FIB-4 index and NAFLD fibrosis score are useful indicators for screening high-risk groups of non-viral hepatocellular carcinoma

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Abstract. Non-viral hepatocellular carcinoma (HCC) tends to appear in non-cirrhotic livers, rendering it difficult to screen for a high-risk group. The present study aimed to identify the most suitable indicator for screening high-risk groups of non-viral HCC. A total of 190 patients with non-viral HCC, including 126 with non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), were enrolled in the present study. A total of two cut-off values, for low and high levels of fibrosis, were set for each of the indicators, including the Child-Pugh score (CPS; 6 and 7), platelet counts (15.8 and $10x10^4/\mu l$), albumin-bilirubin (ALBI) score (-2.60 and -2.27), fibrosis 4 index (FIB-4 index; 1.30 and 2.67) and NAFLD fibrosis score (NFS; -1.455 and 0.675). The ratio of the number of patients who fell outside the cut-off value for all patients was defined as the overlooking rate. The overlooking rates of CPS, platelet counts, ALBI score, FIB-4 index and NFS for the low fibrosis cut-off value were 41.0, 48.9, 35.8, 4.2 and 5.8%, respectively. When performing analysis limited to the NAFLD cases, those of the FIB-4 index and NFS were 4.8 and 6.3%, respectively. Those for the high fibrosis cut-off value were 79.5, 73.2, 62.6, 30.0 and 37.4%, respectively. On the whole, the present study demonstrates that the cut-off values of ≥1.30 for the FIB-4 index or ≥-1.455 for the NFS may be used to screen high-risk groups of HCC among patients with non-viral hepatitis.

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Abbreviations: HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; CPS, Child-Pugh score; ALBI score, albumin-bilirubin score; NFS, NAFLD fibrosis score; HBV, hepatitis B virus; HCV, hepatitis C virus; DM, diabetes mellitus; FIB-4 index, fibrosis 4 index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index

Key words: hepatocellular carcinoma, non-viral hepatitis, FIB-4 index, NAFLD fibrosis score, risk factor

Introduction

Hepatocellular carcinoma (HCC) is frequently observed in patients with cirrhosis caused by persistent hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcohol consumption, obesity and diabetes mellitus (DM)-related metabolic disorders (1). With notable advancements being made in the treatment of HCV with direct-acting antiviral therapy (2) and the marked increase in the number of obese patients worldwide (3), the number of cases of HCV-related HCC has decreased, while that of non-viral HCC cases has increased (4,5). In fact, the population of non-viral HCC for all HCC cases is reported to be 59% in the USA and 28.8% in Japan (5,6). Non-alcoholic fatty liver disease (NAFLD), hepatic manifestations of obesity and metabolic disorders, and non-alcoholic steatohepatitis (NASH), a progressive liver disease with inflammation and fibrosis that can lead to cirrhosis, are of interest in relation to HCC. Patients with NASH are reported to be 5.29 per 1,000 person-years, with risks increasing as liver pathology, such as fibrosis, progresses (7).

Sufficient surveillance with regard to the risk factors for HCC (e.g., etiology, severity of hepatic fibrosis, and its history) is recommended so that it may be detected at an early stage when curative treatment is feasible (8-10). However, screening high-risk groups for HCC among patients with NAFLD/NASH is extremely difficult as their-related HCC tends to appear in non-cirrhotic livers. It has been reported that only 46% of all NAFLD/NASH-related HCC cases were complicated by cirrhosis (6). Furthermore, the numbers of obese patients or patients with NAFLD/NASH are currently markedly higher those of patients with viral hepatitis (11). As a result, a vast number of patients with non-viral hepatitis could be subjected to HCC surveillance, and there is an urgent need to develop a simple, efficient and non-invasive HCC surveillance system for patients with non-viral hepatitis.

The severity of hepatic fibrosis is one of the most critical risk factors for HCC (8-10). The Child-Pugh score (CPS) and platelet counts are established indicators of the severity of cirrhosis, liver functional reserve and hepatic fibrosis. Recently, the albumin-bilirubin (ALBI) score, which can be easily calculated only from serum levels of albumin and total bilirubin, has been reported to have an improved capability compared with the CPS to assess hepatic function reserve in patients with HCC (12). The fibrosis 4 (FIB-4) index, which is based on age,

aspartate aminotransferase (AST) levels, alanine aminotransferase (ALT) levels and the platelet count, is a non-invasive scoring system used to evaluate hepatic fibrosis (13). The NAFLD fibrosis score (NFS), which is calculated by adding the body mass index (BMI) and the presence of DM to the four parameters used in the FIB-4 index, is also a fibrosis scoring system exclusively for patients with NAFLD (14). The American, European and Japanese clinical practice guidelines for NAFLD/NASH recommend that the FIB-4 index or NFS should be used as the first step in evaluating hepatic fibrosis as these two indicators have a high negative predictive value for ruling out advanced fibrosis (15-18). However, it remains unclear as to which cut-off values for each of these indicators would be the most suitable for screening high-risk groups of HCC among non-viral hepatitis in a clinical setting.

In the present study, patients with non-viral HCC treated in Gifu University Hospital (Gifu, Japan) were divided according to the representative cut-off values of each indicator described above. The present study aimed to identify the most suitable indicator for screening high-risk groups of HCC by comparing the possibility that HCC was overlooked in patients outside the cut-off values.

Materials and methods

Enrolled patients. Between May, 2006 and December, 2021, 536 patients with HCC were treated in Gifu University hospital; of these, 346 were found to have virus-related HCC (74 HBV-related, 269 HCV-related and 3 HBV/HCV overlaps). A total of 190 patients (35.4%) with neither a hepatitis B surface antigen nor HCV antibody diagnosed with HCC were enrolled in the present study. The mean age of the enrolled patients was 72.9 years (range, 40-90 years). In this cohort, 105, 100 and 36 patients had diabetes, hypertension and hyperlipidemia, respectively. In total, 160 patients visited the hospitals regularly to undergo treatment for the aforementioned metabolic syndromes or other diseases prior to the diagnosis of HCC. Moreover, 57, 44, 74, 8 and 7 patients underwent liver resection, radiofrequency ablation, transcatheter arterial chemoembolization, radiotherapy and systemic chemotherapy, respectively. These initial treatments for HCC were determined according to the applicable Japanese guidelines (8). All patients were administered standard clinical treatment. Of the 190 patients, 126 patients (53 pathologically and 73 clinically) were diagnosed with NAFLD/NASH, provided that they had metabolic syndromes, such as obesity or DM; patients with other types of non-viral hepatitis, such as alcoholic hepatitis, autoimmune hepatitis, or primary cholangitis were excluded from the study.

HCC was diagnosed based on typical hypervascular tumor staining on angiography and typical dynamic computed tomography or magnetic resonance imaging findings of enhanced staining in the early phase and attenuation in the delayed phase (8). The authors were unable to obtain written, informed consent in advance due to the retrospective design of the study. Instead, by disclosing the details of the study, the study participants were provided with an opportunity to opt-out. The study design was reviewed and approved by the Ethics Committee of the Gifu University School of Medicine on September 5, 2022 (ethical protocol code: 2022-0193).

Study design and scoring. The ALBI score, FIB-4 index and NFS were calculated using the following formulas, as previously described (12-14): i) ALBI score={log10 [17.1 x total bilirubin (mg/dl)] x0.66} + [10x albumin (g/dl) x -0.085]; ii) FIB-4 index=age (years) x AST (U/l)/{platelet count ($10^4/\mu$l) x [√ALT (U/l)]}; iii) NFS=-1.675 + 0.037 x age (years) + 0.094 x BMI (kg/m^2) + 1.13x DM (yes=1, no=0) + 0.99 x AST (U/l)/ALT (U/;) -0.013x platelet counts ($10^4/\mu$l) -0.66x albumin (g/dl).

Two cut-off values for low and high levels of fibrosis, for CPS, platelet count, ALBI score, FIB-4 index and NFS were set based on data at the time of the diagnosis of HCC. The cut-off values for CPS were 6 (grade A) for low levels of fibrosis and 7 (grade B) for levels of high fibrosis. The cut-off values for platelet counts were 15.8x$10^4/\mu$l for low levels of fibrosis and 10.0x$10^4/\mu$l for high levels of fibrosis. These values were determined as a platelet count of <10.0x$10^4/\mu$l is pathologically associated with stage 4 hepatic fibrosis in the case of hepatitis C (19,20) and that of 15.8x$10^4/\mu$l is the lower limit of normal in Gifu University Hospital. The ALBI score was set to low fibrosis at -2.60 and the cut-off value between ALBI grades I and IIa. The score for high fibrosis was set at -2.27 and the cut-off value for ALBI grades IIa and IIb, respectively (12). The cut-off values of low fibrosis and high fibrosis in the FIB-4 index (1.31 and 2.67) and those in the NFS (-1.455 and 0.675) were determined, respectively, according to the NAFLD/NASH guidelines (15).

Analysis of the cut-off values. The ratio of the number of patients who fell outside the above cut-off values to the total number of patients was defined as the overlooking rate. The most appropriate indicator for HCC surveillance was examined in patients with non-viral hepatitis by comparing the overlooking rates of low and high fibrosis cut-off values for each indicator. These comparisons were performed without the use of any formal statistical analyses. Instead, cut-off values were considered preferable when they corresponded to lower overlooking rates.

Results

Baseline characteristics of the patients. The baseline characteristics of all the enrolled patients (n=190) and patients with NAFLD/NASH (n=126) are presented in Table I. Of all the patients, 112, 39, 18, 11, 6, 3 and 1 patients had a CPS of 5, 6, 7, 8, 9, 10 and 12, respectively. The mean platelet count, ALBI score, FIB-4 index and NFS were 15.6±7.5 (range, 9.3-42.2) x$10^4/\mu$l, -2.37±0.55 (range, -3.63 to -0.59), 5.33±4.27 (range, 0.50-27.9) and 1.063±1.668 (range, -4.897-5.429), respectively. Among the 126 patients with NAFLD/NASH, 76, 26, 12, 6, 5 and 1 patients had a CPS of 5, 6, 7, 8, 9 and 10, respectively. The mean platelet count, ALBI score, FIB-4 index and NFS in these patients were 16.7±7.4 (range, 3.8-42.2) x$10^4/\mu$l, -2.38±0.52 (range, -3.38 to -0.760), 4.74±3.39 (range, 0.50-16.8) and 0.944±.656 (range, -4.897-4.146), respectively.

The dot charts with low and high-fibrosis cut-off values for CPS, platelet counts, ALBI score, FIB-4 index and NFS in all the enrolled patients are presented in Fig. 1. The overlooking rates for CPS, platelet counts, ALBI score, FIB-4 index and NFS on the low fibrosis cut-off value were 41.0, 48.9, 35.8,

Table I. Baseline demographic and clinical characteristics of the enrolled patients.

Variable	All patients (n=190)	Patients with NAFLD/NASH (n=126)
Sex (male/female)	135/55	82/44
Age (years)	72.9±9.1	74.3±9.0
Etiology (NAFLD/alcohol/others)	126/50/14	-
BMI (kg/m^2)	24.7±3.7	24.8±3.4
AST (U/l)	53.3±45.7	52.1±38.3
ALT (U/l)	38.0±40.1	40.7±47.3
ALB (g/dl)	3.7±0.6	3.7±0.5
T-Bil (mg/dl)	1.2±1.2	1.2±1.3
PLT (x10^4/μl)	15.6±7.5	16.7±7.4
PT (%)	87.7±19.9	88.8±20.7
Child-Pugh score (5/6/7/8/9/10/11/12)	112/39/18/11/6/3/0/1	76/26/12/6/5/1/0/0
ALBI score	-2.37±0.55	-2.38±0.52
FIB-4 index	5.33±4.27	4.74±3.39
NAFLD fibrosis score	1.063±1.668	0.944±1.656
Diabetes mellitus (yes/no)	105/85	75/51
AFP (ng/dl)	10790±68264	6202±22585
PIVKA-II (mAU/ml)	27207±196026	56733±298328
Stage (I/II/III/IV)	24/66/66/34	12/45/43/26

Values are presented as a mean ± standard deviation. NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; T-Bil, total bilirubin; PLT, platelet count; PT, prothrombin time; ALBI score, albumin-bilirubin score; FIB-4 index, fibrosis 4 index; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonists-II.

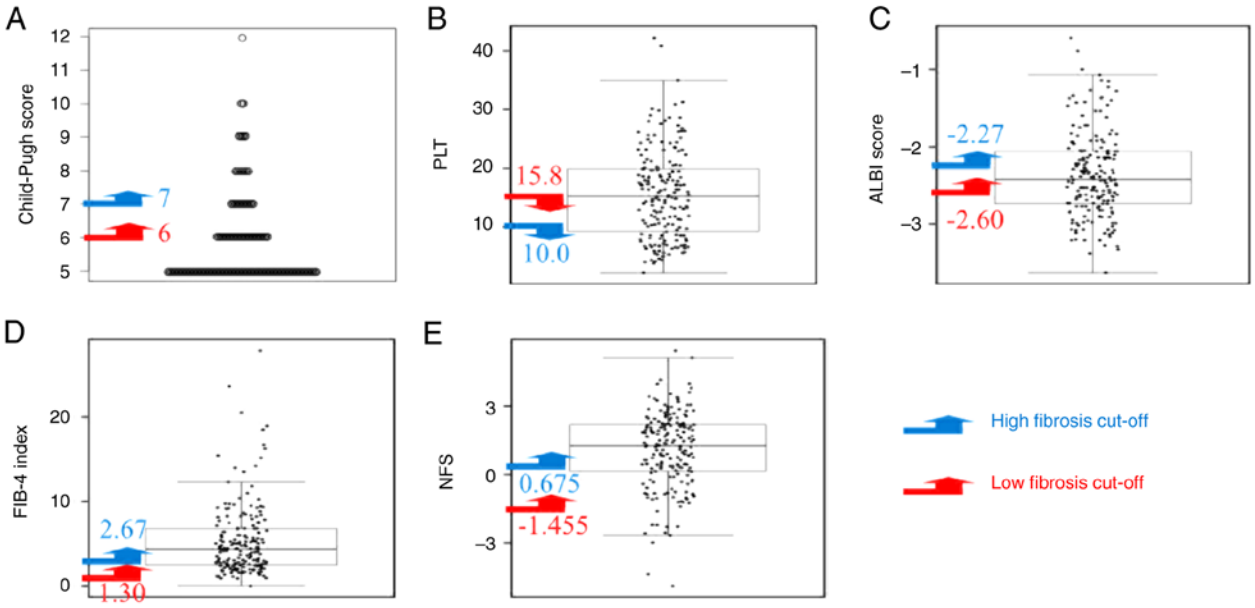

Figure 1. Distribution of patients with non-hepatitis B virus and -hepatitis C virus HCC at cut-off values for each index. The dots indicate the distribution of the patients by low and high fibrosis cut-off values in the (A) Child-Pugh score, (B) platelet count, (C) ALBI score, (D) FIB-4 index, and (E) NFS. PLT, platelet; ALBI score, albumin-bilirubin score; FIB-4 index, Fibrosis 4 index; NFS, non-alcoholic fatty liver disease fibrosis score.

4.2 and 5.8%, respectively, while those on the high fibrosis cut-off value were 79.5, 73.2, 62.6, 30.0 and 37.4%, respectively. Even when the analysis was limited to the 126 cases of NAFLD/NASH, those for the FIB-4 index and NFS on the low fibrosis cut-off value were 4.8 and 6.3%, which were markedly lower than those corresponding to the other cut-off values (31.7 and 81.0%) (Table II). These findings suggest that the overlooking rates of the FIB-4 index (4.2% for all patients and 4.8% for patients with NAFLD/NASH) and NFS (5.8% for all patients and 6.3% for patients with NAFLD/NASH) at

Table II. Overlooking rates of the indicators that represent liver functional reserve and fibrosis among all patients and those with NAFLD.

	All patients (n=190)		Patients with NAFLD/NASH (n=26)	
Variable	Overlooking rate (low fibrosis) (%)	Overlooking rate (high fibrosis) (%)	Overlooking rate (low fibrosis) (%)	Overlooking rate (high fibrosis) (%)
Child-Pugh score	41.0	79.5	60.3	81.0
PLT	48.9	73.2	56.3	80.2
ALBI score	35.8	62.6	34.9	70.6
FIB-4 index	4.2	30.0	4.8	31.7
NAFLD fibrosis score	5.8	37.4	6.3	38.9

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PLT, platelet count; ALBI score, albumin-bilirubin score; FIB-4 index, fibrosis 4 index.

the low fibrosis cut-off value were lower than those of CPS, platelet counts and ALBI score.

Discussion

The results of the present study demonstrated that the overlooking rates of the FIB-4 index and NFS using the low fibrosis cut-off values set here were low enough to screen patients with non-viral HCC, including NAFLD/NASH-related HCC. These cut-off values (≥1.30 for the FIB-4 index or ≥-1.455 for NFS) may be used to screen high-risk groups for HCC in patients with non-viral hepatitis, including NAFLD/NASH. These findings reinforce the findings of previous studies that have demonstrated that both the FIB-4 index and NFS are promising non-invasive scoring systems for assessing the risk of liver fibrosis and ultimately NASH/NAFLD-related HCC (13-15). It should also be noted that these cut-off values of the FIB-4 index and NFS are recommended for selecting cases of advanced fibrosis in the Japanese NAFLD/NASH guidelines (15). A previous meta-analysis revealed that the FIB-4 index and NFS were diagnostically sensitive to advanced fibrosis in patients with NAFLD (21). The negative predictive value for a diagnosis of advanced fibrosis with an FIB-4 index ≥1.30 is 99% (13). These reports indicate again that these systems may be useful in identifying groups at a high risk of developing HCC in non-fibrotic, advanced cases, without cirrhosis. Surveillance for HCC is difficult for patients with non-viral hepatitis as they are rarely followed-up by gastroenterologists, although are often followed-up by general physicians or annual physical examinations. The FIB-4 index and NFS can be easily calculated from AST, ALT, albumin, platelet count, BMI, age and the presence of DM, all of which can be evaluated in general clinical practice. Therefore, general physicians should evaluate the risk of hepatic fibrosis and hepatocarcinogenesis in non-viral hepatitis patients using the FIB-4 index or NFS and consult a gastroenterologist if they find patients with FIB-4 index ≥1.30 or NFS ≥-1.455.

By contrast, in the present study, platelet counts, CPS and ALBI scores were not appropriate indicators for screening high-risk groups of HCC in patients with non-viral hepatitis. For example, 48.9% of the patients with non-viral hepatitis and 56.3% of those with NAFLD/NASH develop HCC before the platelet counts decreases to $<10.0 \times 10^4/\mu l$ (Table II), which is a marker of progression to cirrhosis and the appropriate cut-off value to screen high-risk groups of HCC in HCV-positive patients (19,20). These findings are consistent with those of a previous study which demonstrated that approximately half of patients with non-viral hepatitis had initial HCC emerging in non-cirrhotic livers (6). On the other hand, patients with an FIB-4 index <1.30 or NFS <-1.455 accounted for approximately only 5% of all the patients HCC in the present study. These results, therefore, suggest that high-risk groups could be screened for non-viral HCC by not using platelet counts, CPS, or ALBI, but the FIB-4 index or NFS. These results may help to improve the management of non-viral hepatitis, as platelet counts or CPS, the established risk factors for HCV-related HCC (19,20), are still utilized by most general physicians. Furthermore, as described above in the Materials and methods section, patients with non-viral hepatitis are frequently followed-up by general physicians for presence of metabolic syndrome or other diseases. Among the 190 patients enrolled in the present study, 160 were followed-up in hospitals other than that of the authors.

Obesity-related factors, such as adipose tissue remodeling and pro-inflammatory adipokine secretion, have been reported to function synergistically with liver fibrosis and contribute to liver carcinogenesis (11). In fact, obesity-related disorders, including insulin resistance, excessive accumulation of leptin and increased levels of oxidative stress and visceral adipose tissue, can promote the recurrence of HCC following curative treatment (22-26). Obesity is a global epidemic, including in Japan, and the number of obese individuals is increasing as rapidly as the number of patients with NAFLD/NASH (5). Obese patients with metabolic diseases, such as DM and NAFLD/NASH, tend to be followed-up by general physicians, but non-viral HCC often develops in the non-cirrhotic liver of these patients. General physicians can easily calculate the FIB-4 index and NFS. Therefore, in patients with non-viral hepatitis, particularly those with obesity or NAFLD/NASH, an appropriate HCC surveillance strategy would be for the general physician to first evaluate hepatic fibrosis using the FIB-4 index and NFS, and in the second step for the gastroen-

terologist to screen for HCC with a detailed examination using abdominal ultrasound and tumor markers.

The present study has some limitations. First, this was a retrospective study that only included patients with HCC. Furthermore, the FIB-4 index and the NFS were considered on data based only at the time of the HCC diagnosis in the present study. Sensitivity and the overlooking rate (false-negative rate) were demonstrated, but specificity and a false-positive rate could not be determined, particularly since the present study did not include non-HCC patients with non-viral hepatitis. The receiver operating characteristic curve and Youden index are generally used to determine an optimal cut-off value (27,28). However, these analyses could not be performed in the present study as the specificity was not determined. To validate the efficacy of the cut-off values obtained herein, a time-to-event plot and analysis including non-viral hepatitis patients without HCC needs to be performed. Second, the overlooking rate was simply determined and may not have been sufficient to ensure a high diagnostic accuracy. However, as a false-negative rate is more important than a false-positive rate in disease screening, the low overlooking rate obtained by setting a cutoff value of FIB-4 index ≥1.30 or NFS ≥1.455 was considered to be useful in screening patients at a high risk of developing non-viral HCC, particularly when performed by non-gastroenterologists. Third, it was necessary to verify whether each cut-off value set at this time was appropriate. An FIB-4 of ≥1.30 and NFS of ≥1.455 were considered suitable cut-off values as their corresponding overlooking rates were lower (~5%) than those corresponding to the other cutoff values (from 30.0 to 79.5%). Statistically significant differences were not evaluated in the present. To determine the appropriate cut-off values, it is necessary to consider not only the rate of missed cases, but also the adequacy of the specificity and the economic burden of healthcare.

In conclusion, in the present study, the cut-off values of the FIB-4 index ≥1.30 or NFS ≥1.455 were associated with a low false-negative rate (overlooking rate) of ~5% and may thus be used to screen high-risk groups for HCC in patients with non-viral hepatitis including NAFLD/NASH. A simple setting of cut-off values may be particularly useful in clinical settings which often involve non-gastroenterologists. However, the present study did not include patients with non-viral hepatitis without HCC; thus, a long-term prospective study including a sufficient cohort of such patients is required to examine the usefulness of this cut-off value in the real world.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors (KI, KT, SU, TM, TH, AS and MS) designed the study. KI analyzed the data and drafted the manuscript. KT supervised the treatment of the participants. KT, SU, TM, TH and AS contributed to the selection of the participants and collected the data. KT, SU, TM, TH and AS revised the manuscript, and MS mainly reviewed and amended the manuscript. KT and MS confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study design was reviewed and approved by the Ethics Committee of the Gifu University School of Medicine on September 5, 2022 (ethical protocol code: 2022-0193). The authors were unable to obtain written informed consent in advance due to the retrospective design of our study. Instead, by disclosing the details of the study, the study participants were provided with an opportunity to opt-out

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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