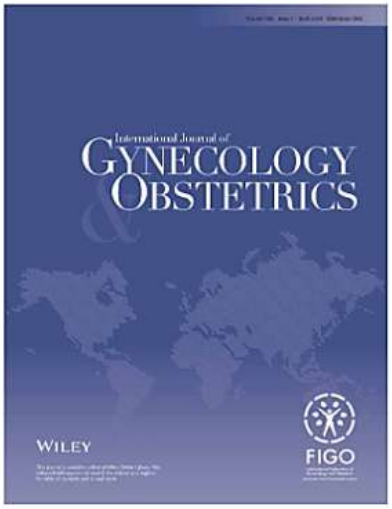


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DOI: https://doi.org/10.1002/ijgo.15513

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Received: 19 December 2023 | Revised: 13 March 2024 | Accepted: 18 March 2024

DOI: 10.1002/ijgo.15513

CLINICAL ARTICLE

Gynecology

Expression of netrin-1 in uterine serous carcinoma and its association with prognosis

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Funding information
Kocaeli Üniversitesi, Grant/Award Number: TSA-2022-2921

Abstract

Background/Objectives: At present, there are few biomarkers used to predict the prognosis of uterine serous carcinoma (USC). Netrin-1 may be a promising biomarker candidate. We investigated netrin-1 expression in USC tissues and healthy endometrial tissues to determine its relevance to disease prognosis.

Materials and Methods: Netrin-1 expression was examined in the tissues of 48 patients with USC and 30 patients with healthy benign endometrial tissues via immunohistochemistry.

Results: None of the healthy tissues were stained with netrin-1. In tumor tissues, the overall positivity rate of netrin-1 was 75%, detected as high expression in 17 patients (35%) and low in 19 (40%). Patients who had tumors with no netrin-1 expression ($n=12$) had a median overall survival (OS) of 60.0 months (95% confidence interval [CI], 47–98), whereas patients who had tumors with low to strong netrin-1 expression ($n=33$) had a lower median OS of 50 months, but the difference was not statistically significant (95% CI, 58–108; $P=0.531$). Disease-free survival (DFS) was not statistically significant between the groups (95% CI, 67.7–115.9; $P=0.566$). Patients with a tumor diameter ≥2 cm had higher netrin-1 expression than those with a tumor diameter of 2 cm ($P=0.027$). We did not find any difference in overall and DFS when age, tumor stage, histology, tumor diameter, p53 status, lymphovascular space invasion, myometrial invasion, and lymph node metastasis were compared according to netrin-1 expression ($P>0.05$).

Conclusion: Netrin-1 was expressed in USC but not in healthy tissues. Its expression was not associated with OS or DFS.

KEYWORDS
biomarker, immunohistochemistry, netrin-1, prognosis, uterine serous carcinoma

1 | INTRODUCTION

Estimates from GLOBOCAN 2020 showed that endometrial uterine carcinoma is the fifth most common malignancy in women in Turkey and the most common gynecological tumor worldwide.[1] Uterine serous carcinoma (USC) is a highly aggressive endometrial cancer (EC); it accounts for 5% to 10% of all endometrial malignancies. Although patients with USC are more likely to be diagnosed

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at an earlier stage of the disease than those with the endometrial subtype, they have a higher tendency to experience recurrence and have poor overall prognosis.[2] Accounting for only a small percentage of EC cases, USC is responsible for almost 40% of disease-related deaths.[3,4] Despite maximal surgery, adjuvant radiation, and chemotherapy, patients usually die because of distant metastasis.[5] If the disease recurs, there is no effective chemotherapy or targeted therapies with proven efficacy other than carboplatin and paclitaxel.[6] Furthermore, there is an extremely low number of prognostic biomarkers identified in the literature.[7]

Biomarkers are powerful tools for determining cancer status and progression as well as efficacy and safety of new treatments.[8] If used to monitor drug response, they could provide important therapeutic benefits in clinical oncology. However, very few biomarkers are used for the clinical diagnosis and prognosis prediction of EC.[9] Furthermore, most of these biomarkers have low sensitivity and specificity and cannot be used effectively. They may also be nonspecifically elevated in noncancerous diseases. Therefore, the development of effective biomarkers for EC diagnosis and therapy is urgently needed.

Netrin-1 is an important biomarker candidate for predicting cancer prognosis and improving therapy.[10] It is a laminin-related protein that functions as neuronal guidance during nervous system development. Netrin-1 exerts its biological effects by binding to two familial receptors belonging to the DCC (deleted in colorectal cancer) and UNC5H (uncoordinated-5 homolog) families. Studies have reported that netrin-1 expression is not limited to the nervous system. It also plays a role in the developmental pattern of epithelial tissues in organs such as the mammary glands, pancreas, and lungs by regulating adhesion, motility, proliferation, and apoptosis.[11,12] Moreover, it regulates inflammation, angiogenesis, and apoptosis. Netrin-1 is highly expressed in many cancer tissues, and inhibition (downregulation) of its expression results in the progression of tumor cell apoptosis, leading to tumor regression.[13]

At present, there are no data in the literature regarding netrin-1 expression in USC tissue. We hypothesized that netrin-1 expression is associated with patient survival. Therefore, we investigated netrin-1 expression in USC and analyzed its relevance as a prognostic marker for future studies.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

We retrospectively analyzed patients pathologically diagnosed with USC (both serous and mixed serous) who underwent surgery between January 2009 and December 2021 at Kocaeli University Hospital (Kocaeli, Turkey). The USC diagnosis was confirmed by three expert pathologists (B.Y.B., C.V., and E.B.T.). The same patients' healthy endometrial tissues were chosen to serve as the control group. Netrin-1 did not stain the healthy endometrial tissue in those patients. We also established a control group with healthy endometrial tissue found by biopsy but who did not have a cancer diagnosis in order to increase consistency.

Patients with FIGO (the International Federation of Gynecology & Obstetrics) stage I to III EC were included, whereas those with stage IV EC at the time of diagnosis were excluded. The study protocol was approved by the institutional review board of Kocaeli University School of Medicine (ethics approval number: KU GOKAEK-2022/03). The requirement for informed consent was waived due to the retrospective nature of the study. Clinical information was obtained from existing medical records, including demographic, surgical, and pathological details (e.g. histology, FIGO stage, tumor diameter, p53 status, lymphovascular space invasion [LVSI], myometrial invasion [MI], and pelvic and para-aortic lymph node status) and follow-up data. Overall survival (OS), local recurrence, distant metastasis, and disease-free survival (DFS) were calculated from the date of surgery.

2.2 | Immunohistochemistry

An immunoreaction kit was used for the streptavidin–biotin–peroxidase complex (Leica Biosystems). Paraffin-embedded tissues were divided into 4-mm-thick sections, which were subsequently dewaxed in xylene and dehydrated in varying degrees of ethanol. The normal method was followed for antigen retrieval. To inhibit endogenous peroxidase activity, the sections were chilled and submerged in 0.3% hydrogen peroxide solution for 15 min. Subsequently, the sections were washed with phosphate-buffered saline for 5 min. Incubation with 5% bovine serum albumin at room temperature for 30 min prevented nonspecific labeling. Then, the sections were incubated with primary rabbit anti-human antibody against netrin-1 (bs-1858R Ntn1/netrin-1 antibody, diluted in 1:200; BIOSS Antibodies Inc.) at 4°C overnight, washed with phosphate-buffered saline, and then incubated with a secondary goat anti-rabbit IgG antibody conjugated to horseradish peroxidase. This antibody was developed using peroxidase-conjugated streptavidin and diaminobenzidine. The sections were stained with hematoxylin and then dehydrated and clearly sealed. Subsequently, they were examined under a microscope using the known positive sections as positive control and the phosphate-buffered saline as negative control instead of the primary antibody.

2.3 | Scoring system

For the double-blind pathological and clinical data, two pathologists selected the visual fields and recorded the proportion of positively stained cells relative to the total number of tumor and normal cells. Separate calculations were made, and the ultimate confirmation of the results came from the discussion. In each patient sample, five high-power fields (×400) were randomly selected, and the staining intensity and proportion of positive cells were used as the reference indices by the relevant references.[14–16] The staining intensity was scored as follows: 0 for no

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coloring; 1 for pale yellow; 2 for brown yellow; and 3 for brown; the proportion of positive cells was graded as follows: 0 for <10%; 1 for 11% to 25%; 2 for 26% to 50%; and 3 for >50% (Figure 1). The basis for judgment was the sum of the two scores. A value >3 indicates high expression, whereas a value ≤3 indicates low expression.

2.4 | Statistical analysis

The main primary outcome of the study was to show netrin-1 expression in USC but not in healthy tissue. A semiquantitative evaluation scale was developed based on the percentage of endometrial netrin-1 expression and was therefore classified as having no (<10%), low (11%–50%), or high (>50%) expression. The other primary outcome was to investigate the relationship of netrin-1 expression with OS and DFS. The OS and DFS were defined as the time from surgery until the patient's last clinic visit. Comparing clinicopathologic features with netrin-1 expression was the secondary outcome. These features were age, stage, tumor size, p53, LVSI, MI, and pelvic and para-aortic lymph node status. For statistical analysis, the conformity of the variables to the normal distribution was examined using the Kolmogorov–Smirnov test. Descriptive statistics are expressed as mean, standard deviation, median, and minimum–maximum. Categorical variables are expressed as frequencies (numbers) and percentages. To compare categorical variables, χ^2 test was employed. OS and DFS were analyzed using the Kaplan–Meier method. Furthermore, the median survival times were compared using log-rank test. Data were analyzed using SPSS version 20 software (IBM), and $P < 0.05$ was considered to indicate statistical significance.

3 | RESULTS

A total of 54 consecutive patients diagnosed with serous or mixed USC who underwent primary surgery at our institution between January 2009 and December 2021 were analyzed. Among them, 48 whose pathology specimens were available for immunohistochemistry (IHC) analysis and 30 with resected healthy endometrial tissue, used as the control group, were included in the study. Patient and treatment characteristics are summarized in Table 1.

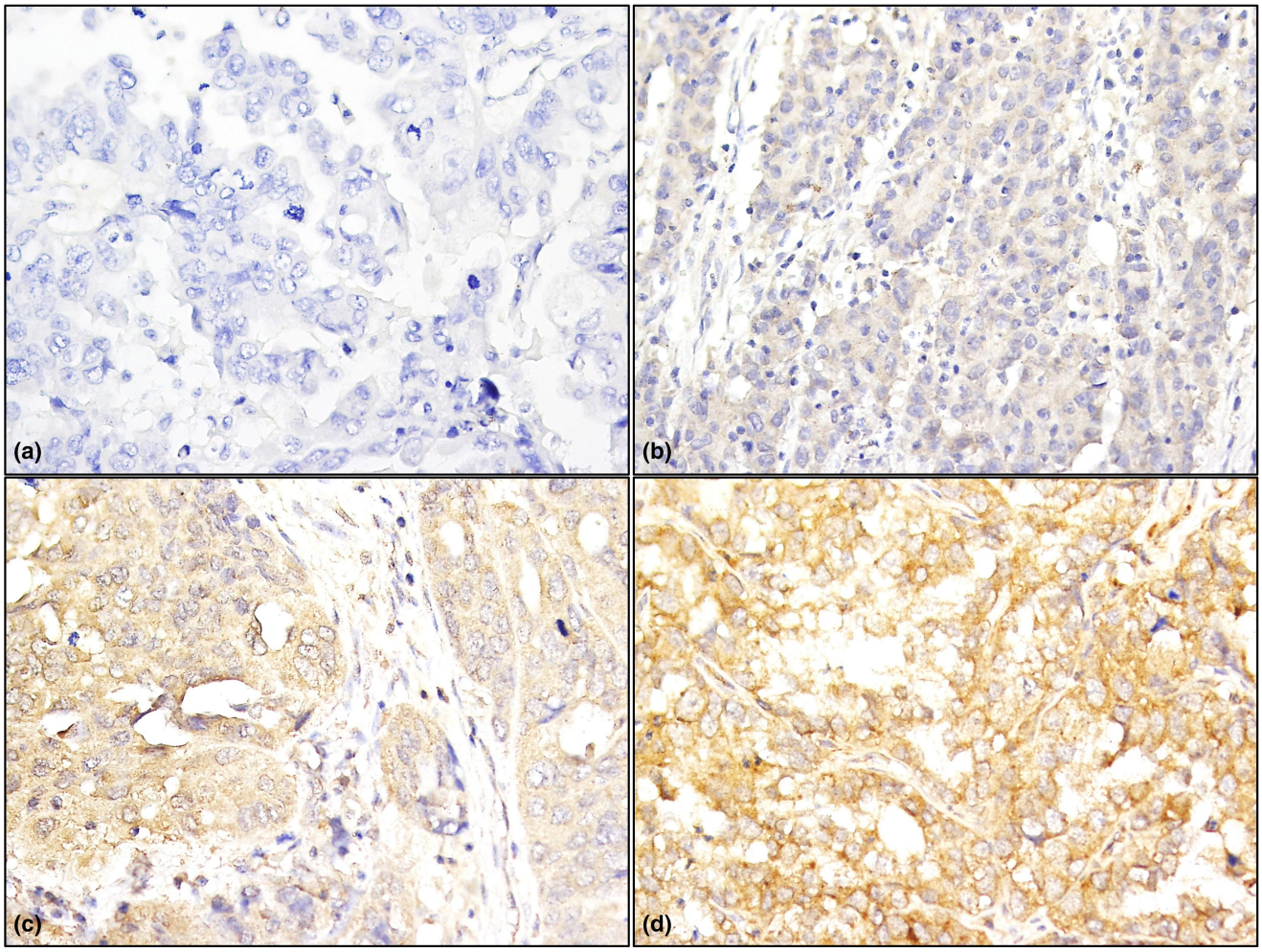


FIGURE 1 Light microscopy images of immunohistochemical staining for netrin-1 detected in endometrial serous carcinoma cells (a) with a staining intensity score of 0 (×400); (b) with a staining intensity score of 1 (×400); (c) with a staining intensity score of 2 (×400); and (d) with a staining intensity score of 3 (×400).

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TABLE 1 Clinicopathological and treatment characteristics of patients with USC.

Characteristic	No. of patients	Percentage
Age at surgery (year)		
Mean ± SD	63.87 ± 9.55	
Range	34–84	
≤60	21	44
>60	27	56
Tumor stage (FIGO)		
1A	15	31
1B	7	15
2	8	17
3A/B	6	12
3C	12	25
Tumor diameter		
<2 cm	19	40
≥2 cm	29	60
Lymphovascular invasion		
Yes	12	25
No	36	75
Myometrial invasion		
Yes	20	42
No	28	58
p53 Status		
Mutant	24	50
Wild	24	50
Positive lymph nodes		
Pelvic	6	13
Paraaortic	12	25
Adjuvant treatment		
Chemotherapy+EBRT	6	13
Chemotherapy+EBRT+VBT	25	52
Only EBRT+VBT	14	29
Only EBRT	3	6
Local recurrence		
Yes	5	10
No	43	90
Distant recurrence		
Yes	24	50
No	24	50

Abbreviations: EBRT, external beam radiation therapy; FIGO, the International Federation of Gynecology & Obstetrics; USC, uterine serous carcinoma; VBT, vaginal brachytherapy.

3.1 | Survival data and relationship with netrin-1 expression

The median follow-up was 45 months (range, 6–182 months). The 3- and 5-year OS rates were 60% and 43.9% and the DFS rates were 52.8% and 44.8%, respectively. According to the FIGO stage, the 3- and 5-year OS rates for the early stage (stages I or II) were 69.7% and 51.1% and the DFS rates were 65.5% and 56.1%, respectively. For stage III, the 3- and 5-year OS rates were 44.4% and 31.7% and the DFS rates were 33.3% and 27.8%, respectively. The median OS (60 vs 33 months, $P=0.05$) was lower in stage III than in the early stages (Figure 2). The median DFS was not reached in stages I and II, whereas the median DFS was lower in stage III and at 18 months (standard error [SE], 7.42 [95% CI, 3.44–32.55]). This difference was significant for DFS ($P=0.03$) (Figure 2).

In the control group, it was observed that netrin-1 did not show any staining in healthy endometrial tissues (Figure 3). The overall positivity rate of netrin-1 in USC tissues was 75%, detected as high expression in 17 patients (35%) and low expression in 19 (40%). Patients with high and low expression intensities were pooled together, and two groups (netrin-1 expressed and not expressed) were established for statistical comparison. Patients who had tumors with no netrin-1 expression ($n=12$) had a median OS of 60.0 months (95% CI, 47–98), whereas patients who had tumors with low to strong expression ($n=36$) had a lower median OS of 50 months, but the difference was not statistically significant (95% CI, 70.3–114.6 [$P=0.531$]). No significant difference was observed between the groups in terms of DFS rates (95% CI, 67.7–115.9; $P=0.566$). The survival curves are shown in Figure 4. Furthermore, no significant difference in OS and DFS was observed when age, tumor stage, histology, tumor diameter, LVSI, MI, p53 status, lymph node metastasis, and adjuvant chemotherapy were compared according to netrin-1 expression ($P>0.05$).

3.2 | Clinical and treatment characteristics of the patients and relationship with netrin-1 expression

The mean age of the patients was 63.8 years (range, 34–84 years). FIGO staging was performed. More than half of the patients (63%) were classified as having early-stage EC (FIGO stage IA–B/II). The median tumor diameter was 4.5 cm (±2.47; 1–12 cm). The tumor histology was serous in 37 patients (77%) and mixed serous in 11 (23%). Furthermore, LVSI was present in 12 patients (25%) and MI in 20 (42%). Lymph node metastasis was detected in 18 patients (37%). Most of the patients were given adjuvant chemotherapy (65%), and all of them underwent adjuvant radiotherapy. Local and distant recurrence was detected in five and 24 patients, respectively.

A statistically significant correlation was observed only between tumor diameter (≥2 cm) and netrin-1 expression. The other correlation results between netrin-1 expression and clinicopathological characteristics are shown in Table 2.

4 | DISCUSSION

USC is an aggressive and rare subtype of EC. However, the best adjuvant treatment for this disease has not yet been established, particularly

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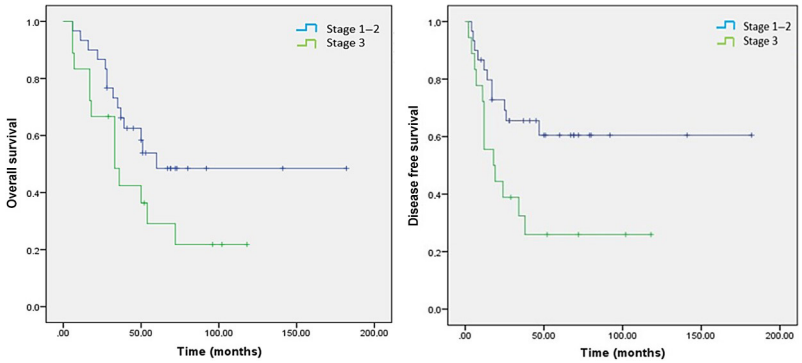


FIGURE 2 Kaplan–Meier overall survival and disease-free survival analysis curve of patients with uterine serous carcinoma according to disease stage grouping (stages 1 and 2 vs stage 3).

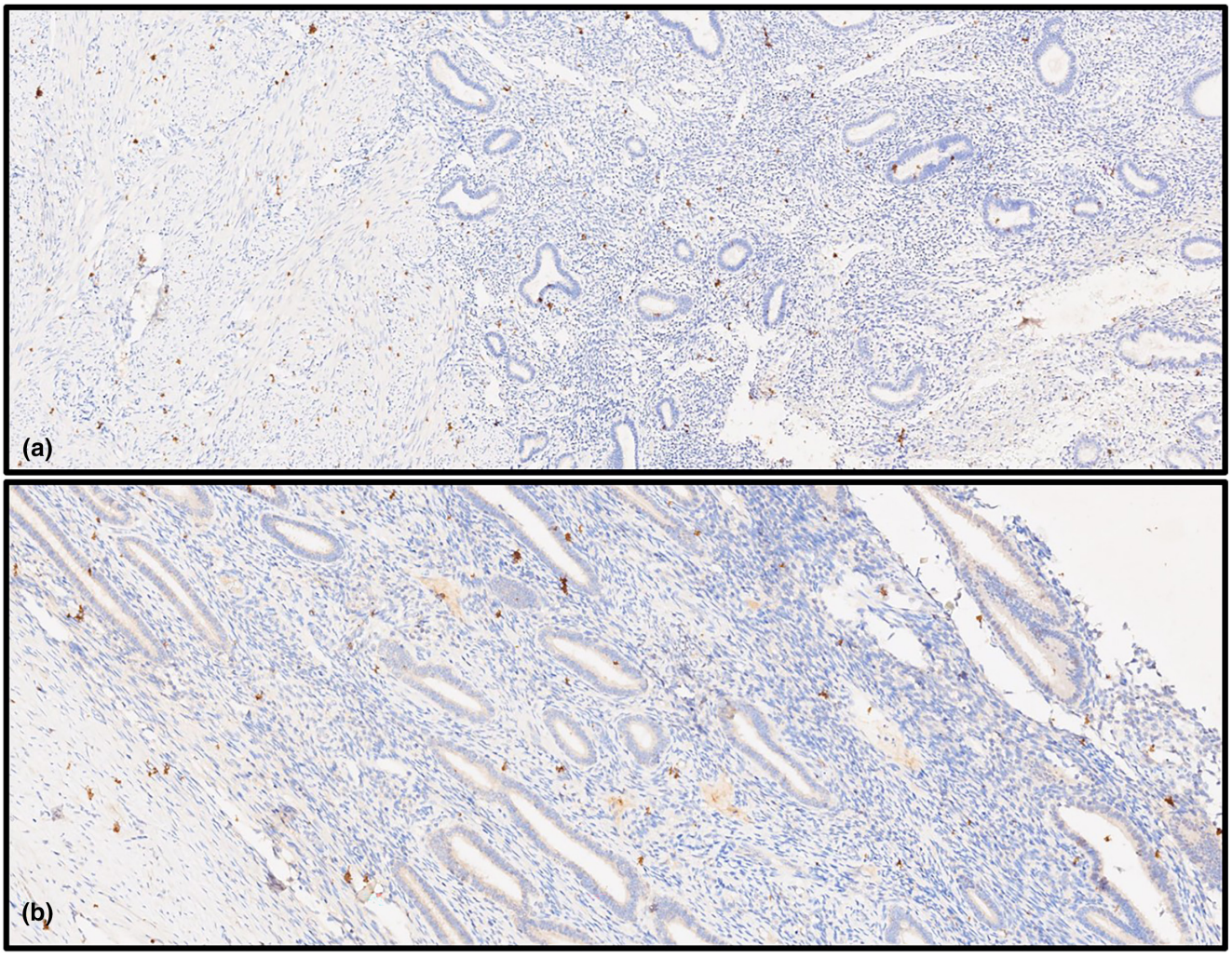


FIGURE 3 Netrin-1 showing negative staining in normal endometrial tissue: (a) ×100 and (b) ×200.

for early-stage carcinoma, because of inadequate clinical trial results. These trials are retrospective, and USC constitutes a minority of patients, thus leading to inconclusive results.[17,18] In a National Cancer Database Study including 7325 patients, although the use of chemotherapy and vaginal brachytherapy was associated with decreased mortality among patients with stage IB and II tumors, patients with stage IA tumors did not benefit from adjuvant treatment.[19] Regardless of these results, multimodal treatment with surgery, radiotherapy, and chemotherapy is usually administered because of the propensity of these tumors for distant spread and local recurrence. At our center, most patients with USC usually receive adjuvant chemotherapy after surgery and always receive radiotherapy. Despite the given multimodal

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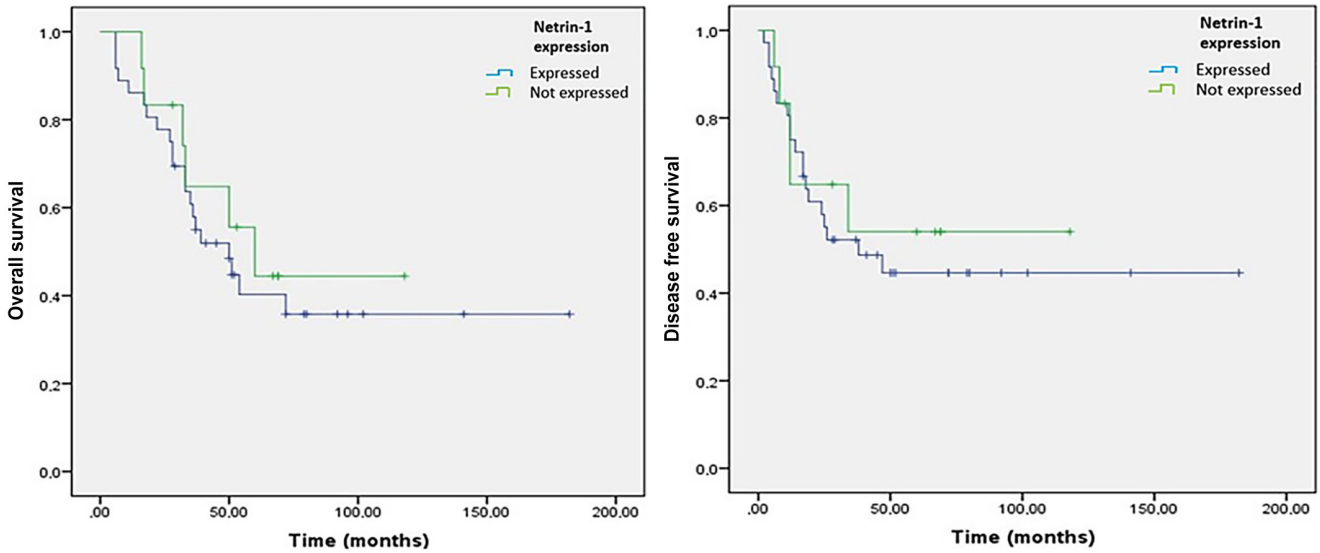


FIGURE 4 Kaplan–Meier overall survival and disease-free survival analysis curve of patients with uterine serous carcinoma according to netrin-1 expression.

TABLE 2 Correlations between netrin-1 expression in tumor tissue and clinicopathologic characteristics.

	No. of events (netrin-1 expression)		Test of significance	
Characteristic	No expression	Expression	χ^2	*P* Value
Age at surgery (year)				
≤60	5	16	0.028	0.867
>60	7	20		
Tumor stage (FIGO)				
1–2	8	22	0.119	0.731
3	4	14		
Tumor diameter				
<2 cm	8	11	4.907	0.027*
≥2 cm	4	25		
Tumor histology				
Serous	10	27	0.354	0.552
Mixed serous	2	9		
p53 Status				
Mutant	5	19	0.000	0.991
Wild	7	17		
Lymphovascular invasion				
Yes	5	7	2.370	0.124
No	7	29		
Myometrial invasion				
Yes	5	15	0.01	0.919
No	7	21		
Positive lymph nodes				
Pelvic	2	4	0.119	0.731
Paraaortic	2	10		

Abbreviation: FIGO, the International Federation of Gynecology & Obstetrics.

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treatments, the 5-year DFS rates of patients with early-stage USC were relatively low (44.8%), according to the literature.

Therefore, in addition to determining the stage, it is important to increase our understanding of molecular biology and examine prognostic biomarkers so as to personalize treatment. This study demonstrated for the first time that netrin-1 is highly expressed in most patients with USC, as detected via IHC. The overall positivity rate of netrin-1 in USC tissues was 75% (high expression in 17 [35%] and low expression in 19 [40%]). Netrin-1 and DCC expressions were first examined by Kato et al. in 2004 both in healthy endometrial tissues and tumor tissues via reverse transcription polymerase chain reaction and IHC.[20] Five of the six cancer cell lines studied had preserved netrin-1 expression, whereas all of them lost normal DCC expression. Dependence receptors are known to promote tumor cell survival by promoting proliferation, angiogenesis, invasiveness, and chemoresistance when activated but actively induce apoptosis when not bound by ligands.[21] The proapoptotic properties of DCC and UNC5H receptors in the absence of netrin-1 have led to the idea that they are tumor suppressor genes.[10] Netrin-1 overexpression inhibits DCC and UNC5H receptor apoptotic activities in metastatic cells, providing them with a survival advantage. This has been shown in studies on metastatic breast cancer and brain metastasis, where it was also correlated with poor prognosis.[22,23]

Netrin-1 was also overexpressed in 76% of ovarian cancer specimens and correlated with advanced stage and grade.[24] Moreover, some studies have demonstrated that the presence of netrin-1 in human fluids is an important biomarker and a predictor of gastric, bladder, pancreatic, and lung cancer recurrence.[25–28]

This study did not find any difference between netrin-1 overexpression and OS, which could be due to the low number of patients with tumor not expressing netrin-1 (25%). We also did not detect any relationship between clinicopathologic tumor characteristics (age, stage, histology, p53 status, LVSI, MI, positive lymph nodes) except tumor diameter. Netrin-1 expression rises with tumor size (≥2 cm), indicating a potential involvement for this protein in carcinogenesis.

This study also had major limitations. First, the number of patients included was small ($n=48$). Second, only netrin-1 was evaluated via IHC, and the presence of netrin-1 in plasma or other fluids and its correlation with USC were not investigated.

In a recent study, a comprehensive analysis of more than 30 tumor types was conducted to analyze netrin-1 expression, epigenetic and pathway relationships, and the correlation between the expression of these proteins and drug susceptibility.[29] The study found that the mutation rates in the netrin family were low in pan-cancers, but, among patients who had tumor with netrin mutations, most had uterine EC, accounting for 13.6% of the cases. Therefore, in this context, patients with EC could be an important group for studying drugs that inhibit interactions between netrin-1 and its receptors. Recently, Cassier et al. reported that blocking netrin-1 with an anti–netrin-1 antibody (NP137) effectively reduced tumor progression in a mouse model of EC.[30] Furthermore, in a phase I trial including 14 patients with advanced EC, the best response observed was eight stable diseases (57.1%) and one partial response (7.1%). They found a 51.16% reduction in target lesions at 6 weeks and up to a 54.65% reduction during the following 6 months. To evaluate the mechanism of action of NP137, mouse tumor gene profiling was performed. In addition to inducing cell death, NP137 inhibited epithelial to mesenchymal transition (EMT). EMT has been associated with various stages of tumorigenesis, such as tumor initiation, progression, and metastasis.[31] Evidently, EMT can contribute to poor outcomes and treatment resistance.[32] Unfortunately, standard treatments as well as targeted therapy, irradiation, and surgery can promote EMT. Therefore, developing therapeutic approaches to prevent or reverse EMT is crucial to improving patient outcomes. NP137 treatment led to decreased EMT features in EC.[30]

A phase Ib/II study is currently underway to assess the combination of NP137, which is a humanized neutralizing monoclonal antibody against netrin-1, and pembrolizumab and/or chemotherapy for the treatment of gynecological cancers (GYNET [Gynecological Cancers Treated With Netrin mAbs in Combination With Chemotherapy and/or Pembrolizumab]; NCT04652076).

5 | CONCLUSIONS

In the current study, it was discovered that the majority of our patients with USC expressed netrin-1. While netrin-1 holds immense potential as a therapeutic target for numerous cancer types, analysis of its expression could yield prognostic biomarkers in USC. As the use of molecular-based therapy expands, more studies on EC and USC are warranted.

AUTHOR CONTRIBUTIONS

Conception: A.K., U.K., and B.Y.B. *Interpretation and analysis of data*: A.K., U.K., B.Y.B., E.B.T., and C.V. *Preparation of the manuscript*: A.K., H.I.S., and U.K. *Revision for important intellectual content*: U.K. and M.G.A. *Supervision*: A.K., B.Y.B., U.K., and M.G.A.

FUNDING INFORMATION

This work has been supported by Kocaeli University Scientific Research Projects Coordination Unit under grant number TSA-2022-2921.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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REFERENCES

1. Ferlay J, Ervik M, Lam F, et al. Global CancerObservatory: Cancer Today. Lyon, France: International Agency for Research onCancer. 2024. Accessed April 4, 2024. https://gco.iarc.who.int/today/en
2. Bogani G, Ray-Coquard I, Concin N, et al. Uterine serous carcinoma. *Gynecol Oncol*. 2021;162(1):226-234.
3. Ferriss JS, Erickson BK, Shih IM, Fader AN. Uterine serous carcinoma: key advances and novel treatment approaches. *Int J Gynecol Cancer*. 2021;31(8):1165-1174.
4. McGunigal M, Liu J, Kalir T, Chadha M, Gupta V. Survival differences among uterine papillary serous, clear cell and grade 3 endometrioid adenocarcinoma endometrial cancers: a national cancer database analysis. *Int J Gynecol Cancer*. 2017;27(1):85-92.
5. Fader AN, Boruta DM, Olawaiye AB, Gehrig PA. Uterine papillary serous cancer: epidemiology, pathogenesis, and management. *Curr Opin Obstet Gynecol*. 2012;22:21-29.
6. Miller D, Filiaci V, Fleming G, et al. Randomized phase III noninferiority trial of first-line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2012;125:771.
7. Dinoi G, Mariani A, Martinelli E, et al. In search for biomarkers and potential drug targets for uterine serous endometrial cancer. *J Cancer Res Clin Oncol*. 2021;147:1647-1658.
8. Henry NL, Hayes DF. Cancer biomarkers. *Mol Oncol*. 2012;6(2):140-146.
9. Werner HMJ, Salvesen HB. Current status of molecular biomarkers in endometrial cancer. *Curr Oncol Rep*. 2014;16(9):403.
10. Kefeli U, Ucuncu Kefeli A, Cabuk D, et al. Netrin-1 in cancer: potential biomarker and therapeutic target? *Tumour Biol*. 2017;39(4):1010428317698388.
11. Arakawa H. Netrin-1 and its receptors in tumorigenesis. *Nat Rev Cancer*. 2004;4:978-987.
12. Bernet A, Fitamant J. Netrin-1 and its receptors in tumour growth promotion. *Expert Opin Ther Targets*. 2008;12:995-1007.
13. Ramesh G, Berg A, Jayakumar C. Plasma netrin-1 is a diagnostic biomarker of human cancers. *Biomarkers*. 2011;16(2):172-180.
14. Gong BS, Feng Q. Netrin-1: the new tumor markers in renal clear cell carcinoma. *Asian Pac J Trop Med*. 2015;8(6):489-493.
15. Yan W, Han P, Zhou Z, et al. Netrin-1 induces epithelial-mesenchymal transition and promotes hepatocellular carcinoma invasiveness. *Dig Dis Sci*. 2014;59(6):1213-1221.
16. Frees S, Zhou B, Han KS, et al. The role of netrin-1 in metastatic renal cell carcinoma treated with sunitinib. *Oncotarget*. 2018 Apr 27;9(32):22631-22641.
17. Fader AN, Nagel C, Axtell AE, et al. Stage II uterine papillary serous carcinoma: carboplatin/paclitaxel chemotherapy improves recurrence and survival outcomes. *Gynecol Oncol*. 2009;112:558-562.
18. Kelly MG, O'malley DM, Hui P, et al. Improved survival in surgical stage I patients with uterine papillary serous carcinoma (UPSC) treated with adjuvant platinum-based chemotherapy. *Gynecol Oncol*. 2005;98(3):353-359.
19. Cham S, Huang Y, Tergas AI, et al. Utility of radiation therapy for early-stage uterine papillary serous carcinoma. *Gynecol Oncol*. 2017;145:269-276.
20. Kato HD, Kondoh H, Inoue T, et al. Expression of DCC and netrin-1 in normal human endometrium and its implication in endometrial carcinogenesis. *Gynecol Oncol*. 2004;95(2):281-289.
21. Brisset M, Grandin M, Bernet A, Mehlen P, Hollande F. Dependence receptors: new targets for cancer therapy. *EMBO Mol Med*. 2021;13(11):e14495.
22. Fitamant J, Guenebeaud C, Coissieux MM, et al. Netrin-1 expression confers a selective advantage for tumor cell survival in metastatic breast cancer. *Proc Natl Acad Sci USA*. 2008;105(12):4850-4855.
23. Harter PN, Zinke J, Scholz A, et al. Netrin-1 expression is an independent prognostic factor for poor patient survival in brain metastases. *PLoS One*. 2014;9(3):e92311.
24. Papanastasiou AD, Pampalakis G, Katsaros D, Sotiropoulou G. Netrin-1 overexpression is predictive of ovarian malignancies. *Oncotarget*. 2011;2(5):363-367.
25. Kefeli U, Yildirim ME, Aydin D, et al. Netrin-1 concentrations in patients with advanced gastric cancer and its relation with treatment. *Biomarkers*. 2012;17(7):663-667.
26. El-Gamal R, Mokhtar N, Ali-El-Dein B, Baiomy AA, Aboazma SM. Netrin-1: a new promising diagnostic marker for muscle invasion in bladder cancer. *Urol Oncol*. 2020;38(7):640.e1-640.e12.
27. Link BC, Reichelt U, Schreiber M, et al. Prognostic implications of netrin-1 expression and its receptors in patients with adenocarcinoma of the pancreas. *Ann Surg Oncol*. 2007;14(9):2591-2599.
28. Yıldırım ME, Kefeli U, Aydın D, Sener N, Gümüş M. The value of plasma netrin-1 in non-small cell lung cancer patients as diagnostic and prognostic biomarker. *Tumour Biol*. 2016;37(9):11903-11907.
29. Hao W, Yu M, Lin J, et al. The pancancer landscape of netrin family reveals potential oncogenic biomarkers. *Sci Rep*. 2020;10(1):5224.
30. Cassier PA, Navaridas R, Bellina M, et al. Netrin-1 blockade inhibits tumour growth and EMT features in endometrial cancer. *Nature*. 2023;620(7973):409-416.
31. Brabletz S, Schuhwerk H, Brabletz T, Stemmler MP. Dynamic EMT: a multi-tool for tumor progression. *EMBO J*. 2021;40(18):e108647.
32. Shibue T, Weinberg RA. EMT, CSCs, and drug resistance: the mechanistic link and clinical implications. *Nat Rev Clin Oncol*. 2017;14(10):611-629.

How to cite this article: Ucuncu Kefeli A, Yaprak Bayrak B, Betul Tunce E, et al. Expression of netrin-1 in uterine serous carcinoma and its association with prognosis. *Int J Gynecol Obstet*. 2024;00:1-8. doi:10.1002/ijgo.15513

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