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ORIGINAL ARTICLE

Effect of abdominal aortic calcification on long-term outcomes after the first liver resection in very old patients with hepatocellular carcinoma

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Abstract

Aim: We previously reported that abdominal aortic calcification is associated with poor overall and recurrence-free survival after hepatectomy for hepatocellular carcinoma (HCC). However, the effect of abdominal aortic calcification on cancer-specific prognosis in very old patients with several comorbidities remains unknown. This multicenter study aimed to evaluate the impact of abdominal aortic calcification on the cumulative recurrence rate and recurrence-free survival in patients with HCC aged >80 years.

Methods: We retrospectively analyzed the data of 128 patients (aged ≥80 years) who underwent liver resection for hepatocellular carcinoma at seven hospitals belonging to Hiroshima Surgical Study Group of Clinical Oncology between January 2014 and December 2018. Patients were divided into two groups: high and low abdominal aortic calcification groups. The primary endpoints were cumulative recurrence rate and recurrence-free survival.

Results: Kaplan–Meier survival curve analysis demonstrated that the cumulative recurrence rate in the high abdominal aortic calcification group was significantly higher than that in the low abdominal aortic calcification group, and the high abdominal aortic calcification group had a significantly lower recurrence-free survival rate. In the multivariate analysis, high abdominal aortic calcification ($p = 0.03$), high des-gamma-carboxyprothrombin score ($p = 0.04$), and multiple tumors ($p < 0.01$) were independent predictive factors for recurrent HCC, and high abdominal aortic calcification ($p = 0.01$) and high des-gamma-carboxyprothrombin ($p = 0.01$) were independent predictive factors for poor cancer-specific survival.

Conclusions: Our results indicate that the abdominal aortic calcification score is associated with cumulative recurrence rate and recurrence-free survival in very old patients with HCC.

KEYWORDS
abdominal aortic calcification, hepatocellular carcinomas, prognosis, survival analysis, very old patients

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies and the third leading cause of cancer-related death worldwide.[1–3] Although hepatectomy is considered curative for HCC, its recurrence rate remains high. Systemic inflammation plays an important role in promoting metastasis and cancer progression as it promotes the release inflammatory cytokines from tumor cells and inflammatory cells coexisting in the tumor microenvironment.[4–6] Inflammatory cells such as macrophages and T lymphocytes, which are the primary cells releasing inflammatory cytokines, are known to be involved in the progression of vascular calcification.[7,8]

Abdominal aortic calcification (AAC) can be readily assessed using abdominal computed tomography (CT) as a marker of atherosclerosis and is associated with an increased relative risk of cardiovascular events and cardiovascular death.[9,10] Additionally, we have previously demonstrated that AAC had a strong relationship with poor overall survival (OS) and recurrent-free survival (RFS) after hepatectomy for HCC.[11] However, background factors and the degree of arterial calcification differ between older and younger patients. In addition, higher AAC scores in very old patients are associated with an increased risk of atherosclerosis-related complications and are independently associated with cardiovascular events.[12–15] Therefore, it is important to evaluate whether AAC is independently associated with cancer-related survival, separate from its association with cardiovascular event-related mortality, in very old patients.

We collected data from multiple centers and evaluated cumulative recurrence rates, RFS, and cancer-specific survival (CSS) to examine the effect of AAC on cancer-specific prognosis in patients aged ≥80 years. This study also aimed to evaluate the consistency of the computed tomography (CT)-based AAC score measurement across institutions.

2 | METHODS

2.1 | Patient recruitment and study protocol

This retrospective cohort study included patients with HCC who underwent primary liver resection between January 2014 and December 2018 at seven hospitals belonging to the Hiroshima Surgical study group of Clinical Oncology (HiSCO). The HiSCO database contains detailed clinical information on patients who underwent liver resection for HCC at the seven institutions. Tumor recurrence and metastasis were determined using CT or magnetic resonance imaging. Patients who underwent R1/R2 resection and those who died were excluded. The primary endpoints were the cumulative recurrence rate, RFS, and CSS. RFS refers to the period after HCC surgery until recurrence or death from any cause, while CSS refers to the period until death from HCC. The study design is shown in Figure 1.

2.2 | Data collection

The HiSCO database was used to identify eligible patients and extract demographics, clinical information, perioperative factors, and long-term outcomes for each case. The patient demographics included age, sex, body mass index, history of diabetes, and Child–Pugh grade. Clinical factors included hepatitis background, preoperative blood test results, indocyanine green retention rate at 15 min, tumor size, and number of tumors. The perioperative factors included blood loss, operation time, and pathological findings. Long-term outcomes were evaluated in terms of cumulative recurrence rate, RFS, and CSS.

Informed consent was obtained from the recruited patients, and the Institutional Review Board of each institution approved this study (E-1639). This study was performed in accordance with the principles of the Declaration of Helsinki and is reported in accordance with the STROBE guidelines.

2.3 | Aortic abdominal calcification measurement method

Abdominal CT images were obtained using a 64-channel multidetector row CT system for standardized preoperative assessment. AAC was defined as the calcification of the abdominal aorta from the renal artery bifurcation to the common iliac artery bifurcation. The AAC score was calculated using SYNAPSE VINCENT software (FUJFILM, Tokyo, Japan). The calcified area was manually selected from the 3D image, and the volume of the area was automatically calculated. The selected calcified areas changed to green in the axial image, confirming that they were accurately selected (Figure 2). The cutoff value was set at 21.0 mL using the receiver operating characteristic (ROC) curve of recurrent HCC. Patients were divided into two groups: low ACC group (<21 mL; $n = 107$) and high ACC group (≥21 mL; $n = 17$).

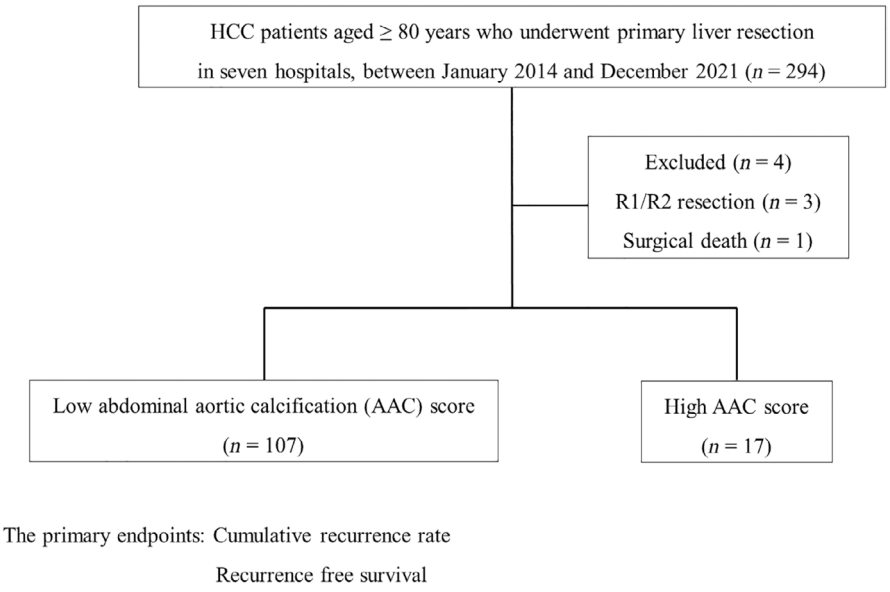

FIGURE 1 Flow chart of the participant selection. None of the patients underwent biliary reconstruction. HCC, hepatocellular carcinoma.

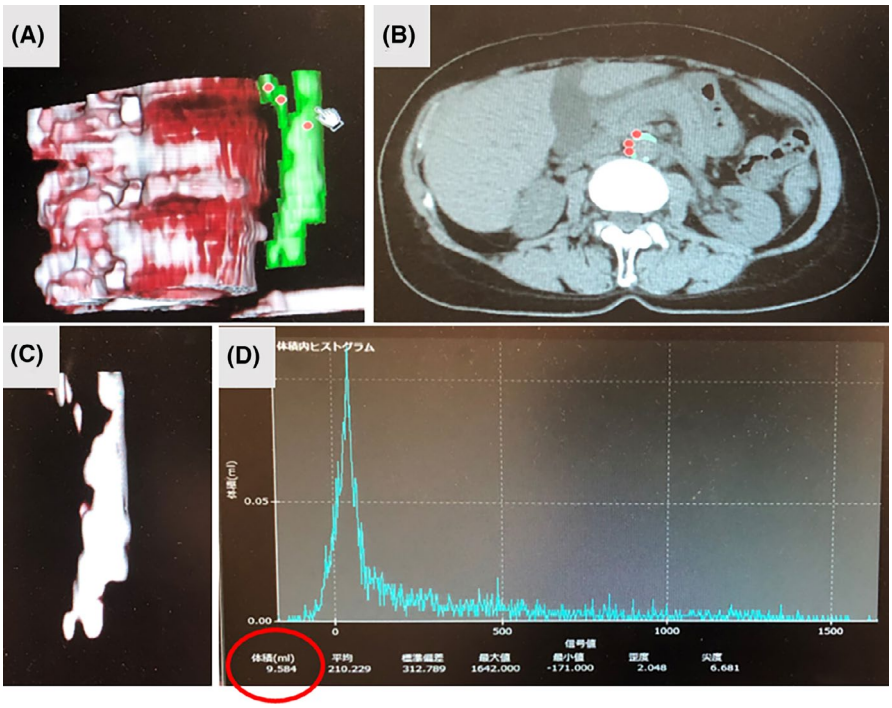

FIGURE 2 Calculation of abdominal aortic calcification score using SYNAPSE VINCENT (FUJFILM, Tokyo, Japan). (A) The calcified area is manually selected in the 3D image, and the selected calcified areas are changed to green, (B) change of all calcified areas to green is confirmed in the axial image, (C) calcified areas are extracted, (D) and the volume of the calcified area is automatically calculated.

2.4 | Statistical analysis

Data were analyzed using JMP software version 16 (SAS Institute, Inc., Cary, NC, USA). Descriptive statistics for categorical and continuous variables are reported as absolute numbers and medians (ranges), respectively. Categorical variables were analyzed using Fisher's exact test, and continuous variables were analyzed using the Student's *t*-test for normally distributed variables and the Wilcoxon test for non-normally distributed variables. Cumulative recurrence rate, RFS, and CSS were calculated using the Kaplan–Meier method and compared using the log-rank test. Multivariate analyses were performed for variables independently associated with the occurrence of recurrent HCC, RFS, and CSS using the Cox proportional hazards model. All variables were included in the multivariate models and the backward elimination method (removal criterion $p = 0.05$ was used to select covariates). The receiver operating characteristic (ROC) curve was used to determine the cut-off value for each continuous variable. Statistical significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Comparison of AAC scores for each institution

Figure 3 shows a box-and-whisker plot of the AAC score for each institution. There was no significant difference in the AAC scores from each institution, suggesting that the AAC score measurement was consistent between institutions.

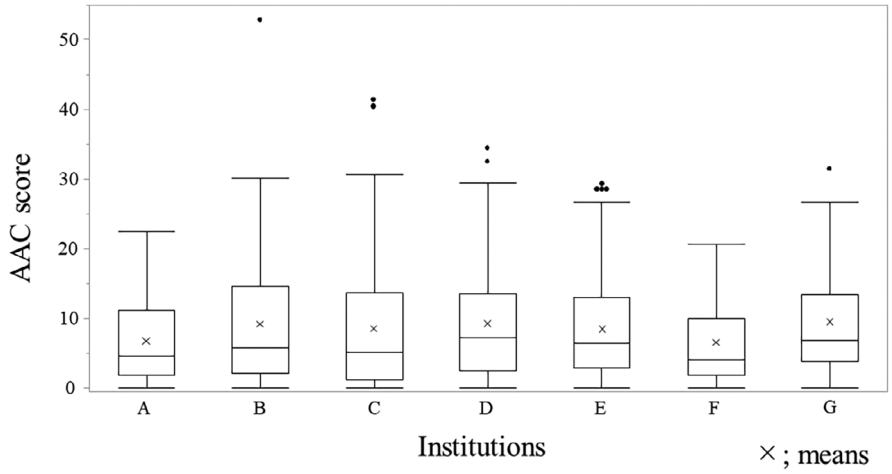

FIGURE 3 Box-and-whisker plot of the AAC score by institution. There are no significant differences in the AAC scores between institutions (median [range]: A, 4.5 [0–22.5]; B, 5.8 [0–52.8]; C, 5.1 [0–41.3]; D, 7.3 [0–34.3]; E, 6.5 [0–29.1]; F, 4.1 [0–20.7]; and G, 6.9 [0–31.4]). AAC, abdominal aortic calcification.

TABLE 1 Comparison of patient background according to age.

	Aged <80 years $n = 597$ (82.8%)	Aged ≥80 years $n = 124$ (17.2%)	*p* value
Age (years), median (range)	70 (35–79)	82 (80–92)	<0.01
Male, *n* (%)	476 (79.7)	87 (70.1)	0.06
Body mass index (kg/m^2), median (range)	23.3 (13.1–45.4)	22.4 (16.9–32.6)	0.04
Diabetes, *n* (%)	217 (36.4)	46 (37.0)	0.65
Child–Pugh B, *n* (%)	39 (6.5)	7 (5.6)	0.91
HBV/HCV, *n* (%)	350 (58.6)	56 (45.1)	0.01
Total bilirubin (mg/L), median (range)	0.8 (0.3–3.0)	0.7 (0.2–2.5)	<0.01
Albumin (g/L), median (range)	4.0 (2.5–5.0)	4.0 (2.5–4.1)	0.17
PT-INR, median (range)	1.07 (1.0–2.0)	1.08 (0.88–2.40)	0.11
ICG-R15 (%), median (range)	12.5 (2.0–76)	12.0 (2.6–50)	0.98
Creatinine (mL/min), median (range)	0.79 (0.34–11.0)	0.89 (0.46–3.39)	<0.01
CRP (mg/dL), median (range)	0.13 (0.01–13.9)	0.13 (0.01–2.0)	0.67
AFP (ng/mL), median (range)	8.0 (0.5–99 430)	6.4 (0.7–2922)	0.26
DCP (ng/mL), median (range)	54 (15–838 500)	60 (15–149 500)	0.72
Tumor size (mm), median (range)	25 (1.2–200)	30 (5–150)	0.14
Multiple tumors, *n* (%)	157 (26.2)	34 (27.4)	0.89
AAC score, median (range)	5.4 (0–40.3)	7.3 (0.2–52.8)	<0.01

Abbreviations: AAC, abdominal aortic calcification; AFP, alpha fetoprotein; CRP, C-reactive protein; DCP, des-gamma-carboxyprothrombin; HBV, hepatitis B virus; HCV, hepatitis C virus; ICG-R, indocyanine green retention rate at 15 min; PT-INR, prothrombin time-international normalized ratio.

3.2 | Comparison of the background characteristics of patients aged <80 years and ≥80 years

A total of 721 patients were included in this study, of whom 124 were aged ≥80 years. Table 1 shows the background characteristics, including AAC scores, according to age. Compared with patients aged <80 years, patients aged ≥80 years had a significantly lower median BMI and prevalence of HBV and HCV positivity, and significantly higher total bilirubin and creatinine levels, as well as AAC scores (Table 1).

3.3 | Relationship between patient characteristics and AAC in patients aged ≥80 years

Table 2 presents the AAC scores and baseline clinical characteristics of the patients. Significantly more patients in the high AAC group had a history of cardiac disease ($p < 0.01$). The high AAC group had significantly lower albumin ($p < 0.01$), significantly higher creatinine ($p < 0.01$), and higher CRP levels ($p < 0.01$). There were no significant differences in intraoperative, postoperative, or tumor factors (Table 2).

TABLE 2 Demographics and clinical characteristics of patients aged ≥80 years.

	High AAC $n=17$ (13.7%)	Low AAC $n=107$ (86.3%)	p value
Age (years), median (range)	82 (80–87)	82 (80–92)	0.86
Male, *n* (%)	14 (82.3)	73 (68.2)	0.21
Body mass index (kg/m^2), median (range)	23.6 (16.9–30.1)	21.9 (17.1–32.6)	0.70
Diabetes, *n* (%)	7 (41.2)	39 (36.4)	0.70
History of cardiovascular disease, *n* (%)	5 (29.4)	6 (5.6)	<0.01
Child–Pugh B, *n* (%)	3 (17.6)	4 (3.7)	0.04
HBV/HCV, *n* (%)	6 (35.3)	50 (46.7)	0.37
Total bilirubin (mg/L), median (range)	0.6 (0.2–1.5)	0.7 (0.3–2.5)	0.05
Albumin (g/L), median (range)	3.6 (2.5–4.4)	4.1 (2.5–4.1)	<0.01
PT-INR, median (range)	1.1 (0.98–2.40)	1.07 (0.88–2.07)	0.11
ICG-R15 (%), median (range)	12.7 (5–50)	12.2 (2.6–41)	0.91
Creatinine (mL/min), median (range)	1.03 (0.59–1.40)	0.83 (0.46–3.39)	<0.01
CRP (mg/dL), median (range)	0.38 (0.02–1.88)	0.12 (0.01–2.0)	0.02
AFP (ng/mL), median (range)	5.8 (1.0–2922)	6.1 (0.7–2487)	0.99
DCP (ng/mL), median (range)	175 (15–51 221)	49 (22–149 500)	0.11
Tumor size (mm), median (range)	30 (18–82)	28 (5–150)	0.15
Multiple tumors, *n* (%)	4 (23.5)	30 (28.0)	0.69
Operation time (min), median (range)	255 (94–541)	291 (82–698)	0.13
Blood loss (mL), median (range)	207 (34–1217)	260 (1–3935)	0.67
Vascular invasion, *n* (%)	4 (23.5)	37 (34.5)	0.35
Anatomical liver resection, *n* (%)	7 (41.1)	32 (29.9)	0.36
Postoperative complications, *n* (%)	4 (23.5)	13 (12.2)	0.17

Abbreviations: AAC, abdominal aortic calcification; AFP, alpha fetoprotein; CRP, C-reactive protein; DCP, des-gamma-carboxyprothrombin; HBV, hepatitis B virus; HCV, hepatitis C virus; ICG-R, indocyanine green retention rate at 15 min; PT-INR, prothrombin time-international normalized ratio.

3.4 | Relationship between AAC and cumulative recurrence rate, RFS, and CSS in patients aged ≥80 years

Figure 4 presents the relationship between AAC and cumulative recurrence rate, RFS, or CSS rates. Kaplan–Meier survival curve analysis demonstrated that the cumulative recurrence rate in the high AAC group was significantly higher than that in the low AAC group (Figure 4A). Additionally, the high AAC group had significantly lower RFS and CSS than the low AAC group (Figure 4B,C).

3.5 | Risk factors for recurrent HCC or recurrence-free survival in patients aged ≥80 years

Table 3 presents the risk factors for HCC recurrence. Univariate analysis revealed that a high AAC level ($p<0.01$), Child–Pugh grade B ($p<0.01$), des-gamma-carboxyprothrombin level >40 mAU/mL ($p<0.01$), intraoperative blood loss >400 mL ($p=0.04$), multiple tumors ($p=0.02$), and tumor size >50 mm ($p=0.01$) were predictive factors for recurrent HCC. In the multivariate analysis, high AAC level (Hazard ratio [OR]: 2.07; 95% CI: 1.04–4.10; $p=0.03$), des-gamma-carboxyprothrombin level >40 mAU/mL (HR: 1.83; 95% CI: 1.00–3.33; $p=0.04$), and multiple tumors (HR: 2.16; 95% CI: 1.23–3.79; $p<0.01$) were independent predictive factors for the recurrent HCC. Regarding the risk factors for poor RFS, high AAC level ($p<0.01$), Child–Pugh grade B ($p=0.02$), des-gamma-carboxyprothrombin level >40 mAU/mL ($p<0.01$), intraoperative blood loss ($p=.01$), tumor size >50 mm ($p<0.01$), and vascular invasion ($p<0.01$) were predictive factors in the univariate analysis. In the multivariate analysis, high AAC level (OR: 2.16; 95% CI: 1.15–4.05; $p=0.01$) and des-gamma-carboxyprothrombin level >40 mAU/mL (OR: 1.97; 95% CI: 1.13–3.42; $p=0.01$) were independent predictive factors of poor RFS (Table 4). For poor CSS, high AAC level ($p<0.01$), Child–Pugh grade B ($p<0.01$), des-gamma-carboxyprothrombin level >40 mAU/mL ($p<0.01$), tumor size >50 mm ($p=0.01$), and vascular invasion ($p<0.01$) were predictive factors according to the results of univariate analysis. In the multivariate analysis, high AAC level (OR: 2.74; 95% CI: 1.07–7.01; $p=0.03$), des-gamma-carboxyprothrombin level >40 mAU/mL (OR: 3.44; 95% CI: 1.07–10.9; $p=0.03$), and vascular invasion (OR: 3.29; 95% CI: 1.33–8.12; $p<0.03$) were independent predictive factors for poor CSS (Table S1).

4 | DISCUSSION

Herein, we demonstrated that high AAC levels were significantly associated with cumulative recurrence rate, RFS, and CSS after the

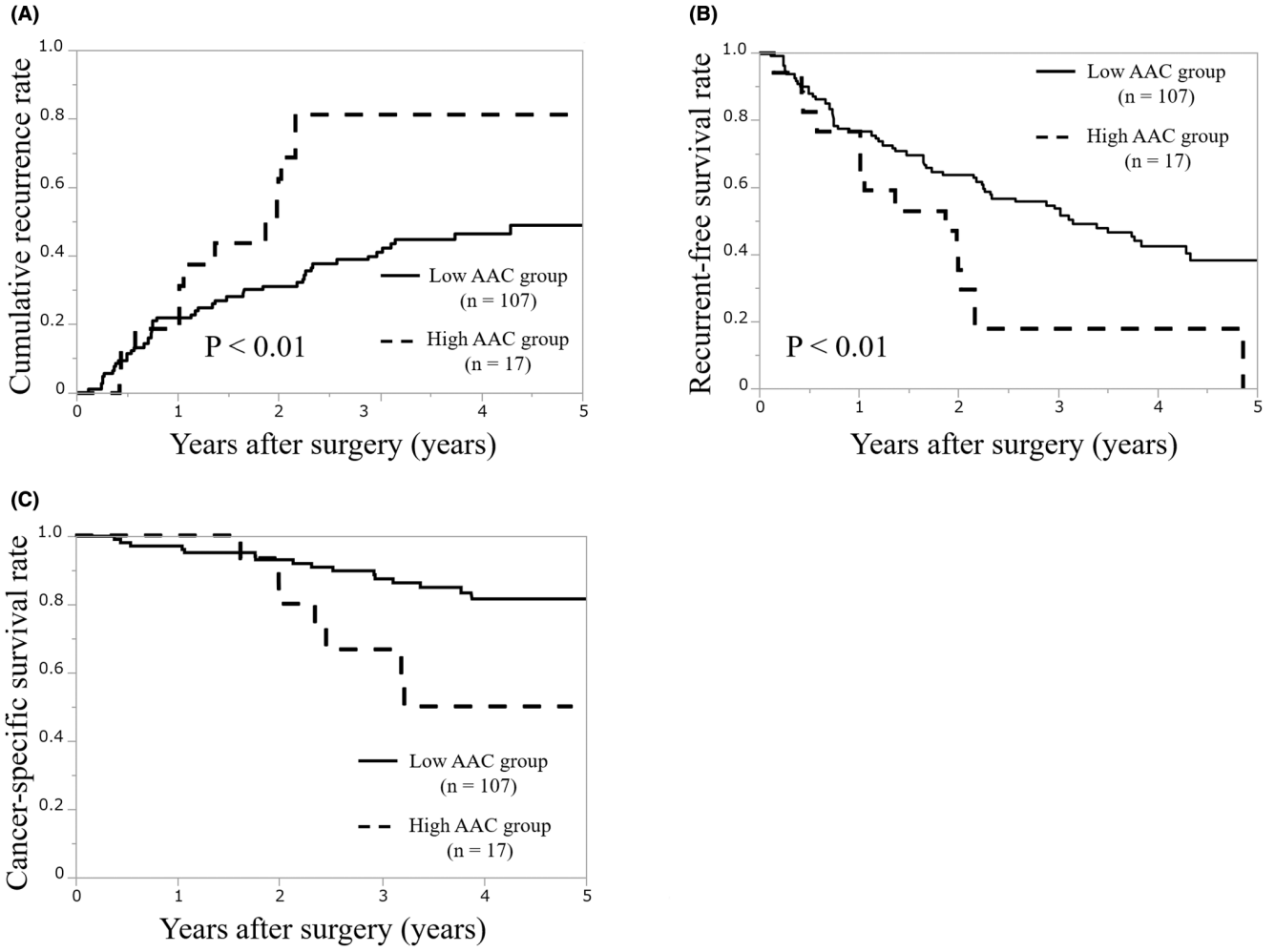

FIGURE 4 Comparison of survival curves for the high and low abdominal aortic calcification (AAC) groups. (A) The cumulative recurrence rate was significantly higher in the high AAC group compared with the low AAC group, (B, C) Kaplan–Meier survival curve analysis demonstrated significantly worse recurrence-free survival and cancer-specific survival in the high AAC group than in the low AAC group.

first liver resection in very old patients with HCC. We have previously demonstrated that high AAC levels are associated with postoperative HCC survival.[11] However the background characteristics of older patients, including the degree or arterial calcification, differ from those of younger patients, and AAC has been shown to be associated with cardiovascular events. It remains unclear whether AAC is associated with cancer-specific survival. Therefore, we demonstrated that high AAC levels were associated with cancer-related prognosis in old patients, suggesting that AAC may be useful in predicting prognosis after liver resection in patients with HCC. The study also showed that AAC measurements using CT was consistent between institutions.

AAC is often used as a predictor of cardiovascular events, such as coronary artery calcification and abdominal aortic aneurysms[16,17]; however, several reports have also shown an association between AAC and systemic inflammation.[18,19] Recently, AAC was observed to be associated with the pyrin domain-containing protein 3 (NLRP3) inflammasome.[20] The NLRP3 inflammasome is a multimeric cytoplasmic protein complex that promotes the release of inflammatory cytokines such as interleukin-1β (IL-1β) and activation of inflammatory responses.[21,22] By recruiting macrophages, cholesterol crystals and vessel wall damage are generally considered to be the first and central trigger of the activation of the NLRP3 inflammasome.[23,24] IL-1β released as a result of NLRP3 activation promotes vascular calcification, plaque rupture, and vessel wall stiffening, suggesting that AAC is a consequence of NLRP3 activation and IL-1β release.[20] In addition, through the formation of an inflammatory microenvironment, NLRP3 is involved in cancer development and progression.[25] Wang et al. reported that high NLRP3 expression was associated with poor OS in patients with HCC.[26] Furthermore, IL-1β promotes malignant tumor progression by promoting immune escape and hematogenous metastasis; therefore, the AAC score may be a prognostic marker in patients with HCC.[27,28] Additionally, given that NLRP3 is a potential therapeutic target for HCC, the AAC score may be useful in assessing the therapeutic response, and AAC itself may be a potential therapeutic target.[29]

However, among very old patients with high comorbidities, those with high AAC scores may have a poorer prognosis due to comorbidities. Indeed, higher AAC scores in very old patients have

TABLE 3 Risk factors for recurrent hepatocellular carcinoma in patients aged ≥80 years.

	Univariate analysis		Multivariate analysis	
	OR [95% CI]	*p* value	OR [95% CI]	*p* value
Male	1.13 (0.64–2.02)	0.65		
HBV/HCV	1.32 (0.79–2.20)	0.28		
Diabetes, *n* (%)	1.43 (0.85–2.40)	0.16		
History of cardiovascular disease, *n* (%)	1.39 (0.59–3.26)	0.44		
Child–Pugh grade B	3.13 (1.33–7.37)	<0.01	2.08 (0.68–6.33)	0.19
ICG-R15 >15%	1.32 (0.79–2.21)	0.28		
AFP >20 ng/mL	1.43 (0.85–2.43)	0.17		
DCP >40 mAU/mL	2.25 (1.29–3.93)	<0.01	1.83 (1.00–3.33)	0.04
Operation time >300 min	1.43 (0.85–2.39)	0.16		
Intraoperative blood loss >400 mL	1.70 (1.01–2.85)	0.04	1.35 (0.74–2.46)	0.32
Multiple tumors	1.82 (1.06–3.10)	0.02	2.16 (1.23–3.79)	<0.01
Tumor size >50 mm	2.26 (1.16–4.39)	0.01	1.86 (0.85–4.07)	0.11
Vascular invasion	1.62 (0.95–2.76)	0.07		
High AAC level	2.36 (1.26–4.40)	<0.01	2.07 (1.04–4.10)	0.03

Abbreviations: AAC, abdominal aortic calcification; AFP, alpha fetoprotein; DCP, des-gamma-carboxyprothrombin; HBV, hepatitis B virus; HCV, hepatitis C virus; ICG-R, indocyanine green retention rate at 15 min.

TABLE 4 Risk factors for recurrence-free survival in patients aged ≥80 years.

	Univariate analysis		Multivariate analysis	
	HR [95% CI]	*p* value	HR [95% CI]	*p* value
Male	1.18 (0.70–1.97)	0.52		
HBV/HCV	1.20 (0.76–1.89)	0.43		
Diabetes, *n* (%)	1.11 (0.69–1.78)	0.65		
History of cardiovascular disease, *n* (%)	1.59 (0.75–3.34)	0.21		
Child–Pugh grade B	2.63 (1.12–6.14)	0.02	1.52 (0.50–4.60)	0.45
ICG-R15 >15%	1.09 (0.68–1.75)	0.54		
AFP >20 ng/mL	1.45 (0.90–2.33)	0.12		
DCP >40 mAU/mL	2.51 (1.52–4.15)	<0.01	1.97 (1.13–3.42)	0.01
Operation time >300 min	1.35 (0.85–2.14)	0.19		
Intraoperative blood loss >400 mL	1.76 (1.10–2.80)	0.01	1.47 (0.87–2.47)	0.14
Multiple tumors	1.80 (0.89–3.62)	0.09		
Tumor size >50 mm	2.23 (1.21–4.11)	<0.01	1.36 (0.68–2.70)	0.37
Vascular invasion	1.90 (1.19–3.04)	<0.01	1.55 (0.92–2.60)	0.09
High AAC level	2.14 (1.21–3.80)	<0.01	2.16 (1.15–4.05)	0.01

Abbreviations: AAC, abdominal aortic calcification; AFP, alpha fetoprotein; DCP, des-gamma-carboxyprothrombin; HBV, hepatitis B virus; HCV, hepatitis C virus; ICG-R, indocyanine green retention rate at 15 min.

been demonstrated to be associated with atherosclerosis-related complications and independently associated with cardiovascular events.[12–15] Additionally, several reports have suggested that high AAC scores are associated with postoperative complications.[27–29] However, it remains unclear whether AAC has a direct impact on cancer-specific survival in very old patients because postoperative complications are an important prognostic factor in such patients. Therefore, in the present study, we evaluated the effect of AAC

using cancer-specific prognostic markers such as CSS and RFS in super-elderly patients. As a result, the AAC score was associated with CSS and RFS, and we considered that the AAC score can be used as a predictive index of prognosis after HCC surgery, even in super-elderly patients with high comorbidities.

Several reports have focused on old patients with HCC and analyzed their prognosis. Hamaoka et al. reported Child–Pugh grade, tumor markers, and multiple tumors were prognostic factors,[30] while Xu et al. reported Child–Pugh grade, tumor markers, multiple tumors, and intraoperative blood loss as prognostic factors.[31] Herein, univariate analysis of RFS demonstrated similar results; however, only the AAC score and tumor markers were independent prognostic factors in the multivariate analysis. Multivariate analysis of recurrent HCC also demonstrated AAC score to be a significant predictor; this result indicated that AAC score was a strong marker of cancer-related prognosis in patients with HCC aged ≥80 years. The AAC score is a simple non-invasive measurement and was measured consistently across institutions. This suggests that it may be suitable for use as a new prognostic marker after HCC surgery.

The present study has several limitations. First, this was a retrospective study. Second, we could not completely exclude the effects of comorbidities. To resolve this issue, in future studies, the number of cases should be increased further, and propensity score matching should be performed. However, despite these limitations, we believe that the AAC score is associated with cumulative recurrence rate and RFS after HCC surgery in super-elderly patients. The decision of the analysis software used for calculating the AAC score should also be evaluated. The AAC score is evaluated by calculating the volume of arterial calcification from CT images. Various reports have utilized analysis software other than the SYNAPSE VINCENT software, which was employed in this study.[11,15,32,33] Although the AAC score can be calculated using many types of analysis software, it remains unclear whether all such software are equally effective for this calculation.

In conclusion, our results indicate that the AAC score is associated with the cumulative recurrence rate and RFS in very old patients with HCC. To our knowledge, these results are novel findings regarding HCC and may aid the development of novel biomarkers and therapeutic strategies.

AUTHOR CONTRIBUTIONS

Yosuke Namba: study design, data analysis and interpretation, drafting of the manuscript. Masahiro Ohira: project administration, study design, review of the manuscript. Yuki Imaoka: study resign. Michinori Hamaoka: data collection. Masakazu Hashimoto: data collection. Takashi Onoe: data collection. Daisuke Takei: data collection. Koichi Oishi: data collection. Megumi Yamaguchi: data collection. Tomoyuki Abe: data collection. Naruhiko Honmyo: review of the manuscript. Shintaro Kuroda: review of the manuscript. Hiroyuki Tahara: review of the manuscript. Tsuyoshi Kobayashi: study design, review of the manuscript. Kentaro Ide: review of the manuscript. Hideki Ohdan: review of the results, overall study oversight, and guarantor of the manuscript. All authors approved the final version of the manuscript. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

Hideki Ohdan is an editorial board member of *AGS*. Other authors declare no conflict of interests for this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Approval of the research protocol: This research will be conducted in accordance with the 1975 Declaration of Helsinki.

Informed Consent: All patients must be given written informed consent to a member of the study team before inclusion in this study, and the Institutional Review Board of each institution approved this study (E-1639).

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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