Efficacy and safety of app-based remote warfarin management during COVID-19-related lockdown: a retrospective cohort study

Shaojun Jiang[1] · Meina Lv[1] · Zhiwei Zeng[1] · Zongwei Fang[1] · Mingrong Chen[1] · Jiafen Qian[1] · Tingting Wu[1] · Wenjun Chen[1] · Jinhua Zhang[1]

Abstract

This study aimed to explore the effectiveness, and safety of internet-based warfarin management during the pandemic. In this single-center retrospective cohort study, we compared the safety and efficacy of online warfarin management using a smartphone app (the Alfalfa app) versus conventional outpatient clinic management from January 1, 2020 to March 31, 2020. Patients in the online management group used the Alfalfa app to communicate coagulation test results and other relevant information to a doctor or clinical pharmacist, who then responded with the dose adjustment plan and the date of the next blood test. The outcomes examined were the time in therapeutic range (TTR), incidence of clinical events (i.e., bleeding events, thrombotic events, warfarin-related emergency department visits, and warfarin-related hospital admissions), and the distribution of international normalized ratio (INR) values. Data from 117 patients were analyzed in this study. TTR was significantly higher in the online group than in the offline group (61.0% vs. 39.6%, P < 0.01). Incidence of major bleeding events, thrombotic events, and warfarin-related hospital admissions were comparable between the online and offline groups. However, minor bleeds (5.3% vs. 28.3%, P < 0.01) and warfarin-related emergency department visits (1.8% vs. 23.3%, P = 0.02) were significantly fewer in the online group than in the offline group. The proportion of INR values in the therapeutic range (53.8% vs. 40.1%, P < 0.01) was significantly higher in the online group. Warfarin management using the Alfalfa app appears to be a safe and effective method for warfarin management when patients cannot physically visit hospitals for follow-up.

Keywords Telemedicine · COVID-19 · Warfarin · Remote consultation · Healthcare delivery

Abbreviations

COVID-19	Coronavirus disease-2019
INR	International normalized ratio
TTR	Time in therapeutic range
WHO	World Health Organization

Highlights

- Patients managed offline have difficulty accessing effective anticoagulation therapy during the lockdown.

- Online management through the Alfalfa app can improve patients' TTR and reduce anticoagulation-related clinical events.

Shaojun Jiang and Meina Lv contributed to the work equally and should be regarded as co-first authors.

✉ Jinhua Zhang
pollyzhang2006@126.com

1 Department of Pharmacy, Fujian Medical University Union Hospital, Fuzhou, Fujian, China

Introduction

In late December 2019, several cases of pneumonia caused by the new coronavirus virus were reported from many hospitals in Wuhan City, Hubei Province, China [1]. To control the spread of COVID-19, the Chinese government imposed emergency response measures, first in Wuhan City and subsequently in 14 other cities in Hubei Province [2, 3]. On January 23, 2020, China initiated Level I response to public health incidents nationwide, which is the highest level in China's public health management system [4]. Despite this, COVID-19 was still spreading rapidly throughout the country and the world. As of February 13, 2020, a total of 25 countries had an outbreak of COVID-19, with a total of 55,748 confirmed cases and 1318 deaths in China [5,

6]. On March 1, the WHO officially defined the COVID-19 outbreak as a pandemic [7]. More than a year after the new coronavirus outbreak was declared a pandemic, the global fight against it has not stopped, and some countries are experiencing the third wave of the virus. Globally, as of August 31, 2021, there have been 215,714,824 cumulative confirmed cases of COVID-19, including 4,490,753 deaths [8]. COVID-19 has had a profound impact on citizens' quality of life, mental state, and even clinic attendance behavior [9–11].

Warfarin is the most widely used anticoagulant drug and has been in use for over 60 years [12, 13]. The anticoagulant effect of warfarin—which is commonly used for thrombosis prevention after heart valve replacement surgery or orthopedic surgery and for patients with atrial fibrillation—is affected by a variety of factors. The inter-individual factors include age, gender, weight, genotype, comorbidities, comorbid medications, diet and lifestyle habits, etc. [14–16]. Except for relatively fixed factors such as genotype and gender, other factors may change over time, which causes the instability of the pharmacokinetic and pharmacodynamic characteristics of warfarin. Inadequate dosing will not achieve sufficient anticoagulation effect, while excessive dosing will increase the risk of bleeding. Therefore, patients need to have their coagulation function checked regularly and their drug dosage adjusted periodically so that INR values remain within the narrow therapeutic range. Unfortunately, COVID-19-induced lockdowns and social distancing and isolation measures have made it difficult for patients to visit outpatient clinics for blood tests and advice on warfarin dose adjustment [17–19].

Over the past 5 years, China has been committed to promoting the use of the Internet to deliver healthcare services, although this is still in the exploratory stage [20]. The spread of COVID-19 has brought unprecedented attention to "Internet + medical health", and along with telemedicine and online consultation, it has ushered in explosive growth within a few months [21]. By the end of December 2020, China has more than 1000 Internet hospitals, an increase of nearly 500 compared to 2019 [22]. Many tertiary hospitals in China have already built their own apps or used the apps—WeChat and Alipay—to deliver healthcare services. Those telemedicine services include paying healthcare service fees, scheduling appointments with doctors, prescribing low-risk medical examinations, receiving medical reports, and ect. Telemedicine is considered an effective alternative to chronic disease management [23]. A pre-pandemic retrospective study has demonstrated the efficacy of remote warfarin management using a smartphone app—the Alfalfa app [24]. With the use of the Alfalfa app, time in therapeutic range (TTR) was higher, and incidence of major bleeding events, warfarin-related emergency visits, and hospital admissions lower, than with the traditional management

model. However, in order to reduce the risk of exposure to COVID-19, patients have consciously reduced the number and frequency of visits to the hospital [25]. In addition, some hospitals also cancelled outpatient services during the peak of the epidemic [18]. As a result, the patient's behavior and medical environment have changed significantly from the pre-pandemic period. Whether the Alfalfa app can provide patients with safe and effective anticoagulation management in this situation is still unknown. This paper aimed to explore the safety, and efficacy of using a smartphone app for remote anticoagulation management during the COVID-19 pandemic.

Methods

Study design and participants

This single-center retrospective observational cohort study was conducted at the Fujian Medical University Union Hospital, Fuzhou, Fujian, China. The study participants were selected from among the patients receiving long-term warfarin from January 1, 2020, to March 31, 2020—a period of COVID-19-induced restrictions in China. Patients were eligible for inclusion in this study if they (1) received warfarin treatment for at least 3 months; (2) received warfarin management through the Alfalfa app or via conventional outpatient clinic visits; (3) consented to regular follow-up; (4) had no serious bleeding or thrombotic events in the 3 months prior to warfarin treatment. The exclusion criteria were (1) pregnancy, (2) change to another anticoagulant during the study period, and (3) two or fewer INR records during the follow-up period. A total of 138 patients who met these criteria were included in this study. Patients were divided into two groups according to the warfarin management method: an "offline group" comprising patients whose dose adjustments were through the routine outpatient approach and an "online group" comprising patients who received remote anticoagulation management through the Alfalfa app.

This study was approved by the Ethics Committee of Fujian Medical University Union Hospital and the need for informed consent was waived as this was a retrospective study.

The Alfalfa app

The Alfalfa app (Alfalfa Health Management Co., Ltd., Fuzhou, Fujian, China) was used for remote warfarin management in the online group; a detailed description of the app has been published earlier [24]. Figure 1 shows the screenshots of the Alfalfa app. Briefly, the Alfalfa app is a smartphone application that be accessed through the
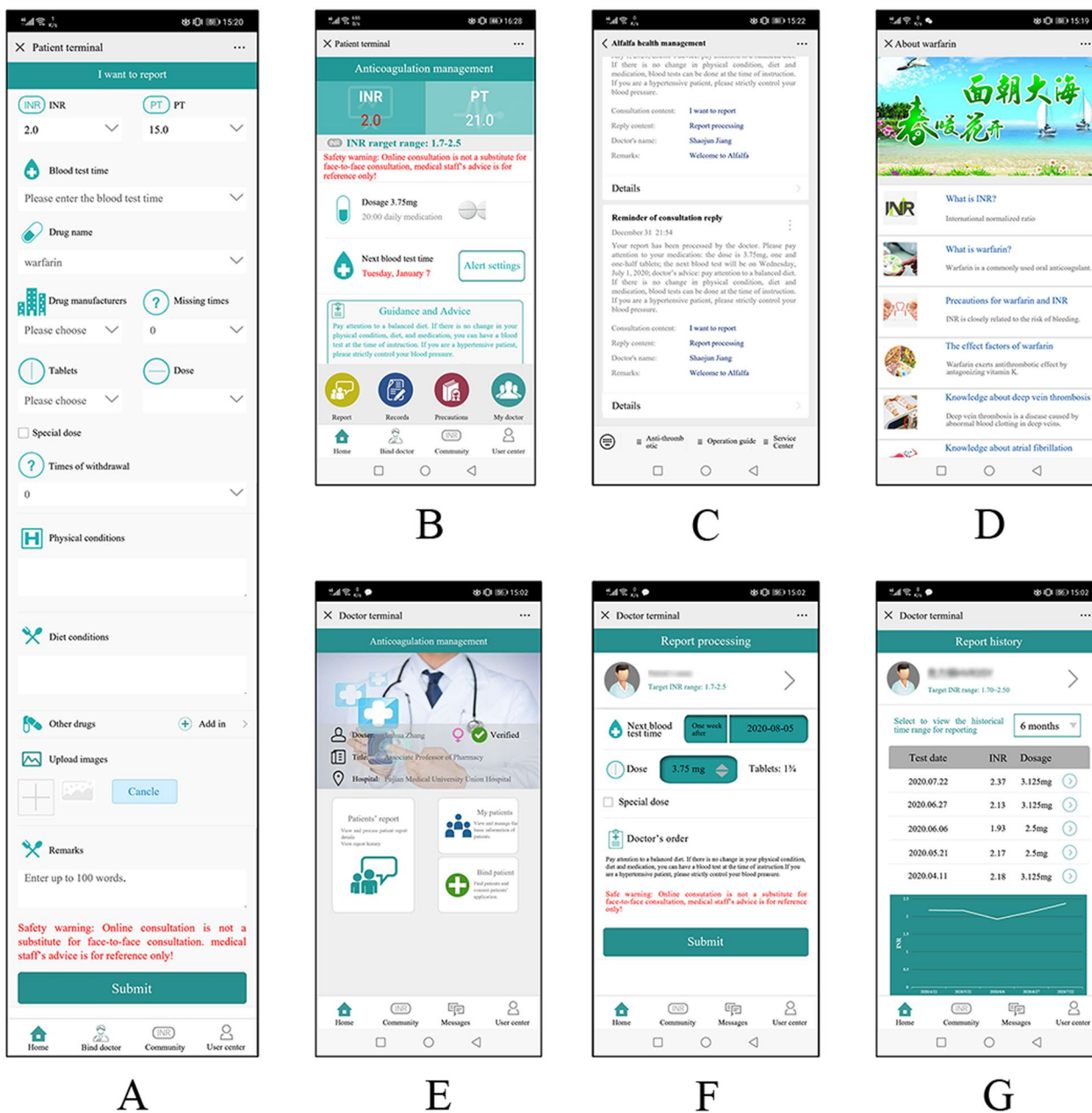
Fig. 1 Screenshots of Alfalfa app. **A** Report Interfacem **B** home page of patient terminal, **C** doctor's reply, **D** patient education, **E** home page of doctor terminal, **F** medical strategy development, **G** checking patient's report records

WeChat public platform. The patient used the app to report the results of the latest coagulation test, recent physical and dietary status, current medications, and adverse events. An anticoagulation management team of Fujian Medical University Union Hospital analyzed the information and responded with the recommended dose of warfarin and the date of the next blood test. The coagulation management team was composed of a total of 8 cardiologists and clinical pharmacists specializing in anticoagulation from Union Hospital of Fujian Medical University. They replied to the

patients' reports before 6:00 pm that day. Alfalfa app can also automatically remind patients to take medication to improve medication compliance.

The dose adjustment strategy

Generally speaking, the therapeutic ranges of INR were 1.5–2.5 for patients who experienced heart valve surgery and 2.0–3.0 for patients with venous thromboembolism or

atrial fibrillation. For patients in both groups, we would educate them on the basic knowledge of warfarin, including the individualized INR therapeutic range, the need to regularly adjust the dose, the concerns about abnormal bleeding, etc. After that, offline patients obtained INR results from clinics or hospitals, and adjusted the dosage under the guidance of the local physicians. For patients in online group, their INR results were also derived from INR draws at clinics or hospitals. Subsequently, they obtained the dosage, the time for the next blood test and other medical orders through the Alfalfa app. In terms of INR test, the time and frequency of blood test for the offline group is determined by the local physicians. Management strategies for patients in the online group were as follows: INR value was rechecked once a week when patient start taking warfarin. In the absence of serious clinical events or extreme values of INR, the frequency of blood checks would remain the same. Whenever 2–3 consecutive INR values were in the therapeutic range, the blood test interval could be extended by one week. The longest INR check interval we recommend was once a month. In other words, a longer blood check interval means that the patient's INR value is more stable.

Data collection

The patients' demographic and clinical data were collected through the hospital information system. The INR results and clinical events of the online group and the offline group were obtained through the back-end management system of the Alfalfa app and through telephone follow-up, respectively. The collected data did not contain personally identifiable information. In addition, we regained basic information such as height and weight that were missing from the database during the follow-up. Follow-up began on the second day of the study and continued until the end of the study or until change to another anticoagulant or until occurrence of major bleeding event or thromboembolic event.

Study outcomes

The quality of anticoagulation management in the two groups was assessed by the TTR, which was calculated using the Rosendaal method of linear interpolation [26]. Safety and efficacy were assessed by the occurrence of clinical events. The safety parameters included minor bleeding events (epistaxis, bleeding from gums/mouth, skin ecchymosis, fundus hemorrhage, excessive or prolonged menstrual bleeding) and major bleeding events (gastrointestinal hemorrhage and cerebral hemorrhage). Efficacy parameters were symptomatic thrombotic events (i.e., minor stroke, transient ischemic attack, venous thromboembolism, valve thrombosis, and cerebral infarction). Other clinical events

of interest were warfarin-related emergencies and warfarin-related hospitalizations.

The distribution of INR values was also examined. According to the patient's target range, the INR values were divided into five categories referring to past studies [27–29]: extreme subtherapeutic, subtherapeutic, therapeutic, supratherapeutic, and extreme supratherapeutic. The definitions of the five categories can be found in the Appendix. Patients with two or more indications for anticoagulation were given the highest INR target corresponding to the indication.

Statistical Analysis

SPSS 20.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. All continuous variables are normally distributed as demonstrated by Kolmogorov–Smirnov test. So continuous variables were summarized as the means $\pm$ standard deviations and compared between groups by the independent-samples t-test. Categorical variables were summarized as the number of cases (and the percentages) and compared by the chi-square test or the Fisher exact test. $P \leq 0.05$ was considered to indicate statistically significant difference. Cases with incomplete data were handled by case-wise deletion instead of multiple imputation in the data analysis, referring to the method described by Zhu et al. [30].

Results

Characteristics of patients

We conducted follow-up of 138 patients, and 21 patients were excluded from this study: one patient because of change of anticoagulant and twenty patients because of two or fewer INR records. Table 1 presents the baseline characteristics of the remaining 117 patients (60 patients in the offline group and 57 in the online group). The mean age of the study population was 50.4 ± 13.1 years. The sex distribution was similar in the two groups. Mean age was slightly higher in the offline group than in the online group, but the difference was not statistically significant (52.7 years vs. 48.1 years, P = 0.06). Hypertension was the most common comorbidity in both groups. In 87 of 117 patients (74%), the indication for anticoagulation was single valve replacement or valvuloplasty. Overall, demographic characteristics, comorbidities, and indications for anticoagulation were comparable between the groups.

Table 1 Characteristics of the study population

Characteristics	Total (n=117)	Offline group (n=60)	Online group (n=57)	P
Demographic characteristic				
Age (year)	50.4 ± 13.1	52.7 ± 12.8	48.1 ± 13.1	0.06
Male (%)	55 (47.0)	29 (48.3)	26 (45.6)	0.79
Height (cm)	161.5 ± 18.1	159.1 ± 22.7	164.4 ± 9.4	0.77
Weight (kg)	59.4 ± 9.78	58.4 ± 8.9	60.6 ± 10.8	0.24
Smoking (%)	75 (64.1)	37 (61.7)	38 (66.7)	0.57
Alcohol (%)	30 (25.6)	16 (26.7)	14 (24.6)	0.79
Duration of anticoagulation at baseline (days)	53.9 ± 17.8	54.2 ± 15.0	53.7 ± 20.5	0.89
Mean warfarin dose (mg/d)	3.81 ± 0.56	3.87 ± 0.53	3.73 ± 0.59	0.18
Comorbidity n (%)				
Hypertension	22 (18.8)	14 (23.3)	8 (14.0)	0.20
Diabetes	2 (1.7)	1 (1.7)	1 (1.7)	> 0.99
Gout or hyperuricemia	6 (5.1)	3 (5.0)	3 (5.3)	0.95
Previous major thrombosis	6 (5.1)	3 (5.0)	3 (5.3)	0.95
Previous major bleeding	1 (0.8)	0 (0.0)	1 (1.8)	0.49
Indication n (%)				
Single valve replacement or valvuloplasty	87 (74.4)	41 (68.3)	46 (80.6)	0.13
Double valves replacement or valvuloplasty	23 (19.7)	15 (25.0)	8 (14.0)	0.14
Triple valves replacement or valvuloplasty	5 (4.3)	4 (6.7)	1 (1.8)	0.37
NVAF	1 (0.8)	0 (0.0)	1 (1.8)	0.49
VTE or PE	1 (0.8)	0 (0.0)	1 (1.8)	0.49

NVAF nonvalvular atrial fibrillation, *VTE* venous thromboembolism, *PE* pulmonary embolism

Table 2 Study outcomes

Outcomes	Total (n=117)	Offline group (n=60)	Online group (n=57)	P	OR (95% CI)
TTR, mean ± SD (%)	49.4 ± 27.2	39.6 ± 23.1	61.0 ± 26.5	< 0.01	0.980 (0.965, 0.994)
Minor bleeding events, n (%)	20 (17.1)	17 (28.3)	3 (5.3)	< 0.01	7.116 (1.666, 17.391)
Major bleeding events, n (%)	1 (0.8)	1 (1.7)	0 (0)	> 0.99	0.983 (0.951, 1.016)
Thromboembolic events, n (%)	2 (1.7)	1 (1.7)	1 (1.8)	> 0.99	0.949 (0.058, 15.543)
Warfarin-related emergency department visits, n (%)	18 (15.4)	14 (23.3)	1 (1.8)	0.02	17.043 (2.159, 134.514)
Warfarin-related hospital admissions, n (%)	2 (1.7)	1 (1.7)	1 (1.8)	> 0.99	0.949 (0.058, 15.543)

OR odds ratio, *CI* confidence interval, *SD* standard deviation

Clinical outcomes

Table 2 summarizes the outcomes. The TTR was significantly lower in the offline group than in the online group (39.6% vs. 61.0%, P < 0.01). Minor bleeding events (28.3% vs. 5.3%, P < 0.01) and warfarin-related emergency hospital visits (23.3% vs. 1.8%, P = 0.02) were significantly more common in the offline group. Major bleeding events, thrombotic events, and warfarin-related hospital admissions were not significantly different between the two groups. One serious bleeding event (gastrointestinal bleeding in a patient in the offline group) and two thrombotic events (cerebral infarctions; one each in the two groups) occurred. In all three patients, serious clinical events were occurring for the first time and led to hospital admission. No patient died during the follow-up period. The clinical events are shown in Fig. 2. Gum or month bleeding and epistaxis are the most common minor bleeding, accounting for 75% of all minor bleeding.

The distribution of INR values

The average frequency of INR checks for patients in the offline and online groups were 2 and 3 weeks, respectively. A total of 582 valid INR records were collected: 359 in the offline group and 223 in the online group. Table 3 shows the distribution of INR values. The proportion of INRs within
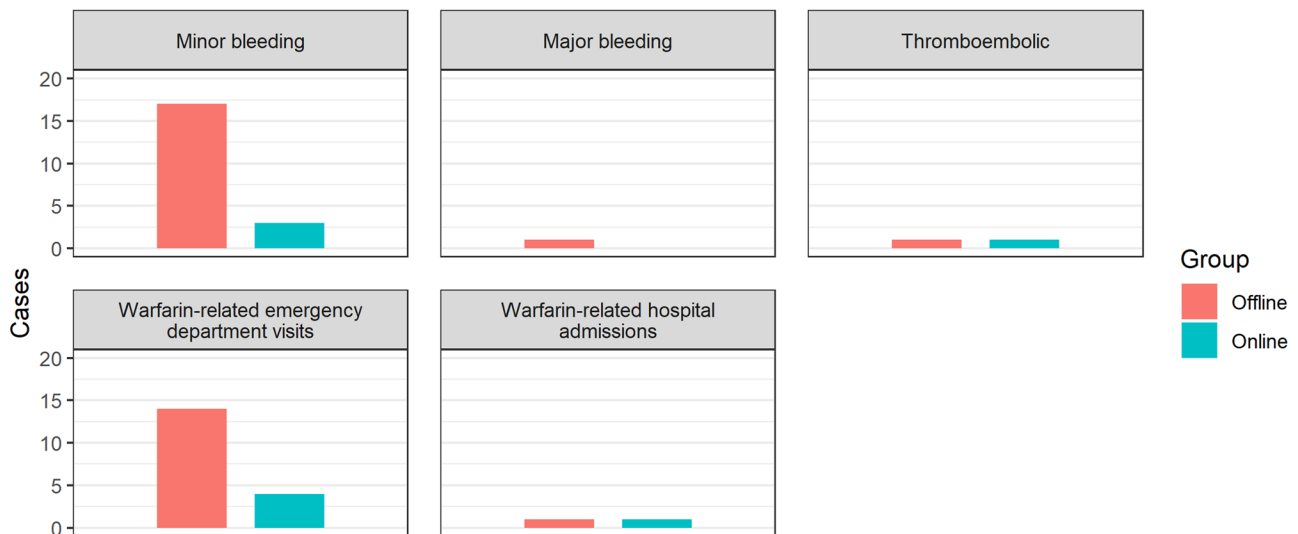
Fig. 2 Composition of clinical events

the therapeutic range was significantly higher in the online group than in the offline group (53.8% vs. 40.1%, P < 0.01). The proportion of INR values in the subtherapeutic range and supratherapeutic range were higher in the offline group than in the online group (10.2% vs. 5.8% and 22.2% vs. 17.9%, respectively), but the differences between the groups were not statistically significant. Extreme supratherapeutic INR values (> 4.5) were not found in either group.

Discussion

This retrospective study was performed to determine the safety and efficacy of a smartphone application for remote management of warfarin therapy during the COVID-19 pandemic. Generally, a TTR of 65% or higher is considered to indicate effective anticoagulation management [31]. In this study, the TTR was only 39.6% among patients receiving offline anticoagulation management versus 61.0% in patients managed via the Alfalfa app. Although the TTR in the online group was significantly better, it was still short of the target of ≥ 65%. The study conducted before the pandemic found TTR of 52.4% in the offline group versus nearly 80% in the online group [24]. Thus, in this study, the cohort followed during the pandemic had worse anticoagulation control. Another part of the reason for the lower TTR during the lockdown may be a change in patients' diets. Studies from China show that 25–30% of the population increased their intake of fresh vegetables, including leaf vegetables and melon/solanaceous vegetables, during the lockdown [32, 33]. The anticoagulant effect of warfarin is mainly exerted by inhibiting the synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X [34]. These additional vitamin K prevents the original dose of warfarin

from producing the same anticoagulant strength and may ultimately lead to an increased risk of thrombosis.

In terms of the distribution of INR values, the proportion of INR values in the therapeutic range was significantly higher in the online group than in the offline group. This finding is consistent with the results of the pre-epidemic cohort study [24]. No extremely high INR values were observed in either of the two groups in our study, meaning that the pandemic did not seem to lead to extremely high INR values. Similar results were reported in the studies of Cope et al. and Singh et al. [35, 36]. However, Pearson et al. compared the INR results from 11 centers and found that the number of abnormal high INR (> 3.5) in 2020 increased by up to 27.3% compared with the same period in 2019 [37]. Furthermore, a UK study (n = 3214 INR samples) by Speed et al. reported that the percentage of blood samples with extreme high INR values (> 8) is nine times higher than during the same period in the previous year (0.9% vs. 0.1%, P < 0.01) [38]. The above opposing results may be due to discrepancies in study population, study design, sample size, and dose adjustment plan. Therefore, the prevention of extreme high INR values should not be neglected in clinical practice.

It is worth noting that the ages of the offline group and the online group are not as close as expected (P = 0.06). The possible reason for this is that in actual clinical practice, there is a preference for management style among patients of different ages and education levels. Although we encouraged younger family members to help older and less educated people to complete the steps of online management, which reduced the age restriction of online management to some extent, there were still some patients living alone who were

Table 3 The distribution of INR values

Outcomes	Total (n = 582)	Offline group (n = 359)	Online group (n = 223)	P
Extreme subtherapeutic, n (%)	149 (25.6)	99 (27.5)	50 (22.4)	0.17
Subtherapeutic, n (%)	39 (8.4)	36 (10.2)	13 (5.8)	0.08
Therapeutic, n (%)	264 (45.4)	144 (40.1)	120 (53.8)	< 0.01
Supratherapeutic, n (%)	120 (20.6)	80 (22.2)	40 (17.9)	0.21
Extreme supratherapeutic, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	> 0.99

INR international normalized ratio

unable to use online management, leading to selection bias. In terms of the reliability of the study, since the p-values for all baseline indicators except age were greater than 0.10, the effect of age alone on the outcome should be minimal and the conclusions is still reliable. At the same time, we hope that there will be randomized controlled studies on the management of warfarin during the epidemic in the future.

The present study reveals benefits with the use of the Alfalfa app. In addition to improving the quality of anticoagulation, online management may also have contributed to prevention and control of COVID-19 by reduce the times for patients to travel to the hospital. Specifically, patients receiving online management had a higher proportion of TTR values within the therapeutic range, indicating more stable INR values; therefore, they could reduce the frequency of hospital visits and the consequent risk of exposure to COVID-19. An additional benefit of online management is the reduced workload on the medical staff [39]. One study showed that the online warfarin management model reduced the average time to process each patient from 30 min to less than 1 min compared to the traditional anticoagulation clinic [40].

Researchers around the world have proposed and practiced several protocols for ensuring the quality of anticoagulation management during the pandemic. Several authors have recommended a combination of point-of-care devices and self-management by the patient [18, 31, 41]. The biggest drawback of this approach is the high cost of the point-of-care device [42]. Moreover, as far as we know, the actual clinical efficacy of this management model in lockdown conditions has not been tested. Drive-up INR testing combined with remote assessment and follow-up has been proposed as a warfarin management model during an outbreak [43]. The patient drives in to the anticoagulation clinic for the INR test, after which the medical staff communicates the dosing recommendation and follow-up appointment date over the phone. Zobeck et al. practiced this management model in a rural area of Illinois and were able to maintain TTR values around 70% [11]. However, the requirements of this method for private cars make it unfriendly to patients in less economically developed areas.

In China, remote management via the Alfalfa app may be ideal for anticoagulation management during the COVID-19

pandemic, especially because there is no need for any equipment other than a smartphone. As of August 31, 2021, more than 215 million people worldwide have been infected with COVID-19 [8]. Six of the ten countries with the worst outbreaks are developing countries, where there is a greater need to make the best use of available medical resources. Healthcare practitioners in these countries may take inspiration from the Alfalfa app and design remote warfarin management software suited for specific local conditions.

There are several limitations to this study. First, as this was a single-center retrospective cohort study, a selection bias is inevitable. Second, the sample size of this study is small, which may cause some clinical endpoints to fail to show significant statistical differences. Third, this study was conducted in Fujian Province in southeastern China where the severity of COVID-19 was relatively low. More background information of the lockdown in Fujian is provided in the Appendix. Overall, further studies are needed to determine whether the Alfalfa app can provide safe and effective anticoagulation management in areas with stricter lockdowns.

Conclusion

In conclusion, remote management of warfarin therapy through the Alfalfa app appears to be feasible, safe, and effective. During the lockdown period, patients managed through the app had higher TTR, greater likelihood of having INR within the therapeutic range, and lower incidences of minor bleeding and warfarin-related emergency hospital visits than patients managed by conventional outpatient visits.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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