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ORIGINAL ARTICLE

Geriatric prognostic scoring system predicts survival after hepatectomy for elderly patients with liver cancer

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Abstract

Aim: The number of elderly patients with liver cancer is increasing with the aging society. The Geriatric Prognostic Scoring System is useful in predicting the postoperative prognosis for elderly patients with gastrointestinal cancer. The aim of the present study was to assess the predictive ability of the geriatric prognostic scoring system for postoperative survival in elderly patients with liver cancer.

Methods: Eighty-eight patients aged ≥75 years who were treated for primary liver cancer and metastatic liver tumor were retrospectively analyzed. The Geriatric Prognostic Score (GPS) was created by several clinical parameters such as age, sex, type of cancer, stage, performance status, body mass index, and comprehensive geriatric assessment. Each patient was divided into two groups of high-risk to low-risk according to their GPS: ≧30 high-risk group and <30 low-risk. The predictive ability of geriatric prognostic scoring system for postoperative survival was assessed in univariate and multivariate analyses.

Results: Of the 88 patients, 75 were diagnosed as hepatocellular carcinoma and 13 as colorectal liver metastasis. After geriatric prognostic scoring system assessments, 26 patients were diagnosed as high-risk and the remaining 62 as low-risk. The 3-year overall survival rates were 78.5% in the low-risk group and 35.1% in the high-risk group ($p < 0.001$). The univariate and multivariate analyses of overall survival identified high GPS as an independent significant factor ($p < 0.001$).

Conclusions: We could conclude that the geriatric prognostic scoring system is useful in predicting patients' prognosis after hepatectomy and it can provide helpful information to surgeons for determining treatment strategies for elderly patients with liver cancer.

KEYWORDS
elderly patients, hepatectomy, liver cancer, prognosis, score

1 | INTRODUCTION

With a rapidly aging society, the number of elderly patients with malignant tumors is increasing.[1,2] The number of surgeries for elderly patients with malignant tumors is also increasing with advancements in surgical instruments and perioperative management of elderly patients. However, elderly patients are often considered to be at a higher risk for postoperative complications of major surgery, such as hepatectomy, and the long hospital stay caused by postoperative complications may lead to worse physical functioning and quality of daily life, resulting in unfavorable surgical outcomes.[3,4] Therefore, it is important to classify the risk status and predict postoperative outcomes before surgery for elderly patients.[5,6]

The comprehensive geriatric assessment (CGA) is a multidisciplinary diagnostic tool that simultaneously assesses cognitive function and frailty. Therefore, CGA is widely utilized as a useful tool to detect problems in the daily lives of the elderly.[7–9] Several reports have shown that CGA is an effective assessment tool for chemotherapeutic toxicity and risk status of postoperative complications in elderly patients receiving chemotherapy and surgery.[10–12] We have also reported that CGA is useful for forecasting delirium and complications after surgery in elderly patients with gastrointestinal cancer.[13,14] Although there are several models predicting prognoses such as overall survival (OS) in elderly non-cancer patients, preoperative geriatric nutritional risk, and the prognostic nutrition index, the models adaptable for gastrointestinal cancer are very limited[15,16] and scattered reports indicate that CGA is useful for predicting OS in elderly patients with gastrointestinal cancer.[9,17] In the field of liver surgery, preoperative frailty is associated with an increased risk of postoperative mortality and morbidity, as well as longer hospital stays.[10,18]

In a previous study, we evaluated the feasibility and outcomes of surgical treatment for elderly patients with various types of cancer in terms of physical and mental status and oncology. Then, we established the geriatric prognostic scoring system for gastrointestinal cancer.[19] The geriatric prognostic scoring system is helpful in forecasting postoperative prognosis and determining the treatment strategy for elderly patients. In recent years, the incidence of hepatocellular carcinoma has been increasing in the elderly, and there is a clinical question of whether liver resection should be performed for elderly patients with poor performance status (PS) or advanced malignancy. In addition, liver cancer is frequently accompanied by chronic liver disease, such as chronic hepatitis or liver cirrhosis. Thus, the long-term prognosis of patients with liver cancer is often influenced by liver function, as indicated by the Child–Pugh classification or albumin–bilirubin score.[20] The geriatric prognostic scoring system does not contain any factor of the classification, grading, or values related to liver function. Therefore, another clinical question is whether the novel prediction system could predict the prognosis of patients with liver cancer. Therefore, we focused on using the geriatric prognostic scoring system in elderly patients with hepatocellular carcinoma to evaluate its usefulness for predicting the prognosis after surgery.

2 | METHODS

2.1 | Patients

From 2010 to 2018, 124 patients aged ≥75 years had the treatment for primary liver cancer and metastatic liver tumor at Osaka University Hospital. Out of 124 patients, 36 were excluded for the following reasons: repeat hepatectomy, benign liver tumors, noncurative resection, or past history of psychological disorders, such as dementia. In this study, 88 patients were analyzed (Figure 1A). This study was approved by the Ethics Committee of Osaka University Hospital. Written informed consent for gastrointestinal surgery was obtained from each patient.

2.2 | Comprehensive geriatric assessment

The geriatricians in Osaka University Hospital performed the CGA before surgery as previously reported.[19] Briefly, the CGA included five evaluation items following the Mini-Mental State Examination (MMSE), the Geriatric Depression Score (GDS), the Barthel Index, the Vitality Index (VI), and instrumental activities of daily living (IADL). All patients were classified based on the CGA as those with a total MMSE score of 30 (normal function >24; cognitive dysfunction ≦23), those with a total GDS of 15 (normal function <6; mild-to-moderate depression 6–10; severe depression ≧11), those with a total Barthel Index of 100 (functional status using activities of daily living [ADL]), those with a total VI of 10, and those with a total IADL score. The cumulative index of the CGA was calculated by each geriatric assessment domain. The score was the sum of each domain (total score = 5), with a score of 5 indicating normal function (robust), 4 indicating mild dysfunction (pre-frail), and ≤3 indicating severe dysfunction (frail) (Figure 1B).

2.3 | Geriatric prognostic scoring system

The GPS was calculated as reported previously.[19] Briefly, the formula for GPS was: $GPS = X(\text{Age})i + X(\text{Sex})i + X(\text{cancer type})i + X(\text{cStage})i + X(\text{PS})i + X(\text{body mass index, BMI})i + X(\text{CGA})I$, where $X()i$ is the score of each predictor in patient i. The score was assigned as described previously.[19] The scores 75–80 years old, 80–84 years old, and ≥85 years old were 0, 6, and 8 points, respectively. In the scores for sex, female patients were 0 points and male patients 3 points. The score for hepatocellular carcinoma was 9 points and colorectal cancer 0 points. The scores for clinical Stage (cStage) were 0, 5, 14, and 22 points for I, II, III, and IV, respectively. The score for patients with PS ≥1 was 7 points, and the others were 0 points. The patients with low BMI (<18.5 kg/m^2) were higher risk than patients with high BMI, and patients with normal BMI were lower risk than patients with high BMI (<18.5, 18.5–25, and >25 were 5, −1, and 0 points, respectively). The frail and pre-frail patients were at higher risk than robust patients (frail, pre-frail, and robust were 8, 6, and 0 points, respectively). The GPS for patient i was obtained from the sum of the scores of each predictor (Figure 1C). Our

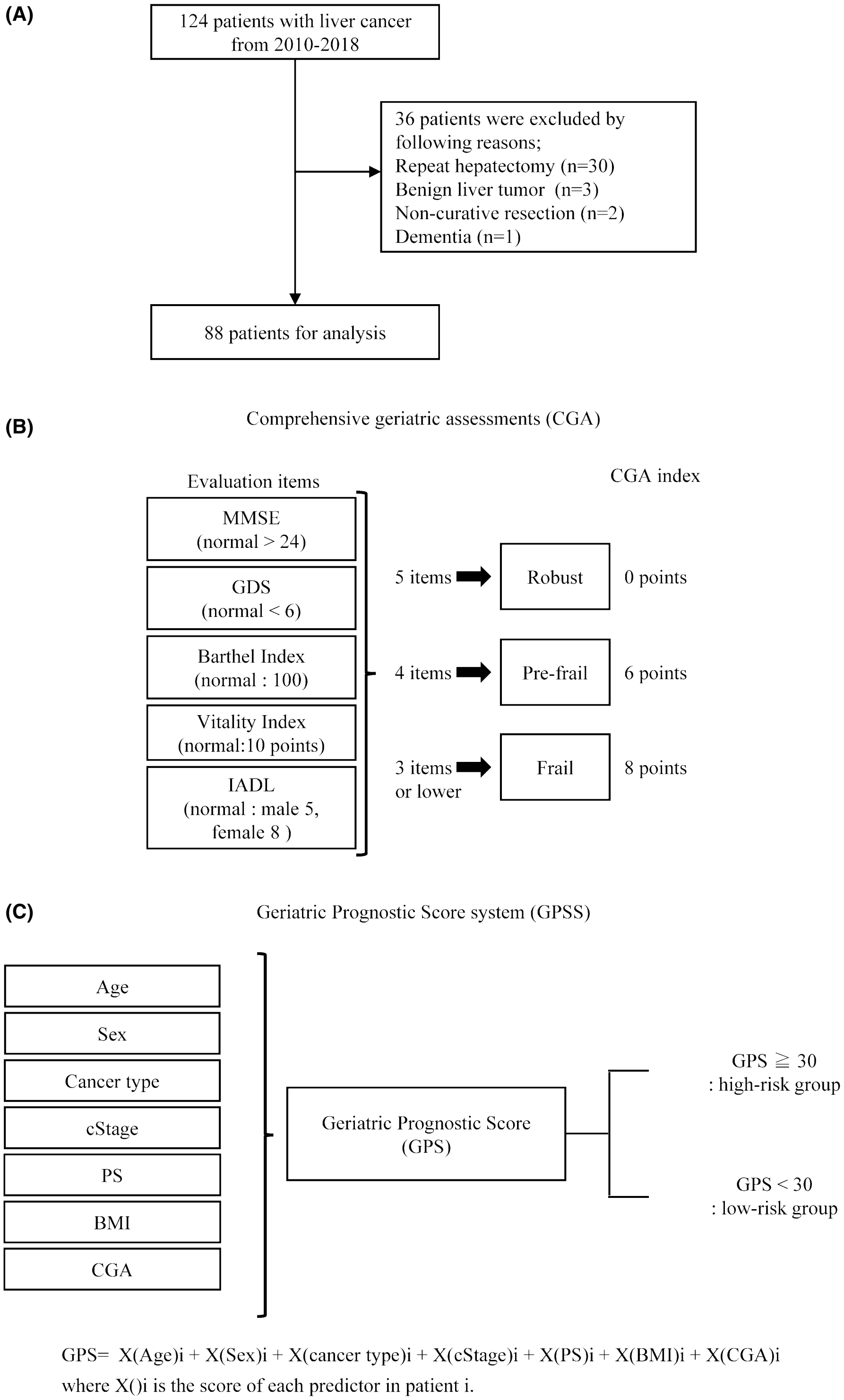

FIGURE 1 (A) Flowchart of patient inclusion in the analysis. (B) Comprehensive geriatric assessments (CGAs) contained the following evaluation items: Mini-Mental State Examination (MMSE), Geriatric Depression Score (GDS), Vitality Index (VI), Barthel Index, and instrumental activities of daily living (IADL). The cumulative CGA index was calculated based on the results for each evaluation item, and each patient was classified as robust with a score of 5, pre-frail with a score of 4, and frail with a score ≤3. (C) The Geriatric Prognostic Score (GPS) was measured by each predictor score.

previous study showed that the optimal cutoff value of GPS as 30 was useful for the prognosis of postoperative survival.[19] In this study, the GPS for each patient was classified into high-risk group or low-risk group using this cut-off (GPS <30 = low-risk, GPS ≥30 = high-risk). The usefulness of the GPS was also examined in elderly patients with liver cancer according to the OS rate and patient background. To assess the distinguishing power of the GPS in forecasting patients' survival, a logistic regression model was used separately to compute the area under the receiver operating characteristic (ROC) curve for 3-year survival after surgery.

2.4 | Follow-up evaluation

All patients were followed up at 3-month intervals for the 2 years after surgery and then every 6 months for 5 years. For screening of tumor recurrence, the patients received the computed tomography scan or ultrasound sonography. The last general follow-up of survivors was performed at the end of September 2020.

2.5 | Statistical analysis

Statistical analyses were performed by using JMP 17.0.0 (SAS, Cary, NC, USA). Continuous variables were expressed as the mean and standard deviation and statistically analyzed by the Student's *t* test. Categorical data were compared by the chi-squared test or Fisher's exact test. Prognostic variables were assessed by the log-lank test, and survival curves was analyzed by the Kaplan–Meier method. Cox's proportional hazard regression model was adopted to identify independent prognostic factors.

3 | RESULTS

3.1 | Patient characteristics

Table 1 summarizes the patients' backgrounds and surgical outcomes, including age, sex, cancer type, cStage, PS, BMI, cumulative CGA index, tumor size, tumor number, Child–Pugh classification, indocyanine green retention rate at 15 min ($ICGR_{15}$), type of hepatectomy, surgical method, operating time, blood loss, and hospital stay. The mean age of all patients was 80 years (range 75–92 years). Twenty patients were female, and 68 patients were male. Of the 88 patients, 13 were diagnosed with colorectal liver metastasis and 75 with hepatocellular carcinoma. Approximately two-thirds of the patients had a diagnosis of stage I or II malignancy, and the PS of nearly 90% patients was 0 or 1. In the cumulative CGA index, 42 patients were classified as robust, 24 as pre-frail, and 22 as frail. The median tumor size and tumor number were 3.8 cm (range, 0.9–14.5 cm) and 1 (range, 1–5), respectively. For liver function, 82 patients were classified as Child–Pugh A and six as Child–Pugh B. The median value of ICGR15 was 15.6%. Among the surgical procedures, 41 patients underwent non-anatomical liver resection, 47 anatomical liver resection, 53 open hepatectomy, and 35 laparoscopic hepatectomy. In addition, 41 patients underwent partial hepatectomy, 23 segmentectomy, 16 sectionectomy, and eight hemihepatectomy. The median operating time and blood loss were 253 min (range, 122–656 min) and 200 mL (range, 5–8300 mL), respectively. The median hospital stay was 17 days (range, 7–144 days). The mean GPS for all patients was 25 (range, 8–46).

3.2 | Association between patient's clinical factors and GPS

Using the optimal GPS cutoff of 30, 26 patients (30%) were diagnosed as high-risk and the remaining 62 (70%) as low-risk (Figure 2A). Table 2 compares the backgrounds of the high-risk and low-risk groups. The high-risk group was significantly older than the low-risk group ($p = 0.007$). The numbers of female patients, patients with colorectal cancer liver metastasis, cStage III or greater, high PS,

TABLE 1 Patient backgrounds and surgical outcomes ($N = 88$).

Age, years (75–79/80–84/≥85)	44/40/4
Sex (female/male)	20/68
Cancer type (colorectal liver metastasis/hepatocellular carcinoma)	13/75
cStage (I/II/III/IV)	12/52/9/15
PS (0/1/≥2)	79/5/4
BMI (>25/18.5–25/<18.5)	17/67/4
CGA cumulative index (robust/pre-frail/frail)	42/24/22
Tumor size (≦2/>2 cm)	17/71
Tumor number (1/2/≥3)	74/8/6
Child–Pugh (A/B)	82/6
$ICGR_{15}$ (%)	15.6 (3–38)
Type of hepatectomy (non-anatomical/segmentectomy/sectionectomy/hemihepatectomy)	41/23/16/8
Operation method (open/laparoscopic)	53/35
Operation time, min	253 (122–656)
Blood loss, mL	200 (5–8300)
Hospital stay, days	17 (7–144)
GPS	25 (8–46)

Note: Values are given as number of patients or mean (range).

Abbreviations: BMI, body mass index; CGA, comprehensive geriatric assessment; GPS, Geriatric Prognostic Score; $ICGR_{15}$, indocyanine green retention rate at 15 min; PS, performance status.

low BMI, frail status, tumor size ≥2 cm, and more than three tumors were significantly higher in the high-risk group than in the low-risk group. On the other hand, there were no significant clinical factors between the high- and low-risk groups in regard to the liver function, the type of hepatectomy, surgical method, operating time, blood loss, and hospital stay.

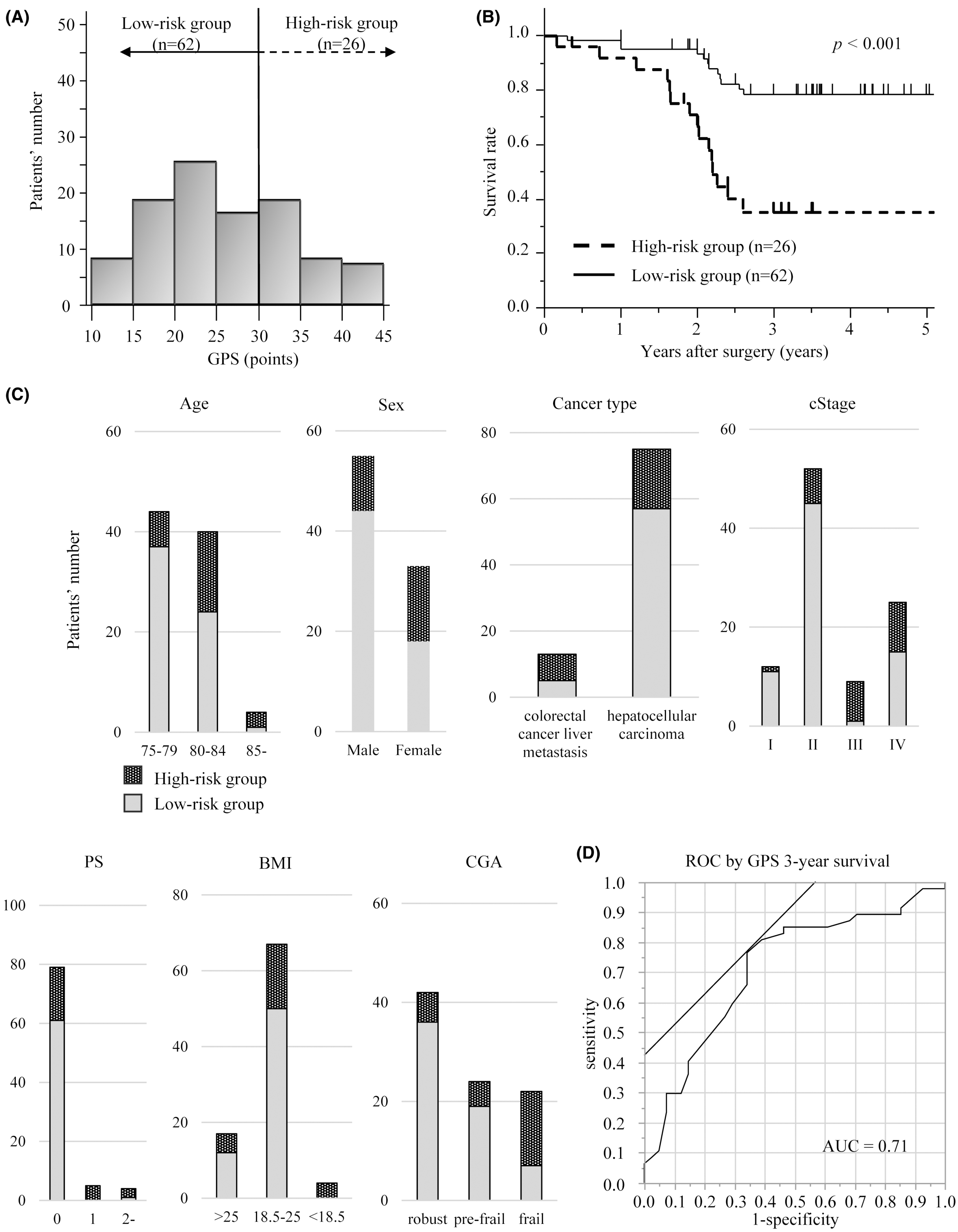

FIGURE 2 (A) Geriatric Prognostic Score (GPS) distribution. (B) Overall survival curves according to the GPS risk groups. (C) Distribution of patients in the high-risk and low-risk groups based on age, sex, cancer type, stage, PS, BMI, and CGA. (D) ROC curve for 3-year postoperative survival.

3.3 | Association between OS and GPS

We validated the ability of geriatric prognostic scoring system to predict OS in this cohort. The GPS had a bimodal distribution (Figure 2A). Kaplan–Meier analysis of OS based on the GPS risk group status also showed a linear separation of the survival distributions across risk categories. The 1-year, 2-year, and 3-year OS rates were 95.1%, 93.3%, and 78.5%, respectively, in the low-risk group compared with 91.8%, 66.8%, and 35.1% in the high-risk group (Figure 2B). The OS rate was significantly lower in the high-risk group than the low-risk group ($p<0.001$). The OS rates were significantly lower in the high-risk group for both hepatocellular carcinoma ($p<0.001$) and colorectal cancer liver metastasis ($p=0.0375$; Figure S1A,B).

Regarding age, sex, cancer type, stage, PS, BMI, and CGA, the distributions of the patients in the high-risk and low-risk groups are shown in Figure 2C. The number of patients in the high-risk group was seven (16%) for 75–79 years old, 16 (40%) for 80–84 years old, and three (75%) for more than 85 years old, and 11 (20%) were male and 15 (45%) were female. Regarding cancer type and clinical stage, the number of patients in the high-risk group was eight (62%) for colorectal cancer liver metastasis and 18 (24%) for hepatocellular carcinoma, and one (8%) in cStage I, seven (13%) in cStage II, eight (89%) in cStage III, and 10 (40%) in cStage IV. The number of patients in the high-risk group with a particular PS were as follows: 18 (23%) in PS0, five (100%) in PS1, and three (75%) in PS2 or greater. Regarding BMI, five patients (29%) had BMI >25 kg/m^2, 17 (25%) 18.5–25 kg/m^2, and four (100%) BMI <18.5 kg/m^2, respectively. Using the cumulative CGA index, the patients in the high-risk group were categorized as follows: six patients (14%) robust, five patients (21%) pre-frail, and 15 patients (68%) frail.

Table 3 presents the results of the univariate and multivariate analyses of prognostic factors in OS. The univariate analysis of OS identified the following two unfavorable factors to be significant: PS (1 or 2) and GPS (≧30). The multivariate analysis revealed only one independent significant factor, high GPS ($p=0.002$). The cutoff of 30 for the GPS was applied to predict 3-year mortality with a sensitivity of 80% and a specificity of 61%. The positive predictive value was 67.8%, and the negative predictive value was 69.6% (Figure 2D). The area under the ROC curve was 0.71.

4 | DISCUSSION

Recently, the number of elderly patients with liver cancer has been increasing. As a result, surgeons have more of a chance to perform hepatectomy for elderly patients.[12,21,22] However, elderly patients are often considered to be at higher risk for postoperative complications of major surgery, such as hepatectomy, and satisfactory surgical outcomes could not be expected for some patients. However, no definitive criteria are known to determine whether surgeons should perform hepatectomy in elderly patients. Thus, our group has established the novel and useful geriatric prognostic scoring system for elderly cancer patients to predict the surgical outcomes

TABLE 2 Comparison of backgrounds of high-risk and low-risk patients.

	High-risk group (GPS ≧ 30) ($n=26$)	Low-risk group (GPS < 30) ($n=62$)	p-value
Age, years (75–79/80–84/≥85)	7/16/3	37/24/1	0.007
Sex (female/male)	15/11	18/44	0.012
Cancer type (colorectal cancer liver metastasis/hepatocellular carcinoma)	8/18	5/57	0.009
cStage (I/II/III/IV)	1/7/8/10	11/45/1/5	<0.001
PS (0/1/≥2)	18/5/3	61/0/1	<0.001
BMI (>25/18.5–25/<18.5)	5/17/4	12/50/0	0.002
CGA cumulative index (robust/pre-frail/frail)	6/5/15	36/19/7	<0.001
Child–Pugh (A/B)	26/0	56/6	0.012
$ICGR_{15}$ (%)	16.1 (3–38)	14.5 (6–24)	0.341
Tumor number (1/2/≥3)	16/6/4	58/2/2	0.002
Tumor size (≦2/>2 cm)	3/23	14/48	0.213
Type of hepatectomy (non-anatomical/segmentectomy/sectionectomy/hemihepatectomy)	14/8/2/2	27/15/14/6	0.333
Operation method (open/laparoscopic)	17/9	36/26	0.520
Operation time, min	244 (152–596)	253 (122–659)	0.333
Blood loss, mL	190 (5–8300)	265 (3–2550)	0.209
Hospital stay, days	17 (11–49)	17 (7–144)	0.350

Note: Values are given as number of patients or mean (range).

Abbreviations: BMI, body mass index; CGA, comprehensive geriatric assessment; $ICGR_{15}$, indocyanine green retention rate at 15 min; PS, performance status.

TABLE 3 Univariate and multivariate analysis of prognostic factors.

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (≦80/>80)	1.005	0.460–2.196	0.989			
Sex (male/female)	1.352	0.512–3.571	0.543			
Cancer type (colorectal cancer liver metastasis/hepatocellular carcinoma)	1.185	0.410–3.427	0.754			
cStage (II, III, IV/I)	1.597	0.717–3.558	0.252			
PS (1.2/0)	3.996	1.605–9.947	0.003	1.971	0.732–5.312	0.180
BMI (≦23/>23)	1.936	0.886–4.231	0.098			
CGA cumulative index (pre-frail or frail/robust)	1.534	0.711–3.309	0.275			
Tumor size (>3.8/≦3.7 cm)	1.272	0.595–2.720	0.534			
Tumor number (multiple/single)	1.717	0.648–4.546	0.277			
Child–Pugh (A/B)	2.123	0.288–15.644	0.460			
$ICGR_{15}$ (≧15/<15%)	1.459	0.670–3.178	0.339			
Operation type (non-anatomical/anatomical)	1.206	0.567–2.566	0.627			
Surgery type (laparoscopic/open)	1.931	0.907–4.113	0.088			
Operation time (≦253/>253 min)	1.503	0.697–3.240	0.298			
Blood loss (≦245/>245 mL)	1.622	0.753–3.498	0.217			
Hospital stay (≦17/>17 days)	1.050	0.493–2.235	0.900			
GPSS (≧30/<30)	4.412	2.053–9.480	<0.001	3.690	1.607–8.472	0.002

Abbreviations: BMI, body mass index; CGA, comprehensive geriatric assessment; CI, confidence interval; GPSS, Geriatric Prognostic Scoring System; HR, hazard ratio; $ICGR_{15}$, indocyanine green retention rate at 15 min; PS, performance status.

in gastrointestinal cancer.[13,19] Liver function influences survival in patients with liver malignancy,[23] but the geriatric prognostic scoring system does not include the elements of liver function. Therefore, we evaluated the usefulness of geriatric prognostic scoring system for survival prognosis in elderly patients with liver cancer.

The geriatric prognostic scoring system could divide the patient cohort into two groups using the cut-off of 30. The non-cancer mortality rates were significantly higher in the high-risk group than in the low-risk group. The high GPS indicated that the rate of death from non-cancerous causes, such as aspiration pneumonitis, was higher in elderly patients with liver cancer. This provides useful information for the surgeons in deciding on surgical treatment or alternative treatment for elderly patients with liver cancer. In univariate analyses, PS was identified as a significant factor in patients' prognosis. PS is the most commonly used method for assessing the operability of patients, but there have been many reports that PS alone is insufficient for a comprehensive assessment of operability, especially in older patients. The geriatric prognostic scoring system contains PS; thus, the geriatric prognostic scoring system would be more useful and predictive than PS alone regarding the prognosis of elderly patients. The previous reports showed that the cumulative CGA index is an important indicator of the prognosis in elderly patients with gastrointestinal cancer who undergo curative surgery.[14,24] However, our data demonstrated that the cumulative CGA index is not an independently significant factor for OS. We speculated that, as the CGA includes five evaluation items (MMSE, GDS, Barthel Index, VI, and IADL), it may not be sufficient for predicting the prognosis of elderly patients with liver cancer.

For the patients with liver cancer in all range of ages, the cancer-related factor and the liver function have been reported to predict postoperative prognosis in many studies.[25,26] However, in this report, no cancer-related factor was identified as independent predictors of postoperative prognosis in elderly patients aged ≥75 years. In this present study, non-cancer-related cause of postoperative death was frequently observed in high-risk group. Pneumonia and cardiovascular disorders were frequently observed. Kamiya et al. reported that postoperative pneumonia was frequently observed in the elderly patients who underwent curative surgery for gastric cancer and preoperative sarcopenia was associated with pneumonia.[27] Guan et al. also reported that cardiovascular disease-related death exceeded primary neoplasm death in older patients with several types of cancers.[28] It was speculated that the physical influence of hepatectomy might affect the atrophy of skeletal muscle and lead to respiratory complications such as pneumonia, and liver dysfunction such as liver cirrhosis might be related with cardiovascular disease in elderly patients. We suspected that this is the reason that tumor-related factors were not identified as prognostic factors in the present cohort.

For liver cancer, preoperative sarcopenia and frailty have been reported to predict prognosis in older patients.[29,30] Sarcopenia is characterized by an age-related decline of skeletal muscle plus low muscle strength and physical performance, and is one of the geriatric syndrome.[31] Frailty is defined as a biological syndrome of decreased reserve and resistance to stressors resulting from cumulative decline across multiple physiological systems.[32] In this study, the novel geriatric prognostic scoring system covered frailty because the frailty was judged by the CGA index. The American Association for the Study of Liver Diseases published the 2021 practice guidance for malnutrition, frailty, and sarcopenia in patients with cirrhosis.[33] In this guidance, malnutrition, cirrhosis-related complications, systemic inflammation, physiological inactivity, and environmental factors contribute to frailty and sarcopenia. In addition, frailty and sarcopenia could contribute to each other. For example, impaired muscle contractile function would accelerate loss of muscle mass. Based on this guidance, the geriatric prognostic scoring system would cover both frailty and sarcopenia.

In this study, the criteria of the patients' age was set as 75 years old. The indications for liver resection by the geriatric prognostic scoring system would be applicable for the elderly patients aged ≥75 years. We could raise the question, was this indication the same as those for younger patients or not? Tanaka et al. reported that the assessment of frailty in elderly patients aged ≥65 years could predict postoperative age-related events after hepatic resection.[10] Yamada et al. also reported that frailty indicated by clinical frailty scale score ≥4 in hepatocellular carcinoma patients >75 years old could estimate the prognosis.[29] These previous reports varied the division of elderly patients by age. Many oncology studies have used ≥70 years as the age for implementing geriatric assessment.[34] However, a recent study applied older age cutoffs (age ≥75 years) due to the aging of the population and the increase in average life expectancy.[5,35] The cutoff of age was various in the previous studies, but the assessment by the geriatric prognostic scoring system for patients aged under 75 years could provide helpful information for the surgeon before liver resection. However, the results of the assessment by the geriatric prognostic scoring system were not established in younger patients and the validation analysis of the geriatric prognostic scoring system for the patients aged from 70 to 75 years would be necessary in the further clinical study.

There are some limitations in the present study. This research was performed as a single-institutional clinical study and selection bias could not be avoided because our hospital is an academic center and some of the patients with several risk factors of postoperative complications such as severe diabetes, immunodeficiency, pulmonary or cardiovascular disorders had been introduced to perform the hepatectomy. However, the GPS had discriminative power to predict the postoperative survival. Further studies using larger cohorts at multiple centers might be needed to validate the utility of the geriatric prognostic scoring system for elderly patients with liver cancer.

In conclusion, the GPS may be an independent prognostic factor in elderly patients with primary liver cancer or metastatic liver cancer. The geriatric prognostic scoring system is useful in forecasting postoperative prognosis and may help surgeons determine treatment strategies for elderly patients with liver cancer.

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CONFLICT OF INTEREST STATEMENT

Yoshihiro Sakano, Takehiro Noda, Shogo Kobayashi, Hiroshi Akasaka, Kazuya Kato, Kazuki Sasaki, Yoshifumi Iwagami, Daisaku Yamada, Yoshito Tomimaru, Hidenori Takahashi, Tadafumi Asaoka, Junzo Shimizu, Hiromi Rakugi, Yuichiro Doki, and Hidetoshi Eguchi have no conflicts of interest or financial ties to disclose. Yuichiro Doki is an editorial board member of *AGS*.

ETHICS STATEMENT

Approval of the research protocol: This retrospective study was approved by the Institutional Review Board of Osaka University Hospital and each institution (No: 08226-10). The study was conducted in accordance with the Declaration of Helsinki and good clinical practice.

Informed consent: Written informed consent for research use of their clinicopathological data was obtained from all patients.

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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