Examination of Etiology and Laboratory Data in Involuntary Weight Loss: Does Prognostic Nutritional Index (PNI) Predict Malignancy?

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ABSTRACT

Background: Many examinations are performed to elucidate the etiology of involuntary weight loss and it is important not to miss any type of malignancy. In this study, we aimed to investigate the guiding feature of prognostic nutritional index (PNI) as a simple marker in determining the etiology of weight loss.

Methodology: 121 patients who were admitted to the internal medicine clinic due to their weight loss and hospitalized to investigate the etiology, were included in the study. "Multivariant Analysis" and "ROC Analysis" were performed to determine the factors affecting weight loss. The determining effect of PNI on etiology was evaluated.

Results: In 121 patients with weight loss, malignancy was detected in 30.5% of the etiology, while 69.5% of patients had chronic diseases or infectious diseases. PNI was found to be determinant in predicting malignancy (AUC: 741; 95% Cl 0.770-0.930; p <0.001). PNI optimal cut-off value for malignant diseases was determined as 33 (86% sensitivity, 50% specificity; youden index: 0.3642).

Conclusion: PNI is thought to be the guide in predicting malignancy in the etiology and in the examination plan in patients presenting with involuntary weight loss. In our study, low PNI was found to be an independent risk factor for malignancy.

Keywords: Involuntary Weight Loss; Malignancy; PNI

Abbreviations: ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CBC: Complete Blood Count; CRP: C- Reactive Protein; ESR: Erythrocyte Sedimentation Rate; FOBT: Fecal Occult Blood Test; HbA1C: Hemoglobin A1C; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; LDH: Lactate Dehydrogenase; MPV: Mean Platelet Volume; N/L: Neutrophil / Lymphocyte; PNI: Prognostic Nutritional Index; TSH: Thyroid Stimulating Hormone; WBC: White Blood Cell

Background

Involuntary weight loss is defined as the loss of more than 5% of the body weight within 6-12 months, without the treatment of a chronic disease or not as a known result of a disease. It is associated with increased mortality rates, healthcare costs and workload [1-3].

There are many reasons for weight loss, but whein it is involuntary, it often indicates serious physiological or psychiatric disorders. Various studies investigating the causes of involuntary weight loss have revealed that malignancy is the most common cause and is found in 15% to 37% of patients. While non-malignant causes include gastrointestinal causes (15-37%), psychiatric disorders (10-23%), no cause

can be found in 25% of them [4]. Given the broad differential diagnosis of involuntary weight loss, there is no single diagnostic approach for all patients. After the history and physical examination to reveal a possible diagnosis, basic laboratory examinations are performed.

Tests should include; electrolytes, glucose, hemoglobin A1C (HbA1C), calcium, kidney and liver function tests, thyroid stimulating hormone (TSH), erythrocyte sedimentation rate (ESR), complete blood count (CBC), C-reactive protein (CRP), urinalysis, fecal occult blood test (FOBT), human immunodeficiency virus (HIV) and hepatitis C virüs (HCV) serology in risky patients and chest radiography, and age-appropriate cancer screening in patients with additional risk factors. Further evaluation should be based on the results of these initial tests. If no abnormality is detected at the initial assessment, the patient can be re-evaluated within one to six months [5,6]. When no reason is found, patients are followed up at frequent intervals. The important point here is that a life-threatening cause such as cancer is not missed [7].

Therefore, it is important to determine the parameters that can predict malignancy. Old age factor, presence of anemia, and high levels of ESR may be useful in demonstrating the association of involuntary weight loss with malignancy. In the presence of anemia and high ESR, the probability of involuntary weight loss due to malignancy is 64% in patients over 62 years of age, while the probability of malignancy in patients under 63 years of age is 9% in the presence of normal levels of hemoglobin and ESR. Various prediction scores have been developed that can predict malignancy in involuntary weight loss. One of them is the Hernandez Score. Independent predictive factors for malignancy in this scoring include being over 80 years of age, high alkaline phosphatase (ALP), lactate dehydrogenase (LDH), white blood cell (WBC) and low albumin levels [8,9].

PNI is a simple and comprehensive index that shows immunological and nutritional status calculated according to serum albumin levels and peripheral lymphocyte count. Albumin levels are affected by nutrition, kidney and liver function. Lymphocytes, on the other hand, provide insight into inflammatory and immune system activation [10]. PNI was first used by Buzby et al. in 1980, to evaluate the prognosis of patients undergoing gastrointestinal surgeryIt was revised by Onodera in 1984 [11]. It has also been used to predict prognosis in various malignancies, pulmonary embolism and cardiac diseases [12]. It has been shown to be associated with prognosis in many cancers such as esophagus, prostate, kidney, breast, lung, and colorectal. Numerous studies have been conducted that reveal its relationship with cardiac diseases. PNI is an effective indicator for evaluating the nutritional and immunological conditions of patients with cancer [13]. Albumin and CBC tests are required for every patient with involuntary weight loss. In this study, we aimed to demonstrate the role of PNI as a simple index in predicting malignancy in the etiology of involuntary weight loss.

Patients and Methods

Files of 4554 patients hospitalized in Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital Internal Medicine Clinic between January 2015 and June 2020, were retrospectively analyzed. 121 patients who applied to the internal medicine outpatient clinic with a complaint of weight loss and were hospitalized to investigate the etiology were included in the study. Patients aged 18 and over, who had an involuntary weight loss of more than 5% in the last 6-12 months were included in the study. The diagnosis of involuntary weight loss was made according to the diagnostic criteria. Weight loss was determined by the presence of 5% loss in those whose previous weight was known in the last 6-12 months, while in those whose weight could not be documented, it was confirmed by the abundance of clothes and belts or by confirmation from relatives [1,14,15].

Those who were under 18 years of age, who had voluntary weight loss, patients with a previously known diagnosis of malignancy, those who lost weight due to use of certain drugs, and those who did not want to participate in the study were excluded. Sociodemographic data and laboratory parameters of the patients were obtained by examining the files and system data of the patients. Patients with involuntary weight loss were divided into two groups as malignant and non-malignant groups, according to the etiological reasons. The non-malignant group consisted of endocrine, gastrointestinal, cardiopulmonary and infectious causes. The age and gender information of the patients were recorded. WBC counts, mean platelet volume (MPV), alanine aminotransferase (ALT), aspartate aminotransferase (AST), ESR, albumin, calcium, magnesium, phosphorus, CRP, vitamin D, Ferritin, LDH, uric acid levels were determined by laboratory tests.

Neutrophil / lymphocyte (N/L) ratio and PNI values were calculated. PNI was calculated using the following formula.

$$PNI = 10 \times serum\ albumin\ value \left(\frac{g}{dl} \right) + 0.005 \times total\ lymphocyte\ count\ in\ the\ peripheral\ blood\ (per\ mm\ 3)$$

[11]. Sociodemographic and laboratory data of 121 patients were analyzed between malignant and nonmalignant two groups. Our study was approved by the Clinical Research Ethics Committee of University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date:03.02.2020, Decision:81/13). The research was carried out in accordance with the Helsinki Declaration.

Statistical Analysis

Statistical analysis was performed using the SPSS version 21.0 (IBM®, Chicago, USA) package program. The conformity of the variables to the normal distribution was examined by using visual (histogram and probability charts) and analytical methods (Shapiro-Wilk test). Descriptive statistics were expressed as mean and standard deviation in normally distributed numerical data, and as number and

percentage in nominal data. Normally distributed numerical variables were compared between two groups with the "Independent Samples T test" and between three groups with the "One way ANOVA test". Numerical variables that did not show normal distribution were compared using the "Mann Whitney U test" between two groups and the "Kruskal Wallis test" between three groups. "Multivariant analysis" and "ROC analysis" were used to determine the factors affecting weight loss. In the statistical analyzes in the study, comparisons with a p value of less than 0.05 were considered statistically significant.

Results

121 patients with involuntary weight loss were included in the study. The mean age of all patients was 61.5 ± 14.3 years, 68.4 years for the malignant group and 58.4 years for the non-malignant group. Average weight loss was 10.5 (4-30) kg. While age, WBC count, platelet count, N/L ratio, CRP, ESR, ferritin, LDH, uric acid were higher; hemoglobin, albumin, vitamin D and PNI values were lower in the group with malignancy. These values were higher in the non-malignant group. The difference between the two groups in terms of laboratory data was statistically significant (p <0.05). The comparison of laboratory values between groups is given in (Table 1). In 121 patients with involuntary weight loss, malignancy was detected at a rate of 30.5%, and chronic diseases and infectious diseases were found at a rate of 69.5%. The most common malignancy was originating from the gastrointestinal system (3.6%). In the non-malignant disease group, the most common cause were endocrine system diseases (55%). Involuntary weight loss reasons are summarized in (Table 2). In the multivariant analysis, low PNI was found to be an independent risk factor for malignancy (OR: 1.196; 95% CI: 1.091-1.312; p <0.001) (Table 3). Other factors were age and LDH (p <0.05). PNI was found to be determinative for malignancy (AUC: 741; 95% Cl 0.770-0.930; p <0.001). The optimal cut-off value for malignant diseases was determined as 33 (86% sensitivity, 50% specificity; youden index: 0.3642) (Figure 1).

Table 1: Distribution of sociodemographic characteristics and laboratory parameters by malignancy.

		All cases (N=121)	Malign (N=37)	Non-malign (N=84)	p value
Age, years [†]	Mean±sd	61.5±14.3	68,4±10,5	58,4±14,8	<0,001
Haemoglobin (g/dL) [†]	Mean±sd	12.5±2.2	11±1,9	13,1±2	<0,001
White Cell Count (109/L) [††]	Med (min-max)	7.5(2.2-28.9)	8,2 (2,2-28,9)	7,3 (3,3-15,3)	0,060
Mean Platelet Volume (fl) [†]	Mean±sd	8.2±1.2	7,7±1,2	8,5±1,1	<0,001
Platelet count (10^9/L) [††]	Med (min-max)	268.8±113	288(146-610)	232(84-635)	0,005
Neutrophil/lymphocyte [††]	Med (min-max)	2.3 (0.4-14)	3,4 (1,5-14)	2 (0,4-11)	<0,001
Alanine aminotransferase(U/L) [††]	Med (min-max)	15 (4-607)	15 (6-480)	15 (4-607)	0,598
Aspartate aminotransferase(U/L) [††]	Med (min-max)	18 (6-757)	22 (12-154)	17 (6-757)	0,013
Albumin (g/L) [†]	Mean±sd	3.5±0.6	3,1±0,6	3,7±0,5	<0,001
Calcıum (mg/dl) [††]	Med (min-max)	9.2 (7,3-15)	9 (7,3-15)	9,2 (7,6-10,6)	0,059
Magnesıum (mg/dl) [†]	Mean±sd	1.8±0.2	1,8±0,3	1,9±0,2	0,862
Phosphorus (mg/dl) [†]	Mean±sd	3.5±0.8	3,3±0,6	3,5±0,8	0,103
C-Reaktive Protein (g/L) [††]	Med (min-max)	7 (0.7-380)	28 (0,7-380)	4,3 (1-116)	<0,001
Sedimentation (ml/h) [††]	Med (min-max)	19 (2-120)	47 (4-120)	13 (2-81)	<0,001
Vitamin D (ng/ml) [††]	Med (min-max)	12 (1.5-58)	9,1 (2,4-47)	14,1 (1,5-58)	0,031
Ferritin (µg/L) [††]	Med (min-max)	79 (3.3-9349)	171 (3,3-9349)	67,5 (3,9-962)	0,030
Lactate dehydrogenase (U/L) [††]	Med (min-max)	173.5 (95-1410)	211 (125-1410)	163 (95-411)	0,001
Urıc Acid (mg/dl) [††]	Med (min-max)	4.8 (1.6-11.6)	5,7 (2,6-8,4)	4,4 (1,6-11,6)	0,003
Prognostic Nutritional Index (PNI) [†]	Mean±sd	35.7±6	31,9±5,9	37,2±5,4	<0,001

Note:

a)   [†] İndependent Samples T-test.

b)   [††] Mann-Whitney U test.

Table 2: Causes of involuntary weight loss in 121 patients.

		N (%)
Malignancies	Gastrointestinal tract	9 (3.6)
	Renal cell carcinoma	1 (0.4)
	Prostate cancer	1 (0.4)
	Over cancer	1 (0.4)
	Pancreas cancer	4 (1.6)
	Mezotelyoma	1 (0.4)
	Lenfoma	4 (1.6)
	Respiratory tract	8 (3.2)
	Cholangiocellular carcinoma	2 (0.8)
	Unknown primary	7 (2.8)
Non-malignant diseases	Endocrinological disorders	55 (22)
	Infectious diseases	1 (0.4)
	Gastrointestinal disorders	6 (2.4)
	Cardiopulmonery disorders	34(13.6)

Table 3: Regression analysis of determinants in malignity prediction.

	B	SE	p	OR	%95Cl	
Age	-,144	,067	,032	,866	,759	,988
Haemoglobin (g/dl)	-,055	,387	,888	,947	,444	2,021
Mean Platelet Volume (fL)	1,390	,683	,042	4,014	1,053	15,311
Platelet count (x10	,005	,005	,404	1,005	,994	1,015
Neutrophil/lymphocyte	,127	,245	,603	1,136	,703	1,835
Aspartate aminotransferase (U/L)	,027	,078	,726	1,028	,882	1,198
Albumin (mg/L)	2,692	1,667	,106	14,761	,563	387,317
Sedimentation (ml/h)	-,030	,027	,272	,971	,921	1,023
Vitamin D (ng/ml)	-,003	,055	,959	,997	,895	1,111
Ferritin (µg/L)	-,001	,004	,693	,999	,991	1,006
Lactate dehydrogenase (U/L)	-,031	,013	,015	,969	,946	,994
Urıc Acid (mg/dl)	-,082	,343	,812	,922	,470	1,806
Prognostic Nutritional Index (PNI)	0,179	0,047	<0,001	1,196	1,091	1,312

Note: Binary logistic regression.
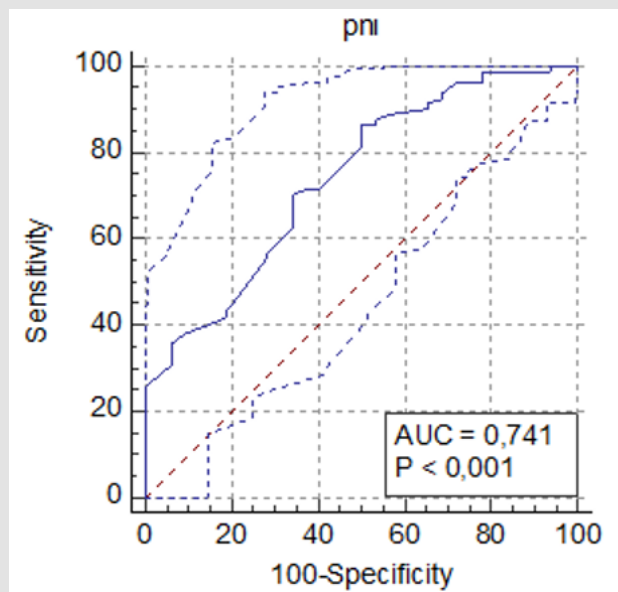
Figure 1: Receiver-operating characteristic curves of PNI for malignant diseases.

Discussion

Various factors have been proposed to predict malignancy in patients with involuntary weight loss. In fact, various scoring systems have been developed. However, more sensitive markers are needed for a predictive scoring based on the relationship between weight loss and malignancy. For this purpose, we aimed to evaluate the PNI value, which is the combination of nutrition and inflammation markers, in our study. In the literature, there is no study evaluating PNI in patients with involuntary weight loss. Our study is important in that it is the first study on this subject. Involuntary weight loss is a health problem that requires a large number of diagnostic tests, as it does not have a standardized guide. This situation causes increased workload and healthcare costs. The most important point here is that malignancy should not be ignored as an etiological cause. In our study for this purpose, we think that PNI is a guide as a simple marker in predicting malignancy in etiology.

There are many studies evaluating PNI in many cancers such as lymphoma, glioblastoma, stomach, colon and pancreas carcinomas. In a study by Xiao et al. comparing the B-cell lymphoma group and the healthy control group, they found that the PNI value in the lymphoma group was significantly lower than the healthy control group [16]. In a study by Karşıyakalı et al., it shows that PNI is a potential preoperative predictor of tumor and an independent risk factor for predicting tumor stage in patients with primary bladder cancer. Low PNI levels were found to be associated with high-stage disease [17]. In the study conducted by Xing-Wang Zhou et al. it was found that PNI> 44.4 is an independent prognostic parameter in evaluating the overall survival and the efficacy of adjuvant therapy in patients with glioblastoma [18]. Lower preoperative PNI values were significantly associated with more tumor growth, lymph node metastasis, lymphatic permeation and venous invasion in patients with gastric carcinoma. In addition, PNI value has been proven to be an independent prognostic indicator in gastric carcinoma [19]. In the meta-analysis in which Kai-yu Sun et al. examined the prognostic significance of PNI in cancer: fourteen studies with a total of 3,414 participants were analyzed. Low PNI has been associated with poor overall survival in cancer patients and the presence of postoperative complications. PNI has also been found to be associated with the depth of invasion and lymph node metastasis in gastric cancer [20].

In conclusion, PNI has been evaluated as a prognostic factor in many studies, especially in malignancies. In our study designed based on these studies, we evaluated PNI as a simple marker in predicting malignancy in the etiology of involuntary weight loss. We identified it as an independent predictive factor in patients with malignancies. We found the cut-off value of 33 in malignant patients. Various scoring systems have been developed to predict malignancy in the etiology of involuntary weight loss. Many laboratory parameters have been analyzed to reveal which of these are guiding. LDH, ESR, CRP, albumin and ALP are the most emphasized values. In cancer cachexia, there is no reduction in energy expenditure despite reduced calorie intake. There is a hypermetabolic condition characterized by an increase in biochemical processes such as gluconeogenesis, protein degradation, and lipolysis [21]. Therefore, laboratory parameters can be guiding.

In a study conducted by Metadilis et al. in which 101 patients with involuntary weight loss were evaluated, they showed that the possibility of malignancy is low, if physical examination and laboratory values such as CBC, CRP, AST, ALT are normal. On the other hand, in all 22 patients diagnosed with malignancy; an abnormality was found in at least one of the ALP, LDH albumin, ferritin tests, chest radiograph and abdominal ultrasound [22]. It has been shown that energy expenditure increases at rest in patients with lung cancer and is associated with higher CRP levels [23]. In our study, we found that these laboratory parameters were associated with malignancy, which supports the literature data [22,23]. Albumin was lower in malignant patients but was not detected as a predictive factor in multivariant analysis.

In the study by Xavier Bosch et al. in examined 2677 patients with involuntary weight loss, 37% non-malignant, 33% malignant and 16% psychosocial causes were found in the etiology. 14In our study, we found the most common non-malignant causes with a rate of 69.5% and malignant causes at a rate of 30.5%, in accordance with the literature. Unlike the literature, the most common non-malignant causes consist of endocrinological issues such as newly diagnosed diabetes, diabetes with irregular blood sugar and thyroid dysfunction [4,15]. Our main limitations were that our study was retrospective, the number of patients was small and it was a single-center study. In terms of revealing the factors that will enable us to predict malignancy in patients with involuntary weight loss, PNI can be a guide as a simple and inexpensive method that does not increase the cost and workload. In this study, we aimed to shed light on new studies in terms of usability in new scoring system. However, we think that prospective and multi-center studies are needed with larger patient groups.

Conclusion

PNI is an easily accessible and easily calculated parameter that has been used to predict prognosis in many diseases. In our study, we determined that this simple index is an independent predictor factor for malignancy in the etiology of involuntary weight loss. This simple test can save time, workload and healthcare costs to elucidate the etiology of involuntary weight loss, diagnose or rule out malignancy, one of the most important causes in the etiology.

Declarations

Availability of Data and Materials

All data are freely available for scientific purpose.

Competing Interests

The authors declare that they have no competing interests.

Funding

No funding sources for research.

Author Contributions

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