Zhongshan Hospital, Fudan University

Investigator-Initiated Observational Clinical Study Protocol

Chinese Title: Consistency Study of Multiple Measurement Methods for Left Diaphragmatic Excursion in Critically Ill Patients

English Title: Consistency Study of Multiple Measurement Methods for Left Diaphragmatic Excursion in Critically Ill Patients

Study Site	Zhongshan Hospital, Fudan University
Principal Investigator	Liu Kai
Sponsor	Zhongshan Hospital, Fudan University
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Version / Revision History

Document	**Version**	**Date**	**Reason for Revision / Summary of Changes**
Protocol	V1.0	December 4, 2025	Initial version
Protocol	V1.1	January 8, 2026	Revision of the statistical methods

Investigator Statement

I will perform or directly supervise this clinical study in accordance with the China GCP requirements. I have read and confirmed this protocol and agree with its scientific and ethical basis. I will fulfill all responsibilities required by applicable Chinese laws and regulations, the Declaration of Helsinki, China GCP, and this protocol. The study will not be implemented until approval has been obtained from the relevant academic and ethics committees, except when measures are necessary to protect the safety, rights, and welfare of study participants. I will keep this protocol confidential.

Study Institution: Zhongshan Hospital, Fudan University

Principal Investigator: Liu Kai

Signature: _____

Date: January 8, 2026

1. Protocol Summary

Project Title: Consistency Study of Multiple Measurement Methods for Diaphragmatic Excursion in Critically Ill Patients

Background: In critically ill patients, it is often necessary to determine bilateral diaphragmatic excursion. Measurement of the left diaphragm has long been difficult. Several surrogate approaches have been reported, but their agreement in critically ill patients has not been established.

Objective: To use ultrasound to measure bilateral diaphragmatic ultrasound indices in critically ill patients, with a focus on the left diaphragm, and to evaluate the agreement and reliability among multiple ultrasound-based methods for assessing diaphragmatic excursion.

Endpoint: Agreement between bilateral diaphragmatic excursion measured by the standard procedure and other alternative methods.

Study Design: Single-center, prospective, observational study.

Sample Size: Thirty-five patients will be analyzed, divided into two groups according to respiratory support: invasive ventilation group (n=17) and non-invasive/spontaneous breathing group (n=18).

Key Eligibility Criteria: Inclusion: adults >=18 years; invasive group switched to 5 L/min oxygen by T-piece or tracheostomy mask during measurement; non-invasive group switched to face-mask oxygen at 5 L/min during measurement; signed informed consent. Exclusion: large wound at the ultrasound window preventing image acquisition; inability to obtain images in any diaphragmatic view; poor image quality in any view; known phrenic nerve injury or diaphragmatic paralysis; pregnancy; neuromuscular disorders affecting spontaneous breathing assessment such as ALS or myasthenia gravis; any condition deemed unsuitable by the investigator.

Expected Study Period: December 2025 to December 2027.

2. Background

Diaphragm is the primary respiratory muscle and contributes approximately 60%-80% of the work of breathing during active inspiration in healthy individuals. Diaphragmatic disuse atrophy, phrenic nerve conduction impairment, and related factors can markedly affect respiratory function. In patients with unilateral or bilateral muscle weakness (for example, stroke, phrenic nerve injury, or severe limb trauma), diaphragmatic function may decline to varying degrees because of immobility and nerve injury.

Traditional tools for evaluating diaphragmatic structure and function, such as computed tomography, chest radiography, and transesophageal transdiaphragmatic pressure monitoring, are limited by invasiveness and operational complexity. In recent years, ultrasound assessment of diaphragm function has gained increasing clinical attention. By dynamically measuring diaphragmatic excursion during breathing, ultrasound provides important information for evaluation of diaphragm function and guidance of rehabilitation training. Diaphragm ultrasound is noninvasive, convenient, and repeatable, and has gradually been accepted in intensive care, emergency medicine, rehabilitation, and respiratory departments.

However, ultrasound assessment of left diaphragmatic excursion remains difficult because the left side is affected by interference from the stomach, bowel gas, and lung air. At the conventional scanning site (between the midaxillary line and midclavicular line along the subcostal margin), image acquisition and respiratory-motion measurement of the left diaphragm are often challenging. Some authors have therefore suggested using right diaphragmatic function as a surrogate for overall diaphragm function, but this is not suitable for patients with bilateral asymmetry or unilateral surgery.

Based on extensive clinical practice and previous research, this study applies several modified ultrasound measurement approaches to bilateral diaphragm assessment and clinically evaluates the accuracy of these improved methods for measuring diaphragmatic excursion, with the goal of developing more practical measurement strategies and advancing diaphragm ultrasound assessment techniques.

3. Objective

This study will use ultrasound to measure bilateral diaphragmatic ultrasound indices in critically ill patients, focusing primarily on the left diaphragm, and will explore the agreement and reliability among multiple ultrasound indices used to evaluate diaphragmatic excursion.

4. Study Overview

4.1 Overall Design and Plan

This is a single-center, prospective, observational study. Patients admitted to the intensive care unit of our hospital on or after May 1, 2026 will be enrolled. Multiple ultrasound methods will be used to monitor diaphragmatic excursion, and agreement and accuracy will be evaluated.

4.2 Number of Cases and Grouping

A total of 35 patients are planned for analysis, divided into an invasive group and a non-invasive group.

The invasive group includes 17 patients receiving mechanical ventilation via endotracheal tube or tracheostomy.

The non-invasive group includes 18 patients receiving noninvasive mechanical ventilation, high-flow oxygen therapy, or conventional oxygen therapy.

4.3 Randomization and Blinding

Randomization is not required.

4.4 Study Flowchart

[Flowchart not reproduced in the translated text version.]

5. Study Population

5.1 Data Source

Patients admitted to the intensive care unit on or after May 1, 2026 will be screened. All ultrasound examinations will be performed using the same GE machine by a single operator who has more than 3 years of diaphragm-ultrasound experience, has completed standardized training, has performed at least 100 diaphragm ultrasound examinations, and is not involved in clinical decision-making. Each measurement will be repeated three times and averaged.

5.2 Diagnostic Criteria

Patients admitted to the intensive care unit who meet the inclusion criteria.

5.3 Inclusion / Exclusion / Withdrawal Criteria

Inclusion criteria

1. Adult patients (>=18 years), regardless of sex.

2. For the invasive group, measurements will be performed after switching intubated or tracheostomized patients to oxygen at 5 L/min via T-piece or tracheostomy mask.

3. For the non-invasive group, measurements will be performed after switching patients to face-mask oxygen at 5 L/min.

4. Willingness to participate and signed informed consent.

Exclusion criteria

1. Large wound at the ultrasound operating site preventing image acquisition.

2. Inability to obtain images in any diaphragmatic view.

3. Poor ultrasound image quality in any view.

4. Known phrenic nerve injury or diaphragmatic paralysis.

5. Pregnant women.

6. Neuromuscular diseases such as ALS or myasthenia gravis that affect assessment of spontaneous breathing.

7. Any other condition judged by the investigator to make the patient unsuitable.

Withdrawal criteria

1. If obvious respiratory distress occurs during measurement, the examination will be stopped immediately, respiratory support will be reconnected, and measurement may be repeated after the patient becomes stable again.

2. Respiratory distress is defined as SpO2 <94% under conventional oxygen at 5 L/min; HR >140 beats/min; systolic blood pressure >180-200 mmHg or blood pressure change >20%; or respiratory rate >35 breaths/min.

6. Study Grouping

No intervention-based grouping is required.

7. Study Endpoints

7.1 Primary Endpoint

Agreement between the standard left diaphragmatic excursion measurement (L-DDrp) and the modified alternative method (L-DDap).

7.2 Secondary Endpoints

1. Agreement between L-DDrp and pleural sliding displacement measured by the edge-distance 2D method (L-PSD2D-mode).

2. Agreement between L-DDrp and pleural sliding displacement measured by M-mode (L-PSDM-mode).

3. Agreement between L-DDrp and splenic displacement at the splenic hilum-venous region (SD).

4. Agreement between L-DDrp and renal displacement at the upper pole capsule of the left kidney (L-RD).

5. Agreement between standard right diaphragmatic excursion (R-DDrp) and modified-position diaphragm excursion (R-DDap).

6. Agreement between R-DDrp and pleural sliding displacement measured by the edge-distance 2D method (R-PSD2D-mode).

7. Agreement between R-DDrp and pleural sliding displacement measured by M-mode (R-PSDM-mode).

8. Agreement between R-DDrp and liver displacement at the first hepatic hilum (LD).

9. Agreement between R-DDrp and renal displacement at the upper pole capsule of the right kidney (R-RD).

7.3 Safety Endpoint

None.

7.4 Exploratory Endpoint

None.

8. Baseline Variables and Important Covariates

None.

9. Study Procedures

9.1 Study Procedures

1. Screening phase: obtain informed consent from ICU patients and collect age and diagnosis to determine eligibility.

2. Treatment/assessment phase: collect demographic and clinical data including sex, age, height, weight, BMI, past history, chief complaint, primary diagnosis, mechanical ventilation parameters, other respiratory therapy parameters, complete blood count, arterial blood gas, APACHE II score, and SOFA score. Personal identifiers such as real name, inpatient number, and outpatient number will not be recorded.

3. All examinations will be performed by a qualified operator with more than 3 years of diaphragm ultrasound experience, standardized theoretical and practical training, and certification through examination, using the designated study ultrasound machine.

4. Patient position: semi-recumbent position with the head of bed elevated 30 degrees.

5. In the invasive group, a uniform oxygen supply of 5 L/min will be used during the off-ventilator measurement period; in the non-invasive group, a face-mask oxygen flow of 5 L/min will be used .

6. For the left diaphragm, the operator will first obtain the standard view and then use M-mode to select the upper and lower diaphragm margins for excursion measurement. Measurements will be repeated three times and averaged, and all images will be archived with time-point labels.

7. The operator will then obtain five additional alternative methods at the corresponding left diaphragmatic position, repeat each measurement three times, and archive all images with time-point labels.

8. On the right side, standard-view excursion and the five alternative methods will also be collected, each repeated three times and averaged, with all images archived and time stamped.

9. All ultrasound image data will undergo a second blinded interpretation by an independent expert ultrasound team.

10. Patient data will be entered into the CRF.

9.2 Investigational Product

Not applicable.

9.3 Concomitant Medication and Treatment

Not applicable.

9.4 Dose Adjustment

Not applicable.

9.5 End of Study

The study will end after all planned participants have been enrolled and assessed.

9.6 Early Termination or Suspension

If severe missing data are observed when 50% of the sample has been collected, or if withdrawals/data loss exceed 10%, the study will be suspended.

9.7 Clinical Observation, Follow-up, and Measures to Ensure Compliance

Participants or their family members will receive prior explanation and education about the study procedures and potential discomfort. They will be informed that the study is beneficial for clinical observation, does not create additional injury or trauma risk, and does not involve any charge.

10. Adverse Event Collection and Reporting

10.1 Definitions

An adverse event (AE) is any unfavorable medical occurrence during the clinical study, regardless of whether it is related to the study medical device. A serious adverse event (SAE) is an event that results in death or serious deterioration in health, including life-threatening illness or injury, permanent impairment of body structure or function, hospitalization or prolongation of hospitalization, or medical/surgical intervention to prevent permanent impairment. In this study, participants undergo ultrasound examination only, and no study-related risk is anticipated.

10.2 Recording and Reporting

If a serious adverse event occurs during the study, the investigator shall immediately take appropriate treatment measures and report it in writing to the clinical trial management department of the institution. The department shall notify the sponsor in writing and report to the sponsor, the institution management department, and the ethics committee within 24 hours. Follow-up SAE reports shall be submitted according to the protocol. For device-related SAEs involving death or life-threatening risk, the sponsor shall report within 7 days; for non-fatal/non-life-threatening device-related SAEs and other major safety risks, within 15 days, to participating institutions, ethics committees, principal investigators, and the competent regulatory authorities, and shall take risk-control measures. SAEs judged definitely unrelated or probably unrelated to the investigational device do not require reporting. Device defects that may lead to SAEs shall be reported within 5 working days to the filing authority and the corresponding health authority, and other participating institutions and investigators shall be informed accordingly.

10.3 Risk Prevention and Management

Throughout the study, investigators will continuously monitor participants' vital signs and equipment status. If any event may cause actual or potential harm, the study procedure will be stopped immediately and the medical team will provide timely treatment. Risk-control measures include: (1) investigators should be fully aware of the participant's condition and current status; (2) dynamic changes in the study equipment should be closely monitored during use; (3) the study equipment should be checked regularly, maintained in good condition, and maintenance records kept; and (4) when serious adverse events or adverse reactions occur, investigators should promptly take necessary actions to ensure participant safety and report to the supervisory authorities, while informing other investigators involved in the same clinical study.

11. Data Management

Study data will be recorded in two parts. One part includes participants' basic information, start and end times of examination, vital-sign parameters, and investigator operation records, which will be recorded by the investigator in the case report forms described in the appendix. The other part consists of ultrasound machine data collected and saved by the equipment and exported by the investigator; therefore, no separate EDC system is required. This study has no project funding. Data will be used only within the department and will not be shared externally.

12. Statistical Analysis

12.1 Sample Size Estimation

Sample size was estimated using PASS 2025 software (NCSS, LLC, Kaysville, Utah, USA). The study aims to assess agreement between two diaphragm ultrasound measurement methods using Bland-Altman analysis and the confidence-interval method for the limits of agreement. The confidence level was set at 0.95 and the central proportion covered at 0.95. Based on pilot data, the standard deviation of the differences between the two methods was 0.081 cm in the invasive ventilation group. Because diaphragmatic motion in intubated patients is very small, the expected half-width of the confidence interval for the limits of agreement was set at 0.25 cm. In the non-invasive ventilation group, the SD was 0.23 cm; because spontaneous breathing produces a larger range of motion, the expected half-width was set at 0.70 cm. The calculated effective sample sizes were 17 and 18 for the invasive and non-invasive groups, respectively.

12.2 Definition and Selection of Analysis Sets

Because this is an observational study with no intervention or randomization, the analysis sets are defined as follows: Enrolled Set (ES): all participants who sign informed consent and are screened into the study; used to describe enrollment and baseline demographic characteristics. Full Analysis Set (FAS): participants in the ES who meet all inclusion criteria, do not meet any exclusion criteria, complete bilateral diaphragm ultrasound examinations (standard and alternative views), have acceptable image quality, and have complete primary-endpoint data. Primary and secondary endpoint analyses will be performed in the FAS. Participants for whom clear ultrasound images cannot be obtained because of poor cooperation or anatomical abnormalities, or for whom data are missing, will not be included in the FAS. Safety Set (SS): all enrolled participants who undergo at least one ultrasound examination; used to summarize any discomfort or adverse events during examination, although the risk of ultrasound is minimal.

12.3 Statistical Methods

Statistical analysis will be performed using SPSS 26.0 or SAS 9.4. Continuous data with normal distribution will be expressed as mean +- standard deviation; non-normally distributed data as median (interquartile range) [P25, P75]. Categorical data will be expressed as frequency and percentage (N, %). The primary endpoint is agreement between the standard measurement view and alternative methods. Bland-Altman analysis will be used. The mean difference (bias) and standard deviation of the differences will be calculated, and the 95% limits of agreement (LoA) will be constructed as Bias +- 1.96 x SD. The 95% confidence intervals of the bias and LoA will also be calculated. Participants will be stratified into the invasive ventilation group and the non-invasive/spontaneous breathing group, and the above agreement and correlation analyses will be performed separately. Between-group comparisons for continuous variables will use the independent-samples t test for normally distributed data or the Mann-Whitney U test for non-normal data; categorical variables will use the chi-square test. Safety analysis will summarize and tabulate all adverse events during the study (for example, vital-sign fluctuation due to position change or skin discomfort) and calculate incidence. Because ultrasound is noninvasive, no dedicated safety hypothesis testing is planned. Unless otherwise specified, all statistical tests will be two-sided and $P < 0.05$ will be considered statistically significant.

13. Ethical Considerations

13.1 Ethics Committee Review

This protocol, the written informed consent form, and all materials directly related to participants must be submitted to the ethics committee and approved in writing before the study can officially begin. The investigator must submit a continuing review report one month before the ethics approval expires to request an extension. If

the study is suspended or completed, the investigator must notify the ethics committee in writing. Any changes in study conduct, including revisions to the protocol and/or informed consent form, must be promptly reported to the ethics committee and may not be implemented before approval, unless the change is necessary to eliminate an immediate and obvious risk to participants. In such cases, the ethics committee will be informed.

13.2 Informed Consent

The investigator must provide the participant or legally authorized representative with an easy-to-understand informed consent form approved by the ethics committee and sufficient time to consider participation. No participant may be enrolled before signed written informed consent is obtained. During participation, updated versions of the informed consent form and written information will be provided as needed. The informed consent form will be retained as an essential study document for inspection.

14. Confidentiality

Results from this study may be published in medical journals. However, participants' personal information will be kept confidential in accordance with applicable laws and regulations, and will not be disclosed unless required by law. When necessary, government authorities, the hospital ethics committee, and relevant personnel may access participant records as permitted by regulations. If cooperation with other institutions is involved (for example, in a multicenter study), personal information will be de-identified before being shared with collaborators.

15. Expected Timeline and Completion Date

1. December 2025-April 2026: scientific review and ethics process, project workflow training, staff training, and competency assessment.

2. May 2026-May 2027: data collection and organization.

3. June 2027-December 2027: data analysis and manuscript preparation.

16. References

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