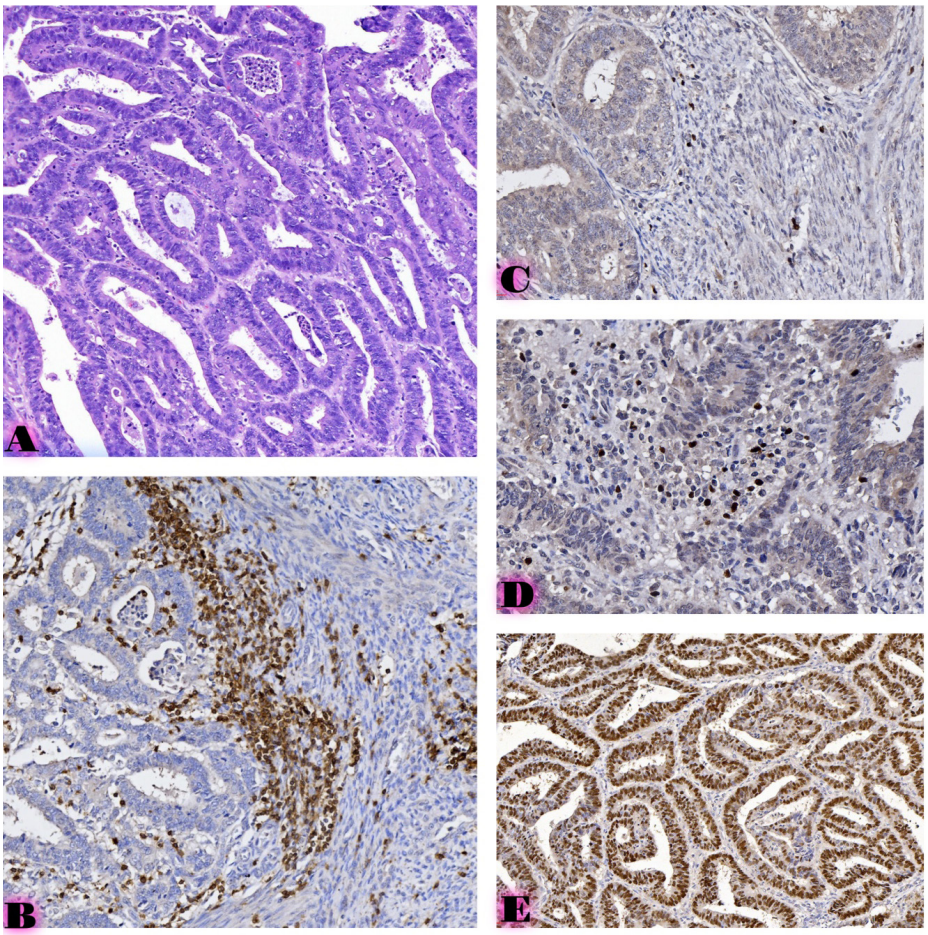


Fig. 2. Representative histopathology and immune marker expression in endometrial lesions. **A.** Endometrioid Carcinoma, FIGO Grade II, H&E, 150×; **B.** CD3+ T-cell expression in Endomerioid Carcinoma, 100×; **C.** FOXP3+ T-cell infiltration in Endomerioid Carcinoma, 400×; **D.** FOXP3+ expression in atypical hyperplasia, 400×; **E.** Estrogen receptor (ER) expression in Endomerioid Carcinoma, 200×.

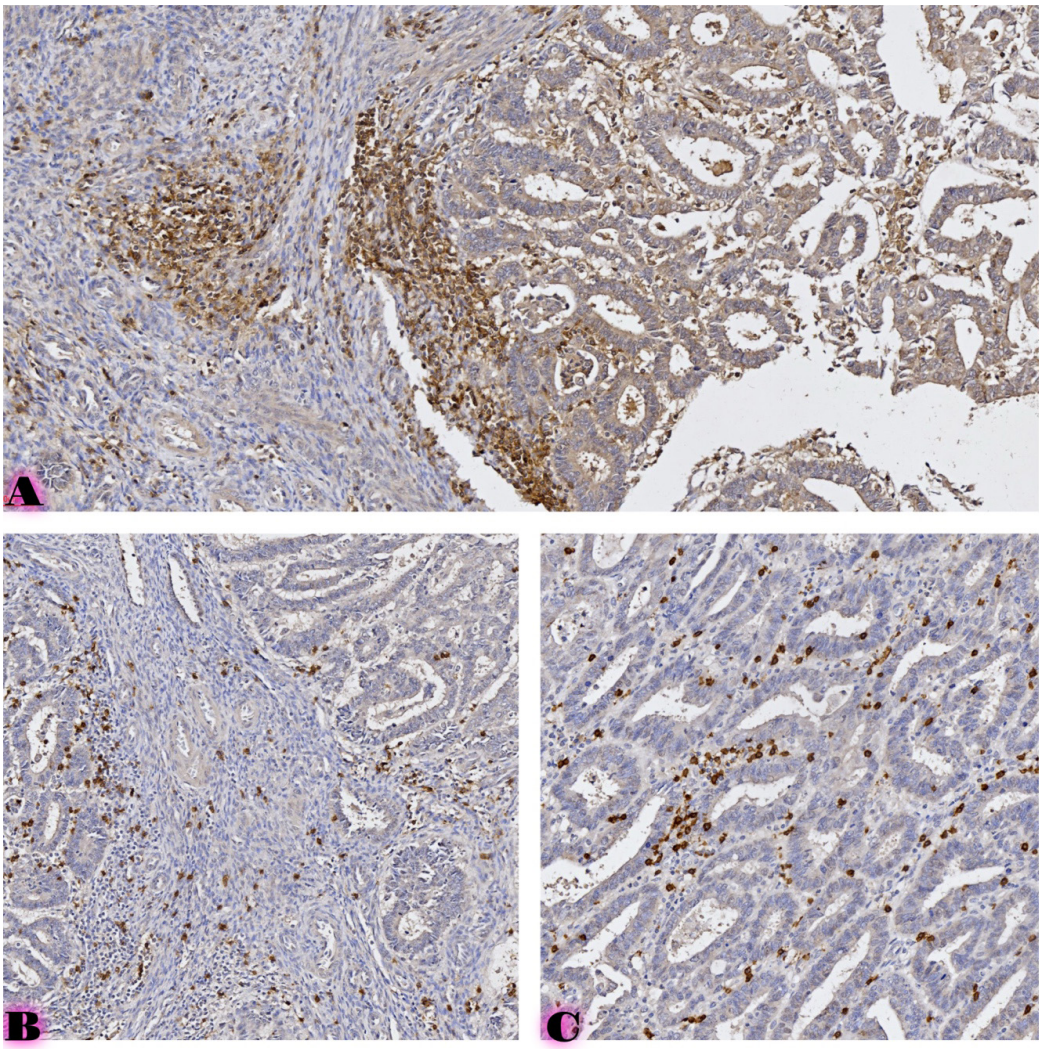


Fig. 3. CD8+ T-cell spatial distribution across compartments. **A.** CD4+ T-cell expression in Endometrioid Carcinoma, 200×; **B.** Peritumoral CD8+ T-cell expression, 150×; **C.** Intratumoral CD8+ T-cell expression, 200×.

values appear as outliers; therefore these findings should be interpreted cautiously.

These findings suggest that a subset of endometrial hyperplasia cases that progress to carcinoma retain peritumoral immune exclusion patterns despite the transition to malignancy, potentially impacting immune surveillance and therapeutic response.

Correlation Between Immune Markers and Hormonal Receptor Expression (ER, PR): CD8+ IT and PT densities exhibited a significant inverse correlation with ER and PR expression (r=−0.76, P<0.001), suggesting a link between estrogen signalling and diminished cytotoxic immune infiltration.

A subset of 27 cases with a prior history of endometrial hyperplasia (with or without atypia) and subsequent diagnosis of endometrioid carcinoma was analysed separately. The mean CD8+ IT density was 13.8 cells/mm^2, whereas the mean CD8+ PT density was 21.2 cells/mm^2, indicating that residual immune exclusion may persist in some cases even after progression. FOXP3+ T cell density demonstrated a moderate positive correlation with ER and PR expression (r=0.50–0.56, P<0.001), suggesting a role in hormone-mediated immune suppression. M2 CD163+ macrophages exhibited an inverse correlation with ER expression (r=–0.49, P <0.01) reinforcing their role in immune modulation during disease progression.

M1 CD68+/iNOS macrophages showed no strong association with ER/PR, whereas M2 CD163+ macrophages demonstrated a negative correlation with ER expression (r=−0.49, P<0.01), indicating potential immune escape mechanisms mediated by tumor-associated macrophages.

These findings indicate that CD8+ T cell infiltration significantly increases in malignant lesions, transitioning from peritumoral immune exclusion in hyperplasia to robust intratumoral infiltration in carcinoma.

A subset of endometrial hyperplasia cases that progress to carcinoma exhibit persistent immune exclusion, characterised by higher peritumoral CD8+ densities.

FOXP3+ regulatory T cells are enriched in ER/PR-positive tumours, supporting a role in hormonal modulation of immune suppression.

M2 macrophages exhibit an inverse relationship with ER expression, suggesting their potential role in shaping the immunosuppressive tumour microenvironment. (Fig. 5A–C).

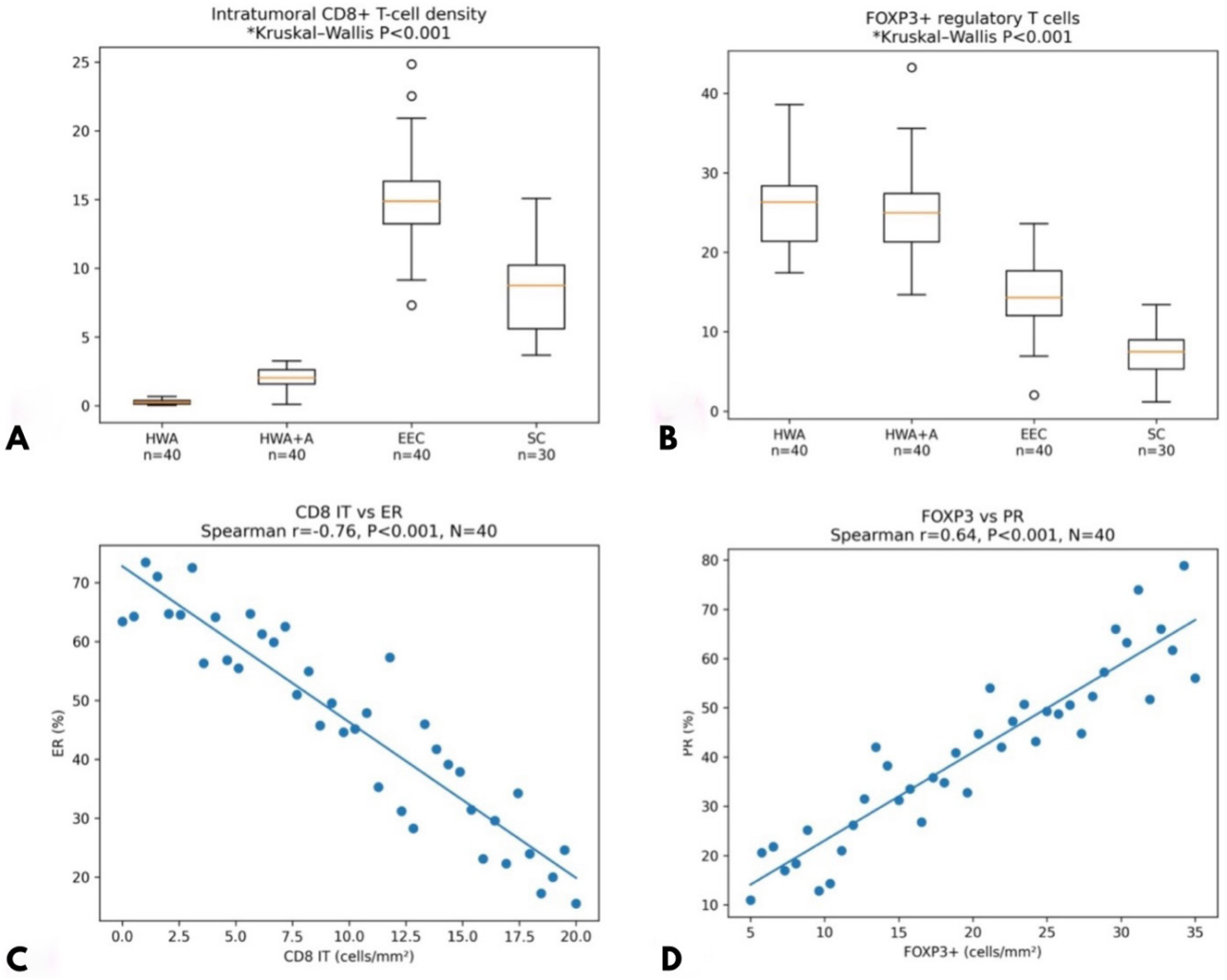


Fig. 4. Quantitative immune marker analyses. **A.** Intratumoral CD8+ T-cell density across histological groups; **B.** FOXP3+ regulatory T-cell densities across histological groups; **C.** Correlation between CD8+ intratumoral density and ER expression; **D.** Correlation between FOXP3+ T-cell density and PR expression. Boxplots show median and interquartile range; whiskers indicate minimum–maximum values. Group comparisons were performed using Kruskal–Wallis test with Dunn's post hoc correction. Correlations were assessed using Spearman's rank test. Regression lines are shown. Sample sizes (n), *P* values, and statistically significant differences (**P*<0.05) are indicated.

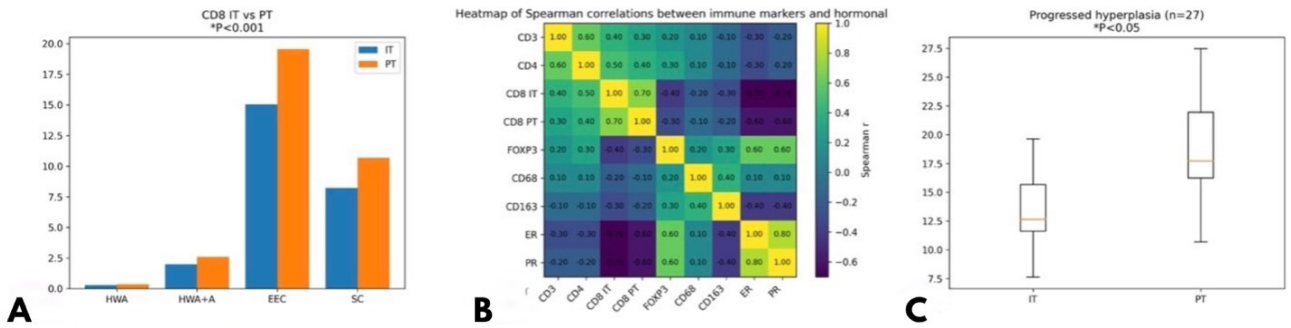


Fig. 5. Immune exclusion and correlation heatmap. **A.** Comparison of CD8+ intratumoral (IT) and peritumoral (PT) densities across lesions; **B.** Heatmap of Spearman correlation coefficients between immune markers and hormonal receptors; **C.** IT vs PT CD8+ density in hyperplasia cases that progressed to carcinoma (n=27).
Bars represent mean values. Statistical significance is indicated (**P*<0.05). In panel A, comparison of $CD8^+$ intratumoral (IT) versus peritumoral (PT) densities across diagnostic groups demonstrated a statistically significant differenc e (*P*<0.001, Kruskal–Wallis test with Dunn's post hoc correction).

DISCUSSION

Endometrial neoplastic progression is closely tied to dynamic alterations within the immune microenvironment, which varies across molecular subtypes and influences clinical behavior[1]. Our findings demonstrate a stepwise shift in immune composition from hyperplasia to carcinoma, characterized by increasing FOXP3$^+$ regulatory T-cell infiltration, variable CD8$^+$ penetration, and enhanced macrophage polarization – features consistent with previously described immunosuppressive profiles in endometrial cancer[1,4,5]. These findings provide novel insights into the immunological landscape of endometrial lesions and highlight potential biomarkers for disease progression risk stratification. Further investigations incorporating functional immune assays and transcriptomic profiling are warranted to elucidate the mechanistic underpinnings of immune-tumor interactions in endometrial neoplasia.

Atypical hyperplasia, recognized as a precursor lesion with substantial malignant potential[3], showed partial immune exclusion characterized by peritumoral clustering of CD8$^+$ T cells with limited intratumoral entry. This aligns with proposed immune escape pathways active during early neoplastic transformation[5]. The persistence of immune exclusion in a subset of cases that progressed to carcinoma highlights heterogeneity in immune barrier breakdown and suggests that immune accessibility may differ among lesions with similar morphology.

The role of hormonal signaling in modulating immune infiltration has been increasingly acknowledged. High ER/PR expression has been associated with reduced T-cell infiltration[6], and our results similarly demonstrate an inverse correlation between CD8$^+$ density and hormonal receptor expression. Moreover, ER and PR expression patterns vary across carcinoma subtypes and have been linked to tumor behavior and differentiation[7]. These observations imply that hormonal signaling may contribute to shaping the tumor immune environment, potentially affecting immunogenicity and progression.

FOXP3$^+$ regulatory T cells showed strong positive associations with ER and PR in our cohort, supporting mechanistic data indicating that estrogen receptor activation can directly modulate FOXP3 transcription and Treg function[12]. This immune–hormonal crosstalk may contribute to the potent local immune suppression observed in hormone-responsive disease states. The enrichment of FOXP3$^+$ cells in endometrioid carcinomas relative to serous subtypes further reflects molecular diversity in immune regulation across histologies.

Macrophage polarization also contributes significantly to immune remodeling. M2-like CD163$^+$ macrophages are known to promote angiogenesis, stromal remodeling, and immune tolerance[10], and increased CD163$^+$ density has been associated with clinical outcomes in several malignancies, including gynecologic tumors[13]. In our study, CD163$^+$ macrophage densities inversely correlated with ER expression, suggesting that loss of hormonal signaling may favor an immunosuppressive M2 phenotype. This shift may enhance tumor progression by fostering microenvironments less conducive to cytotoxic immune activity.

Cytotoxic CD8$^+$ infiltration remains a strong prognostic indicator in endometrial carcinoma, with high intratumoral CD8$^+$ density linked to improved outcomes[11]. In our cohort, intratumoral CD8$^+$ cells increased from hyperplasia to carcinoma but displayed significant heterogeneity. Endometrioid carcinomas exhibited higher IT CD8$^+$ levels compared to serous carcinomas, a finding consistent with prior evidence that early-stage, low-grade tumors may elicit stronger cytotoxic responses[9]. Serous carcinomas, conversely, demonstrated greater immune suppression with reduced CD8$^+$ presence despite higher proliferative and mutational potential.

The overall pattern observed, progressive immune suppression, increasing regulatory and macrophage populations, and variable cytotoxic infiltration, aligns with established models of the tumor microenvironment as a suppressive milieu that obstructs antitumor immunity[10]. This framework supports the interpretation that immune remodeling in endometrial cancer is not linear but rather influenced by the interplay of hormonal status, subtype-specific molecular features, and microenvironmental architecture[8].

By integrating proliferative, hormonal, and immune parameters across the continuum from hyperplasia to carcinoma, this study contributes to refining risk stratification and offers insights into mechanisms that may inform therapeutic decision-making. Understanding these transitions may aid in identifying candidates for immunomodulatory or hormone-targeted interventions and enhance prognostic accuracy for patients with endometrial precursor lesions.

CONCLUSION

This study demonstrates a transition from immune exclusion in hyperplasia to increased intratumoral immune infiltration in carcinoma, although this shift is not universal. A subset of progressing lesions maintains persistent exclusion, suggesting variability in immune accessibility that may depend on molecular subtype or stromal architecture. Hormone receptor–positive tumours exhibit enriched FOXP3+ Tregs and CD163+ macrophages, indicating possible, but not definitive, hormonal modulation of immune suppression. These findings suggest potential biomarkers for progression risk and support further investigation into therapeutic strategies combining hormonal modulation and immune-based therapy.

ABBREVIATIONS

CD, Cluster of Differentiation; EEC, Endometrioid Endometrial Carcinoma; ER, Estrogen Receptor; FOXP3, Forkhead Box P3; HWA, Hyperplasia Without Atypia; HWA+A, Hyperplasia With Atypia; IHC, Immunohistochemistry; IT, Intratumoral; PR,

Progesterone Receptor; PT, Peritumoral; SC, Serous Carcinoma; TILs, Tumor-Infiltrating Lymphocytes.

Author contributions: PJ: conceptualisation of the study, supervision of research workflow, and critical revision of the manuscript for important intellectual content; ZB: methodological guidance, histopathological evaluation, and verification of diagnostic accuracy across all included cases; GB: study design oversight, interpretation of immunohistochemical findings, and scientific editing of the manuscript; SK: data collection, digital pathology analysis, statistical analysis, preparation of figures and tables, and drafting and finalising the manuscript.

Conflict of interest statement: The authors declare no conflicts of interest.

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