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Current and Emerging Prognostic Biomarkers in Endometrial Cancer

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Endometrial cancer is the most common gynaecological malignancy in high income countries and its incidence is rising. Whilst most women with endometrial cancer are diagnosed with highly curable disease and have good outcomes, a significant minority present with adverse clinico-pathological characteristics that herald a poor prognosis. Prognostic biomarkers that reliably select those at greatest risk of disease recurrence and death can guide management strategies to ensure that patients receive appropriate evidence-based and personalised care. The Cancer Genome Atlas substantially advanced our understanding of the molecular diversity of endometrial cancer and informed the development of simplified, pragmatic and cost-effective classifiers with prognostic implications and potential for clinical translation. Several blood-based biomarkers including proteins, metabolites, circulating tumour cells, circulating tumour DNA and inflammatory parameters have also shown promise for endometrial cancer risk assessment. This review provides an update on the established and emerging prognostic biomarkers in endometrial cancer.

Keywords: endometrial cancer, prognosis, biomarkers, risk stratification, treatment

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INTRODUCTION

Endometrial cancer is the sixth most frequently diagnosed cancer in females and the gynaecological malignancy with the greatest incidence in high-income countries. In 2020, there were an estimated 417,000 incident cases and 97,000 deaths from the disease worldwide (1). The incidence of endometrial cancer is rising alongside the growing obesity epidemic (2). In the United Kingdom (UK), there are around 9,700 cases and 2,400 endometrial cancer-associated deaths every year (3). Over the last decade, deaths have increased by 25%, a trend that has been reported in other high income countries. It is projected that mortality rates for endometrial cancer will rise by a further 19% in the UK between 2014 and 2035, despite improvements in overall survival (3).

Most endometrial cancers are sporadic, with an estimated 5% occurring in the context of a hereditary predisposition, most commonly Lynch syndrome (4). Lynch syndrome is an autosomal dominant condition that arises from a defect in the DNA mismatch repair (MMR) system, predisposing to a constellation of malignancies, including endometrial cancer (5). There are currently no evidence–based screening options for endometrial cancer in either the general population or in high-risk women (6). Most women are diagnosed following routine investigations for post-menopausal bleeding, the cardinal symptom of the disease. In current

clinical practice, symptomatic women are investigated by sequential tests that include transvaginal ultrasound scan, endometrial biopsy and hysteroscopy (7). Most women with endometrial cancer are diagnosed at an early stage and have highly curable disease, reflected in excellent 5-year survival rates (3). A significant minority present with adverse clinico-pathological characteristics including biologically aggressive endometrial cancer phenotypes, and have a poor prognosis. The management of endometrial cancer is primarily surgery, with total hysterectomy and bilateral salpingo-oophorectomy as standard of care worldwide. Women with high-risk features are offered adjuvant therapy with chemotherapy and/or radiotherapy, aimed at reducing risk of recurrence (8). A significant minority are managed conservatively including those of reproductive age or those for whom surgery carries considerable risk such as the frail or medically unfit (7).

Identifying those with endometrial cancer at highest risk of recurrence and cancer-related death is important to ensure women receive appropriate evidence-based care whilst avoiding the harms and costs of unnecessary treatments for those at lowest risk. Clinical, sociodemographic, histopathological and molecular factors all impact on endometrial cancer outcomes (9). A validated risk-stratification model that accurately defines risk of disease recurrence and death will guide clinical care by allowing for treatment de-escalation for those at lowest risk and intensification for those at high risk (10). Such a model may also help define the optimal follow-up programme for recurrence and guide decisions regarding alternative primary treatments for the fraction of women who are managed conservatively. This review provides an update of the current and emerging prognostic biomarkers and risk-stratification algorithms in endometrial cancer. Further, we highlight the challenges in clinical translation and offer fresh perspectives on endometrial cancer biomarker research.

CURRENT ENDOMETRIAL CANCER PROGNOSTIC BIOMARKERS

What Are Prognostic Biomarkers?

Prognostic biomarkers are clinical or biological characteristics that can be objectively assessed and evaluated to predict the course of a disease regardless of therapy (11). Prognostic biomarkers are used in clinical practice to identify the likelihood of a clinical event (mortality, disease recurrence or progression) occurring amongst those with the condition of interest (12, 13). Examples of prognostic biomarkers include clinical, tumour specific molecular and histopathological characteristics.

Bokhman Dualistic Model of Endometrial Cancer

In 1983, Bokhman proposed a dualistic model of endometrial cancer based on clinical, epidemiologic and prognostic features (14). Type I tumours are by far the most common and are low-grade, oestrogen driven tumours that are associated with obesity and have a favourable prognosis. By contrast, type II tumours are relatively rare, high-grade, biologically aggressive tumours that are more common in healthy weight women and act independently of oestrogen (14). This model was of value several decades ago but has been shown to lack sufficient discriminatory ability to justify its continued use in the classification and management of endometrial cancers today (15). For example, ~20% of women with type I endometrial cancer experience a relapse while ~50% of those with type II do not, suggesting that the precision with which this dualistic model guides receipt of adjuvant therapy is moderate at best (16).

Histopathological Biomarkers and Current Risk Stratification Algorithms

Histological subtype, FIGO stage, disease grade, presence of lympho-vascular space invasion (LVSI) and deep myometrial invasion are established prognostic biomarkers in endometrial cancer (17) (**Figure 1**). The histological subtypes of endometrial cancer include endometrioid tumours, which have a favourable prognosis, and non-endometrioid tumours (serous, clear cell, carcinosarcomas and mixed), which are biologically aggressive and associated with poor outcomes. Endometrioid tumours make up over 80% of newly diagnosed endometrial cancers, while serous, clear cell and carcinosarcomas make up 10%, 3% and <2% respectively (18, 19). Low grade endometrioid tumours are type I and high grade endometrioid and non-endometrioid histological subtypes are type II tumours. The mutational profiles of the different histological subtypes vary. *PTEN* mutations portend a favourable prognosis are more common in endometrioid endometrial cancers, while *TP53* mutations are associated with a poor prognosis and are common in serous tumours (20). Surgical staging provides important prognostic information in the management of endometrial cancer and is based on the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system (21) (**Table 1**). Women with early stage (FIGO I/II) endometrial cancer have a favourable prognosis compared to those with advanced disease (FIGO III/IV). The 5-year survival rate is >90% in early stage disease and <20% in late stage disease (17, 21). Disease grade is also an important prognostic parameter (22). Studies have been consistent in suggesting a correlation between tumour grade and depth of myometrial invasion, presence of extra-uterine disease and lymph node metastasis (23). Depth of myometrial invasion is a component of FIGO staging for stage I tumours and is an independent predictor of endometrial cancer outcomes across all stages. A recent meta-analysis of 79 studies involving 68,870 women concluded that deep myometrial invasion is associated with high endometrial cancer recurrence risk and poor outcomes (24). LVSI is also an important prognostic parameter, being linked to an increased risk of nodal spread, disease recurrence and poor outcomes (25, 26).

Current endometrial cancer risk stratification is based on a consensus algorithm by the three major endometrial cancer consortiums: European Society for Medical Oncology, European Society of Gynaecological Oncology, and European Society for radiotherapy & Oncology (ESMO, ESTRO and ESGO) (8). This was recently updated by ESGO, ESTRO and the European Society

TABLE 1 | FIGO staging of endometrial cancer (21).

FIGO Staging	Carcinoma of the endometrium
Stage I	Tumour confined to the uterus
IA	No or <50% myometrial invasion
1B	≥50% myometrial invasion
Stage II	Cervical stromal invasion, but not beyond the uterus
Stage III	Local and/or regional tumour spread
IIIA	Tumour invades serosa and/or adnexa
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastases to pelvic and/or para-aortic lymph nodes
IIIC1	Pelvic node involvement
IIIC2	Para-aortic lymph node involvement ± positive pelvic lymph nodes
Stage IV	Tumour invades bladder and/or bowel, and/or distant metastases
IVA	Tumour invasion of bladder and/bowel mucosa
IVB	Distant metastases including abdominal metastases and/inguinal nodes

Adapted based on the 2009 revised staging by the FIGO Committee on Gynecologic Oncology.

of Pathology (ESP) to also include prognostic risk groups where endometrial cancer molecular classification information(described in detail in section 3.0) is known (27). Women are classed as low, intermediate, high-intermediate, high -risk and advanced metastatic based on histological subtype, FIGO stage, and grade, depth of myometrial invasion, presence of LVSI and molecular grouping (27) (**Table 2**). The classification system based on histopathological parameters is used to guide receipt of adjuvant treatment but has been shown to have sub-optimal ability in defining endometrial cancer outcomes (9, 28). Histological subtype and grade have poor reproducibility even amongst expert pathologists, while FIGO stage and LVSI are only available post-hysterectomy, and thus cannot inform decisions regarding surgical management (29–31). A pathology review of patients with high-risk endometrial cancer as part of the PORTEC-3 trial found significant disagreement in the assignment of several risk defining parameters including histological subtype, grade, cervical stromal invasion, LVSI and depth of myometrial invasion (32). It is therefore not surprising that the currently used risk-stratification algorithm leads to imprecise estimation of the risk of recurrence and death in women with endometrial cancer (33). Furthermore, a small minority of women with endometrial cancer are managed conservatively for fertility-sparing and surgical fitness reasons, and so cannot be surgically staged. Imaging with MRI +/-CT are limited in their ability to define risk stratifiers. Novel prognostic biomarkers that guide decisions regarding the type and suitability of alternative primary treatments in this group of women has the potential to transform patient care.

EMERGING ENDOMETRIAL CANCER PROGNOSTIC BIOMARKERS

TCGA Endometrial Cancer Molecular Classification

Molecular subtyping offers a more objective and reproducible classification of endometrial cancer when compared with histopathological evaluation and has the potential to revolutionise patient care (33). Recently, the TCGA proposed four distinct endometrial cancer molecular subgroups based on mutational burden, microsatellite instability and copy number alterations observed in 373 endometrial cancer cases: copy number high, copy number low, MSI hypermutated, and *POLE* ultra-mutated (34) (**Table 3**). This classification has been validated in subsequent studies and shown to have prognostic and therapeutic implications (29, 38–41).

The copy number high (serous-like) cancers have the worst progression-free survival and are characterised by widespread genomic alterations with extensive copy number aberrations (34, 35). Patients in this subgroup have mostly high-grade and

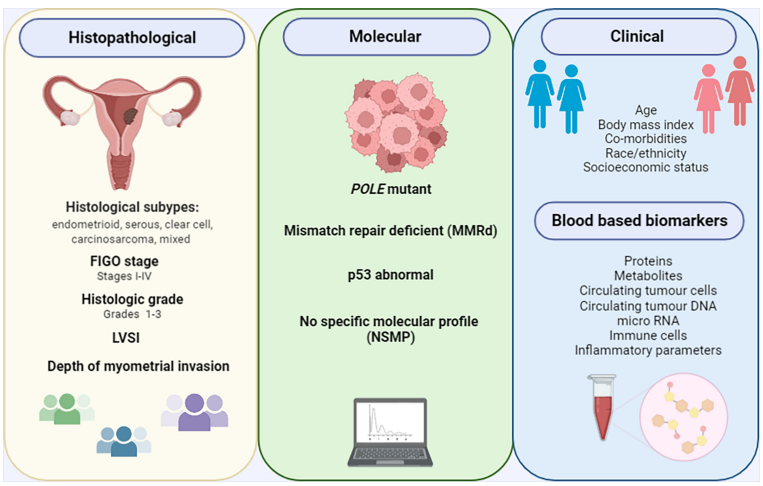

FIGURE 1 | Current and emerging endometrial cancer prognostic biomarkers.

TABLE 2 | Updated ESMO, ESTRO and ESGO endometrial cancer risk stratification algorithm (27).

Risk group	Molecular classification unknown	Molecular classification known
Low	• Stage IA endometrioid + low-grade + LVSI negative or focal	• Stage I–II ***POLE***-mutant endometrial carcinoma, no residual disease • Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade + LVSI negative or focal
Intermediate	• Stage IB endometrioid + low-grade + LVSI negative or focal • Stage IA endometrioid + high-grade + LVSI negative or focal • Stage IA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion	• Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade + LVSI negative or focal • Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade + LVSI negative or focal • Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High-intermediate	• Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion • Stage IB endometrioid high-grade regardless of LVSI status • Stage II	• Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion • Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade regardless of LVSI status • Stage II **MMRd/NSMP** endometrioid carcinoma
High	• Stage III–IVA with no residual disease • Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	• Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease • Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease • Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	• Stage III–IVA with residual disease • Stage IVB	• Stage III–IVA with residual disease of any molecular type • Stage IVB of any molecular type

Focal LVSI refers to the presence of a single focus around the tumour. Key: p53abn, p53-abnormal; MMRd, MMR-deficient; NSMP, no specific molecular profile.

biologically aggressive tumours including serous endometrial cancers and 25% of the grade 3 endometrioid tumours (34, 35). Mutations commonly observed in copy number high tumours include those in *TP53* and *PIK3CA*. Other mutations involving *FBXW7* and *PPP2RIA* are unique to copy number high tumours (34). Amplifications of *CCNE1* and *ERBB2* are also commonly observed (42, 43).

Copy number low endometrial cancers have few copy number aberrations and no increased mutation burden.They comprise low grade, microsatellite stable, endometrioid tumours (34, 35). Whilst tumours in this subgroup generally have a favourable prognosis, they have specific unique molecular features that are associated with poor prognosis, namely *CTNNB1* mutations and amplification of chromosome arm1q, thus making the group an interesting one for future stratified clinical trials (44, 45).

Microsatellite instable endometrial cancers have mismatch repair deficiency (MMR-d), high mutation rates and few copy number aberrations (34). They are characterised by mutations or epigenetic silencing affecting the MMR genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Other commonly mutated genes in this subgroup include *PTEN*, *ARIDIA*, *PIK3CA*, *PIK3RI*, and *RPL22* (34, 35). These tumours are usually endometrioid although their histological morphology can be unusual, making characterisation challenging (35).

The final subgroup of the TCGA classification is the *POLE* ultra-mutated group. This subgroup is characterised by high mutation rates and hotspot mutations in the *POLE* exonuclease domain (EDM) of polymerase-ε (34). *POLE* ultra-mutated tumours exhibit few copy number aberrations and have mutations in *PTEN, PIK3RI, PIK3CA, FBXW7* and *KRAS* genes. These tumours have an excellent prognosis with the best progression free survival (46). They are characterised by dense immune cell infiltrates. Whilst previously thought not to recur, there is emerging evidence that the *POLE* tumours can recur but at a much lower rate compared to other molecular subtypes (35, 46). The recent proteogenomic characterisation of endometrial cancer by the National Cancer Institute's Clinical Proteomic Tumour Analysis Consortium (CPTAC) provides further insights into the proteomic markers of endometrial cancer clinical and genomic tumour subgroups (47).

Whilst the TCGA classification substantially advanced our understanding of the molecular diversity of endometrial cancer and the associated prognostic implications, its clinical applicability in terms of refining surgical staging, guiding decisions about adjuvant therapy and intensity of post-treatment surveillance is limited (35). Barriers include the need for fresh-frozen tumour specimens, high costs and technical and methodological complexities.

Simplified and Pragmatic Endometrial Cancer Molecular Classifiers

Novel molecular classification tools have been developed and validated based on the use of surrogate markers to define four distinct subgroups of endometrial cancer that are analogous but not identical to the TGCA classification (40). The classifiers include the TransPORTEC (48) and ProMisE models (49).These novel classifiers utilise immunohistochemistry to identify MMR and p53 abnormalities and targeted sequencing to identify *POLE* mutations (40, 48). In contrast to the fresh-frozen tumour specimens required for TCGA classification, these pragmatic classifiers can be used on formalin-fixed, paraffin-embedded tumour materials, thus enhancing their clinical utility (29). There is good evidence to support their potential applicability to endometrial biopsy and curettage diagnostic specimens (50–

52) and the inter laboratory concordance is high (51). Studies have been consistent in confirming the prognostic value and potential clinical utility of these classifiers across unselected patient populations (53–56).

In the TransPORTEC initiative, the four molecular subgroups are p53-abnormal, MSI-high, *POLE*-mutant and those with no specific molecular profile (NSMP) (48) (**Figure 2A**). Of 116 high-risk endometrial cancer specimens analyzed by the TransPORTEC group, p53-abnormal (n=36) and NSMP (n=44) subgroups had significantly higher rates of distant metastases and lower 5-year relapse free survival than MSI-high (n=19) and *POLE*-mutant (n=14) tumours (48) (**Table 4**). The 5-year recurrence-free survival rates were 93% and 95% for the *POLE*-mutant and MSI-high subgroups respectively, compared with 42% (p53-abnormal) and 52% (NSMP) (48). A refined version of the TransPORTEC classifier has since been developed that incorporates the presence of LVSI and other molecular parameters such as L1CAM expression and the presence of *CTNNB1* mutation (57). This model is being prospectively tested in a cohort of women with high-to-intermediate risk endometrial cancer as part of the PORTEC-4a trial.

ProMisE stratifies women with endometrial cancer based on sequential molecular testing for aberrations in the order of MMR-D, *POLE* mutation and p53 status (**Figure 2B**). The four molecular groupings based on ProMisE are MMR-deficient (MMRd; analogous to MSI-high subgroup), *POLE EDM* (analogous to *POLE* ultramutated), p53-abnormal (p53 abn, analogous to the copy number high group) and p53-wild type (p53 wt, analogous to the copy number low group) (40, 49). These molecular subgroupings have also been shown to correlate with disease-free and overall survival even after adjusting for known risk parameters (35, 49). Women in the p53 abn group have the worst prognosis with a 3- to -5 fold higher risk of mortality or progressive/recurrent disease than the p53 wt group, and a 2-fold higher risk following adjustment for clinico-pathological parameters (35, 49). Those in the MMR-D subgroup have a 1.5 to 2-fold increase in mortality compared with the p53 wt subgroup; the survival benefit was non-significant following adjustment for confounding. The *POLE* EDM subgroup have the best prognosis and are least influenced by clinico-pathological features (35, 49).

Other Molecular Prognostic Parameters and Risk Algorithms

Other molecular parameters that are prognostic in endometrial cancer include overexpression of L1CAM and loss of oestrogen (ER) and/or progesterone receptors (PR), both of which are linked to a higher risk of recurrence and death (58–61). L1CAM expression strongly correlates with non-endometrioid histology, LVSI and lymph node metastasis (58). Loss of ER/PR expression is linked to high-grade disease, deep myometrial invasion and lymph node metastasis (62). DJ-1 protein distinguishes low-grade from high-grade endometrial cancer (63) while *CTNNBI* mutations have shown potential in identifying those low-grade, early stage, endometrial cancers at higher risk of recurrence and death (44).

A number of risk-prediction models, incorporating clinical, histological and molecular parameters, have been developed to aid prediction of survival outcomes in endometrial cancer. ENDORISK, a validated risk algorithm based on four pre-operative molecular markers, namely L1CAM, PR, ER, and p53 status, predicted risk of lymph node metastasis and survival in a multi-centric cohort of 763 women with endometrial cancer

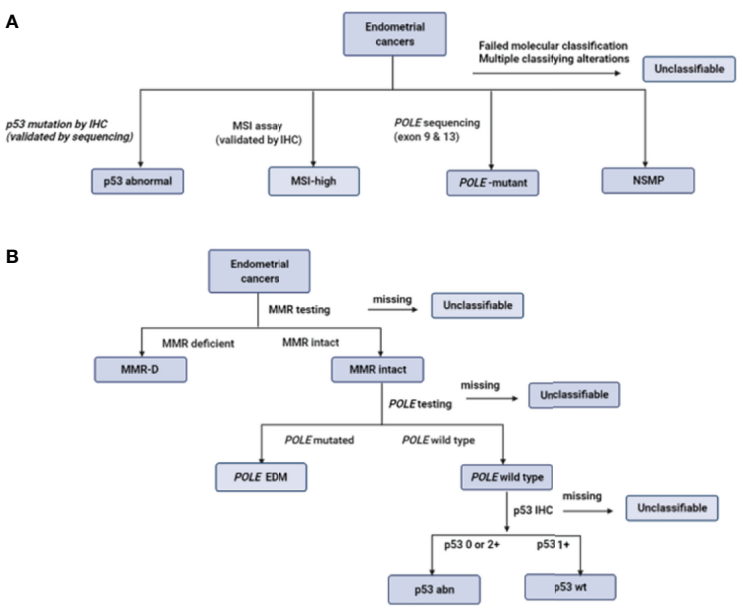

FIGURE 2 | Defining the molecular subgroups of endometrial cancer based on the TransPORTEC classifier **(A)** and ProMisE **(B)**. Adapted from (48, 49, 51).

TABLE 3 | Characteristics of the TCGA molecular classification of endometrial cancer.

Type	*POLE* (ultramutated)	MSI (hypermutated)	Copy number low (endometrioid)	Copy number high (serous like)
Prevalence	7%	28%	39%	26%
Mutation frequency	Very high (>100 mutations/Mb)	High 100-10 mutations/Mb	Low <10 mutations/Mb	Low <10 mutations/Mb
Commonly mutated genes	*POLE* (100%), *PTEN* (94%)	*PTEN* (88%) *PIK3CA* (54%)	*PTEN* (77%) *CTNNB (52%)*	*TP53* (92%) *PIK3CA (47%)*
Copy number aberrations	Very low	Low	Low	High
MSI/*MLH1* methylation	Mixed high and low MSI, stable	High MSI (*MLH1*, *PMS2*, *MSH2*, and/or *MSH6* deficiency)	MSI stable	MSI stable
Histological subtype	Endometrioid	Mostly endometrioid	Endometrioid	Serous, 25% high-grade endometrioid and mixed
Grade	G1-3	G1-3	G1-2	G3
Other features	Ambiguous histo-morphology Dense immune infiltrates	Display tumour-infiltrating lymphocytes	*CTNNB* mutations are associated with poor prognosis Subgroup with amplification of chromosome arm 1q has poor prognosis	Similar to high-grade serous ovarian carcinoma L1 cell adhesion molecule (L1CAM) expression associated with poor prognosis
Prognosis	Good	moderate	moderate	Poor

Adapted from (35–37).

across Europe, and 2 independent cohorts from the Netherlands and Norway (64). In a similar study, a model incorporating L1CAM, PR, ER and p53 status demonstrated a 48% sensitivity and 89% specificity for high-risk endometrial cancer (65). Ravegnini and colleagues found better stratification of NSMP patients with *CTNNB1* mutation alongside miR-499a-5p status (66).

Therapeutic Implications and Additional Benefits of the Molecular Classification of Endometrial Cancer

The molecular classification of endometrial cancer has prognostic and therapeutic implications. The p53-abnormal endometrial cancers are the most biologically aggressive and would ideally be managed with complete/aggressive surgical treatment. These tumours generally require adjuvant treatment. A retrospective molecular analysis of the PORTEC-3 trial for high-risk endometrial cancer confirmed that women with p53-abnormal endometrial cancer had significantly improved recurrence-free survival when platinum-based chemotherapy was used alongside radiation, compared with radiation alone (67). This survival benefit was not observed in the other molecular categories, although the PORTEC-3 trial was not originally powered for these subgroup analyses (67). The finding of several molecular similarities between the TCGA p53 endometrial cancer group and both high grade serous tubo-ovarian cancer (HGSOC) and basal-like breast cancer, has sparked interest in the potential for therapeutics that target homologous recombination in these tumours (33, 34). A number of clinical trials assessing the efficacy of PARP inhibitors alone or in combination with anti-angiogenics/immune checkpoint inhibitors for recurrent or metastatic endometrial cancer are under way (68). The TransPORTEC Refining Adjuvant treatment IN endometrial cancer Based On molecular features (RAINBO) suite of clinical trials is evaluating the role of adjuvant chemo-radiation with or without a DNA

TABLE 4 | Prognostic performance of ProMisE and TransPORTEC classifiers, adapted from (49) and (48), respectively.

Subgroups	N (%)	Overall survival		Disease specific survival		Progression free survival	
ProMisE		**HR(95%CI)**	**LRT p**	**HR(95%CI)**	**LRT p**	**HR(95%CI)**	**LRT p**
p53 wt	139 (45.6%)	Comparator group					
MMR-D	64 (20.1%)	1.90 (0.88-4.04)	0.0211	1.32 (0.51-3.35)	0.0156	0.64 (0.25-1.60)	0.011
POLE EDM	30 (9.4%)	1.01(0.26-2.99)		0.42 (0.04-1.88)		0.19 (0.02-0.81)	
P53 abn	86 (27.0%)	2.61 (1.27-5.72)		2.28 (1.02-5.58)		1.75 (0.84-3.96)	
TransPORTEC		**5-year overall survival**		**Distant recurrence rates**		**5-year recurrence free survival**	
NSMP	44 (38%)	61%	<0.001	39%	<0.001	52%	<0.001
MSI-high	19 (16%)	63%		0%		95%	
POLE mutant	14 (12%)	93%		0%		93%	
p53 abnormal	39 (34%)	40%		50%		42%	

ProMisE data are based on multivariable analysis in a validation cohort of 319 cancers. Variables included in model are age, BMI, grade, histology, any treatment received. TransPORTEC data included 116 high risk endometrial cancer patients. HR, hazard ratio; LRP, likelihood ratio test.

damage response targeting agent in women with p53-abnormal endometrial cancer (39). Women with p53 wild type disease have lower metastatic potential and surgical treatment alone may suffice (69). Those with POLE mutant tumours have such a good prognosis that adjuvant treatment is unlikely to improve survival outcomes and de-escalation of therapy may be appropriate. The MMR-D molecular group is highly immunogenic, providing therapeutic opportunities for the use of immunotherapy. Marebella and colleagues, in the KEYNOTE-158 study reported an objective response rate of 57.1% in 49 endometrial cancer patients with previously treated unresectable or metastatic MMR-D disease who were treated with pembrolizumab (70). The GARNET trial, a phase 1b trial of anti-PD1 dostarlimab reported an objective response rate of 42.3% for women with recurrent or advanced MMR-D endometrial cancer that had progressed after treatment with platinum-based chemotherapy (71). Both pembrolizumab and dostarlimab have been FDA approved (71, 72).

The incorporation of endometrial cancer molecular testing into routine clinical care has several additional advantages. It will allow for the early identification of women with an inherited defect affecting one of the four MMR genes (Lynch syndrome) for whom cancer surveillance and aspirin chemoprevention may help to prevent future cancers, and cascade testing may identify other affected family members (5). For women of reproductive age who are considering non-surgical management, molecular classification of endometrial biopsy specimens can guide treatment decisions as p53 abnormal status would discourage a conservative approach to management (69).

BLOOD-BASED ENDOMETRIAL CANCER PROGNOSTIC BIOMARKERS

A blood-based prognostic biomarker has strong appeal to clinicians and patients alike. 'Can a blood test be used in predicting survivorship and/or recurrent disease?' ranked 5th most important research priority in the James Lind Alliance endometrial cancer priority setting partnership, representing the views of patients, clinicians, and members of the general public (73). A blood-based test that can accurately detect deep myometrial invasion and lymph node metastasis pre-operatively could inform surgical management. Such a test may also have utility in risk stratifying within endometrial cancer molecular groups, since women whose tumours fall within MMR-D or NSMP groupings have overlapping survival outcomes and adjuvant therapy may be beneficial for some but not all (74). Several blood-based biomarkers, including proteins, metabolites, circulating tumour cells, cell-free DNA, immune cells and inflammatory parameters have shown potential for refining endometrial cancer risk assessment. However, the evidence to enable clinical translation is limited.

The most commonly reported blood-based protein prognostic markers include cancer antigen 125 (CA125) and Human Epididymis protein 4 (HE4) (75, 76). Serum CA125 was first shown to be elevated in women with recurrent and advanced endometrial cancer by Niloff and colleagues in 1984 (77). Subsequent studies have been consistent in suggesting an association between serum CA125 concentration and adverse endometrial cancer clinico-pathological parameters and outcomes (78–82). Jiang and colleagues, in an analysis of 995 patients with endometrial cancer, found that elevated CA125 significantly correlated with lymph node metastasis, myometrial invasion, FIGO stage but not histological subtype, and was an independent prognostic factor (83). This study was limited by its retrospective design and selection bias, as almost 20% of endometrial cancer patients were excluded due to lack of pre-operative serum CA125 (83). There is good evidence of an association between serum HE4 levels and endometrial cancer outcomes. The meta-analysis by Dai and colleagues, involving 4235 patients, reported that elevated HE4 levels were significantly associated with worse overall, disease-free and progression-free survival (84). Serum HE4 has also been shown to correlate with adverse endometrial cancer histopathological parameters, although the evidence has been limited by marked heterogeneity across the various studies, small sample sizes and significant variation in the prognostic thresholds used (74). Several blood-based metabolites have also been linked to adverse endometrial cancer clinico-pathological factors and poor outcomes (13). As yet, none have been translated into routine clinical practice.

There is emerging evidence of a correlation between circulating cell-free tumour DNA levels and endometrial cancer prognosis (85–88). Cicchillitti and colleagues found elevated levels of cell-free DNA in grades 2 and 3 endometrial cancer compared to grade 1 disease (86). These findings align with the report by Vizza and colleagues of a significantly increased level of total cell-free DNA in high grade endometrial cancer (85). In addition, serum DNA integrity (the ratio between long and short cell free DNA fragments) was found to be higher in women with LVSI (85). Tanaka and colleagues, on the other hand, did not find a significant change in cell-free DNA by endometrial cancer grade or stage (89). Further studies are thus needed to confirm the potential prognostic utility of circulating tumour DNA in endometrial cancer. Circulating tumour DNA have also been suggested as potential tools for the early detection of recurrence in endometrial cancer (88, 90). The small pilot study by Moss and colleagues found that ctDNA could detect endometrial cancer recurrence and progression earlier than imaging or clinical presentation with a median lead time of 2.5 months (88). Specific blood-based tumour mutations have also been associated with endometrial cancer prognosis. Dobrzycka and colleagues found an association between circulating cell-free DNA p53 antibody and *KRAS* mutation status and high-grade endometrial cancer (87). Bolivar and colleagues found a significant association between the presence of plasma ctDNA mutation (*CTNNBI, KRAS, PTEN*, or *PIK3C*) and advanced stage, deep myometrial invasion, LVSI, and primary tumour size (91). Circulating tumour cells have also been linked to endometrial cancer prognosis. Lemech and colleagues, in a feasibility study of 30 patients with advanced endometrial cancer found an association

between circulating tumour cell positivity and non-endometrioid histology, tumour size, disease stage and survival (92). The small prospective study by Bogani and colleagues, involving 28 patients with grade 3 endometrial cancer reported a significant correlation between the presence of circulating tumour cells and deep myometrial invasion and lymph node positivity (93). Studies exploring how best to incorporate circulating tumour markers into routine clinical care are needed.

Systemic inflammatory parameters have shown potential as prognostic biomarkers in endometrial cancer (94). Chronic low-grade inflammation is one of the biological mechanisms underpinning endometrial carcinogenesis. Inflammation is known to damage DNA and potentiates pro-proliferative and anti-apoptotic processes that contribute to tumour development and progression. A recent study from our group found that women with elevated CRP at a decision threshold of 5.5mg/L had a two-fold increase in cancer-specific mortality risk (95). These findings need to be validated in an independent cohort prior to clinical translation. Other inflammatory parameters that are prognostic in endometrial cancer include neutrophil to lymphocyte ratio, monocyte to lymphocyte ratio, systemic inflammatory index, and Glasgow prognostic score (**Table 5**). However, there is insufficient evidence to enable clinical translation at present.

RADIOMIC PROGNOSTIC PROFILING OF ENDOMETRIAL CANCER

Radiomic-based risk-stratification models are emerging prognostic systems in endometrial cancer (118). Radiomics deals with the high-throughput mining of quantitative tomographic image parameters and their application in clinical decision making (119). There is growing evidence for the potential utility of radiomic techniques in improving cancer diagnostic, prognostic and predictive accuracy across various tumour sites (118, 119). This has been made possible by the advances in artificial intelligence and machine learning techniques, thus allowing for an in-depth tumour characterisation. Studies have been consistent in suggesting the potential utility of radiomic signatures in endometrial cancer risk-stratification and prediction of outcomes (118, 120–123). Increasingly, radiomics is combined with genomic data (radiogenomics) to aid the prediction of genetic variants including microsatellite instability. Veeraravaghan and colleagues proposed an integrated radiomic-clinical classification algorithm that distinguishes MMR-D endometrial tumours from copy number low and copy number high tumours with an AUC of 0.78 (121). Chen and colleagues found that an MRI-based radiomic model had better discrimination than clinical and conventional MRI parameters in predicting low risk endometrial cancer (124). Yan and colleagues showed that radiomic based models can aid the prediction of pelvic lymph node metastasis in endometrial cancer (120). A high-quality, robust and generalizable radiomic risk-prediction model is dependent on the optimal collection and integration of data from multimodal sources and rigor in model development and implementation (119, 125).

CLINICAL PARAMETERS AND ENDOMETRIAL CANCER PROGNOSIS

Several clinical parameters have been associated with endometrial cancer survival outcomes. They include age at diagnosis, body mass index (BMI) and the presence of comorbidities (126). Age at diagnosis is universally accepted as prognostic for most adult cancers, with older patients having worse outcomes. In the UK, endometrial cancer mortality rates were highest in women aged 85 to 89 between 2016 and 2018, with over 50% of all endometrial cancer deaths occurring in those aged 75 and over (3). An important consideration is whether this association is purely related to age or other unfavourable prognostic factors that are associated with age (126). Studies have been consistent in reporting an association between advancing age and the presence of adverse tumour related parameters (127–129). For example, Lachance and colleagues studied 396 women with endometrial cancer and reported a higher prevalence of aggressive disease, specifically higher grade, late stage, non-endometrioid endometrial cancers in those >65 years of age (129). In a retrospective analysis of 551 endometrial cancer patients, Son and colleagues found that age ≤40 years was associated with non-invasive cancers, less lympho-vascular space invasion and a higher body mass index (130). Lee et al, in a study of over 15,000 women with endometrial cancer, reported a higher rate of serous histology in those >40 years and a 5-year disease-specific survival rate of 86.4% compared to 93.2% in women <40 years (127). Following adjustment for histology and adjuvant therapy, the survival disadvantage persisted. Other factors including differential treatment and treatment-related morbidity may be contributory to these trends. Koul and colleagues found that older women (≥75 years) were less likely to be offered adjuvant therapy and had a significantly lower 5-year cancer-specific survival rate compared to those <75 years (128). Zeng and colleagues reported a higher rate of post-operative morbidity in elderly endometrial cancer patients undergoing robotic surgery (131). These findings are consistent with previously published data where age has been reported to independently impact on endometrial cancer outcomes, including risk of recurrence (130, 132–135).

Obesity is the most important modifiable risk factor in endometrial cancer, with every 5kg/m^2 increase in BMI conferring a 60% increased risk of the disease (136). Obesity-driven endometrial cancers are usually low grade, early stage, endometrioid tumours with a favourable prognosis when compared with the biologically aggressive non-endometrioid endometrial cancer phenotypes (136–138). Despite the survival advantages offered by favourable tumour biology, obesity is associated with higher all-cause mortality due to comorbid health conditions, particularly cardiovascular disease (139). Indeed, cardiovascular disease is the leading cause of death among endometrial cancer survivors (140). Arem and colleagues found that women with BMI ≥35kg/m^2 had an almost 5-fold higher risk of cardiovascular-related mortality 10 years post diagnosis compared with those with BMI <25kg/m^2

TABLE 5 | Circulating endometrial cancer prognostic biomarkers.

Category	Biomarker	Prognostic features
Proteins	Elevated CA125	Linked to poor survival (96, 97) Higher stage (83, 98) Higher grade (83, 98) Deep myometrial invasion (83, 98) Lymph node metastasis (83, 98) LVSI (98)
	Elevated HE4	Poor overall, disease-specific and recurrence free survival (74, 84) Deep myometrial invasion (99, 100) Advanced stage (100–102) Presence of LVSI (66, 103) Tumour size (100) Lymph node metastasis (99, 103) Recurrence (103)
	High Estriol (E3) High Estrone sufate (E1-S)	Non-myoinvasive tumours, low risk of recurrence and improved overall survival (104) Increased relapse (104)
Metabolites	Bradykinin, heme, lactic acid, homocysteine, myristic acid, valine, progesterone, threonine, stearic acid, sarcosine, glycine etc	Associated with histological subtype (13, 105, 106)
	Hydroxysphingomyelins, phospatidylcholines, estrogen metabolites	Associated with deep myometrial invasion (13, 106–108)
	Hexadecadienyl carnitine, phosphatidylcholines	Associated with LVSI (13, 107)
	Spermine, acylcholines, sphingolipids, linoleic acid, myristic acid, polyamines, ceramides	Associated with recurrence (13, 105)
	Methionine sulfoxide	Poor survival (109)
Circulating tumour cells (CTC)	Detection of CTC	Poor progression-free survival (92) Association with non-endometrioid cancer (92) Large tumour size (>5cm) (92) Lymph node involvement (93) Deep myometrial invasion (93)
Circulating tumour DNA (ctDNA)	Presence of ctDNA	Associated with type II tumours (87). Elevated in grades 2 and 3 endometrial cancer (85, 86)
	Serum ctDNA integrity	Elevated in LVSI (85)
	Plasma p53 antibody	Linked to serous tumours (87) Linked to higher grade in Type I tumours (87)
	Plasma *KRAS* mutation	Elevated in grade 2 of type I tumours (87)
	Presence of plasma mutation (*CTNNBI, KRAS, PTEN*, or *PIK3CA*)	Linked to tumour stage (91) Deep myometrial invasion (91) LVSI (91) Large tumour size (91)
Immune/inflammatory parameters	Elevated CRP	Associated with poor overall and cancer-specific survival (65, 80, 81, 110) Stage (111, 112) Lymph node involvement (112)
	Glasgow prognostic score	Survival and recurrence (113)
	Inflammatory parameters (NLR,MLR,PLR,SII etc)	Adverse clinico-pathological features and outcomes (94, 95, 114–117)

(141). Secord and colleagues, in a meta-analysis involving 665,694 endometrial cancer cases reported significantly higher odds of all-cause mortality with increasing BMI, with the highest risk for those with class III obesity (BMI≥40kg/m^2) (139). Obesity may also influence cancer-specific mortality from treatment-related factors (142). As an example, women with class III obesity are less likely to be offered hysterectomy, have a higher risk of perioperative morbidity and are more likely to receive suboptimal doses of chemotherapy from dose capping (142–146). Obesity may also impact on the optimal delivery of adjuvant radiation due to physical, technical and dosimetric constraints, thus contributing to poorer outcomes (147). Whilst obesity certainly impacts on endometrial outcomes, it is unclear whether weight loss interventions can improve survival and work in this space is on-going (148).

Studies have shown that women with a higher Age-adjusted Charlson-Comorbidity (AAC) index scores are at a greater risk of overall mortality, but not cancer-specific mortality or disease recurrence (149). Robbins and colleagues, in an analysis of 671 patients with FIGO stage I-II endometrioid endometrial cancer, report that high AAC scores independently predict short overall survival (149). It remains unclear whether lifestyle changes, including weight loss and dietary modifications, can reduce cardiovascular risk in endometrial cancer survivors, although

this is a tantalizing concept our group seeks to explore further. There is growing evidence that thyroid dysfunction may be linked to survival outcomes in endometrial cancer. The small study by Seebacher and colleagues reported poor disease-specific survival in women with TSH>2.5 mU/L (150). Our group recently found that endometrial cancer patients with comorbid hypothyroidism have significantly improved overall, cancer-specific and recurrence-free survival than those who are euthyroid (151). A prospective validation of these findings is warranted and the underlying mechanisms will need to be elucidated prior to clinical translation. Whether type 2 diabetes mellitus (T2DM) status impacts endometrial cancer survival outcomes is unclear. The meta-analysis by Zhang and colleagues involving 12,195 endometrial cancer cases and 575 deaths found no evidence of an association between T2DM status and endometrial cancer mortality (152). A more recent meta-analysis of five cohort studies by Laio and colleagues concluded that the data linking T2DM status and endometrial cancer-specific mortality are inconsistent. This analysis was limited by considerable clinical and methodological heterogeneity of included studies (153). In two of the included studies, a pooled relative risk of 1.32 (95% CI 1.10, 1.60. p=0.003) was reported. One study reported a hazard ratio of 1.64 (95% CI 0.17, 9.60, p=0.58) while the other three studies reported SMRs that could not be quantitatively synthesized (153). Further research is needed to clarify the prognostic impact of T2DM status on endometrial cancer outcomes.

SOCIODEMOGRAPHIC ASSOCIATIONS WITH PROGNOSIS

There is good evidence to suggest that ethnicity affects outcomes from endometrial cancer (154, 155). In the USA, Black women are more likely to be diagnosed with late stage disease and biologically aggressive endometrial cancer phenotypes (high grade, non-endometrioid cancers) than women of White ethnicity (154, 156–159). Park and colleagues found that non-Hispanic Black women had significantly shorter overall survival than non-Hispanic White women in an equal access healthcare system, despite correcting for traditional clinico-pathological characteristics, suggesting that other factors including molecular phenotypic differences might be contributing (155). It has been postulated that differential expression of specific tumour markers such as p53, *PTEN*, *HER2/neu* and *PIK3R1* mutations may explain some of the racial disparities (160, 161). *PTEN* mutation portends a favourable prognosis and has been reported to be less common in Black women compared to White women (162). *TP53* mutations, on the other hand, portend an unfavourable prognosis and are more common in Black women (163). Studies have also shown that women of Black ethnicity are less likely to undergo hysterectomy (160, 164) or receive adjuvant therapy than their White counterparts (165, 166). A review of the US National Cancer Database found that 47% of the 19,594 endometrial cancer patients who met the criteria for adjuvant radiation failed to receive radiation. The omission of adjuvant radiation was more common amongst Black, Asian and Hispanic women as well as those of lower socioeconomic status (166). Differences in comorbid conditions may also contribute to racial disparities in outcomes. Studies have been consistent in suggesting a higher comorbidity burden amongst Black women compared to women of White ethnicity (167, 168). Tarney and colleagues found that Black women <65 years with endometrial cancer are more likely to die from non-cancer related causes than White women (169).

Socioeconomic status has been linked with endometrial cancer outcomes too. Factors such as differential access to health care, level of income, educational status and areal-level economic deprivation may be contributory. Bedir and colleagues analyzed data on 21,602 German women with endometrial cancer and found differences in survival according to district level socioeconomic deprivation (170). In a Swedish study, women from the higher social groups were less likely to be diagnosed with advanced stage disease and non-endometrioid cancers, and had more favourable outcomes than women from the lower social groups (171). These findings are consistent with those reported in several high-income countries (149, 164, 172, 173). In the UK, results have been conflicting (174–176). Donkers and colleagues found no evidence of a socioeconomic disparity in survival after adjusting for confounding factors (175). Using the English multiple indices of deprivation, Njoku and colleagues found that women from more deprived neighbourhoods were more likely to present with fatal recurrence than those from less deprived areas (176). Further research is needed to confirm these findings and identify modifiable contributing factors.

CONCLUSION

Several clinical, sociodemographic and tumour specific parameters have emerged as important endometrial cancer prognostic biomarkers. The Cancer Genome Atlas and subsequent clinically translatable molecular classification systems, in particular, hold great promise to refine current endometrial cancer risk stratification systems. The clinical utility of endometrial cancer molecular classification in guiding adjuvant therapy and recurrence monitoring is yet to be defined and must now be prioritised. Blood-based markers including systemic inflammatory parameters, proteins and metabolites, and circulating tumour cells have also shown potential to refine endometrial cancer risk stratification algorithms and their prospective validation in larger study cohorts is warranted. The impact of socioeconomic status and ethnicity on endometrial cancer outcomes is becoming more apparent and studies exploring the factors underlying these disparities are urgently needed.

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Conceptualization- KN and EJC. Writing- original draft preparation KN. Writing- review and editing KN, CEB, and

EJC. Supervision- EJC. Funding acquisition- EJC. All authors read and approved the final version for submission.

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