



Italian Journal of
Gynæcology & Obstetrics
September 2026 - Vol. 38 - N. 3 - Quarterly - ISSN 2385 – 0868

Metabolomic analysis of gynaecological cancer: identification of novel biomarkers using gas chromatography-mass spectrometry

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ARTICLE INFO

History

Received: 18 September 2025

Received in revised form: 22 November 2025

Accepted: 18 December 2025

Available online: 10 September 2026

DOI: 10.36129/jog.2026.260

Key words

Biomarker; cervical neoplasm; endometrial neoplasm; gas chromatography-mass spectrometry; ovarian neoplasm.

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ABSTRACT

Objective. This study aimed to identify novel biomarkers for gynaecological cancers – including ovarian, cervical, and endometrial cancers – using gas chromatography-mass spectrometry.

Materials and Methods. A case-control study was conducted with 16 Japanese women as controls and 73 women diagnosed with gynaecological cancers. Urine and serum samples were analysed for 90 metabolites, including amino acids, organic acids, sugars, fatty acids, and tricarboxylic acid cycle components.

Results. Significant variations were observed in numerous metabolites between the control group and patients with ovarian, cervical, and endometrial cancers. Notably, levels of glutamine, 1,5-anhydroglucitol (1,5-AG), and lactate differed significantly according to the Kruskal-Wallis test. Receiver operating characteristic (ROC) analysis showed that the area under the curve (AUC) values for urine and serum glutamine ranged from 0.764 to 0.895 across the three cancer types. For 1,5-AG, the AUC values were 0.852-0.896 for urine samples and 1.000 for serum samples. Lactate yielded AUC values ranging from 0.727 to 0.924 in urine and serum samples.

Conclusions. This study demonstrated clear differences in metabolites between controls and gynaecological cancer patients. Glutamine, 1,5-AG, and lactate may serve as useful biomarkers for ovarian, cervical, and endometrial cancers.

INTRODUCTION

Primary gynaecological cancers – including ovarian, cervical, and endometrial cancers – remain a significant global health concern for women. These malignancies often present with nonspecific symp-

toms in their early stages, making timely and accurate diagnosis critical for improving clinical outcomes. Although conventional tumour markers are widely used for screening and monitoring, their limited sensitivity and specificity have prompted the search for more reliable diagnostic strategies.

Cancer cells exhibit distinct metabolic behaviour, favouring glycolysis over oxidative phosphorylation even in oxygen-rich environments – a phenomenon known as the Warburg effect [1, 2]. This metabolic reprogramming supports rapid proliferation and survival by altering sugar, amino acid, and lipid metabolic pathways [3-5]. Metabolomics has emerged as a powerful tool to investigate these changes, offering insights into cancer biology and potential biomarkers.

Gas chromatography-mass spectrometry (GC/MS) is a widely adopted analytical technique in metabolomics, capable of detecting low-molecular-weight volatile metabolites with high sensitivity and specificity [6, 7]. Although GC/MS has been applied to explore cancer-related metabolites [8-10], comprehensive metabolic profiling in gynaecological cancers remains limited.

Several studies have identified metabolites as promising biomarkers for various malignancies [11]. In addition, molecular markers such as L1CAM have demonstrated prognostic relevance in endometrial cancer [12]. Recent investigations have highlighted diagnostic challenges in cervical adenocarcinoma [13] and evaluated clinical outcomes in ovarian cancer [14], collectively reinforcing the paradigm shift toward individualized care in gynaecologic oncology.

Building on these insights, the present study aimed to identify novel metabolic biomarkers for the early detection of ovarian, cervical, and endometrial cancers using GC/MS-based profiling of urine and serum specimens.

MATERIALS AND METHODS

Patients

This case-control study was approved by the Institutional Review Board of Kanazawa Medical University and conducted between 2017 and 2023. During this period, 38 Japanese women who underwent routine health examinations were screened. Of these, 22 were excluded according to predefined criteria, and 16 women without gynaecological abnormalities were ultimately selected as controls. In addition, 73 Japanese women with histologically confirmed gynaecological cancers who subsequently underwent surgical treatment were enrolled after providing written informed consent. The cancer cohort included patients with ovarian cancer (n = 23; high-grade serous, clear cell, mucinous, and endometrioid carcinomas), cervical cancer (n = 23; squamous cell carcinoma and adenocarcinoma), and endometrial cancer (n = 27; FIGO grades 1-3).

Matching criteria

Controls (healthy women) and cases (ovarian, cervical, and endometrial cancers) were matched based on some parameters. The mean age of the control group was 48.1 years (SD = 6.4), which overlapped with the case groups. No significant differences in BMI were observed between groups, minimizing the influence of obesity-related metabolic variations. The proportions of nulliparous and parous women were balanced, and the prevalence of smoking was comparable between groups.

Exclusion criteria

Controls: individuals with metabolic disorders, recent infections, or medication use that could affect metabolite profiles were excluded. Cases: patients undergoing active treatment, with prior chemotherapy or radiotherapy, or with compromised sample integrity (e.g., haemolysis or contamination) were excluded.

Specimen collection and handling

Fasting morning urine (15 mL) and venous blood (5 mL) samples were collected from each participant. Blood samples were centrifuged at 1,800 rpm for 3 minutes at 4 °C, and both serum and urine samples were aliquoted and stored at -80 °C within 2 hours of collection. Sample integrity was assessed by evaluating haemolysis and measuring total protein concentrations.

Quality control measures

Histopathological diagnoses were independently confirmed by two board-certified pathologists. Sample processing protocols were standardized to minimize batch effects. Clinical data – including age, BMI, tumour histology, disease stage, and laboratory parameters – were systematically extracted from electronic medical records. All analytical procedures were conducted in a blinded fashion to ensure objectivity.

Gas chromatography-mass spectrometry

GC/MS analysis was performed using a JMS-K9 instrument (JEOL, Tokyo, Japan), which enables sensitive and precise detection of trace components in complex biological samples. Urine and serum

metabolites – including amino acids, organic acids, sugars, fatty acids, and tricarboxylic acid (TCA) cycle-related compounds – were separated by gas chromatography and identified by mass spectrometry. Urine metabolites were normalized to creatinine levels, and serum metabolites were corrected using internal standards.

Statistical analysis

A total of 90 metabolites were examined: 28 amino acids, 24 organic acids, 15 sugars, 15 fatty acids, and 8 TCA cycle-related compounds (Table 1). Comparisons between controls and cancer patients were performed using the Mann-Whitney U test and the Kruskal-Wallis test. Receiver operating characteristic (ROC) curve analyses were conducted with EZR (version 1.68; Saitama Medical Center, Jichi Medical University, Japan) to assess the diagnostic performance of selected metabolites. For each metabolite, the area under the curve (AUC) was calculated, and optimal cutoff values were determined using the Youden Index. The statistical significance of AUCs was evaluated with DeLong's method, and P-values were adjusted for multiple testing using the Benjamini-Hochberg procedure to control the false discovery rate. All other statistical analyses were performed with GraphPad Prism 9 (version 9.2.0; GraphPad Software, San Diego, CA, USA). A P-value < 0.05 was considered statistically significant.

RESULTS

The clinical characteristics of the participants' urine and serum samples are summarized in Table 2 and Table 3, respectively. Cervical cancer was more prevalent among multiparous women, whereas endometrial cancer was more common among nulliparous individuals. Additionally, diabetes was more frequently observed in patients with endometrial cancer.

Due to missing urine samples, the final analysis included 16 controls, 11 ovarian cancer patients, 6 cervical cancer patients, and 19 endometrial cancer patients. Serum sample loss was minimal, with samples available from 16 controls, 23 ovarian cancer patients, 23 cervical cancer patients, and 27 endometrial cancer patients.

A total of 90 metabolites were analysed in urine and serum samples from both control and cancer groups. Significant differences in metabolite levels

Table 1. List of analysed metabolites.

Amino acids					
1	Alanine	11	Homoserine	21	Lysine 1
2	Glycine 1	12	Aspartate	22	Glutamine
3	Sarcosine	13	Methionine	23	Tyrosine 1
4	Valine	14	Pyroglutamate	24	Histidine
5	Leucine	15	4-Hydroxyproline	25	Lysine 2
6	Proline	16	Phenylalanine 1	26	Tyrosine 2
7	Isoleucine	17	Ornithine	27	β-Alanine
8	Glycine 2	18	Glutamate	28	Dimethylglycine
9	Serine	19	Phenylalanine 2		
10	Threonine	20	Asparagine		
Organic acids					
1	Glycolate	11	Phenyllactic acid	21	Hypoxanthine
2	3HP	12	Glycerol 3-phosphate	22	Urate
3	Cresol	13	Vitamin C	23	Pseudouridine
4	3HIB	14	Phthalic acid	24	Xanthine
5	2HIV	15	2-ketoisocaproate		
6	3HIV	16	2-hydroxyisobutyrate		
7	Urea	17	3AIB		
8	Phosphate	18	4-Deoxytetronic acid		
9	Glutarate	19	3-Deoxytetronic acid		
10	Erythronate	20	2-Deoxytetronic acid		
Sugars					
1	Erythritol	11	Arabinose		
2	Arabitol	12	Fucose		
3	Fructose	13	Sucrose		
4	Glucose1	14	Lactose		
5	Mannitol	15	1,5-Anhydroglucitol		
6	Chiro-inositol				
7	Glucose2				
8	Epi-inositol				
9	Myo-inositol				
10	Ribose				
Fatty acids					
1	Glycerol	11	C16:0		
2	Adipate	12	C16:1		
3	Suberate	13	C18:0		
4	Sebacate	14	C18:1		
5	C12DC:1	15	C18:2		
6	C6:0				
7	C8:0				
8	C10:0				
9	C12:0				
10	C14:0				
TCA cycle					
1	Lactate				
2	2HB				
3	Pyruvate				
4	3HB				
5	Succinate				
6	Fumarate				
7	Malate				
8	Citrate				

3HP: 3-hydroxypropionic acid; 3HIB: 3-hydroxyisobutyric acid; 2HIV: 2-hydroxyisovaleric acid; 3HIV: 3-hydroxy 3-methylbutyrate; 3AIB: 3-aminoisobutyric acid; 2HB: 2-hydroxybutyric acid; 3HB: 3-hydroxybutyric acid; C6:0: Caproic acid; C8:0: Octanoic acid; C10:0: Decanoic acid; C12:0: Lauric acid; C14:0: Myristic acid; C16:0: Palmitic acid; C16:1: Palmitoleic acid; C18:0: Stearic acid; C18:1: Oleic acid; C18:2: Linoleic acid.

Table 2. Participant characteristics (urine cohort).

Variables (urine)	Control (n = 16)	Ovarian cancer (n = 11)	Cervical cancer (n = 8)	Endometrial cancer (n = 19)
Age, mean (SD)	48.1 (6.4)	53.8 (17.6)	54.9 (17.6)	56.3 (13.7)
Age, range	38 - 59	31 - 84	36 - 82	29 - 74
BMI, median	21.3	20.3	20.4	24.8
Parity				
Nulliparous, 0	0	5	0	8
Multiparous, 1 - 4	16	6	7	11
Smoking status				
Non-smoker	12	10	7	19
Smoker	4	1	1	0
Diabetes mellitus				
No	16	10	7	13
Yes	0	1	1	6
Diagnostic pathology				
Ovarian cancer		High grade serous ca (n = 6) Clear cell ca (n = 3) Mucinous ca (n = 2)		
Cervical cancer			Squamous cell ca (n = 2) Cervical adenoca (n = 6)	
Endometrial cancer				Endometrioid ca G1 (n = 10) Endometrioid ca G2 (n = 7) Endometrioid ca G3 (n = 29)

SD: standard deviation; BMI: Body mass index; Ca: carcinoma.

Table 3. Participant characteristics (serum cohort).

Variables (serum)	Control (n = 16)	Ovarian cancer (n = 23)	Cervical cancer (n = 23)	Endometrial cancer (n = 27)
Age, mean (SD)	48.1 (6.4)	57.1 (16.4)	53.5 (15.8)	55.9 (14.1)
Age, range	38 - 59	31 - 84	31 - 82	29 - 75
BMI, median	21.3	20.9	21.0	24.2
Parity				
Nulliparous, 0	0	9	2	10
Multiparous, 1 - 4	16	14	21	17
Smoking status				
Non-smoker	12	22	19	25
Smoker	4	1	4	2
Diabetes mellitus				
No	16	18	20	20
Yes	0	5	3	7
Diagnostic pathology				
Ovarian cancer		High grade serous ca (n = 12) Clear cell ca (n = 6) Mucinous ca (n = 3) Endometrial ca (n = 2)		
Cervical cancer			Squamous cell ca (n = 13) Cervical adenoca (n = 10)	
Endometrial cancer				Endometrioid ca G1 (n = 15) Endometrioid ca G2 (n = 10) Endometrioid ca G3 (n = 2)

SD: standard deviation; BMI: Body mass index; Ca: carcinoma.

Table 4. Metabolite levels in controls and patients with gynaecological cancer.

Metabolites	Control vs Ovarian cancer	Control vs Cervical cancer	Control vs Endometrial cancer
Amino acids			
Urine-Glutamine	0.0003***	0.0001***	< 0.0001****
Serum-Glutamine	< 0.0001****	0.0023**	0.0035**
Organic acids			
Urine-PLA	0.0004***	0.0066**	0.0009***
Serum-PLA	0.0001***	0.0695	0.0327*
Sugars			
Urine-1,5-AG	0.0007***	0.0005***	< 0.0001****
Serum-1,5-AG	< 0.0001****	< 0.0001****	< 0.0001****
Fatty acids			
Urine-C14:0	< 0.0001****	0.0002***	< 0.0001****
Serum-C14:0	0.0094**	0.0086**	0.0076**
Urine-C18:2	0.0002***	0.0002***	0.0005***
Serum-C18:2	< 0.0001****	0.0134*	0.0003***
TCA related			
Urine-Lactate	0.0501	0.0028**	< 0.0001****
Serum-Lactate	< 0.0001****	< 0.0001****	< 0.0001****

PLA: phenyllactic acid; 1,5-AG: 1,5-anhydroglucitol; C14:0: myristic acid; C18:2: linoleic acid. Statistical significance was assessed using the Mann-Whitney U test. Asterisks indicate significance levels: $p < 0.05$ *, $p < 0.01$ **, $p < 0.001$ ***, $p < 0.0001$ ****.

were observed between cancer patients and controls. Glutamine was consistently elevated in both urine and serum across all cancer types. As shown in **Table 4**, phenyllactic acid (PLA), 1,5-anhydroglucitol (1,5-AG), myristic acid (C14:0), and linoleic acid (C18:2) also exhibited notable changes. Lactate was elevated in serum for all cancers, while urine lactate was increased in cervical and endometrial cancers, with only a borderline trend in ovarian cancer. These results suggest that these metabolites may serve as useful biomarkers for gynaecological cancers. Among the metabolites examined, glutamine, 1,5-AG, and lactate showed statistically significant differences according to the Kruskal-Wallis test (**Figure 1**).

Urine glutamine levels were significantly higher in patients with ovarian ($p = 0.0080$), cervical ($p = 0.0142$), and endometrial cancer ($p = 0.0015$) compared with controls. Serum glutamine levels were elevated in ovarian cancer ($p < 0.0001$) and cervical cancer ($p = 0.0322$). In endometrial cancer, levels showed a slight increase, but this was not statistically significant ($p = 0.0504$). ROC analysis revealed AUC values for urine and serum glutamine of 0.838 and 0.891 (ovarian), 0.895 and 0.783 (cervical), and 0.841 and 0.764 (endometrial), respectively.

For 1,5-AG, urine levels were significantly higher in patients with cervical ($p = 0.0020$) and endome-

trial cancer ($p = 0.0001$), but no significant difference was observed in ovarian cancer patients ($p = 0.1233$). Serum 1,5-AG levels showed significant differences across all cancer types ($p < 0.0001$). The corresponding AUC values for urine and serum 1,5-AG were 0.852 and 1.000 (ovarian), 0.879 and 1.000 (cervical), and 0.896 and 1.000 (endometrial), respectively.

Similarly, urine lactate levels were significantly elevated in patients with cervical ($p = 0.0300$) and endometrial cancer ($p = 0.0004$), but not in those with ovarian cancer ($p = 0.2407$). Serum lactate levels differed significantly among all cancer types, with P-values of < 0.0001 , 0.0002, and 0.0001, respectively. AUC values for urine and serum lactate were 0.727 and 0.902 (ovarian), 0.867 and 0.859 (cervical), and 0.891 and 0.924 (endometrial), respectively.

Collectively, these findings (**Table 5**) underscore the diagnostic potential of glutamine, 1,5-AG, and lactate as promising biomarkers for the early detection of ovarian, cervical, and endometrial cancers.

DISCUSSION

Metabolic reprogramming has emerged as a hallmark of gynaecological cancers, reflecting the

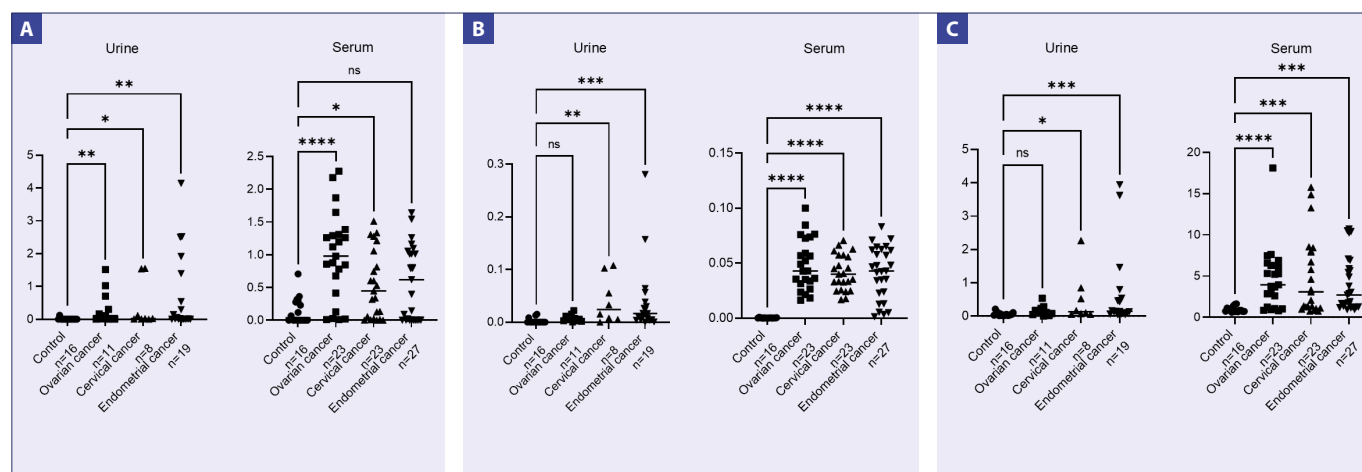


Figure 1. Comparative analysis of urine and serum metabolites in patients with gynaecological cancer.

(A) Glutamine: comparison of urine glutamine levels between the control (n = 16) and ovarian cancer (n = 11) groups; $p = 0.0080$. Comparison of urine glutamine levels between the control (n = 16) and endometrial cancer (n = 19) groups; $p = 0.0015$. Comparison of serum glutamine levels between the control (n = 16) and ovarian cancer (n = 23) groups; $p < 0.0001$. Comparison of serum glutamine levels between the control (n = 16) and cervical cancer (n = 23) groups; $p = 0.0322$. Comparison of serum glutamine levels between the control (n = 16) and endometrial cancer (n = 27) groups; $p = 0.0504$. **(B) 1,5-Anhydroglucitol:** comparison of urine 1,5-anhydroglucitol levels between the control (n = 16) and ovarian cancer (n = 11) groups; $p = 0.1233$. Comparison of urine 1,5-anhydroglucitol levels between the control (n = 16) and cervical cancer (n = 8) groups; $p = 0.0020$. Comparison of urine 1,5-anhydroglucitol levels between the control (n = 16) and endometrial cancer (n = 19) groups; $p = 0.0001$. Comparison of serum 1,5-anhydroglucitol levels between the control (n = 16) and ovarian cancer (n = 23) groups; $p < 0.0001$. Comparison of serum 1,5-anhydroglucitol levels between the control (n = 16) and cervical cancer (n = 23) groups; $p < 0.0001$. Comparison of serum 1,5-anhydroglucitol levels between the control (n = 16) and endometrial cancer (n = 27) groups; $p < 0.0001$. **(C) Lactate:** comparison of urine lactate levels between the control (n = 16) and ovarian cancer (n = 11) groups; $p = 0.2407$. Comparison of urine lactate levels between the control (n = 16) and cervical cancer (n = 8) groups; $p = 0.0300$. Comparison of urine lactate levels between the control (n = 16) and endometrial cancer (n = 19) groups; $p = 0.0004$. Comparison of serum lactate levels between the control (n = 16) and ovarian cancer (n = 23) groups; $p < 0.0001$. Comparison of serum lactate levels between the control (n = 16) and cervical cancer (n = 23) groups; $p = 0.0002$. Comparison of serum lactate levels between the control (n = 16) and endometrial cancer (n = 27) groups; $p = 0.0001$.

Table 5. Diagnostic performance of urine and serum metabolites in gynaecological cancers based on roc analysis.

Cancer type	Sample	AUC	95%CI	Cut-off point	Sensitivity (%)	Specificity (%)
Glutamine						
Ovarian Cancer	Urine	0.838	0.688 – 0.988	> 0.014	72.73	93.75
	Serum	0.891	0.792 – 0.991	> 0.415	78.26	93.75
Cervical Cancer	Urine	0.895	0.747 – 1.000	> 0.010	87.50	93.75
	Serum	0.783	0.637 – 0.928	> 0.449	52.17	93.75
Endometrial Cancer	Urine	0.841	0.723 – 0.957	> 0.0002	73.68	93.75
	Serum	0.764	0.617 – 0.911	> 0.397	55.56	93.75
1,5-Anhydroglucitol						
Ovarian Cancer	Urine	0.852	0.690 – 1.000	> 0.0003	100.0	81.25
	Serum	1.000	1.000 – 1.000	> 0.016	100.0	100.0
Cervical Cancer	Urine	0.879	0.722 – 1.000	> 0.005	87.50	81.25
	Serum	1.000	1.000 – 1.000	> 0.017	100.0	100.0
Endometrial Cancer	Urine	0.896	0.791 – 1.000	> 0.001	94.74	81.25
	Serum	1.000	1.000 – 1.000	> 0.001	100.0	100.0
Lactate						
Ovarian Cancer	Urine	0.727	0.501 – 0.954	> 0.083	72.73	81.25
	Serum	0.902	0.811 – 0.993	> 2.602	73.91	100.0
Cervical Cancer	Urine	0.867	0.724 – 1.000	> 0.059	100.0	68.75
	Serum	0.859	0.745 – 0.973	> 1.128	78.26	81.25
Endometrial Cancer	Urine	0.891	0.787 – 0.996	> 0.063	89.47	75.00
	Serum	0.924	0.847 – 1.000	> 1.141	92.59	81.25

AUC: Area Under the Curve; CI: Confidence Interval.

unique bioenergetic and biosynthetic demands of tumour cells. In this study, we performed comprehensive metabolomic profiling of urine and serum samples to explore their diagnostic potential. Among the 90 metabolites analysed, glutamine, 1,5-AG, and lactate exhibited significant alterations between healthy controls and cancer patients, implicating their involvement in tumour-associated metabolic pathways.

Glutamine, a conditionally essential amino acid, plays a central role in maintaining redox balance and supporting anabolic processes in cancer cells [15-22]. In our cohort, both urine and serum glutamine levels were significantly altered in cancer patients compared with controls, with the most pronounced differences observed in ovarian cancer, where glutamine dependence is well established [19-21]. Elevated expression of SNAT1, a glutamine transporter, has been linked to poor prognosis in cervical cancer. In endometrial cancer, glutamine-driven metabolism promotes tumour growth and inhibits autophagy. These findings underscore glutamine's pivotal role in tumour progression and its potential as a therapeutic target in gynaecological cancers.

1,5-AG, a glucose-like polyol that reflects short-term glycaemic control, competes with glucose for renal reabsorption. In this study, both urinary and serum levels of 1,5-AG were significantly altered in cancer patients, although urinary levels in ovarian cancer did not differ significantly from controls. Previous studies have reported inconsistent associations between 1,5-AG and cancer risk, including its predictive value for cancer mortality and an inverse relationship with pancreatic cancer [23-25]. Our findings suggest a positive association with gynaecological cancers, even after excluding patients with diabetes. These discrepancies may reflect tumour-specific metabolic adaptations and warrant further investigation in larger, more diverse cohorts.

Lactate, a key byproduct of aerobic glycolysis, contributes to tumour progression by modulating immune responses, promoting angiogenesis, and facilitating metastasis [26-29]. In our study, elevated lactate levels were observed in both urine and serum samples from patients with cervical and endometrial cancers, consistent with previous reports of increased lactate production in ovarian cancer cells [30-32]. High plasma lactate has also been associated with cervical lesion severity, poor survival in head and neck cancers [33], and enhanced

proliferation in endometrial cancer as revealed by NMR-based metabolomics [34]. Metabolic studies in cervical cancer further support the roles of lactate and glutamine in tumour progression [35]. These findings suggest that elevated lactate levels may reflect enhanced glycolytic activity and mitochondrial reprogramming in gynaecological cancers.

Beyond metabolic profiling, clinical parameters also influence prognosis. Vizza *et al.* [36] demonstrated that vaginal cuff length in low-risk endometrial cancer surgery correlates with survival and recurrence. Perrone *et al.* [37] emphasized the therapeutic relevance of targeting the BRAF pathway in low-grade serous ovarian cancer. D'Oria *et al.* [38] provided an updated overview of systemic pharmacotherapy for recurrent cervical cancer. These studies highlight the importance of integrating metabolic, molecular, and surgical factors to improve prognostic accuracy and support personalized management in gynaecological cancers.

ROC analysis revealed high AUC values for glutamine, 1,5-AG, and lactate, indicating strong discriminatory power between cancer patients and healthy individuals. These results support their potential utility as non-invasive biomarkers for early detection.

This study has several limitations. First, the relatively small sample size limits the generalizability of our findings. Second, sample subdivision and repeated GC/MS analyses may have introduced minor variability. Third, the study population consisted exclusively of Japanese women, which may limit applicability to other ethnic groups. Finally, the cross-sectional design precludes assessment of longitudinal metabolic changes during disease progression or treatment. Larger, multicentre prospective studies are needed to validate these findings and enhance diagnostic robustness.

CONCLUSIONS

In conclusion, the metabolites glutamine, 1,5-AG, and lactate exhibited significant alterations in both urine and serum samples from patients with gynaecological cancers. Supported by ROC analysis with high AUC values, these metabolites reflect key aspects of cancer metabolism and hold promise as robust non-invasive biomarkers for early detection and prognostic assessment in gynaecological cancers.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

H.T.: Conceptualization, formal analysis, writing – original draft, writing – review & editing. S.S., E.T.: Data curation. C.Z.: Formal analysis, writing – review & editing. M.T., T.S.: Formal analysis.

Funding

None.

Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

This study was approved by the Institutional Review Board of Kanazawa Medical University [approval number: I282].

Informed consent

All participants signed an informed consent statement before participating in the study.

Data sharing

Data are available under reasonable request to the corresponding author.

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