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Evaluation of an ARIMA-Based Algorithm for Detecting Respiratory Events After Lung Transplantation: Case-Crossover Analysis with Descriptive Comparison to a Deviation-Based Model

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Incorporated Association, a non-profit organization in Japan. The remaining authors declare that they have no competing interests.

Abstract

Background:

Home spirometry enables longitudinal monitoring of lung transplant recipients, but its utility is limited by measurement variability and reliance on fixed reference thresholds, which may fail to capture clinically relevant changes. We evaluated an autoregressive integrated moving average (ARIMA)-based algorithm for detecting respiratory events from daily home spirometry, alongside exploratory analyses of diagnosis-specific pre-event trends.

Methods:

We developed an ARIMA-based algorithm to identify abnormalities in daily FEV1 trajectories implemented within a web-based application. Performance was evaluated using a nested case-crossover design among 21 patients who experienced acute or chronic respiratory events. Case windows were defined as the 7 days preceding event onset, and control windows as 7-day periods occurring 90 days before the event. For each window, we assessed whether abnormalities were detected by the ARIMA-based algorithm and by a previously reported deviation-based algorithm. Associations between algorithm-detected abnormalities and respiratory events were estimated separately for two algorithms using conditional logistic regression. Additionally, we explored the number of detected events by specific clinical diagnoses. As an exploratory analysis, we examined the linear trends over three predefined pre-event intervals (0–14, 14–45, and 14–90 days before the event) for each individual to explore whether patterns differed by event type.

Results:

Of 21 events, both the ARIMA-based and deviation-based algorithms detected 11 events overall. Abnormalities identified by the ARIMA-based algorithm were strongly associated with respiratory events (OR 10.0; 95% CI 1.28–78.1; p = 0.028). The ARIMA-based algorithm identified most acute events (10/15; pneumonia and acute rejection) but detected few chronic or slowly progressive events (1/6; CLAD-related or pleural effusion). In contrast, the deviation-based algorithm detected fewer acute events (7/15) but captured more chronic or slowly progressive events (4/6). Exploratory trend analyses suggested that gradual FEV1 declines often preceded chronic events, indicating that trend features may aid discrimination diagnosis for events.

Conclusions:

The ARIMA-based algorithm may help detect acute respiratory events based on individual daily home spirometry FEV1 trend after lung transplantation. Incorporating trend features may complement detection of chronic or slowly progressive events. Combining short-term deviation detection with longer-term trend characterization may potentially support early event detection in home spirometry-based post-transplant surveillance.

Clinical trial number: Not applicable.

Background

Lung transplantation is an established therapeutic option for patients with end-stage lung diseases; however, long-term outcomes remain limited by acute respiratory events such as rejection and infection. Early detection of these events is clinically crucial, as delayed intervention may lead to irreversible graft injury and progression to chronic lung allograft dysfunction (CLAD) [1].

To facilitate early identification of graft dysfunction, home-based pulmonary function monitoring has been widely implemented in lung transplant recipients. Daily measurements of forced expiratory volume in one second (FEV1) allow closer surveillance than conventional hospital-based pulmonary function tests. Nevertheless, despite the increasing availability of longitudinal home spirometry data, there is no universally established algorithm for detecting clinically meaningful declines in pulmonary function that reliably indicate acute respiratory events [2].

We previously developed and evaluated a deviation-based algorithm implemented in the LT-FollowUp Version 3 system, in which abnormal FEV1 decline was defined using patient-specific mean values and standard deviations over the past three months. That algorithm demonstrated a strong association between detected FEV1 abnormalities and clinically confirmed acute respiratory events [3]. However, several limitations were identified. In particular, the algorithm may be less sensitive during periods of postoperative improvement in pulmonary function, such as within the first year after transplantation, and during slowly progressive declines observed in conditions such as CLAD, where acute superimposed events may be difficult to distinguish from long-term trends [4].

Autoregressive Integrated Moving Average (ARIMA) models are widely used to analyze time-series data characterized by trends, autocorrelation, and stochastic variability. By explicitly modeling temporal structure, ARIMA-based prediction intervals may offer an alternative framework for identifying abnormal deviations from expected pulmonary function trajectories in lung transplant recipients. Such an approach has the potential to accommodate postoperative recovery trends and gradual long-term changes in lung function [5].

The primary objective of this study was to evaluate an ARIMA-based algorithm for detecting respiratory events using home spirometry data in lung transplant recipients, employing the same case-crossover framework and dataset as our previous study to enable direct comparison with a validated deviation-based algorithm [6]. Detection performance by clinical diagnostic categories (acute respiratory events such as acute rejection and infection, and chronic respiratory events such as CLAD) was also compared. In addition, an exploratory analysis was conducted in which individual FEV1 trajectories were examined to identify trend patterns according to clinical event type.

Methods

This study received approval from the Research Ethics Committee of the Faculty of Medicine, The University of Tokyo (approval date: July 17, 2025; approval number: 2406-(12)). Informed consent was obtained using an opt-out approach. Information regarding the study, including its objectives and procedures, was made publicly available on the institutional website, enabling individuals to decline participation if they so wished. As no opt-out requests were submitted, informed consent was deemed to have been obtained from all participants included in the study.

Study Design and Data Source

This study used the same dataset as our previously published study of lung transplant recipients monitored with the LT-FollowUp system [3]. LT-FollowUp is a web-based platform that enables home-based spirometry with twice-daily measurements and real-time data transmission to clinicians. The present analysis reused the original cohort without modification to inclusion criteria, follow-up period, or outcome definitions, thereby isolating the impact of an alternative anomaly detection algorithm.

The primary analysis employed a nested case-crossover design to estimate the association between abnormalities detected by an ARIMA-based algorithm and the respiratory events confirmed by physicians. The magnitude of association was compared with that of a previously reported deviation-based method. We further examined the number of events detected by the two algorithms descriptively across major clinical diagnostic categories. In addition, an exploratory analysis was performed to explore whether pre-event FEV1 trajectory patterns depending on event diagnosis.

Study Population

All lung transplant recipients at the University of Tokyo Hospital who used the LT-FollowUp system during the study period were screened for inclusion. Only the first acute respiratory event after initiation of LT-FollowUp was analyzed for each patient.

Eligibility criteria, exclusion criteria, and data completeness requirements were identical to those described in the prior study [3]. In brief, patients were eligible if they (1) had undergone lung transplantation at the University of Tokyo Hospital and (2) had a data filling rate of at least 30% in either morning or evening measurements, defined as the number of days with recorded inputs divided by the total number of follow-up days. To ensure stability of longitudinal estimation, this filling rate threshold was required to be met during both the 0–90 day and 91–180 day periods preceding an acute respiratory event.

Patients were excluded if spirometry data were missing during the week immediately prior to the event or if an acute respiratory event occurred within three months of initiating LT-FollowUp. Follow-up was conducted from October 2020 through December 2023.

Description of the ARIMA-based Algorithm

We developed an algorithm based on the ARIMA model (hereinafter, ARIMA-based algorithm) to help detect abnormalities for lung transplant patients based on their daily FEV1 by home spirometry. In this study, longitudinal FEV1 measurements were modeled using a non-seasonal ARIMA (1,1,1) model, applied uniformly across all patients. The model specification was defined a priori based on clinical considerations.

First-order differencing (d = 1) was applied to render the FEV_1 time series approximately stationary by removing non-stationary trends. This approach assumes that first-differenced FEV_1 values (i.e., changes between consecutive measurements) form a stationary process, which is appropriate for modeling short-term fluctuations in post-transplant pulmonary function. Importantly, differencing removes the underlying clinical trajectory – including postoperative improvement and long-term decline – from the series; consequently, the ARIMA model captures deviations from this local trend rather than the trend itself. Formal stationarity testing, such as the Augmented Dickey–Fuller or KPSS tests, was not performed. This decision reflects the study's focus on identifying deviations from expected short-term trajectories rather than establishing strict stationarity for long-term prediction. Higher-order differencing ($d \geq 2$) was not pursued, as over-differencing can introduce spurious autocorrelation. Given the objective of short-term deviation detection, d = 1 was deemed appropriate. The autoregressive (p = 1) and moving average (q = 1) terms were chosen to capture short-term temporal dependence and residual autocorrelation while maintaining model simplicity and robustness. Higher-order autoregressive or moving average components were not incorporated to avoid overfitting, to preserve interpretability, and to ensure stable performance across patients with varying data density.

The ARIMA model was used pragmatically to generate one-step-ahead predictions and corresponding prediction intervals. To mitigate the influence of acute deterioration on baseline estimation and to avoid contamination of the predictive model by early pathological changes, the most recent 14 days of FEV1 observations prior to each evaluation point were excluded from model fitting.

Definition of CASE: Respiratory Events Confirmed by Physicians

Respiratory events were defined according to established clinical diagnostic criteria, including pneumonia, acute rejection, anastomotic complications, pleural effusion and other graft-related conditions requiring hospitalization or bronchoscopy. Diagnostic procedures were consistent with the prior analysis to ensure comparability. Respiratory events were categorized based on final clinical diagnosis into acute-onset events (e.g., infection, acute rejection, stent obstruction) and chronic/delayed-onset events (e.g., CLAD, pleural effusion) for the additional and exploratory analyses.

Definition of EXPOSURE: Abnormality detected by the ARIMA-based Algorithm

We used the ARIMA-based algorithm described above to identify abnormalities for patients. First, an abnormal FEV1 value was defined as an observed measurement falling below the lower bound of the model-based prediction interval, calculated as: Observed FEV1 < Predicted FEV1 − 2 × SE. To reduce false alerts attributable to isolated measurement noise, a temporal aggregation rule was applied. Specifically, abnormality was defined as the presence of ARIMA-based abnormal FEV1 on at least three days within a 7-day window. When fewer than seven FEV1 measurements were available during a given window, exposure was defined as the occurrence of alerts in at least the same proportion (≥ 3/7) of available measurements, consistent with the criteria used in the previous deviation-based analysis [3].

Definition of Case and Control Windows

The conceptual schema of case-crossover design is shown in Supplementary Fig. 1. Case windows were defined as the 7-day period immediately preceding hospitalization for an acute respiratory event, while control windows were defined as the 7-day period 90 days prior to hospitalization, allowing each patient to serve as their own control, consistent with the prior study.

Statistical Analysis

For the primary analysis examining the association between the abnormalities detected by an ARIMA-based algorithm and the respiratory events confirmed by physicians, we used a conditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs). This OR was compared with that from the previously reported deviation-based algorithm descriptively. Then, we described the number of events detected by the two algorithms (ARIMA-based, deviation-based) for each event type. Given the limited number of cases per category, no formal inferential testing or interaction analysis was performed; thus, this analysis was intended solely to characterize algorithm behavior rather than support statistical inference. As an exploratory analysis, individual pre-event FEV1 trajectories were examined by estimating linear slopes over three predefined intervals (0–14, 14–45, and 14–90 days before the event). Slope estimates were treated as continuous measures and used descriptively to characterize patterns of pulmonary function change preceding respiratory events. Rather than applying predefined thresholds or binary classifications, we focused on the direction and relative magnitude of FEV1 change across intervals to explore whether characteristic trajectory patterns differed according to physician-confirmed diagnoses. This analysis was intended to provide a clinically intuitive description of longitudinal trends without imposing arbitrary cutoffs or diagnostic rules. All analyses were conducted using R (version 4.3.3). Conditional logistic regression was performed using the survival package.

Results

Study Population and Event Characteristics

The study population, inclusion and exclusion criteria, follow-up period, and data completeness were identical to those reported in our previous deviation-based analysis and are summarized in Supplemental Fig. 1. Of 163 lung transplant recipients screened, 95 patients met inclusion criteria for this analysis.

Among these, 21 patients experienced acute or chronic respiratory events: seven cases of acute rejection, seven cases of pneumonia, four cases of CLAD-related events, two cases of pleural effusion, and one case of bronchial stent obstruction, as detailed in Supplemental Table 1.

Overall Performance of the ARIMA-Based Algorithm

Among the 21 case windows, ARIMA-based algorithm detected 11 cases (i.e., 11/21 exposure-positive case windows, true positive), whereas two abnormalities were detected in 21 control windows (i.e., 2/21 exposure-positive control windows, false positive). Conditional logistic regression accounting for within-patient matching indicated a significant association between ARIMA-detected abnormalities and respiratory events (OR, 10.0; 95%CI, 1.28 to 78.1; p = 0.028). In contrast, the deviation-based algorithm detected 11 abnormalities out of 21 case windows and 1 out of 21 control windows, also showing a statistically significant association with acute events (OR, 5.42×10^{5}; 95%CI, 3.79×10^{-193} to 7.74×10^{203}; p = 0.0002). The extremely large OR may reflect sparse data and should be interpreted with caution. Results are summarized in Table 1.

Table 1
Results from the Case-Crossover Analysis

Algorithm	Cases window (n = 21)	Control window (n = 21)	OR (95%CI)	P value
ARIMA-based	11 (52%)	2 (10%)	10 (1.28 to 78.1)	0.028
Deviation-based	11 (52%)	1 (5%)	5.42×10^{5} (3.79×10^{-193} to 7.74×10^{203})	0.0002

Stratified Performance by Clinical Diagnosis

Detection of respiratory events by event type and specific diagnosis is summarized in Table 2.

Table 2
Detection of respiratory events by event type and specific diagnosis.

Clinical diagnosis	No. of events	ARIMA-based algorithm, n (%)	Deviation-based algorithm, n (%)
Acute-onset events	**15**	**10 (67)**	**7 (47)**
Pneumonia	7	5 (71)	1 (14)
Acute rejection	7	4 (57)	5 (71)
Bronchial stent obstruction	1	1 (100)	1 (100)
Chronic/delayed-onset events	**6**	**1 (17)**	**4 (67)**
CLAD-related events	4	1 (25)	3 (75)
Pleural effusion	2	0 (0)	1 (50)
Total	**21**	**11 (52)**	**11 (52)**

- **Acute-onset events (n = 15)**: The ARIMA-based algorithm detected 10 of 15 events, while the deviation-based algorithm detected 7 of 15 events. Specifically, among pneumonia cases (n = 7), ARIMA detected 5 events versus 1 by the deviation-based model; among acute rejection cases (n = 7), ARIMA detected 4 versus 5 by the deviation-based model; the single bronchial stent obstruction case was detected by both algorithms.
- **Chronic/delayed-onset events (n = 6)**: The ARIMA-based algorithm detected 1 of 6 events, whereas the deviation-based model detected 4 of 6 events. No pleural effusion (0/2) and only one CLAD event (1/4) were detected by the ARIMA-based algorithm, compared with 1 of 2 pleural effusions and 3 of 4 CLAD events by the deviation-based model.

Exploratory Analysis of FEV1 patterns for different events

Table 3 presents the slopes of three pre-event intervals and the diagnosis for each individual. Slope estimates of the three pre-event intervals revealed heterogeneous patterns of FEV1 change across diagnostic categories. Acute-onset events such as pneumonia and acute rejection were frequently characterized by abrupt short-term declines, whereas chronic or delayed-onset events, including CLAD-related conditions, tended to exhibit more gradual and sustained downward trends over longer intervals. Considerable inter-individual variability was observed, and no single slope pattern uniquely defined a specific diagnosis.

Table 3

ARIMA-based alerts and FEV1 decline preceding acute respiratory events after lung transplantation

Patient index	Event Type	Slope 0-14d (m*) ‰	Slope 14-45d (m*) ‰	Slope 14-90d (m*) ‰	Slope 0-14d (e*) ‰	Slope 14-45d (e*) ‰	Slope 14-90d (e*) ‰
1	pneumonia	4.84	6.2	-1	12.58	-2.1	-1.14
2	pneumonia	-25	-1.43	-0.88	-14.96	-1.37	-0.71
3	pneumonia	1.37	-0.25	-0.04	2.97	-1.06	-0.33
4	pneumonia	-3.08	-2.55	0.24	1.76	-1.18	-0.67
5	pneumonia	-7.64	4	1.08	-12.75	5.06	1.73
6	pneumonia	-6.54	-1.81	0.51	-0.71	-1.52	0.2
7	pneumonia	-18.85	9.32	4.59	-8.18	8.03	3.88
8	effusion	-7.49	-7.17	-3.17	-13.01	NA	-1.71
9	effusion	NA	-2.28	-0.95	1.17	-2.08	-0.94
10	stent obstruction	-8.9	-2.15	-0.94	-5.82	-0.81	-1.06
11	acute rejection	2.58	-1.15	-1.67	17.75	-1.1	-0.16
12	acute rejection	0.49	-0.04	-0.06	0.6	-0.18	-0.09
13	acute rejection	-4.27	-0.23	-0.51	-1.81	-1.01	-0.48
14	acute rejection	-25.28	-4.02	-1.58	-24.18	-4.62	-1.73
15	acute rejection	-42.09	-0.46	3.69	-43.78	-1.62	3.33
16	acute rejection	-0.44	-0.29	-0.8	-6.42	-0.28	-1.02
17	acute rejection	-9.12	-5.05	-1.69	-10.44	-2.93	-1.52
18	CLAD	-2.64	-3.3	-4.07	NA	-9.73	-4.01
19	CLAD	0.6	0.99	-0.95	-2.75	0.76	-1.14

*FEV1 decline slopes are expressed in permille per day (‰/day). Morning (m) and evening (e) measurements are reported separately.

CLAD, chronic lung allograft dysfunction.

Patient index	Event Type	Slope 0-14d (m*) ‰	Slope 14-45d (m*) ‰	Slope 14-90d (m*) ‰	Slope 0-14d (e*) ‰	Slope 14-45d (e*) ‰	Slope 14-90d (e*) ‰
20	CLAD	-14.05	1.14	1.19	-10.48	3.58	0.62
21	CLAD	-0.44	-0.5	-0.52	0.05	-0.21	-0.49
*FEV1 decline slopes are expressed in permille per day (‰/day). Morning (m) and evening (e) measurements are reported separately.							
CLAD, chronic lung allograft dysfunction.							

Discussion

In this study, we described an ARIMA-based algorithm implemented in a web application to help detect respiratory events based on daily home spirometry trajectory for lung transplant recipients. The nested case-crossover analysis indicated that the ARIMA-based algorithm preferentially detected acute respiratory events characterized by rapid, short-term declines in FEV1. While the previously reported deviation-based algorithm identified more events with slow, progressive declines such as CLAD, this higher detection rate reflects its reliance on historical averages rather than true sensitivity to acute changes. Exploratory analyses further suggested that incorporating certain pre-event patterns depending on the event type, suggesting that relative slope patterns across multiple time windows may provide contextual information complementary to algorithm-based alerts.

Interpreting longitudinal home spirometry data poses two fundamental challenges. First, measurements obtained in the home setting are subject to greater variability than laboratory-based spirometry, due to differences in patient technique, effort, and device handling. Second, conventional alert algorithms typically rely on deviations from a fixed reference value, which require frequent recalibration and may fail to capture clinically meaningful changes during recovery or gradual decline. By modeling each patient's expected FEV1 trajectory and short-term variability, the ARIMA-based approach may address these limitations and emphasizes abrupt declines likely to reflect acute pathological events.

When comparing the ARIMA-based algorithm with the deviation-based method, distinct detection patterns emerged. ARIMA-based algorithm was more effective at identifying events with abrupt, short-term declines, while the deviation-based algorithm detected a higher proportion of slow, rightward-downward trends. This advantage may be attributable to the deviation-based algorithm's assumption of a stable mean; in cases with sustained FEV1 decline, the historical average may overestimate expected values, leading to more abnormalities being detected. In contrast, the higher detection rate for chronic events by the deviation-based algorithm may reflect its responsiveness to long-term downward shifts in FEV1, including those associated with CLAD.

While ARIMA was less effective at detecting chronic or slowly progressive declines such as those related to CLAD, the exploratory analyses showed that pre-event FEV1 trajectories across multiple time intervals

may help distinguish different event types. Combining short-term deviation detection with explicit trend-based features may provide comprehensive coverage of both acute and chronic respiratory events, thereby overcoming limitations inherent to each individual approach. Because this analysis is only descriptive and hypothesis generating, future studies should evaluate whether these patterns can reliably discriminate among different types of clinical events.

Overall, these results highlight the feasibility and potential clinical value of individualized, time-series-based monitoring of home spirometry data. Although further optimization is necessary, anchoring alerts to each patient's recent variability rather than fixed reference values appears to allow ARIMA-based algorithms to detect clinically actionable acute events while minimizing false alerts.

This study has several limitations that should be considered when interpreting the results. First, the analysis was conducted at a single center with a limited sample size, which may restrict generalizability and precluded extensive subgroup analyses. However, the use of a within-patient nested case-crossover design mitigates between-patient heterogeneity and allows robust estimation of associations despite the modest sample size. Second, the retrospective design does not allow direct evaluation of how algorithm-detected abnormalities influenced clinical decision-making or patient outcomes in real time; nonetheless, the study was designed to evaluate the detection characteristics of the algorithm rather than its clinical impact, which was appropriately addressed within this framework. Third, the exploratory analyses of pre-event FEV1 trajectories were descriptive in nature and were not intended to establish diagnostic or predictive criteria; rather, they provide clinically interpretable summaries of longitudinal patterns that complement the primary case-crossover analysis. Finally, not all abnormalities detected by the algorithms corresponded to clinically actionable events, emphasizing the need for contextual interpretation; however, this reflects a common trade-off in surveillance systems and underscores the importance of clinician oversight when integrating algorithm-based monitoring into clinical practice. These issues warrant further evaluation in prospective studies to determine how algorithm-based monitoring can be optimally integrated into clinical practice.

Conclusion

In conclusion, this ARIMA-based algorithm applied to daily home spirometry data after lung transplantation demonstrated strength in detecting acute respiratory events characterized by short-term functional deterioration. Chronic or slowly progressive events, such as CLAD or pleural effusion, were less frequently captured by ARIMA algorithm alone, but could be partially identified through pre-event FEV1 trajectory trends. The findings highlight the potential value of integrating short-term event detection with longer-term trend characterization for comprehensive post-transplant monitoring.

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Faculty of Medicine, The University of Tokyo (approval number: 2406-(12)).

Consent for publication

Not applicable.

Availability of data and materials

Data are available from the corresponding author upon reasonable request.

Competing interests

KY is affiliated with the Institute for Airway Disease, which has received funding from the University of Tokyo for the development and maintenance of the LT-FollowUp system. YL is employed in the Department of Next-Generation Organ Transplantation, The University of Tokyo Hospital, which is an endowed department supported by the N28 General Incorporated Association, a non-profit organization in Japan. The remaining authors declare that they have no competing interests.

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Authors' contributions

KY: Conceptualization, methodology, software development, statistical analysis, data interpretation, and drafting of the manuscript.
YS: Study design, clinical supervision, interpretation of results, and critical revision of the manuscript.
MY: Clinical data interpretation, validation of outcomes, and manuscript review.
MW: Contribution to system testing, data curation support, and manuscript review.
YL: Clinical interpretation, domain expertise, and critical revision of the manuscript.
MS: Overall supervision of the project, funding acquisition, and final approval of the manuscript.

All authors read and approved the final manuscript.

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