Efficacy and Safety of Deep Sedation in Percutaneous Radiofrequency Ablation for Hepatocellular Carcinoma

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Abstract

Introduction: Radiofrequency ablation (RFA) has been accepted as safe and effective for treating early-stage hepatocellular carcinoma (HCC). However, it often causes severe pain. Therefore, in this study, we performed RFA under deep sedation and investigated its efficacy and safety.

Methods: We conducted a retrospective study including 511 HCC patients who received approximately 886 RFA treatments between December 2014 and November 2016 at our institution. Respiratory depression was defined as oxygen saturation of <90%; and severe body movement was defined as movement caused by pain, which was managed by lowering the power of the generator. Factors associated with respiratory depression and severe body movement were examined via univariate and multivariate regression analyses.

Results: Respiratory depression occurred in 15.3% of the patients and severe body movement in 26.5% of the patients. In the multivariate analysis, BMI (≥25 kg/m^2, odds ratio [OR] = 1.75, P = 0.035) and longer ablation (≥10 min, OR = 2.59, P = 0.002) were significant respiratory depression-related factors. Male sex (OR = 2.02, P = 0.005), Child-Pugh class A (odds ratio = 1.96, P = 0.018), and longer ablation (≥10 min, OR = 3.03, P < 0.001) were significant factors related to severe body movement.

Conclusion: Deep sedation for RFA can be performed safely and effectively. Higher BMI and longer ablation were risk factors for respiratory depression and male sex, Child-Pugh class A, and longer ablation were independent predictors of severe body movement during RFA under deep sedation.

Keywords: Deep sedation; Hepatocellular carcinoma; Percutaneous radiofrequency ablation; Respiratory depression; Severe body movement

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignant neoplasm in the world [1]. Percutaneous radiofrequency ablation (RFA) is a radical treatment for HCC and is a safe procedure; it is less invasive than surgical resection and can shorten hospitalization time. Moreover, several investigators have reported that RFA has reliable antitumor efficacy, a low morbidity rate, and promising long-term results [2-8]. RFA uses a high-frequency alternating current that disrupts solid tumor tissue [8]. The radio frequency energy produced from the exposed tip of the electrode is converted into heat. Substantial heat is carried homogeneously in all directions. RFA results in local inflammation. It releases neo-tumor associated antigens (neo-TAAs) and influences the immune response. Neo-TAAs are drained to secondary lymphoid organs, such as the lymph nodes and spleen, through afferent lymphatic vessels, where they prime immature dendritic cells to present antigen to and activate T cells. Overall survival (OS) is significantly influenced by the liver function, defined as Child-Pugh class, high baseline serum alpha fetoprotein level, and the existence of portosystemic collaterals. OS is not defined by long-term potentiation, because new circulating biomarkers are urgently needed as non-invasive tools to monitor response to treatment and to identify HCC recurrence after RFA treatment [9]. Thus, RFA is considered one of the best treatments for early-stage HCC.

Patients who undergo RFA often complain of severe pain during the procedure, and body movement associated with severe pain becomes problematic for interventional radiologists. Many other studies

for conventional conscious sedation for RFA have demonstrated that intraprocedural pain occurs often [10-12]. Hence, the demand for deep sedation during RFA has increased.

However, there is no consensus on the best technique of sedation during RFA. The drugs most widely used for endoscopic sedation are benzodiazepines and analgesics [13]. Thus, we performed RFA under deep sedation using these drugs to reduce pain. Deep sedation is usually accompanied by a high incidence of cardiovascular and respiratory depression. The dose of sedative drugs is often increased to suppress body movements, leading to over-sedation, potentially causing respiratory depression during RFA.

To the best of our knowledge, no study has determined the safety of deep sedation for RFA. The aim of our retrospective study was to investigate the efficacy and safety of deep sedation for RFA. In addition, we assessed the independent factors that affect respiratory depression and severe body movement during the procedure.

Methods

Patients

Between December 2014 and November 2016, we performed 886 RFA treatments for 511 consecutive patients with HCC under deep sedation at our institution, which is a tertiary referral hospital. Of these patients, 22 were excluded owing to lack of data; the remaining 489 patients were

included in the study (Figure 1). The clinical data of each patient who underwent RFA in our department were stored in a prospectively designed and maintained database to evaluate the efficacy and safety of RFA treatment. Patients were identified using electronic medical records and the RFA database. We evaluated patient characteristics, including demographics such as age and sex, body mass index (kg/m^2), HCC etiology, Child-Pugh classification, tumor size, tumor number, and total duration of ablation. Anesthesia records were accessed to record the total midazolam and pentazocine doses (mg). Sedation-related adverse events for all patients were recorded electronically by one investigator. This study was conducted according to the ethical guidelines of the Declaration of Helsinki and approved by Hospital Ethics Committee Juntendo University Hospital (No.:17-303), and the requirement for written informed consent was waived.

HCC diagnosis

We diagnosed HCC according to the American Association for the Study of Liver Diseases (AASLD) guidelines [14]. Based on these guidelines, we confirmed HCC diagnosis upon observing early enhancement in the arterial phase and wash out in the portal phase or delay phase using computed tomography (CT) or magnetic resonance imaging (MRI). In the absence of such typical findings, we performed a liver biopsy to confirm the diagnosis pathologically.

Anesthetic management

Patients received supplemental oxygen (2 L/min) via a nasal cannula during the RFA procedure as their vital signs and oxygen saturation were continuously monitored every 5 min using a standard 3-lead electrocardiogram, pulse oximetry, and automatic blood pressure equipment. Before the procedure, 2 mg midazolam, 30 mg pentazocine, 25 mg hydroxyzine for anti-emetic use, and 0.5mg atropine for prevention of the vasovagal reflex were administered intravenously. A bolus of 1 mg midazolam was added when the patient was not sedated sufficiently, and a bolus of 15 mg pentazocine was added if the patient showed signs of discomfort, restlessness, or agitation that were related to intraprocedural pain. Approximately 5-10 mL of 2% lidocaine was provided via a percutaneous injection along a specified insertion route from the skin to the liver capsule. In the procedure room, there was a nurse and three gastroenterologists. Sedation was administered by a dedicated gastroenterologist who was responsible for monitoring the patient, managing any sedation-related adverse events, and data recording. The Modified Observer's Assessment of Alertness and Sedation (MOAA/S) scale is a subjective sedation assessment scale used as a standard for the measurement of sedation levels. The independent investigator assessed the depth of sedation using the MOAA/S score, which ranges from 0 to 6 (0 = does not respond to deep stimulus, 1 = does not respond to mild prodding or shaking, 2 = responds only after mild prodding or shaking, 3 = responds only after name is called loudly and/or repeatedly, 4 = lethargic response to name spoken in normal tone, 5 = responds readily to name spoken in normal tone (alert), and 6 = agitated) [13]. Deep sedation was defined as 0-1 point on the MOAA/S scale. At least one physician with advanced

training in basic and cardiac life support was present during each procedure, and the resuscitation equipment was always available in the treatment room.

Treatment methods

Our RFA indications were as follows: total bilirubin <3 mg/dL, platelet count >50 × 10^3/mm^3, and prothrombin activity >50%. Patients with portal vein tumor thrombus, refractory ascites, or extrahepatic metastatic were excluded. In general, we performed RFA on patients with Child-Pugh class A or B, a single tumor ≤5 cm in diameter, or those with three or fewer tumors ≤3 cm in diameter. In other circumstances, however, we performed RFA on patients who were likely to benefit from this procedure as a possible cure or prolongation of life after treatment. The RFA technique has been described meticulously [2]. All RFA procedures were performed in the presence of three physicians. One physician inserted the electrode under ultrasound guidance while another assisted the procedure; at least one physician had 20 years of experience in RFA. The remaining physician was responsible for giving sedation and monitoring the patient. A 17-gauge cooled-tip electrode (Cool Tip, Medtronic, Minneapolis, MN) was inserted after the administration of sedatives and local anesthesia. Radio frequency energy was delivered for 3 to 12 min per application. Artificial pleural effusion [15] or artificial ascites [16] was performed for tumors in the hepatic dome or those adjacent to the gastrointestinal tract. One to three days after RFA, we performed enhanced CT to assess whether the targeted tumors were ablated completely. When CT showed possible residual tumor, we

performed additional RFA until we achieved adequate ablation.

Study endpoints

The primary endpoint was the efficacy of deep sedation, factors that influence respiratory depression, and severe body movement under deep sedation during RFA. In addition, the following secondary endpoints were assessed: sedation-related adverse events and RFA complications.

Outcome measurement and definitions

Efficacy was analyzed based on the proportion of complete procedures, the patient's level of consciousness, and the frequency of patients' complaint of pain during RFA. The success of sedation was defined in the cases where the patient did not complain of pain during the procedure, due to administration of the sedative drug or analgesic and the procedure was completed. Respiratory depression was defined as oxygen saturation of <90% and unresponsiveness to the jaw-thrust maneuver for 15 s. Severe body movement was defined as movement caused by pain, which was managed by lowering the power of the generator during RFA. Major complications were defined as those that, if left untreated, would be life-threatening to the patient, would lead to substantial morbidity and disability, or result in hospital admission or considerable long-term hospitalization according to the previously described guidelines [17]. All other complications were considered as minor. Sedation-related adverse events were defined as hypotension, bradycardia, and post-procedure

aspiration pneumonia. Hypotension was defined as a ≥20% reduction in baseline mean arterial pressure or a systolic arterial pressure of <90 mmHg. Bradycardia was defined as a 25% decrease in initial heart rate or a heart rate <50 beats per minute.

Statistical analyses

Parametric data are presented as means ± standard deviation and were analyzed using the Student's *t* test. Nonparametric data are presented as medians (ranges) and analyzed by the Mann-Whitney U test. Qualitative variables are expressed as frequencies and percentages, and proportions were compared using χ^2 tests with continuity correction or the Fisher's exact test, when appropriate. Statistical significance was considered as $P < 0.05$. Odds ratios and their 95% confidence intervals were calculated to assess the univariable associations between the potential risk factors and the occurrences of respiratory depression and severe body movement. Multivariate logistic regression analyses were performed to study the risk factors of interest. In the multivariate analysis for respiratory depression, age [18, 19], sex, BMI [20, 21], Child-Pugh class, total duration of ablation [20, 21], and total midazolam dose were considered for inclusion in the final model. In addition, age, sex, BMI, Child-Pugh class, and total duration of ablation [10, 12, 22] were included in the final model for severe body movement. We excluded tumor size and number because these factors were highly correlated with total duration of ablation. Among the 489 patients, if more than one treatment was administered, the first RFA was included in the regression analysis. Statistical analyses were

134 performed using JMP (version 12; SAS Institute Inc, Cary, NC).

135

136 **Results**

137 **Baseline characteristics of patients**

138 The baseline characteristics of the patients and their technical RFA details are shown in Table 1. The
139 mean age was 72.3 years ± 9.5 [standard deviation]; age range, 42-93 years. Patients were mostly male
140 (68.9%) and many of them were HCV positive. The mean tumor diameter was 19.4 ± 9.7 mm (range,
141 4-61 mm) and the mean tumor number was 1.7 ± 1.2 (range, 1-9).

142

143 **Clinical findings and therapeutic effects**

144 All patients exhibited depressed consciousness and did not complain of pain during RFA under deep
145 sedation. In addition, they completed the procedure using the proposed sedation scheme. The
146 therapeutic data and RFA complications are shown in Table 2. Four major complications and four
147 minor complications were observed. There were no deaths. Side effects such as moderate pain
148 controlled by analgesics, nausea, or fever unrelated to infection relieved by antipyretics, were not
149 included in these analyses. Regarding the major complications, intraperitoneal hemorrhage was
150 observed in one patient (0.2%). After transfusion, the patient sufficiently recovered under careful
151 observation. Hepatic abscess formation was found in one patient (0.2%) and antibiotics were
152 administered. Hemothorax occurred in one patient (0.2%) and percutaneous drainage was performed

without transfusion. Pneumothorax occurred in one patient (0.2%) and thoracic drainage was performed.

Use of sedation agents and adverse events of sedation

The use of sedatives during RFA and sedation-related adverse events are shown in Table 3. Hypotension occurred in five patients (1.0%) who were treated using a saline infusion; in two patients (0.4%), intravenous ephedrine was also administered. Bradycardia occurred in two patients (0.4%). The patients were treated using intravenous atropine. Aspiration was generally treated by increasing oxygen, after which antibiotic therapy was started. Post-procedure aspiration pneumonia occurred in one patient (0.2%). There were no life-threatening adverse events, including cardiorespiratory arrest and myocardial infarction.

Predictive factors of respiratory depression for RFA in patients under deep sedation

Respiratory depression occurred in 15.3% of the patients (75/489) and included those with unresponsiveness to the chin lift/jaw thrust maneuver, bag valve mask ventilation, and nasal airway. Only two patients (0.4%) required bag valve mask ventilation. There was no need for intubation in all 75 patients. Univariate analysis identified BMI (≥25 kg/m^2) (P = 0.049), tumor size (P = 0.035), and total ablation time (≥10 min) (P = 0.0018) as significant factors for respiratory depression during the procedure (Table 4). Multivariate analysis showed BMI (≥25 kg/m^2) (P = 0.035; OR, 1.75; 95% CI:

1.04-2.95) and total ablation time (≥10 min) (P = 0.002; OR, 2.59; 95% CI: 1.38-5.16) as significant factors of respiratory depression during the procedure (Table 4).

Predictive factors of severe body movement for RFA in patients under deep sedation

Severe body movement occurred in 26.5% of the patients (130/489). Univariate analysis identified male sex (P = 0.0024), Child-Pugh class B/C (P = 0.014), and total ablation time (≥10 min) (P < 0.001) as significant factors for severe body movement during the procedure (Table 5). Multivariate analysis also showed that male sex (P = 0.005; OR, 2.02; 95% CI: 1.24-3.36), Child-Pugh class B/C (P = 0.018; OR, 0.51; 95% CI: 0.27-0.89), and total ablation time (≥10 min) (P < 0.001; OR, 3.03; 95% CI: 1.85-5.16) were significant factors for severe body movement during the procedure as presented in Table 5.

Discussion

All patients underwent the complete RFA procedure under deep sedation and did not complain of pain during the procedure. Furthermore, none of the procedures in this study required delay or termination, and our dose calculations and sedation scheme were both safe and effective without any serious adverse events.

Image-guided percutaneous ablation is thought to be the best treatment for early-stage HCC. RFA is superior to ethanol injection, in terms of treatment response, cures for local tumors, and OS.

Microwave ablation can generate a larger ablation volume in a shorter time. More studies are required to confirm findings on irreversible electroporation, a non-thermal ablation method that uses short electric pulses to elicit apoptotic cell death [8]. RFA was related to a higher long-term OS rate than that associated with transcatheter arterial chemoembolization-treated patients with HCC [23]. There is still controversy about whether surgery or ablation is better for small HCC. Several meta-analyses have indicated that RFA and surgical resection are similar in terms of their impact on OS [9]. RFA can also be applied as a bridge to liver transplantation. RFA is possibly curative, minimally invasive, and readily repeatable for recurrence [8].

RFA is a complex procedure. Pain often occurs during RFA when a tumor in a subcapsular location that abuts the parietal peritoneum or a central tumor that is in contact with a large vessel is being treated [22]. Thus, a high level of patient collaboration is required to promote a meticulous intervention. Teratani et al. [24] demonstrated that 32.5% of 636 patients had at least one nodule in a high-risk location, defined as a location adjacent to a large vessel or an extrahepatic organ. Therefore, adequate patient sedation is indispensable for the procedure.

Sedation options include conscious sedation, deep sedation, and general anesthesia (GA). Conscious sedation is commonly administered using a benzodiazepine/analgesics combination and is employed in many endoscopic and intervening procedures. However, it is often inadequate for RFA. In previous studies, the total percentage of patients under conscious sedation who reported the intensity of pain as severe during RFA were over 40% [10-12]. A prospective study of pain control to

compare intravenous (i.v.) one-shot delivery of fentanyl plus i.v. diazepam with continuous i.v. infusion of fentanyl plus i.v. diazepam in patients with HCC treated by RFA showed that the continuous infusion of fentanyl provided effective and safe analgesia. Furthermore, the median visual analogue scale (VAS) score was 4.0±1.8 in i.v. one-shot group and 3.4±1.9 in continuous i.v. infusion group; the difference was not statistically significant [11]. Another prospective study to compare the efficacy and safety of propofol and dexmedetomidine, which were given during RFA for hepatic neoplasm, showed that dexmedetomidine provided better respiratory strength and decreased opioid consumption when compared to propofol [25].

In Westernized countries, such as the United States and European nations, liver tumor ablation is performed under GA in many cases. A retrospective study showed that RFA under GA reduced the number of treatment sessions required to achieve complete tumor ablation of early HCC and shortened hospitalization time [26]. Another retrospective study assessed factors that affected the periprocedural anesthetic management and complication during and after RFA under GA or conscious sedation. The results showed that this procedure required good anesthetic support in the form of sedation-analgesia or full GA, and these anesthetics provided maximum patient comfort and technical success of the procedure [27]. However, there are some limitations with this sedation option. The time required for each procedure is often longer because the time required for patient preparation, induction of anesthesia, endotracheal intubation/extubation, and recovery are increased. In addition, RFA under GA may result in complications such as nausea and vomiting, sore throat,

229 cardiopulmonary dysfunction, and delay in normal mental function of the patient. Furthermore, GA
230 causes severe complications such as myocardial infarction, stroke, or malignant hyperthermia. Thus,
231 patients still require complicated examination and rigorous evaluation of the risk factors related to
232 GA before the procedure.

233 Deep sedation prevents the extension of the set-up time required for GA and does not require a
234 complicated preoperative examination. In addition, deep sedation can be carried out only by simple
235 examination at the time of admission and questionnaire in our country. Furthermore, deep sedation
236 provides a better procedure condition than conscious sedation. Yang et al. [21] demonstrated a 28%
237 incidence of transient hypoxia and hypotension in patients undergoing endoscopic retrograde
238 cholangiopancreatography (ERCP) under deep sedation. The present study showed that 15.3% of
239 patients had respiratory depression and transient hypotension. In addition, no fatal cardiopulmonary
240 events were observed. In a previous study, the major RFA complications rate ranged from 2.2 to
241 3.1% [22]. In comparison with this report, our complication rate was lower, at 1.2%. Overall, our
242 results suggested that adverse events occurred during several procedures under deep sedation, but
243 they were usually minor and rarely led to the discontinuation of the procedure or to major
244 complications. Even if tumors are in the hepatic dome or adjacent to the gastrointestinal tract, it is
245 possible to treat them by inserting an electrode during exhalation under free breathing, using
246 artificial pleural effusion or artificial ascites. Shiina et al demonstrated complete tumor ablation in
247 99.4% of 2982 treatments performed for the 1170 primary HCC patients [2].

Multivariate regression analysis of our 489 patients demonstrated that increasing BMI and a longer duration of ablation were independent predictors of respiratory depression during the procedure. Because patients with high BMI are obese, they may have a higher incidence of sleep apnea and a higher risk of developing respiratory depression. Many other studies have demonstrated that longer procedure duration was associated with adverse events, including respiratory depression in ERCP, under deep sedation [20, 21]. It can be estimated that longer procedures may increase the likelihood of respiratory depression, which might prolong a procedure. Our result was consistent with those of other studies, which evaluated the risk factors for airway complications in patients undergoing ERCP. Our study demonstrated that older age was not a risk factor for respiratory depression during RFA. One interpretation is that the elderly patients had a significantly lower consumption of the sedative than younger patients ($P < 0.001$). Old age is a controversial risk factor for hypoxemia. Adverse event rate was increased in some studies due to old age [28, 29], but age was not included as an independent risk factor in ours and another study [30]. This may be due to the differences in patient backgrounds, underlying diseases, the definition of hypoxemia, and statistical analyses.

On multivariate regression analysis, male sex, longer duration of ablation, and Child-Pugh class A were independent predictors of severe body movement during RFA. In some studies, patients who underwent a longer duration of ablation showed a higher level of intraprocedural pain [10, 12, 22, 31]. Consistent with this, we demonstrated that longer duration of ablation was relevant to severe body movement, which was a result of intraprocedural pain. Midazolam clearance was reduced in patients

with hepatic impairment [32]. Liver cirrhosis impairs protein synthesis, alters drug metabolites, and decreases hepatic blood flow. All of these factors may affect the pharmacokinetics of sedatives. A previous study has shown that pentazocine should be administered with caution in patients with severe hepatic impairment [33]. It can be presumed that body movement caused by severe pain was rarely observed when the patient's liver function was decreasing because the drug was more effective. In addition, severe body movement did not increase the frequency of complications. Even if severe body movement occurred during the RFA procedure, complete ablation was achieved in all patients.

Our report has several limitations. First, data were collected from a single, tertiary care referral center. Treatment outcomes may depend on the physicians' expertise and the institution's volume of care. This study was based on a retrospective single-center experience and our results might not reflect the results of other institutions where physicians have limited experience. To extrapolate the findings of this study to patients at other institutions, multicenter prospective studies would be needed. A second limitation is that we did not compare the outcomes of anesthesiologist-administered sedation and those of conscious sedation. However, it is not realistic to conduct a randomized controlled trial comparing deep sedation with conscious sedation because patients who underwent RFA under deep sedation several times would loathe the severe pain and may be unwilling to undergo the procedure under conscious sedation. Thus, prospective, randomized trials to evaluate clinical factors that are potentially estimative of post-RFA recurrence and pain control are needed in this field.

286

287 **Conclusions**

288 This is the first study that analyzed the efficacy and safety of deep sedation using midazolam and
289 pentazocine during RFA. In summary, deep sedation with midazolam and pentazocine for RFA was
290 safe and effective for patients with HCC. Deep sedation could be performed safely by a trained non-
291 anesthesiologist physician skilled in airway management, who could provide sedative anesthesia. It
292 was apparent that the incidence of sedation-related adverse events was lower when sedatives were
293 administered by trained anesthesia personnel. In addition, high BMI (≥25 kg/m^2) and longer duration
294 of ablation were risk factors for respiratory depression during RFA under deep sedation. Moreover,
295 male sex, Child-Pugh class A, and longer duration of ablation (≥10 min) were independent predictors
296 of severe body movement during the procedure.

297

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305

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309

310 **Compliance with Ethics Guidelines.** All procedures performed in studies involving human
311 participants were in accordance with the ethical standards of Hospital Ethics Committee Juntendo
312 University Hospital and with the 1964 Helsinki declaration and its later amendments or comparable
313 ethical standards. The requirement for written informed consent was waived.

314

315 **Data Availability.** The datasets generated during and/or analyzed during the current study are
316 available from the corresponding author on reasonable request.

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Table 1 Baseline characteristics of the 489 patients who underwent radiofrequency ablation for hepatocellular carcinoma

Variable	
Age, years, mean ± SD	72.3 ± 9.5
Male, n (%)	337 (68.9)
BMI, kg/m^2, mean ± SD	24.2 ± 3.8
Viral infection, n (%)	
HBs-Ag positive	42 (8.5)
Anti-HCV positive	293 (60.0)
Both positive	3 (0.6)
Both negative	154 (31.5)
Child-Pugh class, n (%)	
A	382 (78.1)
B	96 (19.6)
C	11 (2.3)
Tumor size, mm, mean ± SD	19.4 ± 9.7
Tumor number, mean ± SD	1.7 ± 1.2

SD, standard deviation; BMI, body mass index; HBs-Ag, hepatitis B serum antigen; Anti-HCV, anti-hepatitis C virus.

Table 2 Therapeutic data and complications of radiofrequency ablation

Total duration of ablation, min, mean ± SD	18.9 ± 15.5
Major complication, n (%)	
Liver abscess	1 (0.2%)
Hemoperitoneum	1 (0.2%)
Hemothorax	1 (0.2%)
Pneumothorax	1 (0.2%)
Minor complication, n (%)	
Skin burn	4 (0.8%)

SD, standard deviation.

Table 3 Use of sedation agents during the radiofrequency ablation

Sedation	
Pentazocine, mg, mean ± SD	56.8 ± 19.2
Midazolam, mg, mean ± SD	5.8 ± 3.2
Adverse events of sedation, n (%)	
Hypotension	5 (1.0%)
Bradycardia	2 (0.4%)
Post-procedure aspiration pneumonia	1 (0.2%)

SD, standard deviation.

Table 4 Univariate and multivariate analyses of factors that predict respiratory depression

Variable	Univariate		Multivariate	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age (≥70 years)	1.19 (0.71-2.01)	0.51	1.02 (0.58-1.80)	0.95
Male sex	0.67(0.40-1.13)	0.129	0.70 (0.41-1.20)	0.19
BMI (≥25 kg/m^2)	1.64 (0.99-2.70)	0.049	1.75 (1.04-2.95)	0.035
HBs-Ag positive	0.82 (0.36-1.66)	0.60		
Anti-HCV positive	0.78 (0.48-1.28)	0.33		
Both negative	1.51 (0.90-2.50)	0.12		
Child B/C	1.19 (0.64-2.11)	0.58	1.03 (0.54-1.88)	0.92
Tumor size (mm)	0.97 (0.95-0.99)	0.035		
Tumor number	1.09 (0.89-1.39)	0.43		
Total duration of ablation (≥10 min)	2.54 (1.39-4.97)	0.0018	2.59 (1.38-5.16)	0.002
Midazolam (mg)	1.49 (0.18-16.8)	0.73	1.04 (0.96-1.14)	0.31

CI, confidence interval; BMI, body mass index; HBs-Ag, hepatitis B serum antigen; Anti-HCV, anti-hepatitis C virus

Table 5 Univariate and multivariate analyses of factors that predict severe body movement

Variable	Univariate		Multivariate	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age (≥70 years)	0.89 (0.59-1.35)	0.59	0.91 (0.59-1.42)	0.82
Male sex	2.04 (1.28-3.33)	0.0024	2.02 (1.24-3.36)	0.005
BMI (≥25 kg/m^2)	1.47 (0.98-2.21)	0.06	1.43 (0.93-2.20)	0.1
HBs-Ag positive	1.08 (0.59-1.89)	0.79		
Anti-HCV positive	0.93 (0.63-1.40)	0.75		
Both negative	0.99 (0.64-1.53)	0.97		
Child B/C	0.51 (0.28-0.88)	0.014	0.51 (0.27-0.89)	0.018
Tumor size (mm)	3.12 (0.88-10.94)	0.078		
Tumor number	3.47 (0.98-12.03)	0.054		
Total duration of ablation (≥10 min)	2.77 (1.71-4.65)	< 0.001	3.03 (1.85-5.16)	< 0.001

CI, confidence interval; BMI, body mass index; HBs-Ag, hepatitis B serum antigen; Anti-HCV, anti-hepatitis C virus.

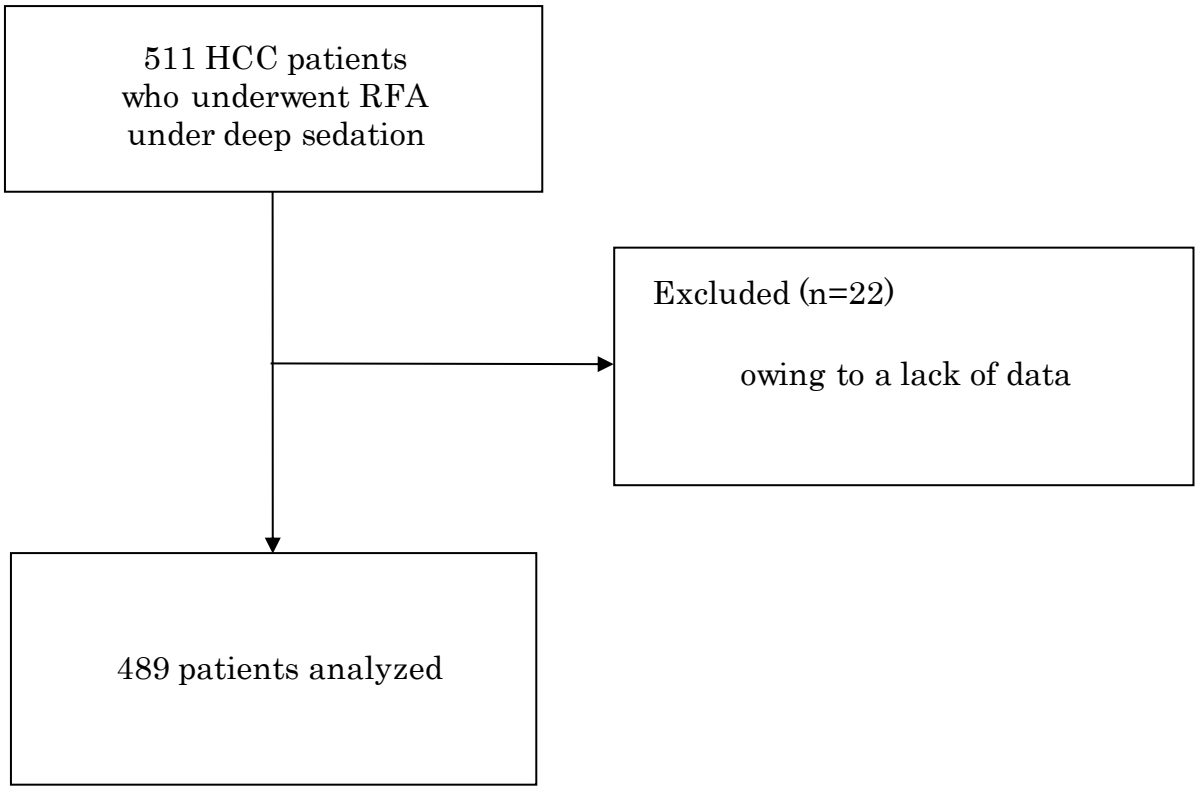

Figure 1. Flow diagram of the study.
HCC hepatocellular carcinoma; RFA radiofrequency ablation.