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OPEN PEER REVIEW

# Telemedicine-Based Functional Monitoring in Pulmonary Alveolar Proteinosis: A Pilot Experience of Post-Whole-Lung Lavage Follow-up

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## About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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## 1 Original submission

6 comments · 18 Jul 2026 – 24 Jul 2026

### Referee 1 Reviewer

MAJOR REVISION 18 Jul 2026

Dear Editor and Author

Journal of Cellular & Molecular Anesthesia

Thank you for the opportunity to review this manuscript, "Predictive value of the six-minute walk test for telemedicine-based monitoring of pulmonary alveolar proteinosis patients undergoing whole-lung lavage." The topic is clinically relevant, and the telemedicine-based approach is of practical interest. However, my review of the text, statistical analyses, and language identified a number of concerns, listed below as Major and Minor.

A) Major Revisions

1. Incorrect statistical model for the outcome variable

• The primary outcome ("need for repeat WLL") is described as binary (yes/no), yet the authors used "Multiple Linear Regression" to model it. For a binary outcome, logistic regression is the appropriate method. Using linear regression for a dichotomous outcome is statistically incorrect, and the β coefficients, SE, and t-values reported in Table 3 are not valid as presented.
• If the outcome was actually intended as a continuous score, this must be clearly defined in the Methods; as written, there is significant ambiguity.
2. Inadequate predictor-to-sample-size ratio (overfitting risk)

• With only 21 patients and 6 predictors in the regression model (Table 3), the ratio is approximately 3.5 observations per predictor, far below the accepted minimum of 10–15 per predictor. This creates a serious risk of overfitting and unstable coefficient estimates, which should be explicitly acknowledged as a limitation and factored into the interpretation of $R^2 = 0.540$.
• The authors should either reduce the number of predictors (e.g., via univariate preselection) or explicitly state this statistical limitation and avoid definitive claims of "independent predictor" status.
3. Group sample sizes (WLL vs. No-WLL) not reported

• Table 2 and the text compare the WLL and No-WLL groups, but the number of patients in each group (n) is never stated. This is essential for judging statistical power and the validity of the reported p-values and should be added.
4. Statistical tests not specified

• The Statistical Analysis section refers only generically to "appropriate statistical tests" without naming the specific test used for each comparison in Table 2 (independent t-test, Mann-Whitney U, chi-square, etc.). Given the small sample size (n = 21), normality testing and justification for the choice of parametric vs. nonparametric tests are needed.
5. Inconsistent section numbering

• The Methods section appears as "3. Methods2.1" and the Results section as "4. Results3.1," indicating a merge error between two different numbering schemes (main section numbers and internal subnumbering). These headings should be corrected and made consistent.
6. Outcome definition not fully specified in Methods

• The Methods do not clearly state how the decision to repeat WLL was made (strictly based on the criteria in section 2.5, physician judgment, or a combination). This is essential for reproducibility.

7. No confidence intervals reported

• For all comparisons in Table 2 and all regression coefficients in Table 3, only p-values are given; 95% CIs are not reported. Given the small sample size, CIs are important for correct clinical interpretation.

8. Study limitations not adequately addressed

• Despite the very small sample size (n = 21), the observational design, and the absence of an independent control group, the Discussion lacks a distinct, explicit Limitations paragraph. This should be added as its own subsection.

B) Minor Revisions

1. Redundant sentence in Abstract/Objectives

• The sentence "This study evaluated the predictive value of the Six-Minute Walk Test (6 MWT) for monitoring functional status and guiding clinical decisions after WLL" is repeated verbatim in both the Background/end of Abstract and the Objectives section. Rephrasing is recommended.

2. Language and grammar issues

• "Patients walked for six minutes" in the Background uses past tense amid otherwise general/definitional present-tense sentences, creating a tense inconsistency; consider changing to "Patients walk..."
• The phrase "WLL decisions should follow the body's functional signal, not isolated laboratory numbers" in the Conclusion uses an informal/metaphorical register ("body's functional signal") that is not appropriate for a research article and should be rewritten more formally.
• The term "double-lumen tube lavage" in the Discussion (around lines corresponding to sections 233 and 241) is conceptually unclear; the intended meaning is likely "lavage performed via double-lumen endotracheal tube," which should be stated explicitly.
• The sentence beginning "So, 6MWT captures global physiological burden" uses "So" as a sentence-initial connector, which is not standard in formal scientific writing ("Thus" or "Therefore" is preferable).
• There is inconsistent spacing between the number and unit throughout the manuscript (e.g., "6 MWT" in some places vs. "6MWT" without a space elsewhere, particularly in Results and Discussion). This should be standardized.

3. Minor inconsistency between title-page keywords and in-text keywords

• On the title page, the keyword appears as "six-minute walk test." (with an extraneous period), whereas in the main text it appears as "Six-Minute Walk Test" without a period. Please correct for consistency.

4. Redundant citation of the same claim

• The statement that WLL "remains the mainstay of treatment... technically feasible, safe, and clinically effective" is repeated almost verbatim at the start of the Discussion (ref. 12) and again a few paragraphs later (refs. 14-16). This repetition is unnecessary, and the two passages should be merged.

5. Measurement scale not specified for some Table 2 variables

• The variables "Oxygen dependence," "Cough severity," and "Fatigue" in Table 2 are reported as numerical means ± SD, but the underlying measurement scale (Likert scale — what range? 0–3? 0–4?) is not specified in the text.

6. Table 3 — regression intercept not reported

• The multiple regression table does not report the model intercept, which is needed for a complete presentation of the regression model.

7. Title page "Informed Consent" and "Data Availability" fields left blank

• These fields are empty on the title page even though the text describes obtaining written informed consent. These fields should be completed.

Thank you again, and best regards,

**Referee 2** Reviewer

MAJOR REVISION 20 Jul 2026

Dear Authors,

I have reviewed the manuscript. The comments below provide additional scientific-review points that are not assigned to the editorial-screening assessment. Major comments address substantive scientific, methodological, interpretive, and STROBE reporting issues; minor comments address editorial clarity and presentation.

This observational study follows 21 patients with pulmonary alveolar proteinosis after whole-lung lavage using a home-based telemedicine protocol. Six-minute walking distance, oxygen saturation, heart-rate response, dyspnea, oxygen dependence, and symptoms were recorded, and patients who underwent repeat WLL were compared with those who did not. The manuscript reports that shorter walking distance was associated with repeat WLL and proposes home-based 6MWT monitoring as a tool for detecting functional deterioration.

The study addresses a clinically relevant problem in a rare disease and uses a low-cost functional measure that may benefit geographically dispersed patients. Consecutive sampling, a defined study period, eligibility criteria, weekly-to-monthly follow-up, and several clinically meaningful measures are reported.

Major Comments:

1. Outcome definition and temporal sequence (STROBE Items 6–8):

> *"Need for repeat WLL," "decision to perform WLL," and "patients requiring WLL" are used as though they represent an objective outcome, but the manuscript does not provide explicit criteria for the decision or establish whether the predictor measurements preceded that decision. Because the in-person evaluation and WLL decision may have incorporated functional performance, dyspnea, imaging, oxygenation, or clinician judgment, the reported association may partly reflect incorporation bias rather than independent prediction (source: Methods—Remote Monitoring Protocol and Criteria for Clinical Referral; Results; Table 3).*
>
> *Author to-do list:*
>
> ** Define the primary outcome precisely as repeat WLL performed, recommended, scheduled, or judged clinically necessary (source: Methods—Criteria for Clinical Referral).*
> ** State the follow-up interval within which repeat WLL was assessed after the predictor measurement (source: Methods; Results).*
> ** Identify the clinicians who made the WLL decision and specify whether they were aware of the home 6MWT results (source: Methods—Criteria for Clinical Referral).*
> ** Report the complete clinical criteria used to recommend repeat WLL (source: Methods—Criteria for Clinical Referral).*
> ** Clarify whether each predictor was recorded before, during, or after the clinical decision (source: Methods—Data Collection; Results).*

2. Inappropriate regression model for a binary outcome (STROBE Items 12 and 16):

> *Table 3 uses multiple linear regression to model what appears to be a binary outcome: WLL versus no WLL. Linear regression is generally unsuitable for a dichotomous outcome because it can produce invalid probability estimates, heteroscedastic residuals, and coefficients that are difficult to interpret clinically. The reported $\beta$ of −0.0022 is consequently not adequate evidence that walking distance independently predicts repeat WLL (source: Abstract—*

*Author to-do list:*

** Reanalyze the binary outcome using an appropriate logistic regression model or justify a different valid model (source: Statistical Analysis; Table 3).*
** Report odds ratios with 95% confidence intervals for every retained predictor (source: Results; Table 3).*
** Describe model assumptions, diagnostics, calibration, discrimination, and influential-observation assessment (source: Statistical Analysis).*
** Replace the linear-model $R^2$ with measures appropriate to the revised model (source: Results 3.3).*
** Revise all interpretations after completing the corrected analysis (source: Abstract; Results; Discussion; Conclusion).*

3. Severe model overfitting in a cohort of 21 patients (STROBE Items 10 and 12):

*The multivariable model includes six predictors in only 21 patients, while the number of repeat-WLL events is not reported. This sample is unlikely to support stable estimation of six independent effects. The unusually precise claims about a "sole independent predictor" may therefore reflect overfitting, sparse data, and model instability (source: Methods—Study Population and Statistical Analysis; Results 3.3; Table 3).*

*Author to-do list:*

** Report the exact number of repeat-WLL events and non-events (source: Results; Tables 1 and 2).*
** Provide the rationale for the number of candidate predictors relative to the number of events (source: Statistical Analysis).*
** Reduce the model to a small set of prespecified clinically justified variables or use an appropriate penalized approach (source: Statistical Analysis).*
** Report internal validation using a method suitable for the small dataset if predictive modeling is retained (source: Statistical Analysis).*
** Reframe the analysis as exploratory if adequate model stability cannot be demonstrated (source: Abstract; Discussion; Conclusion).*

4. Home-based 6MWT protocol and measurement validity (STROBE Items 7 and 8):

*The home-based test differs materially from standardized supervised field-walking procedures, but the path length, path configuration, encouragement, walking aids, oxygen use, supervision, safety response, device validation, environmental conditions, and test repeatability are not reported. Patients apparently counted laps and calculated distance themselves, creating substantial measurement variability and possible differential error (source: Methods—Remote Monitoring Protocol).*

*Author to-do list:*

** Report the required path length and configuration and how each home path was measured (source: Methods—Remote Monitoring Protocol).*
** State whether a caregiver or clinician remotely supervised each test (source: Methods—Remote Monitoring Protocol).*
** Describe standardized instructions, encouragement, rest rules, oxygen use, walking aids, and stopping criteria (source: Methods—Remote Monitoring Protocol).*
** Identify the pulse-oximeter specifications and any validation or quality-control procedure (source: Methods—Remote Monitoring Protocol).*
** Report adverse events, aborted tests, and missing or technically invalid assessments (source: Methods; Results).*
** Explain how the home protocol differed from the cited ERS/ATS technical standard (source: Background; Methods).*

5. Longitudinal data structure is not described (STROBE Items 8, 12, and 15):

*Monitoring occurred weekly during the first month and monthly thereafter, implying repeated observations for each patient. The analysis, however, presents one value per variable without explaining whether it represents a baseline, most recent, worst, mean, or pre-decision measurement. Ignoring within-patient correlation and variable follow-up duration can bias estimates and discard the longitudinal information central to the study (source: Methods—Remote Monitoring and Data Collection; Results; Tables 2 and 3).*

*Author to-do list:*

** Define the observation used for every variable in Tables 2 and 3 (source: Results; Tables 2 and 3).*
** Report the number and timing of assessments per patient (source: Methods—Remote Monitoring; Results).*
** Report follow-up duration separately for the repeat-WLL and no-WLL groups (source: Results).*
** Describe how repeated observations and within-patient correlation were handled (source: Statistical Analysis).*
** Use a longitudinal or time-to-event analysis if the research question concerns deterioration leading to repeat WLL (source: Statistical Analysis).*

6. Participant flow, missing data, and group denominators (STROBE Items 13 and 14):

*The manuscript states that all eligible patients were enrolled but does not report how many were assessed, excluded, lost to follow-up, unable to complete home testing, or included in each analysis. The number of patients in the repeat-WLL and no-WLL groups is also absent from the tables, preventing evaluation of selection, attrition, and sparse-data bias (source: Methods—Study Population and Eligibility Criteria; Results; Tables 1–3).*

*Author to-do list:*

** Report the numbers assessed, excluded with reasons, enrolled, followed, and analyzed (source: Methods; Results).*
** Provide a participant flow diagram (source: Methods—Study Population).*
** Add group sample sizes to Tables 2 and 3 (source: Tables 2 and 3).*
** Report missing observations for every predictor and outcome (source: Results).*
** Explain the method used to handle missing data (source: Statistical Analysis).*

7. Candidate predictors and statistical procedures are incompletely reported (STROBE Items 12 and 16):

*The methods state only that "appropriate statistical tests" were used, while the results present univariate group comparisons and multivariable coefficients without naming the tests, describing distribution checks, defining coding, reporting confidence intervals, or explaining variable selection. "Marginally significant" and "clinically important" labels are applied based on P values without a prespecified evidentiary basis (source: Methods—Data Collection and Statistical Analysis; Tables 2 and 3).*

*Author to-do list:*

** Name the statistical test used for each comparison in Table 2 (source: Statistical Analysis; Table 2).*
** Define the coding and scale of oxygen dependence, symptoms, WLL outcome, and all model variables (source: Methods; Tables 2 and 3).*
** Describe distributional assessment and the use of parametric or nonparametric procedures (source: Statistical Analysis).*
** Report effect estimates with 95% confidence intervals rather than P values alone (source: Results; Tables 2 and 3).*
** Remove post hoc labels such as "marginally significant" and "clinically important" unless supported by prespecified criteria and effect estimates (source: Results 3.3; Table 3).*

8. Unsupported predictive threshold and lack of validation (STROBE Items 11, 16, and 20):

*The manuscript states that walking approximately 300 m or less identifies patients at highest risk, but no threshold-selection method, sensitivity, specificity, predictive values, ROC analysis, or validation is reported. The value appears to derive from the mean of the WLL group rather than a validated decision threshold. The study therefore establishes, at most, an exploratory association—not a clinically usable cutoff (source: Results—Clinical Interpretation; Discussion; Conclusion).*

*Author to-do list:*

** Remove the 300-m clinical threshold unless it is derived using a stated method and validated (source: Results 3.4; Conclusion).*
** If threshold analysis is retained, report sensitivity, specificity, predictive values, and confidence intervals (source: Statistical Analysis; Results).*
** Distinguish model development from model validation (source: Methods; Discussion).*
** State explicitly that external validation is required before clinical implementation (source: Discussion; Conclusion).*

9. Telemedicine effectiveness is not directly evaluated (STROBE Items 7, 15, and 20):

*The conclusion asserts that telemedicine enabled timely detection and may enhance surveillance, but the study does not compare telemedicine with conventional follow-up, report detection times, referral delays, adherence, acceptability, technical failures, access barriers, or adverse events. The design can describe a remotely monitored cohort but cannot establish that telemedicine improved timeliness or outcomes (source: Abstract—Conclusion; Methods—Remote Monitoring; Discussion; Conclusion).*

*Author to-do list:*

** Define telemedicine process outcomes, including adherence, completed contacts, missing contacts, and technical failures (source: Methods; Results).*
** Report the interval from detected deterioration to in-person assessment and repeat WLL (source: Results).*
** Remove comparative effectiveness claims not supported by a control group (source: Abstract; Discussion; Conclusion).*
** Present feasibility conclusions as preliminary and descriptive (source: Discussion; Conclusion).*

Minor Comments:

1. Tables and figures:

*The manuscript contains three tables and no figures or images. Tables 1–3 are all explicitly cited in the main text. Add the repeat-WLL and no-WLL sample sizes to Tables 2 and 3; define all abbreviations and variable coding in footnotes; replace "Significance" labels with estimates and confidence intervals; standardize negative signs and decimal precision; and clarify whether "oxygen dependence" is binary, ordinal, or continuous (source: Tables 1–3).*

2. Early-stage editorial and language red flags:

*The manuscript requires focused language editing. "Patients walked for six minutes" in the Background should be "Patients walk for six minutes" when describing the general test; "mean age was 36.7 ± 14.9 years old" should be "mean age was 36.7 ± 14.9 years"; "This underscores the PAP's continued central role in care" should be "This underscores WLL's continued central role in PAP care"; and "WLL decisions should follow the body's functional signal" should be replaced with neutral scientific wording such as "WLL decisions should incorporate validated measures of functional decline." Correct "Methods2.1," "Results3.," and ") Table 3(" and remove conversational transitions such as "So" (source: Background; Methods heading; Results heading; Discussion; Conclusion).*

3. Terminology and abbreviation consistency:

> *Standardize "6MWT," "6 MWT," and "6 MWD"; use "repeat WLL" consistently rather than alternating among "WLL," "need for WLL," and "WLL indication"; and distinguish home-based, remotely supervised, telemonitored, and clinic-based assessments accurately. Define GM-CSF, COPD, IPF, $SpO_2$, HR, and PAP at first use as applicable (source: Abstract; Background; Methods; Results).*

4. Redundant background and discussion:

> *The first and fourth Discussion paragraphs repeat that WLL was introduced in the 1960s, remains the principal treatment, is safe and effective, and provides durable benefit. Consolidate this material into one concise paragraph and use the space to discuss study-specific limitations (source: Discussion paragraphs 1 and 4).*

5. Reference currency:

> *Ten references were published in 2011 or earlier: Refs 1, 2, 4, and 7–14. Review these sources for replacement with more recent and directly relevant evidence where appropriate, while retaining Ref 1 or other genuinely seminal sources with explicit justification. The citation attributed in the text to "Bois et al. (2010)" should be corrected to "du Bois et al." and reconciled with the reference-list year of 2011 (source: Background; References 1, 2, 4, and 7–14).*

The study addresses a potentially useful remote-monitoring strategy in a rare disease, but the binary outcome has been modeled incorrectly, the small cohort cannot support the current multivariable claims, and the temporal, longitudinal, and decision-making structure is insufficiently reported. Substantial reanalysis and major revision are required before the proposed predictive or clinical conclusions can be evaluated.

Best regards,
Scientific Reviewer

**Referee 3** Reviewer

MAJOR REVISION 20 Jul 2026

Dear Authors,

Thank you for submitting your manuscript to the journal. Following our initial editorial screening, the issues below must be corrected before the submission can be considered complete for further evaluation.

Please note that references are very important for publication, and all cited sources must include a DOI/PMID when supplied, be cited appropriately in the manuscript text, and be suitable for the journal.

2-1- Author identification and declaration sections are incomplete:

* What the author wrote: The submission metadata contains four full author names, contributions, ethics approval, funding, and conflict-of-interest information, but the manuscript does not provide a visible author byline, affiliations, corresponding-author details, or complete declaration sections. (source: manuscript front matter; embedded submission metadata)
* Why correction is required: This must be corrected because the manuscript is not compliant with basic editorial requirements regarding author identification, correspondence, ethics, funding, competing interests, and contribution disclosure. (source: manuscript front matter; embedded submission metadata)
* To do: Add the complete author byline, affiliations, corresponding-author details, ethics approval, informed consent, funding, competing-interest, and author-contribution sections to the manuscript. (source: manuscript front matter; embedded submission metadata)

2-2- Data-availability information is missing:

embedded metadata)
* Why correction is required: This must be corrected because the manuscript is not compliant with basic editorial requirements regarding research-data transparency and reproducibility. (source: entire manuscript)
* To do: Add a data-availability statement specifying what de-identified data and analytic materials are available, from whom, under what conditions, and subject to which ethical restrictions. (source: entire manuscript)

2-3- Reference-list integrity requires correction:

* What the author wrote: The manuscript contains 17 references with DOI or PMID identifiers, but 10 require further internal review because they were published in 2011 or earlier or lack an exact standalone in-text citation. (source: manuscript body; References)
* References with DOI/PMID: Ref 1 - Rosen et al., Ref 2 - Trapnell et al., Ref 3 - Leth et al., Ref 4 - Luisetti et al., Ref 5 - Kiani et al., Ref 6 - Holland et al., Ref 7 - Enright et al., Ref 8 - Lama et al., Ref 9 - Hallstrand et al., Ref 10 - Lederer et al., Ref 11 - du Bois et al., Ref 12 - Ben-Abraham et al., Ref 13 - Beccaria et al., Ref 14 - Michaud et al., Ref 15 - Jouneau et al., Ref 16 - Tay et al., Ref 17 - Fijołek et al. (source: References)
* References requiring further review:

* Ref 1 - Rosen et al. — published in 1958; retain only with explicit justification as the seminal description of PAP. (source: Reference 1)
* Ref 2 - Trapnell et al. — published in 2003; replace with a newer source unless its retention is specifically justified. (source: Reference 2)
* Ref 4 - Luisetti et al. — published in 2010; replace with a newer treatment review unless its retention is justified. (source: Reference 4)
* Ref 7 - Enright et al. — published in 2003; replace with newer functional-test evidence unless its retention is justified. (source: Reference 7)
* Ref 8 - Lama et al. — published in 2003; replace with newer disease-relevant evidence unless its retention is justified. (source: Reference 8)
* Ref 9 - Hallstrand et al. — published in 2005; replace with newer evidence unless its retention is justified. (source: Reference 9)
* Ref 10 - Lederer et al. — published in 2006 and not cited in the manuscript text; no exact standalone in-text citation to this reference was found. (source: manuscript body; Reference 10)
* Ref 11 - du Bois et al. — published in 2011; replace with newer validation evidence unless its retention is justified. (source: Reference 11)
* Ref 12 - Ben-Abraham et al. — published in 2002; replace with current perioperative WLL guidance unless its retention is justified. (source: Reference 12)
* Ref 13 - Beccaria et al. — published in 2004; replace with more recent long-term outcome evidence unless its retention is justified. (source: Reference 13)
* Ref 14 - Michaud et al. — published in 2009 and not cited in the manuscript text; no exact standalone in-text citation to this reference was found. (source: manuscript body; Reference 14)
* Ref 15 - Jouneau et al. — not cited in the manuscript text; no exact standalone in-text citation to this reference was found. (source: manuscript body; Reference 15)
* Why correction is required: This must be corrected because the manuscript is not fully verifiable without current evidence and a consistent relationship between in-text citations and reference-list entries. (source: manuscript body; References)
* To do: Verify every affected reference, add exact in-text citations where justified, replace outdated sources with newer and directly relevant literature where appropriate, and remove any unused entry. (source: manuscript body; References)

Please revise the manuscript accordingly and submit a corrected version together with any required supporting material.

Kind regards,
Screening Reviewer

**Seyyedeh Masumeh Hashemi** Reviewer

MINOR REVISION 23 Jul 2026

Thank you for presenting your interesting article entitled “Predictive value of the six-minute walk test for telemedicine-based monitoring of pulmonary alveolar proteinosis patients undergoing whole-lung lavage”. This manuscript addresses an important clinical question in a rare disease and evaluates the potential role of a simple, cost-effective, and remotely applicable functional assessment tool for the follow-up of patients with pulmonary alveolar proteinosis (PAP). The topic is clinically relevant, and the manuscript is generally well written with a good standard of English.
However, several issues should be addressed to improve the scientific rigor and clarity of the study:
First, as this study represents an observational case series, the study design should be explicitly stated in the title.
Second, the diagnostic criteria for PAP are insufficiently described. The manuscript currently states only that patients had a "confirmed diagnosis" (Line 84). The authors should clearly specify how the diagnosis was established, including whether bronchoalveolar lavage findings, lung biopsy, anti-GM-CSF antibody testing, or other accepted diagnostic methods were used.
Third, the indications for performing whole-lung lavage (WLL) require clarification. The criteria used to initiate the first WLL, as well as those guiding the decision for repeat WLL during follow-up, should be explicitly defined.
Fourth, if available, the number of prior WLL procedures for each patient should be reported, as previous interventions may influence both disease severity and functional outcomes.
Fifth, in the Abstract (Line 15), the abbreviation mMRC should be written in full at first mention as "modified Medical Research Council dyspnea scale."
Sixth, in Line 233, the manuscript refers to "double-lumen tube lavage," whereas "whole-lung lavage (WLL)" is used consistently elsewhere. Terminology should be standardized throughout the manuscript to avoid confusion.
Seventh, given the small sample size and the case series design, the statistical analysis should be carefully reviewed by a statistician. In particular, the use of multiple linear regression to identify predictors of WLL recurrence requires justification and assessment of its appropriateness.
Finally, as one of the key strengths of this study is the use of telemedicine, the remote monitoring protocol should be described in greater detail. Additional information regarding the telemedicine platform, patient training, standardization of the home-based six-minute walk test, monitoring procedures, and quality assurance measures would enhance the reproducibility and clinical applicability of the study.

**Associate Editor**

MAJOR REVISION 24 Jul 2026

Dear EIC
The manuscript needs major revisions before proceeding. Please ask the authors to consider the reviewers' comments and revise the manuscript.

**Editor-in-Chief** MAJOR REVISION 24 Jul 2026

Dear authors
The manuscript needs major revisions before we can proceed. Please consider the reviewers' comments and revise the manuscript accordingly.

2

# Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

# Response to Reviewer Comments

## #Reviewer1

**Comment 1:** 1. Outcome definition and temporal sequence (STROBE Items 6–8):

> “Need for repeat WLL,” “decision to perform WLL,” and “patients requiring WLL” are used as though they represent an objective outcome, but the manuscript does not provide explicit criteria for the decision or establish whether the predictor measurements preceded that decision. Because the in-person evaluation and WLL decision may have incorporated functional performance, dyspnea, imaging, oxygenation, or clinician judgment, the reported association may partly reflect incorporation bias rather than independent prediction (source: Methods—Remote Monitoring Protocol and Criteria for Clinical Referral; Results; Table 3).
>
> Author to-do list:
>
> * Define the primary outcome precisely as repeat WLL performed, recommended, scheduled, or judged clinically necessary (source: Methods—Criteria for Clinical Referral).
> * State the follow-up interval within which repeat WLL was assessed after the predictor measurement (source: Methods; Results).
> * Identify the clinicians who made the WLL decision and specify whether they were aware of the home 6MWT results (source: Methods—Criteria for Clinical Referral).
> * Report the complete clinical criteria used to recommend repeat WLL (source: Methods—Criteria for Clinical Referral).
> * Clarify whether each predictor was recorded before, during, or after the clinical decision (source: Methods—Data Collection; Results).:

**Author’s response 1:** Thank you for the valuable comment. These points have been incorporated into the revised manuscript.

**Comment 2:** Inappropriate regression model for a binary outcome (STROBE Items 12 and 16):

> Table 3 uses multiple linear regression to model what appears to be a binary outcome: WLL versus no WLL. Linear regression is generally unsuitable for a dichotomous outcome because it can produce invalid probability estimates, heteroscedastic residuals, and coefficients that are difficult to interpret clinically. The reported β of −0.0022 is consequently not adequate evidence that walking distance independently predicts repeat WLL (source: Abstract—Methods and Results; Results 3.3; Table 3).
>
> Author to-do list:
>
> * Reanalyze the binary outcome using an appropriate logistic regression model or justify a different valid model (source: Statistical Analysis; Table 3).

> * Report odds ratios with 95% confidence intervals for every retained predictor (source: Results; Table 3).
> * Describe model assumptions, diagnostics, calibration, discrimination, and influential-observation assessment (source: Statistical Analysis).
> * Replace the linear-model $R^2$ with measures appropriate to the revised model (source: Results 3.3).
> * Revise all interpretations after completing the corrected analysis (source: Abstract; Results; Discussion; Conclusion).

**Author's response 2:** Thank you for this important methodological comment. We agree that repeat WLL represents a binary outcome (performed vs. not performed), and that logistic regression is more appropriate for modeling dichotomous outcomes. Accordingly, we have reanalyzed the data using binary logistic regression and revised the statistical analysis, Table 3, and the corresponding interpretations throughout the manuscript. The results are now presented as odds ratios (ORs) with 95% confidence intervals rather than regression coefficients. We have also added appropriate model performance measures and revised our conclusions to describe 6MWT distance as a functional marker associated with repeat WLL rather than a definitive independent predictor.

**Reviewer Comments 3:** Severe model overfitting in a cohort of 21 patients (STROBE Items 10 and 12):

> The multivariable model includes six predictors in only 21 patients, while the number of repeat-WLL events is not reported. This sample is unlikely to support stable estimation of six independent effects. The unusually precise claims about a "sole independent predictor" may therefore reflect overfitting, sparse data, and model instability (source: Methods—Study Population and Statistical Analysis; Results 3.3; Table 3).
>
> Author to-do list:
>
> * Report the exact number of repeat-WLL events and non-events (source: Results; Tables 1 and 2).
> * Provide the rationale for the number of candidate predictors relative to the number of events (source: Statistical Analysis).
> * Reduce the model to a small set of prespecified clinically justified variables or use an appropriate penalized approach (source: Statistical Analysis).
> * Report internal validation using a method suitable for the small dataset if predictive modeling is retained (source: Statistical Analysis).
> * Reframe the analysis as exploratory if adequate model stability cannot be demonstrated (source: Abstract; Discussion; Conclusion).

**Author's response3:** Thank you for the valuable comment. These points have been incorporated into the revised manuscript.

.

**Reviewer Comments 4:** Home-based 6MWT protocol and measurement validity (STROBE Items 7 and 8):

> The home-based test differs materially from standardized supervised field-walking procedures, but the path length, path configuration, encouragement, walking aids, oxygen use, supervision, safety response, device validation, environmental conditions, and test repeatability are not reported. Patients apparently counted laps and calculated distance themselves, creating substantial measurement variability and possible differential error (source: Methods—Remote Monitoring Protocol).
>
> Author to-do list:
>
> * Report the required path length and configuration and how each home path was measured (source: Methods—Remote Monitoring Protocol).
> * State whether a caregiver or clinician remotely supervised each test (source: Methods—Remote Monitoring Protocol).
> * Describe standardized instructions, encouragement, rest rules, oxygen use, walking aids, and stopping criteria (source: Methods—Remote Monitoring Protocol).
> * Identify the pulse-oximeter specifications and any validation or quality-control procedure (source: Methods—Remote Monitoring Protocol).
> * Report adverse events, aborted tests, and missing or technically invalid assessments (source: Methods; Results).
> * Explain how the home protocol differed from the cited ERS/ATS technical standard (source: Background; Methods).

**Author's response 4:** Thank you for the valuable comment. The method section has been revised based on your valuable comment.

**Reviewer Comments 5:** Longitudinal data structure is not described (STROBE Items 8, 12, and 15):

> Monitoring occurred weekly during the first month and monthly thereafter, implying repeated observations for each patient. The analysis, however, presents one value per variable without explaining whether it represents baseline, most recent, worst, mean, or pre-decision measurements. Ignoring within-patient correlation and variable follow-up duration can bias estimates and discard the longitudinal information central to the study (source: Methods—Remote Monitoring and Data Collection; Results; Tables 2 and 3).
>
> Author to-do list:
>

> * Define the observation used for every variable in Tables 2 and 3 (source: Results; Tables 2 and 3).
> * Report the number and timing of assessments per patient (source: Methods—Remote Monitoring; Results).
> * Report follow-up duration separately for repeat-WLL and no-WLL groups (source: Results).
> * Describe how repeated observations and within-patient correlation were handled (source: Statistical Analysis).
> * Use a longitudinal or time-to-event analysis if the research question concerns deterioration leading to repeat WLL (source: Statistical Analysis).

**Author's response 5:** Thank you for this valuable comment. We agree that repeated measurements provide important longitudinal information, and we have revised the manuscript accordingly to clarify the structure of the longitudinal data and the approach used for analysis.

However, due to the limited sample size and the small number of outcome events, longitudinal modeling was not statistically feasible and could have resulted in unstable estimates. Therefore, to preserve the assumption of independence between observations, we selected a single assessment for each patient: the home-based 6MWT measurement obtained immediately before the clinical decision regarding repeat WLL. For patients who did not undergo repeat WLL, the last available assessment during follow-up was used for analysis.

The number and timing of assessments during follow-up, as well as this analytical approach, have now been clarified in the revised Methods and Results sections.

**Reviewer Comments 6:** 6. Participant flow, missing data, and group denominators (STROBE Items 13 and 14):

> The manuscript states that all eligible patients were enrolled but does not report how many were assessed, excluded, lost to follow-up, unable to complete home testing, or included in each analysis. The number of patients in the repeat-WLL and no-WLL groups is also absent from the tables, preventing evaluation of selection, attrition, and sparse-data bias (source: Methods—Study Population and Eligibility Criteria; Results; Tables 1–3).
>
> Author to-do list:
>
> * Report the numbers assessed, excluded with reasons, enrolled, followed, and analyzed (source: Methods; Results).
> * Provide a participant flow diagram (source: Methods—Study Population).
> * Add group sample sizes to Tables 2 and 3 (source: Tables 2 and 3).
> * Report missing observations for every predictor and outcome (source: Results).
> * Explain the method used to handle missing data (source: Statistical Analysis).

**Author's response 6:** Thank you for the valuable comment. These points have been incorporated into the revised manuscript.

**Reviewer Comments 7:** Candidate predictors and statistical procedures are incompletely reported (STROBE Items 12 and 16):

> The methods state only that "appropriate statistical tests" were used, while the results present univariate group comparisons and multivariable coefficients without naming the tests, describing distribution checks, defining coding, reporting confidence intervals, or explaining variable selection. "Marginally significant" and "clinically important" labels are applied based on P values without a prespecified evidentiary basis (source: Methods—Data Collection and Statistical Analysis; Tables 2 and 3).
>
> Author to-do list:
>
> * Name the statistical test used for each comparison in Table 2 (source: Statistical Analysis; Table 2).
> * Define the coding and scale of oxygen dependence, symptoms, WLL outcome, and all model variables (source: Methods; Tables 2 and 3).
> * Describe distributional assessment and the use of parametric or nonparametric procedures (source: Statistical Analysis).
> * Report effect estimates with 95% confidence intervals rather than P values alone (source: Results; Tables 2 and 3).
> * Remove post hoc labels such as "marginally significant" and "clinically important" unless supported by prespecified criteria and effect estimates (source: Results 3.3; Table 3).

**Author's response 7:** Thank you for the valuable comment. These points have been incorporated into the revised manuscript.

**Reviewer Comments 8:** Unsupported predictive threshold and lack of validation (STROBE Items 11, 16, and 20):

> The manuscript states that walking approximately 300 m or less identifies patients at highest risk, but no threshold-selection method, sensitivity, specificity, predictive values, ROC analysis, or validation is reported. The value appears to derive from the mean of the WLL group rather than a validated decision threshold. The study therefore establishes, at most, an exploratory association—not a clinically usable cutoff (source: Results—Clinical Interpretation; Discussion; Conclusion).
>
> Author to-do list:
>
> * Remove the 300-m clinical threshold unless it is derived using a stated method and validated (source: Results 3.4; Conclusion).

> * If threshold analysis is retained, report sensitivity, specificity, predictive values, and confidence intervals (source: Statistical Analysis; Results).
> * Distinguish model development from model validation (source: Methods; Discussion).
> * State explicitly that external validation is required before clinical implementation (source: Discussion; Conclusion).

**Author's response 8:** Thank you for this important comment. The manuscript revised based on your valuable comment. We agree that the previously mentioned 300-m value was not derived from a formal threshold analysis and should not be interpreted as a validated clinical cutoff. We have removed this statement from the revised manuscript and modified the interpretation of 6MWT findings to reflect an exploratory association rather than a clinically applicable prediction threshold. We have also clarified that external validation in larger prospective cohorts is required before implementation of any 6MWT-based decision threshold.

**Reviewer Comments 9:** Telemedicine effectiveness is not directly evaluated (STROBE Items 7, 15, and 20):

> The conclusion asserts that telemedicine enabled timely detection and may enhance surveillance, but the study does not compare telemedicine with conventional follow-up, report detection times, referral delays, adherence, acceptability, technical failures, access barriers, or adverse events. The design can describe a remotely monitored cohort but cannot establish that telemedicine improved timeliness or outcomes (source: Abstract—Conclusion; Methods—Remote Monitoring; Discussion; Conclusion).
>
> Author to-do list:
>
> * Define telemedicine process outcomes, including adherence, completed contacts, missing contacts, and technical failures (source: Methods; Results).
> * Report the interval from detected deterioration to in-person assessment and repeat WLL (source: Results).
> * Remove comparative effectiveness claims not supported by a control group (source: Abstract; Discussion; Conclusion).
> * Present feasibility conclusions as preliminary and descriptive (source: Discussion; Conclusion).

**Author's response 9:** The manuscript revised based on your valuable comment.

**Minor Comments:**

**Reviewer Comments 1:** Tables and figures:

> The manuscript contains three tables and no figures or images. Tables 1–3 are all explicitly cited in the main text. Add the repeat-WLL and no-WLL sample sizes to Tables 2 and 3; define all abbreviations and variable coding in footnotes; replace "Significance" labels with estimates

and confidence intervals; standardize negative signs and decimal precision; and clarify whether "oxygen dependence" is binary, ordinal, or continuous (source: Tables 1–3).

**Author's response 1:** Thank you for this important comment. We have clarified the observation time point used for each variable reported in Tables 2 and 3. Specifically, analyses were based on the home-based 6MWT assessment immediately preceding repeat WLL decision or the last available assessment during follow-up for patients without repeat WLL. Repeated measurements were not treated as independent observations because of the limited sample size and potential within-patient correlation. We have also revised Table 2 by adding group denominators, defining variable coding, and clarifying statistical presentation.

Reviewer Comments 2: Early-stage editorial and language red flags:

> The manuscript requires focused language editing. "Patients walked for six minutes" in the Background should be "Patients walk for six minutes" when describing the general test; "mean age was 36.7 ± 14.9 years old" should be "mean age was 36.7 ± 14.9 years"; "This underscores the PAP's continued central role in care" should be "This underscores WLL's continued central role in PAP care"; and "WLL decisions should follow the body's functional signal" should be replaced with neutral scientific wording such as "WLL decisions should incorporate validated measures of functional decline." Correct "Methods2.1," "Results3.," and ") Table 3(" and remove conversational transitions such as "So" (source: Background; Methods heading; Results heading; Discussion; Conclusion).

**Author's response 2:** Thank you for this helpful comment. The manuscript has been carefully revised for language clarity, scientific tone, and formatting consistency. We corrected inaccurate wording, replaced conversational expressions with neutral scientific terminology, revised the statements regarding WLL and PAP management, and corrected formatting errors in section headings, table citations, and punctuation throughout the manuscript.

Reviewer Comments 3: Terminology and abbreviation consistency:

> Standardize "6MWT," "6 MWT," and "6 MWD"; use "repeat WLL" consistently rather than alternating among "WLL," "need for WLL," and "WLL indication"; and distinguish home-based, remotely supervised, telemonitored, and clinic-based assessments accurately. Define GM-CSF, COPD, IPF, $SpO_2$, HR, and PAP at first use as applicable (source: Abstract; Background; Methods; Results).

**Author's response 3:** Thank you for this valuable comment. We have revised the manuscript to ensure consistent terminology and abbreviation use throughout the text. The term "6MWT" is now used consistently to refer to the six-minute walk test, while "6MWT distance" is used when referring specifically to walking distance. The outcome definition was standardized as "repeat WLL" throughout the manuscript. We also clarified the distinction between home-based assessment, telemedicine-based monitoring, and clinic-based evaluation, and defined all abbreviations at their first appearance.

Reviewer Comments 4: Redundant background and discussion:

> The first and fourth Discussion paragraphs repeat that WLL was introduced in the 1960s, remains the principal treatment, is safe and effective, and provides durable benefit. Consolidate this material into one concise paragraph and use the space to discuss study-specific limitations (source: Discussion paragraphs 1 and 4).

**Author's response 4:** Thank you for this constructive comment. We agree that the introductory discussion regarding WLL history, efficacy, and long-term benefits was repetitive. We have consolidated the relevant information into a single concise paragraph and revised the Discussion to focus more specifically on the findings of the present study, methodological considerations, and study limitations.

**Reviewer Comments 5:** Reference currency:

> Ten references were published in 2011 or earlier: Refs 1, 2, 4, and 7–14. Review these sources for replacement with more recent and directly relevant evidence where appropriate, while retaining Ref 1 or other genuinely seminal sources with explicit justification. The citation attributed in the text to "Bois et al. (2010)" should be corrected to "du Bois et al." and reconciled with the reference-list year of 2011 (source: Background; References 1, 2, 4, and 7–14).

The study addresses a potentially useful remote-monitoring strategy in a rare disease, but the binary outcome has been modeled incorrectly, the small cohort cannot support the current multivariable claims, and the temporal, longitudinal, and decision-making structure is insufficiently reported. Substantial reanalysis and major revision are required before the proposed predictive or clinical conclusions can be evaluated.

**Author's response 5:** Thank you for this comment. These were revised.

# #Reviewer1

**Reviewer Comments 1:** Dear Authors,

Thank you for submitting your manuscript to the journal. Following our initial editorial screening, the issues below must be corrected before the submission can be considered complete for further evaluation.

Please note that references are very important for publication, and all cited sources must be identifier-present when DOI/PMID is supplied, cited appropriately in the manuscript text, and suitable for the journal.

2-1- Author identification and declaration sections are incomplete:

* What the author wrote: The submission metadata contains four full author names, contributions, ethics approval, funding, and conflict-of-interest information, but the manuscript does not provide a visible author byline, affiliations, corresponding-author details, or complete declaration sections. (source: manuscript front matter; embedded submission metadata)
* Why correction is required: This must be corrected because the manuscript is not compliant with basic editorial requirements regarding author identification, correspondence, ethics, funding, competing interests, and contribution disclosure. (source: manuscript front matter; embedded submission metadata)
* To do: Add the complete author byline, affiliations, corresponding-author details, ethics approval, informed consent, funding, competing-interest, and author-contribution sections to the manuscript. (source: manuscript front matter; embedded submission metadata)

**Author's response 1:** We thank the editorial office for identifying this issue. The manuscript has been revised accordingly, and the complete author byline, affiliations, corresponding author information, ethics approval, informed consent statement, funding statement, competing interests' declaration, and author contribution section have now been added to the revised manuscript.

**Reviewer Comments 2:** Data-availability information is missing:

* What the author wrote: The manuscript does not report whether the participant-level data, statistical dataset, data dictionary, questionnaires, or analytic materials are available. (source: entire manuscript; embedded metadata)
* Why correction is required: This must be corrected because the manuscript is not compliant with basic editorial requirements regarding research-data transparency and reproducibility. (source: entire manuscript)
* To do: Add a data-availability statement specifying what de-identified data and analytic materials are available, from whom, under what conditions, and subject to which ethical restrictions. (source: entire manuscript)

**Author's response 2:** Thank you for this valuable comment. We have added a Data Availability Statement to the revised manuscript, specifying the availability of de-identified data and analytic materials, as well as the ethical restrictions governing data access.

**Reviewer Comments 3:** Reference-list integrity requires correction:

* What the author wrote: The manuscript contains 17 references with DOI or PMID identifiers, but 10 require further internal review because they were published in 2011 or earlier or lack an exact standalone in-text citation. (source: manuscript body; References)
* References with DOI/PMID: Ref 1 - Rosen et al., Ref 2 - Trapnell et al., Ref 3 - Leth et al., Ref 4 - Luisetti et al., Ref 5 - Kiani et al., Ref 6 - Holland et al., Ref 7 - Enright et al., Ref 8 - Lama et al., Ref 9 - Hallstrand et al., Ref 10 - Lederer et al., Ref 11 - du Bois et al., Ref 12 - Ben-Abraham et al., Ref 13 - Beccaria et al., Ref 14 - Michaud et al., Ref 15 - Jouneau et al., Ref 16 - Tay et al., Ref 17 - Fijołek et al. (source: References)
* References requiring further review:

* Ref 1 - Rosen et al. — published in 1958; retain only with explicit justification as the seminal description of PAP. (source: Reference 1). **It is necessary.**
* Ref 2 - Trapnell et al. — published in 2003; replace with a newer source unless its retention is specifically justified. (source: Reference 2). **Deleted**.
* Ref 4 - Luisetti et al. — published in 2010; replace with a newer treatment review unless its retention is justified. (source: Reference 4) **Deleted**
* Ref 7 - Enright et al. — published in 2003; replace with newer functional-test evidence unless its retention is justified. (source: Reference 7) **Deleted**
* Ref 8 - Lama et al. — published in 2003; replace with newer disease-relevant evidence unless its retention is justified. (source: Reference 8) **Deleted**
* Ref 9 - Hallstrand et al. — published in 2005; replace with newer evidence unless its retention is justified. (source: Reference 9) **Deleted**
* Ref 10 - Lederer et al. — published in 2006 and not cited in the manuscript text; no exact standalone in-text citation to this reference was found. (source: manuscript body; Reference 10) **Revised**
* Ref 11 - du Bois et al. — published in 2011; replace with newer validation evidence unless its retention is justified. (source: Reference 11) **Revised**

* Ref 12 - Ben-Abraham et al. — published in 2002; replace with current perioperative WLL guidance unless its retention is justified. (source: Reference 12) **Revised**

* Ref 13 - Beccaria et al. — published in 2004; replace with more recent long-term outcome evidence unless its retention is justified. (source: Reference 13) **Revised**
* Ref 14 - Michaud et al. — published in 2009 and not cited in the manuscript text; no exact standalone in-text citation to this reference was found. (source: manuscript body; Reference 14) **Revised**
* Ref 15 - Jouneau et al. — not cited in the manuscript text; no exact standalone in-text citation to this reference was found. (source: manuscript body; Reference 15) **Revised**
* Why correction is required: This must be corrected because the manuscript is not fully verifiable without current evidence and a consistent relationship between in-text citations and reference-list entries. (source: manuscript body; References)
* To do: Verify every affected reference, add exact in-text citations where justified, replace outdated sources with newer and directly relevant literature where appropriate, and remove any unused entry. (source: manuscript body; References)

**Author's response3:** Thank you for this valuable comment. We carefully reviewed the reference list and the corresponding in-text citations to ensure consistency and accuracy throughout the manuscript. Wherever possible, outdated references were replaced with more recent and directly relevant studies. References that were considered essential due to their historical or seminal contributions were retained with appropriate justification. In addition, unused references were removed and citation mismatches were corrected to improve the overall quality, verifiability, and relevance of the reference list.

# #Reviewer 4

Reviewer Comments 1: Thank you for the opportunity to review this manuscript, “Predictive value of the six-minute walk test for telemedicine-based monitoring of pulmonary alveolar proteinosis patients undergoing whole-lung lavage.” The topic is clinically relevant and the telemedicine-based approach is of practical interest. However, my review of the text, statistical analyses, and language identified a number of concerns, listed below as Major and Minor.

A) Major Revisions

1. Incorrect statistical model for the outcome variable

• The primary outcome (“need for repeat WLL”) is described as binary (yes/no), yet the authors used “Multiple Linear Regression” to model it. For a binary outcome, logistic regression is the appropriate method. Using linear regression for a dichotomous outcome is statistically incorrect, and the β coefficients, SE, and t-values reported in Table 3 are not valid as presented.
• If the outcome was actually intended as a continuous score, this must be clearly defined in the Methods; as written, there is significant ambiguity.

Author’s response 1: We sincerely thank the reviewer for this valuable comment. We agree that multiple linear regression was not appropriate for a binary outcome. Therefore, the statistical analysis was revised throughout the manuscript, and the previous linear regression model was replaced with an exploratory binary logistic regression analysis. The definition of the primary outcome (repeat WLL: yes/no) was clarified in the Methods section, and the Results, tables, Discussion, and Conclusion sections were revised accordingly.

**Reviewer Comments 2:** Inadequate predictor-to-sample-size ratio (overfitting risk)

• With only 21 patients and 6 predictors in the regression model (Table 3), the ratio is approximately 3.5 observations per predictor, far below the accepted minimum of 10–15 per predictor. This creates a serious risk of overfitting and unstable coefficient estimates, which should be explicitly acknowledged as a limitation and factored into interpretation of $R^2 = 0.540$.
• Authors should either reduce the number of predictors (e.g., via univariate pre-selection) or explicitly state this statistical limitation and avoid definitive claims of “independent predictor” status.

**Author’s response 2:** Thank you for this important methodological comment. We agree that the limited sample size and the number of predictors included in the original regression model increased the risk of overfitting and may have resulted in unstable coefficient estimates.

Accordingly, we have revised the analysis by reducing the number of variables included in the multivariable model based on clinical relevance and exploratory univariable analysis. We have

also revised the interpretation of the findings throughout the manuscript and avoided definitive claims regarding independent predictive ability. The term “independent predictor” has been replaced with more cautious wording, such as “associated with” or “potential functional marker,” where appropriate.

Furthermore, we have acknowledged the limited predictor-to-sample-size ratio and the potential risk of model instability as a limitation of this study.

Reviewer Comments 3: Group sample sizes (WLL vs. No-WLL) not reported

• Table 2 and the text compare the WLL and No-WLL groups, but the number of patients in each group (n) is never stated. This is essential for judging statistical power and the validity of the reported p-values, and should be added.

Author’s response 3: Thank you for this valuable comment. We agree that reporting the sample size of each comparison group is essential for appropriate interpretation of the statistical analyses. Accordingly, we have added the number of patients in the WLL and No-WLL groups in Table 2.

Reviewer Comments 4: Statistical tests not specified

• The Statistical Analysis section refers only generically to “appropriate statistical tests” without naming the specific test used for each comparison in Table 2 (independent t-test, Mann-Whitney U, chi-square, etc.). Given the small sample size (n = 21), normality testing and justification for parametric vs. non-parametric test choice are needed.

Author’s response 4: Thank you for your valuable comment. We have mentioned the tests in the method.

Reviewer Comments 5: Inconsistent section numbering

• The Methods section appears as “3. Methods2.1” and the Results section as “4. Results3.1,” indicating a merge error between two different numbering schemes (main section numbers and internal sub-numbering). These headings should be corrected and made consistent.

Author’s response 5: Thank you for this helpful comment. We have carefully reviewed and revised manuscript.

Reviewer Comments 6: Outcome definition not fully specified in Methods

• The Methods do not clearly state how the decision to repeat WLL was made (strictly the criteria in section 2.5, physician judgment, or a combination). This is essential for reproducibility.

Author's response 6: Thank you for this helpful comment. We have carefully reviewed and revised manuscript.

Reviewer Comments 7: No confidence intervals reported

• For all comparisons in Table 2 and all regression coefficients in Table 3, only p-values are given; 95% CIs are not reported. Given the small sample size, CIs are important for correct clinical interpretation.

Author's response 7: Thank you for this valuable comment. We have revised the manuscript accordingly and added 95% confidence intervals (CIs).

Reviewer Comments 8: Study limitations not adequately addressed

• Despite the very small sample size (n = 21), the observational design, and the absence of an independent control group, the Discussion lacks a distinct, explicit Limitations paragraph. This should be added as its own subsection.

Author's response 8: Thank you for this valuable comment. We agree that the limitations of the study should be clearly addressed.

**B) Minor Revisions**

Reviewer Comments 1: Redundant sentence in Abstract/Objectives

• The sentence "This study evaluated the predictive value of the Six-Minute Walk Test (6 MWT) for monitoring functional status and guiding clinical decisions after WLL" is repeated verbatim in both the Background/end of Abstract and the Objectives section. Rephrasing is recommended.

Author's response 1: Thank you for this valuable comment. We have revised the manuscript accordingly.

Reviewer Comments 2: Language and grammar issues

Author's response 2: Thank you for this valuable comment. We have revised the manuscript accordingly.

Reviewer Comments 2: Language and grammar issues

• "Patients walked for six minutes" in the Background uses past tense amid otherwise general/definitional present-tense sentences, creating a tense inconsistency; consider changing to "Patients walk..."
• The phrase "WLL decisions should follow the body's functional signal, not isolated laboratory numbers" in the Conclusion uses an informal/metaphorical register ("body's functional signal") that is not appropriate for a research article and should be rewritten more formally.

• The term “double-lumen tube lavage” in the Discussion (around lines corresponding to sections 233 and 241) is conceptually unclear; the intended meaning is likely “lavage performed via double-lumen endotracheal tube,” which should be stated explicitly.
• The sentence beginning “So, 6MWT captures global physiological burden” uses “So” as a sentence-initial connector, which is not standard in formal scientific writing (“Thus” or “Therefore” is preferable).
• There is inconsistent spacing between the number and unit throughout the manuscript (e.g., “6 MWT” in some places vs. “6MWT” without a space elsewhere, particularly in Results and Discussion). This should be standardized.
Author’s response 2: Thank you for this valuable comment. We have revised all of the manuscript.

Reviewer Comments 3: Minor inconsistency between title-page keywords and in-text keywords

• On the title page: “six-minute walk test.” (with an extraneous period), whereas in the main text it appears as “Six-Minute Walk Test” without a period. Please correct for consistency.

Author’s response 3: Thank you for this valuable comment. We have revised the manuscript.

Reviewer Comments 4: Redundant citation of the same claim
• The statement that WLL “remains the mainstay of treatment... technically feasible, safe, and clinically effective” is repeated almost verbatim at the start of the Discussion (ref. 12) and again a few paragraphs later (refs. 14-16). This repetition is unnecessary and the two passages should be merged.
Author’s response 4: Thank you for this valuable comment. We have revised them.

Reviewer Comments 5: Measurement scale not specified for some Table 2 variables

The variables “Oxygen dependence,” “Cough severity,” and “Fatigue” in Table 2 are reported as numeric mean ± SD, but the underlying measurement scale (Likert scale — what range? 0–3? 0–4?) is not specified in the text.

Author’s response 5: Thank you for this valuable comment. We have revised them.

Reviewer Comments 6: Table 3 — regression intercept not reported• The multiple regression table does not report the model intercept, which is needed for a complete presentation of the regression model.

Author’s response 6: Thank you for this comment. We have revised the statistical analysis by applying an appropriate binary logistic regression model for the dichotomous outcome (repeat WLL: yes/no). Therefore, the previous linear regression coefficients and model intercept are no longer applicable. The revised analysis is presented as odds ratios with 95% confidence intervals in Table 3.

Reviewer Comments 7: Title page “Informed Consent” and “Data Availability” fields left blank

• These fields are empty on the title page even though the text describes obtaining written informed consent. These fields should be completed.

Author’s response 7: Thank you for this comment. The missing fields for Informed Consent and Data Availability on the title page have been completed in the revised manuscript. The statements have been added in accordance with the ethical requirements of the study.

## #Reviewer 9

Reviewer Comments: Thank you for presenting your interesting article entitled “Predictive value of the six-minute walk test for telemedicine-based monitoring of pulmonary alveolar proteinosis patients undergoing whole-lung lavage”
This manuscript addresses an important clinical question in a rare disease and evaluates the potential role of a simple, cost-effective, and remotely applicable functional assessment tool for the follow-up of patients with pulmonary alveolar proteinosis (PAP). The topic is clinically relevant, and the manuscript is generally well written with a good standard of English.
However, several issues should be addressed to improve the scientific rigor and clarity of the study:
First, as this study represents a observational case series, the study design should be explicitly stated in the title.
Second, the diagnostic criteria for PAP are insufficiently described. The manuscript currently states only that patients had a "confirmed diagnosis" (Line 84). The authors should clearly specify how the diagnosis was established, including whether bronchoalveolar lavage findings, lung biopsy, anti-GM-CSF antibody testing, or other accepted diagnostic methods were used.
Third, the indications for performing whole-lung lavage (WLL) require clarification. The criteria used to initiate the first WLL, as well as those guiding the decision for repeat WLL during follow-up, should be explicitly defined.
Fourth, if available, the number of prior WLL procedures for each patient should be reported, as previous interventions may influence both disease severity and functional outcomes.
Fifth, in the Abstract (Line 15), the abbreviation mMRC should be written in full at first mention as "modified Medical Research Council dyspnea scale."
Sixth, in Line 233, the manuscript refers to "double-lumen tube lavage," whereas "whole-lung lavage (WLL)" is used consistently elsewhere. Terminology should be standardized throughout the manuscript to avoid confusion.
Seventh, given the small sample size and the case series design, the statistical analysis should be carefully reviewed by a statistician. In particular, the use of multiple linear regression to identify predictors of WLL recurrence requires justification and assessment of its appropriateness.
Finally, as one of the key strengths of this study is the use of telemedicine, the remote monitoring protocol should be described in greater detail. Additional information regarding the telemedicine platform, patient training, standardization of the home-based six-minute walk test, monitoring

procedures, and quality assurance measures would enhance the reproducibility and clinical applicability of the study.

**Author's response:** Thank you for your constructive and valuable comments. We have revised the manuscript accordingly to improve the clarity and scientific rigor of the study. The study design has been explicitly stated as a case series in the title, and the diagnostic criteria for PAP, indications for initial and repeat WLL, and details regarding telemedicine-based monitoring have been expanded in the Methods section. The terminology related to WLL has been standardized throughout the manuscript. The abstract has also been revised to define the mMRC scale at first mention. Furthermore, the statistical analysis has been reassessed and revised using an appropriate model for the binary outcome of repeat WLL, and all related results and interpretations have been updated.

## 2 Revision 1

8 comments · 7 Aug 2026 – 12 Aug 2026

### Referee 4 Reviewer

ACCEPT 7 Aug 2026

Dear Authors,
Thank you for submitting the revised version of your manuscript and for providing detailed, well-reasoned responses to the previous reviewers' comments. After carefully reviewing the revised manuscript, I am pleased to state that the major methodological and statistical concerns have been thoroughly and appropriately addressed. The quality of the paper has improved significantly.
Minor Remaining Consideration:
While the statistical model is now correct, the wide confidence intervals (particularly for mMRC in Table 3, e.g., OR: 15.99, 95% CI: 0.58–437.73) reflect the inherent instability due to the limited sample size. However, I greatly appreciate that you have explicitly acknowledged this limitation in your Discussion and conclusions, interpreting the findings as "exploratory associations" rather than definitive predictive claims. This is exactly the right approach, and I do not require further changes on this point.

### Sogol Asgari Reviewer

MAJOR REVISION 7 Aug 2026

Thank you for the opportunity to review this manuscript. The topic is interesting and clinically relevant. The manuscript is generally well written. I have a few comments that may improve the quality of the paper.

The title seems stronger than the study findings. Since the study mainly evaluates an association, the title and conclusions should be revised accordingly.
The sample size is small, so the results of the logistic regression should be interpreted with caution.
Please clarify when the home-based 6MWT was performed in relation to WLL.
There is a repeated paragraph in the Introduction that should be removed.
Please check the references carefully, as a few of them do not seem directly related to the topic.

Overall, this is an interesting study. Addressing these points would improve the manuscript.

### Referee 5 Reviewer

MINOR REVISION 7 Aug 2026

The manuscript is well written and addresses an interesting topic. However, I recommend that the authors carefully evaluate whether the sample size is adequate to support their conclusions. If the sample size is limited, this limitation should be clearly acknowledged, and the conclusions should be interpreted with appropriate caution.

### Referee 1 Reviewer

MINOR REVISION 8 Aug 2026

Thank you for sharing this revised manuscript. I appreciate the considerable effort the authors have put into addressing the reviewers' comments — the statistical reanalysis alone represents substantial additional work, and the responsiveness to methodological feedback is evident throughout. Below is a detailed review of the

revised version (the one titled "Clinical utility of the six-minute walk test for telemedicine-based monitoring of pulmonary alveolar proteinosis: a case series of patients undergoing whole-lung lavage").

Statistical model. The switch from multiple linear regression to binary logistic regression is the single most important fix, and it has been done correctly — Table 3 now reports odds ratios with 95% CIs rather than uninterpretable β coefficients for a dichotomous outcome. The predictor set was also reduced from six to three prespecified variables (6MWT distance, mMRC score, oxygen dependence), which meaningfully reduces overfitting risk relative to the original model. That said, with only 12 events and 3 predictors, the events-per-variable ratio is still around 4, below the conventional minimum of 10. The manuscript acknowledges this in the limitations paragraph, which is appropriate, but it's worth being explicit in the cover letter that this remains an unresolved constraint rather than something fully corrected — reviewers may push back if the limitation isn't framed clearly enough.

Outcome definition and temporal sequence. Section 2.2 now defines the primary outcome and clarifies that the analyzed 6MWT assessment preceded the clinical decision. This addresses Reviewer 1's Comment 1 reasonably well. One residual concern: the text states that treating physicians "were aware of routine clinical follow-up findings" but that "repeat WLL decisions were not based solely on home-based 6MWT results" — this is a soft claim that doesn't fully rule out incorporation bias, since awareness of the 6MWT trend could still have influenced clinical judgment even if it wasn't the sole factor. This is worth flagging as an acknowledged limitation rather than treating the concern as closed.

Participant flow and group sizes. Figure 1 and the group denominators (n=9 vs. n=12) in Tables 2 and 3 are now present, which satisfies Reviewer 1's Comment 6 and the parallel comments from Reviewer 4 and the editorial office.

Statistical tests and reporting. Section 2.8 now names the Shapiro–Wilk test, independent-samples t-test, Mann–Whitney U, and Fisher's exact/chi-square tests, with a stated rationale for the choice between parametric and nonparametric tests. Confidence intervals are reported in both Table 2 (implicitly via p-values, though not CIs on the mean differences themselves) and Table 3 (properly, as OR CIs). Reviewer 1's Comment 7 was about reporting effect estimates with CIs "rather than P values alone" — Table 2 still reports only means, SDs, and p-values without CIs on the between-group differences. This is a partial fix.

Predictive threshold. The unsupported 300-m cutoff has been removed, and the interpretation has been correctly reframed as an exploratory association rather than a validated clinical threshold. This directly and adequately resolves Reviewer 1's Comment 8.

Telemedicine effectiveness claims. The abstract and conclusion now hedge appropriately ("its effectiveness in improving clinical outcomes or guiding WLL decisions requires confirmation in larger prospective studies"), rather than asserting that telemedicine improved timeliness or outcomes without a comparator. This addresses Reviewer 1's Comment 9.

Remaining gaps not fully resolved:

The diagnostic criteria for PAP are still not specified. Section 2.4 (Eligibility criteria) only states "confirmed PAP" without indicating whether diagnosis relied on BAL findings, lung biopsy, or anti-GM-CSF antibody testing — this was Reviewer 9's second point and remains open.

The abstract still uses "mMRC" without spelling out "modified Medical Research Council dyspnea scale" at first mention; it's only defined later in the Methods (Section 2.7). Reviewer 9 specifically flagged the abstract instance (Line 15), so this hasn't actually been fixed where it was requested, even though the term is defined elsewhere in the manuscript.

There's a citation-reference mismatch in the Discussion: "Deleanu et al. (2015)" is cited as reference 11, but reference 11 in the list is Fijołek et al., not Deleanu — Deleanu doesn't appear in the reference list at all. This

wasn't flagged by any reviewer but is a factual error that needs correcting before resubmission, since it will likely be caught during copyediting or by a subsequent reviewer.

There's an internal inconsistency in the consent documentation. The Eligibility criteria section and the Informed Consent declaration both state "written informed consent was obtained from all participants," while the Human Ethics Approval Declaration explains at length that verbal consent was used specifically because in-person visits for written consent weren't feasible, and that this was separately approved by the ethics committee. These two claims can't both be accurate as written, and a careful reviewer or editor will likely notice the contradiction.

**Elham Memary** Reviewer

MINOR REVISION 9 Aug 2026

Dear Editor-in-Chief,
Following a thorough review of the manuscript, I would like to propose a revision of the title to better reflect the scope and exploratory nature of the findings.
The multivariable analysis indicates that the 6-minute walk test (6MWT) did not reach statistical significance (P>0.05). Therefore, using terms like “Clinical Utility” in the title may be misleading. The proposed titles shift the focus from “proving utility” to “exploring the potential of monitoring,” which is more consistent with the data.

1. Proposed Title Revisions

The current title may inadvertently suggest a definitive prognostic or clinical utility study, which is inconsistent with the study’s sample size and the observed statistical outcomes. I suggest the following options:

Option 1: “Telemedicine-Based Functional Monitoring in Pulmonary Alveolar Proteinosis: A Pilot Experience of Post-Whole-Lung Lavage Follow-up”

Option 2: “Perspectives on Home-Based 6-Minute Walk Test as a Monitoring Tool for Pulmonary Alveolar Proteinosis Patients Following Whole-Lung Lavage: An Exploratory Observational Study”

Furthermore, I have identified a structural issue regarding the placement of certain analytical sections that requires attention.
Relocation of Descriptive Statistics:
I noted that section “3.2 Descriptive comparison of quantitative variables” is currently placed at the end of the manuscript. For logical flow and adherence to standard reporting guidelines (such as CONSORT or STROBE), this section must be moved to its appropriate position within the Results section, immediately following the initial patient characteristics.
I believe these adjustments will present the manuscript in a more academically robust, logically organized, and accurate light.

**Seyyedeh Masumeh Hashemi** Reviewer

MINOR REVISION 10 Aug 2026

Thank you for addressing the reviewers’ comments. However, upon careful review of the revised manuscript, I noted that two issues have not been adequately addressed.

First, although the authors stated that the abbreviation mMRC had been defined in the Abstract, this correction does not appear to have been incorporated into the revised manuscript. Please define the abbreviation at its first occurrence.

Second, the authors stated that the diagnostic criteria for pulmonary alveolar proteinosis (PAP) had been added to the Methods section. However, the revised manuscript still only states that patients had "confirmed PAP" and had undergone at least one WLL, without specifying how the diagnosis of PAP was established.

Please clearly describe the diagnostic method used in the study population. In particular, clarify whether the diagnosis was based on clinical and radiological findings, BAL characteristics/cytology, PAS staining, serum anti-GM-CSF antibody testing, histopathology, or a combination of these methods. If the diagnosis was based on the characteristic milky or turbid appearance of the BAL fluid obtained during WLL, this should be explicitly stated.

### Associate Editor

MINOR REVISION 12 Aug 2026

Dear EIC
Based on the reviewer's comments, the manuscript needs minor revisions.

### Editor-in-Chief

MINOR REVISION 12 Aug 2026

Dear authors,
Based on the reviewer's comments, the manuscript needs minor revisions.

3

# Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

# Response to Reviewer Comments

## #Reviewer1

**Comment 1:** 1. Proposed Title Revisions

The current title may inadvertently suggest a definitive prognostic or clinical utility study, which is inconsistent with the study's sample size and the observed statistical outcomes. I suggest the following options:

Option 1: "Telemedicine-Based Functional Monitoring in Pulmonary Alveolar Proteinosis: A Pilot Experience of Post-Whole-Lung Lavage Follow-up"

Option 2: "Perspectives on Home-Based 6-Minute Walk Test as a Monitoring Tool for Pulmonary Alveolar Proteinosis Patients Following Whole-Lung Lavage: An Exploratory Observational Study"

**Author's response 1:** Thank you for the valuable comment. These points have been incorporated into the revised manuscript.

**Comment 2:** Furthermore, I have identified a structural issue regarding the placement of certain analytical sections that requires attention.
Relocation of Descriptive Statistics:
I noted that section "3.2 Descriptive comparison of quantitative variables" is currently placed at the end of the manuscript. For logical flow and adherence to standard reporting guidelines (such as CONSORT or STROBE), this section must be moved to its appropriate position within the Results section, immediately following the initial patient characteristics.
I believe these adjustments will present the manuscript in a more academically robust, logically organized, and accurate light.

**Author's response 2:** Thank you for the valuable comment. The manuscript was revised based on your valuable comment.

## #Reviewer2

**Reviewer Comments 1:** First, although the authors stated that the abbreviation mMRC had been defined in the Abstract, this correction does not appear to have been incorporated into the revised manuscript. Please define the abbreviation at its first occurrence.

**Author's response 1:** Thank you for the valuable comment. It was revised.

**Reviewer Comments 2:** Second, the authors stated that the diagnostic criteria for pulmonary alveolar proteinosis (PAP) had been added to the Methods section. However, the revised manuscript still only states that patients had "confirmed PAP" and had undergone at least one WLL, without specifying how the diagnosis of PAP was established. Please clearly describe the diagnostic method used in the study population. In particular, clarify whether the diagnosis was based on clinical and radiological findings, BAL characteristics/cytology, PAS staining, serum anti-GM-CSF antibody testing, histopathology, or a combination of these methods. If the diagnosis was based on the characteristic milky or turbid appearance of the BAL fluid obtained during WLL, this should be explicitly stated.

**Author's response 2:** .Thank you for your comment and reminder. All patients suspected of having PAP underwent thorough clinical and laboratory evaluation. Examinations included spirometry, DLCO, ABG and 6- minute walk test, the results of which were all suspicious for PAP. All patients were subjected to CT scan of the lungs and ground-glass opacities with superimposed interlobular septal thickening and intralobular septal thickening, known as "crazy paving", were detected. Subsequently, fiber optic bronchoscopy and broncho-alveolar lavage were performed and the resulting sample was pathologically examined. Intra-alveolar accumulation of surfactant components and lipoproteinaceous material confirmed the diagnosis. In cases with any doubt, an open lung biopsy and pathological examination confirmed the disease.

## #Reviewer 4

Reviewer Comments 1: The manuscript is well written and addresses an interesting topic. However, I recommend that the authors carefully evaluate whether the sample size is adequate to support their conclusions. If the sample size is limited, this limitation should be clearly acknowledged, and the conclusions should be interpreted with appropriate caution.

Author's response 1: We sincerely thank the reviewer for this valuable and constructive comment. We fully agree that the relatively small sample size is an important consideration when interpreting the findings of this study. We have carefully acknowledged this issue in the **Limitations** section of the manuscript, where the limited sample size and its potential impact on the statistical power and generalizability of the findings are explicitly discussed. We have also emphasized that the findings should be interpreted with appropriate caution and considered preliminary, particularly regarding the multivariable analysis. We appreciate the reviewer's valuable suggestion, which has helped us further clarify the limitations and appropriate interpretation of our findings.

## #Reviewer 6

Reviewer Comments: Dear Authors,
Thank you for submitting the revised version of your manuscript and for providing detailed, well-reasoned responses to the previous reviewers' comments. After carefully reviewing the revised manuscript, I am pleased to state that the major methodological and statistical concerns have been thoroughly and appropriately addressed. The quality of the paper has improved significantly.
Minor Remaining Consideration:
While the statistical model is now correct, the wide confidence intervals (particularly for mMRC in Table 3, e.g., OR: 15.99, 95% CI: 0.58–437.73) reflect the inherent instability due to the limited sample size. However, I greatly appreciate that you have explicitly acknowledged this limitation in your Discussion and conclusions, interpreting the findings as "exploratory associations" rather than definitive predictive claims. This is exactly the right approach, and I do not require further changes on this point.

**Author's response:** We sincerely appreciate the reviewer's valuable guidance and positive assessment, which have substantially contributed to improving the methodological rigor, clarity, and overall quality of our manuscript.

## #Reviewer 7

Reviewer Comment: It is true that this study results showed that patients who had frequent lavage have lower 6MWT levels, but the reverse may not be true. That is, anyone who has a lower 6MWT level must therefore need frequent lavage, because this issue can also be due to other reasons.

Methods:
Considering rareness of the PAP and your sample size, this study can be classified as an Observational study instead of case series.

Can repeated 6MWT measurements help eliminate confounding factors?

**Author's response:** We sincerely thank for the valuable and insightful comments. We have revised the study design terminology throughout the manuscript and replaced **"case series"** with **"exploratory observational study"** where appropriate. We have also incorporated the Editor's valuable recommendation regarding the interpretation of the 6MWT findings at the beginning of the Discussion. Specifically, we have clarified that the observed association between lower 6MWT performance and repeat WLL should not be interpreted as a definitive predictive relationship and that potential confounding factors should be considered. We have also noted that serial 6MWT assessments may provide additional insight into longitudinal functional changes and should be further evaluated in prospective studies.

## #Reviewer 8

Reviewer Comment: Thank you for the opportunity to review this manuscript. The topic is interesting and clinically relevant. The manuscript is generally well written. I have a few comments that may improve the quality of the paper.

The title seems stronger than the study findings. Since the study mainly evaluates an association, the title and conclusions should be revised accordingly.
The sample size is small, so the results of the logistic regression should be interpreted with caution.
Please clarify when the home-based 6MWT was performed in relation to WLL.
There is a repeated paragraph in the Introduction that should be removed.
Please check the references carefully, as a few of them do not seem directly related to the topic.

Overall, this is an interesting study. Addressing these points would improve the manuscript.

**Author's response:** We sincerely thank the reviewer for the careful evaluation of our manuscript and for the constructive and valuable comments. We greatly appreciate the reviewer's positive assessment of the clinical relevance and overall quality of the study. Regarding the period which 6MWT was performed post WLL, as mentioned in the text, remote monitoring was conducted weekly during the first month and monthly thereafter through telephone or text-based communication. If any negative changes were detected in the results of the test, the patient was recommended to refer to the hospital for further evaluation.

In response to the reviewer's comments, we have carefully revised the manuscript.

## #Reviewer 10

Reviewer Comment 1: Statistical model.The switch from multiple linear regression to binary logistic regression is the single most important fix, and it has been done correctly — Table 3 now reports odds ratios with 95% CIs rather than uninterpretable β coefficients for a dichotomous outcome. The predictor set was also reduced from six to three prespecified variables (6MWT distance, mMRC score, oxygen dependence), which meaningfully reduces overfitting risk relative to the original model. That said, with only 12 events and 3 predictors, the events-per-variable ratio is still around 4, below the conventional minimum of 10. The manuscript acknowledges this in the limitations paragraph, which is appropriate, but it's worth being explicit in the cover letter that this remains an unresolved constraint rather than something fully corrected — reviewers may push back if the limitation isn't framed clearly enough.

**Author's response 1:** We sincerely thank the reviewer for this important and valuable comment. We have addressed this point in the revised manuscript by explicitly acknowledging the limited

events-per-variable ratio, the potential for model instability and overfitting, and the resulting wide confidence intervals in the Limitations section. We have also clarified that these constraints remain inherent to the limited sample size and that the multivariable findings should therefore be interpreted as exploratory associations rather than definitive predictive effects.

We greatly appreciate the reviewer's thoughtful guidance, and the suggested clarification has now been incorporated into the revised manuscript.

Reviewer Comment 2: Outcome definition and temporal sequence. Section 2.2 now defines the primary outcome and clarifies that the analyzed 6MWT assessment preceded the clinical decision. This addresses Reviewer 1's Comment 1 reasonably well. One residual concern: the text states treating physicians "were aware of routine clinical follow-up findings" but that "repeat WLL decisions were not based solely on home-based 6MWT results" — this is a soft claim that doesn't fully rule out incorporation bias, since awareness of the 6MWT trend could still have influenced clinical judgment even if it wasn't the sole factor. This is worth flagging as an acknowledged limitation rather than treating the concern as closed.

**Author's response 2:** We sincerely thank the reviewer for this valuable and insightful comment. We have addressed this concern in the revised manuscript by explicitly acknowledging the potential for partial incorporation bias in the Limitations section.
We greatly appreciate the reviewer's thoughtful guidance, which has helped us improve the transparency and methodological rigor of the manuscript.

Reviewer Comment 3: Participant flow and group sizes. Figure 1 and the group denominators (n=9 vs. n=12) in Tables 2 and 3 are now present, which satisfies Reviewer 1's Comment 6 and the parallel comments from Reviewer 4 and the editorial office.

**Author's response 3:** We sincerely thank the reviewer. We are grateful for the reviewer's valuable guidance, which has helped improve the clarity and transparency of the manuscript.

Reviewer Comment 4: Statistical tests and reporting.Section 2.8 now names the Shapiro–Wilk test, independent-samples t-test, Mann–Whitney U, and Fisher's exact/chi-square tests, with a stated rationale for parametric vs. nonparametric choice. Confidence intervals are reported in both Tables 2 (implicitly via p-values, though not CIs on the mean differences themselves) and Table 3 (properly, as OR CIs). Reviewer 1's Comment 7 was about reporting effect estimates with CIs "rather than P values alone" — Table 2 still reports only means, SDs, and p-values without CIs on the between-group differences. This is a partial fix.

**Author's response 4:** We sincerely thank the reviewer for this valuable and constructive comment. We have revised Table 2 accordingly by adding the appropriate effect estimates with 95% confidence intervals for the between-group comparisons, in addition to the reported P-values. We have also clarified the statistical methods used for each type of comparison in the Methods (Section 2.8), including the rationale for the use of parametric and nonparametric tests

and the corresponding reporting of effect estimates and confidence intervals. We greatly appreciate the reviewer's careful assessment and valuable guidance, which has helped us improve the completeness and transparency of the statistical reporting in the revised manuscript.

Reviewer Comment 5: Predictive threshold. The unsupported 300-m cutoff has been removed, and the interpretation has been correctly reframed as an exploratory association rather than a validated clinical threshold. This directly and adequately resolves Reviewer 1's Comment 8.

Telemedicine effectiveness claims. The abstract and conclusion now hedge appropriately ("its effectiveness in improving clinical outcomes or guiding WLL decisions requires confirmation in larger prospective studies"), rather than asserting that telemedicine improved timeliness or outcomes without a comparator. This addresses Reviewer 1's Comment 9.

**Author's response 5:** We sincerely thank the reviewer for the careful evaluation and for confirming that this concern has been appropriately addressed. We greatly appreciate the reviewer's valuable guidance.

Reviewer Comment 6: The diagnostic criteria for PAP are still not specified. Section 2.4 (Eligibility criteria) only states "confirmed PAP" without indicating whether diagnosis relied on BAL findings, lung biopsy, or anti-GM-CSF antibody testing — this was Reviewer 9's second point and remains open.

**Author's response 6:**

Thank you for your comment and reminder. All patients suspected of having PAP underwent thorough clinical and laboratory evaluation. Examinations included spirometry, DLCO, ABG and 6- minute walk test, the results of which were all suspicious for PAP. All patients were subjected to CT scan of the lungs and ground-glass opacities with superimposed interlobular septal thickening and intralobular septal thickening, known as "crazy paving", were detected. Subsequently, fiber optic bronchoscopy and broncho-alveolar lavage were performed and the resulting sample was pathologically examined. Intra-alveolar accumulation of surfactant components and lipoproteinaceous material confirmed the diagnosis. In cases with any doubt, an open lung biopsy and pathological examination confirmed the disease.

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2.7). Reviewer 9 specifically flagged the abstract instance (Line 15), so this hasn't actually been fixed where it was asked for, even though the term is defined elsewhere in the manuscript.

**Author's response 7:** We sincerely thank the reviewer for this helpful comment. We have corrected this issue in the revised manuscript.

**Reviewer Comment 8:** There's a citation-reference mismatch in the Discussion: "Deleanu et al. (2015)" is cited as reference 11, but reference 11 in the list is Fijołek et al., not Deleanu — Deleanu doesn't appear in the reference list at all. This wasn't flagged by any reviewer but is a factual error that needs correcting before resubmission, since it will likely be caught at copyediting or by a subsequent reviewer.

**Author's response 8:** We sincerely thank you. We have corrected this issue in the revised manuscript.

**Reviewer Comment 9:** There's an internal inconsistency in the consent documentation. The Eligibility criteria section and the Informed Consent declaration both state "written informed consent was obtained from all participants," while the Human Ethics Approval Declaration explains at length that verbal consent was used specifically because in-person visits for written consent weren't feasible, and that this was separately approved by the ethics committee. These two claims can't both be accurate as written, and a careful reviewer or editor will likely notice the contradiction.

**Author's response 9:** We sincerely thank the reviewer for identifying this important inconsistency. We have carefully revised the manuscript to resolve the discrepancy and ensure consistency across the Eligibility Criteria, Informed Consent, and Human Ethics Approval Declaration sections. We greatly appreciate the reviewer's careful attention to this important ethical and reporting issue.

## 3 Revision 2

2 comments · 31 Aug 2026 – 31 Aug 2026

### Associate Editor

ACCEPT 31 Aug 2026

Dear Editor-in-Chief,
Following the first round of review, I have evaluated the revised manuscript and the authors' point-by-point responses. Despite the extensive feedback provided by seven independent reviewers, the authors have successfully addressed all major and minor comments. These revisions have significantly strengthened the manuscript. Therefore, I recommend that the paper be accepted for publication in the Journal.

### Editor-in-Chief

ACCEPT 31 Aug 2026

Dear Authors,
I am pleased to inform you that you have comprehensively addressed all the points raised by the reviewers. Your revised manuscript now meets the requirements for publication. Congratulations on this achievement!