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ORIGINAL ARTICLE

Impact of Prognostic Nutritional Index on Clinical Outcomes in Hereditary Angioedema: A single-center experience

Herediter Anjiyoödemde Prognostik Nutrisyonel İndeksin Klinik Sonuçlar Üzerine Etkisi: Tek Merkez Deneyimi

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ABSTRACT

Background/Aim: This study aims to evaluate the impact of the Prognostic Nutritional Index (PNI) on clinical outcomes in hereditary angioedema (HAE) patients. HAE is a rare genetic disorder (prevalence approximately 1:50,000) marked by recurrent episodes of severe swelling due to a deficiency in the C1 inhibitor (C1-INH) protein, affecting the complement and contact systems. PNI, a measure of nutritional and immune status, has been used to predict clinical outcomes in various chronic diseases, but its role in HAE remains unclear.
Methods: A single-center retrospective cohort of 60 patients was analyzed. Clinical characteristics and PNI were assessed and calculated using the formula: [Serum Albumin (g/L)] + [5 × Peripheral Blood Lymphocyte Count (×10□/L)]. Patients were stratified into low and high PNI groups based on a cut-off value of 51.725, derived from receiver operating characteristic (ROC) curve analysis (AUC = 0.902, p < 0.001). Statistical significance was set at p < 0.05.
Results: Low PNI was significantly associated with increased attack frequency (p < 0.001), extended diagnostic delays (p = 0.022), and greater laryngeal (p = 0.003) and gastrointestinal involvement (p = 0.005). Furthermore, low PNI was negatively correlated with monthly attack frequency (Spearman's rho = -0.653, p < 0.001) and positively correlated with the C1-INH function (Spearman's rho = 0.408, p = 0.001).
Conclusion: These findings underscore the importance of incorporating nutritional evaluations into HAE management, as poor nutritional status may exacerbate disease severity. Further prospective studies are needed to validate these associations and explore nutritional interventions as a complementary strategy in HAE treatment.

Keywords: C1 inhibitor protein, hereditary angioedema, immune system diseases, nutritional status, prognostic nutritional index

ÖZ

Giriş/Amaç: Bu çalışmanın amacı, Prognostik Nutrisyonel İndeksin (PNI), HAE hastalarındaki klinik sonuçlar üzerindeki etkisini değerlendirmektir. Herediter anjiyoödem (HAE), C1 inhibitör (C1-INH) protein eksikliğine bağlı olarak kompleman ve kontakt sistemlerini etkileyen, yaklaşık 1:50.000 prevalans ile seyreden nadir bir genetik hastalıktır. Hastalık, tekrarlayan ciddi şişlik atakları ile karakterizedir. Prognostik Nutrisyonel İndeks (PNI), beslenme ve immün durumun bir göstergesi olarak çeşitli kronik hastalıklarda klinik sonuçları öngörmek amacıyla kullanılmaktadır; ancak, HAE üzerindeki etkisi henüz netlik kazanmamıştır.
Yöntem: Tek merkezli retrospektif bir kohort çalışması kapsamında 60 hasta analiz edilmiştir. Hastaların klinik özellikleri ve PNI değerleri incelenmiş, PNI şu formülle hesaplanmıştır: [Serum Albümini (g/L)] + [5 × Periferik Kan Lenfosit Sayısı (×10□/L)]. Alıcı çalıştırma özellik (ROC) eğrisi analiziyle belirlenen 51.725 kesim değeri esas alınarak hastalar düşük ve yüksek PNI gruplarına ayrılmıştır (AUC = 0.902, p <0.001). İstatistiksel anlamlılık seviyesi p <0.05 olarak kabul edilmiştir.
Bulgular: Düşük PNI, artmış atak sıklığı (p <0.001), uzamış tanı gecikmesi (p = 0.022), ve daha sık larinks (p = 0.003) ve gastrointestinal tutulum (p = 0.005) ile anlamlı olarak ilişkilendirilmiştir. Ayrıca, düşük PNI ile aylık atak sıklığı arasında negatif bir korelasyon (Spearman rho = -0.653, p < 0.001) ve C1-INH fonksiyonu ile pozitif bir korelasyon (Spearman rho = 0.408, p = 0.001) bulunmuştur.
Sonuç: Bu bulgular, HAE yönetiminde beslenme değerlendirmelerinin önemini vurgulamaktadır. Zayıf beslenme durumu, hastalık şiddetini artırabilir. Bu ilişkilerin doğrulanması ve HAE tedavisinde tamamlayıcı bir strateji olarak beslenme müdahalelerinin etkilerinin araştırılması için ileriye dönük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Beslenme durumu, C1 inhibitör protein, herediter anjiyoödem, immün sistem hastalıkları, prognostik nutrisyonel indeks

Introduction

Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent episodes of severe swelling, primarily due to a deficiency or dysfunction of the C1 inhibitor (C1-INH) protein, playing a crucial role in regulating the complement and contact systems of the immune response (1). The clinical manifestations of HAE can lead to significant morbidity, affecting various tissues including the skin, gastrointestinal (GI) tract, and respiratory airways, and can result in life-threatening complications, if not managed appropriately (2).

The pathophysiology of HAE is primarily linked to mutations in the SERPING1 gene, which encodes the C1-INH protein, resulting in decreased plasma levels of functional C1-INH and subsequent dysregulation of bradykinin production (1, 3). This dysregulation is responsible for the characteristic swelling episodes, which can occur spontaneously or be triggered by

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various factors, including trauma, stress, and certain medications (2).

The management of HAE has evolved significantly over recent years, with the introduction of targeted therapies, such as bradykinin B2-receptor antagonists (e.g., icatibant) and C1-INH concentrates, which have shown to improve treatment outcomes for patients experiencing acute attacks (4, 5). Current guidelines recommend a tailored approach to treatment, considering the frequency and severity of attacks, with options for on-demand therapy and long-term prophylaxis (6, 7).

Despite these advancements, challenges remain in the clinical management of HAE, particularly in accurately diagnosing acute attacks, as there are currently no specific laboratory markers for HAE episodes (8). Recent studies propose that increased levels of prothrombin fragment F1+2 and D-dimer could serve as diagnostic tools for acute attacks, pointing to the need for further validation through rigorous research (8). Moreover, the quality of life (QoL) for patients with HAE is significantly impacted by the unpredictability and severity of attacks, necessitating the development of patient-reported outcome measures to better assess the burden of the disease and the effectiveness of treatment strategies (9). As the understanding of HAE continues to evolve, ongoing research is essential to refine treatment protocols and improve clinical outcomes for affected individuals.

The Prognostic Nutritional Index (PNI) has emerged as a significant tool in assessing the nutritional status of patients, particularly in the context of chronic diseases. Originally developed to predict surgical outcomes, PNI has been correlated with disease severity and immune function in various chronic inflammatory and autoimmune disorders (10, 11).

However, its relevance in HAE remains largely unexplored, with limited data on how nutritional status may influence the clinical manifestations of this condition. Nutritional deficiencies can exacerbate the severity of chronic diseases, potentially leading to increased frequency and severity of HAE attacks (6).

Given that HAE is characterized by recurrent episodes of swelling, understanding the interplay between nutritional status and immune response could provide insights into disease management (12). Patients with HAE may experience nutritional deficiencies due to recurrent GI attacks, leading to impaired nutrient absorption and reduced dietary intake. Additionally, chronic inflammation and increased metabolic demand may further contribute to malnutrition, exacerbating disease severity and attack frequency. Recent studies suggest that nutritional assessments, including PNI, may offer valuable prognostic information for patients with chronic conditions, indicating a need for further exploration in the context of HAE (11).

This study aims to investigate the potential impact of nutritional status, as measured by PNI, on clinical outcomes in patients with HAE, thereby highlighting an under-researched area that could enhance patient care strategies. Understanding the relationship between nutritional status and disease activity in HAE could offer novel perspectives for patient management, potentially guiding more personalized therapeutic strategies incorporating nutritional assessments as part of routine care.

Materials and Methods

Study design and patient selection

This study is a single-center, retrospective cohort analysis. The study cohort comprised HAE patients followed at the immunology outpatient clinic from 2019 to 2023. Patients were included in the study if they had a confirmed diagnosis of HAE based on clinical and laboratory findings, had complete clinical and biochemical data, and were 18 years or older at the time of evaluation. The exclusion criteria for this study included chronic liver disease, malignancy, severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m²), or any chronic inflammatory or autoimmune disorder that could potentially influence nutritional status and immune function. Additionally, patients with incomplete medical records were excluded.

Data collection and assessments

Assessment of patients' data

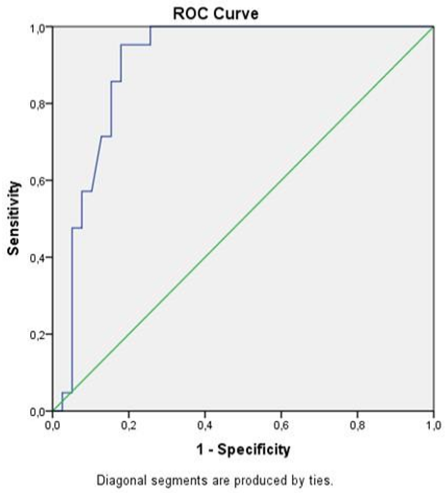
Demographic data collected for the patients encompassed age, gender, type of HAE, age of symptom onset related to HAE, and age at diagnosis. The diagnostic delay was determined by subtracting the age of symptom onset from the age at diagnosis. Data regarding the functional level of the C1 esterase inhibitor at the time of diagnosis was documented. Supplementary laboratory parameters comprised white blood cell (WBC) count, neutrophil count, lymphocyte count, hemoglobin concentration,

platelet count, creatinine concentration, aspartate aminotransferase (AST) level, alanine aminotransferase (ALT) level, albumin concentration, and C-reactive protein (CRP) level. These laboratory values were acquired from patients during asymptomatic intervals.

Calculation of the optimal cut-off for the prognostic nutritional index

PNI was determined using the formula: serum albumin concentration (g/L) + 5 × peripheral blood lymphocyte count (×10□/L) (13). The ROC curve analysis revealed that the area under the curve (AUC) for the PNI level's capacity to differentiate clinical conditions was 0.902. The AUC value obtained was statistically significant ($p < 0.001$), with a 95% confidence interval of 0.822 to 0.982 (Figure 1). As a result, the patients were categorized into two groups according to a PNI threshold of 51.725.

Figure 1. ROC curve for determining the optimal cut-off value of the prognostic nutritional index.



Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as median (interquartile range) for numerical variables and as numbers and percentages for categorical variables. The Mann–Whitney U test was employed to analyze differences between variables according to their distribution patterns. The chi-squared ($\chi 2$) and Fisher's exact tests were used for comparing percentages. Receiver Operating Characteristic (ROC) curve analysis was used to ascertain the optimal cut-off value for the PNI. The ROC curve visually represents the correlation between the sensitivity and specificity of the test, facilitating the assessment of the model's discriminative capability. Youden's Index was calculated to determine the optimal cut-off value derived from the ROC analysis. Spearman correlation analysis was conducted to assess the relationship between PNI levels and the annual frequency of attacks. $p<0.05$ was considered statistically significant.

Ethical Approval

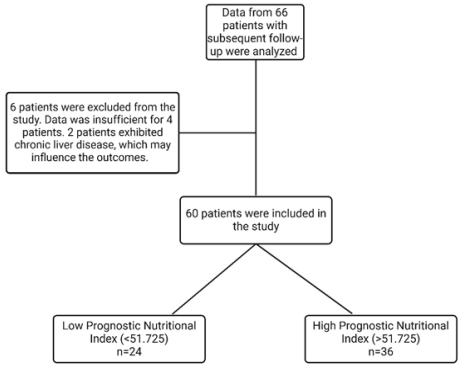
This study was approved by the Ethics Committee of Necmettin Erbakan University (Approval Number: 2024/5336). All data collection and analysis were conducted in compliance with ethical standards and the Declaration of Helsinki.

Results

Study population

Of the 66 patients initially monitored, two were excluded from the study due to chronic liver disease, which could potentially influence the outcomes, and four others were excluded due to incomplete data. A study cohort of 60 patients was established, excluding these six individuals. The low PNI group comprised 24 patients, while the high PNI group included 36 patients. The clinical and demographic data of these two patient groups were compared and analyzed (Figure 2).

Figure 2. Flowchart of patient selection and categorization based on prognostic nutritional index threshold.



The median age of the patients was 41 years, and 36 of the patients were female. In the comparison between patients with low (<51.725) and high (>51.725) PNI levels, no significant difference was found between the two groups in terms of age ($p = 0.774$). Gender distribution analysis revealed a significantly higher proportion of males in the high PNI group compared to the low PNI group, with this difference being statistically significant ($p = 0.013$). No significant difference was observed between the groups concerning the type of

HAE. However, the diagnostic delay was found to be significantly longer in the low PNI group (Table 1).

Table 1. Comparison of demographic and clinical characteristics between low and high prognostic nutritional index groups in patients with hereditary angioedema

	PNI Low (<51.725) (n=24)	PNI High (>51.725) (n=36)	p
Age (years) (median, IQR)	41.5 (30.25-49)	40.5 (28-51)	0.774*
Gender			
Female (n) (%)	19 (79.2)	17 (47.2)	**0.013****
Male (n) (%)	5 (20.8)	19 (52.8)	
Hereditary Angioedema Type			
Type 1 (n) (%)	15 (62.5)	22 (61.1)	0.914**
Type 2 (n) (%)	9 (37.5)	14 (38.9)	
Diagnostic delay (years) (median, IQR)	16.5 (5.5-21.8)	8.5 (4.3-14.5)	**0.022***

*Mann–Whitney U test (data are shown as median with IQR). **χ^2 test (data are shown as numbers and percentages). IQR: Interquartile range,

PNI: Prognostic nutritional index

Evaluation of attack frequency, involvement patterns, and clinical parameters concerning PNI levels

In the comparison between groups with low and high PNI levels, the frequency of attacks was significantly higher in the low PNI group (30.0% vs. 5.0%; p < 0.001). No significant differences were observed between the groups regarding mucocutaneous involvement (40.0% vs. 58.3%; p = 0.410). However, laryngeal involvement was significantly more prevalent in the low PNI group compared to the high PNI group (26.7% vs. 16.7%; p = 0.003). Additionally, GI involvement was significantly more frequent in the low PNI group (35.0% vs. 31.7%; p = 0.005). Furthermore, the median number of attacks per month was notably higher in the low PNI group (5 [IQR: 3.25-8]) compared to the high PNI group (1 [IQR: 0.4-2]; p < 0.001) (Table 2).

Table-2. Clinical outcomes, attack frequency, and involvement patterns in hereditary angioedema patients categorized by prognostic nutritional index levels

	PNI Low (<51.725) (n=24)	PNI High (>51.725) (n=36)	p
Presence of Frequent Attacks (n) (%)	18 (75.0)	3 (8.3)	**<0.001***
Mucocutaneous Involvement (n) (%)	24 (100.0)	35 (97.2)	**1***
Gastrointestinal Involvement (n) (%)	21 (87.5)	21 (58.3)	**0.005***
Laryngeal Involvement (n) (%)	16 (66.7)	10 (27.8)	**0.003***
Number of Attacks per Month (median, IQR)	5 (3.25-8)	1 (0.4-2)	**<0.001****

*χ^2 test (data are shown as numbers and percentages). **Mann–Whitney U test (data are shown as median with IQR). IQR: Interquartile range, PNI: Prognostic nutritional index **Mann–Whitney U test (data are shown as median with IQR)

Biochemical and hematological differences based on PNI levels

In the comparison between the groups with low (<51.725) and high (>51.725) PNI levels, significant differences were observed in several biochemical and hematological parameters. The C1-INH function was significantly lower in the low PNI group (p=0.001). There was no statistically significant difference in WBC count and neutrophil count between the two groups (p = 0.940 and p = 0.357, respectively). The lymphocyte count was significantly lower in the low PNI group compared to the high PNI group (p=0.001). No significant differences were found between the two groups in terms of hemoglobin levels, platelet count, creatinine, AST, and ALT levels (p > 0.05 for all). However, albumin levels were significantly lower in the low PNI group compared to the high PNI group (p<0.001) No statistically significant difference was observed in CRP levels between the groups (p = 0.561) (Table 3).

Table-3. Comparison of biochemical and hematological parameters in hereditary angioedema patients stratified by prognostic nutritional index levels

	PNI Low (<51.725) (n=24)	PNI High (>51.725) (n=36)	p*
C1 inhibitor function (%) (median, IQR)	8.85 (5.25-12)	11.4 (10-19.55)	**0.001**
White Blood Cell count (10^3/μL) (median, IQR)	7.39 (6.99-8.57)	7.61 (6.60-9.02)	0.940
Neutrophil count (10^3/μL) (median, IQR)	4.52 (4.19-5.51)	4.41 (3.59-5.80)	0.357
Lymphocyte count (x10^3/mL) (median, IQR)	1.86 (1.38-2.16)	2.22 (1.99-2.41)	**0.001**
Hemoglobin (g/dL) (median, IQR)	13.7 (12.9-15.0)	14.3 (13.2-15.4)	0.287
Platelet count (10^3/μL) (median, IQR)	276 (226-323)	264 (231-308)	0.597
Creatinine (mg/dL) (median, IQR)	0.75 (0.66-0.88)	0.77 (0.68-0.91)	0.602
Aspartate Aminotransferase (U/L) (median, IQR)	15.9 (13.3-19.8)	17.1 (13.0-21.8)	0.551
Alanine Aminotransferase (U/L) (median, IQR)	13.1 (10.8-22.6)	16.7 (12.2-24.9)	0.216
Albumin (g/L) (median, IQR)	39 (36-40)	44 (42-47)	**<0.001**
C-reactive protein (mg/L) (median, IQR)	2.24 (1.48-3.60)	2.45 (1.18-4.48)	0.561

*Mann–Whitney U test (data are shown as median with IQR). IQR: Interquartile range,

PNI: Prognostic nutritional index

Correlation analysis between PNI levels and attack frequency, clinical and laboratory parameters

Spearman correlation analyses were performed to assess the relationships between PNI levels and various clinical parameters, including monthly attack

frequency, disease duration, the C1-INH function, and age at symptom onset (complaint age). The analysis showed a significant negative correlation between PNI levels and monthly attack frequency (Spearman's rho = -0.653, p < 0.001), associating lower PNI levels with more frequent attacks. By contrast, the relationship between PNI levels and disease duration was weak and not statistically significant (Spearman's rho = -0.155, p = 0.237), indicating a lack of meaningful association. A moderate positive correlation was found between PNI levels and the C1-INH function (Spearman's rho = 0.408, p = 0.001), indicating that higher PNI levels were associated with the improved C1-INH function. There was not a statistically significant correlation between PNI levels and age at symptom onset (Spearman's rho = 0.141, p = 0.284) (Table 4).

Table-4. Spearman correlation analysis between prognostic nutritional index levels and clinical and laboratory parameters in hereditary angioedema patients

Clinical Parameter	Spearman's rho	p	Interpretation
Monthly attack frequency	-0.653	< 0.001	Significant negative correlation
Duration of disease	-0.155	0.237	Weak negative, not statistically significant
Age at the onset of symptoms	0.141	0.284	Weak positive, not statistically significant
C1 inhibitor function	0.408	0.001	Moderate positive correlation, significant

Discussion

This study is one of the initial investigations to thoroughly assess the influence of prognostic nutritional index (PNI) levels on clinical outcomes in individuals with HAE. Our findings indicate that diminished PNI levels correlate with elevated attack frequencies, heightened laryngeal and GI involvement, and prolonged diagnostic delays. These findings offer a novel viewpoint on the impact of HAE and the role of nutritional status.

The observation of elevated monthly attack frequencies in patients with diminished PNI levels highlights the significance of nutritional status in affecting disease progression. This corresponds with the guideline established by Maurer et al. which underscores the essential influence of nutritional factors in the pathogenesis of chronic inflammatory diseases (14).

Research on prognostic nutritional indices in alternative conditions offers supplementary context. Jiang et al. discovered that diminished PNI levels in gastric cancer patients were significantly correlated with postoperative complications and reduced long-term survival (15). This highlights the essential connection between malnutrition and clinical decline. Zhang et al. similarly indicated that PNI is a reliable predictor of diabetic nephropathy progression (16). Lower PNI was associated with heightened renal dysfunction and inflammation. Nergiz et al. demonstrated that in patients with acute ischemic stroke, a lower PNI predicted increased infection rates (17). This underscores its value as an indicator of immune competence and systemic susceptibility.

The heightened incidence of laryngeal involvement in patients with diminished PNI levels emphasizes the necessity of vigilant monitoring of nutritional status to avert potentially fatal respiratory complications. Laryngeal edema presents a considerable threat of airway obstruction. Our results corroborate those of Zanichelli et al. who underscored the necessity of prompt identification and assertive treatment of high-risk individuals with C1-INH deficiency (18).

Moreover, research conducted by Wiednig et al. indicates that nutritional interventions may directly mitigate the severity of mucosal edema by enhancing systemic inflammatory regulation (5). This suggests that targeted dietary modifications may play a role in reducing the risk of laryngeal attacks in HAE patients.

This study identifies a significant association between low PNI levels and GI involvement in patients with HAE, underscoring the interplay between nutritional status and disease severity. GI symptoms, including recurrent abdominal pain, vomiting, and diarrhea, may contribute to a detrimental cycle of malabsorption, protein depletion, and heightened inflammatory responses (19). Increased vascular permeability and mucosal edema in the GI tract may further impair nutrient absorption, exacerbate weight loss, and disrupt metabolic homeostasis (20). Lumry et al. reported that persistent GI symptoms in HAE significantly reduce dietary intake, exacerbating malnutrition and inflammation (21). Similarly, Santos et al. demonstrated that targeted nutritional interventions, including specialized dietary modifications and supplementation, alleviated symptom severity and improved overall health outcomes in HAE patients (22). These findings suggest that nutritional deficiencies are not merely a consequence of HAE but may actively contribute to disease progression and symptom

exacerbation.

Given these observations, routine nutritional assessments and proactive interventions are imperative in the clinical management of HAE. Longhurst et al. highlighted the benefits of personalized dietary strategies in mitigating GI distress, enhancing patient resilience to acute episodes, and improving QoL (23). Specifically, monitoring PNI levels and addressing deficiencies through targeted supplementation, particularly of proteins, vitamins, and essential micronutrients, may play a crucial role in optimizing disease management (24). Our findings underscore the necessity of integrating nutritional monitoring into the standard clinical approach for HAE, considering its potential impact on disease severity and treatment outcomes.

The correlation between diminished PNI levels and GI involvement underscores the complex effects of nutritional deficiencies in HAE. GI symptoms, including abdominal pain, vomiting, and diarrhea, diminish QoL and may aggravate nutritional deficiencies in a detrimental cycle.

Lumry et al. highlighted that recurrent GI symptoms in patients with HAE substantially diminish their nutritional intake, exacerbating malnutrition and inflammatory responses (21). Santos et al. observed that GI-focused nutritional interventions, including targeted supplementation and dietary alterations, diminished symptom severity and enhanced overall health in their cohort of HAE patients (22). Longhurst et al. emphasized the significance of personalized nutritional care in mitigating GI distress (23). Their findings indicated enhanced resilience to acute episodes and improved patient-reported outcomes post-intervention. These studies collectively emphasize the imperative to tackle GI-related nutritional challenges in the management of HAE.

The noted decline in the C1-INH function linked to inadequate nutritional status reinforces the hypothesis that PNI may intensify complement system dysfunction. The activity of the complement system is influenced by systemic inflammation, which is exacerbated in malnourished conditions (14). This interaction may elucidate the heightened severity and frequency of attacks noted in patients with a low PNI.

Additionally, Ishiguro et al. emphasized the significance of lymphocyte count within the PNI framework, suggesting its potential as a dependable biomarker for immune competence (25). These findings suggest that improving nutritional status could positively impact complement regulation and immune function in HAE patients.

These findings indicate that nutritional status must be prioritized as a critical factor in the management of HAE patients. Nutritional interventions aimed at sustaining elevated PNI levels may decrease attack frequency, enhance the C1-INH functionality, and improve overall patient outcomes. Wiednig et al. established that nutrition-oriented therapeutic strategies improve long-term patient satisfaction and adherence to treatment (5).

Routine evaluation of PNI should be incorporated into clinical practice to enable the prompt identification of at-risk patients. Customized nutritional approaches, encompassing dietary guidance and supplementation, may alleviate the disease burden. Santos et al. emphasized the beneficial impact of nutritional education in managing chronic diseases (22). This could be tailored for HAE patients to improve adherence and results.

Moreover, interdisciplinary cooperation among immunologists, dietitians, and psychologists is essential for formulating a comprehensive strategy for patient care. This strategy could tackle the physical dimensions of nutritional deficiencies and the psychosocial obstacles encountered by HAE patients. Research by Bonner et al. has highlighted the significance of patient-reported outcomes in informing treatment strategies (9). This could potentially facilitate the implementation of customized nutritional interventions.

Utilizing technological innovations like digital health tools and mobile applications may enable real-time tracking of nutritional status and patient compliance with dietary plans. These tools have demonstrated the potential to improve patient engagement and outcomes in various chronic diseases. They may be modified for HAE management (23). Shi et al. demonstrated the prognostic significance of integrated nutritional indices and digital monitoring in chronic disease management, which may be beneficial for HAE patients (26).

Ultimately, catering to the distinct requirements of subpopulations, such as pediatric or geriatric patients with HAE, may enhance treatment strategies. Farkas et al. emphasized the unique challenges encountered by pediatric HAE patients, wherein nutritional deficiencies may negatively affect growth and development (27). Customizing nutritional interventions for these at-risk

populations may avert long-term complications and enhance overall disease outcomes.

The retrospective design of this study limits the ability to establish causal relationships between nutritional status and clinical outcomes in HAE. Future studies with expanded sample sizes and longitudinal designs are necessary to validate these findings. Additionally, research evaluating targeted dietary and nutritional interventions in HAE patients could address critical gaps in knowledge. For instance, investigating the effects of protein-rich diets on the C1-INH function—a hypothesis grounded in the role of albumin (a key component of PNI) in maintaining immune and inflammatory balance—may provide mechanistic insights. While no direct studies have yet explored protein intake's impact on C1-INH activity in HAE, the rationale stems from the observation that hypoalbuminemia, often linked to malnutrition, correlates with systemic inflammation and complement dysregulation (14, 22). Similarly, micronutrient supplementation trials (e.g., vitamin D, zinc) could assess their potential to reduce attack frequency, given emerging evidence of their immunomodulatory roles in other inflammatory conditions (16, 24). Such investigations would clarify whether nutritional optimization directly modulates disease pathophysiology or simply reflects broader systemic health.

In addition to PNI and C1-INH levels, investigating the roles of additional biomarkers (such as albumin, cytokines, and inflammatory mediators) in forecasting clinical outcomes may yield a more thorough comprehension of disease mechanisms. Maurer et al. emphasize that the relationship between bradykinin-induced inflammation and nutritional status requires additional examination (14).

Ultimately, investigating the psychosocial aspects of nutritional deficiencies in HAE is essential. Lumry et al. underscored that inadequate nutritional status and frequent episodes substantially contribute to depression and diminished productivity in HAE patients (21). This highlights the necessity for comprehensive management strategies. Moreover, incorporating patient-reported outcomes into forthcoming studies may yield an enhanced understanding of the effects of nutritional interventions on QoL (9).

This study highlights the substantial influence of nutritional status, as evaluated by PNI, on the clinical outcomes of HAE patients. Regular PNI monitoring and focused nutritional interventions may significantly decrease the attack frequency and disease burden while enhancing QoL. Prospective studies are crucial to validate these findings and discover new therapeutic targets. Healthcare providers can formulate more tailored and effective management strategies to enhance patient outcomes and long-term health by addressing the complex relationship between nutrition and HAE.

Key Findings of the Study

Reduced PNI levels were significantly correlated with elevated attack frequency, extended diagnostic delays, and increased laryngeal and GI involvement in patients with HAE.

Low PNI levels exhibited a negative correlation with monthly attack frequency (Spearman's rho = -0.653, $p < 0.001$) and a positive correlation with the C1-INH function (Spearman's rho = 0.408, $p = 0.001$).

Laryngeal involvement was significantly more common in the low PNI group than in the high PNI group (66.7% vs. 27.8%; $p = 0.003$), suggesting an increased risk of potentially fatal airway obstruction.

GI involvement occurred more frequently in the low PNI group (87.5% vs. 58.3%; $p = 0.005$), significantly affecting patients' QoL.

The findings underscore the essential importance of nutritional status in HAE management. Consistent assessment of PNI levels may enhance clinical outcomes and guide individualized treatment approaches.

Authors' Contributions

Study design, supervision of work and task distribution, interpretation of results: Dr. MEG; ehmet Emin Gerek:Statistical analysis and data interpretation: Associate Professor Dr. Fatih CÇ;ölkesen: Data collection and initial data processing: Dr. TO;uğba Önalan: Data collection and statistical validation: Dr. FAA;atma Arzu Akkuş: Data curation and quality control: Dr. RE;ecep Evcen: Data collection and manuscript drafting support: Dr. MK;ehmet Kılınç: Data curation and literature review: Dr. SK;elim Kahraman: Supervision of work, critical revision of the manuscript, and interpretation of results: SAProfessor Dr. Şevket Arslan:

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