RESEARCH ARTICLE

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2022.2021-241
Cyprus J Med Sci 2022;7(5):628-632

Prognostic Nutritional Index as a Predictor of In-Hospital Mortality in Patients with Ischemic Hepatitis

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Abstract

BACKGROUND/AIMS: Ischemic hepatitis (IH), a life-threatening medical disease, requires treatment in the shortest possible time. The present study aimed to investigate the clinical significance of the prognostic nutritional index (PNI) for IH.

MATERIALS AND METHODS: We retrospectively analyzed 40 patients admitted to our hospital with a diagnosis of IH. The patients were classified into two groups (survivals and non-survivals) and they were compared according to their clinical and laboratory characteristics. PNI was calculated as 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (per mm^3). We also used a logistic regression to identify any risk factors of in-hospital mortality.

RESULTS: The mean age of the study cohort was 72±12 years. Of the patients, 25 (64.1%) were male, and 21 (52.5%) died during their intensive coronary unit stay. The PNI levels were significantly lower in the non-survival group than in the survival group (40.9±6.7 vs 32.9±5.8, $p<0.001$). Multivariate analysis showed that the PNI [odds ratio (OR): 0.98, 95% confidence interval (CI): 0.97-0.99, $p\leq0.001$], glucose (OR: 2.54, 95% CI: 1.64-4.29, $p\leq0.001$), albumin (OR: 0.93, 95% CI: 0.91-0.996, $p\leq0.001$), red cell distribution width (OR: 0.99, 95% CI: 0.98-0.99, $p\leq0.001$) independently predicted in-hospital mortality.

CONCLUSION: The PNI is an independent predictor of in-hospital mortality in patients with a diagnosis of IH.

Keywords: Hepatitis, in-hospital mortality, nutritional index

INTRODUCTION

Ischemic hepatitis (IH) is a life-threatening syndrome characterized by a rapid, massive and transient rise in the plasma aminotransferase level [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] as a result of predisposing conditions, such as cardiac failure, sepsis and respiratory failure. In its diagnosis, other causes of higher transaminase levels need to be excluded, including acute viral hepatitis, metabolic liver diseases and toxic hepatitis.[1-3] IH is a frequent cause of acute liver injury in intensive care units, with previously reported incidences of nearly 2.5%, but it has also been reported in some studies that its incidence can be as high as 10% and it results in a mortality rate of 56% to 59% depending on the awareness of the clinical picture.[4]

To cite this article: Vural A, Taşargöl Ö, Günaydın ZY, Akagün T, Özbaş HM, Ayvaz MA, Yakarışık M. Prognostic Nutritional Index as a Predictor of In-Hospital Mortality in Patients with Ischemic Hepatitis. Cyprus J Med Sci 2022;7(5):628-632

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Received: 05.12.2021
Accepted: 16.02.2022

Evidence suggests that the cross-impact between the liver and other organ systems is a major factor in the development of IH, but the pathophysiologic mechanisms are not fully understood yet.

The prognostic nutritional index (PNI) is a derivative of the total lymphocyte count and serum albumin, reflecting the nutritional and inflammatory status of the patients.[5] PNI is a prognostic score and it has a very close relationship with prognosis in a variety of clinical settings including cardiovascular diseases, infectious diseases and cancer.[6-11] In this study, we aimed to investigate the prognostic value of PNI in patients with IH.

MATERIALS AND METHODS

Study Population

Between January, 2017 and November, 2019, 52 patients with the diagnosis of IH were hospitalized in the intensive care, gastroenterology, or cardiology departments of our hospital. The medical records of these patients were retrospectively evaluated. Twelve patients were excluded from this study; one patient was under the age of 18; two patients were diagnosed with cancer and nine patients had missing information in their hospital data.

The diagnostic criteria for IH were determined as follows: rapid, massive and transient increases in either AST or ALT up to 10 times the upper limit of normal, and the presence of predisposing factors such as cardiac, circulatory and/or respiratory failures. Additionally, some tests were examined in terms of the diagnosis and differential diagnosis of IH. Echocardiographic findings including measurements of ventricular and valve functions, heart size and pulmonary artery pressure were examined for cardiac causes. Liver size and condition, vascular structures and flow conditions, and the spleen were evaluated by abdominal ultrasonography. When necessary, liver and vascular structures were evaluated, pancreatitis was ruled out, and cirrhosis symptoms were examined by computed tomography.

Other causes in the differential diagnosis of acute liver enzyme elevation, and tests related to toxic, viral and autoimmune hepatitis were examined.

- Information obtained from the patients and their relatives about toxins, drugs and/or herbal medicines which cause acute serum aminotransferase elevation were considered. When necessary, toxicological examinations which could be compatible with the clinic were performed.

- Since autoimmune hepatitis can also present with acute hepatitis clinic, tests such as anti-nuclear antibodies, anti-smooth muscle antibodies, anti-liver-kidney-microsomal, anti-soluble liver antigen, globulin profile, anti-neutrophil cytoplasmic antibody, HLA typing were performed.

- Hepatitis A, hepatitis B, hepatitis C, cytomegalovirus and Ebstein-Barr virus tests were requested in relation to viral hepatitis.

This study was approved by the Ethics Committee for Clinical Research of the Ordu University Faculty of Medicine (approval number: 2020/207).

Laboratory Analysis

In the retrospective analysis of the patients' records, the diagnosis of IH was made considering the highest ALT-AST levels detected during their hospitalization. Other biochemical and hematological parameters, viral markers, infectious diseases, hepatobiliary ultrasound and transthoracic echocardiography were also examined to evaluate the reasons which may have caused liver enzyme elevation. For each case, the PNI was calculated with the following equation; PNI = [10 x albumin (mg/dL)] + [0.005 x lymphocyte count (per mm^3)].

Statistical Analysis

All statistical analyses were performed with the SPSS 21 software package (SPSS Inc., Chicago, Illinois). Quantitative variables with a normal distribution are given as mean (± standard deviation), while those without a normal distribution are presented as median and minimum-maximum values. Categorical variables are shown as percentage. The normality of the data was determined using the Kolmogorov-Smirnov test. The t-test was used to compare quantitative variables with the normal distribution, while the Mann-Whitney U test was employed to compare data without normal distribution. The chi-square test was performed to compare categorical variables. Independent predictors of in-hospital mortality were identified using logistic regression analysis. All variables showing significance values of less than 0.10 in the univariate analysis were included in the model. Two-tailed p-values of less than 0.05 were considered as statistically significant.

RESULTS

The study population included 40 patients with IH. The mean age of the study cohort was 72±12 years. Of the patients, 25 (64.1%) were male, and 21 (52.5%) died during their stay in the intensive care unit. Heart failure was the main factor for the development of IH in 24 patients (62%). Sepsis caused IH in eight patients (20%). Four patients (10%) developed IH due to hemorrhage and hypovolemia. There was no significant difference between the 2 groups in terms of hypoperfusion etiologies. The PNI levels were significantly lower in the non-survival group compared to the survival group (40.9±6.7 vs 32.9±5.8, $p<0.001$). The clinical characteristics of all patients enrolled in the study are shown in Table 1. The multivariate analysis showed that the PNI [odds ratio (OR): 0.98, 95% confidence interval (CI): 0.97-0.99, $p\leq0.001$], glucose (OR: 2.54, 95% CI: 1.64-4.29, $p\leq0.001$), albumin (OR: 0.93, 95% CI: 0.91-0.996, $p\leq0.001$), and red cell distribution width (OR: 0.99, 95% CI: 0.98-0.99, $p\leq0.001$) independently predicted in-hospital mortality (Table 2).

DISCUSSION

In our study, we determined that the PNI value was significantly lower in the non-survival group than in the survival group, and that PNI was a predictor for mortality due to IH.

IH is a serious and uncommon form of hypoxic hepatitis accompanied by elevated liver enzymes, and increased lactate dehydrogenase (LDH) levels due to life threatening predisposing factors including heart failure, respiratory diseases and sepsis. Physicians need to consider this diagnosis in unexplained extreme elevations of liver transaminases where there are elevations up to 10 times the upper limit of normal, especially in the presence of risk factors. As a general rule, transaminitis occurs 1 to 3 days after the acute disturbing event and generally normalizes 7 to 10 days later. In addition, the ALT to LDH ratio is almost always less than 1.5.[6]

Previous studies have shown that impaired liver function tests are common in patients with acute heart failure and they are associated

Table 1. Baseline characteristics of the study population at admission

Variables	Survivors (n=19)	Non-survivors (n=21)	p-value
Age (years)	70.4 ±13.1	74.6±11.1	0.27
Glucose (mg/dL)	128.15 (55.67)	187.09 (88.23)	0.17
AST (U/L)	1,155.47 (1652.26)	1,268.90 (1014.62)	0.22
ALT (U/L)	800.78 (786.33)	734.71 (524.99)	0.75
Alkaline phosphatase (U/L)	128.15 (72.04)	157.14 (140.5)	0.64
Total protein (g/dL)	6.22 (0.69)	5.76 (1.22)	0.23
Albumin (g/dL)	3.67 (0.63)	2.82 (0.69)	0.001
Total bilirubin (mg/dL)	2.48 (1.91)	2.18 (1.83)	0.94
Direct bilirubin (mg/dL)	1.43 (1.17)	1.60 (1.59)	0.71
GGT (U/L)	129.23 (154.11)	165.71 (375.71)	0.12
LDH (U/L)	1,011.05 (921.65)	1,102.31 (815.12)	0.75
C-reactive protein (mg/dL)	32.31 (45.4)	24.01 (32.87)	0.50
Urea (mg/dL)	90.15 (44.87)	144.71 (78.32)	0.11
Creatinine (mg/dL)	2.17 (1.52)	3.2 (2.77)	0.27
Hemoglobin, (g/dL)	11.99 (2.23)	10.44 (2.41)	0.43
Hematocrit, (%)	36.6±6.3	32.6±7.4	0.76
White blood cell count ($X10^3$/µL)	9.75 (3.08)	15.03 (10.96)	0.26
Lymphocyte ($X10^3$/µL)	1.05 (0.45)	1.01 (0.82)	0.35
Neutrophyl ($X10^3$/µL)	7.99 (3.11)	13.3 (10.4)	0.38
Platelet ($X10^3$/µL)	191.73 (102.87)	154.33 (73.77)	0.19
RDW, (%)	31.6 (17.08)	25.71 (15.33)	0.51
TSH (mU/L)	1.26 (1.84)	0.64 (1.48)	0.25
Troponin T (µg/L)	0.16 (0.27)	0.91 (2.18)	0.13
Creatinine kinase (U/L)	259.27 (447.51)	661.61 (1363.38)	0.45
PH	7.3±0.7	7.2±0.1	0.48
Lactate (mmol/L)	3.16 (1.62)	5.64 (3.81)	0.36
Bicarbonate (mEq/L)	21.2±3.4	19.3±5.82	0.33
PNI	40.9±6.7	32.9±5.8	0.01
Ejection fraction, (%)	40.5±15.7	38.6±13.9	0.76
sPAP (mmHg)	41.8±12.5	51.4±11.3	0.17
Length of stay (days)	8.83 (6.41)	21.57 (25.68)	0.48
Etiology			
Heart failure (n, %)	10 (52.6)	14 (66.6)	0.38
Sepsis (n, %)	3 (15.7)	5 (23.3)	
Hypovolemia (n, %)	3 (15.7)	1 (4.7)	
Other (n, %)	3 (15.7)	1 (4.7)	

The differences were regarded as significant when p<0.05.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase, LDH: lactate dehydrogenase, PNI: prognostic nutritional index, RDW: red cell distribution width, sPAP: systolic pulmonary artery pressure, TSH: thyroid-stimulating hormone.

Table 2. Independent predictors of in-hospital mortality in patients with ischemic hepatitis: logistic regression analysis

Variables	Univariate OR, 95% CI	p-value	Multivariate OR, 95% CI	p-value
Glucose	3.12 (1.92-4.54)	<0.001	2.54 (1.64-4.29)	<0.001
PNI	0.98 (0.97-0.99)	<0.001	0.98 (0.97-0.99)	<0.001
Albumin	0.92 (0.90-0.94)	<0.001	0.93 (0.91-0.96)	<0.001
RDW	0.99 (0.98-0.99)	<0.001	0.99 (0.98-0.99)	<0.001

The results were regarded as significant when p<0.05.
RDW: red cell distribution width, PNI: prognostic nutritional index, OR: odds ratio, CI: confidence interval.

with an increased risk of mortality, readmission, and in-hospital HF worsening.[7] In our study, the mean ejection fraction decreased in both groups. The ejection fraction was found to be slightly lower in the non-survival group than in the survival group, but this difference was not statistically significant.

Nutritional condition reflects the patients' health status. Previous studies have reported the use of multiple tools in screening for nutritional parameters in patients, such as PNI, the geriatric nutritional risk index (GNRI) and controlling nutritional status score (CONUT). Numerous studies have reported that these parameters are associated with adverse outcomes such as heart failure,[7] various cancers,[12,13] pulmonary embolism,[14] stroke[15] and chronic kidney disease.[16]

It is difficult to assess the nutritional status of patients. The data obtained by examination may differ according to the practitioner, or the verbal information obtained from the patients and/or their relatives may be misleading. Therefore, we preferred the PNI as a more objective nutritional marker. Based on laboratory data, the most commonly used nutrition indexes are CONUT, GNRI and PNI. All three indexes contain the albumin component. Albumin is a protein with a long half-life and it indicates a chronic nutritional status. IH is an acute condition. However, we examined the effect of chronic malnutrition on acute IH by measuring the PNI of patients at the time of admission. Malnutrition is a complex condition involving the depletion of protein and energy stores, resulting in a weakened immune defense.

The present study revealed that the PNI value and serum albumin level on admission were independently associated with mortality. PNI is derived from an equation including the albumin value and the lymphocyte count. Multivariate analysis revealed that PNI and serum albumin were significant predictors of mortality in IH patients. In our study, no difference was found between the survival and non-survival groups in terms of their lymphocyte levels. The factor making the difference between the PNI values was the albumin levels.

Recent studies have shown that low serum albumin levels, which are used as an indicator of nutritional status in clinical practice, predict hospitalization and mortality. Various mechanisms may mediate low serum albumin levels in IH. Since it is synthesized in hepatocytes, low albumin levels indicate impaired liver function. Albumin levels may also be altered with inflammation. Proinflammatory cytokines, such as interleukin-6 or tumor necrosis factor-alpha, affect albumin synthesis in hepatocytes leading to malnutrition.[17,18] In addition, inflammatory responses accelerate catabolism, resulting in low albumin levels.[19] In critical illnesses, decreased appetite, inadequate intake, and malabsorption also lead to low albumin levels.[20]

Study Limitations

The limited sample size and retrospective design are the limitations of our study. As it was conducted retrospectively, we were not able to determine vital signs at admission, treatments and nutritional support during hospitalization. The inability to compare the hypoperfusion time is an important limitation of our study. Since our study was retrospective, we could not obtain data on this subject. However, in a previous study of IH, only 51% of the patients had a documented hypotensive event or shock state.[21] Namely, the hypoferfusion time would be very difficult to determine.

CONCLUSION

In conclusion, lower PNI values are independently associated with in-hospital mortality in IH patients. The PNI may be a useful parameter for predicting mortality in IH patients.

MAIN POINTS

- IH is a serious and uncommon form of hypoxic hepatitis accompanied by elevated liver enzymes, and increased LDH levels due to life threatening predisposing factors including heart failure, respiratory diseases or sepsis.
- The PNI is a prognostic score reflecting immune and inflammatory status and it has a very close relationship with the prognosis in a variety of clinical settings such as cardiovascular diseases, infectious diseases, and cancer.
- In our study, we found that the PNI value was significantly higher in the non-survival group than in the survival group, and also, it was a predictor for mortality due to IH.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee for Clinical Research of the Ordu University Faculty of Medicine (approval number: 2020/207).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.Y., Design: A.V., M.Y., Supervision: Ö.T., Materials: H.M.Ö., Data Collection and/or Processing: M.A.A., Analysis and/or Interpretation: A.V., Literature Search: Z.Y.G., Writing: A.V., T.A., Critical Review: A.V.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The author declared that this study had received no financial support.

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