



Research article

Simultaneous multi-slice diffusion weighted imaging of hepatocellular carcinoma at 3.0 T: Comparison of breath-hold, free-breathing, and respiratory-triggered techniques

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ABSTRACT

Purpose: This study aimed to evaluate the performance of simultaneous multi-slice diffusion weighted imaging (SMS-DWI) using breath-hold (BH), free-breathing (FB), and respiratory-triggered (RT) breathing schemes in patients with hepatocellular carcinoma (HCC), focusing on image quality and apparent diffusion coefficient (ADC) repeatability.

Methods: This prospective study consecutively enrolled HCC patients between October 2020 and March 2023, based on specific inclusion and exclusion criteria. The patients underwent BH-SMS-DWI, FB-SMS-DWI and RT-SMS-DWI at b-values of 50, 400, and 800 s/mm². Image quality was assessed qualitatively using a 5-point Likert scale. Besides, signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR), and ADC values were quantitatively measured. To evaluate the ADC repeatability, SMS-DWI scans were performed twice for each breathing scheme. The intraclass correlation coefficient (ICC) and test-retest variability (TRV) were used for assessment.

Results: A total of 172 HCC patients with 189 HCC lesions were included for analysis. BH-SMS-DWI showed the shortest scan time but reduced image quality at high b-values (b = 800 s/mm²) compared to RT-SMS-DWI and FB-SMS-DWI. At b = 800 s/mm², BH-SMS-DWI exhibited significantly lower overall image quality (3.37 ± 0.67 , $P < 0.001$) compared to both RT-SMS-DWI (3.65 ± 0.69) and FB-SMS-DWI (3.63 ± 0.65), with no significant difference between them ($P > 0.990$). In addition, it also demonstrated inferior SNRs for both liver and tumor compared to RT-SMS-DWI (liver: 118.36 vs. 183.08, $P < 0.001$; tumor: 247.41 vs. 389.23, $P < 0.001$) and FB-SMS-DWI (liver: 118.36 vs. 161.52, $P < 0.001$; tumor: 247.41 vs. 323.48, $P < 0.001$). There were no significant differences in tumor ADC values across three breathing schemes. BH-SMS-DWI demonstrated the highest ADC repeatability (ICC: 0.86, 95% CI: 0.84–0.91; TRV: 9.17, 95% CI: 7.21–16.23), followed by FB-SMS-DWI (ICC: 0.83, 95% CI: 0.76–0.87; TRV: 14.27, 95% CI: 11.34–21.17), and RT-SMS-DWI (ICC: 0.80, 95% CI: 0.75–0.86; TRV: 14.36, 95% CI: 12.57–23.31).

Conclusion: FB-SMS-DWI is recommended as the most reliable and efficient option for clinical HCC imaging. BH-SMS-DWI, with superior ADC repeatability, is preferred for treatment monitoring and longitudinal follow-up in patients with sufficient breath-holding capability.

Abbreviations: ADC, apparent diffusion coefficient; BH, breath-hold; CI, confidence interval; CNR, contrast-to-noise ratio; DWI, diffusion weighted imaging; FB, free-breathing; HCC, hepatocellular carcinoma; ICC, intraclass correlation coefficient; NEX, number of excitations; RT, respiratory-triggered; SNR, signal-to-noise ratio; SMS, simultaneous multi-slice; TRV, test-retest variability.

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1. Introduction

Hepatocellular carcinoma (HCC) is the most prevalent pathological type of primary liver cancer, characterized by high morbidity and mortality rates worldwide [1]. Early detection and accurate characterization of HCC are crucial for improving prognosis, as the disease is often diagnosed at an advanced stage when treatment options are limited [1,2]. Diffusion weighted imaging (DWI), along with the apparent diffusion coefficient (ADC), plays a critical role in the detection, characterization and staging of HCC. Moreover, DWI is essential in monitoring treatment response and predicting outcomes in HCC patients, providing non-invasive insights into tumor biology and treatment efficacy [3–5].

In clinical practice, liver DWI is typically performed using breath-hold (BH), free-breathing (FB), or respiratory-triggered (RT) breathing schemes. The choice of breathing scheme significantly affects the image quality and the accuracy of ADC measurements, and each scheme comes with its own set of advantages and challenges [6]. For instance, BH-DWI could shorten scan time and minimize motion artifacts but may lead to a lower signal-to-noise ratio (SNR) and decreased spatial resolution, which could limit the detection of small lesions [7]. On the other hand, FB-DWI offers a more relaxed scanning process but is susceptible to blurring and image degradation caused by continuous respiratory motion [8]. Moreover, RT-DWI is able to address these issues by synchronizing the acquisition with the patient's respiratory cycle, but it often leads to unpredictable longer scan time [9]. The use of accelerated technique may optimize the acquisition process in this regard, and therefore improving image quality and ensuring the reliability of ADC measurements in liver DWI.

Simultaneous multi-slice (SMS) technique was proposed as an accelerated method to simultaneously excites and acquires multiple slices, allowing for acquisition time reduction or higher image resolution in DWI [10]. Recent studies found that SMS-DWI, especially with motion correction, showed superior image quality and clearer lesion delineation than tradition DWI in liver imaging [6,11,12]. Similarly, Xu et al. [13] demonstrated that SMS-DWI with an acceleration factor of 2 significantly reduced scan time while preserving image quality and maintaining comparable ADC values to conventional DWI. In addition, Pei et al. had applied SMS technique to three breathing schemes of liver DWI, including breath-hold (BH-SMS-DWI), free-breathing (FB-SMS-DWI) and respiratory-triggered (RT-SMS-DWI), and indicated the feasibility of hepatic SMS-DWI [6]. They compared SMS-DWI with conventional DWI in three breathing schemes, showing that BH-SMS-DWI can effectively shorten scan time with satisfactory image quality and ADC repeatability in volunteers. Despite these promising results, further research with larger sample sizes and specific patient populations, particularly HCC patients, is needed to determine the most effective breathing scheme of SMS-DWI in routine clinical practice.

Therefore, the aim of this study was to assess liver SMS-DWI with three breathing schemes in HCC patients, including BH-SMS-DWI, FB-SMS-DWI and RT-SMS-DWI, and explore the optimal breathing scheme by comparing the image quality and ADC repeatability.

2. Methods and materials

2.1. Study Participants

This prospective study was approved by the Institutional Review Board of our hospital, and written informed consent was obtained from all subjects. Patients with high-risk HCC were consecutively enrolled between October 2020 and March 2023. The inclusion criteria were as follows: (1) age ≥ 18 years; (2) suspected primary HCC by clinical history, prior imaging or laboratory tests; (3) without any liver disease-related treatment before the examination (such as radiofrequency ablation, transcatheter arterial chemoembolization, hepatectomy, radiotherapy, targeted therapy, etc.); (4) without any MRI

contraindications. Subjects were excluded if any of the following criteria applied: (1) suspicious liver lesions were confirmed as non-HCC by pathological confirmation or comprehensive diagnostic assessment; (2) incomplete MRI images.

2.2. Diagnostic criteria for HCC

This study used a composite diagnostic standard for HCC, incorporating both pathological examination and clinical diagnosis. For lesions lacking pathological results, the following clinical criteria were applied: For patients with hepatitis B or C, or liver cirrhosis of any etiology: (1) For liver lesions with a diameter ≤ 2 cm, a clinical diagnosis of HCC can be made if at least two of the following imaging modalities show typical features: multiparametric MRI, dynamic contrast-enhanced computed CT, contrast-enhanced ultrasound, or liver-specific contrast agent-enhanced MRI using Gd-EOB-DTPA. Typical features include significant enhancement during the arterial phase and reduced enhancement compared to liver tissue in the portal venous and/or equilibrium phases, indicating a “wash-in, wash-out” pattern. (2) For liver lesions with a diameter > 2 cm, a clinical diagnosis of HCC can be made if at least one typical feature is present in any of the above imaging tests.

2.3. MRI protocol

All examinations were performed on a 3.0 T MRI scanner (MAGNETOM Skyra, Siemens Healthcare, Germany) equipped with an 18-channel anterior body coil and the spine coil. All patients underwent axial SMS-DWI sequences with three different breathing schemes (BH, FB and RT) and routine clinical sequences. Three b-values of 50, 400, and 800 s/mm² were sampled in three orthogonal diffusion directions (three-scan trace). Detailed MRI protocol and acquisition parameters are provided in Table 1. RT-SMS-DWI is based on FB-SMS-DWI with the addition of respiratory triggering, while all other parameters remain the same. RT-SMS-DWI acquires images at the end of each expiration. Additionally, SMS-DWI scans were performed twice under each breathing schemes to evaluate the repeatability, yielding a total of six SMS-DWI scans in each participant. Patients completed multiple sets of breathing exercises under the guidance of experienced technicians. In specific, breath-hold sequence acquisition was performed at the end of exhalation. During free-breathing sequence acquisition, patients were instructed to breathe normally and evenly. During respiratory-triggered

Table 1
MRI acquisition parameters.

Parameters	BH-SMS-DWI	FB-SMS-DWI	RT-SMS-DWI
TR/TE (ms)	1100/63	2000/63	2000/63
FOV (mm ²)	400 × 288	400 × 288	400 × 288
Matrix	128 × 94	128 × 94	128 × 94
Slice thickness/gap (mm)	5/1.5	5/1.5	5/1.5
Number of slices	22	22	22
Bandwidth (Hz/pixel)	2442	2442	2442
Fat suppression	Fat Sat	Fat Sat	Fat Sat
Acceleration factor	GRAPPA 2 + SMS 2	GRAPPA 2 + SMS 2	GRAPPA 2 + SMS 2
b value (s/mm ²)	50, 400, 800	50, 400, 800	50, 400, 800
NEX	1, 2, 2	1, 2, 4	1, 2, 4
Acquisition time (s)	24	52	52*

Abbreviations: SMS = simultaneous multi-slice, DWI = diffusion weighted imaging, BH = breath-hold, FB = free-breathing, RT = respiratory-triggered, TE = echo time, TR = repetition time, FOV = field of view, GRAPPA = generalized autocalibration partially parallel acquisition, NEX = number of excitations.

* RT-SMS-DWI built upon FB-SMS-DWI by incorporating respiratory triggering, with all other scanning parameters remaining the same. Therefore, in theory, the acquisition times for both sequences should be identical. However, in practice, the patient's respiratory rhythm may influence the respiratory triggering, leading to a deviation between the actual acquisition time and the sequence's planned duration.

sequence acquisition, patients were instructed to breathe shallowly and evenly, while a respiratory pressure pad was used to monitor the breathing curve.

2.4. Image analysis

2.4.1. Qualitative image analysis

Two experienced-abdominal radiologists (M.Z. and Z.Y.) conducted a qualitative assessment of image quality for the first scan of BH-SMS-DWI, FB-SMS-DWI and RT-SMS-DWI (b value = 50, 400 and 800 s/mm²) in a randomized order. The images at each b value were assessed separately. They conducted the evaluation in a blinded manner, without any knowledge of the image groups, imaging parameters, or patient information. The image quality was assessed using a 5-point Likert scale from various aspects, including the overall image quality, clarity of intrahepatic vessel, sharpness of liver edge, conspicuity of left lobe, image artifact, and lesion conspicuity. The detailed scoring criteria are shown in Table 2.

2.4.2. Quantitative image analysis

In this study, the signal-to-noise ratio (SNR) of liver, the SNR of tumor and the contrast-to-noise ratio (CNR) between liver tissue and tumor were calculated based on the first scan of BH-SMS-DWI, FB-SMS-DWI and RT-SMS-DWI images (b value = 800 s/mm²). All quantitative measurements were independently performed by two observers (observer 1: T.Y., observer 2: H.L.), and the results from each were averaged to produce the final value for analysis. First, the images were adjusted to the section showing portal venous of the liver, with an effort to maintain consistency in the level. Three circular regions of interest (ROIs) were delineated in the right lobe of the liver of the same section, avoiding intrahepatic lesions, blood vessels, and artifacts. The mean value of the average signal intensity (SI) within three ROIs was recorded as the SI of liver. A circular ROI was placed in the air region on the same side, and the standard deviation (SD1) within the ROI was recorded as the background noise of this section.

In addition, the images were also adjusted to the slice showing the largest cross-section of the tumor, and placed a circular ROI at the center of the tumor, avoiding the areas of hemorrhage, necrosis and calcification. The mean SI within the ROI was recorded as the SI of tumor. Meanwhile, at the same slice, another circular ROI was placed on the normal liver tissue, recording its mean SI as the SI of contrast liver tissue. A circular ROI was placed in the air region on the same side, and the standard deviation (SD2) within the ROI was recorded as the background noise of this section. Subsequently, the SNRs and the CNR between liver tissue and tumor were calculated as follows:

$$\text{SNR}_{\text{liver}} = \frac{\text{SI}_{\text{liver}}}{\text{SD1}} \quad \text{SNR}_{\text{tumor}} = \frac{\text{SI}_{\text{tumor}}}{\text{SD2}}$$

$$\text{CNR} = \frac{|\text{SI}_{\text{contrast liver tissue}} - \text{SI}_{\text{tumor}}|}{\text{SD2}}$$

2.4.3. Repeatability analysis of ADC measurements

ADC parameter maps were generated using a mono-exponential model. This process included six sets of images, with twice scans con-

ducted under each of the three breathing schemes. In this study, the repeatability of tumor ADC measurements was assessed using the intraclass correlation coefficient (ICC), specifically the two-way random effects model [ICC(2,1)], along with test-retest variability (TRV), based on the six sets of ADC parameter maps [6,12]. Notably, TRV is an indicator to measure the variation in results for the same sample across multiple tests. High TRV indicates measurement instability, with a large difference between test results, while low TRV reflects high consistency, with a small difference between repeated tests. The SMS-DWI images (b value = 800 s/mm²) were adjusted to the slice displaying the largest cross-section of tumor, with an effort to maintain consistency in the level, placing a circular ROI at the center of the tumor and avoiding areas of hemorrhage, necrosis, and calcification within the tumor. Then, the ROIs were copied from the SMS-DWI images to ADC parameter maps, and the mean value within ROI was recorded as ADC value. Subsequently, the TRV of tumor for each breathing schemes was calculated as follow:

$$\text{TRV} = 2 \times \frac{|\text{ADC}_{\text{first}} - \text{ADC}_{\text{second}}|}{|\text{ADC}_{\text{first}} + \text{ADC}_{\text{second}}|} \times 100\%$$

2.5. Statistical analysis

The Kolmogorov-Smirnov test was used to assess the normality of all data in the study. The Friedman test and post hoc test with Bonferroni adjustment were conducted to compare SNR of liver, SNR of tumor, CNR between liver tissue and tumor, ADC values of tumor, TRV and qualitative scores between three different breathing schemes, respectively. The interobserver agreements for qualitative scores were assessed using κ statistics. The strength of agreement for the κ values was as follows: 0.2 or less, poor; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.00, almost perfect agreement.

The agreement of repeated ADC measurements was evaluated by calculating the ICC and its 95% confidence interval (CI). The ICC (2,1) was calculated using a two-way random effects model with absolute agreement for single measurements. The strength of agreement for the ICC values was as follows: An ICC below 0.50 indicated poor agreement, 0.50 to 0.75 indicated moderate agreement, 0.75 to 0.90 indicated good agreement, and an ICC greater than 0.90 indicated excellent agreement. A P value less than 0.05 indicated a statistically significant difference. Statistical analyses were conducted using SPSS software (version 27.0; IBM).

3. Results

3.1. Participant characteristics

This prospective study initially included 351 patients. After excluding 150 patients with non-HCC lesions and 29 patients without complete MRI, a final of 172 eligible patients with 189 HCC lesions were enrolled in the study for analysis. The patient population included 143 males and 29 females (mean age ± standard deviation, 62.85 ± 13.52 years), and 97 patients with pathologically confirmed HCC and 75 patients with clinically diagnosed HCC. Among these patients, 156

Table 2
Image quality assessment using the 5-point Likert scale.

Score	Overall image quality	Clarity of intrahepatic vessel	Sharpness of liver edge	Conspicuity of left lobe	Image artifact	Lesion conspicuity
1	Non-diagnostic	Non-diagnostic	Non-diagnostic	Non-diagnostic	Non-diagnostic	Non-diagnostic
2	Poor image quality	Poor clarity	Severe blurring	Barely conspicuous	Severe artifacts	Barely conspicuous
3	Moderate image quality	Moderate clarity	Moderate blurring	Moderately conspicuous	Moderate artifacts	Moderately conspicuous
4	Good image quality	Good clarity	Mild blurring	Well seen	Mild artifacts	Well seen
5	Excellent image quality	Excellent clarity	Sharp and no blurring	Very well and sharply defined	No artifacts	Very well and sharply defined

(90.70%) patients were diagnosed with chronic hepatitis B virus infection, and 131 (76.16%) patients had cirrhosis.

3.2. Image analysis

3.2.1. Qualitative image analysis

Fig. 1 presents typical SMS-DWI images and ADC maps at different b-values (50, 400 and 800 s/mm²) for each breathing mode. Figs. 2–4 show the classic comparisons of SMS-DWI across the three breathing modes at b = 800 s/mm². The detailed results of qualitative scores of BH-SMS-DWI, FB-SMS-DWI and RT-SMS-DWI with different b values (b value = 50, 400 and 800 s/mm²) are demonstrated in Table 3. Likewise, the interobserver agreement indicated fair-to-substantial levels ($\kappa = 0.422–0.783$).

For the images with b value of 50 s/mm², the image artifact scores of BH-SMS-DWI were significantly lower than those of RT-SMS-DWI ($P = 0.009$) and FB-SMS-DWI ($P < 0.001$) and there was no statistically significant difference between the other two ($P = 0.618$).

For the images with b value of 400 s/mm², the clarity of intrahepatic vessel, the sharpness of liver edge and the image artifact of FB-SMS-DWI were significantly lower than those of BH-SMS-DWI ($P = 0.005$, $P < 0.001$ and $P < 0.001$, respectively) and RT-SMS-DWI ($P < 0.001$ for all). Additionally, the conspicuity of left lobe of BH-SMS-DWI was significantly higher than that of FB-SMS-DWI ($P = 0.011$).

For the images with b value of 800 s/mm², the overall image quality and the conspicuity of left lobe of BH-SMS-DWI were significantly lower than those of RT-SMS-DWI ($P < 0.001$ for both) and FB-SMS-DWI ($P < 0.001$ and $P = 0.006$, respectively), and the conspicuity of left lobe of RT-SMS-DWI was significantly higher than that of FB-SMS-DWI ($P = 0.042$). Besides, the clarity of intrahepatic vessel and the sharpness of liver edge and the image artifact of RT-SMS-DWI were significantly higher than those of BH-SMS-DWI ($P < 0.001$ for both) and FB-SMS-DWI ($P < 0.001$ for both), and the lesion conspicuity of RT-SMS-DWI was also significantly higher than that of BH-SMS-DWI ($P = 0.022$). Furthermore,

the image artifact of FB-SMS-DWI was significantly higher than that of BH-SMS-DWI ($P < 0.001$) and RT-SMS-DWI ($P < 0.001$).

3.2.2. Quantitative image analysis

In our study, for the b = 800 s/mm² images of all patients, the tumor signal intensity was higher than that of the surrounding liver tissue. For the three indices (SNR of liver, SNR of tumor, CNR between liver tissue and tumor), there were all statistically significant differences in the overall distribution across three different breathing schemes in SMS-DWI ($P < 0.001$ for all). Pairwise multiple comparisons revealed that the SNR of liver, SNR of tumor and CNR for BH-SMS-DWI were significantly lower than those for RT-SMS-DWI ($P < 0.001$ for all) and FB-SMS-DWI ($P < 0.001$ for all). The difference of the three indices between RT-SMS-DWI and FB-SMS-DWI were not statistically significant ($P = 0.083$ for SNR of liver; $P = 0.067$ for SNR of tumor; $P = 0.211$ for CNR). The corresponding results are presented in Fig. 5, and the detailed results are shown in Table 4.

3.2.3. Repeatability analysis of ADC measurements

The results of tumor ADC values, ICC and TRV are presented in Table 5. In the first and second scans, there were both no statistically significant difference in the overall distribution of tumor ADC values among the different breathing schemes in SMS-DWI ($P = 0.438$ for the first scan; $P = 0.840$ for the second scan). Additionally, the repeatability analysis results demonstrated that BH-SMS-DWI had the highest ICC value (0.86; 95% CI: 0.84–0.91), followed by FB-SMS-DWI (0.83; 95% CI: 0.76–0.87) and RT-SMS-DWI (0.80; 95% CI: 0.75–0.86). Meanwhile, the TRVs across the three different breathing schemes showed a statistically significant difference ($P < 0.001$). Pairwise multiple comparisons revealed that the TRV of BH-SMS-DWI (9.17; 95% CI: 7.21–16.23) was significantly lower than that of FB-SMS-DWI (14.27; 95% CI: 11.34–21.17; $P = 0.001$) and RT-SMS-DWI (14.36; 95% CI: 12.57–23.31; $P < 0.001$). There was no statistically significant difference between TRV of RT-SMS-DWI and FB-SMS-DWI ($P = 0.427$).

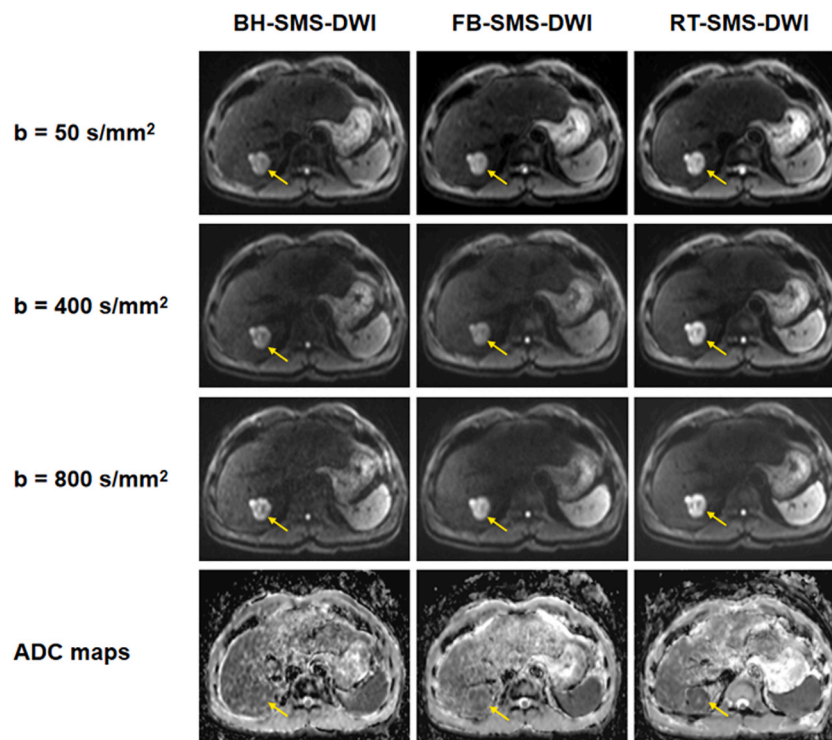


Fig. 1. A 58-year-old male patient with hepatocellular carcinoma, presenting a lesion diameter of 3.47 cm (yellow arrowheads). The graph presents the simultaneous multi-slice diffusion weighted imaging (SMS-DWI) at b value of 50, 400, 800 s/mm² and the apparent diffusion coefficient (ADC) maps, which were conducted with three different breathing schemes. BH, breath-hold; FB, free-breathing; RT, respiratory-triggered.

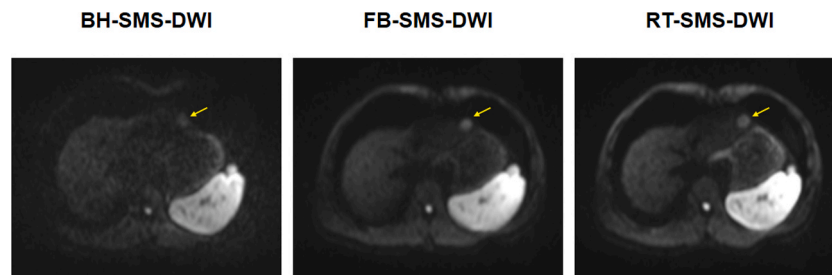


Fig. 2. A 44-year-old male patient with hepatocellular carcinoma, presenting a lesion diameter of 1.50 cm (yellow arrowheads). The graph presents the simultaneous multi-slice diffusion weighted imaging (SMS-DWI) at b value of 800 s/mm² across three different breathing schemes. Compared with the breath-hold SMS-DWI (BH-SMS-DWI), the free-breathing SMS-DWI (FB-SMS-DWI) and respiratory-triggered SMS-DWI (RT-SMS-DWI) both demonstrate superior overall image quality and lesion conspicuity, with RT-SMS-DWI being the most optimal. Compared to FB-SMS-DWI, RT-SMS-DWI provides clearer clarity of intrahepatic vessel and sharper delineation of the liver edge.

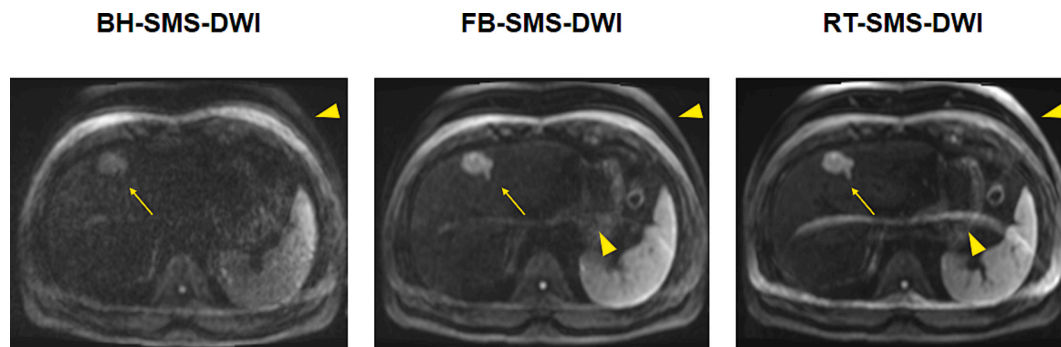


Fig. 3. A 67-year-old male patient with hepatocellular carcinoma, presenting a lesion diameter of 3.62 cm (yellow arrowheads). The graph presents the simultaneous multi-slice diffusion weighted imaging (SMS-DWI) at b value of 800 s/mm² across three different breathing schemes. The breath-hold SMS-DWI (BH-SMS-DWI) has the least chemical shift artifact, but its high noise and unclear liver structures make it overall image quality worst. The respiratory-triggered SMS-DWI (RT-SMS-DWI) shows the most pronounced artifact but excels in lesion conspicuity, clarity of intrahepatic vessel, and sharpness of liver edge, outperforming the free-breathing SMS-DWI (FB-SMS-DWI) overall. While the FB-SMS-DWI is slightly inferior to RT-SMS-DWI, its image quality remains sufficient for diagnostic purpose. The yellow triangles indicate the chemical shift artifact.

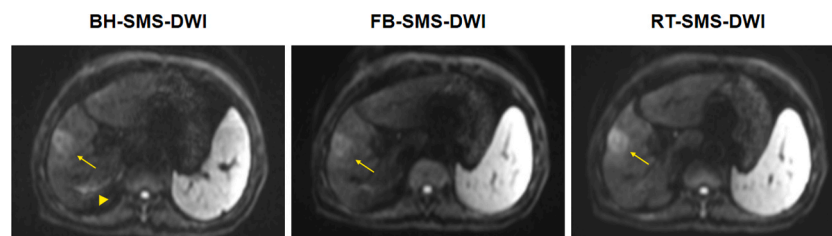


Fig. 4. A 69-year-old male patient with hepatocellular carcinoma, presenting a lesion diameter of 2.49 cm (yellow arrowheads). The graph presents the simultaneous multi-slice diffusion weighted imaging (SMS-DWI) at b value of 800 s/mm² across three different breathing schemes. The respiratory-triggered SMS-DWI (RT-SMS-DWI) shows the best performance in lesion conspicuity and visualization of the left hepatic lobe. In contrast, the breath-hold SMS-DWI (BH-SMS-DWI) exhibits relatively poorer conspicuity of the lesion and intrahepatic structures, and shows the most pronounced artifact (yellow triangle). FB-SMS-DWI, free-breathing SMS-DWI.

Although ideal TRV has been suggested to be 3–4%, a TRV within 15% is generally considered acceptable for abdominal DWI [12]. These results comprehensively indicated that BH-SMS-DWI had the highest repeatability in ADC measurements, while RT-SMS-DWI and FB-SMS-DWI showed similar repeatability.

4. Discussion

SMS-DWI has been proven to be equal to or superior to conventional DWI in terms of overall image quality and lesion detection conspicuity [6,11]. However, in clinical practice, the optimal acquisition protocol of SMS-DWI for HCC patients across different breathing schemes still requires further investigation. In this study, we evaluated the image quality, the difference and repeatability of ADC measurements of BH-

SMS-DWI, FB-SMS-DWI, and RT-SMS-DWI for HCC patients, aiming to explore the optimal breathing scheme for SMS-DWI in clinical scenario.

Our qualitative results indicated that BH-SMS-DWI, FB-SMS-DWI, and RT-SMS-DWI images across different b values each had their own advantages with different evaluation criteria. For the low and moderate b values, there were no significant differences in overall image quality among the three breathing schemes which was aligned with previous study [6]. However, with high b value ($b = 800 \text{ s/mm}^2$), the overall image quality, clarity of intrahepatic vessel and conspicuity of left lobe of BH-SMS-DWI were significantly lower than those of RT-SMS-DWI and FB-SMS-DWI, and the sharpness of liver edge and lesion conspicuity of BH-SMS-DWI were also significantly lower than those of RT-SMS-DWI. From a clinical standpoint, the reduced conspicuity of the left lobe and the poorer delineation of intrahepatic vessels on BH-SMS-DWI at

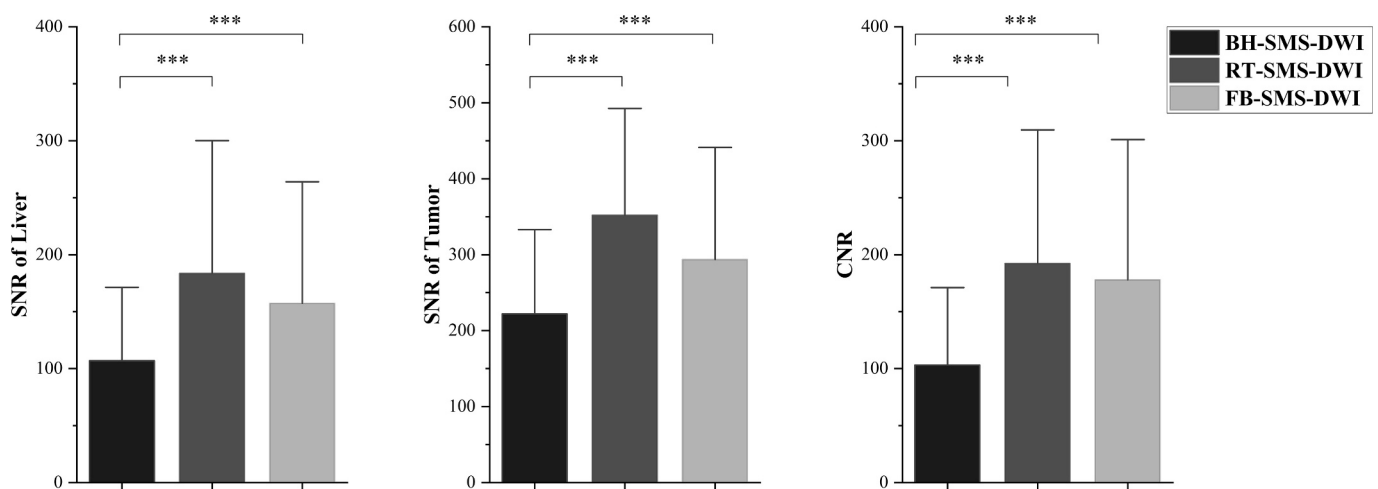
Table 3

Qualitative assessment for SMS-DWI with three different breathing techniques.

	BH-SMS-DWI (1)	RT-SMS-DWI (2)	FB-SMS-DWI (3)	P value Overall	(1) vs. (2)	(1) vs. (3)	(2) vs. (3)
Overall image quality							
b = 50 s/mm ²	4.77 ± 0.37	4.83 ± 0.53	4.78 ± 0.43	> 0.990	/	/	/
b = 400 s/mm ²	4.54 ± 0.61	4.56 ± 0.65	4.53 ± 0.57	> 0.990	/	/	/
b = 800 s/mm ²	3.37 ± 0.67	3.65 ± 0.69	3.63 ± 0.65	<0.001*	<0.001*	<0.001*	> 0.990
Clarity of intrahepatic vessel							
b = 50 s/mm ²	4.83 ± 0.44	4.83 ± 0.57	4.81 ± 0.53	> 0.99	/	/	/
b = 400 s/mm ²	4.43 ± 0.51	4.56 ± 0.59	4.22 ± 0.53	<0.001*	0.332	0.005*	<0.001*
b = 800 s/mm ²	3.53 ± 0.72	4.10 ± 0.81	3.70 ± 0.74	<0.001*	<0.001*	0.043*	<0.001*
Sharpness of liver edge							
b = 50 s/mm ²	4.88 ± 0.35	4.92 ± 0.29	4.86 ± 0.36	0.737	/	/	/
b = 400 s/mm ²	4.55 ± 0.47	4.58 ± 0.47	4.23 ± 0.51	<0.001*	0.506	<0.001*	<0.001*
b = 800 s/mm ²	3.93 ± 0.59	4.28 ± 0.64	4.01 ± 0.65	<0.001*	<0.001*	0.065	<0.001*
Conspicuity of left lobe							
b = 50 s/mm ²	4.81 ± 0.45	4.80 ± 0.42	4.77 ± 0.45	0.232	/	/	/
b = 400 s/mm ²	4.13 ± 0.63	3.92 ± 0.69	3.81 ± 0.69	<0.001*	0.072	0.011*	0.533
b = 800 s/mm ²	3.35 ± 0.79	3.78 ± 0.75	3.65 ± 0.77	<0.001*	<0.001*	0.006*	0.042*
Image artifact							
b = 50 s/mm ²	4.24 ± 0.39	4.58 ± 0.41	4.63 ± 0.38	<0.001*	0.009*	<0.001*	0.168
b = 400 s/mm ²	3.78 ± 0.57	3.84 ± 0.63	4.45 ± 0.69	<0.001*	> 0.99	<0.001*	<0.001*
b = 800 s/mm ²	3.43 ± 0.67	3.48 ± 0.65	3.98 ± 0.71	<0.001*	> 0.99	<0.001*	<0.001*
Lesion conspicuity							
b = 50 s/mm ²	4.77 ± 0.53	4.82 ± 0.55	4.77 ± 0.57	> 0.990	/	/	/
b = 400 s/mm ²	4.65 ± 0.69	4.70 ± 0.71	4.63 ± 0.70	0.375	/	/	/
b = 800 s/mm ²	4.21 ± 0.73	4.45 ± 0.76	4.27 ± 0.76	<0.001*	0.022*	0.635	0.089

Abbreviations: SMS = simultaneous multi-slice, DWI = diffusion weighted imaging, BH = breath-hold, FB = free-breathing, RT = respiratory-triggered.

* P value for comparison of SMS-DWIs across three breathing schemes at different b values, calculated using the Friedman test and post hoc test with Bonferroni adjustment, indicating statistical significance.

**Fig. 5.** Comparison of the signal-to-noise (SNR) of liver, SNR of tumor, and contrast-to-noise ratio (CNR) between them in simultaneous multi-slice diffusion weighted imaging (SMS-DWI) across different breathing schemes. BH-SMS-DWI, breath-hold SMS-DWI; RT-SMS-DWI, respiratory-triggered SMS-DWI; FB-SMS-DWI, free-breathing SMS-DWI.

high b values are of particular concern, as these limitations may directly impair the detection and characterization of lesions in the left lobe and perivascular regions, potentially reducing diagnostic confidence in BH-SMS-DWI. This was primarily due to the limited scan time and fewer signal excitations in breath-hold protocol compared to non-breath-hold protocols. Similarly, previous studies on conventional DWI have found that breath-hold scanning led to increased image noise, reduced clarity of hepatic anatomical details, and decreased contrast between lesions and liver compared to non-breath-hold DWI, where these findings were

also consistent with our quantitative results [14,15]. Moreover, the sharpness of liver edge of FB-SMS-DWI was significantly lower than that of RT-SMS-DWI, which was probably due to the free-breathing acquisition method with no correction for respiratory motion, resulted in blurred liver edge. For the image artifact, the FB-SMS-DWI showed significantly superior performance than BH-SMS-DWI and RT-SMS-DWI, which was obtained after considering susceptibility artifacts, respiratory artifacts, and chemical shift artifacts. This advantage in artifact control suggests that FB-SMS-DWI may offer greater robustness across different

Table 4The SNR and CNR analysis for BH-SMS-DWI, RT-SMS-DWI and FB-SMS-DWI at b value of 800 s/mm².

	BH-SMS-DWI (1)	RT-SMS-DWI (2)	FB-SMS-DWI (3)	P value* Overall	(1) vs. (2)	(1) vs. (3)	(2) vs. (3)
SNR _{Liver}	118.36 (56.87–160.85)	183.08 (87.45–280.72)	161.52 (72.48–246.56)	<0.001*	<0.001*	<0.001*	0.083
SNR _{Tumor}	247.41 (108.2–312.66)	389.23 (226.37–468.39)	323.48 (189.96–403.53)	<0.001*	<0.001*	<0.001*	0.067
CNR	82.75 (48.62–159.9)	175.53 (86.85–289.21)	163.59 (82.86–281.23)	<0.001*	<0.001*	<0.001*	0.211

Abbreviations: SMS = simultaneous multi-slice, DWI = diffusion weighted imaging, BH = breath-hold, FB = free-breathing, RT = respiratory-triggered, SNR_{Liver} = signal-to-noise ratio of liver, SNR_{Tumor} = signal-to-noise ratio of tumor, CNR = contrast-to-noise ratio. The data is presented as the median and interquartile range (IQR).

* P value for comparison of SMS-DWIs across three breathing schemes at b value of 800 s/mm², calculated using the Friedman test and post hoc test with Bonferroni adjustment, indicating statistical significance.

Table 5

The difference and repeatability analyses of tumor ADC measurements for BH-SMS-DWI, RT-SMS-DWI and FB-SMS-DWI.

	BH-SMS-DWI (1)	RT-SMS-DWI (2)	FB-SMS-DWI (3)	P value* Overall	(1) vs. (2)	(1) vs. (3)	(2) vs. (3)
ADC ₁ (×10 ⁻³ mm ² /s)	0.97 (0.89–1.15)	1.06 (0.93–1.21)	1.04 (0.91–1.19)	0.101	/	/	/
ADC ₂ (×10 ⁻³ mm ² /s)	0.98 (0.90–1.15)	1.05 (0.94–1.20)	1.04 (0.90–1.18)	0.093	/	/	/
ICC	0.86 (0.84–0.91)	0.80 (0.75–0.86)	0.83 (0.76–0.87)	/	/	/	/
TRV (%)	9.17 (7.21–16.23)	14.36 (12.57–23.31)	14.27 (11.34–21.17)	<0.001*	<0.001*	0.001*	0.427

Abbreviations: SMS = simultaneous multi-slice, DWI = diffusion weighted imaging, BH = breath-hold, FB = free-breathing, RT = respiratory-triggered, ADC₁ = apparent diffusion coefficient from the first scan, ADC₂ = apparent diffusion coefficient from the second scan, TRV = test–retest variability.

* P value for comparison of SMS-DWIs across three breathing schemes, calculated using the Friedman test and post hoc test with Bonferroni adjustment, indicating statistical significance.

patient conditions, particularly in individuals who have difficulty maintaining breath-holds or who are prone to respiratory-related artifacts.

In our study, BH-SMS-DWI exhibited significantly lower SNR of liver, SNR of tumor and CNR compared to FB-SMS-DWI and RT-SMS-DWI. Meanwhile, there was no statistically significant difference between RT-SMS-DWI and FB-SMS-DWI, which was consistent with the comparative results of liver SNR from the previous study [11]. The discrepancy between BH and non-BH sequences was primarily attributed to the shorter breath-hold acquisition time and fewer signal excitations. Choi et al. found that the SNRs of liver and focal hepatic lesions and the CNR for standard BH-DWI with b value of 800 s/mm² were significantly lower than standard non-BH-DWI [16]. Furthermore, Pei et al. [6] analyzed the SNR of liver in SMS-DWI with b value of 600 s/mm² across three breathing schemes, and reported that the SNR of liver of BH-SMS-DWI was slightly higher than that of FB-SMS-DWI and RT-SMS-DWI. However, their study involved young healthy volunteers with excellent breath-hold capacity and no underlying liver diseases, suggesting that differences in experimental populations may account for the different results. Moreover, the employment of parallel acquisition techniques could result in non-uniform spatial distribution of image noise, potentially introducing bias into the measurements.

In clinical application, quantitative ADC values were often measured to further assess the disease condition [17]. This study found no significant differences in the ADC values for HCC lesions among BH-SMS-DWI, FB-SMS-DWI, and RT-SMS-DWI. A possible explanation for this consistency may be attributed to the inherent characteristics of the simultaneous SMS technique itself. Currently, the impact of SMS technique on quantitative parameters in abdominal DWI remained a subject of debate. Xu et al. [13] and Obele et al. [18] have suggested that there was no significant difference in liver ADC values between SMS-DWI and conventional DWI. However, Taron et al. found that SMS-DWI yields lower ADC values in abdominal organs compared to conventional DWI [11,19,20]. The discrepancy was probably attributed to two main aspects: first, the SMS technique shortened the repetition time, leading to

incomplete recovery of the longitudinal magnetization vector (T1 saturation effect), which may systematically affect signal intensity and ADC calculations. Second, the noise level in SMS-DWI differs from that of conventional DWI. Since all three acquisition strategies in our study utilized the SMS technique, the potential influencing factors, such as the T1 saturation effect and altered noise properties, were present across all BH, FB, and RT conditions. Consequently, the systematic influence of the SMS technique likely outweighed the subtle differences in respiratory patterns, contributing to the similarity in ADC values. These sources of variability highlight the need for consistent scanning protocols when making comparisons in SMS-DWI studies, especially with different breathing schemes.

For the repeatability of ADC measurements, BH-SMS-DWI had the highest ICC and the lowest TRV indicating the high consistency and low variability between the two measurements, thus demonstrating its superior repeatability. This could be due to the relatively stable position of the liver during breath-hold, resulting in lower variability in quantitative parameters during repeated scans. Meanwhile, the ICC of FB-SMS-DWI was slightly higher than that of RT-DWI-SMS, and there was no significant difference in TRV between the two breathing schemes. Kwee et al. [21] reported similar findings in conventional DWI, showing that the stability of liver ADC values was significantly better in breath-hold and free-breathing DWI compared to respiratory-triggered sequences. They hypothesized that this could be due to respiratory-triggered DWI capturing image data only at the end of expiration. During different respiratory cycles, it was challenging for the liver to maintain a completely consistent position. Even slight variations in position could result in poor image registration, thereby affecting the accuracy of ADC measurements.

There were several limitations in our study. First, to ensure a feasible breath-hold duration, both the number of excitations (NEX) and the repetition time (TR) were shortened compared to the other two respiratory patterns, which may affect the comparability. However, even with the trade-offs, the breath-hold duration remains relatively long for clinical practice. Future studies may consider optimizing parameters to

balance breath-hold time and image quality. Second, SNR was estimated using an air-placed ROI. Although the current ROI-based method was consistently applied across all three breathing modes, this method is suboptimal with multi-channel coils and SMS acquisition technique, as these can cause non-uniform noise distribution, potentially affecting the measurements. Future research should adopt pixel-wise standard deviation method for more robust SNR evaluation. Third, there is no gold standard for determining the true diffusion coefficient in patient lesions, which is a common challenge to majority of DWI researches, as in vivo histopathological validation is rarely available. Finally, not all HCC patients in this study were confirmed by pathology, and some were diagnosed through comprehensive clinical assessments. However, current guidelines support clinical diagnosis of HCC, ensuring reliable accuracy in preoperative evaluation. Moreover, future studies should investigate how participant characteristics (e.g., tumor size) influence the feasibility and repeatability of each breathing scheme, and whether the observed ADC differences across the three breathing schemes affect diagnostic performance for HCC.

In conclusion, each breathing scheme of SMS-DWI had its strengths, and the choice of the scanning protocol should be adjusted to the specific objectives of HCC research. Overall, non-breath-hold SMS-DWI images scored higher in both quantitative and qualitative assessment compared to breath-hold acquisitions, with FB-SMS-DWI demonstrating faster image acquisition than RT-SMS-DWI. Therefore, FB-SMS-DWI is recommended as the optimal breathing scheme for HCC patients in clinical scenarios. Additionally, the repeatability of ADC value of breath-hold acquisition is notably superior to non-breath-hold acquisitions, making BH-SMS-DWI the preferred option for patients with good breath-holding capacity in studies involving HCC treatment evaluation and longitudinal follow-up.

CRedit authorship contribution statement

Meng Zhang: Writing – original draft, Methodology, Formal analysis. **Hanyu Li:** Writing – review & editing, Formal analysis. **Ting Yang:** Investigation, Formal analysis. **Ting Yin:** Resources. **Zhenlin Li:** Supervision. **Zheng Ye:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Ting Yin is an employee of Siemens Healthineers and is responsible for providing technical support in this work. She was not involved in participant recruitment, image acquisition, data analysis, or paper

writing. None of the other authors have a conflict of interest to disclose.].

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