Impact of muscle volume and muscle function decline in patients undergoing surgical resection for hepatocellular carcinoma

Atsushi Hiraoka,* Yasuhiro Otsuka,† Hideki Kawasaki,‡ Hirofumi Izumoto,* Hidetaro Ueki,* Shogo Kitahata,* Toshihiko Aibiki,* Tomonari Okudaira,* Hiroka Yamago,* Yuji Miyamoto,* Ryuichiro Iwasaki,* Hideomi Tomida,* Kenichiro Mori,* Hideki Miyata,* Eiji Tsubouchi,* Masatoshi Hirooka,* Masanori Abe,* Tomonari Okudaira,* Hiroka Yamago,* Yuji Miyamoto,* Ryuichiro Iwasaki,* Hideomi Tomida,* Atsushi Hiraoka,* Yasuhiro Otsuka,† Izumi Mori,‡ Hirofumi Izumoto,* Hidetaro Ueki,* Shogo Kitahata,* Toshihiko Aibiki,* Tomonari Okudaira,* Hiroka Yamago,* Yuji Miyamoto,* Ryuichiro Iwasaki,* Hideomi Tomida,* Kenichiro Mori,* Hideki Miyata,* Eiji Tsubouchi,* Masatoshi Hirooka,* Masanori Abe,* Tomonari Okudaira,* Hiroka Yamago,* Yuji Miyamoto,* Ryuichiro Iwasaki,* Hideomi Tomida,* Bunzo Matsuura,§ Tomoyuki Ninomiya,* Izumi Mori,† Yoichi Hiasa§ and Kojiro Michitaka*†

Gastroenterology Center,†Department of Laboratory,‡Department of Surgery, Ehime Prefectural Central Hospital, Matsuyama, and§Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Toon, Japan

Key words
hepatocellular carcinoma, muscle function, muscle volume loss, peak expiratory flow rate, prognosis, sarcopenia.

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Correspondence
Dr Atsushi Hiraoka, Gastroenterology Center, Ehime Prefectural Central Hospital, 83 Kasugacho, Matsuyama, Ehime 790-0024, Japan.
Email: hirage@m.ehime-u.ac.jp

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Abstract

Background and Aim: This study investigated the prognostic impact of muscle volume loss (MVL) and muscle function decline in patients undergoing resection for hepatocellular carcinoma (HCC).

Methods: This study enrolled 171 naïve HCC patients treated with resection from 2007 to 2015, after excluding those lacking spirometry or computed tomography findings, who had received non-curative treatments, or with restrictive or obstructive lung disorders. The median peak expiratory flow rate (%PEF) was set as the cut-off value for muscle function decline, and MVL was diagnosed using a previously reported value. Clinical backgrounds and prognosis were retrospectively evaluated.

Results: Overall survival rate was lower in the MVL (n = 35) as compared with the non-MVL (n = 136) group (1/3/5-year overall survival rate = 88.2%/81.6%/55.6% vs 91.0%/81.5%/74.8%, respectively; P = 0.0083), while there were no differences regarding hepatic function or tumor burden between the groups. Child–Pugh class B (hazard ratio [HR] 3.510, 95% confidence interval [CI]: 1.558–7.926, P = 0.0025), beyond Milan criteria (HR 1.866, 95%CI: 1.024–3.403, P = 0.042), and presence of MVL (HR 1.896, 95%CI: 1.052–3.416, P = 0.033) were significant prognostic factors. The decreased %PEF group (n = 84) showed a higher rate of postoperative delirium than the others (n = 87) (27.4% vs 11.5%, P = 0.0088). The cut-off values for %PEF and age for postoperative delirium were 63.3% (area under receiver operating characteristic [AUROC] 0.697) and 73 years old (AUROC 0.734), respectively. Delirium was observed in 50.0% (14/28) of patients with both factors, 23.8% (15/63) of those with 1 factor, and 5.0% (4/80) of those without either factor.

Conclusion: Muscle volume loss is an independent prognostic factor in HCC patients treated with surgical resection, while advanced age and decreased muscle function might indicate high risk for postoperative delirium.

Introduction

Recently, muscle volume loss (MVL) and muscle function have been shown to be related to quality of life and survival in patients with chronic liver disease (CLD). In the criteria presented by the European Working Group on Sarcopenia in Older People (EWGSOP),1 Asian Working Group for Sarcopenia (AWGS),2 and Japan Society of Hepatology (JSH),3 sarcopenia has been reported as age-related muscle atrophy that appears in combination with MVL and/or physical performance condition in patients with CLD. Furthermore, sarcopenia diagnosed using those criteria is related to increased risk of physical limitations and/or mortality.4 Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death worldwide5 and often develops in patients with CLD. In patients with both liver cirrhosis and HCC, MVL has been reported to be an independent risk factor for death.6–10 However, there have been few investigations of the relationship of muscle function with prognosis of HCC patients treated with surgical resection. Here, we investigated the clinical impacts of MVL and muscle function decline on survival of patients with HCC who underwent a resection procedure.
Methods
From 2007 to 2015, 282 patients with naïve HCC were treated with surgical resection as the initial treatment at Ehime Prefectural Central Hospital. After exclusion of those lacking spirometry or computed tomography (CT) findings, who received non-curative treatments, with a restrictive lung disorder shown by an abnormal forced expiratory volume 1.0 s (1.0%) value of 70% or less, or with an obstructive lung disorder shown by percent vital capacity of 80% or less, 171 were enrolled. All were living independently without obvious symptoms of dementia. Clinical backgrounds and prognosis were evaluated in a retrospective manner.

Evaluations of muscle atrophy and function. We used previously reported cut-off values for MVL, which were calculated based on the psoas muscle area at the level of the middle of the third lumbar vertebra of the healthy cohort and height [psoas index: males = 4.24, females = 2.50 cm²/m²].11 Peak expiratory flow (PEF) was measured, and predicted PEF was automatically calculated with a CHESTAC-8800 (CHEST M.I., Inc., Tokyo, Japan) for each gender using age, height (cm), and body weight (kg). PEF rate (%PEF) was also calculated (PEF/predicted PEF) and used for evaluation of muscle function. All enrolled patients underwent CT and spirometry examinations within 1 month of undergoing surgical resection.

Patients were divided into those with (n = 35) and without (n = 136) MVL. In both groups, overall survival rate (OSR) and adverse events following surgical resection were analyzed. The median value for %PEF (74.4%) was set as the cut-off for decreased muscle function.

Diagnosis of hepatocellular carcinoma. Hepatocellular carcinoma was diagnosed based on an increasing course of alpha-fetoprotein (AFP), as well as dynamic CT,12 magnetic resonance imaging, contrast enhanced US with perflubutane (Sonazoid®, Daiichi Sankyo Co., Ltd. Tokyo, Japan),13 and/or pathological findings. Tumor node metastasis stage (TNM) was determined using criteria reported in studies for staging of HCC conducted by the Liver Cancer Study Group of Japan (LCSGJ, 6th edition).

All treatments were performed following the Japanese practical guidelines for HCC15,16 whenever possible after obtaining written informed consent from each patient.

Etiology of hepatocellular carcinoma. Patients positive for the hepatitis B virus surface antigen were judged to have HCC due to the presence of the hepatitis B virus, while those positive for the anti-hepatitis C virus were judged to have HCC due to hepatitis C virus.

Evaluation of delirium and infection. Postoperative delirium was diagnosed based on clinical records (e.g. disorientation, self-removal of drip infusion and/or drain tube, and complaint of auditory hallucinations) and scored using the Intensive Care Delirium Screening Checklist.17 Postoperative infection was defined as grade 2 or more according to the classification of surgical complications by Dindo.18

The study protocol was performed in compliance with the Helsinki Declaration and approved by the Institutional Ethics Committee of Ehime Prefectural Central Hospital (No. 29-2).

Statistical analysis. Statistical analyses were performed using the Kaplan–Meier method with a log–rank test, Pearson’s correlation test, Student’s t-test, Mann–Whitney’s test, or Fischer’s exact test, as appropriate. Statistical significance was defined as P < 0.05. Receiver operating characteristic (ROC), and area under ROC (AUROC) values were calculated for definition of cut-off values of postoperative delirium. Calculations were performed using EZR,19 a graphical user interface for R, version 1.29 (The R Foundation for Statistical Computing, Vienna, Austria).

Results
When we compared patients with and without MVL, there was a significant difference in regard to body mass index (21.9 ± 3.2 vs 24.2 ± 3.2 kg/m², P = 0.0001), while there were no significant differences for age, gender, etiology, platelet count, transaminase, total-bilirubin, albumin, prothrombin time, Fib-4 index,20 tumor size, tumor number, TNM, frequency of beyond Milan criteria (less than three tumors and 3 cm, or single tumor less than 5 cm),21 tumor markers [AFP, fucosylated-AFP (AFP-L3), protein induced by vitamin K absence or antagonist-II (PIVKA-II)], %PEF, frequency of postoperative delirium, frequency of infection, positive for diabetes mellitus, hospital period, and observation period (Table 1). OSR was lower in the MVL group (n = 35) as compared with the non-MVL group (n = 136) (1-, 3-, 5-year OSR: 88.2%, 81.6%, 55.6% vs 91.0%, 81.5%, 74.8%, respectively; P = 0.0083) (Fig. 1), whereas there were no significant differences between the groups when divided by median %PEF value into the decreased (n = 84) and non-decreased (n = 87) %PEF groups (1-, 3-, 5-year OSR: 90.1%, 81.1%, 72.7% vs 90.6%, 81.9%, 69.3%, respectively; P = 0.614) (Fig. 2). When additional analysis was performed after exclusion of patients with beyond Milan criteria, patients with MVL (n = 16) showed a lower OSR as compared with those without MVL (n = 76) (1-, 3-, 5-year OSR: 93.8%, 87.1%, 43.0% vs 94.6%, 85.6%, 79.5%, respectively; P = 0.0095), while there were no significant differences for age, gender, Child-Pugh classification, and TNM (data not shown). Although the percentage of patients with a postoperative infection and delirium were higher in those with than without MVL (11.4% vs 2.9%, and 28.6% vs. 16.9%), there were no significant differences in postoperative infection and delirium between those groups (P = 0.056 and P = 0.121, respectively).

Child-Pugh class B (hazard ratio [HR] 3.191, 95% confidence interval [CI]: 1.48–6.88, P = 0.003), beyond Milan criteria (HR 1.785, 95%CI: 1.034–3.069, P = 0.036), elevated PIVKA-II (≥ 100 mAU/mL; HR 1.784, 95%CI: 1.010–3.151, P = 0.046), and presence of MVL (HR 2.149, 95%CI: 1.201–3.844, P = 0.010) were significant prognostic factors for death shown in univariate Cox-hazard analysis. In multivariate Cox-hazard analysis, Child-Pugh class B (HR 3.510, 95%CI: 1.558–7.926, P = 0.0025), beyond Milan criteria (HR 1.866, 95%CI: 2018) 1271–1276
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Table 1  Patient characteristics

|                         | Total (n = 171) | With MVL (n = 35) | Without MVL (n = 136) | P value |
|-------------------------|-----------------|-------------------|-----------------------|---------|
| Age, years (SD)         | 70.4 (9.2)      | 72 (9.1)          | 69.9 (9.2)            | 0.238   |
| Gender, male:female     | 130:41          | 31:4              | 99:37                 | 0.052   |
| Performance status, 0:1:2:3 | 138:27:4:2      | 29:5:0:1          | 109:22:4:1            | 0.723   |
| Etiology of CLD, HCV:HBV:alcohol:others | 96:17:8:50     | 22:3:2:8          | 74:14:6:42            | 0.344   |
| BMI, kg/m² (SD)         | 23.8 (3.3)      | 21.9 (3.2)        | 24.3 (3.2)            | <0.001  |
| AST, IU/L (SD)          | 53.7 (39.3)     | 58.4 (66.1)       | 52.5 (33.9)           | 0.555   |
| ALT, IU/L (SD)          | 47.6 (39.5)     | 42.4 (28.2)       | 48.9 (33.9)           | 0.277   |
| Platelets, x10⁶ cells/μL (SD) | 14.6 (6.0)     | 15.2 (6.0)        | 14.4 (6.1)            | 0.508   |
| Fib-4 index (SD)        | 4.73 (3.6)      | 5.03 (4.54)       | 4.66 (3.36)           | 0.655   |
| Total-bilirubin, mg/dL (SD) | 0.78 (0.38)    | 0.68 (0.34)       | 0.80 (0.39)           | 0.064   |
| Albumin, g/dL (SD)      | 3.94 (0.51)     | 3.78 (0.52)       | 3.98 (0.50)           | 0.053   |
| Child-Pugh class, A:B   | 158:13          | 31:4              | 127:9                 | 0.342   |
| AFP, ng/mL (SD)         | 1962.8 (12192.7)| 5421.3 (25078.2)  | 1066.1 (4897.2)       | 0.314   |
| PIVKA-II, nAU/mL (SD)   | 3813.3 (12687.6)| 7594.5 (15855.6)  | 2839.3 (11608.6)      | 0.109   |
| Tumor size, cm (SD)     | 4.45 (2.77)     | 5.13 (3.50)       | 4.27 (2.53)           | 0.179   |
| %PEF, % (SD)            | 4.1 (0.9)       | 1.5 (1.0)         | 1.4 (0.9)             | 0.710   |
| Beyond Milan criteria at enrollment, % (n) | 54.4% (93) | 45.7% (16) | 56.6% (77) | 0.152 |
| TNM stage of HCC, I:II:III:IV† | 17:104:39:11 | 3:21:9 | 14:83:30:9 | 0.736 |
| %PEF, % (SD)            | 74.0 (15.5)     | 72.2 (16.6)       | 74.5 (15.2)           | 0.462   |
| Postoperative infection, % (n) | 4.1% (7) | 11.4% (4) | 2.9% (4) | 0.056 |
| Postoperative delirium, % (n) | 19.3% (33) | 28.6% (10) | 16.9% (23) | 0.121 |
| Hospital period, days (SD) | 17.4 (11.9) | 20.4 (17.4) | 16.6 (9.9) | 0.227 |
| Observation period, months (SD) | 52.5 (35.6) | 47.3 (31.0) | 53.8 (36.6) | 0.293 |

†Liver Cancer Study Group of Japan, 6th edition.

AFP, alpha-fetoprotein; AFP-L3, fucosylated AFP; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CLD, chronic liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MVL, muscle function loss; PIVKA-II, protein induced by vitamin K absence or antagonist-II; TNM, tumor node metastasis stage; TNM stage, tumor-node-metastasis stage; %PEF, rate of peak expiratory flow.

Figure 1  Overall survival rate (OSR) of patients with and without muscle volume loss. OSR was lower in the muscle volume loss (MVL) (n = 35) as compared with the non-MVL (n = 136) group (1-, 3-, 5-year OSR: 88.2%, 81.6%, 55.6% vs 91.0%, 81.5%, 74.8%, respectively; P = 0.0083). [Color figure can be viewed at wileyonlinelibrary.com]

Figure 2  Overall survival rate (OSR) of patients with and without muscle function decline. There were no significant differences for OSR between patients divided based on the median value for peak expiratory flow rate (%PEF) (74.4%) into the with (n = 84) and without (n = 87) %PEF decline groups (1-, 3-, 5-year OSR: 90.1%, 81.1%, 72.7% vs 90.6%, 81.9%, 69.3%, respectively; P = 0.614). [Color figure can be viewed at wileyonlinelibrary.com]
95%CI, 95% confidence interval; AFP, alpha-fetoprotein; AFP-L3, fucosylated AFP; BMI, body mass index; DM, diabetes mellitus; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; MVL, muscle volume loss; PIVKA-II, protein induced by vitamin K absence or antagonist-II; %PEF, rate of peak expiratory flow.

1.024–3.403, P = 0.042), and presence of MVL (HR 1.896, 95%CI: 1.052–3.416, P = 0.033) remained significant (Table 2).

Postoperative delirium was observed in 33 (19.3%) of the 171 patients. In a sub-analysis performed to compare between patients with and without %PEF decline, those with such a decline (n = 84) showed a higher rate of postoperative delirium than those without (n = 87) (27.4% vs 11.5%, P = 0.0088), while there were no differences in regard to frequency of postoperative infection (3.6% vs 5.7%, P = 0.720) (with %PEF decline: abscess in 2, cellulitis in 1; and without %PEF decline: abscess in 3, urinary tract infection in 1, aspiration pneumonia in 1), period of postoperative oxygenation (3.3 ± 2.4 vs 3.3 ± 5.6 days, P = 0.954), and hospital period (16.9 ± 10.8 vs 17.9 ± 12.9 days, P = 0.619). There were also no significant differences for liver function, number of tumors (data not shown), and Intensive Care Delirium Screening Checklist points (5.4 ± 1.3 vs 5.6 ± 1.6, P = 0.719), while the difference was significant for frequency of male gender (65.5% vs 86.2%, P = 0.002), between patients with and without %PEF decline. There was also a significant relationship found between age and %PEF (r = −0.321, 95% CI: −0.449−0.179, P < 0.0001). The cut-off values for %PEF and age of delirium after resection were 63.3% (AUROC 0.697, 95%CI: 0.591–0.802) and 73 years old (AUROC 0.734, 95% CI: 0.652–0.816), respectively. When patients had two positive factors (cut-off value for %PEF 63.3% or less, cut-off value for age 73 years or more), delirium was observed in 50.0% (14/28), while that was observed in 23.8% (15/63) of the patients with 1 factor and in only 5.0% (4/80) of those without any factors (Fig. 3).

**Table 2** Cox-hazard analysis for prognostic factors for death

|                  | Univariate | Multivariate |
|------------------|------------|--------------|
|                  | HR         | 95%CI        | P value | HR        | 95%CI        | P value |
| Age (≥ 65 years) | 1.146      | 0.622–2.112  | 0.661   | —         | —            | —       |
| Gender (female)  | 0.623      | 0.304–1.277  | 0.817   | —         | —            | —       |
| BMI (≥ 25 kg/m²) | 0.799      | 0.439–1.455  | 0.463   | —         | —            | —       |
| Positive for HCV | 1.481      | 0.844–2.601  | 0.172   | —         | —            | —       |
| Platelet (≤ 10 × 10⁶ cells/µL) | 0.770      | 0.431–1.376  | 0.378   | —         | —            | —       |
| Child-Pugh classification B | 3.191      | 1.480–6.880  | 0.003   | 3.510     | 1.558–7.926  | 0.003   |
| Beyond Milan criteria | 1.785      | 1.034–3.069  | 0.036   | 1.866     | 1.024–3.403  | 0.042   |
| AFP (≥ 100 ng/mL) | 1.014      | 0.531–1.938  | 0.967   | —         | —            | —       |
| AFP-L3 (≥ 10%)   | 1.495      | 0.852–2.624  | 0.162   | —         | —            | —       |
| PIVKA-II (≥ 100 mAU/mL) | 1.784      | 1.010–3.151  | 0.046   | 1.355     | 0.741–2.480  | 0.324   |
| Positive for MVL | 2.149      | 1.201–3.844  | 0.010   | 1.896     | 1.052–3.416  | 0.033   |
| Positive for decline of %PEF (≤ 74.4%) | 0.870      | 0.506–1.498  | 0.614   | —         | —            | —       |
| Positive for DM   | 0.936      | 0.536–1.637  | 0.817   | —         | —            | —       |

**Figure 3** Distribution of postoperative delirium. When analysis was performed using two factors cut-off value for %PEF ≤ 63.3%; cut-off value for age ≥ 73 years), the rate for patients with postoperative delirium (black circle) was higher as the number of positive factors increased (2 factors = 50.0%, 1 factor = 23.8%, 0 factors = 5.0%). White circle indicates patients without postoperative delirium.

**Discussion**

It is well known that HCC occurs in patients with CLD. Surgical resection and radiofrequency ablation have been developed as curative treatments for HCC, which has improved the prognosis of affected patients. In addition, transcatheter arterial chemoembolization and oral multikinase inhibitors (sorafenib and regorafenib) given as palliative therapy have prolonged the survival of patients with unresectable HCC. Nevertheless, patient prognosis is also dependent on hepatic function and tumor burden.

European Working Group on Sarcopenia in Older People, AWGS, and JSH have defined sarcopenia as MVL coexisting with muscle strength decline. In patients with CLD, sarcopenia, MVL, and muscle strength decline are not rare, even in an early stage. In addition, MVL has recently been reported as a prognostic factor for survival in HCC patients treated with liver transplantation, surgical resection, or sorafenib, although few reports have elucidated the relationship between muscle function and prognosis of HCC patients following surgical resection. Although the difference was not statistically significant, the rate of postoperative infection was higher in patients with...
MVL than in those without that in the present study (11.4% vs 2.9%, \(P = 0.056\)), and our results also showed that MVL is an independent risk factor for death in HCC patients treated with resection. On the other hand, decreased muscle function of respiratory muscles (%PEF decline) was not a risk factor for death but rather for postoperative delirium. In a previous report, handgrip strength was reported to be a strong predictor of all-cause and cardiovascular mortality.\(^\text{33}\) Handgrip strength is also noted in the definition of sarcopenia provided by EWGSOP,\(^\text{1}\) AWGS,\(^\text{2}\) and JSH.\(^\text{3}\) Unfortunately, we were unable to obtain data for handgrip strength as an evaluation of muscle function in the present patients. Additional analyses of the relationship between muscle function and prognosis in HCC patients using %PEF, handgrip strength, and walking speed are needed.

Peak expiratory flow is determined based on the strength of respiratory muscles in patients without disorders\(^\text{1}\); thus, we used %PEF, calculated by PEF/predicted PEF, for evaluation of muscle function decline in each of the present patients. It has been reported that sarcopenia has a relationship with cognitive decline,\(^\text{34}\) and it is feasible that high age is a risk factor for incidence of postoperative delirium.\(^\text{35}\) Although activities of daily living were maintained in the enrolled patients, respiratory function (%PEF) decline is thought to be another risk factor. In our study, we investigated postoperative delirium using only age and %PEF, and patients positive for both factors (cut-off value for %PEF \(\leq 63.3\%\) [AUROC 0.697]; cut-off value for age, \(\geq 73\) years old [AUROC 0.734]) were considered to be in the high-risk group for postoperative delirium.

In a previous meta-analysis, the incidence of postoperative delirium was 36.8% (range 0% to 73.5%), with decreased incidence noted in patients who underwent preoperative psychiatric counseling or participated in a structured perioperative program.\(^\text{38}\) In the present study, 19.3% of the patients experienced postoperative delirium. Although the specificity of detection of delirium by attending nurses is high, their sensitivity for detection is lower than that of a specialized researcher\(^\text{39}\); thus, slight changes in cognitive disorder may not have been evaluated in a detailed manner. Patients considered to be at high risk for postoperative delirium should be interviewed preoperatively by a psychiatric counselor or participate in a structured perioperative program. On the other hand, prevention of progression of MVL and muscle function decline is important in the early stages of CLD. A few reports for intervention with nutritional guidance and exercise for improvement of muscle strength or prevention of decline and MVL have been reported.\(^\text{40–42}\) To improve the prognosis and quality of life in CLD patients with and without HCC, establishment of nutritional and exercise programs is needed.

This study has some limitations, including its retrospective nature. Although a relationship between reduced muscle function (handgrip strength) and cognitive function has been reported with use of the Mini Mental State Examination (MMSE) tool,\(^\text{43}\) we did not perform preoperative cognitive function assessment with the MMSE in the present study. A future analysis of the relationship between %PEF and MMSE is needed. In addition, an additional investigation is needed to confirm whether %PEF can be used as an evaluation method for muscle function instead of handgrip strength or walking speed. Also, a prospective study with a larger cohort treated at multiple institutions is necessary.

In conclusion, MVL was found to be an independent prognostic factor in HCC patients treated with surgical resection. Furthermore, older patients with decreased muscle function might be at high risk for postoperative delirium as a complication.

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