Original Paper

Changes in Background Liver Function in Patients with Hepatocellular Carcinoma over 30 Years: Comparison of Child-Pugh Classification and Albumin Bilirubin Grade

Takashi Kumada^a Hidenori Toyoda^b Toshifumi Tada^b Satoshi Yasuda^b
Junko Tanaka^c

^aDepartment of Nursing, Faculty of Nursing, Gifu Kyoritsu University, Ogaki, Japan;

^bDepartment of Gastroenterology and Hepatology, Ogaki Municipal Hospital, Ogaki, Japan;

^cDepartment of Epidemiology, Infectious Disease Control, and Prevention, Hiroshima University Institute of Biomedical and Health Sciences, Hiroshima, Japan

Keywords

Albumin-bilirubin (ALBI) grade · Child-Pugh classification · Hepatocellular carcinoma · Modified ALBI (mALBI) grade · FIB-4 index

Abstract

Background: Background liver function in patients with hepatocellular carcinoma (HCC) has improved remarkably with advances in various treatments. Recently, the Child-Pugh classification (CPC) system has been recognized as limited in its ability to assess patients with good hepatic reserve. We compared the albumin-bilirubin (ALBI) grade, which is suitable for a more detailed evaluation of patients with good liver function, with CPC over a 30-year period. **Methods:** A total of 2,347 patients were analyzed. Patients were stratified by year of diagnosis into 6 groups: Group A (1990–1994, $n = 376$), Group B (1995–1999, $n = 434$), Group C (2000–2004, $n = 438$), Group D (2005–2009, $n = 444$), Group E (2010–2014, $n = 392$), and Group F (2015–2018, $n = 263$). We compared ALBI grade and CPC across the groups. **Results:** The prevalence of patients with CPC A at diagnosis increased throughout the study period, reaching nearly 80% in Groups E and F ($p < 0.001$). By contrast, the percentage of patients with ALBI grade 1 disease remained approximately 50% in Groups E and F ($p < 0.001$). Modified ALBI (mALBI) grade 2a corresponds to patients with CPC A who have poor hepatic function. There were

Takashi Kumada, MD
Department of Nursing, Faculty of Nursing
Gifu Kyoritsu University, 5-50, Kitagata-cho
Ogaki-shi, Gifu-ken 503-8550 (Japan)
takashi.kumada@gmail.com

significant survival differences between patients with mALBI grade 1 versus 2a, 1 versus 2b, and 2a versus 2b disease, respectively ($p < 0.0001$), in patients with CPC A. **Conclusions:** CPC is not suitable for assessing patients with recently diagnosed HCC and good remnant hepatic function. In such patients with HCC, the prognosis can be stratified by ALBI grade rather than CPC.

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Introduction

In 1964, Child and Turcotte, two surgeons who performed portacaval shunt surgery, created a new liver function index known as the Child-Pugh classification (CPC) for patients with cirrhosis [1]. The CPC system has been the most extensively used method for assessing the remnant liver in patients with hepatocellular carcinoma (HCC). This classification system is simple and easy to use; it was suitable for evaluating the background liver in HCC until the end of the 20th century. CPC A, B, and C status corresponded to minimally, moderately, and severely altered hepatic functional reserve, respectively. This classification system was based on 5 variables: 3 clinical (ascites, encephalopathy, and nutritional status) and 2 biochemical (serum albumin and bilirubin) [1]. The Child-Turcotte classification system was modified by Pugh et al. in 1973 by substituting prothrombin time for nutritional status, arbitrarily adjusting limits for serum albumin, and better defining the encephalopathy grading system [2]. However, the CPC system was not specifically designed for HCC. It was developed empirically and conventionally used in patients with cirrhosis. It includes some subjective components, such as ascites and encephalopathy, and interrelated factors, such as serum albumin and ascites.

There are more than 30 versions in the literature worldwide. Some variable scores are different in different versions and difficult to apply consistently between regions and investigators. Most importantly, the majority of patients with recently diagnosed HCC have CPC A background liver function. We do not take into account liver dysfunction when assigning stage or prognosis in most cases of HCC. Therefore, easier and more accurate methods to assess hepatic function are needed. Recently, the albumin-bilirubin (ALBI) grade was developed as a new method for assessing hepatic function [3]. This classification has already been reported to be more useful for predicting prognosis in patients with HCC than CPC in many previous studies [3–10].

In this study, our aim was to compare ALBI grade and CPC for assessing changes in the background liver of patients with HCC over 30 years and demonstrate whether ALBI grade is superior to CPC for evaluating hepatic function.

Methods

Patients

The entire study protocol was approved by our hospital's Ethics Committee and carried out in compliance with the Declaration of Helsinki (approval No.: 20190228-9), and written informed consent was obtained from each patient included in the study. At Ogaki Municipal Hospital, 2,350 patients have been diagnosed with new HCCs between January 1990 and December 2019. Of these 2,350 patients, 2,347 met the eligibility criteria: both hepatitis B surface antigen (HBsAg) levels and anti-hepatitis C virus (HCV) antibody titers were measured; data on CPC, including data on total bilirubin, albumin, prothrombin time, and presence or absence of hepatic encephalopathy or ascites were available; and tumor node metastasis (TNM) stage based on the Liver Cancer Study Group of Japan (LCSGJ) criteria [11, 12] was available. The diagnosis of HCC was based on radiologic findings from computed tomography (CT) or selective hepatic angiography including hypervascularity in the late arterial phase and washout on portal venous and/or delayed phases on dynamic CT, or hypervascularity on angiography. When findings indicative of HCC were not obtained with dynamic CT

or angiography, CT during hepatic arteriography and CT during arterial portography or histological examination of US-guided needle biopsy specimens were performed. Gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid-enhanced magnetic resonance imaging (MRI) was performed after February 2008 [13].

The patients were stratified by year of diagnosis into 6 groups: Group A (1990–1994, $n = 376$), Group B (1995–1999, $n = 434$), Group C (2000–2004, $n = 438$), Group D (2005–2009, $n = 444$), Group E (2010–2014, $n = 392$), and Group F (2015–2019, $n = 263$). Underlying liver disease was classified into 4 groups: hepatitis B virus (HBV), HBV + HCV, HCV, and non-HBV/non-HCV. Platelet count, prothrombin time, and levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, α -fetoprotein (AFP), and indocyanine green retention test after 15 min (ICGR-15) were also measured at the time of HCC diagnosis. CPC, Child Pugh-score (CPS), and ALBI grade were determined as an indicator of liver function [3]. ALBI grade was based on the formula

$$(\log_{10} \text{bilirubin } [\mu\text{mol/L}] \times 0.66) + (\text{albumin } [\text{g/L}] \times -0.0852),$$

with grade 1 corresponding to values ≤ -2.60 , grade 2 corresponding to values > -2.60 and ≤ -1.39 , and grade 3 corresponding to values > -1.39 . Moreover, ALBI grade was divided into 4 levels (1, 2a, 2b, and 3; modified ALBI [mALBI]) according to Hiraoka et al. [5]. The FIB-4 index was calculated as

$$(\text{age } [\text{years}] \times \text{AST } [\text{U/L}]) / ((\text{platelet count } [10^9/\text{L}]) \times (\text{ALT } [\text{U/L}])^{1/2})$$

and classified into mild fibrosis (<1.45), moderate fibrosis (1.45–3.25), and advanced fibrosis (>3.25) [14]. Tumor staging was performed according to the LCSG's TNM staging system [11].

Selection of therapy for each patient was based on consultation among surgeons and physicians before 2004. Starting in 2005, treatment policy was primarily based on treatment guideline for HCC in Japan [15]. Patients were initially assessed for eligibility for hepatic resection. When patients declined or were deemed not to be candidates for surgical treatment, they underwent non-surgical treatment. Patients were first considered for locoregional ablative therapies such as percutaneous ethanol injection therapy, percutaneous microwave coagulation therapy, and radiofrequency ablation therapy. Patients who were ineligible for both surgery and locoregional ablative therapy were offered transcatheter arterial chemoembolization. Nucleos(t)ide analogue (NA) therapy for HBV began in December 2000. Patients taking NAs during periods A and B were used from December 2000 after drug approval. Indications for NA therapy followed the guidelines of the American Association for the Study of Liver Diseases (AASLD) [16] or the European Association for the Study of the Liver (EASL) [17]. Interferon (IFN) therapy with or without ribavirin was performed between January 1990 and August 2014. Oral direct-acting antivirals (DAAs) were used in all patients except decompensated cirrhosis since September 2014. IFN was used in patients who were relatively young and had a good performance status, but it was not used in patients with decompensated cirrhosis. DAAs were administered to all patients judged to be able to take medications regularly. Sustained virologic response (SVR) was defined as undetectable serum HCV RNA at 24 weeks after the end of IFN or DAA therapy. Non-SVR was defined as the presence of HCV RNA after antiviral therapy.

Statistical Analysis

Continuous variables were expressed as medians (interquartile range). The Mann-Whitney U test or Jonckheere-Terpstra test was used for continuous variables. The χ^2 test or Fisher's exact test was used for categorical variables. Actuarial analysis of cumulative survival was carried out using the Kaplan-Meier method, and differences were tested using the log-rank test with Bonferroni correction. All p values were derived from two-tailed tests, with $p < 0.05$ accepted as statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria) [18]. More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics.

Results

Comparison of Patient Characteristics among the Groups

Table 1 shows the characteristics of all patients according to the time period. Median age at diagnosis clearly rose in recent years ($p < 0.001$); Groups A and F had a difference of 11 years.

Table 1. Patient characteristics

	Group A 1990–1994 (n = 376)	Group B 1995–1999 (n = 434)	Group C 2000–2004 (n = 438)	Group D 2005–2009 (n = 444)	Group E 2010–2014 (n = 392)	Group F 2015–2019 (n = 263)	p value
Age, years	63 [57–69]	65 [60–70]	68 [62–74]	70 [63–76]	72 [65–78]	74 [67–80]	<0.001
Gender							
Female	111 (29.5%)	104 (24.0%)	116 (26.5%)	132 (29.7%)	127 (32.4%)	67 (25.5%)	0.084
Male	265 (70.5%)	330 (76.0%)	322 (73.5%)	312 (70.3%)	265 (67.6%)	196 (74.5%)	
Etiology							
HBV	61 (16.2%)	64 (14.7%)	67 (15.3%)	71 (16.0%)	53 (13.5%)	30 (11.4%)	<0.001
HBV + HCV	3 (0.8%)	8 (1.8%)	9 (2.1%)	3 (0.7%)	0 (0.0%)	1 (0.4%)	
HCV	280 (74.5%)	312 (71.9%)	322 (73.5%)	293 (66.0%)	224 (57.1%)	110 (41.8%)	
NBNC	32 (8.5%)	50 (11.5%)	40 (9.1%)	77 (17.3%)	115 (19.3%)	122 (46.4%)	
NA therapy							
Yes	3 (4.7%)	4 (5.6%)	35 (46.1%)	55 (74.3%)	51 (92.7%)	26 (83.9%)	<0.001
No	61 (95.3%)	68 (94.4%)	41 (53.9%)	19 (25.7%)	4 (7.3%)	5 (16.1%)	
IFN or DAA therapy							
SVR	1 (0.4%)	7 (2.2%)	23 (6.9%)	30 (10.1%)	79 (35.3%)	68 (61.3%)	<0.001
Non-SVR	4 (1.4%)	19 (5.9%)	29 (8.8%)	27 (9.1%)	27 (12.1%)	5 (4.5%)	
No therapy	278 (98.2%)	294 (91.9%)	279 (84.3%)	239 (80.7%)	118 (52.7%)	38 (34.2%)	
ALT, IU/L	51 [31–82]	58 [32–96]	54 [32–100]	49 [29–82]	47 [26–84]	31 [17–69]	<0.001
AST, IU/L	67 [41–105]	75 [45–123]	72 [42–119]	59 [37–110]	59 [35–117]	43 [26–89]	<0.001
Total bilirubin, mg/dL	1.0 [0.7–1.6]	0.8 [0.6–1.2]	0.8 [0.6–1.2]	0.9 [0.6–1.3]	0.9 [0.6–1.2]	0.8 [0.6–1.1]	<0.001
Platelet count, $\times 10^4/\mu\text{L}$	9.8 [6.9–14.0]	10.1 [7.0–15.4]	10.7 [7.1–15.4]	11.4 [8.1–16.3]	13.1 [9.5–18.4]	15.0 [11.2–19.1]	<0.001
Albumin, g/dL	3.2 [2.8–3.6]	3.3 [2.9–3.8]	3.5 [3.1–3.9]	3.7 [3.2–4.1]	3.8 [3.4–4.2]	4.0 [3.6–4.3]	<0.001
PT, %	80 [66–93]	81 [70–94]	85 [73–94]	87 [76–97]	85 [73–97]	89 [78–100]	<0.001
AFP, ng/mL	49.0 [15.0–439.3]	36.1 [9.9–349.2]	31.1 [8.1–304.0]	18.1 [6.1–211.3]	13.5 [5.5–97.4]	8.8 [3.6–45.5]	<0.001
ICGR-15, %	19.4 [12.5–32.6]	20.0 [12.2–31.1]	18.3 [11.1–27.9]	18.6 [11.8–32.6]	18.3 [10.2–29.6]	14.1 [9.5–21.9]	<0.001
ALBI score	–1.86 [–2.33 to –1.49]	–2.11 [–2.53 to –1.61]	–2.28 [–2.66 to –1.81]	–2.40 [–2.74 to –1.91]	–2.54 [–2.88 to –2.04]	–2.66 [–2.96 to –2.26]	<0.001
FIB-4 index	6.69 [4.04–10.65]	6.84 [4.37–10.64]	6.22 [3.62–10.38]	5.54 [3.16–10.30]	5.20 [2.96–9.26]	4.15 [2.64–7.33]	<0.001
CPS	6 [6–8]	6 [5–8]	6 [5–7]	5 [5–7]	5 [5–6]	5 [5–6]	<0.001
Stage							
1	79 (21.0%)	80 (18.4%)	114 (26.0%)	96 (21.6%)	111 (28.3%)	72 (27.4%)	<0.001
2	111 (29.5%)	154 (35.5%)	145 (33.1%)	183 (41.2%)	156 (39.8%)	117 (44.5%)	
3	85 (22.6%)	98 (21.4%)	111 (25.3%)	92 (20.7%)	71 (18.1%)	47 (17.9%)	
4a	85 (22.6%)	79 (22.6%)	50 (11.4%)	62 (14.0%)	43 (11.0%)	20 (7.6%)	
4b	16 (4.3%)	20 (4.6%)	18 (4.1%)	11 (2.5%)	7 (2.7%)	7 (2.7%)	
Treatment							
HR	58 (15.4%)	80 (18.4%)	156 (35.6%)	157 (35.4%)	169 (43.1%)	135 (51.3%)	<0.001
LAT	99 (26.3%)	111 (25.6%)	121 (27.6%)	108 (24.3%)	90 (23.0%)	41 (15.6%)	
TACE	133 (35.4%)	130 (30.0%)	72 (16.4%)	80 (18.0%)	71 (18.1%)	42 (16.0%)	
Other	32 (8.5%)	33 (7.6%)	22 (5.0%)	20 (4.5%)	20 (5.1%)	19 (7.2%)	
None	54 (14.4%)	80 (18.4%)	79 (17.8%)	79 (17.8%)	42 (10.7%)	26 (9.9%)	

Continuous values are expressed as medians [interquartile range]; categorical values are expressed as n (%). HBV, hepatitis B virus; HCV, hepatitis C virus; HBV + HCV, HBV and HCV; NBNC, negative for both HBV and HCV; ALT, alanine aminotransferase; NA therapy, nucleos(t)ide analogue therapy for HBV; IFN or DAA therapy, interferon or direct acting antiviral therapy for HCV; SVR, sustained virologic response; AST, aspartate aminotransferase; PT, prothrombin time; AFP, α -fetoprotein; ICGR-15, indocyanine green retention rate at 15 minutes; ALBI score, albumin-bilirubin score; Stage, Liver Cancer Study Group of Japan tumor node metastasis stage; HR, hepatic resection; LAT, locoregional ablative therapies including percutaneous ethanol injection, percutaneous microwave coagulation therapy, or radiofrequency ablation; TACE, transarterial chemoembolization; CPS, Child-Pugh score.

Fig. 1. Changes in Child-Pugh classification (CPC) and Child-Pugh score (CPS) over time ($n = 2,347$). The prevalence of patients with CPC A and CPS 5 at diagnosis increased throughout the study period ($p < 0.0001$), reaching approximately 80 and 70% in 2010–2019, respectively.

Regarding the etiology of liver disease, the proportion of patients with non-HBV and non-HCV HCC increased significantly, while the proportion of patients with HCV infection decreased significantly ($p < 0.001$, online suppl. Fig. 1; see www.karger.com/doi/10.1159/000507933 for all online suppl. material). Levels of ALT, AST, AFP, total bilirubin, ICGR-15, ALBI score, FIB-4 index (online suppl. Fig. 2), and CPS decreased significantly throughout the study period ($p < 0.001$). By contrast, platelet count and albumin levels increased significantly ($p < 0.001$). There was a good correlation between ICGR-15 and ALBI score (online suppl. Fig. 3; Spearman's rank correlation coefficient 0.613, $p < 0.0001$). The percentage of patients with stage I disease increased until 1999 and reached a plateau after 2000 ($p < 0.001$). The percentage of patients who underwent hepatic resection as the initial treatment increased from Group A to Group F ($p < 0.001$). By contrast, the proportion of patients who underwent transcatheter arterial chemo-embolization decreased from over 30% in Groups A and B to under 20% in Groups C–F ($p < 0.001$). Among the patients with HBV infection, NAs were administered to approximately half of the patients in Group C and over 80% of the patients in Groups E and F ($p < 0.001$). During 1995–2009, less than 20% of the patients with HCV infection received IFN-based therapy; after 2010, over 50% of the patients received IFN-free therapy ($p < 0.001$). In Group F, over 90% of the patients with HCV infection who received IFN-free therapy achieved SVR.

Comparison of CPC and ALBI Grade among the Groups

Figure 1 shows the changes in CPC and CPS over time. The prevalence of patients with CPC A and CPS 5 at diagnosis increased throughout the study period, reaching approximately 80 and 70% in 2010–2019, respectively. Figure 2 shows the increase in the proportion of

Fig. 2. Changes in albumin-bilirubin (ALBI) grade and Child-Pugh score (CPS) over time ($n = 2,347$). The prevalence of patients with ALBI grade 1 disease increased throughout the study period ($p < 0.0001$). However, the percentage of patients with grade 1 disease remained approximately 50% in 2010–2019.

patients with ALBI grade 1 disease throughout the study period. However, the percentage of patients with grade 1 disease remained approximately 50% in 2010–2019, while ALBI grade 2 disease accounted for 45–60% of the patients (Fig. 2). Figure 3 shows a comparison between CPC and mALBI grade, when grade 2 was divided into 2a and 2b [5]; mALBI grade 2a disease is indicative of poor liver function associated with CPC A. Figure 4 shows a comparison of mALBI grade and serum albumin values. A serum albumin level of 3.5 g/dL is considered to be the cutoff value separating ALBI grade 2a and 2b.

Comparison between ALBI Grade and CPC for Predicting Prognosis

Figure 5 shows cumulative survival curves by mALBI grade in patients with CPC A (Fig. 5a). There were significant differences between patients with ALBI grade 1 versus 2a disease ($p < 0.0001$), ALBI grade 1 versus 2b disease ($p < 0.0001$), and ALBI grade 2a versus 2b disease ($p < 0.0001$). Figure 5 shows cumulative survival curves by CPS in patients with ALBI grade 1 disease (Fig. 5b). There was a significant difference between patients with CPS 5 versus 6 disease ($p = 0.0004$).

Discussion

Antiviral therapies such as NAs for HBV infection and DAAs for HCV infection with minimal treatment-related side effects have been developed. Viral suppression of HBV using NAs or eradication of HCV using DAAs substantially improves liver function in patients with

Fig. 3. Comparison of Child-Pugh classification (CPC) and modified albumin-bilirubin (mALBI) grade over time ($n = 2,347$). ALBI grade 2 had a very wide range; therefore, it was divided into 2a and 2b at the cutoff value of -2.270 . Approximately 20% of the patients had ALBI grade 2a disease throughout the study period. ALBI grade 2a corresponds to patients with CPC A who have poor hepatic reserve.

chronic hepatitis virus infection [19–24]. Most HCC patients have complications including cirrhosis and malnutrition. The efficacy of nutritional supplementation with oral branched-chain amino acids in HCC patients undergoing interventions has been recognized [25, 26]. It seems that this advance in supportive care for cirrhosis may play a role in improving liver function in non-HBV and non-HCV cirrhosis. It is well known that prognosis in patients with HCC is dependent on tumor burden and hepatic function. More recently, the prevalence of non-viral HCC associated with aging has increased [27]; Group F had the highest proportion of patients with non-viral HCC. Therefore, CPC A is the most common pattern of liver function among patients with naïve HCC in Japan. CPC A disease accounted for approximately 80% of the patients in Groups E and F in our study (Fig. 1). With this high proportion of patients with CPC A disease, the significance of CPC as an indicator of hepatic function is extremely low. Thus, a more detailed evaluation of hepatic function in patients with CPC A disease and good liver function is needed based on recent clinical trends.

ALBI grade gradually increased over time; ALBI grade 1 disease accounted for approximately half of the patients in Group F (Fig. 2). As shown in Figure 5(a), the mALBI classification system was able to clearly distinguish the prognosis of patients with CPC A into 3 groups. On the other hand, as shown in Figure 5(b), CPS was unable to properly differentiate the prognosis of patients with ALBI grade 1 disease. ALBI grade was found to be suitable for assessing liver function in patients with good hepatic reserve function. However, ALBI grade has some weaknesses. ALBI grade has been reported to have insufficient power as a prog-

Fig. 4. Comparison of modified albumin-bilirubin (mALBI) grade and serum albumin levels over time ($n = 2,347$). A serum albumin level of 4.0 g/dL is considered the cutoff value separating ALBI grades 1 and 2a, and 3.5 g/dL is considered the cutoff value separating ALBI grades 2a and 2b.

nostic factor in patients with decompensated cirrhosis. In a comparison between ALBI grade and the model for end-stage liver disease score performed by Khabbaz et al. in patients undergoing creation of a transjugular intrahepatic portosystemic shunt due to complications of portal hypertension, only the model for end-stage liver disease score was associated with transplant-free survival [28].

As shown in Figure 2, ALBI grade 2 disease encompasses a very wide range, similar to CPC B disease. Thus, ALBI grade 2 should be divided into subgrades for a more detailed assessment of hepatic reserve function. Since ALBI scores are strongly correlated with ICGR-15 ($\gamma = 0.563$; 95% confidence interval [CI], 0.550–0.570; $p < 0.0001$), Hiraoka et al. suggested ALBI grade could be modified into 4 grades: mALBI 1, 2a, 2b, and 3, using ICGR-15 results of 30% (cutoff value for ALBI score = -2.270 ; area under curve, 0.828; 95% CI, 0.823–0.833) [5]. They showed prognosis was well stratified by mALBI grade for each LCSGJ TNM stage ($p < 0.001$). In addition, Hiraoka et al. showed mALBI grade (1/2a) was a better hepatic function assessment tool than CPC or CPS in patients with initial molecular targeting agent therapy [29–31]. In the near future, we think ALBI grade will be more useful when the combination therapy with immune check-point drug and molecular targeting agents for unresectable HCC will become available [32].

Jaundice is less likely to be found with HCC because of advances in antiviral therapy for underlying liver disease and early detection of HCC. Therefore, ALBI grade is greatly influenced by serum albumin levels. As shown in Figure 4, the serum albumin level of 4.0 g/dL is consistent with the cutoff for ALBI grade 1 and 2a disease, and the serum albumin level of 3.5 g/dL has good

Fig. 5. Comparison of cumulative survival by Child-Pugh classification (CPC) A and albumin-bilirubin (ALBI) 1 grade for predicting prognosis. **a** There were significant differences between patients with CPC A who had modified ALBI (mALBI) grade 1 versus 2a disease, mALBI grade 1 versus 2b disease, and mALBI grade 2a versus 2b disease ($p < 0.0001$). **b** There was a significant difference between patients with ALBI grade 1 disease who had Child-Pugh scores (CPS) of 5 versus 6 ($p = 0.0004$).

agreement with the cutoff for ALBI grade 2a and 2b disease. It seems that the serum albumin value of 3.5 g/dL and ICGR-15 of 30% are in agreement with each other. The measurement method of serum albumin changed from the bromocresol green (BCG) method which was used for conventional measurement to the modified bromocresol purple (BCP) method which was highly specific for albumin. This method was introduced at our institution in June 2017. The overestimation of albumin by the BCG method resulted in a low albumin level (<3.5 g/dL). If the serum albumin level is <3.5 g/dL using the BCG method, the result is 0.3 g/dL higher than that of the modified BCP method [33, 34]. However, as shown in Figure 4, the cutoff value for distinguish mALBI grade 2a from mALBI grade 2b is 3.5 g/dL, and there is no need for a correction in the modified BCP method for the evaluation of ALBI grade 1 and 2a, which are indicators of good liver function. Serum albumin level is known to be higher in the sitting or standing position than in the prone position [35]. In this study, blood was collected in a sitting position in all cases.

The proportion of patients with advanced fibrosis decreased gradually throughout the study period (online suppl. Fig. 2). Age became markedly higher during this study period, with a difference of 11 years between Groups A and F (Table 1). We believe that the FIB-4 index has decreased despite having an age-dependent component [14], indicating that the prevalence of truly advanced fibrosis has decreased. This phenomenon seems to be related to improvement in liver function. The levels of ALT, AST, AFP, total bilirubin, ICGR-15, ALBI score, FIB-4 index, and CPS decreased during the study period. By contrast, platelet count and albumin increased. All of these events are thought to be due to good background liver function.

In conclusion, the CPC system was originally proposed over 50 years ago by Dr. Child, Dr. Turcotte, and Dr. Pugh. Its continued use should be reconsidered according to the current situation, especially in patients with good hepatic function. In such patients with HCC, the prognosis can be well stratified by ALBI grade rather than CPC.

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Statement of Ethics

The entire study protocol was approved by the hospital's Ethics Committee and carried out in compliance with the Declaration of Helsinki (approval No.: 20190228-9), and written informed consent was obtained from each patient included in the study.

Conflict of Interest Statement

Takashi Kumada (Gilead Sciences and AbbVie), Hidenori Toyoda (AbbVie, Merck Sharp & Dohmen, and Bayer), and Junko Tanaka (AbbVie and Gilead Sciences).

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Author Contribution

All authors have contributed to and agreed on the content of the manuscript. *Concept and study design:* Takashi Kumada and Hidenori Toyoda. *Data acquisition:* All authors. *Analyses of the data:* Junko Tanaka and Toshifumi Tada. *Statistics:* Junko Tanaka. *Supervise:* Hidenori Toyoda. *Preparing manuscript:* Takashi Kumada. *Review and approval:* All authors.

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