

MIOTIC study: a prospective, multicenter, randomized study to evaluate the long-term efficacy of mobile phone-based Internet of Things in the management of patients with stable COPD

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Abstract: Chronic obstructive pulmonary disease (COPD) is a common disease that leads to huge economic and social burden. Efficient and effective management of stable COPD is essential to improve quality of life and reduce medical expenditure. The Internet of Things (IoT), a recent breakthrough in communication technology, seems promising in improving health care delivery, but its potential strengths in COPD management remain poorly understood. We have developed a mobile phone-based IoT (mIoT) platform and initiated a randomized, multicenter, controlled trial entitled the 'MIOTIC study' to investigate the influence of mIoT among stable COPD patients. In the MIOTIC study, at least 600 patients with stable GOLD group C or D COPD and with a history of at least two moderate-to-severe exacerbations within the previous year will be randomly allocated to the control group, which receives routine follow-up, or the intervention group, which receives mIoT management. Endpoints of the study include (1) frequency and severity of acute exacerbation; (2) symptomatic evaluation; (3) pre- and post-bronchodilator forced expiratory volume in 1 second (FEV_1) and FEV_1 /forced vital capacity (FVC) measurement; (4) exercise capacity; and (5) direct medical cost per year. Results from this study should provide direct evidence for the suitability of mIoT in stable COPD patient management.

Keywords: Internet of Things, mobile phone, chronic obstructive pulmonary disease, efficacy

Introduction

Chronic obstructive pulmonary disease (COPD) is a global disease that causes high mortality in urban and rural People's Republic of China and substantial economic and social burden in Chinese health care.¹⁻³ The acute exacerbation of COPD (AECOPD) is one of the most important adverse events in the natural history of COPD, and accounted for 1.6% of all hospital admissions in the People's Republic of China in 2008.²

Effective management of stable COPD is essential to delay disease progression, reduce acute exacerbation, and improve quality of life. However, at least one-third of stable COPD patients are under-treated, partly due to a lack of resources in contrast to increased COPD incidence and insufficiency of pulmonary medical staff in less developed localities (regional inequality).

Technological improvement suggests a potential for telehealthcare in COPD management. Telehealthcare, defined as delivery of clinical care at a distance, includes real-time (synchronous) and store-and-forward (asynchronous) interaction between electronic communications and information technology.⁴ Current evidence favors telehealthcare in COPD patients, but its potential in general application remains largely

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unknown. In a Cochrane review, McLean et al⁵ showed how telehealthcare could reduce COPD exacerbations and improve the quality of life of COPD patients. It was found to significantly reduce emergency department visits and hospital admissions without changes in morbidity and costs. Polisena et al⁶ also obtained similar results in a systematic review of nine original studies but concluded that the telephone support group incurred increased mortality with insignificantly different quality of life compared with the usual care group. Additionally, Wootton et al⁷ cast doubt on the practical efficacy of telehealthcare as study results were marred by short study durations (<6 months), inattention to cost effectiveness, and the possibility of publication bias in most telehealthcare trials. In this regard, further investigation is essential to verify the long-term efficacy of telehealthcare in cost reduction and improved quality of life among COPD patients.⁸

In recent years, 'Internet of Things' (IoT) technology has risen as a promising aid in telehealthcare delivery to resolve health care problems.^{9,10} IoT links the virtual world to the real world through connections between sensors and working devices. To improve the feasibility of telehealthcare application in the management of stable COPD patients, a real seamless platform, entitled mobile phone-based IoT

(mIoT), has been established. By mIoT, we mean interactive communication among patients and health care providers in medical centers and communities. Confronted with the need for large data processing in modern medicine (eg, imaging analysis, daily surveillance, and frequent feedback response between physician and patients), cloud computing is crucial to improve data processing efficiency, which justifies the involvement of a calculation center with recruitment of data processing and data mining in the current system. As shown in Figure 1, the mIoT platform integrates sensor networks, the mobile communication network, and cloud computing to detect physiological parameters that are transmitted to our cloud platform for analysis. Patients may access the mIoT platform via their mobile terminals to complete a COPD questionnaire at regular intervals, obtain instant and personalized services, or visit medical experts for advice. In addition to patient monitoring, the platform offers health promotion advice, including smoking-cessation services and digital educational materials. Designed in plain Chinese language, the system is user friendly and widely applicable in urban and rural regions.

The purpose of this study is to evaluate the effect of mIoT management on the prevention of acute exacerbations, symptom control, lung function measurement, exercise

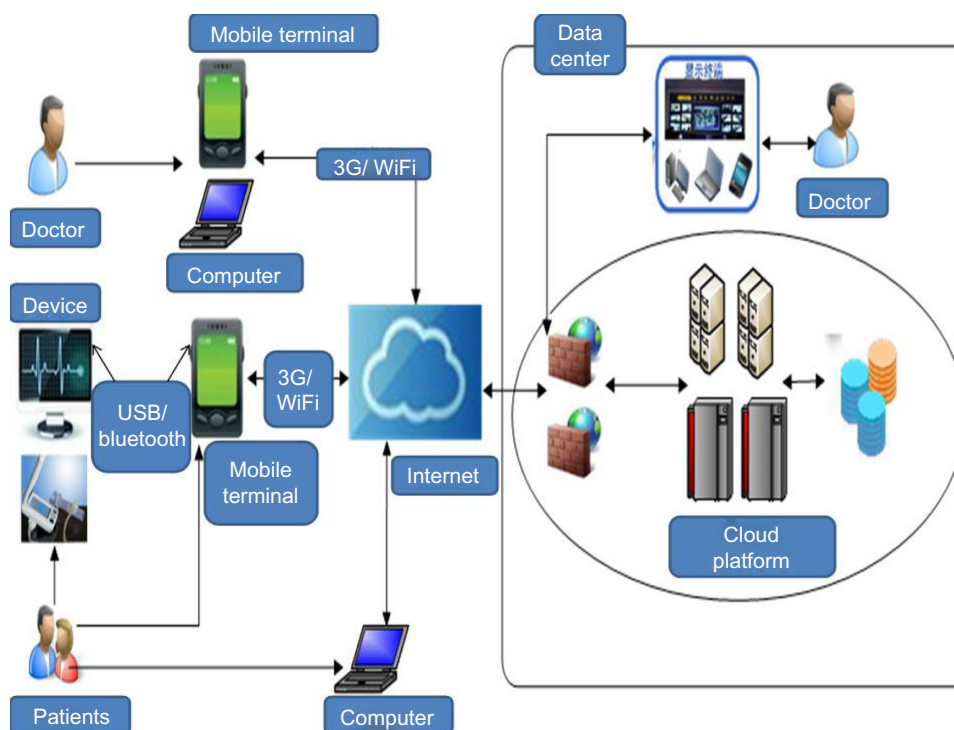


Figure 1 Overview of the mobile phone-based Internet of Things (mIoT) platform. Physiological parameters are collected from a patient and transmitted through Bluetooth to the patient's mobile terminal. It is further transmitted from the mobile device to the mIoT platform via WiFi or the third generation (3G) network. The platform software analyzes data and yields results, which are stored in the system and transmitted to the physician's mobile terminals. Medical staff may then modify the results and provide feedback to patients. Patients, general practitioners in community hospitals, and specialists in medical centers may communicate via mobile terminals.

capacity quantification, and medical costs compared with routine management.

Patients and methods

Trial design

This clinical trial is designed to investigate the effect of mIoT on the management of patients with stable COPD. The primary study outcome is the rate of moderate to severe acute exacerbations over 1 year; other endpoints include symptomatic evaluation, pre- and post- bronchodilator spirometry, exercise capacity, and direct medical costs over 1 year.

This trial has been registered in the Chinese Clinical Trials Registry (ChiCTR-TRC-13003257).

Inclusion criteria

Patients with COPD belonging to stable Global initiative for chronic Obstructive Lung Disease (GOLD) group C or D who receive treatment in participating hospitals will be recruited. The definition and classification of COPD follows the GOLD definition.¹ Subjects must meet the following criteria: (1) 40–80 years old; (2) post-bronchodilator forced expiratory volume in first second of expiration (FEV_1)/forced vital capacity (FVC) ratio less than 0.70; (3) two or more moderate-to-severe acute exacerbations in the previous year, including at least one exacerbation requiring hospitalization or emergency visit; (4) stable COPD, indicating those without exacerbation or recovering from exacerbation at the time of enrollment; (5) patients should be capable of using an mIoT device after training.

In accordance with the Declaration of Helsinki, written informed consent will be obtained from all participants after an explanation of the complete trial. This study has been approved by the Institutional Review Board of Zhongshan Hospital, Fudan University, Shanghai, People's Republic of China.

Exclusion criteria

Exclusion criteria include chronic kidney disease (stage 4 and 5), severe liver dysfunction, malignancies, psychiatric diseases, and life expectancy less than 2 years. Patients who could not perform the spirometry test and/or could not use inhaled corticosteroids, long-acting beta agonist inhalers, or long-acting muscarinic antagonist inhalers are also excluded from the study.

Study outline

The flow chart of the study design is shown in Figure 2. After enrollment, participants are randomly assigned into

two groups: the mIoT group and the routine management group. For both groups, patients receive medications, oxygenation, or non-invasive ventilation at home according to GOLD guideline recommendations. Follow-up at 4-weekly intervals is arranged for the routine management group.

For the mIoT group, data acquisition software based on the android phone system is installed in the patient's cell-phone for free and all patients are trained to use the software. They are allowed to practice until accurate data submission and collection is ascertained. A trouble-shooting booklet is also provided, with one engineer ready for consultation in case of any technical problems. The following measures are carried out via the mIoT platform: (1) medication reminders are delivered at a fixed time according to the treatment plan; (2) patients are asked to report their symptomatic changes once a week via the smart phone application installed on the patient's mobile terminal; (3) health education, including smoking cessation, knowledge of COPD, appropriate exercise plan, and advice regarding coping with anxiety, depression, and stress are pushed to the patient's mobile terminal; (4) communication with medical staff during work hours is available remotely through the mobile device.

Patients are allowed to make unscheduled clinic visits and emergency visits as necessary. The study period is 1 year. The outcomes will be recorded and the effect of mIoT in the management of stable COPD will be evaluated.

Randomization

Enrollment and random allocation are performed by central registration at Zhongshan Hospital of Fudan University. Managers of each institute will enroll participants after examining their eligibility and obtaining informed consent. Patients will be assigned into two groups via randomization (randomization numbers generated by central registration center) in a 1:1 fashion to the intervention and control groups. The arm assignment will be notified within 6 hours of enrollment.

Endpoints

The primary endpoint is frequency (per year) of moderate to severe AECOPD.

An AECOPD involves worsening of respiratory symptoms that goes beyond day-to-day variations, typically lasts for several days, and warrants a change in medication.¹ While two examiners independently determine the onset and severity of an exacerbation, a third party is engaged when discrepancies arise. Any unscheduled clinic/emergency room visits,

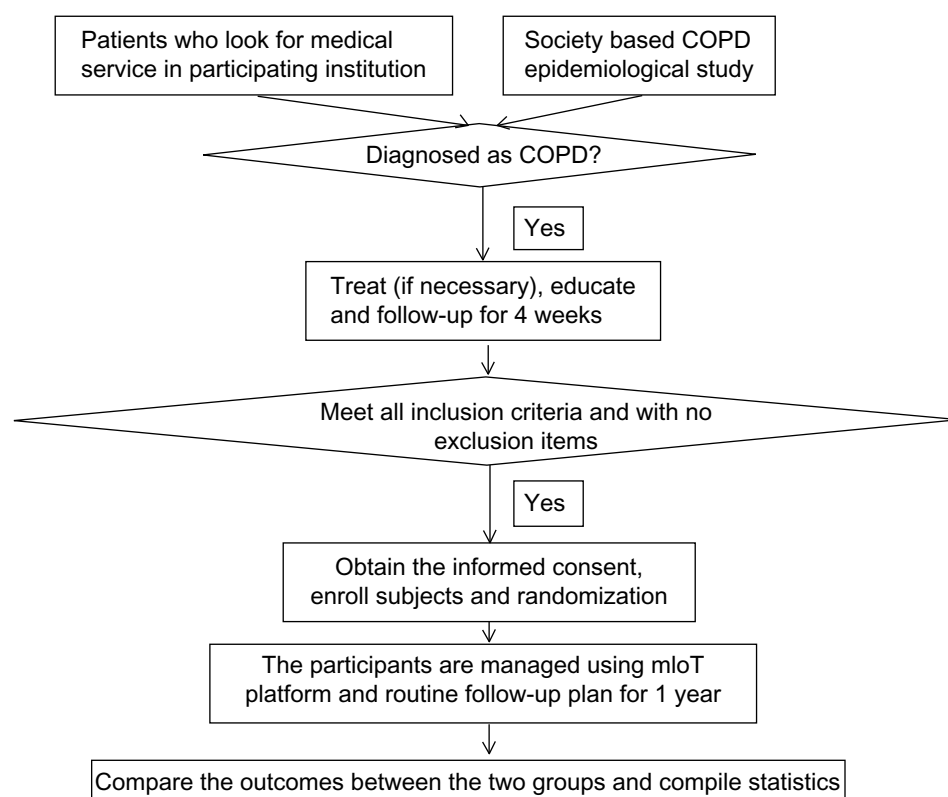


Figure 2 Flow diagram of the study.

Abbreviations: mIoT, mobile phone-based internet of things; COPD, chronic obstructive pulmonary disease.

hospitalization (including duration of hospital stay and use of intensive care unit), or medication related to an exacerbation will be recorded. A moderate exacerbation is defined as an acute event requiring the use of oral corticosteroids and/or antibiotics, and a severe exacerbation is defined as one that requires an emergency room visit or hospitalization. Rates of all acute exacerbations over 1 year and time to first moderate or severe exacerbation will also be recorded.

Secondary endpoints include symptomatic evaluation, spirometry, exercise capacity, and direct medical costs per year.

The symptoms of participants are evaluated by the COPD assessment test (CAT).¹¹ The CAT score is collected remotely via mobile application once a week in the mIoT group and face-to-face once a month during clinic follow-up in the routine management group.

Spirometry and exercise capacity are examined by post-bronchodilator FEV₁ value and 6-minute walking distance (6MWD), respectively, during onsite visits at the beginning and by the end of the study period.

The direct medical costs per subject are the total costs of medication (including clinic registration fee) for stable disease treatment and acute exacerbations.

Data acquisition

All attempts at spirometry and 6MWD are performed in a community center or onsite clinic guided by an experienced technician/trained physician/trained nurse and reports submitted to the cloud calculation center. CAT score and other online consultations are carried out online. Medical expenditure will be calculated based on the medical record and precise cost for each patient.

Statistical analysis

To power mIoT for superiority and to detect a 25% difference between the mIoT and the routine groups for the primary endpoint, at least 300 patients are required for each group.

Statistics will be compared in both groups by unpaired *t*-tests for continuous variables. For discrete variables and ranked variables, a chi-squared (χ^2) test or rank sum test will be used. In time-to-event analysis, the time to first moderate-to-severe exacerbation will be described with Kaplan–Meier curves, and the difference in average event-free time during follow-up between the two groups will be compared. Further description of treatment differences will be obtained with a Cox proportional hazards model. Analysis will be by intention to treat. All statistical analysis will be performed using

SPSS version 17.0 (IBM, Armonk, NY, USA). Values are considered to be significant when $P < 0.05$.

Study organization and study period

Six institutes (the Zhongshan Hospital of Fudan University, Qingpu Center Hospital, Zhabei Center Hospital, and three relevant community hospitals) are participating in this study as of May 10, 2013. A growing number of medical centers and community hospitals are to be involved. The 'mIoT COPD Management Workshop' was organized by these institutes in January 2012 to permit entry of other facilities before August 31, 2014. The study period will be extended under the approval of the Workshop and the ethical committee.

Discussion

Conventional medical modality has been challenged by limited medical resources and increased demand. As a breakthrough in information technology that enhances organization of equipment, patient management, and doctor–patient communication, IoT serves as a potential supplement to the current medical service modality and acts as an alternative to management of stable chronic disease (eg, COPD).

Recently, IoT has been investigated in the People's Republic of China.¹² For example, Cao et al¹³ proposed a wireless, portable monitoring system for respiratory diseases using a microthermal flow sensor, a tri-axis micro accelerometer, and a micro photoelectric sensor, which monitor essential physiological parameters. In this project, Bluetooth via mobile cellular networks or the Internet is utilized as a data communication approach to achieve ubiquity. A cellphone or personal computer connected to the Internet, remote center, and physicians will be used to analyze test results.

Our research group has proposed the establishment of a cellphone-based IoT e-health platform. As a pioneer system for Chinese clinical settings, it will integrate sensor networks, mobile communication networks, and cloud computing to detect physiological parameters that will be transmitted to the cloud platform for analysis and data mining. Patient monitoring, disease prevention, and treatment may be conducted via the cellphone accordingly. Patients may access the mIoT platform for instant and personalized services through applications installed in their smart mobile phones. We plan to test our mIoT platform in sample case studies through intervention of risk factors (smoking behavior), disease monitoring, and standard treatment and rehabilitation.

In addition to the urban population that may conveniently access our platform, inter-hospital communication and medical training have been implemented to improve health care delivery

in the rural population. Furthermore, inter-hospital connection also allows medical professionals to exchange opinions and refine management plans. A medical center–community pattern for COPD management has thus been established.

Limitations

Selection bias cannot be avoided since the study population only involves patients in rural and urban Shanghai who seek medical services in community or university hospitals. Another limitation is the exclusion of GOLD group A and B patients, who will only be included in further studies.

Conclusion

The MIOTIC study investigates the effect of mIoT in stable COPD patients, including the frequency and severity of acute exacerbation, symptomatic evaluation (CAT score), pre- and post-bronchodilator airflow limitation (FEV₁), exercise capacity (6MWD), and direct medical costs over a 1-year period. We expect a significantly reduced risk of AECOPD through the use of mIoT, which will support its application in stable COPD management.

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Disclosure

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