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Novel algorithm including CA-125, HE4 and body mass index in the diagnosis of endometrial cancer☆

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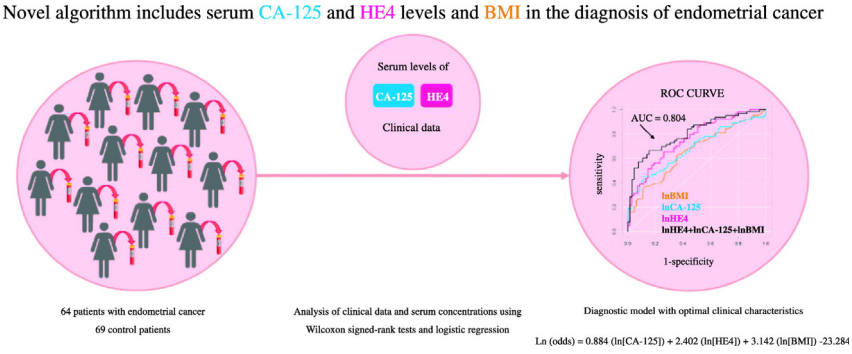
HIGHLIGHTS

- Serum CA-125 and HE4 levels are significantly higher in endometrial cancer patients.
- Model to distinguish endometrial cancer from benign gynaecological diseases is proposed.
- Diagnostic algorithm includes serum CA-125 and HE4 levels and BMI (AUC = 0.80).
- Serum HE4 levels differentiate patients with lymphovascular invasion (AUC = 0.81).
- Serum HE4 levels stratify patients with deep myometrial invasion (AUC = 0.78).

GRAPHICAL ABSTRACT



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ABSTRACT

Objectives. To evaluate the diagnostic and prognostic potential of preoperative serum CA-125 and HE4 levels in patients with endometrial cancer.

Methods. Prospective case–control study of 133 women who underwent surgical treatment at the University Medical Centre Ljubljana (64 patients with endometrial cancer, 69 control patients with prolapsed uterus or myoma). Serum CA-125 and HE4 levels were determined using electrochemiluminescent assays.

Results. Serum CA-125 and HE4 levels were significantly higher in patients with endometrial cancer, compared to the controls ($p = 2.67 \times 10^{-4}$, 1.36×10^{-7}, respectively). A diagnostic model that combines serum CA-125 and HE4 levels and body mass index separated patients with endometrial cancer from controls, with AUC of 0.804, sensitivity of 66.7%, and specificity of 84.6%. Serum HE4 levels showed good prognostic potential and stratified the patients according to presence/absence of deep myometrial invasion ($p = 0.001$) or lymphovascular invasion ($p = 0.003$), with AUCs of 0.78 and 0.81, respectively. In low-risk patients with grade

Abbreviations: AIC, Akaike Information Criteria; AUC, area under the curve; BMI, body mass index; ECLIA, electrochemiluminescent immunoassay; ROC, receiver operating characteristics.

☆ Contributions: TLR and JO designed the study; TLR contributed to the final version of the manuscript. TK performed the experiments and the statistical analysis, and drafted the manuscript. SFG evaluated the histology and tumour grading. ŠS and IT collected the patient clinical data. AB and KV supervised the statistical modelling and contributed to the final version of the manuscript. All of the authors reviewed the manuscript before submission.Funding: This study was supported by a J3-6799 Grant to T.L.R., and a Young Researcher Grant to T.K., both from the Slovenian Research Agency.Conflict of interest: The authors have nothing to disclose.

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Prognosis
Logistic regression

1 and 2 endometrioid cancer for whom lymphadenectomy can be avoided, HE4 allowed stratification according to deep myometrial invasion ($p = 3.39 \times 10^{-4}$), with AUC of 0.84. Although median HE4 levels were higher in patients with lymphovascular invasion, this difference did not reach significance ($p = 0.06$).

Conclusions. A model based on preoperative serum CA-125 and HE4 levels and body mass index has good diagnostic accuracy for separation of patients with endometrial cancer and control patients. In patients with endometrial cancer, serum HE4 levels allow prediction of deep myometrial and lymphovascular invasion.

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1. Introduction

Endometrial cancer is the fifth most common gynaecological malignancy in Slovenia, with the highest incidence in women between the ages of 50 and 64 years [1]. Worldwide, endometrial cancer accounts for 76,000 deaths and there are an estimated 320,000 new cases per year [2]. Risk factors for the development of endometrial cancer include obesity, diabetes mellitus, arterial hypertension, early menarche and/or late menopause, anovulation, nulliparity, hyperandrogenism, use of exogenous oestrogens unopposed by progestins, excessive endogenous production of oestrogens, and genetic predisposition [3]. Additionally, the high-risk population includes patients treated with tamoxifen, which is the standard therapy for the majority of the 1.6 million women with breast cancer who are identified yearly worldwide [2], and of the patients with Lynch syndrome, with over 1.0 million cases in Europe alone [4]. The standard treatments for endometrial cancer include hysterectomy and bilateral salpingo-oophorectomy [5] however, there is still no consensus regarding lymphadenectomy as a part of the complete surgical staging procedure, as it carries additional risk for developing lymphedema, deep vein thrombosis, and neurological and vascular injuries [6]. Blood biomarkers that can predict the presence of deep myometrial and lymphovascular invasion preoperatively would thus allow selection of patients who will need lymphadenectomy [7,8]. Clinical assessment and imaging techniques have been exploited as prognostic markers of endometrial cancer [9], although they lack sensitivity and specificity for the detection of deep myometrial invasion and extra-uterine disease [10,11]. These shortcomings would be overcome with a non-invasive disease-specific biomarker. Although several prognostic biomarkers for endometrial cancer have been studied, with some of them indicated promising results, none of these have been accepted into clinical practice [9,12,13].

Cancer antigen 125 (CA-125) is an epithelial-cell surface antigen that is expressed in many different types of tumour cells, and it is usually used in the evaluation and follow-up processes for patients with ovarian cancer [14]. In 1984, Niloff reported elevated CA-125 levels in patients with recurrent and advanced endometrial cancer [15]. Indeed, in recent years there have been several studies that have evaluated CA-125 as a potential diagnostic and prognostic biomarker for endometrial cancer [13,16]. Considering its greater prognostic than diagnostic characteristics, CA-125 has been suggested as a prognostic marker for preoperative evaluation of patients with endometrial cancer [17,18].

There has also been a growing interest in the role of human epididymis protein 4 (HE4) in endometrial cancer. Serum HE4 levels are elevated in patients with serous and endometrioid ovarian carcinomas, and also in those with recurrent ovarian cancer [19–22]. Serum HE4 levels are also higher in patients with endometrial cancer, compared to healthy controls, and they show potential as a diagnostic biomarker for endometrial cancer [20–22]. Several studies have reported superior diagnostic characteristics of HE4 in combination with CA-125, as compared to CA-125 alone, for the detection of endometrial cancer, where addition of age further increased the diagnostic value [23]. The published studies thus support the potential of both of these biomarkers in preoperative evaluation of endometrial cancer patients.

The aims of the present study were two-fold: (i) to evaluate preoperative serum CA-125 and HE4 levels in endometrial cancer and control patients, and to examine their diagnostic and/or prognostic potential as single biomarkers and as the combination of both biomarkers with patient clinical characteristics; and (ii) to construct a model with the optimal diagnostic and/or prognostic characteristics. To the best of our knowledge there have been only four case–control studies that investigated the diagnostic and prognostic potentials of serum CA-125 and HE4 levels combined with statistical modelling [21–24].

2. Methods

2.1. Patient enrolment

Patient enrolment took place from June 2012 to December 2014 at the Department of Obstetrics and Gynaecology, University Medical Centre Ljubljana, Slovenia. In this case–control study, we included 133 women who underwent surgical treatment. Based on clinico-histopathological findings, the study participants were stratified as patients with endometrial cancer ($n = 64$) and as the control group of women with prolapsed uterus or myoma ($n = 69$). Within a week prior to surgery, morning blood samples were collected and additional information was obtained regarding their life-style and gynaecological and clinical status (Table 1). For sample collection and processing, strict and detailed standard operating procedures were followed, and serum samples were stored at −80 °C until further analysis. The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (Nr. 0120-127/2016-2), and all of the participants signed written informed consent before being included in this study. The depth of myometrial invasion was assessed by two independent gynaecological pathologists (SFG, MB). The Cancer Registry of the Republic of Slovenia was searched for the vital status of the patients, with the cut-off point of 15 November 2016.

2.2. Measurement of CA-125 and HE4

Specimens were analysed using electrochemiluminescent immunoassays (ECLIAs) specific for CA-125 and HE4, on a Cobas e411 immunoassay analyser (Roche Diagnostics GmbH, Manheim, Germany). The measuring ranges for serum CA-125 and HE4 levels with these ECLIAs were 0.600–5000 U/mL and 15.0–1500 pmol/L, respectively, and the quality control data are present as Supplementary Data (Supplementary Table 1). CA-125 quantitative determination kits (REF: 11776223190, LOT: 139788-01) and HE4 detection kits (REF: 05950929190, LOT: 112732-01) were used, along with calibrators, such as CA125IICalSet (REF: 07030207190 LOT: 134830-01), HE4 CalSet (REF: 05950945190, LOT: 187553-01), ElecsysPreciControl HE4 (REF: 05950953190, LOT: 187791-02), and ElecsysPreciControlTumor Marker (REF: 11776452, LOT: 187283-02).

2.3. Statistical analysis

The data was numerically anonymised and was collected in Microsoft Office Excel 2013 spreadsheets. All the data was first analysed descriptively. Serum levels were compared between the case and control groups using two-sided Wilcoxon rank-sum tests (Mann-Whitney *U* tests), as the data was not normally distributed. Non-parametric Kruskal-Wallis H tests were used for comparisons of more than two groups. Pairwise Wilcoxon tests with Holm corrections were used as *post-hoc* tests to determine the difference within each group. Fisher's

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