Evaluation of mobile supervision application and electronic medicine box for tuberculosis patients: Implementation experience from Tianjin during 2019-2020

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Abstract

Background

Poor tuberculosis (TB) medication adherence increases the risk of treatment failure and development of drug-resistant TB, while universal implementation of directly observed therapy (DOT) is not feasible in China. EHealth technologies were reported to be promising patient-centered tools for improving adherence. However, only pilot studies have assessed patients’ experiences and the results were discrepant.

Methods

This cross-sectional study was conducted among TB patients at the outpatient department from 3 March 2019 to 30 May 2020 in Tianjin, China. Data were downloaded from the Tuberculosis doctor App and TB Information Management System (TBIMS), and merged them using the TBIMS notification number. Logistic regression analysis was used to analyze the factors associated with regular drug-intake. Odds ratios and 95% confidence intervals were estimated with and without adjustment for age, gender, ethnicity, and occupation.

Results

A total of 1193 TB patients were recruited, of whom 33.28% (397) patients were regular drug-intake. The whole drug-intake rate was 84.84%, except for the first month, the drug-intake rate decreased with the increase of monthly treatment sequence. After adjustment by age, gender, ethnicity, and occupation, tuberculosis pleurisy (aOR: 0.42, 95CI%=0.26-0.69) and retreated patients (aOR: 0.40, 95CI% =0.27-0.59) were more likely to have poor medication compliance. Local resident tend to have better medication compliance (aOR: 1.80, 95CI% =1.16-2.79).

Conclusions

The medication adherence at the first month should be noticed. Medication adherence was poor in tuberculosis pleuritis and retreated patients, while local resident tend to have better medication adherence. To make full use of the application of eHealth in TB patient management, more incentive measures should be adopted for patients and doctors respectively.

Keywords: Tuberculosis; electronic medicine box; APP; medication adherence
Introduction

Tuberculosis is a global public health problem. According to the estimates by the World Health Organization (WHO), there were 9.96 million new cases of TB globally in 2019, with an incidence of 130/100,000 and 1.21 million deaths due to TB [1]. China ranks the third in terms of TB burden in the world; accounting for 8.4% of the estimated new cases and 14% of multiple drug resistant tuberculosis (MDR-TB) patients. The occurrence of MDR-TB is closely related to the patient's treatment adherence. Treatment adherence refers to the degree to which the patient's treatment-related behaviors (such as taking medication, regular review, et al.) are consistent with the doctor's suggestions [2]. Poor treatment adherence of TB patients will lead to prolonged disease, recurrence, aggravation, and even the extensive spread of drug-resistant tuberculosis bacilli [3]. This problem has became one of the obstacles to the control of the global tuberculosis epidemic [4]. Therefore, improving patient adherence is still one of the effective public health measures to reduce the spread of tuberculosis and control the epidemic of TB[5].

Directly observed therapy (DOT) by health care workers recommended by WHO has been shown to ensure TB patient treatment adherence[6]. However, due to the high cost of healthcare, level of economic development, availability of transportation, medical resources and patient privacy issues, it is difficult for many developing countries to fully implement DOT management for the treatment of TB[7]. The DOT Short-course strategy was implemented in 1992 in China and covered the entire country by 2005[8], only 20% TB patients were supervised by health workers, while others were on self-administered treatment or by family members [7,9]. Thus, in the 2017 WHO’s TB treatment guidelines, eHealth technology was suggested to be applied in the management of TB patients [10].

As a new mobile communication and network technology in the healthcare industry, eHealth technology not only provide humanized, convenient and high-quality services for patients, but also improve the quality and efficiency of medical service [11-13]. Short messaging service (SMS), video supervision, electronic
medicine box, wirelessly observed therapy (WOT) and mobile supervision application (APP) were reported to apply on TB patients management [14-16], although those measures contributed to improved patient compliance compared to the traditional DOT, no eHealth technology was widely promoted due to the cost, privacy issues, operation and technical problems [17-23]. APP supervision has shown its potential application due to its low cost, convenience and high acceptance. However, at present, only a small range of pilot studies have reported the effect of APP on the management of TB patients [24].

In Tianjin, after early pilot applications and continuous improvement in 2015-2018, the APP and electronic medicine boxes have been promoted and used in all districts since March 2019. To evaluate the effect of APP and electronic medicine boxes in the management of TB patients, we analyzed the data of TB patients who completed the course of treatment.

Methods
Study design
This is a cross sectional study. The APP and electronic medicine boxes have been promoted and used in all districts since March 2019. After diagnosis, the patients were instructed to install the TB assistant APP by the doctors of the community healthcare center where they currently live; electronic medicine boxes were given to those patients who do not use the APP, and community doctors binded the box to those patients on the TB doctor App. The electronic medicine box and TB assistant App could remind the patient to take medicine and visit the hospital to get medicine according to the set time. On the day of taking medicine, the information of taking medicine was uploaded when the patient open the electronic medicine box or sign in the TB assistant App. Open the electronic medicine box or sign in the TB assistant APP were equivalent to taking medicine. During the study, if the patients lost to follow-up, refused treatment, died, rule out of TB, default due to adverse reactions, their data would be treated as invalid.

The community doctor visited each patient within 72 hours after diagnosis, and
contacted them once a month during the intensive and continuous phases. The doctor evaluated the drug adherence, given advice about timely and regular drug intake. If a patient does not sign in the App or open the electronic medicine box, the community doctor should remind the patient through the TB doctor App or phone; if a patient does not visit the hospital 3 days after the scheduled time, the community doctor was required to call or visit patient to supervise him/her to visit the designated medical institution to get medications or receive relevant examination within 24 h.

**Study population**

The study population comprises a consecutive enrolled pulmonary TB patients diagnosed at clinic. Inclusion criteria were as follows: 1) ≥18 years old; 2) Patients with no communication impairment (mental, visual, auditory, or speech); 3) Patients or family members agreed to download and use App or electronic medicine box after training; 4) Patients lived in Tianjin during treatment and were able to persist in receiving treatment.

All TB patients were given standard 6-8 months short-course chemotherapy and managed as outpatients. The chemotherapy regimens included isoniazid, rifampin, ethambutol, and pyrazinamide for 2 mo, followed by isoniazid and rifampin for 4 or 6 mo; The therapy used every day dosing for the entire treatment course. At each monthly visit, patients went to hospital to get enough medications for a 1-mo period according to his doctor’s prescription.

**Introduction of electronic medicine box and APP**

**APP**

App was developed by Beijing SINOVO POWER Technology Co., Ltd. and Beijing Chest Hospital. It consists of two parts: Tuberculosis Assistant App and Tuberculosis Doctor App. Tuberculosis Assistant App is available for TB patients, which could provide reminders of drug taking and examination, Q&A consultation, patient forum and communication with management doctors. Tuberculosis Doctor App is the management doctor terminal, including the mobile APP and the web system. Doctors
can view medication feedback, respond to patients' questions, communicate with patients instantly, send messages and irregularly push health information, etc.

**Electronic medicine box**
Electronic medicine box is a medication monitor that holds a 1-month supply of medication and has three key functions: as an audio reminder for TB patients to take their daily medication, reminds a patient of upcoming monthly visit, and records date and time whenever the box is opened.

**Data collection**
We downloaded the data from the Tuberculosis doctor App and TB Information Management System (TBIMS), and merged them using the TBIMS notification number.

Observation indicators: (1) drug-intake rate: the drug-intake rate of patients in different treatment months was calculated. The calculation formula was as follows: the monthly drug-intake rate = the actual times of drug-intake in the month/the times of drug should be taken in the month × 100%; the whole drug-intake rate = the actual times of drug-intake during the whole course/the times of drug should be taken during the whole course × 100% (2) Determination of regular drug-intake: The whole course of drug-intake rate ≥ 90% was determined as regular drug-intake.

Case finding was classified as active treatment; while referral, follow-up, health examination and contact examination were classified as passive treatment.

**Statistical analysis**
All analyses were performed using SPSS software (version 16.0; SPSS Inc., Chicago, IL, USA). Normality test was performed first for continuous variables, data that was not conforming to the normal distribution were represented as median (quartile), and non-parametric Kruskal-Wallis test was performed. Categorical data were evaluated by Chi-square test as appropriate. Univariate and multivariate logistic regression analysis was used to analyze the association between the risk factors and regular drug-intake. Odds ratios and 95% confidence intervals were estimated by logistic regression with and without adjustment for age, gender, ethnicity and occupation. All tests were two-sided and \( P < 0.05 \) was considered statistically significant.
Ethics
The study was approved by the review board of Tianjin Center for Tuberculosis Control and written informed consent was obtained from the patients.

Results
Patient characteristics
From 3 March 2019 to 30 May 2020, a total 1284 pulmonary TB patients were informed and agreed to receive the APP or electronic medicine box to finish their whole course of anti-tuberculosis treatment management. Of those, 91 patients were excluded: 36 patients were loss follow-up, 23 patients subsequently refused to use the APP or electronic medicine box, 21 patients moved away, 6 patients received a non-TB diagnosis from their physician and 5 patients died of other disease. Finally 1193 (92.91%) patients met the enrollment criteria.

Among the 1193 study patients, 799 (66.97%) were male and 394 (33.03%) were females. The median age was 48 years old, the minimum age was 14 years old and the maximum age was 95 years. 318 (26.66%) patients were student and employee, 1052 (88.18%) were local residents, 861 (72.17%) were active case finding, 350 (29.34%) were diagnosed as negative and 756 (63.37%) were positive, 1071 (89.77%) were new TB patients (Table 1).

Results of drug-intake rate
397(33.28%) TB patients were regular drug-intake. During the study period, the times that all patients should take medicine were 238815, while the actual times recorded by APP or electronic medicine box were 202602, the whole drug-intake rate was 84.84%. The first drug-intake rate was only 51.84%, and the drug-intake rate decreased with the increase of monthly treatment sequence, this decreasing trend was significant (P <0.01) (Fig. 1).
Comparison of patient characteristics

The demographic characteristics of the TB patients are presented in Table 1. The proportion of 48 years old and over, migrants, new patients, and negative patients in irregular drug-intake group were all higher than those in the regular drug-intake group, the differences were statistically significant ($P < 0.05$).

Table 1. Characteristics of patients

| Characteristic              | Irregular drug-intake | Regular drug-intake | Chi-square | P   |
|----------------------------|-----------------------|---------------------|------------|-----|
| Gender                     |                       |                     |            |     |
| Male                       | 524 (65.83%)          | 275 (69.27%)        | 1.42       | 0.24|
| Female                     | 272 (34.17%)          | 122 (30.73%)        |            |     |
| Age                        |                       |                     | 6.25       | 0.01|
| <48                        | 440 (55.28%)          | 189 (47.61%)        |            |     |
| ≥48                        | 356 (44.72%)          | 208 (52.39%)        |            |     |
| Ethnicity                  |                       |                     | 0.50       | 0.48|
| Han                        | 784 (98.49%)          | 393 (98.99%)        |            |     |
| Others                     | 12 (1.51%)            | 4 (1.01%)           |            |     |
| Occupation                 |                       |                     | 5.04       | 0.17|
| Student and employee       | 220 (27.64%)          | 98 (24.69%)         |            |     |
| Farmers                    | 191 (23.99%)          | 86 (21.66%)         |            |     |
| Retired                    | 90 (11.31%)           | 61 (15.37%)         |            |     |
| Unemployed                 | 295 (37.06%)          | 152 (38.29%)        |            |     |
| Residence                  |                       |                     | 10.37      | 0.001|
| Migrants                   | 111 (13.94%)          | 30 (7.56%)          |            |     |
| Local                      | 685 (86.06%)          | 367 (92.44%)        |            |     |
Factors associated with irregular drug-intake

As shown in Table 2, univariate logistic regression analysis showed that 48 years old and over were more likely to have poor adherence (OR:0.74, 95CI%=0.56-0.94). Also, retired TB patients more often demonstrated poor adherence (OR: 0.66, 95CI%=0.44-0.98). Compared with negative and positive TB patients, tuberculosis pleuritis were more likely to have poor adherence (OR: 0.40, 95CI%=0.25-0.64). Retreated patients tend to have poor medication compliance than new patients (OR: 0.38, 95CI%=0.26-0.56). While local resident were related to good medication compliance (OR: 1.98, 95CI%=1.30-3.03). After adjustment by age, gender, ethnicity and occupation, tuberculosis pleurisy (aOR: 0.42, 95CI%=0.26-0.69) and retreated patients (aOR: 0.40, 95CI% =0.27-0.59) were more likely to have poor medication compliance. Local resident tend to have better medication compliance than migrants (aOR: 1.80, 95CI% =1.16-2.79).

Table 2.  Factors associated with regular drug-intake

| Variables       | Unadjusted OR | Adjusted OR |
|-----------------|---------------|-------------|
|                 | OR(95%CI)     | P-value     | aOR(95%CI) | P-value |
| Gender          |               |             |            |         |
| Male            | 1.00          | 1.00        | 1.00       | 1.00    |
| Female          | 0.17(0.90-1.52) | 0.23    | 1.10(0.84-1.42) | 0.53   |
| Age             |               |             |            |         |
| <48             | 1.00          | 1.00        | 1.00       | 1.00    |
| ≥48             | 0.74(0.56-0.94) | 0.01    | 0.87(0.67-1.14) | 0.31   |
| Ethnicity       |               |             |            |         |
| Han             | 1.00          | 1.00        | 1.00       | 1.00    |
| Others          | 0.66(0.21-2.08) | 0.48    | 0.69(0.22-2.23) | 0.54   |
| Occupation      |               |             |            |         |
|                        | 1.00      | 1.00      | 0.99(0.70-1.40) | 0.24 | 1.05(0.71-1.53) | 0.49 | 0.66(0.44-0.98) | 0.04 | 0.82(0.51-1.31) | 0.27 | 0.87(0.64-1.18) | 0.98 | 1.01(0.72-1.41) | 0.67 |
|------------------------|-----------|-----------|----------------|------|----------------|------|----------------|------|----------------|------|----------------|------|----------------|------|
| **Residence**          |           |           |                |      |                |      |                |      |                |      |                |      |                |      |
| Migrants               | 1.00      |           |                |      |                |      |                |      |                |      |                |      |                |      |
| Local                  | 1.98(1.30-3.03) | 0.002 | 1.80(1.16-2.79) | 0.009 |
| **Diagnosis**          |           |           |                |      |                |      |                |      |                |      |                |      |                |      |
| Negative               | 1.00      |           |                |      |                |      |                |      |                |      |                |      |                |      |
| Positive               | 0.76(0.58-1.00) | 0.20 | 0.81(0.61-1.08) | 0.12 |
| Pleuritis              | 0.40(0.25-0.64) | 0.0005 | 0.42(0.26-0.69) | 0.0009 |
| **Therapy category**   |           |           |                |      |                |      |                |      |                |      |                |      |                |      |
| New patients           | 1.00      |           |                |      |                |      |                |      |                |      |                |      |                |      |
| Retreated patients     | 0.38(0.26-0.56) | <0.0001 | 0.40(0.27-0.59) | <0.0001 |
| **Case finding**       |           |           |                |      |                |      |                |      |                |      |                |      |                |      |
| Active                 | 1.00      |           |                |      |                |      |                |      |                |      |                |      |                |      |
| Passive                | 1.30(0.98-1.71) | 0.06 | 1.14(0.85-1.53) | 0.37 |

**Discussion**

Effective management is the key to the success chemotherapy after the patient have been given an appropriate treatment plan. Although DOT has achieved great success in past decades, it was reported that in some areas the implementation rate of DOT was only 50% and 20% TB patients were self-administered therapy without any adherence support [7]. Therefore, how to make full use of high-tech methods to achieve accurate management of TB patients is important to improve the level of TB prevention and treatment. At present, electronic medicine boxes and mobile medical APPs were applied in the management of chronic disease. Due to its relatively low cost and simple operation, APP was accessible and affordable even in resource-limited settings. However, its effect on improving the medication adherence of TB patients was discrepant currently [5,14,25-26]. Compared with APP, electronic medicine boxes tend to be applied in elderly persons whose phone does not support APPs or can’t use APPs.

The whole drug-intake rate in our study was 84.84%, and only 33.28% (397) patients were regular drug-intake. The drug-intake rate decreased with the increase of monthly treatment sequence. At the first month, the drug-intake rate was the lowest of
the whole therapy course; some patients often forgot to sign in on the APP after taking the medicine, to improve the compliance of TB patients, 1 rmb/day was given to patients in some districts since Aug 2019, the drug-intake rate of TB patients who diagnosed after Aug 2019 was 98.32% at the first month, so the rate was underestimated. The drug-intake rate at the twice and third month increased compared with the drug-intake rate at the first month. However, from the fourth month, the drug-intake rate decreased. As to the possible reasons, on the one hand, after three months of standardized treatment, some patients stopped to take medicine when they felt relief of symptoms. On the other hand, doctors chosen to ignore the reminders of missing medication on the APP because of lacking sufficient financial incentives [27] and they had other tasks to do. In Tianjin, although according to the government strategy, a doctor can get 7 rmb/day for supervising a patient to take the medicine, however, for various reasons, the doctor actually got less than half of the money, or even none. Hence, improving the financial support of doctors and TB patients were beneficial for improving adherence.

In our study, tuberculosis pleurisy patients tend to have poor medication adherence. Because tuberculosis is a respiratory infectious disease, the TB patients generally carry a psychological burden of being discriminated and lack of confidence in curing the disease [28]. The attitudes of family members and friends were reported to influence the medication adherence [29]. Patients with frequent medication supervision and mentally encouragement by family members, especially spouses, were more likely to have better adherence [30]. Compared with active TB, the therapy course of tuberculosis pleurisy was as long as 12 months, thus tuberculosis pleurisy patients often own more psychological burden, less social support and, therefore, poor medication adherence.

Retreated TB patients were showed to have poor adherence. Similar finding was reported in Ni Wang’ study [31]. As to the possible reason, Due to the long course of medication of retreated TB patients, generally 6 to 12 months, some even as long as 18 months, and the adverse drug effects were more serious than those of the new patients, retreated TB often had negative psychology and less confidence. However,
Retreated patients were reported to be more active to upload medication information during treatment [32]. Further research is required to identify the reasons for this correlation.

Our study noted that local resident were more likely to have better treatment adherence than migrants. Although free anti-tuberculosis drugs were provided by the government, TB patients still need to pay extra fees for medical examinations and liver protection drugs [33]. It was reported that treatment was sometimes interrupted due to financial burden of these additional cost. While migrants tended to have low income and low awareness of TB, they often stopped taking medicines once the symptoms improved. So more financial support was needed for the migrants to help them finish the therapy course.

**Limitations**

There were several limitations that need to be addressed. Firstly, since this study only included TB patients in Tianjin, due to the lack of multi-center data comparison, the extrapolation of the results were limited, but it can provide reliable scientific basis for the further development of community management strategies for TB patients in Tianjin. Secondly, because of the presence of electronic medicine box’s signal and battery failure, and patients' failing to sign-in on APP after taking medicine, the data uploaded in this study cannot truly reflect the patient's actual medication status. However, published data indicated a high correlation between medication monitors’ records and rifampicin detected in urine [15], hence the records of medication monitors were representative to some extent.

**Conclusion**

EHealth technology such as electronic medicine box and mobile phone APP enables community doctors to timely know the treatment of patients and respond accordingly[34]. In this study, medication adherence was poor in tuberculosis pleuritis and retreated patients, while local resident tend to have better medication adherence. During the process of TB patient management, non-adherence data should be noticed by doctors to provide more intensive supervision, in addition, financial support should
be increased to improve the enthusiasm of doctors, so as to ensure the patients’ adhere to complete the course of treatment with the use of eHealth Technology.

**Abbreviations**

TB: Tuberculosis; MTB: Mycobacterium tuberculosis; APP: Application; DOT: Directly observed therapy; WHO: World Health Organization; SMS: Short messaging service; WOT: Wirelessly observed therapy; TBIMS: TB Information Management System.

**Ethics approval and consent to participate**
The study was approved by the review board of Tianjin Center for Tuberculosis Control and written informed consent was obtained from the patients.

**Consent for publication**
Not applicable.

**Availability of data and materials**
The dataset are available from the corresponding author on reasonable request.

**Competing interests**
The authors declare that they have no competing interests.

**Funding**
This study has no funding support.

**Authors' contributions**
XL mainly analyzed the data and wrote the manuscript. XP helped interpret the results and FZ designed the study. All authors revised and approved the final manuscript.

**Acknowledgements**
We thank Shengyu Chen for clinical interpretation of the data.

Reference

1. World Health Organization. Global Tuberculosis Report, 2020. Geneva: WHO; 2020.
2. Coamb RB. Review of the scientific literature on the prevalence, consequences and health costs of non compliance inappropriate use of prescription medication in Canada: health promotion research. Toronto: University of Toronto Press, 1995.
3. Karumbi J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Database Syst Rev, 2015; 29(5): CD003343.
4. Van Den BJ, Lyimo RA, Boeree MJ, Kibiki GS, Aarnoutse RE. Electronic monitoring of treatment adherence and validation of alternative adherence measures in tuberculosis patients: a pilot study. Bull World Health Organ. 2011; 89(9): 632-9.
5. Ma Y, Du J, Liu YH, Li L. The role of mobile health on management of tuberculosis patients. Chin J Antituberc. 2016; 38(7): 527-30.
6. World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care. 2017. Geneva: WHO; 2017.
7. Hou WL, Song FJ, Zhang NX, Dong XX, Cao SY, Yin XX, et al. Implementation and community involvement in DOTS strategy: a systematic review of studies in China. Int J Tuberc Lung Dis. 2012; 16(11):1433–40.
8. Wang L, Liu J, Chin DP. Progress in tuberculosis control and the evolving public-health system in China. Lancet. 2007; 369(9562):691–6.
9. Wang L, Zhang H, Ruan Y, Chin DP, Xia Y, Cheng S, et al. Tuberculosis prevalence in China, 1990–2010: a longitudinal analysis of national survey data. Lancet. 2014; 383(9934):2057–64.
10. Falzon D, Timimi H, Kurosinski P, Migliori GB, Van Gemert W, Denkinger C, et al. Digital health for the End TB Strategy: developing priority products and making them work. Eur Respir J. 2016; 48(1):29–45.
11. Haapala I, Barengo NC, Biggs S, Surakka L, Manninen P. Weight loss by mobile phone: a 1-year effectiveness study. Public Health Nutr. 2009; 12(12):2382-91.
12. Denkinger CM, Grenier J, Stratis AK, Akkihal A, Pant-Pai N, Pai M. Mobile health to improve tuberculosis care and control: a call worth making. Int J Tuberc Lung Dis. 2013; 17(6):719–27.
13. Free C, Phillips G, Galli L, Watson L, Felix L, Edwards P, et al. The effectiveness of mobile-health technology-based health behaviour change or disease management interventions for health care consumers: a systematic review. PLoS Med. 2013; 10(1):e1001362.
14. Huan ST, Chen R, Liu XQ, Ou XC, Jiang SW, Zhao YL, et al. Operational feasibility of medication monitors in monitoring treatment adherence among TB patients. Chin J Antituberculosis. 2012; 34(7):419–424.
15. Chuck C, Robinson E, Macaraig M, Alexander M, Burzynski J. Enhancing management of tuberculosis treatment with video directly observed therapy in New
York City. Int J Tuberc Lung Dis. 2016; 20(5): 588 – 93.

16. Gashu KD, Gelaye KA, Mekonnen ZA, Lester R, Tilahun B. Does phone messaging improves tuberculosis treatment success? A systematic review and meta-analysis. BMC Infect Dis. 2020; 20(1):42.

17. Albino S, Tabb KM, Requena D, Egoavil M, Pineros-Leano MF, Zunt JR, et al. Perceptions and acceptability of short message services technology to improve treatment adherence amongst tuberculosis patients in Peru: a focus group study. PLoS One. 2014; 9(5):e95770.

18. Mohammed S, Glennerster R, Khan A J. Impact of a daily SMS medication reminder system on tuberculosis treatment outcomes: a randomized controlled trial. PLoS One. 2016;11(11): e0162944.

19. Bediang G, Stoll B, Elia N, Abena LJ, Geissbuhler A. SMS reminders to improve adherence and cure of tuberculosis patients in Cameroon (TB-SMS Cameroon): a randomised controlled trial. BMC Public Health. 2018; 18(1):583.

20. Story A, Garfín RS, Hayward A, Rusovich V, Dadu A, Soltan V, et al. Monitoring therapy compliance of tuberculosis patients by using video-enabled electronic devices. Emerg Infect Dis. 2016; 22(3): 538-40.

21. Nguyen TA, Pham MT, Nguyen TL, Nguyen VN, Pham DC, Nguyen BH, et al. Video directly observed therapy to support adherence with treatment for tuberculosis in Vietnam: a prospective cohort study. Int J Infect Dis. 2017; 65: 85-9.

22. Gao L, Qian XJ, Huang SY, Lin SP, Ying LP, Deng YR. The effect of traditional supervision and telephone supervision on treatment compliance of tuberculosis patients in county and township. Inter J Epidemiol Infect Dis. 2016; 43(6): 404-7.

23. Lewis JJ, Liu XQ, Zhang ZY, Thomas BV, Vassall A, Sweeney S, et al. Evaluation of a medication monitor-based treatment strategy for drug-sensitive tuberculosis patients in China: study protocol for a cluster randomised controlled trial. Trials, 2018, 19(1): 398.

24. Xie YT, Du J, Luo P, Wu Y, Zhang K, Yang C, et al. Preliminary report of a mobile supervision application used for treatment management in patients with tuberculosis in Tongzhou District, Beijing in 2016. Chin J Antituberc. 2017; 39(7): 708-12.

25. Promthong K, Kittivoravitkul P, Oer-Areemitr N, Wattanatham A. Tuberculosis treatment with smartphone medical application reminders a randomised control study. Respirology. 2016; 21(Suppl 3): 96.

26. Subbaraman R, de Mondesert L, Musiimenta A, Pai M, Mayer KH, Thomas BE, et al. Digital adherence technologies for the management of tuberculosis therapy: mapping the landscape and research priorities. BMC Glob Heal. 2018; 3(5): e001018.

27. Liu XQ, Lewis JJ, Zhang H, Lu W, Zhang S, Zheng G, et al. Effectiveness of electronic reminders to improve medication adherence in tuberculosis patients: a cluster-randomised trial. PLoS Med. 2015; 12(9): e1001876.

28. Theron G, Peter J, Zijenah L, Chanda D, Mangu C, Clowes P, Rachow A, et al. Psychological distress and its relationship with non-adherence to TB treatment: a multicentre study. BMC Infect Dis. 2015; 15: 253.
29. Xu M, Markstrom U, Lyu J, Xu L. Detection of Low Adherence in Rural Tuberculosis Patients in China: Application of Morisky Medication Adherence Scale. Int J Environ Res Public Health. 2017; 14(3): 248.
30. Xu WG, Lu W, Zhou Y, Zhu LM, Shen HB, Wang JM. Adherence to anti-tuberculosis treatment among pulmonary tuberculosis patients: a qualitative and quantitative study. BMC Health Serv Res. 2009; 9: 169.
31. Wang N, ZhangH, Zhou Y, Jiang H, Dai B, Sun MM, et al. Using electronic medication monitoring to guide differential management of tuberculosis patients at the community level in China. BMC Infect Dis. 2019; 19(1):844.
32. Fang HX, Qin YB, Liu CW, Chen ZC, Yan XF, Yu WL, et al. Preliminary analysis of video observed therapy for management of tuberculosis patients by internet and mobile phones in Longhua District of Shenzhen City. Chin J Antituberc. 2017; 39(7): 684-8.
33. Xu WG, Lu W, Zhou Y, Zhu LM, Shen HB, Wang JM. Adherence to anti-tuberculosis treatment among pulmonary tuberculosis patients: a qualitative and quantitative study. BMC Health Serv Res. 2009;9:169.
34. Chen X, Du L, Wu RH, Xu J, Ji HQ, Zhang Y, et al. The effects of family, society and national policy support on treatment adherence among newly diagnosed tuberculosis patients: a cross-sectional study. BMC Infect Dis. 2020(1); 20: 623.