ORIGINAL PAPER

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Serum Netrin-1 as a biomarker for Endometrium Cancer detection

Netrina-1 en sangre como biomarcador para la detección del cáncer de endometrio

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ABSTRACT

Objective: To investigate the relationship of preoperative netrin-1 with important clinicopathological and prognostic factors and appropriate cut-off levels in patients with endometrial cancer. Material-Methods: In this prospective, observational study, the case and control group were selected among patients who applied to the Gynecological Oncology Clinic. Four mL of venous blood was drawn into a biochemistry tube from each patient during the preoperative period. Netrin values in predicting the presence of malignity were analyzed using ROC (receiver operating characteristics) curve analysis. The cut-off value was calculated according to the Youden index. Results: In the study, the cut-off value of malignancy according to the netrin level was determined as 645.50 mg/dL in the ROC analysis (using the Youden index). The probability of malignancy in individuals with Netrin values above this cut-off was 78.2% (95% CI 0.680-0.884). The sensitivity of netrin in showing the probability of malignancy at this cut-off value was 87.5%, and the specificity 63.6%. Conclusion: Netrin-1 can be a potential biomarker for endometrial cancer detection and prognosis evaluation.

Key words: Netrin-1, Endometrial neoplasms, carcinoma, Biomarkers, Uterine hemorrhage, Apoptosis

RESUMEN

Objetivo. Investigar la relación de la netrina-1 preoperatoria con factores clinicopatológicos y pronósticos importantes y los niveles de corte adecuados en pacientes con cáncer de endometrio. Material y Métodos. En este estudio prospectivo y observacional, el grupo de casos y el de controles se seleccionaron entre las pacientes que acudieron a la Clínica de Oncología Ginecológica. Se extrajeron 4 mL de sangre venosa en un tubo de bioquímica de cada paciente durante el período preoperatorio. Los valores de netrina para predecir la presencia de malignidad se analizaron mediante el análisis de la curva ROC (*receiver operating characteristics*). El valor de corte se calculó según el índice de Youden. Resultados. En el estudio, el valor de corte de malignidad según el nivel de netrina fue determinado en 645,50 mg/dL en el análisis ROC (utilizando el índice de Youden). La probabilidad de malignidad en individuos con valores de netrina superiores a este punto de corte fue del 78,2% (IC 95%: 0,680 a 0,884). La sensibilidad de la netrina para mostrar la probabilidad de malignidad en este valor de corte fue del 87,5% y la especificidad del 63,6%. Conclusiones. La netrina-1 puede ser un biomarcador potencial para la detección del cáncer de endometrio y la evaluación de su pronóstico.

Palabras clave. Netrina-1, Neoplasias de endometrio, carcinoma, Biomarcadores, Hemorragia uterina, Apoptosis

Introduction

Endometrial cancer is the sixth leading cause of cancer death among women in the United States and is the most common gynecological malignancy when evaluated worldwide[(1)]. Although the outcomes of endometrial cancer are better than those of other gynecological malignancies due to presenting early symptoms such as abnormal vaginal bleeding and patients presenting to a healthcare institution with this condition, these women have the opportunity to have early diagnosis and treatment. As a result, the 5-year survival rate reaches 95% in patients with endometrial cancer diagnosed in stage I, while 5-year survival decreases to 69% and 17% for stages III and IV, respectively[(1)]. Endometrial biopsy, the gold standard in the diagnostic evaluation of the

essential symptom abnormal uterine bleeding, can sometimes miss focal pathologies in cases of endometrial cancer[2].

Currently, standard treatments for endometrial cancer include hysterectomy and bilateral salpingo-oophorectomy, and they are widely used[3]. When researched in terms of cancer screening, it is seen that there is no accepted screening test for endometrial cancer in the general population today. Since obesity constitutes the most critical risk factor among endometrial cancer risk factors, many of the biomarkers used to detect and monitor the development of endometrial cancer seem to be associated with metabolic and endocrine changes[4]. The availability of a serum tumor marker to predict lymphatic involvement, advanced disease, or myometrial invasion prior to surgery in endometrial cancer patients would be helpful to for customizing the type of surgery for patients. In addition, using blood biomarkers with the capacity to predict the presence of deep myometrial and lymphovascular invasion before the surgical operation provides better results for lymphadenectomy applications and prevents additional morbidities that may occur[5]. No test or molecular results have been validated as a preoperative prognostic marker of endometrial cancer.

The netrin protein family group plays an essential role in cell and axon migration during embryogenesis[6]. It has been shown that netrin-1, which belongs to this protein family, has several functions in the non-neural system, for example, contributing to inflammation[7], cell migration and adhesion[8], tumor progression, and angiogenesis[9]. Also, when evaluated for tumors, netrin-1 acted as an oncogene that is overexpressed in many cancers such as colorectal cancer[10], hepatic cancer[8], lung cancer[11], and breast cancer[12]. Netrin-1 is found to be over-expressed in more than 80% of endometrial cancer cases[13]. In addition, the DCC and UNC5 receptors of netrin-1 are known to play an active role in the development of endometrial cancer[14,15].

Currently, the role of netrin-1 as a useful tumor marker in the treatment plan and in the pre-surgical evaluation for cancer treatment is still controversial.

This study aimed to investigate the relationship of preoperative netrin-1 with important clinicopathological and prognostic factors and appropriate cut-off levels in patients under study.

Materials and Methods

In this prospective, observational study, the case group and control group were selected from those patients who sought care at the Gynecological Oncology Clinic of Sakarya Training and Research Hospital, affiliated to Sakarya University, between December 2019 and December 2020. Thirty-nine women who presented with abnormal uterine bleeding and had endometrial cancer by pathology were included in the case group, without randomization. All patients with EC underwent frozen section analysis at the time of surgery as well as pelvic or pelvic and para-aortic systemic lymphatic dissection, based on tumor diameter and the presence of myometrial and cervical invasion according to frozen section findings. Once the study group was completed, 47 women with abnormal uterine bleeding similar to the demographic characteristics of the study group and findings of benign pathology were included as a control group. Care was taken to avoid repetition for the case and control groups. Patients with heart disease, cerebrovascular disease, patients <40 and >80 years, smokers, and patients with a history of cancer other than endometrial cancer were excluded from the study. Figure 1 shows the flow diagram regarding the selection of study population. Permission was obtained from the Ethics Committee of Sakarya University to conduct the study. In addition, written consent was obtained from all patients included in the case and control groups.

All participants received fasting venous blood drawn within 24 hours of enrollment. Four mL of venous blood was drawn into a biochemistry tube from each patient during the preoperative period. Once collected, samples were left at room temperature for 30 minutes. The samples were then centrifuged for 5 min at 4,000 rpm and the serum was allocated into Eppendorf tubes and stored at -80 °C until assayed. All samples were thawed and included in the study in the same month on the study day.

Serum netrin-1 levels were measured by ELISA method using kits from Bioassay Technology Laboratory (Zhejiang, China). The intra-measurement coefficient of variation (CV) of the kit was <8% and the inter-measurement coefficient of variation was <10%. The netrin-1 levels of the samples studied with the manual ELISA meth-

od were read and calculated using the Biotek ELX800 (USA) ELISA reader, following the manufacturer's protocols. The set of all biochemical parameters studied in case and control patients were set blinded by the laboratory staff. The laboratory staff did not know to which group the results belonged.

Statistical analyses were performed using the SPSS 21.0 software version. The variables were investigated using analytical methods (Kolmogorov-Smirnov test) to determine distribution. Descriptive analysis was presented using means and standard deviations if the variables were normally distributed medians, and interquartile ranges were used if the variables were not normally distributed. Categorical variables are specified as numbers and percentages.

Univariate analyses were investigated the Chi-square test, Student t-test, Mann Whitney U Test, and Kruskal Wallis test, where appropriate. For the multivariate analysis, the possible factors identified with univariate analysis were further entered into the logistic regression analysis to determine independent predictors of malignity.

Netrin values in predicting the presence of malignity were analyzed using ROC (receiver operating characteristics) curve analysis. The cut-off value was calculated according to the Youden index. Accordingly, specificity and sensitivity values were determined. A 5% type 1 error level was used to infer statistical significance.

Results

A comparison of some marker and biochemical parameters of the patient and control group is provided in Table 1. There were no statistical difference in age, pregnancy status, parity, body mass index (BMI), Ca125 tumor marker, and blood count values in the case and control groups. However, netrin-1 values in the blood of the case group were found to be statistically significantly higher than the control group (Table I).

The distribution of netrin levels with statistically significant differences in the case and control groups is also seen in the box plot graph (Figure 2).

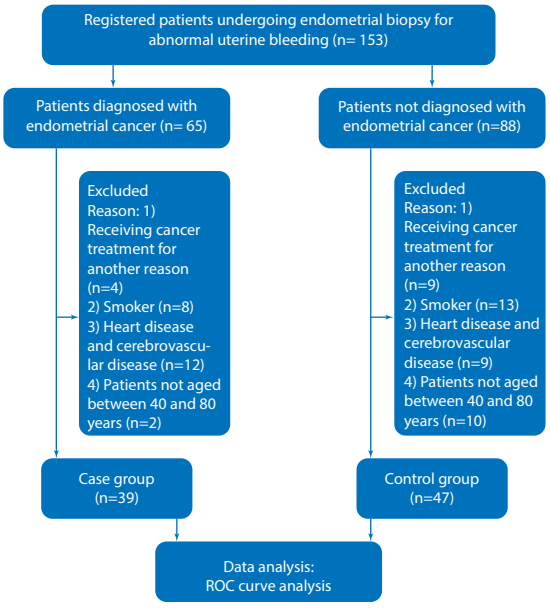
In the study, the cut-off value of malignancy according to the netrin level was determined as 645.50 mg/dL in the ROC analysis (using the

Table 1. Distribution and comparison of some marker and biochemical parameters of the case and control group.

Variables	Case (n=39)	Control (n=47)	p
Age	60.82±9.50	58.28±7.19	0.173*
Parity 1-2 3-4 ≥5	 16 17 6	 19 21 7	0.995**
BMI(kg/m2)	34.28±5.05	33.78±4.20	0.630*
Ca 125 (U/mL)	18.40 [11.40-28.00]	17.60 [14.15-27.32]	0.760‡
CA 19-9 (U/mL)	12.00 [7.08-24.30]	11.60[8.50-16.75]	0.356‡
CEA (ng/mL)	1.54 [1.00-2.25]	2.73 [1.45-3.74]	0.003‡
Netrin-1 (pg/mL)	775.00 [680.00-1024.00]	588.00 [541.50-697.50]	<0.001‡

*BMI= body mass index, *Student t test, **Chi-square test, ‡Mann Whitney U test, CEA= carcinoembryonic antigen*

Figure 1. STARD diagram depicting the study design and classification of study participants.



Youden index). The probability of malignancy in individuals with netrin values above this cut-off was 78.2% (95% CI 0.680-0.884). The sensitivity of netrin in showing the probability of malignancy at this cut-off value was 87.5%, and the specificity 63.6% (Figure 3).

The increase in netrin-1 level caused an increase in the probability of malignancy (p<0.005). In this model, white blood count Ca-125 values did not have a statistical effect on detecting malignancy (Table 2).

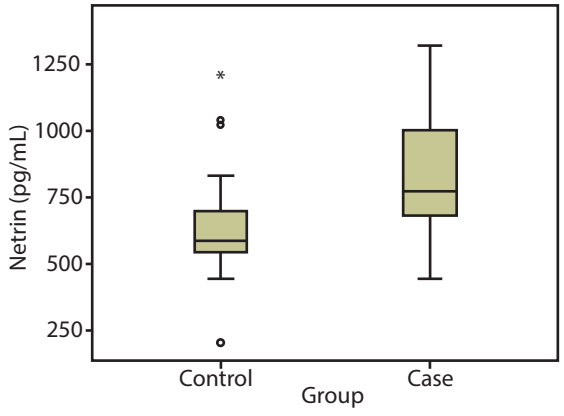
The netrin-1 level was higher in patients with malignancy with cervical invasion than in cases without cervical invasion. This difference was

Table 2. Comparison of some cancer parameters and netrin-1 levels according to cancer staging scores.

	Netrin-1	Ca 125	CEA
MI (%) <50 ≥50	752.50 (662.50-884.00) 895.50 (708.25-1040.50)	20.55 (12.70-30.25) 18.20 (9.80-23.97)	2.15 (1.27-3.30) 3.00 (2.23-13.53)
p	0.101*	0.558*	0.092*
Cervical invasion Yes No	1053.50 (1029.50-1221.50) 763.00 (670.25-939.00)	26.40 (9.03-31.10) 18.20 (11.70-24.27)	3.06 (2.33-41.43) 2.70 (1.41-3.65)
p	0.012*	0.660*	0.266*
FIGO ≤1B >1B	765.00 (667.00-957.00) 1046.00 (862.00-1168.00)	18.00 (11.40-24.30) 22.50 (13.35-31.00)	3.00 (1.45-3.74) 2.73 (1.62-28.75)
p	0.042*	0.542*	0.705*
Histology 1 2	794.00 (685.25-1024.00) 637.50 (542.00--)	20.55 (12.30-28.70) 13.55 (8.70--)	2.86 (1.43-3.48) 11.36 (1.62--)
p	0.181*	0.279*	0.566*
Grade 1 2 3	761.00 (664.00-895.50) 965.50 (721.75-1076.75) 733.00 (542.00--)	17.70 (11.20-22.75) 24.25 (14.97-31.15) 18.40 (8.70--)	2.40 (1.22-5.36) 2.86 (2.07-3.35) 3.00 (1.62-)
p	0.096**	0.219**	0.830**

*CEA= carcinoembryonic antigen, MI= myometrial invasion, FİGO= The International Federation of Gynecology and Obstetrics, *Mann Whitney U test, **Kruskall Wallis test*

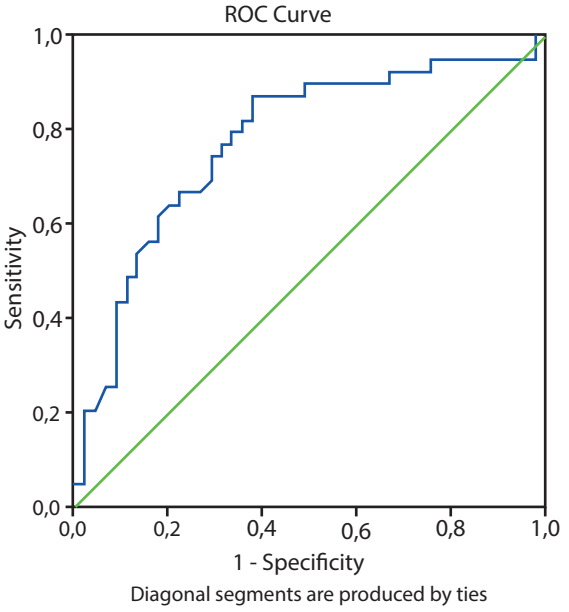
Figure 2. The distribution graph of the level of cases and control groups netrin-1.



also statistically significant. In FIGO (The International Federation of Gynecology and Obstetrics) staging, the netrin level in the blood was found to be statistically significantly higher in malignancy cases graded above 1B than in cases with 1B and below.

On the other hand, the amount of myometrial invasion, histology, or grade staging in malignant cases did not cause a difference in blood

Figure 3. ROC curve for netrin-1 data.



netrin levels (Table 2).

Discussion

Our study aimed to show whether there is a connection between serum netrin-1 levels and endometrial cancer. Despite recent advances, there is no essential biomarker that can be used in the diagnosis and treatment of endometrial cancer[16]. An ideal marker is expected to be directly related to the tissue expression of the marker level in the blood and to be effective in predicting the diagnosis and prognosis of the disease to be evaluated[17]. Various non-invasive gynecological sampling methods and technologies (genomic, epigenomic, and proteomic approaches) to detect endometrial cancer have been described and evaluated in terms of their results. Due to the inconclusive results of these methods, there remains a need to find suitable protein biomarkers that reveal possible targets not only for endometrial cancer diagnosis but also for future treatment modalities. Therefore, the primary purpose of our study was to evaluate preoperative serum netrin-1 levels in endometrial cancer patients who are planned for surgery, to evaluate whether it helps surgical debulking in the context of postoperative findings, and to predict whether lymphadenectomy is needed for the clinical stage.

Since its discovery, the netrin gene family has been shown to contribute to the organization of multiple tissues in addition to neuronal development where

it is mainly found[18]. Netrin-1/deleted in colorectal cancer (DCC) signaling has been found to play a crucial role in the development of the nervous system. DCC was initially shown to play a candidate role in suppresing tumors associated with human colon cancer. Recent studies have determined that netrin-1 is associated with the growth and metastatic potential of many types of cancer, including colorectal and breast cancer[12,19]. When DCC is suppressed in non-neuronal cells, it participates in the apoptosis program and consequently exhibits tumor suppressor activities. When evaluating netrin proteins, DCC was found to be among the receptors used in tissues[18].

Normally functioning endometrial glands express both DCC and netrin-1 in the proliferative and early secretory phases, but DCC expression is arrested in glandular cells in the late secretory phase[20]. Restoration of DCC in cancer cell lines in the absence of netrin-1' indicates induction of apoptosis[20]. Silencing of DCC expression may contribute to the resulting cancer cells' escape from the apoptotic program regulated by this expression and at the same time lead to the development of metastatic and invasive properties.

Many studies have shown that netrin-1 plays a role in inflammation, cell adhesion, migration, tumor, and angiogenesis at different tissue levels[8,10]. Zhan et al. found that netrin-1 was significantly upregulated in all samples obtained from renal tumors[21]. Yin et al. stated that netrin-1 is a regulator of the PI3K/AKT pathway that modulates the proliferation and invasiveness of gastric cancer cells[22].

Netrin-1, which is associated with modulation and invasion of cancer cells through the PI3K/AKT pathway in other types of cancer, shows efficacy in endometrial cancer using the same pathway. Tissue levels of netrin-1 affect serum levels. In our study, the cutoff value for serum netrin-1 was 645.50 mg/dL. This suggests that netrin-1 can be used as an essential marker in the prediction and pre-surgical evaluation of patients with endometrial cancer when corroborated by other studies.

A study with an anti-netrin-1 antibody (NP137) in a mouse model of EC demonstrated its efficacy in reducing tumor progression. Furthermore, in a comparative study of NP137 + carboplatin-paclitaxel and carboplatin-paclitaxel alone in mice with EC, the anti-netrin-1 group had better results[23]. In the same study, a series of 14 patients treated with NP137 in combination with carboplatin-paclitaxel showed disease stabilization in a significant proportion of patients[23].

Overexpression of netrin-1 significantly increases phosphorylation of extracellular signal-regulated kinase and focal adhesion kinase (FAK)[24]. FAK up-regulation has been observed in both endometrial hyperplasia and endometrial carcinoma, implying that FAK may play a vital role in epithelial-mesenchymal transition. FAK is essential in integrin signaling and is highly expressed in endometrial cancer[25]. The potential for metastasis in endometrial cancer is known to be related to the β1/FAK signaling pathway in endometrial cancer cell lines. For this reason, we think that increased netrin-1 levels are related to invasion prior to metastasis due to the relationship between netrin-1 and FAK, and the increased serum netrin-1 level is due to this situation.

Increased netrin-1 gene expression, large tumor dimension, and age are positive predictors associated with an increased likelihood of local bladder tumor recurrence[26]. This raises the possibility of using netrin-1 gene expression in tissue samples as prognostic markers for local bladder tumor recurrence[26]. Since netrin 1, which is associated with recurrence in other cancer types, uses the same pathways, it can be thought that it may also be associated with recurrence in endometrial cancer. However, to reach this conclusion, it is necessary to carry out comprehensive studies in the relevant patient groups in the future.

Our findings show an association between serum netrin-1 levels and the malignant potential of patients with endometrial cancer. As a result, more comprehensive studies with a higher number of cases are needed so that serum netrin-1 level can be used in the evaluation of prognosis for endodontic cancer.

Conclusion

Netrin-1 can be a potential biomarker for endometrial cancer detection and prognosis evaluation.

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