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Domiciliary monitoring of exhaled nitric oxide in the management of asthma: a pilot study

Hongwen Li[1], Jiangtao Lin[2*], Qing Zhang[3], Jingru Wang[4] and Chunxiao Li[2,5]

Abstract

Background Whether asthma patients could benefit from home monitoring for fractional exhaled nitric oxide (flow of 50 mL/s, Fe_{NO50}) is unknown. We explore the application value of home monitoring Fe_{NO50} in daily asthma management.

Methods Twenty-two untreated, uncontrolled asthma patients were selected. Medical history, blood and sputum samples, pulmonary function, Asthma Control Test (ACT), and other clinical data of the subjects were collected. All subjects underwent daily monitoring for four weeks using a Fe_{NO50} monitor and mobile spirometry (mSpirometry). The diurnal differences and dynamic changes were described. Compare the effect-acting time and the relative plateau of treatment between Fe_{NO50} and mSpirometry monitoring.

Results In the first two weeks, the morning median (IQR) level of Fe_{NO50} was 44 (35, 56) ppb, which was significantly higher than the evening median level [41 (32, 53) ppb, $P = 0.028$]. The median (IQR) effect-acting time assessed by Fe_{NO50} was 4 (3, 5) days, which was significantly earlier than each measure of mSpirometry ($P < 0.05$). Fe_{NO50} reached the relative plateau significantly earlier than FEV_1 (15 ± 2 days vs. 21 ± 3 days, $P < 0.001$). After treatment, the daily and weekly variation rates of Fe_{NO50} showed a gradually decreasing trend ($P < 0.05$). The ACT score, sputum eosinophils, and blood eosinophils also significantly improved ($P \leq 0.01$).

Conclusions The daily home monitoring of Fe_{NO50} in asthmatic patients showed significant circadian rhythm, and the sensitivity of Fe_{NO50} in evaluating the response to treatment was higher than mSpirometry. The daily and weekly variation rates of Fe_{NO50} change dynamically with time, which may be used to assess the condition of asthma.

Keywords Asthma, Home monitoring, Fe_{NO50}, Biomarker, Mobile spirometry

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Introduction

Bronchial asthma is a common chronic airway inflammatory disease that causes substantial economic and social burdens [1, 2]. Global Initiative for Asthma (GINA) proposes that the long-term goal of asthma treatment is to achieve symptom control and reduce the risk of acute exacerbations, irreversible airflow limitation, and treatment side effects [3]. At the same time, assessment, adjustment, and monitoring form a continuous cycle in asthma treatment and management strategy. Thus, effective self-assessment and monitoring are vital for asthma patients to achieve long-term treatment goals [4]. However, previous studies have shown that the natural history of asthma is heterogeneous and complex, characterized by circadian rhythms and long-term dynamic changes [5]. Therefore, daily asthma management should include dynamic changes, not just the absolute value of a single measurement.

Studies have shown inconsistencies in symptoms, lung function, and airway inflammation of asthma patients [6]. Self-management based on symptoms and peak expiratory flow (PEF) may still miss patients at risk of severe acute exacerbations in the future [7, 8]. There are also inconsistencies between physician and patient in the assessment of asthma control [9]. So, perhaps more methods are needed for daily asthma assessment. Fractional exhaled nitric oxide (flow of 50 mL/s, Fe_{NO50}) is one of the tools to assess airway inflammation, which is non-invasive, simple, rapid, and is currently mainly used in hospital scenarios [10]. Studies have shown that increasing the number and frequency of Fe_{NO50} monitoring helps predict asthma control status [11]. The daily fluctuation of Fe_{NO50} with different asthma control statuses is different [12]. Studying the long-term variation pattern of Fe_{NO50} measurements makes it possible to identify the risk of acute exacerbations [13–15]. Simultaneous daily monitoring of Fe_{NO50} can also assess compliance [10, 16, 17] and responsiveness to inhaled corticosteroids (ICS) for Type 2 asthma [18–21]. In summary, applying Fe_{NO50} in daily asthma self-monitoring may be significant for asthma management.

More convenient products are applied to self-monitor chronic diseases with the development of science and technology and improved economic levels [7]. The emergence of daily home monitoring devices and innovative applications has made it possible to monitor circadian rhythms and daily changes for asthma patients. However, whether asthma patients could benefit from it is not fully known due to the lack of prognostic data [22]. We attempted to analyze the pattern of longitudinal dynamic changes in Fe_{NO50} after treatment in uncontrolled asthmatic patients who were not regularly treated. To initially explore the value of Fe_{NO50} domiciliary monitoring in the daily management of asthma.

Methods

Subjects

Twenty-two asthma patients who visited the respiratory outpatient of China-Japan Friendship Hospital from October 2019 to December 2021 were prospectively included.

Inclusion criteria: (1) age $\geq$ 18 years old; (2) fulfilled the diagnostic criteria of bronchial asthma defined by GINA 2018 [3]; (3) asthma symptom control was assessed as uncontrolled according to GINA2018 [3].

Exclusion criteria: (1) subjects underwent other interventional clinical trials 30 days before enrollment; (2) subjects with other pulmonary diseases or other severe system diseases that may affect the conduct of the study; (3) subjects with a smoking index > 10 pack-years and a history of smoking for nearly one year; (4) subjects had been on regular asthma therapy within 12 weeks before enrollment; (5) subjects had respiratory tract infection within four weeks before enrollment.

Written informed consent was obtained from each participant. The China-Japan Friendship Hospital ethics committee approved this study (No. 2018-19-k14, approval date: February 6th, 2018).

Study design

Enrollment stage: All subjects performed the asthma control test (ACT) [23], mini-asthma quality of life questionnaire (mini-AQLQ) [24], differential blood count, serum total IgE (enzymatic chemiluminescence, Beckmen Coulter, USA), spirometry, Fe_{NO50} (NIOX Vero, Circassia (Beijing) Medical Device Co., Beijing, China), differential induced sputum count. Mobile spirometry (A1, Breath Home, China) [25] and Fe_{NO50} monitor (NIOX Vero, Circassia (Beijing) Medical Device Co., Beijing, China) were provided to each subject to measure Fe_{NO50} and mSpirometry twice a day over four weeks at home. On the day of enrollment, subjects were trained on using the equipment mentioned above (viewing usage videos and on-site instruction). Subjects were contacted during subsequent use to ensure they correctly mastered the usage methods.

The treatment strategy is not affected by the study, and the patient's treatment plan is formulated by the physician, with medication recommendations based on the GINA 2018 guidelines [3].

Domiciliary monitor stage: Subjects were asked to measure Fe_{NO50} and mSpirometry twice daily during the same period, between 06:00 to 08:00 and 20:00 to 22:00, respectively. Before medication, Fe_{NO50} measurement was first taken, and the results were automatically

recorded on the monitor. When the subjects returned the device, all measurements were transmitted to the computer. Mobile spirometry was taken three times, and the best of the three readings were automatically uploaded to an electronic diary card. Peak expiration flow (PEF), forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), the maximum expiratory flow rate at 75%/50%/25% of the vital capacity (MEF_{75}, MEF_{50}, and MEF_{25}) were collected by mSpirometry.

End of follow-up: ACT, mini-AQLQ, spirometry, Fe_{NO50}, differential blood, and induced sputum count were reviewed again.

Statistical Analysis

The normal distribution data were represented by mean ± standard deviation (sd). Non-normally distributed data were shown as median (interquartile range, IQR). A comparison of each measure before and after follow-up was performed using paired samples t-test and Wilcoxon signed-rank test. The categorical variables were expressed by frequency (composition ratio or percentage) and compared by the chi-square test.

Indicators and calculation formulas representing the variation of Fe_{NO50} and mSpirometry: diurnal variation rate = (highest in a day - lowest in a day)/ (mean of highest versus lowest in a day)×100; mean daily variation rate = mean of diurnal variation rate over 1week; weekly variation rate = (highest over two weeks - lowest over two weeks)/ (mean of highest versus lowest over two weeks)×100.

A repeated-measures analysis of variance was used to compare diurnal differences in Fe_{NO50} logarithmic transformed values and mSpirometry. The least-square method was used to perform curve fitting for each subject's daily monitoring results of Fe_{NO50} and mSpirometry, and the second derivative was used to calculate the inflection point. The inflection point in this study was the transition point for the improvement of Fe_{NO50} and mSpirometry, and its progress slowed down after the inflection point. The relative plateau of treatment was defined as the time to reach the inflection point [26]. The effect-acting time was calculated with a Fe_{NO50} reduction of more than 20% and an improvement in mSpirometry of more than 10% as criteria [10, 27]. ANOVA and Friedman's test were used to compare the relative plateau and the effect-acting of treatment between Fe_{NO50} and mSpirometry. Friedman's test was also used to compare the differences in variation rates of Fe_{NO50} and mSpirometry. A two-tailed p-value of < 0.05 was considered significant. All statistical analyses were performed with SPSS 20 (IBM-SPSS, Armonk, NY, USA) and Matlab software (Mathworks, Inc., Natick, MA, USA).

Table 1 Assessment of the disease condition before and after treatment

	baseline	visit	*P*
ACT (mean ± SD)	16 ± 4	23 ± 2	<0.001
mini-AQLQ (mean ± SD)			
Symptoms	3.84 ± 0.98	5.63 ± 1.22	<0.001
Activity	4.93 ± 1.27	6.01 ± 0.94	0.001
Emotion	3.71 ± 1.34	5.03 ± 1.49	0.002
Environment	3.67 ± 1.49	5.00 ± 1.09	0.001
Overall score	4.06 ± 0.95	5.49 ± 1.04	0.001
Spirometry function			
FEV_1 (L, mean ± SD)	2.47 ± 0.76	2.89 ± 0.60	0.002
FEV_1% (%, mean ± SD)	81.2 ± 20.9	95.9 ± 10.5	<0.001
FEV_1/FVC (%, mean ± SD)	66.4 ± 14.3	72.2 ± 7.8	0.002
PEF (L, mean ± SD)	5.72 ± 1.79	7.27 ± 1.39	<0.001
$MMEF_{75/25}$ (L, mean ± SD)	1.74 ± 0.88	2.15 ± 0.79	0.003
MEF_{75} (L, mean ± SD)	4.00 ± 1.76	5.30 ± 1.26	<0.001
MEF_{50} (L, mean ± SD)	2.06 ± 0.97	2.58 ± 0.81	0.002
MEF_{25} (L, mean ± SD)	0.79 ± 0.44	0.86 ± 0.44	0.026
Fe_{NO50} [ppb, median (IQR)]	80 (56, 117)	27 (18, 47)	<0.001
Sputum eosinophils [%, median (IQR)]	25.8 (15.0, 59.6)	2.8 (1.0, 14.0)	0.004
Blood eosinophils [cells/μL, median (IQR)]	380 (283, 658)	255 (188, 280)	0.001

ACT asthma control test, *mini-AQLQ* mini-asthma quality of life questionnaire, FEV_1 forced expiratory volume in 1-second, *FVC* forced vital capacity, *PEF* peak expiratory flow, $MMEF_{75/25}$ maximum mid expiratory flow, MEF_{75}/ MEF_{50}/ MEF_{25} maximum expiratory flow rate at 75%/ 50%/ 25% of the vital capacity, Fe_{NO50} fractional exhaled nitric oxide (flow of 50 mL/s)

Results

Characteristics of subjects

A total of 22 subjects were included in the study, with 40 ± 14 years old (range 18-64 years). There were slightly more female subjects (n = 14, 63.6%), and the BMI was 23.74 ± 4.60 kg/m^2. The median (IQR) duration of illness was 2.75 (0.84, 8.87) years. The main co-morbidities of the subjects were allergic rhinitis (90.9%), nasal polyps (18.2%), and eczema (22.7%). A history of allergy was present in 59.1% of the subjects, and the median (IQR) serum total IgE level was 185.50 (86.88, 470.75) IU/ml. All subjects received salmeterol/fluticasone (50/250 μg) twice daily, with three subjects receiving montelukast and three subjects receiving tiotropium.

The effective Fe_{NO50} and mSpirometry monitoring were 1035 and 991 times, respectively, and the overall adherence rates were 84.0% (1035/1232) and 80.4% (991/1232), respectively. Of the enrolled subjects, F_{eNO50} baseline level ≥ 50 ppb in 19 (86.4%) patients; sputum eosinophil baseline level ≥ 3% in 21 (95.4%) patients; and 16 (72.7%) patients had blood eosinophils baseline level ≥ 300/μL; 15 patients (68.2%) had FEV_1% baseline level > 80%.

Assessment of the disease condition before and after treatment

After four weeks of treatment, the subjects showed significant improvement in all measurements (Table 1). A significant improvement in the ACT (improvement of more than 3 points) [23] was observed in 17 subjects, with an ACT score ranging from 16 ± 4 points improved to 23 ± 2 points (P < 0.001). In mini-AQLQ, overall score, symptoms, activity, emotion, and environmental scores improved significantly (P < 0.01). The pulmonary function was significantly improved ($P \leq 0.01$). In terms of inflammation, either Fe_{NO50} or sputum and blood eosinophils were significantly reduced (P < 0.01) (Table 1).

Diurnal variation of Fe_{NO50} and mSpirometry

There was a significant diurnal difference in Fe_{NO50} daily monitoring in the first two weeks. The morning median

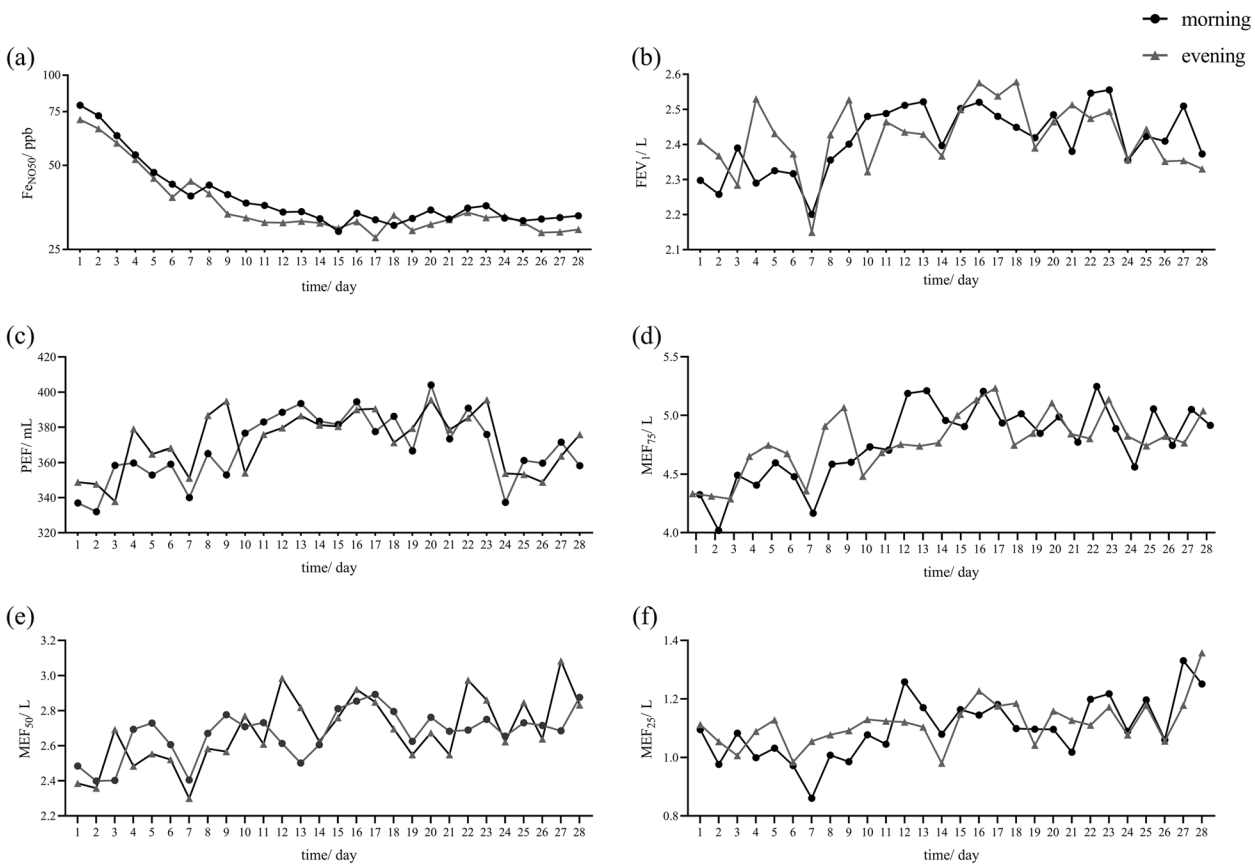

Fig. 1 Diurnal variation curves of domiciliary monitoring. **a** Fe_{NO50} diurnal variation curves, **b** FEV_1 diurnal variation curves, **c** PEF diurnal variation curves, **d** MEF_{75} diurnal variation curves, **e** MEF_{50} diurnal variation curves, **f** MEF_{25} diurnal variation curves. Fe_{NO50}: fractional exhaled nitric oxide (flow of 50 mL/s), FEV_1: forced expiratory volume in 1-second, PEF: peak expiratory flow, MEF_{75}/ MEF_{50}/ MEF_{25}: maximum expiratory flow rate at 75%/ 50%/ 25% of the vital capacity

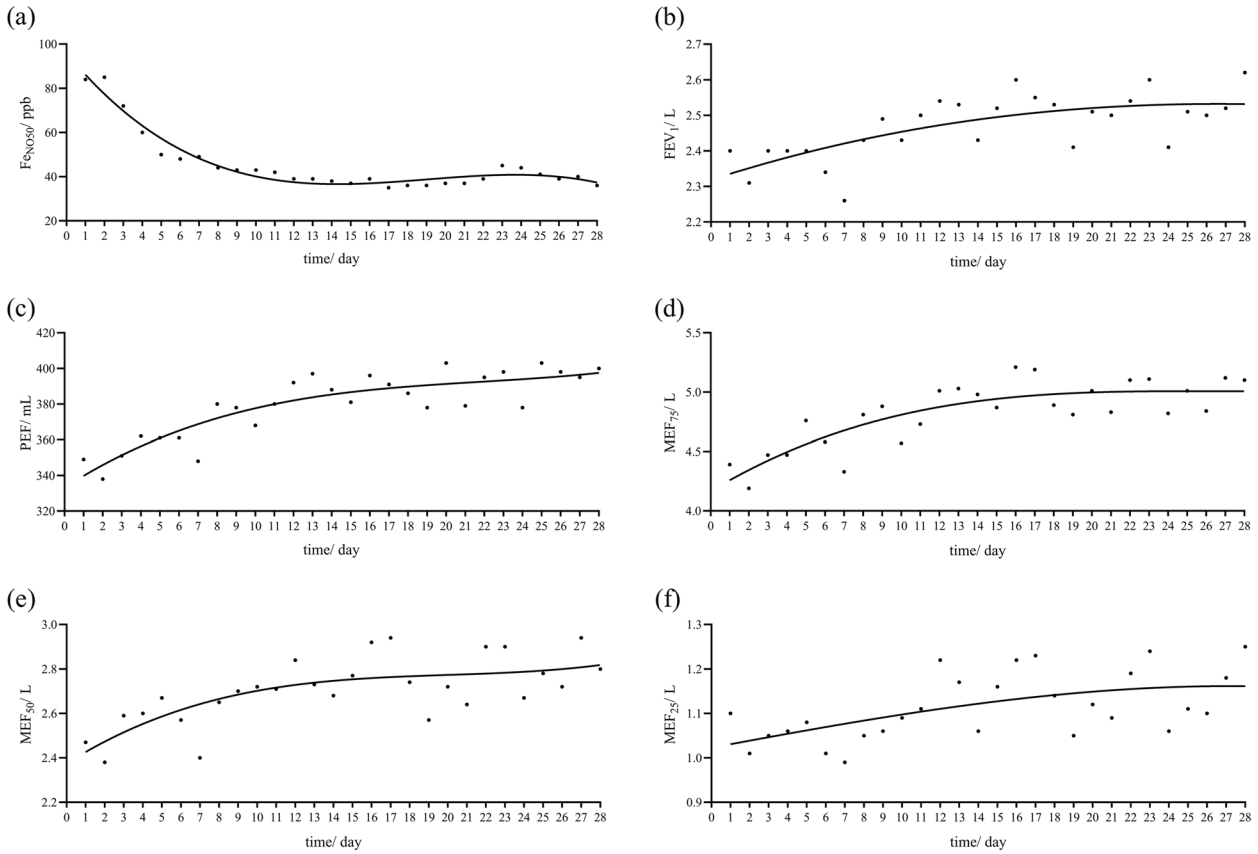

Fig. 2 Fitting curve of domiciliary monitoring. **a** Fitting curve of Fe_{NO50} ($R^2 = 0.698 \pm 0.239$), **b** Fitting curve of FEV_1 ($R^2 = 0.476 \pm 0.270$), **c** Fitting curve of PEF ($R^2 = 0.564 \pm 0.220$), **d** Fitting curve of MEF_{75} ($R^2 = 0.499 \pm 0.203$), **e** Fitting curve of MEF_{50} ($R^2 = 0.503 \pm 0.237$), **f** Fitting curve of MEF_{25} ($R^2 = 0.449 \pm 0.158$). Fe_{NO50}: fractional exhaled nitric oxide (flow of 50 mL/s), FEV_1: forced expiratory volume in 1 second, PEF: peak expiratory flow, MEF_{75}/ MEF_{50}/ MEF_{25}: maximum expiratory flow rate at 75%/ 50%/ 25% of the vital capacity, R^2: coefficient of determination

(IQR) level of Fe_{NO50} was 44 (35, 56) ppb, which was significantly higher than the evening median level [41 (32, 53) ppb, $P = 0.03$]. However, after two weeks of treatment, the significant difference between day and night disappeared ($P = 0.17$). In our study, no significant differences were found in any indicators of mSpirometry between day and night (Fig. 1).

Dynamic fluctuation of Fe_{NO50} and mSpirometry

The best curve fit of the daily monitoring indices of Fe_{NO50} and mSpirometry for the subject is shown in Fig. 2. In general, Fe_{NO50} and Spirometry improved gradually over time with treatment. The median (IQR) effect-acting time assessed by Fe_{NO50} was 4 (3, 5) days, which was significantly earlier than mSpirometry ($P < 0.05$) (Table 2). After Bonferroni correction, Fe_{NO50} reached the relative plateau significantly earlier than FEV_1 (15 ± 2 days vs. 21 ± 3 days, $P < 0.001$), but there was no statistical difference with other indicators of mSpirometry (Table 2).

Table 2 Exhaled nitric oxide fraction and mobile spirometry assessment therapeutic effect

	effect-acting time† [day, median (IQR)]	*P*‡	relative plateau time§ [day, mean ± SD)]	*P*‡
Fe_{NO50}	4 (3, 5)		15 ± 2	
FEV_1	11 (4, 28)	0.001	21 ± 3	<0.001
PEF	8 (4, 20)	0.005	18 ± 3	0.013
MEF_{75}	11 (4, 27)	0.001	14 ± 4	0.754
MEF_{50}	8 (4, 16)	0.009	12 ± 4	0.012
MEF_{25}	12 (4, 28)	<0.001	12 ± 3	0.011

† The effect-acting time was calculated with Fe_{NO50} reduction of more than 20% and mSpirometry improvement of more than 10% as criteria

‡ Fe_{NO50} vs mSpirometry (PEF, FEV_1, MEF_{75}, MEF_{50}, MEF_{25})

§ The relative plateau time in this study was the transition point for improvement of Fe_{NO50} and mSpirometry, and its progress slowed down after the transition point. *Fe_{NO50}*: fractional exhaled nitric oxide (flow of 50 mL/s), *mSpirometry*: mobile spirometry, *PEF*: peak expiratory flow, *FEV_1*: forced expiratory volume in 1-second, *MEF_{75}/ MEF_{50}/ MEF_{25}*: maximum expiratory flow rate at 75%/ 50%/ 25% of the vital capacity

Variation rates of Fe_{NO50} and mSpirometry

After ICS treatment, the daily variation rates of Fe_{NO50} and mSpirometry showed a gradually decreasing trend. The average daily variation rates of Fe_{NO50} and FEV_1 at week 1 were significantly higher than those at week 4 ($P < 0.05$), while there was no significant difference in PEF, MEF_{75}, MEF_{50}, and MEF_{25}. (Fig. 3). There was a substantial reduction in weekly variation rates of Fe_{NO50} and mSpirometry among the participants ($P < 0.05$) (Fig. 4).

Discussion

Through daily domiciliary monitoring of untreated, uncontrolled asthmatic patients, we found significant diurnal differences and daily dynamic changes in Fe_{NO50} and mSpirometry, which can be used to evaluate asthma patients' response to treatment and condition assessment.

Fe_{NO50} is a sensitive biomarker that reflects the inflammation of airway eosinophils [28]. In the early stage of treatment, Fe_{NO50} was significantly higher in the morning than at night in asthmatic patients, consistent with previous findings [21, 29]. Although studies have shown that the decrease of FEV_1 affects the results of Fe_{NO50}, the effect of the change in airway diameter on Fe_{NO50} will be offset when the airway inflammation is higher [30, 31]. However, the disappearance of diurnal differences in asthmatic patients after treatment may be related to airway inflammation and lung function improvement [32, 33].

The primary purpose of this study is to observe the impact of home monitoring on evaluating treatment outcomes. After four weeks of treatment, all participants showed improvement in symptoms and inflammation levels. Therefore, although different treatment plans may cause biases, we believe the impact on the conclusion is relatively tiny.

Peak-trough times of lung function and biomarkers in asthma patients may differ due to individual chronotype differences [34]. Lung function fluctuates between 6-7 days in Fig. 1, but there is no significant difference. Although the measurement period was specified to avoid bias, the personal measurement time or additional measurement period was not selected according to the living habits, thus reducing the reliability of dynamic variation. No significant diurnal differences in lung function were found in this study, which may

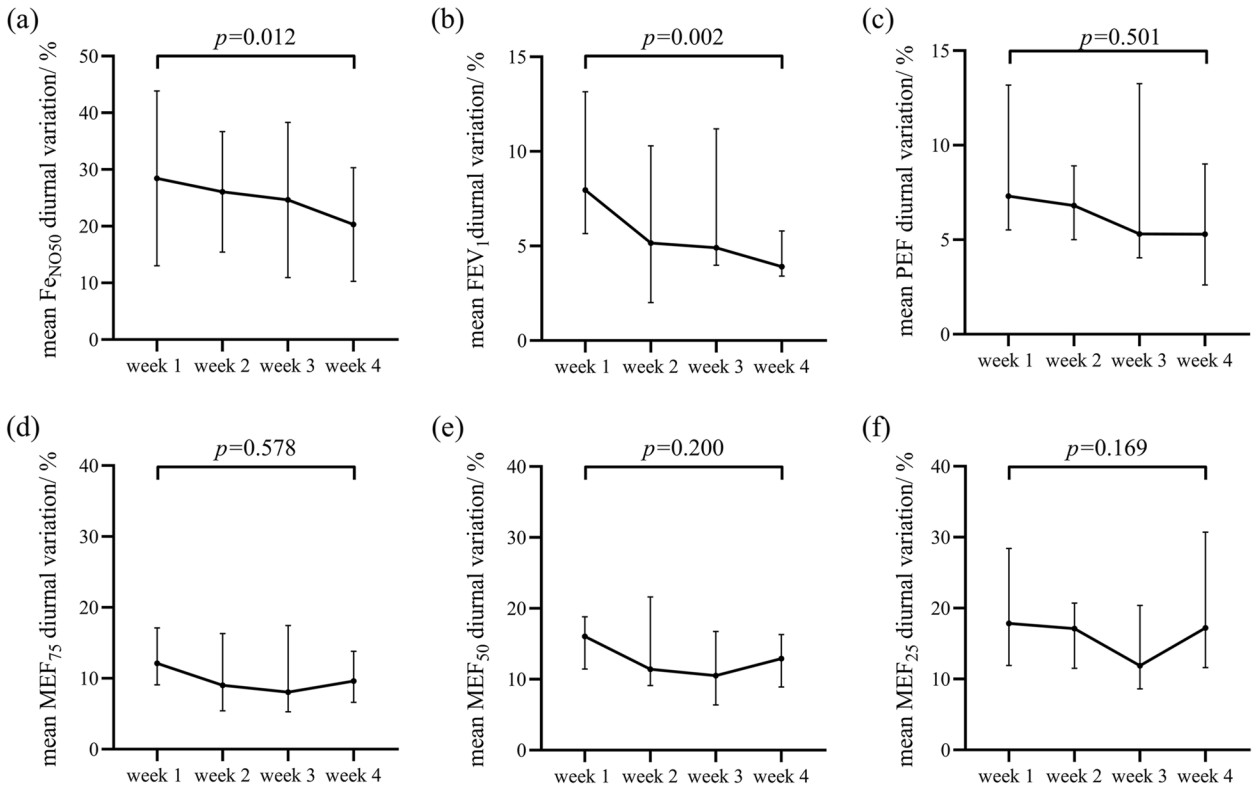

Fig. 3 Daily variation rate curves of domiciliary monitoring. **a** Daily variation rate curves of Fe_{NO50}, **b** Daily variation rate curves of FEV_1, **c** Daily variation rate curves of PEF, **d** Daily variation rate curves of MEF_{75}, **e** Daily variation rate curves of MEF_{50}, **f** Daily variation rate curves of MEF_{25}. Fe_{NO50}: fractional exhaled nitric oxide (flow of 50 mL/s), FEV_1 forced expiratory volume in 1 second, PEF: peak expiratory flow, MEF_{75}/ MEF_{50}/ MEF_{25}: maximum expiratory flow rate at 75%/ 50%/ 25% of the vital capacity

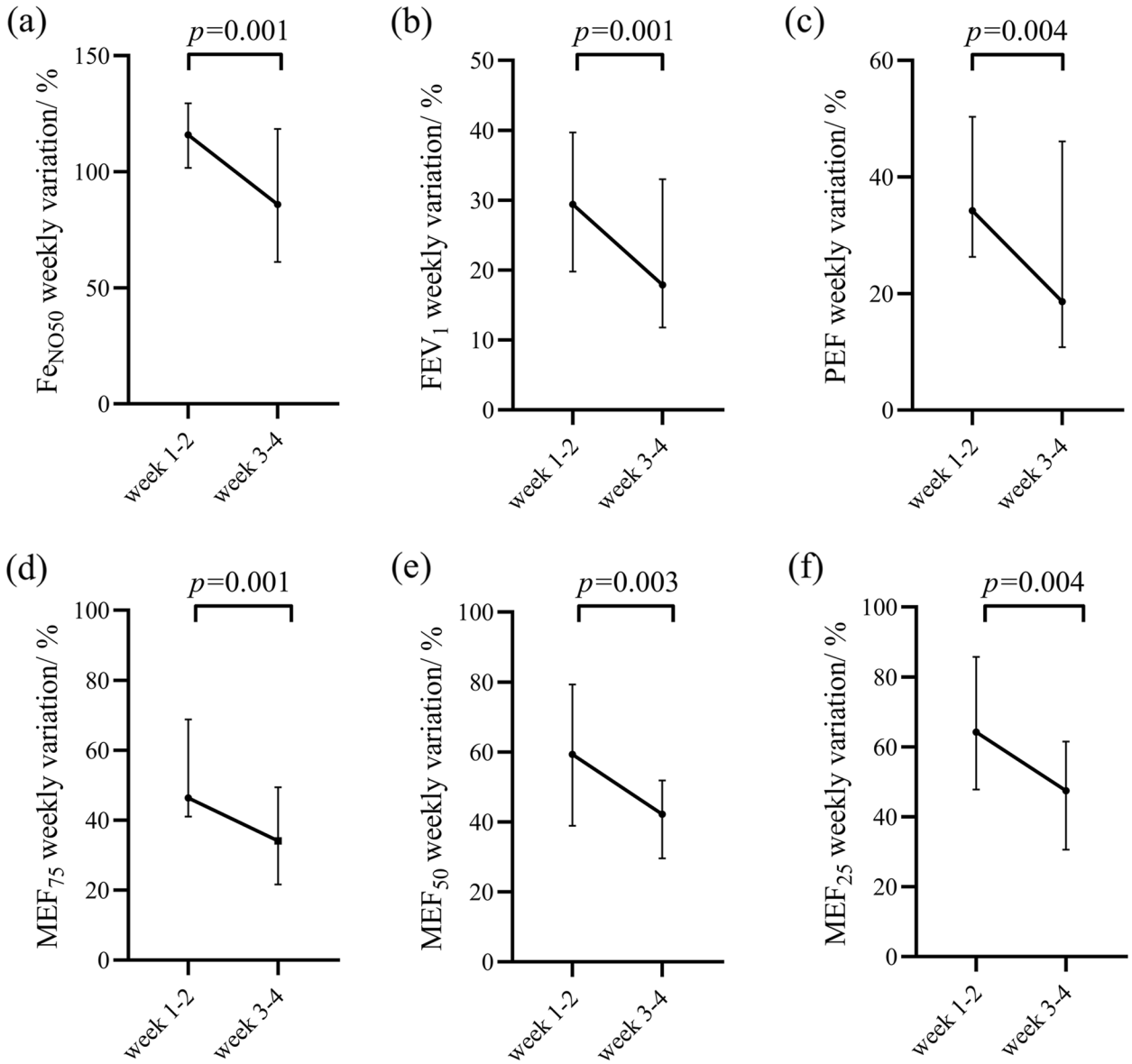

Fig. 4 Weekly variation rates of domiciliary monitoring. **a** Weekly variation rate of Fe_{NO50}, **b** Weekly variation rate of FEV_1, **c** Weekly variation rate of PEF, **d** Weekly variation rate of MEF_{75}, **e** Weekly variation rate of MEF_{50}, **f** Weekly variation rate of MEF_{25}. Fe_{NO50} fractional exhaled nitric oxide (flow of 50 mL/s), FEV_1: forced expiratory volume in 1-second, PEF: peak expiratory flow, MEF_{75}/ MEF_{50}/ MEF_{25}: maximum expiratory flow rate at 75%/ 50%/ 25% of the vital capacity

be related to the relatively good lung function of the included subjects, reducing the sensitivity of diurnal differences.

We characterized the changing trend of Fe_{NO50} in treated Type 2 asthmatic patients. We found that Fe_{NO50} could detect the treatment response for 3-5 days and reached a relative plateau for two weeks. Various indices (PEF, FEV1, MEF_{75}, MEF_{50}, MEF_{25}) of mSpirometry improved gradually, with treatment effect-acting time around 8~12 days and reached a relative plateau of improvement around 2-3 weeks [26, 35]. However, due to the relatively low goodness of fit of the fitting curves for mSpirometry in this study, the treatment turning point of mSpirometry still needs further validation with extensive sample data.

Daily monitoring found that the treatment effect assessed by Fe_{NO50} was significantly earlier than mSpirometry, and the time to reach the relative plateau of treatment was substantially earlier than FEV_1. As we can see, Fe_{NO50} was more sensitive than mSpirometry in assessing responsiveness to asthma therapy. Meanwhile, the latest research indicates that Fe_{NO50} is a risk

biomarker identifying patients at increased risk of lung function decline [36].

After treatment, the daily and weekly variation rates of Fe_{NO50} and mSpirometry showed a decreasing trend. Our study found that the average daily variation of Fe_{NO50} in the first week was significantly higher than in the fourth week. Therefore, the improvement of diurnal variation in Fe_{NO50} can also be used to evaluate the effectiveness of treatment in asthma. This variability over time suggests that the domiciliary monitoring strategy has the advantage of detecting daily and long-term changes in physiology and inflammation, providing substantial evidence to predict future exacerbations and disease assessment. After four weeks of treatment, the participants showed significant improvements in asthma control, quality of life, lung function, and inflammation. With the considerable improvement of symptoms and clinical indicators, the variation rate of domiciliary monitors gradually decreased, which is an essential clinical signal to evaluate the changes in the conditions of asthma patients.

The study had limitations. Firstly, as our study is a pilot study, all admitted patients were untreated type 2 asthma. We did not include patients with severe asthma. Still, previous studies have shown that Fe_{NO50} can also serve as an inflammatory marker for evaluating treatment response in severe asthma populations. [37]. A large sample study was needed to demonstrate the general generalization of the variation pattern. Secondly, complex device use, frequency of daily readings, and strict monitoring times reduce the completion of measures [38, 39]. Still, previous studies have also shown that remote monitoring devices allow subjects to understand their self-control levels and improve patient compliance [40, 41]. Although there was no monitoring of drug adherence, the completion rate of this study exceeded 80%, indirectly indicating that drug adherence is still acceptable. Thirdly, our study could not compare mSpirometry A1 with the lung function laboratory device. The study found that only a portion of mSpirometry A1 (BreathHome, China) met the quality and performance evaluation standards [25]. However, considering this study mainly observed dynamic changes, the research results are still acceptable.

In conclusion, this pilot study of domiciliary monitoring found that Fe_{NO50} in uncontrolled asthma patients has significant diurnal differences and is superior to mSpirometry in assessing sensitivity to treatment response. The dynamic fluctuation of Fe_{NO50} may be available for evaluating disease conditions in asthmatics. Studies with large samples and long observation periods are expected to explore mobile domiciliary monitors in asthma management.

Abbreviations

ACT	Asthma control test
BMI	Body mass index
Fe_{NO50}	Fractional exhaled nitric oxide (flow of 50 mL/s)
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GINA	Global initiative for asthma
ICS	inhaled corticosteroids
IQR	interquartile range
MEF_{75}	Maximum expiratory flow rate at 75% of the vital capacity
MEF_{50}	Maximum expiratory flow rate at 50% of the vital capacity
MEF_{25}	Maximum expiratory flow rate at 25% of the vital capacity
mini-AQLQ	mini Asthma Quality of Life Questionnaire
mSpirometry	mobile spirometry
PEF	peak expiratory flow

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Submission declaration
We confirm that the original manuscript has not been published before, is not currently being considered for publication elsewhere, and has not been posted to a preprint server.

Authors' contributions
H.L. and J.L. designed the study. J.W. and C.L. acquisitions of data or analysis and interpretation of data. Q.Z. and H.L. statistical analysis. H.L. drafting articles. All authors revise the article critically for important intellectual content and final approval of the version to be published.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of China-Japan Friendship Hospital (approval number: 2018-19-k14). Written informed consent was obtained from each participant.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Huang K, Yang T, Xu J, et al. Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. Lancet. 2019;394(10196):407–18.
2. Haselkorn T, Szefler SJ, Chipps BE, et al. Disease Burden and Long-Term Risk of Persistent Very Poorly Controlled Asthma: TENOR II. J Allergy Clin Immunol Pract. 2020;8(7):2243–53.
3. Stewart L, Katial RK. Exhaled nitric oxide. Immunol Allergy Clin North Am. 2012;32(3):347–62.
4. Janson SL, McGrath KW, Covington JK, et al. Individualized asthma self-management improves medication adherence and markers of asthma control. J Allergy Clin Immunol. 2009;123(4):840–6.

5. Wang R, Murray CS, Fowler SJ, et al. Asthma diagnosis: into the fourth dimension. Thorax. 2021;76(6):624–31.
6. Voorend-van Bergen S, Vaessen-Verberne AA, Landstra AM, et al. Fractional Exhaled Nitric Oxide Monitoring Does Not Improve Asthma Management in Children with Concordant and Discordant Asthma Phenotypes. Am J Respir Crit Care Med. 2015;192(8):1016–8.
7. Castner J, Klingman K, Sullivan S, et al. Hitting home with technology development for asthma. Lancet Respir Med. 2016;4(2):102–3.
8. Lo DK, Beardsmore CS, Roland D, et al. Lung function and asthma control in school-age children managed in UK primary care: a cohort study. Thorax. 2020;75(2):101–7.
9. Fuhlbrigge A, Marvel J, Electricwala B, et al. Physician-Patient Concordance in the Assessment of Asthma Control. J Allergy Clin Immunol Pract. 2021;9(8):3080-3088.e3081.
10. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med. 2011;184(5):602–15.
11. Yang S, Park J, Lee YK, et al. Association of longitudinal fractional exhaled nitric oxide measurements with asthma control in atopic children. Respir Med. 2015;109(5):572–9.
12. Saito J, Gibeon D, Macedo P, et al. Domiciliary diurnal variation of exhaled nitric oxide fraction for asthma control. Eur Respir J. 2014;43(2):474–84.
13. van der Valk RJP, Baraldi E, Stern G, et al. Daily exhaled nitric oxide measurements and asthma exacerbations in children. Allergy. 2012;67(2):265–71.
14. Stern G, de Jongste J, van der Valk R, et al. Fluctuation phenotyping based on daily fraction of exhaled nitric oxide values in asthmatic children. J Allergy Clin Immunol. 2011;128(2):293–300.
15. Petsky HL, Cates CJ, Kew KM, et al. Tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils): a systematic review and meta-analysis. Thorax. 2018;73(12):1110–9.
16. McNicholl DM, Stevenson M, McGarvey LP, et al. The utility of fractional exhaled nitric oxide suppression in the identification of nonadherence in difficult asthma. Am J Respir Crit Care Med. 2012;186(11):1102–8.
17. Heaney LG, Busby J, Bradding P, et al. Remotely Monitored Therapy and Nitric Oxide Suppression Identifies Nonadherence in Severe Asthma. Am J Respir Crit Care Med. 2019;199(4):454–64.
18. Buchvald F, Eiberg H, Bisgaard H. Heterogeneity of FeNO response to inhaled steroid in asthmatic children. Clin Exp Allergy. 2003;33(12):1735–40.
19. Cowan DC, Taylor DR, Peterson LE, et al. Biomarker-based asthma phenotypes of corticosteroid response. J Allergy Clin Immunol. 2015;135(4):877-883.e871.
20. Kharitonov SA, Donnelly LE, Montuschi P, et al. Dose-dependent onset and cessation of action of inhaled budesonide on exhaled nitric oxide and symptoms in mild asthma. Thorax. 2002;57(10):889–96.
21. Anderson WJ, Short PM, Williamson PA, et al. Inhaled corticosteroid dose response using domiciliary exhaled nitric oxide in persistent asthma: the FENOtype trial. Chest. 2012;142(6):1553–61.
22. Carpenter DM, Jurdi R, Roberts CA, et al. A Review of Portable Electronic Spirometers: Implications for Asthma Self-Management. Curr Allergy Asthma Rep. 2018;18(10):53.
23. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004;113(1):59–65.
24. Juniper EF, Guyatt GH, Cox FM, et al. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J. 1999;14(1):32–8.
25. Wu Z, Huang R, Zhong L, et al. Technical performance analysis of different types of spirometers. BMC Pulm Med. 2022;22(1):23.
26. Reddel HK, Marks GB, Jenkins CR. When can personal best peak flow be determined for asthma action plans? Thorax. 2004;59(11):922–4.
27. Szefler SJ, Martin RJ, King TS, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. J Allergy Clin Immunol. 2002;109(3):410–8.
28. Nanda CR, Singapuri A, Soares M, et al. Domiciliary exhaled nitric oxide and eosinophilic airway inflammation in adults with asthma. Eur Respir J. 2016;48(1):242–4.
29. Pijnenburg MW, Floor SE, Hop WC, et al. Daily ambulatory exhaled nitric oxide measurements in asthma. Pediatr Allergy Immunol. 2006;17(3):189–93.
30. Garnier P, Fajac I, Dessanges JF, et al. Exhaled nitric oxide during acute changes of airways calibre in asthma. Eur Respir J. 1996;9(6):1134–8.
31. Haccuria A, Michils A, Michiels S, et al. Exhaled nitric oxide: a biomarker integrating both lung function and airway inflammation changes. J Allergy Clin Immunol. 2014;134(3):554–9.
32. Gochicoa-Rangel L, Rojas-Cisneros F, Miguel-Reyes JL, et al. Variability of FeNO in healthy subjects at 2240 meters above sea level. J Clin Monit Comput. 2016;30(4):445–9.
33. Ekroos H, Karjalainen J, Sarna S, et al. Short-term variability of exhaled nitric oxide in young male patients with mild asthma and in healthy subjects. Respir Med. 2002;96(11):895–900.
34. Adan A, Archer SN, Hidalgo MP, et al. Circadian typology: a comprehensive review. Chronobiol Int. 2012;29(9):1153–75.
35. Reddel HK, Jenkins CR, Marks GB, et al. Optimal asthma control, starting with high doses of inhaled budesonide. Eur Respir J. 2000;16(2):226–35.
36. Pavord ID, de Prado Gómez L, Brusselle G, et al. Biomarkers Associated with Lung Function Decline and Dupilumab Response in Patients with Asthma. Am J Respir Crit Care Med. 2024;209(8):1031–3.
37. Couillard S, Shrimanker R, Lemaire-Paquette S, et al. Longitudinal changes in sputum and blood inflammatory mediators during FeNO suppression testing. Thorax. 2022;77(9):933–8.
38. Reddel H, Jenkins C, Woolcock A. Diurnal variability–time to change asthma guidelines? Bmj. 1999;319(7201):45–7.
39. Côté J, Cartier A, Malo JL, et al. Compliance with peak expiratory flow monitoring in home management of asthma. Chest. 1998;113(4):968–72.
40. van Vliet D, van Horck M, van de Kant K, et al. Electronic monitoring of symptoms and lung function to assess asthma control in children. Ann Allergy Asthma Immunol. 2014;113(3):257-262.e251.
41. Feldman JM, Kutner H, Matte L, et al. Prediction of peak flow values followed by feedback improves perception of lung function and adherence to inhaled corticosteroids in children with asthma. Thorax. 2012;67(12):1040–5.

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