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# A PROGNOSTIC BIOMARKERS IN ENDOMETRIAL CANCER-A META ANALYSIS

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**Abstract**

**Introduction:** Endometrial cancer (EC) is the most frequent gynaecological cancer in developed countries, and its prevalence is increasing. While the majority of women with endometrial cancer are identified with highly treatable illness and have acceptable outcomes, a considerable minority have severe clinicopathological features that indicate a bad prognosis. Prognostic biomarkers that reliably identify people at highest risk of disease recurrence and mortality can guide management methods to ensure that patients receive evidence-based and individualised care.

**Materials and Methods:** All selected articles were reviewed, and data were compiled in a comprehensive database that included: general information (first author's name, country, journal, year of publication); number of patients and analytical technique used; association of the described biomarkers with different prognostic factors (histological type, histological grade, FIGO stage, myometrial invasion, lymph node status, LVSI, cervical invasion, metastasis, TCGA molecular classification, A meta-analysis on OS was performed for the five most studied biomarkers. Only studies providing an estimate of the hazard ratio (HR) and the associated 95% CI for the parameter here considered were included.

**Results:** Our initial PubMed, Medline, Scopus, Chochrane and DOAJ search yielded 250 hits, which were reduced to 155 following the first screening phase. 39 of them satisfied our criteria and were considered for this review. Biomarker research on prognostic biomarkers in the EC has expanded over time, with Asia (43%) and Europe (41%) being the largest contributors. At the country level, Japan, China, the United States of America, Turkey, and Norway are the leading countries.

**Conclusion:** According to our meta-analysis, ESR1, TP53, and WFDC2 have the ability to predict overall survival in EC. The limitations of the published research are noted in terms of suitable study design, a lack of high-throughput measurements, and statistical flaws, and novel methodologies and possibilities for the identification and validation of clinically relevant EC prognostic biomarkers are presented.

**Key Words:** Endometrial cancer, Prognostic biomarkers, overall survival.

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## INTRODUCTION

Endometrial cancer (EC) is the most frequent gynaecological cancer in developed countries, and its prevalence is increasing. While the majority of women with endometrial cancer are identified with highly treatable illness and have acceptable outcomes, a considerable minority have severe clinicopathological features that indicate a bad prognosis.[1] Prognostic biomarkers that reliably identify people at highest risk of disease recurrence and mortality can guide management methods to ensure that patients receive evidence-based and individualised care.[2]

Endometrial cancer is the sixth most common cancer in women and the gynaecological cancer with the highest prevalence in high-income nations. There will be a projected 417,000 incident cases and 97,000 fatalities from the disease worldwide in 2020. Endometrial cancer is becoming more common as the obesity pandemic worsens.[3]

The most majority of endometrial malignancies are random, with an estimated 5% developing as a result of a familial susceptibility, most often Lynch syndrome. Lynch syndrome is an autosomal dominant disorder caused by a malfunction in the DNA mismatch repair (MMR) mechanism, which predisposes to a number of cancers, including endometrial cancer. There are no evidence-based screening strategies for endometrial cancer in the general population or in high-risk women at the moment. The majority of women are detected after routine tests for postmenopausal bleeding, the disease's primary symptom. In today's clinical practise, symptomatic women are evaluated using a series of procedures that include a transvaginal ultrasound scan, an endometrial biopsy, and hysteroscopy.[4]

The majority of women with endometrial cancer are detected early and have a relatively treatable illness, as evidenced by outstanding 5-year survival statistics. A considerable minority have poor prognosis due to unfavourable clinicopathological features such as biologically aggressive endometrial cancer morphologies. Endometrial cancer is primarily treated surgically, with complete hysterectomy and bilateral salpingo-oophorectomy being the global standard of care. Women with high-risk characteristics are provided adjuvant chemotherapy and/or radiotherapy to reduce the likelihood of recurrence. A significant percentage, particularly those of reproductive age or those for whom surgery involves significant risk, such as the frail or medically unfit, are handled conservatively.[5]

Clinical or biological variables that may be reliably tested and evaluated to predict the course of a disease regardless of therapy are referred to as prognostic biomarkers. In clinical practise, prognostic biomarkers are used to predict the likelihood of a clinical event (mortality, illness recurrence, or progression) occurring among persons with the condition of interest. Clinical, tumor-specific molecular, and histological characteristics are examples of prognostic biomarkers.[7]

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We extensively analysed the existing literature to compile an overview of the various proteins that are EC prognostic factors connected with or directly related to recurrence and survival in this review. We highlight the proteins that have a strong potential to become prognostic biomarkers in clinical settings after prospective validation. Finally, we explore potential enhancements and novel approaches to EC biomarker research that could speed up the discovery of clinically meaningful biomarkers.

## MATERIALS AND METHODS

From January 2022 to December 2022, literature searches were conducted in Pubmed, Scopus, Embase, Chochrane and DOAJ using the terms "endometrial cancer" or "endometrial neoplasms" or "endometrial carcinoma", "biomarkers" or "markers", and "prognosis or prognostic" or "recurrence" or "survival".

**Inclusion criteria:**

- Studies including endometrial cancer with an epithelial origin.
- Biomarker studies performed at protein level.
- Prognostic biomarker studies, i.e., studies that identify or validate biomarkers that are associated to EC risk factors, recurrence or survival
- Studies performed on any biological human sample, but not on cultured cells or animal models.
- Studies based on the expression of biomarkers.

**Exclusion criteria:**

- Not written in English,
- Based on the characterization of one specific EC subtype,
- Based on response-to-treatment biomarkers,
- Articles performed using less than 10 samples in total,
- Reviews, meta-analyses, opinion articles or case report studies.

All selected articles were reviewed, and data were compiled in a comprehensive database that included: general information (first author's name, country, journal, year of publication); number of patients and analytical technique used; association of the described biomarkers with different prognostic factors (histological type, histological grade, FIGO stage, myometrial invasion, lymph node status, LVSI, cervical invasion, metastasis, TCGA molecular classification, A meta-analysis on OS was performed for the five most studied biomarkers. Only studies providing an estimate of the hazard ratio (HR) and the associated 95% CI for the parameter here considered were included.

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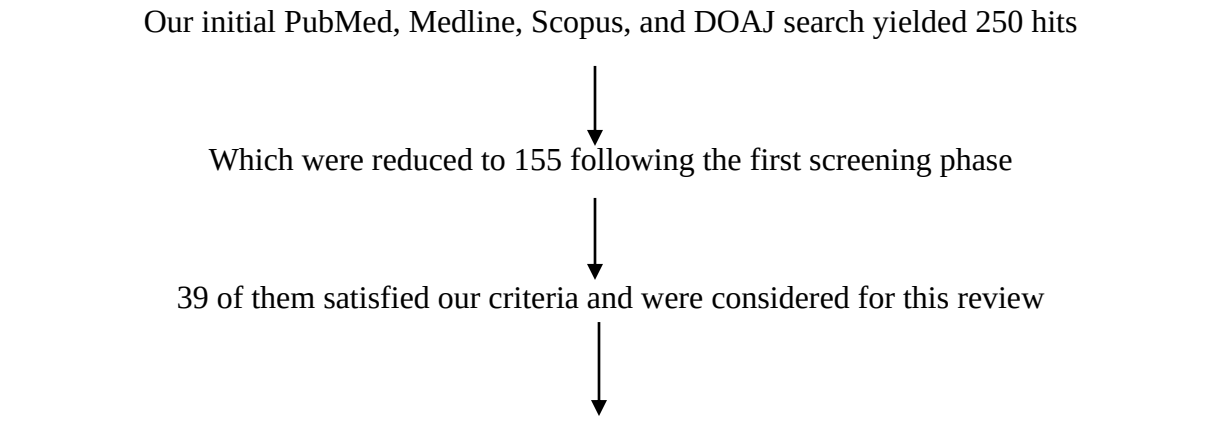


**Figure 1: PRISMA Statement of search results**

## RESULTS

Our initial PubMed, Medline, Scopus, and DOAJ search yielded 250 hits, which were reduced to 155 following the first screening phase. 39 of them satisfied our criteria and were considered for this review. Biomarker research on prognostic biomarkers in the EC has expanded over time, with Asia (43%) and Europe (41%) being the largest contributors. At the country level, Japan, China, the United States of America, Turkey, and Norway are the leading countries.

A total of 25 protein biomarkers were identified as putative predictive biomarkers from the 39 papers examined, defined as proteins linked with one or more of the established clinical prognostic variables in EC, recurrence, or survival. Surprisingly, only 6% of articles classified the recruited patients and/or analysed their data using the TCGA categorization. Only 21% of the 25 protein biomarkers included in this review were validated using an independent approach, an independent cohort, or in an independent study. Surprisingly, 60% of the research focused on a single protein. In terms of clinical samples used, 79% of the research were performed on tissue specimens, with 16% of the studies using serum samples.

The majority of biomarkers identified in this systematic review were associated with histological grade, FIGO stage and OS, with more than 100 biomarkers described for each of these parameters. Other biomarkers were associated with lymph node status, histological type, myometrial invasion, LVSI, DFS, recurrence, DSS, PFS, risk, RFS, metastasis, cervical invasion and the TCGA subgroups. The vast majority of biomarkers are related to more than one of the above-mentioned parameters, indicating that they provide relevant prognostic information but are not specifically linked to one feature in particular. In fact, those that were associated with a specific paramet generally corresponded to those biomarkers that have been scarcely studied. Thus, further research needs to be performed to understand whether they are truly significant as

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prognostic factors and specific of that parameter in particular or might be also related to other parameters.

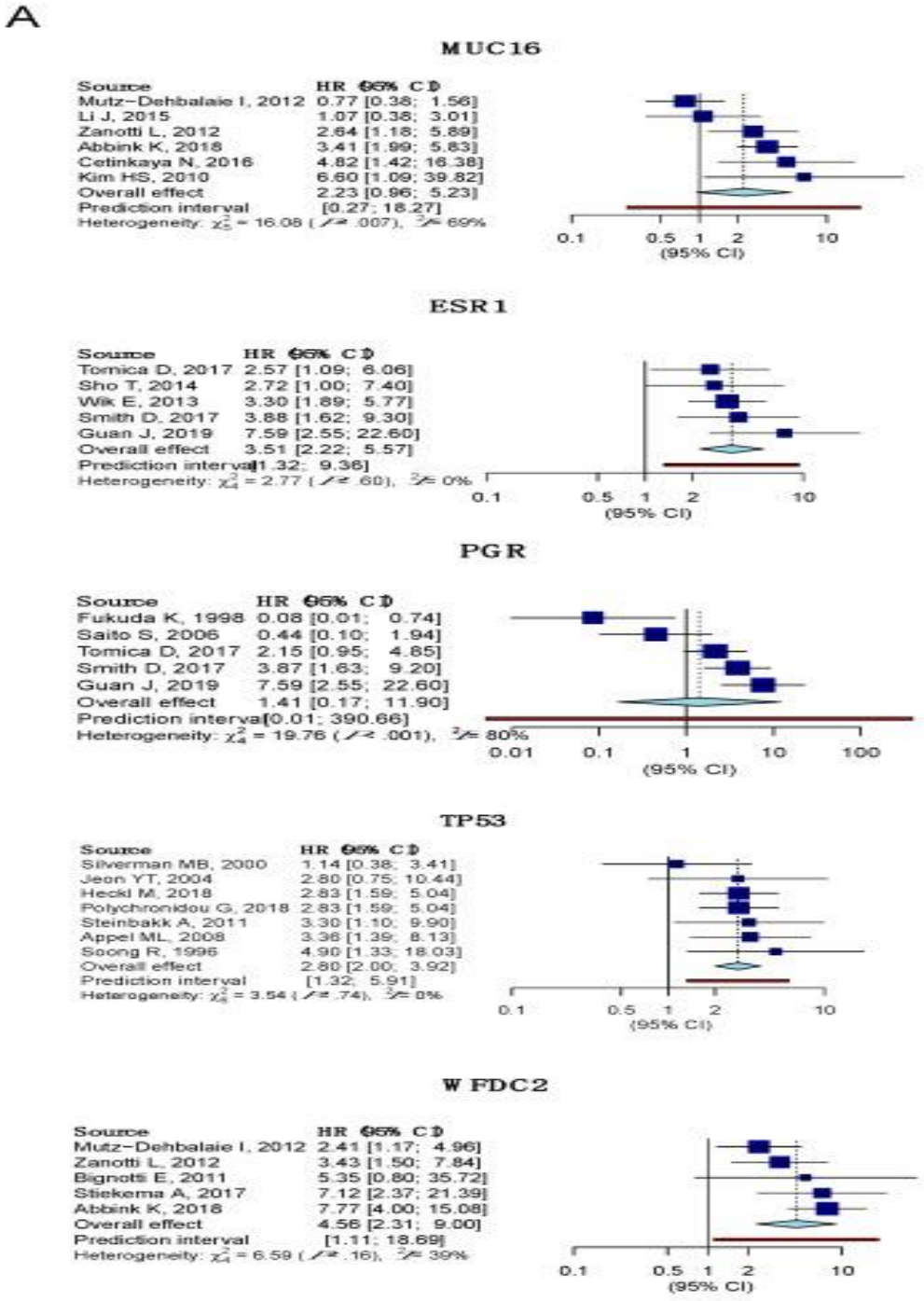


**Figure 2: Meta-analysis on OS of the most studied biomarkers regarding prognosis in EC**

## DISCUSSION

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This systematic review and metanalysis underline the lack of potential prognostic biomarkers of EC. Among the 250 articles identified in this review, 39 were deeply analyzed. As a result, this review compiles information of 25 potential biomarkers, which are related to one or more of the clinical prognostic factors in EC, recurrence or survival. Although a large list of biomarkers is described, there are critical issues that hamper their clinical application and that are discussed in this section, from a conceptual, methodological and analytical point of view. Additionally, new strategies in biomarker research are exposed.[8]

EC study design should include the TCGA classification as an additional parameter to either recruit patients or evaluate the results. In this review, we only identified 11 articles including the TCGA classification. The incorporation of the TCGA molecular classification in research and clinical practice for classifying EC patients should be promoted, especially when studying prognostic biomarkers.[9]

The rapid advances in medical and biomedical sciences have a huge impact on the outcome for patients. This is possible thanks to the tight relation between medical identification of clinical needs and the consequent solution from the research side. However, regarding EC disease, even if the clinical gaps are well-known, more research is needed to provide solutions to all of them. Based on our review we identified the lack of discovery studies as one of the main causes. Discovery studies allow for the identification of de novo biomarkers since they screen for the whole or at least, an abundant part of the proteome of the samples that are being studied. Following our search criteria, we could only identify two discovery studies on prognostic factors in EC.[10]

## CONCLUSION

According to our meta-analysis, ESR1, TP53, and WFDC2 have the ability to predict overall survival in EC. The limitations of the published research are noted in terms of suitable study design, a lack of high-throughput measurements, and statistical flaws, and novel methodologies and possibilities for the identification and validation of clinically relevant EC prognostic biomarkers are presented.

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