

Effect of illness uncertainty on alanine transaminase levels and aspartate aminotransferase levels in patients with nonalcoholic fatty liver disease

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ABSTRACT

Patients with nonalcoholic fatty liver disease (NAFLD) have illness uncertainty. The purpose of this longitudinal study was to investigate the effect of the degree of illness uncertainty in patients with NAFLD on liver function values. We conducted a questionnaire survey and collected blood samples from outpatients with NAFLD. The items in the questionnaire were measured for illness uncertainty using the Japanese version of the Mishel Uncertainty in Illness Scale-Community (MUIS-C). Blood samples were collected at baseline and after 1 year. We divided the patients into two groups: one with high illness uncertainty and the other with low illness uncertainty. We then compared changes in alanine transaminase (ALT) and aspartate aminotransferase (AST) levels over time from baseline using multiple regression analysis. This study analyzed 148 patients with NAFLD; 75 were male and 73 were female, with a mean age of 58.4 ± 12.3 years. The group with higher illness uncertainty had significantly higher ALT and AST levels at 1 year ($\beta = .185$ and $.183$, respectively) than the group with lower illness uncertainty. High illness uncertainty in patients with NAFLD can lead to higher ALT and AST levels. Healthcare providers must focus on reducing illness uncertainty in patients with NAFLD.

Keywords: alanine transaminase, aspartate aminotransferase, nonalcoholic fatty liver disease, uncertainty

Abbreviations:

ALT: alanine transaminase

AST: aspartate aminotransferase

IPAQ-SF: International Physical Activity Questionnaire Short Form

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MUIS-C: Mishel Uncertainty in Illness Scale-Community

NASH: nonalcoholic steatohepatitis

NAFLD: nonalcoholic fatty liver disease

QOL: quality of life

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INTRODUCTION

The incidence of nonalcoholic fatty liver disease (NAFLD) has risen in Japan in recent years, and its prevalence rate, identified during health checkups, is approximately 40% in men and 20% in women.^{1,2}

Lifestyle improvements in diet and exercise are important in patients with NAFLD, and patients should understand the risks associated with disease progression before engaging in self-care. Therefore, healthcare providers must provide opportunities for patients to be informed. However, because most of the symptoms of NAFLD are not subjective,³ the disease often progresses without the patient being aware of it. Patients with NAFLD that has progressed to cirrhosis and liver cancer were found to have illness uncertainty.⁴ Mishel⁵ defines disease uncertainty as “the inability to make a clear sense of a variety of disease-related events,” and it comprises four components: 1) ambiguity of the disease state, 2) complexity of the treatment or healthcare system, 3) lack of information about the name or severity of the disease, and 4) unpredictability of the disease course and prognosis. Some studies have examined the relationship between the degree of pain and self-care behavior and illness uncertainty in chronic diseases.⁶ Illness uncertainty is associated with the quality of life (QOL) in patients with NAFLD.⁷ However, no study has analyzed the relationship between illness uncertainty and liver function parameters. The purpose of this study was to longitudinally examine the effect of the degree of illness uncertainty on liver function in patients with NAFLD.

METHODS

Study design

This prospective cohort study was conducted between July 2019 and September 2020 at Nagoya University Hospital, Japan, a base hospital for the treatment of liver diseases. This study is an addition to a previous study⁷ that clarified the structure of QOL in patients with NAFLD.

Participants

The eligibility criteria for this study were adult patients with NAFLD. We excluded patients with liver cancer, primary biliary cirrhosis, and autoimmune hepatitis, as liver function values could be affected by treatments other than NAFLD treatment. In addition, patients who started, discontinued, or changed the dosage of oral medication that may affect the pathogenesis of NAFLD (hepatic function-improving drugs; vitamin E preparations; insulin; medications for hepatitis virus, hyperlipidemia, and high cholesterol; immunosuppressants; and hormone therapy medicine) during the study period were excluded from the analysis because changes in medication may alter the alanine transaminase (ALT) and aspartate aminotransferase (AST) levels. In total, 158 outpatients diagnosed with NAFLD by gastroenterologists participated in this study. During the study course, 10 participants dropped out due to interruption of hospital visits or termination of consultation; therefore, 148 participants were finally included in the analysis.

Procedure

The gastroenterologist introduced the subjects to the researcher, and the researcher explained the study to the subjects. For baseline assessments, we distributed the questionnaire to patients who agreed to participate and asked them to return the questionnaire by mail. We also reviewed medical record data (baseline and after 1 year) of subjects whose consent was obtained. This study was approved by the ethics committee of Nagoya University Bioethics (approval no. 2019-0062).

Survey items

Illness uncertainty. This study measured illness uncertainty using the Mishel Uncertainty in Illness Scale-Community (MUIS-C). This scale has been used for patients with diseases such as cancer, intractable diseases, and cardiac diseases and has been validated for its reliability and accuracy.^{8,9} One factor consists of 23 items, such as “I do not know what is wrong with my body,” “I do not know how much my condition will worsen in the future,” “I do not know what will happen to my body in the future,” and “I do not understand the explanation of the doctor and the course of illness; therefore, I cannot predict the future.” Items are rated on a 5-point Likert scale ranging from 1 (not at all) to 5 (always), with total scores ranging from 23 to 115, with higher scores indicating higher levels of uncertainty in illness. MUIS-C has been used in various fields of investigation, including liver disease, cardiac disease, cancer, and neurological intractable diseases.^{6,10,11}

Dietary habits. To evaluate the dietary habits of patients with NAFLD, we created a 9-item questionnaire based on previous studies¹²⁻¹⁴ on fatty liver disease, Japanese NAFLD/nonalcoholic steatohepatitis (NASH) practice guidelines, and opinion from nurses in chronic disease nursing, and hepatologists. The questionnaire items were rated on a 5-point Likert scale from 1 (not applicable at all) to 5 (very applicable); total scores ranged from 9 to 45, with higher scores indicating better eating habits. Examples of questionnaire statements are as follows: Eating meals that are considered nutritionally balanced, reducing caloric intake in the diet, etc.

Physical activity. The amount of habitual physical activity was evaluated using the International Physical Activity Questionnaire Short Form (IPAQ-SF). The IPAQ-SF is valid and reliable¹⁵ and assesses the amount of physical activity performed over the past week. It can be calculated as a continuous score by multiplying the number of minutes spent on activities (METs) and the number of days these activities were performed.¹⁵ Total physical activity was assessed according to the usage guidelines.^{16,17}

Statistical analysis

Basic attributes such as sex and illness uncertainty scores were analyzed as binary variables, while age, dietary habits, physical activity, and ALT and AST levels were analyzed as continuous variables. We log-transformed ALT and AST levels into normal distribution values and analyzed them. In this study, the median (57.0) MUIS-C score was used as a cutoff value to divide the patients into two groups: those with high illness uncertainty and those with low illness uncertainty. Data were analyzed using IBM SPSS ver. 26 (IBM, Armonk, NY, USA). In all analyses, significance was set at $p < .05$. The primary endpoint was the degree of change in liver function (ALT and AST levels) values from baseline to 1 year later. We performed t-tests and Pearson's correlation analyses for basic attributes, illness uncertainty, dietary habits, and physical activity, with each outcome as the dependent variable. We conducted a multiple regression analysis using the variable reduction method, with sex, illness uncertainty, eating habits, body mass index, and

experience with nutritional guidance as explanatory variables, which showed significant differences in the correlation analysis. Physical activity and age were added as independent variables because evidence has been established in the literature.¹⁸ We also added baseline liver function values as an independent variable to adjust for differences in liver function values for the degree of illness uncertainty at baseline.

RESULTS

Participant characteristics

Of 183 patients with NAFLD, 166 patients (90.7% response rate) returned the questionnaire. Of these, eight questionnaires had invalid responses. Ten patients either did not have blood samples to evaluate liver function or interrupted their hospital visits from the start of the study until one year later. Ultimately, we included 148 patients in the analysis. The subjects' characteristics are shown in Table 1. Of the participants, 75 were male and 73 were female, with a mean age of 58.4 ± 12.3 years.

The mean values (SD) for each measured variable are shown in Table 2. The illness uncertainty score was 56.5 ± 10.1 , and the median score was 57.0. The dietary habit score was 28.2 ± 5.2 . Physical activity was 2535.6 ± 4220.0 Mets-min/week.

Table 1 Participants' baseline clinical and sociodemographic characteristics (n = 148)

		n (%)
Sex	Male	75 (50.7)
	Female	73 (49.3)
Age	20–29	1 (0.7)
	30–39	10 (6.8)
	40–49	27 (18.2)
	50–59	35 (23.6)
	60–69	45 (30.4)
	70–	30 (20.3)
NASH	Yes	26 (17.6)
	No	122 (82.4)
Hepatitis virus carrier or asymptomatic	Yes	52 (35.1)
	No	96 (64.9)
Illness uncertainty	High	76 (51.4)
	Low	72 (48.6)

NASH: nonalcoholic steatohepatitis

Table 2 Value of each measured variable (n = 148)

	Mean (SD)
Illness uncertainty (score)	56.5 (10.1)
Dietary habits (score)	28.2 (5.2)
Physical activity (Mets-min/week)	2535.6 (4220.0)

Changes in liver function values according to the degree of illness uncertainty

The means (SD) of liver function values according to the degree of illness uncertainty are shown in Table 3. The group with higher illness uncertainty had risen ALT and AST levels from baseline to 1 year later. The group with the lowest illness uncertainty had improved ALT and AST levels from baseline to 1 year later.

Table 3 Mean (SD) of liver function values according to illness uncertainty

		Baseline (SD)	1 year (SD)
ALT	High illness uncertainty	42.4 (25.9)	45.8 (30.5)
	Low illness uncertainty	50.5 (39.5)	42.4 (30.9)
AST	High illness uncertainty	33.1 (15.7)	35.2 (18.9)
	Low illness uncertainty	34.5 (16.9)	30.7 (15.4)

ALT: alanine transaminase

AST: aspartate aminotransferase

Changes in ALT levels

The results of multiple regression analysis on the degree of change in ALT levels from baseline to 1 year is shown in Table 4.

Regarding the degree of change, the higher the illness uncertainty, the more significant was the rise in ALT levels at 1 year ($\beta = .185$, $p = .013$), particularly in men ($\beta = .147$, $p = .047$). ALT levels improved in participants who received nutritional guidance ($\beta = -.169$, $p = .028$).

Table 4 Relationship between each variable with the degree of change in ALT levels from baseline as the dependent variables (multiple regression analysis)

	Degree of change in ALT levels after 1 year	
	Standardized regression coefficient (β)	P value
Illness uncertainty (high)	.185	.013
Physical activity	.112	.137
Sex (male)	.147	.047
Received nutritional guidance	-.169	.028
Coefficient of determination R ²	.255	
Adjusted R ²	.229	
Analysis of variance	<.001	

ALT: alanine transaminase

Changes in AST levels

The results of multiple regression analysis on the degree of change in AST levels from baseline to 1 year is shown in Table 5.

Regarding the degree of change, the higher the illness uncertainty, the more significant was the rise in AST levels at 1 year ($\beta = .183$, $p = .018$). AST levels improved in participants who received nutritional guidance ($\beta = -.157$, $p = .047$).

Table 5 Relationship between each variable with the degree of change in AST levels from baseline as the dependent variables (multiple regression analysis)

	Degree of change in AST levels after 1 year	
	Standardized regression coefficient (β)	P value
Illness uncertainty (high)	.183	.018
BMI \geq 25 (kg/m ²)	-.113	.154
Received nutritional guidance	-.157	.047
Coefficient of determination R ²		.170
Adjusted R ²		.147
Analysis of variance		<.001

AST: aspartate aminotransferase

BMI: body mass index

DISCUSSION

This is the first study to show that illness uncertainty can be a predictor of liver function. Previous studies have provided ample evidence that self-care, such as dietary habits and physical activity, can improve liver function in patients with NAFLD.^{19,20} Katsagoni et al¹⁸ also reported that intervention with guidance on self-care can lead to significant changes in patients' self-care behavior and have a positive impact on their disease status. This indicates the importance of supporting patients' self-care for the treatment of NAFLD.

Several studies have focused on illness uncertainty to promote self-care behavior in patients. Bailey et al²¹ validated illness uncertainty by providing regular self-care guidance and consultation to patients. Mishel²² also stated that the longer the illness uncertainty persists, the more unstable the individual's functioning becomes, leading to significant emotional distress. In addition, high illness uncertainty has been associated with lower self-care compliance.²³ These findings indicate that illness uncertainty is an important factor in self-care support for chronic diseases. In this study, the higher the illness uncertainty, the significantly worse the ALT and AST levels after 1 year. As mentioned earlier, previous studies have shown that liver function worsens in NAFLD when self-care activities such as diet and exercise are not followed.^{19,20} Therefore, the results of this study might indicate that the subjects may not have been able to successfully engage in self-care due to their high level of illness uncertainty. For this reason, it is essential for healthcare providers to understand the illness uncertainty of the NAFLD disease and consider appropriate interventions in order to increase self-care compliance among patients with NAFLD.

This study also found that ALT and AST levels improved in patients receiving nutritional guidance. Previous studies have shown that nutritional guidance can affect liver function in patients with NAFLD.^{24,25} Previous studies have shown that illness uncertainty is reduced by professional interventions.^{26,27} In this study, illness uncertainty may be a mediating variable that connects the experience of receiving nutritional guidance with the liver function values. Therefore, to support self-care of patients with NAFLD, it is necessary for healthcare providers to confirm whether the patient has ever received nutritional guidance and to understand the degree of illness uncertainty in patients with NAFLD.

Limitations

This study had several limitations. First, the independent variables were measured using a

questionnaire survey only at baseline and not over time. Second, because the study was conducted at a single institution, there are limitations in terms of the generalizability and showing causality. In the future, longitudinal studies using more accurate data collection methods should be conducted.

CONCLUSIONS

High illness uncertainty in patients with NAFLD is associated with a rise in ALT and AST levels. It is recommended that healthcare providers focus and work on reducing illness uncertainty in patients with NAFLD.

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CONFLICTS OF INTEREST AND SOURCE OF FUNDING

None declared.

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