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ORIGINAL ARTICLE

Slow Gait Speed Is a Risk Factor for Complications After Hepatic Resection

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Abstract

Purpose The aims of this study were to clarify the relationship of gait speed, hand grip strength, and skeletal muscle mass with complications after hepatic resection and to identify risk factors for complications in patients who underwent hepatic resection.

Methods We evaluated the risk factors for complications after hepatic resection in 154 consecutive patients. Preoperative factors included gait speed, hand grip strength, and skeletal muscle mass. The gait speed and hand grip strength of patients were measured by physical therapists, and skeletal muscle mass was measured by computed tomography. Multivariate logistic regression analyses using preoperative factors were performed to assess predictors of the development of complications after hepatic resection.

Results Thirty-three patients (21.4%) developed complications after hepatic resection. These patients had a significantly lower serum albumin level ($p = 0.015$), slower gait speed ($p = 0.007$), higher rate of hepatic resection ≥ 2 Couinaud segments ($p = 0.014$), and lower rate of laparoscopic hepatic resection ($p = 0.017$) than patients without complications. Multivariate analysis revealed that a gait speed ≤ 1.10 m/s and a serum albumin level of ≤ 4.0 g/dl were independent risk factors for complications after hepatic resection.

Conclusions Slow gait speed and low serum albumin level are significant risk factors for complications after hepatic resection. These data will be helpful for perioperative patient management.

Keywords Gait speed · Complication · Hepatic resection · Frailty

Introduction

Hepatic resection has been established as a safe and effective treatment for liver tumors, including hepatocellular carcinoma.[1–4] Although surgical techniques and preoperative and postoperative management have recently been improved, the relatively high complication rate associated with hepatic resection remains problematic.[5–7]

Frailty is defined as an excess vulnerability to stressors, with decreased physiological reserve and a predictor of surgical outcomes in older patients.[8] Frailty criteria are composed of five aged-associated domains as defined by the Fried scale: shrinking (weight loss), exhaustion, low physical activity, weakness (low hand grip strength), and slowness (slow gait speed).[9] A previous study reported a linkage relationship between frailty phenotypes including these five components, which caused a loss of skeletal muscle mass.[10] We previously reported that loss of skeletal muscle mass was a risk factor for survival after hepatic resection for treatment of hepatocellular carcinoma.[11,12] An association between slow gait speed and postoperative complications after colorectal or cardiac operations was recently reported.[13,14] Nevertheless, the relationship

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between slow gait speed and complications after hepatic resection has not been established. Therefore, we hypothesized that slow gait speed is associated with postoperative complications in patients who have undergone liver surgery.

The aims of this study were to investigate the association of gait speed, hand grip strength, and skeletal muscle mass with complications after hepatic resection and to identify preoperative risk factors for complications in patients who have undergone hepatic resection.

Materials and Methods

Patients

This study included 154 patients (95 with hepatocellular carcinoma, 38 with metastatic liver tumors, 8 with intrahepatic cholangiocarcinoma, 4 with extrahepatic bile duct cancer, and 9 with other primary liver disease) who were treated at the Department of Surgery and Science, Kyushu University Hospital, from July 2014 to February 2016. The study protocol was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the institutional review board (approval codes 26–84).

To assess the usual gait speed, patients were instructed to walk forward over a 10-m straight course at their usual speed. Assistance or the use of crutches or a walker was allowed. Hand grip strength was measured using a digital grip strength dynamometer. The grip strength was measured twice for each hand, and the highest value was used in the analysis. The degree of proportional skeletal muscle mass was measured from patient computed tomography (CT) scans. A transverse CT image at the third lumbar vertebra in the inferior direction was assessed on each scan.[15] Skeletal muscle was identified and quantified by Hounsfield unit (HU) thresholds of − 29 to + 150 (water is defined as 0 HU and air as 1000 HU). Multiple muscles were quantified, including the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal oblique abdominal muscles, and rectus abdominis.[16] CT measurements were calibrated with water and air at fixed intervals. Skeletal muscle mass was measured by manual outlining on CT images.

Surgical Procedures and Postoperative Outcomes

Patients were carefully selected for major hepatic resection based on volumetric analysis of the remnant liver to prevent postoperative liver failure.[5,7] The type of hepatic resection was determined according to the preoperative indocyanine green retention rate at 15 min (ICGR15).[17] Patients with an indocyanine green retention rate ≥ 30% at 15 min were selected for limited resection. Two thirds of nontumorous liver parenchyma could be removed if the ICGR15 was ≤ 10%, and less than a third of it could be resected if it was 10–19%; patients with an ICGR15 of 20–29% received single segmentectomy or less. Intraoperative ultrasonography was performed to mark the plane of transection. Parenchymal transection was performed using the Cavitron Ultrasonic Surgical Aspirator (CUSA) system, (Valleylab Inc., Boulder, CO, USA) and a monopolar dissecting sealer (TissueLink; Salient Surgical Technologies, Portsmouth, NH, USA) powered by a VIO system (VIO 300D; ERBE Elektromedizin, Tubingen, Germany). As for laparoscopic hepatic resection, the surface of the liver was divided using mainly bipolar scissors fitted with a silicone tube dripping saline to the tip, and the liver parenchyma was transected using bipolar scissors or a bipolar clamp (BiClamp; ERBE Elektromedizin).[18,19] Inflow vascular control was performed with the Pringle maneuver with 15 min of occlusion alternating with 5 min of reperfusion. A selective hepatic vein-clamping method was used whenever required. One or two closed-suction drainage tubes were usually placed at near the raw surface of the liver.

Postoperative management was performed as previously described.[6] Postoperative complications were categorized using the Clavien-Dindo classification.[20] In this study, morbidity at 30 days after hepatic resection was classified as grade ≥ 2. Mortality was defined as 90-day mortality.

Statistical Analysis

Continuous variables are presented as the median (range) and were compared using the Mann-Whitney *U* test. Categorical variables were reported as percentages (%) and compared using Fisher's exact test. A logistic regression analysis was performed to identify preoperative variables for complications after hepatic resection. Estimation of the cutoff values for predicting complications was performed by calculating the areas under the receiver operating characteristic (ROC) curves. The ROC curve is a plot of sensitivity versus 1-specificity for all possible cutoff values. The most commonly used index of accuracy is the area under the ROC curve (AUC), where values close to 1.0 indicate high diagnostic accuracy, and 0.5 indicates a test of no diagnostic value. The optimal cutoff values used were selected based on the sensitivity and specificity. The predictive accuracy of selected variables for complications was evaluated by an AUC derived from a ROC curve. The preoperative predictive model for complication was designed using preoperative variables significantly associated with complications after hepatic resection in logistic regression analysis.

A p value < 0.05 was considered statistically significant. Data are expressed as the median and range. All statistical analyses were performed using JMP software (SAS Institute Inc., NC, USA).

Results

Operative Information

In total, 129 patients (83.8%) underwent open hepatic resection, including 56 major hepatic resections (36.3%), and 25 (16.2%) patients underwent laparoscopic hepatic resection. Fourteen patients (9.1%) underwent simultaneous surgery. Of these 14 patients, 4 underwent extrahepatic bile duct resection and reconstruction, 2 underwent partial resection of the right diaphragm, 2 underwent partial gastrectomy, 2 underwent partial resection of the ileum, 1 underwent distal pancreatectomy, 1 underwent partial resection of the colon, 1 underwent right nephrectomy, and 1 underwent bilateral salpingo-oophorectomy.

Complications After Hepatic Resection

Complications after hepatic resections (30-day morbidity; grade ≥ 2 according to the Clavien-Dindo classification[20]) are summarized in Table 1. Fourteen patients (9.1%) developed grade 2 complications, 18 (11.7%) developed grade 3a complications, and 1 (0.6%) developed a grade 3b complication. In total, 33 patients (21.4%) developed complications after hepatic resection, and the 90-day mortality rate was 0.0%.

Table 1 Summary of complications (30-day morbidity; Clavien-Dindo grade ≥ 2) after hepatic resection

Grade	Complication	Number
2		14 (9.1%)
	Cholangitis	3
	Ascites	3
	Portal vein thrombus	2
	Ileus	2
	Pleural effusion	1
	Acute colitis	1
	Acute pneumoniae	1
	Acute renal dysfunction	1
3a		18 (11.7%)
	Bile leakage	7
	Wound infection	5
	Intraabdominal abscess	3
	Ascites	1
	Pleural effusion	1
	Gastrointestinal bleeding	1
3b		1 (0.6%)
	Intestinal ischemia	1

Univariate Risk Factor Analyses for Complications After Hepatic Resection

The clinical characteristics of patients with and without complications after hepatic resection are shown in Table 2. The presence of complications was significantly associated with a low serum albumin concentration ($p = 0.015$), slow gait speed ($p = 0.007$), high rate of hepatic resection ≥ 2 Couinaud segments ($p = 0.014$), and low rate of laparoscopic surgery ($p = 0.017$). The skeletal muscle mass was not significantly associated with complications. The handgrip strength tended to be low in female patients with complications after hepatic resection. Regarding postoperative factors, the presence of complications was significantly correlated with a long operation time ($p = 0.012$), high blood loss ($p = 0.002$), high resection volume ($p < 0.001$), high rate of blood transfusion ($p < 0.001$), and a long postoperative hospital stay ($p < 0.001$).

Multivariate Risk Factor Analyses for Complications After Hepatic Resection

The best cutoff values for the gait speed and serum albumin level for postoperative complications were determined using an ROC curve. For all patients, the median gait speed was 1.23 m/s (range 0.52–1.78 m/s). A gait speed ≤ 1.10 m/s (AUC = 0.659) and a serum albumin level of ≤ 4.0 g/dl (AUC = 0.637) were the best cutoff values for complications after hepatic resection, respectively. Table 3 shows the results of the multivariate analyses used to identify the preoperative factors that were significantly associated with complications after hepatic resection excluding laparoscopic surgery because of the low number of cases. The multivariate analysis revealed that a slow gait speed ($p = 0.003$) and low serum albumin level ($p = 0.025$) remained significant independent predictors of complications after hepatic resection.

Risk Factor Analyses for Complications After Hepatic Resection in Patients with a Gait Speed > 1.1 m/s and ≤ 1.1 m/s

The clinical characteristics of the patients with a gait speed > 1.1 m/s and ≤ 1.1 m/s after hepatic resection are shown in Table 4. Patients with a gait speed ≤ 1.1 m/s were significantly associated with high age ($p < 0.001$) and a low hand grip strength in females ($p = 0.004$). The hand grip strength tended to be low in male patients with a gait speed ≤ 1.1 m/s.

Discussion

This study examined the relationship between preoperative factors (including gait speed, hand grip strength, and skeletal muscle mass) and complications in patients who underwent

Table 2 Characteristics of patients who underwent hepatic resection

Variable	Without complication ($n = 121$)	With complication ($n = 33$)	p value
Age (years)	67 (33–87)	66 (51–91)	0.741
Sex, male/female	81/40	24/9	0.527
BMI (kg/m^2)	22.6 (16.0–31.8)	22.3 (17.3–38.0)	0.956
HBs-Ag positive	15 (12.3%)	3 (9.1%)	0.600
HCV-Ab positive	33 (27.2%)	6 (18.1%)	0.287
Diabetes mellitus	37 (30.5%)	10 (30.3%)	0.741
Child Pugh A/B	121/0	32/1	0.214
MELD score	7 (6–21)	7 (6–20)	0.105
Total bilirubin (mg/dl)	0.8 (0.3–1.9)	0.8 (0.3–2.1)	0.998
Albumin (g/dl)	4.1 (3.2–5.1)	3.9 (2.2–4.6)	0.015
Prothrombin time (%)	94 (71–135)	95 (71–121)	0.241
ICGR15 (%)	9.7 (0.7–36.9)	11.3 (2.3–26.7)	0.558
Total cholesterol (mg/dl)	175 (95–288)	161 (103–280)	0.238
White blood cell	5510 (2590–9560)	5020 (2570–12,720)	0.194
CRP (mg/dl)	0.08 (0.01–2.32)	0.09 (0.01–2.71)	0.143
Skeletal muscle mass (cm^2/m^2); male	49.2 (33.6–67.1)	48.6 (39.4–76.0)	0.939
Skeletal muscle mass (cm^2/m^2); female	39.6 (30.3–51.0)	42.2 (31.3–50.3)	0.856
Hand grip strength (kg); male	36.8 (19.3–46.0)	35.4 (23.2–54.0)	0.948
Hand grip strength (kg); female	21.2 (15.4–28.5)	20.2 (9.1–27.0)	0.093
Gait speed (m/s)	1.26 (0.47–1.78)	1.10 (0.52–1.44)	0.007
Repeat hepatic resection	37 (30.5%)	8 (38.0%)	0.478
Hepatic resection ≥ 2 Couinaud segments	38 (31.4%)	18 (54.5%)	0.014
Laparoscopic surgery	24 (19.8%)	1 (3.0%)	0.017
Operation time (min)	244 (89–571)	317 (117–691)	0.012
Blood loss (ml)	300 (4–2830)	509 (10–5391)	0.002
Blood transfusion	9 (7.4%)	11 (33.3%)	< 0.001
Resected specimen (g)	88.5 (1.5–2010)	218 (6–2755)	< 0.001
Postoperative hospital stay (day)	10 (4–23)	17 (8–65)	< 0.001
90-day mortality	0 (0%)	0 (0%)	–

Data are presented as n (%) or median (range)

BMI, body mass index; *HBs-Ag*, hepatitis B surface antigen; *HCV-Ab*, hepatitis C virus antibody; *MELD*, model for end-stage liver disease; *ICGR15*, indocyanine green retention rate at 15 min; *CRP,* C-reactive protein

hepatic resection. A slow gait speed (≤ 1.1 m/s) and a low serum albumin level (≤ 4.0 g/dl) were associated with a significantly increased occurrence of complications after hepatic resection. Many reports described the rates of and risk factors for postoperative complications in patients undergoing hepatic resection.[21,22] The current study suggests that slow gait speed may be a more powerful predictor of postoperative complications than skeletal muscle mass or hand grip strength.

Our previous study revealed that a loss of skeletal muscle mass was a risk factor for long-term outcomes in patients who had undergone hepatic resection for treatment of hepatocellular carcinoma; however, it was not a risk factor for

Table 3 Multivariate analyses of preoperative factors associated with postoperative complications in patients who underwent hepatic resection (logistic regression analysis)

Variable	Hazard ratio	95% CI	p value
Albumin ≤ 4.0 g/dl	2.62	1.12–6.47	0.025
Gait speed ≤ 1.1 m/s	3.44	1.50–8.05	0.003
Hepatic resection ≥ 2 Couinaud segments, yes	2.27	0.98–5.82	0.052

CI, confidence interval

Table 4 Variables of patients who underwent hepatic resection

Variable	Gait speed > 1.1 m/s ($n = 104$)	Gait speed ≤ 1.1 m/s ($n = 50$)	p value
Age (years)	66 (33–82)	74 (46–91)	< 0.001
Sex, male/female	76/28	29/21	0.060
BMI (kg/m^2)	22.5 (16.0–31.8)	22.4 (17.2–38.0)	0.975
HBs-Ag positive	13 (12.5%)	5 (10.0%)	0.651
HCV-Ab positive	25 (24.0%)	15 (28.0%)	0.280
Diabetes mellitus	34 (32.6%)	13 (26.0%)	0.398
Child Pugh A/B	103/1	50/0	0.486
MELD score	7 (6–20)	7 (6–21)	0.852
Total bilirubin (mg/dl)	0.8 (0.3–2.1)	0.75 (0.3–1.5)	0.404
Albumin (g/dl)	4.1 (3.2–5.1)	4.0 (2.2–4.9)	0.627
Prothrombin time (%)	94 (71–135)	93 (72–115)	0.405
ICGR15 (%)	10.0 (1.9–36.9)	9.8 (0.7–26.7)	0.687
Total cholesterol (mg/dl)	168 (111–284)	175 (95–288)	0.361
White blood cell	5360 (2570–10,060)	5665 (2770–12,720)	0.222
CRP (mg/dl)	0.09 (0.01–2.43)	0.08 (0.01–2.71)	0.809
Skeletal muscle mass (cm^2/m^2); male	49.0 (35.5–67.1)	50.0 (3.6–76.0)	0.698
Skeletal muscle mass (cm^2/m^2); female	38.0 (30.3–51.0)	41.0 (32.5–50.3)	0.225
Hand grip strength (kg); male	36.9 (25.2–57.8)	33.2 (19.3–54.0)	0.061
Hand grip strength (kg); female	21.8 (11.0–28.5)	19.6 (9.1–26.8)	0.004
Repeat hepatic resection	26 (25.0%)	19 (38.0%)	0.096
Hepatic resection ≥ 2 Couinaud segments	36 (34.6%)	20 (40.0%)	0.515
Laparoscopic surgery	18 (17.3%)	7 (14.0%)	0.602
Operation time (min)	250 (89–691)	259 (95–522)	0.929
Blood loss (ml)	340 (5–2900)	380 (4–5391)	0.772
Blood transfusion	13 (12.5%)	7 (14.0%)	0.795
Resected specimen (g)	102.5 (1.5–2755)	151 (2–1302)	0.506
Complication	15 (14.4%)	18 (36.0%)	0.002
Postoperative hospital stay (day)	10 (5–65)	11 (4–63)	0.027
90-day mortality	0 (0%)	0 (0%)	–

Data are presented as n (%) or median (range)

BMI, body mass index; *HBs-Ag*, hepatitis B surface antigen; *HCV-Ab*, hepatitis C virus antibody; *MELD*, model for end-stage liver disease; *ICGR15*, indocyanine green retention rate at 15 min; *CRP*, C-reactive protein

postoperative complications.[11] In the present study, we found no association between skeletal muscle mass and complications in patients who underwent hepatic resection, as described in previous reports.

A simple gait speed test can be used to identify physical frailty.[23] In older adults, a slower walking speed is closely related to decreased survival, poorer health, and reduced function.[24] Robinson et al.[14] reported that a timed up and go score (which is similar to the gait speed) of ≥ 15 s was associated with a significantly increased occurrence of one or more postoperative complications, 30-day readmission, the need for discharge to an institutional care facility, and 1-year mortality in patients who underwent cardiac or colorectal operations. Alfredsson et al.[25] reported that gait speed was independently associated with 30-day mortality and long hospital stays after transcatheter aortic valve replacement in a large cohort of patients with severe aortic stenosis. These findings support the use of the gait speed test for patients who are referred for hepatic resection, given that gait speed adds easy-to-obtain functional information beyond that reflected in established risk scores. This is the first report to show that a slow gait speed in patients considering hepatic resection is a risk for complications after hepatic resection.

Hand grip strength is a good predictor of immune system function, nutrition, aging, bone density, and overall body strength, especially in older patients.[26] Sato et al.[27] recently reported that low hand grip strength, but not low skeletal muscle mass, was a risk factor for morbidity following gastric

cancer surgery. In the present study, we found no significant association between hand grip strength and complications after hepatic resection. In female patients, however, this relationship was marginal. Only 49 female patients were included in this study. Therefore, further studies with higher numbers of female patients are required to determine whether a low handgrip strength is related to complications following hepatic resection.

Previous meta-analyses showed that laparoscopic hepatic resection was associated with less blood loss, less overall and liver-specific complications, and a shorter postoperative hospital stay compared with open hepatic resection.[28] In the current study, we observed a significant association between laparoscopic liver resection and complications. However, during the study period, laparoscopic liver resection was still mostly performed for easily accessible lesions; therefore, only 25 patients (16.2%) underwent laparoscopic liver resection. Further studies with higher numbers of patients are required to clarify whether gait speed is related to complications following laparoscopic hepatic resection.

Several limitations of the current study must be acknowledged. We included a relatively small number of patients that had a diverse range of diseases. The findings are not directly generalizable to other settings because this was a single-center study. The cutoff gait speed of 1.1 m/s is also not directly generalizable to other settings. Because no previous study has assessed the implications of gait speed in liver surgery and the Japanese population, we statistically established our optimal cutoff value.

Despite these limitations, this is the first study, to the best of our knowledge, to investigate the relationship between frailty assessment factors (gait speed and hand grip strength) and complications in patients who undergone hepatic resection. Our findings demonstrated that liver surgeons should take special care for patients with a slow gait speed and a low serum albumin level to reduce the risk of complications after liver resection. These patients would need to undergo prehabilitation or preoperative exercise and preoperative nutritional support. Further studies with a greater number of patients are required to confirm the results of the present study.

In conclusion, a slow gait speed and a low serum albumin level were independently associated with complications in patients who have undergone liver resection. Although these factors must be validated in a larger cohort, our results will be helpful for perioperative patient management.

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Author Contributions S.I. participated in study conception and design, analysis, and drafting of the article.

T.Y. participated in study conception and design, and critical revision of the manuscript.

K.S. participated in acquisition of data, analysis, and interpretation of data.

T.M. participated in acquisition of data, analysis, and interpretation of data.

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N.H. participated in acquisition of data, analysis, and interpretation of data.

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