

Elevated human epididymis protein 4 levels in chronic kidney disease compromise the accuracy of the risk of ovarian malignancy algorithm

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Abstract. The present study aimed to compare the diagnostic accuracy of the risk of ovarian malignancy algorithm (ROMA) for differentiating ovarian tumors in patients with and without chronic kidney disease (CKD), using postoperative histopathological findings as the reference standard among patients who underwent surgery after ROMA testing. The retrospective study included 1,122 patients, including 21 with CKD, who met the inclusion criteria and underwent surgery for ovarian tumors at Gangneung Asan Hospital between August 2015 and August 2025. In patients with CKD, human epididymis protein 4 (HE4) levels were elevated in both benign and malignant groups compared with normal levels, with progressively higher levels observed with increasing CKD severity. Among patients with benign ovarian tumors, median HE4 levels were higher in those with CKD than in those without CKD (210.00 vs. 41.10 pmol/l). Cancer antigen 125 (CA125) levels did not differ significantly according to CKD status. Because of the elevated HE4 levels, ROMA scores were significantly higher in patients with CKD, resulting in low specificity {0.200 [95% confidence interval (CI), 0.066-0.470]} and reduced overall accuracy [0.429 (95% CI, 0.240-0.640)]. Receiver operating characteristic curve analysis demonstrated superior predictive

performance of ROMA in patients without CKD [area under the curve (AUC), 0.724; 95% CI, 0.680-0.768] compared with those with CKD (AUC, 0.467; 95% CI, 0.217-0.717). In conclusion, in patients with CKD and ovarian tumors, ROMA should be interpreted with caution, and CA125 and imaging findings should be considered alongside other clinical information when assessing the risk of ovarian malignancy.

Introduction

Ovarian cancer has a poorer prognosis than other gynecological cancers because approximately 70% of patients are diagnosed at an advanced stage (1). Therefore, distinguishing benign ovarian tumors from ovarian cancer is important for guiding surgical decision-making and preventing disease progression.

Cancer antigen 125 (CA125), a classical biomarker for epithelial ovarian cancer (EOC), is frequently elevated in conditions such as leiomyomas, adenomyosis, infection, liver cirrhosis, pregnancy, and pelvic endometriosis, resulting in false-positive results and low specificity (2,3). To address these limitations, the risk of ovarian malignancy algorithm (ROMA), a risk stratification tool approved by the U.S. Food and Drug Administration, was developed to differentiate benign from malignant ovarian tumors. ROMA integrates serum levels of human epididymis protein 4 (HE4) and CA125 with menopausal status (4-6). HE4 is involved in EOC tumorigenesis and is frequently elevated in ovarian cancer (7,8). Unlike CA125, HE4 is less influenced by physiological conditions or endometriosis and has higher diagnostic specificity (9,10).

However, HE4 levels may also be elevated in noncancerous conditions, particularly in patients with end-stage renal disease, diabetic nephropathy, nephrotic syndrome, kidney cancer, or urosepsis. Such elevations may result from decreased HE4 clearance or increased production in damaged kidneys. HE4 may be expressed in the distal convoluted tubules of the kidney and elevated serum HE4 levels may occur with renal cellular injury or renal fibrosis (11). Significantly elevated serum HE4 levels have been reported in patients with chronic kidney disease (CKD), with median levels of approximately 1,041 pmol/l in women, and a positive correlation between

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Abbreviations: ROMA, risk of ovarian malignancy algorithm; CA125, cancer antigen 125; HE4, human epididymis protein 4; CKD, chronic kidney disease; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic; EOC, epithelial ovarian cancer; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; PI, predictive index

Key words: HE4, ovarian cancer, biomarker, CKD

serum HE4 levels and CKD stage (12,13). Although elevated HE4 levels have been reported in patients with CKD without ovarian cancer, no study has investigated whether this elevation reduces the diagnostic accuracy of ROMA (14). If elevated HE4 levels in patients with CKD and ovarian tumors reduce the accuracy of ROMA results, they may lead to unnecessary ovarian surgery in patients with CKD who are at high surgical risk, resulting in avoidable morbidity and inefficient use of medical resources.

Therefore, this study aimed to compare the diagnostic accuracy of ROMA for differentiating ovarian tumors in patients with and without CKD, using postoperative histopathological findings as the reference standard among patients who underwent surgery after ROMA testing.

Materials and methods

Patients. The Institutional Review Board of Gangneung Asan Hospital determined that this retrospective study was exempt from IRB review and waived the requirement for informed consent (IRB no. 2025-10-003). The medical records of patients who underwent ROMA testing for ovarian tumors and subsequently underwent surgery at Gangneung Asan Hospital between August 2015 and August 2025 were retrospectively reviewed.

Only patients with histologically confirmed diagnoses following surgery were included. All types of borderline tumors were included in the cancer group and analyzed accordingly. A borderline ovarian tumor is an epithelial neoplasm that sits in the 'gray zone' between benign and invasive malignant tumors. It shows active cell proliferation and nuclear atypia, but lacks destructive stromal invasion. Serous borderline tumors share molecular and genetic alterations with low-grade serous carcinomas and can present at higher stages with peritoneal implants and/or lymph node involvement, which validates their borderline malignant potential (15). Revised Korean Standard Classification of Diseases-8 (KCD-8) includes borderline ovarian tumor as general cancer in 2021 (16). Patients with ascites or peritoneal carcinomatosis, which was considered sufficiently predictive of ovarian cancer based on preoperative imaging, were excluded. Patients with isolated hydrosalpinx or paratubal cysts, inclusion cysts resulting from pelvic adhesions, or inflammatory lesions were also excluded because these conditions can typically be distinguished from ovarian cancer based on preoperative imaging or inflammatory testing. Patients were additionally excluded if >3 months had elapsed between ROMA testing and surgery or if they had been diagnosed with other malignancy within the previous 5 years.

Clinicopathological data, including age, menopausal status, preoperative CA125 and HE4 levels, ROMA test results, and histological findings of ovarian tumors, were collected. For patients with CKD, additional laboratory data, including blood urea nitrogen (BUN), serum creatinine, and estimated glomerular filtration rate (eGFR), were obtained. The CKD-Epidemiology collaboration formula was used to calculate Egfr (17). CKD was defined as a structural or functional abnormality of the kidney that persists for ≥ 3 months and has substantial health implications. CKD was classified into GFR categories G1-G5 based on Kidney Disease: Improving Global

Outcomes guidelines (18). Clinicopathological data, including all patients' CKD status and blood test results, were obtained during the preoperative examination and testing process and correspond to the time of ROMA testing.

Methods. Serum HE4 and CA125 levels were determined using the Roche Elecsys® assay (Roche Diagnostics, Basel, Switzerland), a one-step sandwich electrochemiluminescence immunoassay for their quantitative determination. The detection range for HE4 was 15.0-1,500 pmol/l; samples with values >1,500 pmol/l were diluted 1:20 using Elecsys Diluent.

Patients were stratified into low- or high-risk groups based on the ROMA score calculated from laboratory measurements and menopausal status. The predictive index (PI) and predicted probability (ROMA score) were calculated using the algorithms proposed by Moore *et al* (4): Premenopausal, $PI = -12.0 + 2.38 \times \ln(HE4) + 0.0626 \times \ln(CA125)$; postmenopausal, $PI = -8.09 + 1.04 \times \ln(HE4) + 0.7320 \times \ln(CA125)$; ROMA score (%) = $\exp(PI) / [1 + \exp(PI)] \times 100$.

The ROMA thresholds for classifying patients as high risk were $\geq 11.4\%$ for premenopausal women and $\geq 29.9\%$ for postmenopausal women. Postmenopausal status was defined as ≥ 1 year after menstrual bleeding cessation. For patients who underwent hysterectomy before menopause, age ≥ 50 years was used to define postmenopausal status.

Statistical analysis. A two-sample t-test or Wilcoxon rank-sum test was used to compare continuous variables, and Fisher's exact test was used for categorical variables. $P < 0.05$ was considered to indicate a statistically significant difference. Box plots were used to compare serum HE4 levels according to CKD status in the benign and cancer groups. The diagnostic performance of ROMA according to CKD status was evaluated by comparing sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. Wald contrast tests from a logistic regression model were performed to compare the diagnostic performance of ROMA according to CKD status. Receiver operating characteristic (ROC) curves were generated separately for patients with and without CKD, and AUCs were compared between independent groups using the unpaired DeLong's test. All statistical analyses were performed using R statistical software, version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Among the 1,816 patients identified in the initial search, 1,122 patients who met the inclusion criteria were included in the retrospective analysis. Of these, 928 (82.7%) had benign ovarian tumors, 194 (17.3%) had ovarian cancer, and 21 had CKD. Of the total 21 patients with CKD, four were undergoing dialysis around the time of ROMA testing; blood samples were collected from all patients 2 h before dialysis. Patient characteristics are summarized in Table I. Patients with CKD were older in both the benign and cancer groups and were more likely to be postmenopausal in the benign group. CA125 levels did not differ significantly according to CKD status. In contrast, HE4 levels were significantly higher in patients with CKD in both the benign and cancer groups ($P < 0.001$).

Table I. Characteristics of study participants.

Parameter	Benign			Cancer		
	No CKD (n=913)	CKD (n=15)	P-value	No CKD (n=188)	CKD (n=6)	P-value
Mean age, years (SD)	43.00 (14.39)	63.93 (13.34)	<0.001	46.62 (13.76)	60.00 (17.13)	0.021
Menopause, n (%)			<0.001			0.238
Pre	670 (73.4)	4 (26.7)		111 (59.0)	2 (33.3)	
Post	243 (26.6)	11 (73.3)		77 (41.0)	4 (66.7)	
Median CA125, U/ml (IQR)	23.00 (13.50, 54.20)	23.50 (13.25, 30.60)	0.492	46.70 (21.20, 111.67)	23.05 (18.92, 25.75)	0.052
Median HE4, pmol/l (IQR)	41.10 (34.10, 50.20)	210.00 (143.30, 1,862.05)	<0.001	52.65 (40.27, 74.30)	175.35 (170.43, 217.25)	<0.001
ROMA risk, n (%)			<0.001			0.03
Low	765 (83.8)	3 (20.0)		92 (48.9)	0 (0.0)	
High	148 (16.2)	12 (80.0)		96 (51.1)	6 (100.0)	
Median ROMA score (IQR)	5.50 (3.50, 9.10)	58.90 (29.99, 93.00)	<0.001	11.60 (5.88, 34.88)	49.85 (42.33, 59.47)	0.005

CA125, cancer antigen 125; CKD, chronic kidney disease; HE4, human epididymis protein 4; IQR, interquartile range; ROMA, risk of ovarian malignancy algorithm.

Among patients with benign ovarian tumors, the median HE4 level was 210.00 pmol/l in those with CKD, compared with 41.10 pmol/l in those without CKD. Among patients with ovarian cancer, the median HE4 level was 175.35 pmol/l in those with CKD, compared with 52.65 pmol/l in those without CKD. Serum HE4 levels according to CKD status in the benign and cancer groups are shown as box plots (Fig. 1). For comparison, HE4 levels >2,000 pmol/l were censored. ROMA scores were significantly higher in patients with CKD in both the benign and cancer groups, likely owing to elevated HE4 levels. Consequently, only 20% (3/15) of patients with benign ovarian tumors and CKD were classified as low risk.

The CKD stage, cause of CKD, BUN, creatinine, eGFR, CA125, HE4, and ROMA scores of patients with CKD are summarized in Table SI. Patients with CKD stage 5 of unknown etiology were classified as having end-stage renal disease, defined as kidney function reduced to $\leq 10\%$. Among patients with benign ovarian tumors, HE4 levels increased gradually up to CKD stage 3, with levels of 123 pmol/l in stage 2, 130.5 pmol/l (130-131) in stage 3a, and 171.6 pmol/l (137-210) in stage 3b. In contrast, HE4 levels were markedly elevated in patients with stage 5 CKD, reaching 2729.2 pmol/l (547.1-8204.6). Among patients with benign ovarian tumors and CKD, the CA125 level was 22.4 U/ml (5.5-51.8), excluding one outlier (701.2 U/ml), and did not show a significant increase comparable to that observed for HE4. The mean ROMA score of patients with benign ovarian tumors increased with increasing HE4 levels, reaching 40.6 in CKD stage 2, 19.0 (14.4-23.5) in stage 3a, 36.4 (20.6-58.9) in stage 3b, and 92.2 (74-100) in stage 5.

The sensitivity, specificity, PPV, NPV, and accuracy of ROMA were compared according to CKD status (Table II). ROMA scores were significantly higher in patients with CKD,

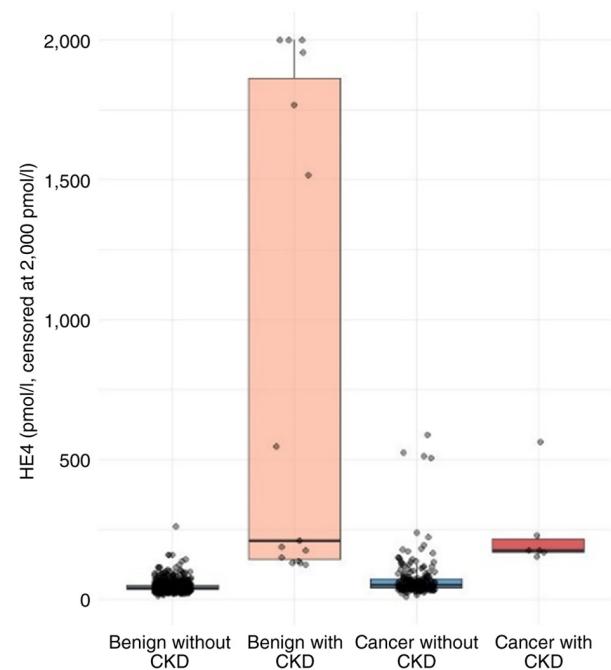


Figure 1. Serum HE4 levels according to CKD status in the benign and cancer groups. In box plots, the central line represents the median, the box represents the interquartile range, and whiskers represent the minimum and maximum values. For comparison, HE4 levels >2,000 pmol/l were censored. CKD, chronic kidney disease; HE4, human epididymis protein 4.

likely owing to elevated HE4 levels, resulting in significantly lower specificity [0.200 (95% CI, 0.066-0.470)] and accuracy [0.429 (95% CI, 0.240-0.640)].

ROC curves for ROMA were generated for patients with and without CKD (Fig. 2). ROMA scores were calculated using the appropriate algorithm according to menopausal status. The diagnostic performance of ROMA was better in

Table II. Diagnostic performance of ROMA according to CKD status.

Parameter	Without CKD (n=1,101)	With CKD (n=21)	P-value
Sensitivity (95% CI)	0.511 (0.439, 0.581)	1	0.968
Specificity (95% CI)	0.838 (0.813, 0.860)	0.200 (0.066, 0.470)	<0.001
PPV (95% CI)	0.393 (0.334, 0.456)	0.333 (0.158, 0.571)	0.615
NPV (95% CI)	0.893 (0.870, 0.912)	1	0.981
Accuracy (95% CI)	0.782 (0.757, 0.805)	0.429 (0.240, 0.640)	<0.001

Wald contrast tests from a logistic regression model were performed to compare the diagnostic performance of ROMA according to CKD status. CI, confidence interval; CKD, chronic kidney disease; NPV, negative predictive value; PPV, positive predictive value.

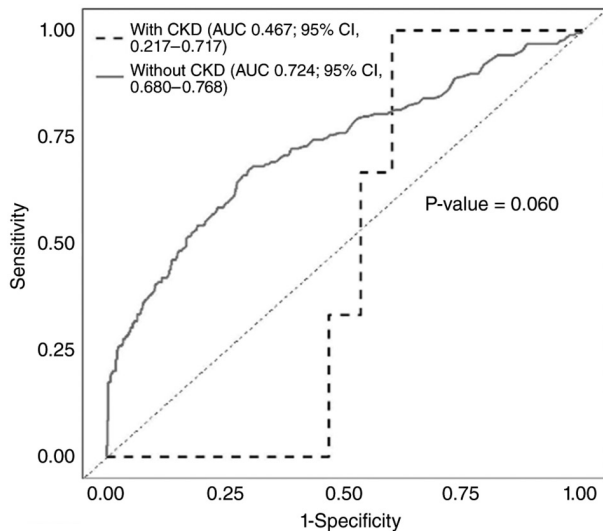


Figure 2. ROC curves of risk of ovarian malignancy algorithm in patients with and without CKD. ROC curves were generated separately for patients with and without CKD, and the P-value for the difference between the two groups was calculated. AUC, area under the curve; CI, confidence interval; CKD, chronic kidney disease; ROC, receiver operating characteristic.

patients without CKD (AUC, 0.724; 95% CI, 0.680-0.768) than in those with CKD (AUC 0.467; 95% CI, 0.217-0.717).

Discussion

CKD is a major health concern in women, with a global prevalence of 11.8% among women aged ≥ 20 years (19). Patients with CKD are more likely to have an adnexal mass detected incidentally than the general population because they undergo imaging, such as noncontrast abdominopelvic computed tomography or abdominal ultrasound, to evaluate renal status. When an ovarian tumor is identified, accurate differentiation between benign ovarian tumors and ovarian cancer is essential for determining the need for surgical intervention.

In patients with CKD, elevated HE4 levels may result from decreased HE4 clearance or increased HE4 production associated with renal dysfunction. Among 913 patients with benign ovarian tumors without CKD, HE4 levels were all <160 pmol/l. In contrast, 66.7% (10/15) of patients with CKD and benign ovarian tumors had HE4 levels >160 pmol/l, with a maximum of 8,205 pmol/l. The markedly elevated HE4 levels

in patients with CKD resulted in substantially higher ROMA scores and poor diagnostic performance for benign ovarian tumors. Patients with CKD and benign ovarian tumors had a higher median HE4 level than those without CKD (1,356.43 vs. 44.85 pmol/l). HE4 levels also increased with CKD progression, with a particularly marked increase in stage 5. These findings are consistent with previous studies (14). ROMA scores of patients with benign ovarian tumors increased with HE4 levels, whereas CA125 levels did not increase significantly. These findings suggest that ROMA does not adequately compensate for elevated HE4 levels in patients with CKD, even when CA125 and menopausal status are incorporated into the calculation.

Recent studies have suggested that urinary assays may provide a noninvasive alternative for evaluating HE4 levels. Urinary HE4 levels are significantly higher in patients with ovarian cancer than in healthy women or those with benign diseases (20,21). Unlike serum HE4, urinary HE4 was reported to be elevated only in patients with ovarian cancer and not in those with CKD, with no significant difference between patients with CKD and healthy controls (22). The urinary-to-serum HE4 ratio was therefore proposed as a potential marker for differentiating ovarian cancer from CKD. However, given the small number of participants in the previous study, prospective study with larger cohorts are needed to validate and standardize this approach before its implementation in clinical practice.

According to a recent meta-analysis of five previous studies, ROMA showed a sensitivity of 0.873 (95% CI, 0.752-0.940) and specificity of 0.855 (95% CI, 0.719-0.932) (23). In the present study, ROMA sensitivity in patients without CKD was lower (0.511; 95% CI, 0.439-0.581). Several factors may explain this difference. First, the present study included only patients with histologically confirmed diagnoses after surgery and excluded advanced ovarian cancer and hydrosalpinx that could be sufficiently characterized by preoperative imaging. Exclusion of patients with preoperative clinical/imaging findings already strongly suggestive of malignancy may have resulted in a more diagnostically challenging study population compared with studies including a broader spectrum of ovarian malignancies, and therefore may have contributed to the lower observed ROMA sensitivity. Second, a relatively large proportion of borderline tumors were classified as cancer. Among 188 patients with ovarian cancer without CKD, 94 had malignant tumors and 94 had borderline tumors. Mucinous

borderline tumors were the most prevalent subtype, and only 15 of the 56 patients were classified as high risk by ROMA, showing a low sensitivity of 26.8%. The frequency of histological subtypes in patients with malignant tumors may also be a contributing factor. HE4 expression in tumors depends on the histological subtype. Drapkin *et al* (24) demonstrated that 100% of endometrioid and 93% of serous EOCs expressed HE4; however, only 50% of clear cell carcinomas and none of the mucinous tumors were HE4-positive. Previous studies have evaluated the efficacy of ROMA according to tumor subtype. In ROC curve analysis, the serous type showed the highest AUC (0.813 in premenopausal and 0.987 in postmenopausal patients), whereas the mucinous type showed the lowest AUC (0.545 and 0.656, respectively) (25). In the present study, all 27 patients with high-grade serous adenocarcinoma were classified as high risk by ROMA, whereas only 8 of the 21 (38.1%) patients with mucinous adenocarcinoma were classified as high risk.

Dialysis status and/or timing relative to dialysis may influence serum HE4 levels and consequently ROMA scores. When blood is drawn after dialysis, serum HE4 levels may be measured lower than when drawn before dialysis due to dilution by the dialysate. In this study, blood samples from all patients undergoing dialysis were collected 2 h before dialysis.

Due to the nature of the disease, patients with CKD were older especially in the benign tumor group. Since age can independently influence HE4 and ROMA scores, this may partly contribute to the higher ROMA values. We reviewed HE4 levels, ROMA scores, and accuracy of ROMA according to age in a total of 305 benign postmenopausal patients aged 50 years or older without CKD. In 147 patients aged 50-59 and 99 patients aged 60-69, the mean HE4 levels were 63.8 and 58.3 pmol/l, the mean ROMA scores were 21.5 and 16.6, and the accuracy of ROMA was 0.809 and 0.747, respectively. However, in 59 patients aged 70 years or older, the mean HE4 levels were 88.2 pmol/l, the mean ROMA score was 24.3, and the accuracy of ROMA was 0.797. Since a rapid increase in HE4 levels and a consequent increase in ROMA scores occur in patients aged 70 years or older, caution is required when using ROMA scores in this age group, and future studies should use age-matched or adjusted analyses.

This study has some limitations. First, its retrospective design precluded assessment of certain clinical factors that may influence CA125 or HE4 levels, such as inflammation, smoking, or rheumatoid arthritis, at the time of testing. Second, the relatively small number of patients with CKD included in the study limited statistical power. Although consistently elevated HE4 levels and ROMA scores were observed among patients with CKD, these findings should be interpreted with caution as the small number of patients reduces the reliability and generalizability of the conclusions. Further studies with larger numbers of patients with CKD are needed to confirm these findings.

In conclusion, the diagnostic accuracy of ROMA was compared for differentiating ovarian tumors in patients with and without CKD. To the best of our knowledge, this is the first study to analyze the discriminatory performance of ROMA in patients with CKD who underwent surgery for ovarian tumors.

In patients with CKD, HE4 levels were elevated, with progressively higher levels observed as CKD advanced. Owing to the elevated HE4 levels in patients with CKD, ROMA scores were markedly elevated, resulting in poor diagnostic performance for differentiating benign from malignant ovarian tumors. The findings demonstrate that ROMA does not adequately compensate for elevated HE4 levels in patients with CKD, even when combined with CA125 and menopausal status. When an ovarian tumor is detected in a patient with CKD, ovarian cancer risk assessment should therefore consider CA125 and imaging findings rather than rely on ROMA alone.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Author's contributions

YJL, DHJ and SSL conceptualized the study and performed the experiments. SWK, SWY and WSS analyzed the data. YJL wrote the original draft. YJL and DHJ confirm the authenticity of all the raw data, reviewed and edited the manuscript and supervised the study. All authors read and approved the final manuscript, and agree to be accountable for all aspects of the work.

Ethics approval and consent to participate

The present study was conducted in accordance with The Declaration of Helsinki. The Institutional Review Board of Gangneung Asan Hospital determined that this retrospective study was exempt from IRB review and waived the requirement for informed consent (IRB no. 2025-10-003).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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