Internet of things-based management versus standard management of home noninvasive ventilation in COPD patients with hypercapnic chronic respiratory failure: a multicentre randomized controlled non-inferiority trial

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Summary

Background Effective monitoring and management are crucial during long-term home noninvasive positive pressure ventilation (NPPV) in patients with hypercapnic chronic obstructive pulmonary disease (COPD). This study investigated the benefit of Internet of Things (IOT)-based management of home NPPV.

Methods This multicenter, prospective, parallel-group, randomized controlled non-inferiority trial enrolled patients requiring long-term home NPPV for hypercapnic COPD. Patients were randomly assigned (1:1), via a computer-generated randomization sequence, to standard home management or IOT management based on telemonitoring of clinical and ventilator parameters over 12 months. The intervention was unblinded, but outcome assessment was blinded to management assignment. The primary outcome was the between-group comparison of the change in health-related quality of life, based on severe respiratory insufficiency questionnaire scores with a non-inferiority margin of −5. This study is registered with Chinese Clinical Trials Registry (No. ChiCTR1800019536).

Findings Overall, 148 patients (age: 72.7 ± 6.8 years; male: 85.8%; forced expiratory volume in 1 s: 0.7 ± 0.3 L; $PaCO_2$: 66.4 ± 12.0 mmHg), recruited from 11 Chinese hospitals between January 24, 2019, and June 28, 2021, were randomly allocated to the intervention group (n = 73) or the control group (n = 75). At 12 months, the mean severe respiratory insufficiency questionnaire score was 56.5 in the intervention group and 50.0 in the control group (adjusted between-group difference: 6.26 [95% CI, 3.71–8.80]; P < 0.001), satisfying the hypothesis of non-inferiority. The 12-month risk of readmission was 34.3% in intervention group compared with 56.0% in the control group, adjusted hazard ratio of 0.56 (95% CI, 0.34–0.92; P = 0.023). No severe adverse events were reported.

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Interpretation Among stable patients with hypercapnic COPD, using IOT-based management for home NPPV improved health-related quality of life and prolonged the time to readmission.

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Keywords: Chronic obstructive pulmonary disease; Noninvasive positive pressure ventilation; Hypercapnia respiratory failure; Internet of things; Telemedicine

Research in context

Evidence before this study

We searched Web of Science, PubMed, and EMBASE using the terms "home noninvasive positive pressure ventilation" and "chronic obstructive pulmonary disease", together with terms such as "telemedicine", "telehealth" and "Internet of Things (IOT)" to identify randomized controlled trials, expert group recommendations and systematic reviews and meta-analyses from database inception through March, 2023, with no language restrictions. Conflicting results have been obtained regarding the effectiveness of home noninvasive positive pressure ventilation (NPPV) in the management of patients with stable chronic obstructive pulmonary disease (COPD) and chronic hypercapnic respiratory failure. More high-quality evidence is required to optimize the follow up, telemonitoring, and management of long-term home NPPV in these patients. Remote monitoring and management of noninvasive ventilation has yielded some promising results for patients with other chronic respiratory diseases, but data are lacking for patients with hypercapnic COPD, particularly concerning the impact of remote interventions on patient health-related quality of life.

Added value of this study

This multicenter, prospective, parallel-group, randomized controlled non-inferiority trial was the first and largest of its kind to be conducted in China to investigate the effect of adding IOT-based monitoring and management to standard home NPPV care in patients with hypercapnic COPD. We established an IOT-based platform that collected clinical information and ventilator parameters for each patient and provided the healthcare team with daily reports and follow-up summaries, allowing the patients to receive comprehensive, integrated, and individualized home NPPV management. Our findings showed that, over the 12-month follow-up period, adding IOT-based management to NPPV improved health-related quality of life and prolonged the time to readmission. No differences in mortality, gas exchange, or lung function were observed between the two study groups and no severe adverse events were reported.

Implications of all the available evidence

The findings of this study provide valuable evidence supporting the effectiveness and safety of IOT-based management of home NPPV in patients with COPD and chronic hypercapnic respiratory failure. The wider implementation of such IOT-based remote management platforms has the potential to improve accessibility to home noninvasive positive pressure ventilation treatment across all regions in China, addressing current imbalances in the availability and use of this treatment. More generalizable studies and more real-world studies to better evaluate the impact of NPPV are also needed.

Introduction

The role of home noninvasive positive pressure ventilation (NPPV) in the management of patients with stable chronic obstructive pulmonary disease (COPD) and chronic hypercapnic respiratory failure (CHRF) has long been controversial, with published studies yielding conflicting results regarding the impact of home NPPV on clinical, physiological, hospital readmission, and survival outcomes.[1,2] However, more promising results have been obtained from randomized controlled trials (RCTs) investigating the effect of high-intensity NPPV on patients with hypercapnic COPD. Indeed, home NPPV with high levels of inspiratory positive airway pressure (IPAP), combined with a high backup respiratory rate to promote a maximal reduction in partial carbon dioxide pressure ($PaCO_2$), may result in significant physiological and clinical benefits.[3,4] On the basis of these results, the 2023 report of the global initiative for chronic obstructive lung disease (GOLD) indicated that NPPV may well improve hospitalization-free survival in patients with pronounced daytime persistent hypercapnia.[5] Moreover, the latest guidelines from the European Respiratory Society[6] and American Thoracic Society[7] support the use of home NPPV for patients with chronic stable hypercapnic COPD.

Telemonitoring of home NPPV is an essential tool for optimizing follow up. In particular, improving the exchange of information between patients and the physicians prescribing NPPV, as well as between health professionals and the external companies performing ventilator servicing, is essential for ensuring treatment adherence and effectiveness.[1,8] Home ventilator devices

are frequently equipped with monitoring software that can collect information about compliance, ventilator parameters and physiological indices. Home NPPV can be considered not only as a treatment, but also as a means for detecting the onset of acute COPD exacerbations.[8,9]

Advances in data transmission and network connectivity, now allow medical devices with sensors that can connect to the internet to send, receive, and store real-time health data wirelessly via a cloud platform. A network of such connected devices is referred to as the Internet of Things (IOT) and it has been predicted that the use of such IOT-based medical platforms will transform patient management, particularly the telemonitoring of patients with chronic diseases.[10,11] Indeed, the emerging use of IOT-based management of continuous positive airway pressure in patients with obstructive sleep apnea has yielded some positive findings.[12–15] In an RCT of stable hypercapnic COPD, the use of telemonitoring during home NPPV initiation was shown to be noninferior to in-hospital NPPV initiation, and was found to be associated with 50% reduction in care costs.[16] However, the potential benefits of long-term IOT-based home NPPV management remain unknown in COPD patients with CHRF. Despite much rhetoric about the potential of long-term management based on telemedicine to reduce healthcare burden of COPD, RCTs have generally been disappointing, showing no effect on quality of life.[1,5] In addition, the safety profiles of IOT-based management have not been fully assessed. Therefore, we conducted a RCT with a classical non-inferiority study design to evaluate the effectiveness of IOT-based management of home NPPV compared to standard home NPPV care.

Methods

Study design

This multicenter, prospective, parallel-group, non-inferiority, RCT involved patients recruited from 11 hospital centers in Shanghai, China (Supplementary Table S1). The trial was approved by the medical ethics committee of Zhongshan Hospital, Fudan University (Shanghai, China; B2017-176R) and by local research and development committees at participating centers. The trial was registered in the Chinese Clinical Trials Registry (ChiCTR1800019536) and the study protocol has been published.[17]

Participants

Patients admitted to any of the participating hospitals with an acute exacerbation of COPD were assessed for eligibility when judged clinically stable. Patients aged between 40 and 80 years with a clear diagnosis of severe or very severe COPD (GOLD stage III or IV[1]) were considered eligible if they had a forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <70% and FEV_1 <50% predicted after receiving 400 μg of a short-acting beta2-agonist (salbutamol), and CHRF with a steady state daytime $PaCO_2$ >50 mmHg, based on previous positive findings in home NPPV.[3,4] In other words, participants in the non-inferiority trial were similar to those in the trials that established efficacy of the reference treatment.[3,4] Patients with unstable cardiac hemodynamics (e.g., acute left heart failure, unstable angina, or cardiogenic shock); typical pulmonary fibrosis, airway tumors, pulmonary tuberculosis sequelae or other lung diseases; and those with neuromuscular diseases or chest wall disorders were excluded. All patients enrolled in the study provided written informed consent.

Randomization and masking

Patients were randomly assigned by an independent data center (School of Public Health, Fudan University), with an allocation ratio of 1:1 to receive either NPPV alone or NPPV plus IOT-based management (Fig. 1), according to a computer-generated random number sequence. An independent statistician who generated the allocation sequence placed allocation codes into sequentially numbered, sealed, opaque envelopes. All investigators at each of the participating hospitals contacted the same researcher to obtain an identification code and a random number unique to this patient who fulfills the inclusion criteria.

As it was not feasible to generate an effective sham intervention for IOT-based management of NPPV, the patients and the clinicians supervising the NPPV and IOT-based management were aware of the treatment assigned from randomization to the end of the trial. However, independent investigators conducting the outcome assessments and statisticians in charge of the analysis were masked to the treatment-group allocations during the entire experimental period. They first became unblinded when the evaluation or analysis was finished.

Procedures

Oxygen therapy and NPPV were initiated in hospital in both groups. Oxygen therapy was initiated using a compact oxygen concentrator (VisionAire 5, CAIRE, Chengdu, China) with a sufficient flow rate to control hypoxemia and maintain oxygen saturation (SpO_2) above the target of 88%. NPPV was initiated using a bi-level positive airway pressure ventilator in the spontaneous/timed mode (Curative Lotus ST30, Suzhou, China), with settings adjusted to provide maximal support for respiration and to achieve either normocapnia or reduce $PaCO_2$ by a target of at least 10 mmHg compared with the average values recorded for each patient during the first night of spontaneous breathing after COPD stabilization. IPAP was gradually increased to the maximal level tolerated by the patient, with the aim of achieving a tidal volume of 8 ml/kg. Positive

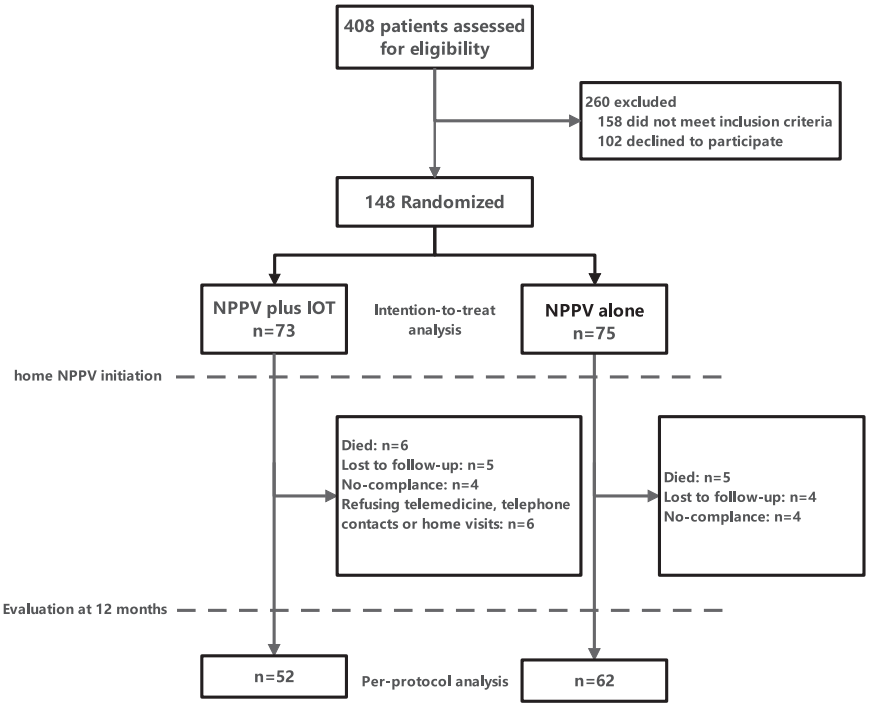

Fig. 1: Trial profile.

end-expiratory pressure was started at 5 cm H_2O. The respiratory rate was set as close as possible to the rhythm of the patient and the inspiration to expiration ratio was set at 1:3. Nasal, oral-nasal or full-face masks were used according to the patient's preference, with humidification to maximize comfort. Patients from both groups were only discharged home once the ventilator parameters had been optimized. All patients were advised to use home oxygen therapy for at least 12 h per day and home NPPV intermittently for at least 8 h per day. Continuous use of NPPV during sleep was recommended but use during daytime was also permitted.

The NPPV alone group received usual home NPPV management. Prior to discharge, patients or their care providers received training on the use NPPV. When necessary, ventilator providers assisted with the home installation of the ventilator. Patients were informed that they could contact their ventilator providers using a helpline in case of technical problems with the ventilator or the oxygen delivery. There was no out-of-hospital management or telemedicine during follow-up. The reference treatment was similar to the way it has been executed in previous home NPPV trials.[3,4]

The NPPV plus IOT-based management group received home NPPV managed in response to data obtained from real-time remote monitoring of each patient using an via IOT cloud platform (Curative Medical Technology Inc., Suzhou, China) as summarized in Fig. 2. The platform included clinical information, ventilator parameters (e.g., usage time, NPPV pressure measurements, mask leaks, breaths per minute, and tidal volume), and follow-up information (Fig. 3). Based on once-daily automatic processing of the collected data, the IOT cloud platform then generated visual summaries of the clinical and follow-up information (Supplementary Figure S1), produced daily reports for medical staff, and highlighted the potential need for risk intervention in the event of data indicating the presence of side effects, leaks or a lack of efficacy (Supplementary Table S2). Automatic alarms based on IOT cloud platform were generated in case of the last 1-week average usage of <5 h/night, mask leak >60 L/min on three consecutive nights or breaths >25/min on two consecutive nights. In case of alarm, healthcare professionals contacted patients by telephone, providing preliminary assessments and case-by-case problem solving. If necessary, emergency home visits were performed and the hospital check-up was recommended. Physicians were responsible for the overall integrated management of care and for recommending appropriate adjustments to the NPPV treatment based on platform information and feedback from the patients. After assessment by physicians, a group of cross-functional healthcare professionals, including family doctors and nurses (from recruiting centre), and healthcare providers (from VitalAire of Air Liquide), cooperated to implement the patients' discharge plans under the close supervision of the third-party investigator (from Shanghai Chest

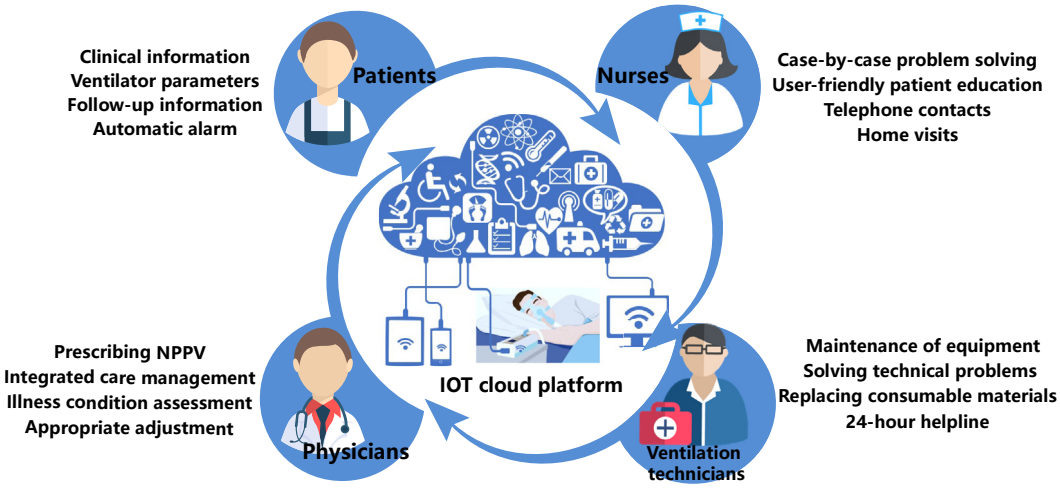

Fig. 2: IOT-based management of NPPV. Reproduced with authorization from the publisher.[17] **Abbreviations**: IOT, Internet of Things; NPPV, noninvasive positive pressure ventilation.

Hospital, Shanghai Jiaotong University). These professionals provided case-by-case problem-solving solutions and specific interventions for minimising side effects and improving compliance. Patients were contacted by telephone every month and home visits were organized 1, 4, and 8 months after NPPV initiation, during which healthcare professionals delivered user-friendly education programs, monitored health status, and ensured adherence to therapy (Supplementary Table S3). Maintenance checks and repairs to the ventilation equipment were also carried out at all follow-up visits. Technicians could be reached via a 24-h helpline in case of technical problems with the ventilator or oxygen treatment.

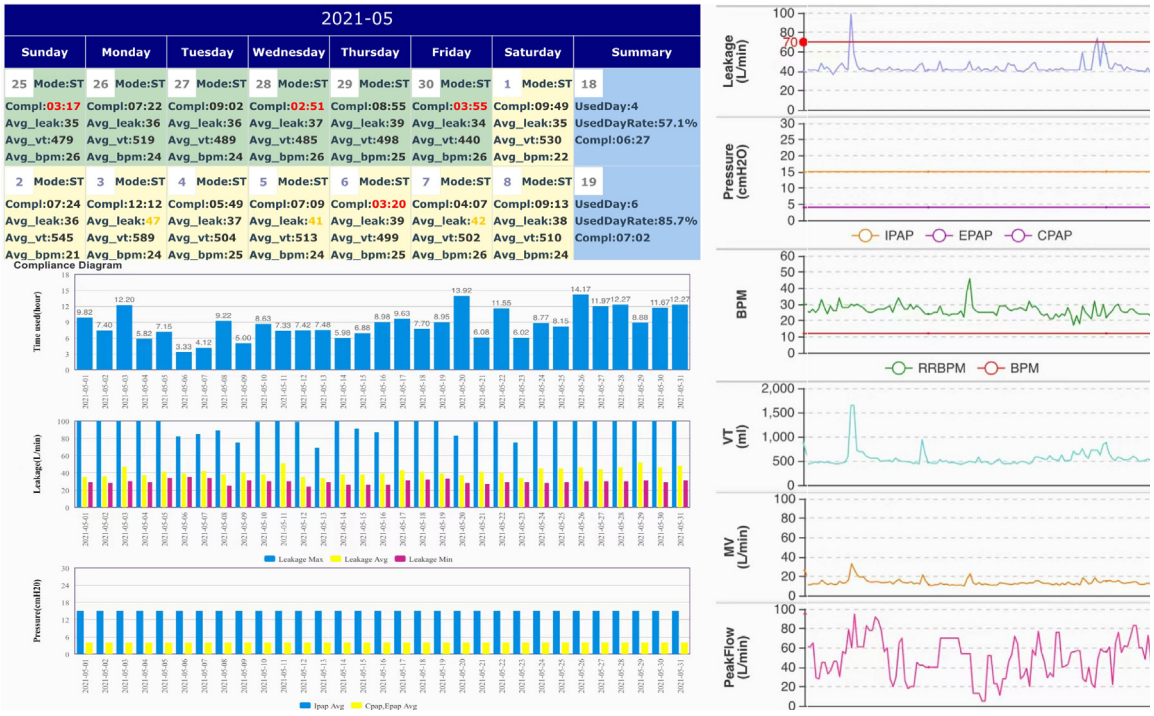

Fig. 3: The IOT cloud platform. **Abbreviations**: Avg leak, average leak volume (L/min); BPM, breaths per minute; compl, Time used (hours); ST, spontaneous/timed; UsedDayRate, percentage of days used per week.

Throughout the study period, patients in both groups also received standard therapy for COPD, such as interventions for smoking cessation and pharmacologic therapy, as recommended by international treatment guidelines.[5] Pharmacologic therapy was guided by symptoms, the risk of exacerbations, side effects, comorbidities and the response to treatment.

All patients were followed up for 12 months. Patient anthropometric data and medical history were collected at baseline. Assessments of health-related quality of life (HRQL) and lung function, as well as chest computed tomography scans, electrocardiograms, echocardiography, routine laboratory tests and daytime gas exchange measurements were performed at baseline. Patients from both groups were admitted to hospital for follow-up assessments at 3, 6, and 12 months at each of the participating hospitals.

Patients were withdrawn from the study and the intervention and follow up terminated if they were lost to follow up, suffered serious adverse events, withdrew consent, or if any of the following endpoints occurred: death; the randomly allocated intervention was not received; endotracheal intubation and invasive ventilation were required during an exacerbation; pneumothorax; active unstable coronary artery disease or cerebrovascular disease; the patient was unable to tolerate noninvasive ventilation due to surgery etc.; or cognitive impairment or unstable psychiatric morbidity.

Outcomes

HRQL was regarded as the most significant patient-centered evaluation in previous research,[2–4] which was a reflection of treatment adherence and effectiveness. Therefore, the primary outcome in this research was a between-group comparison of the change in HRQL between the baseline and the follow-up visits, as centrally assessed using the severe respiratory insufficiency (SRI) questionnaire. The SRI questionnaire was specifically designed for patients with chronic respiratory failure using home mechanical ventilation. The total score was based on the sum of the domain scores calculated by transforming the mean item score into a percentage ranging from 0 (worst quality of life) to 100 (best quality of life).[18]

Secondary outcomes were between-group comparisons of the time to readmission or death within the 12 months following randomization, exacerbation and hospitalization frequency, NPPV compliance, changes in arterial $PaCO_2$ and oxygen pressure (PaO_2) and lung function over the course of the study, assessments of all-cause mortality and safety, and the change in HRQL measured by the modified Medical Research Council score[19] to assess dyspnea (0 = no dyspnea, 4 = dyspnea at rest), the COPD assessment test[20] and the COPD nocturnal symptom assessment test (Supplementary Table S4). NPPV adherence was centrally assessed by monitoring daily usage via the IOT platform for the NPPV plus IOT-based group and by downloading data recorded by the NPPV devices when the observation period ended for the control group. Arterial blood gas analysis was performed on samples collected during the daytime, when the patient was at rest and not receiving oxygen or ventilatory support (except in patients that were deemed unable to stop ventilator support even for short periods). Lung function was assessed according to international guidelines.[5] Data on hospital readmission and survival status were collected from medical records. Safety was assessed by recording the timing, severity, duration, adopted management, and outcome of any adverse events occurring during the study.

Changes to the original protocol are listed in the Supplementary Material.

Statistical analysis

Based on the results of previous trials,[3,4,21] the mean SRI score would be expected to be around 50 for patients receiving standard management of home NPPV after 1 year of treatment, with a between-group difference of around 5 compared to home oxygen therapy alone group. We hypothesized that the IOT-based management would be noninferior to standard management. Therefore, the efficacy of the intervention was at least superior to home oxygen therapy without NPPV and the mean between-group differences in SRI scores of five were judged to be the non-inferiority margin. Assuming a standard deviation (SD) of 10,[16] and a loss to follow up of 25%, a sample size of 100 participants per group would be needed to detect a between-group difference of at least five with a one-sided α of 0.025 and a β of 0.1.

The study was overseen by a steering committee (Supplementary p 2). Recruitment started in January 2019 and the steering committee conducted an interim analysis in June 2021. They recommended that enrollment into the trial be halted because of recruitment and retention difficulties (not for therapeutic futility). In an interim analysis, the mean total SRI score was 55.40 in the NPPV plus IOT group and 52.31 in the NPPV alone group, with an adjusted between-group difference of 3.27 (95% CI, 0.55–5.98; P = 0.019) (Supplementary Tables S5). More specifically, we demonstrated non-inferiority between the two groups. The 12-month follow up of patients who had already been allocated to one of the treatment groups was continued.

Data were presented as the mean (SD), median (interquartile range [IQR]) or as absolute numbers (percentages), as appropriate. Between-group differences were analyzed using the Student t test or the Mann–Whitney U test for continuous variables, and the chi-square test or Fisher exact test for categorical variables, as appropriate. Changes over time were assessed using either a general linear repeated measures analysis of variance with a Bonferroni correction, or a paired t test. Outcome data from all patients randomly allocated to one of the intervention groups were analyzed

according to the intention-to-treat (ITT) principle. Missing data were handled using the "last observation carried forward" method. A linear mixed model was used to analyze the mean difference between the groups after adjustment for minimization variables[4] (baseline values, age, body mass index, and frequency of COPD-related readmissions within the past 12 months). Time from randomization to readmission or death was performed according to the ITT principle using the Kaplan–Meier approach and the log rank test. Hazard ratios (HR) were analyzed using a Cox proportional hazards regression model after adjustment for covariance of the same factors as those identified for the linear mixed model. A per-protocol sensitivity analysis was also performed using outcome data from patients who completed the study according to the protocol.

Two-sided P values of less than 0.05 were considered to be statistically significant. Statistical analyses were performed using SPSS software (version 25.0, IBM SPSS).

Details of cost-effectiveness analysis can be found in the Supplementary Material.

Role of the funding source

The funders played no part in the study design, or in the collection, management, analysis or interpretation of the data.

Results

At total of 148 patients were included in the study between January 24, 2019, and June 28, 2021: 73 patients were randomly allocated to NPPV plus IOT-based management and 75 patients to standard management with NPPV alone (Fig. 1). The final patient follow-up visit occurred on July 27, 2022. In total, 114 patients (52 in the NPPV plus IOT group and 62 in the NPPV alone group) completed the 12-month study and were included in the per-protocol analysis. Overall, 23 patients were withdrawn (dropout rate: 15.5%) and 11 patients (7.4%) died during follow up.

The baseline characteristics of the study population are shown in Table 1. The groups appeared well balanced with no major differences in baseline characteristics. The randomized cohort had severe COPD as evidenced by severe airflow obstruction (mean ± SD FEV1 of 0.66 ± 0.29 L and mean ± SD ratio of FEV1/FVC of 46.36 ± 10.95%) and hypercapnic respiratory failure (mean ± SD PaCO2 of 66.36 ± 12.03 mm Hg).

At 12 months, the mean total SRI score was 56.55 in the NPPV plus IOT group and 50.05 in the NPPV alone group, with an unadjusted between-group difference of 6.31 (95% CI, 3.76–8.86; P < 0.001) and an adjusted between-group difference of 6.26 (95% CI, 3.71–8.80; P < 0.001), satisfying the hypothesis of non-inferiority (lower limit of 95% CI > –5) (Table 2; Fig. 4). Analysis of the individual SRI domains revealed that patients in the NPPV plus IOT group showed greater improvements in the 12-month scores for respiratory complaints, physical functioning, attendant symptoms and sleep, social relationships, anxiety, psychological well-being and social functioning than patients in the NPPV alone group (Supplementary Figure S2 and Table S6).

Significantly greater improvements in adjusted scores for the COPD assessment test, the modified Medical Research Council assessment, and the COPD nocturnal symptom assessment test were also observed in the NPPV plus IOT group than in the NPPV alone group at 12 months (Table 2; Fig. 4).

There were also statistically significant between-group differences in HRQL scores at 6 months, with greater improvements in the NPPV plus IOT group than in the NPPV alone group. In contrast, there were no statistically significant between-group differences at 3 months (Table 2, Fig. 4).

For readmission within 12 months, the unadjusted hazard HR was 0.54 (95% CI, 0.33–0.88; P = 0.014) and the adjusted HR was 0.56 (95% CI, 0.34–0.92; P = 0.023). The 12-month risk of readmission was 34.3% in the NPPV plus IOT group compared with 56.0% in the NPPV alone group, resulting in an absolute risk reduction of 21.9% (95% CI, 4.8%-37.1%) (Fig. 5).

The acute COPD exacerbation-related readmission frequency during the study period was 0.57 (95% CI, 0.34–0.80) for the NPPV plus IOT group and 0.94 (95% CI, 0.68–1.21) for NPPV alone group. The difference between the two groups was close to being statistically significant, with an unadjusted between-group difference of –0.36 (95% CI, –0.71 to –0.01; P = 0.041) and an adjusted between-group difference of –0.34 (95% CI, –0.69 to 0.01; P = 0.053) (Supplementary Table S7).

Five (6.7%) of 75 patients in the control group, and six (8.2%) of 73 patients in the intervention group died within 1 year of randomization (log rank test: P = 0.679), with all causes of death being COPD (Supplementary Figure S3).

In both groups, daytime $PaCO_2$ decreased significantly over the 12-month follow-up period. The adjusted mean between-group difference in the change in $PaCO_2$ at 12 months was 0.47 mmHg (95% CI, –3.47 to 4 41; P = 0.812). The ratio of PaO_2 to the fraction of inspired oxygen (PaO_2/FiO_2) also improved in both groups, without any significant differences between groups (Table 3). In addition, there were no significant between-group differences in FEV_1, FVC, FEV_1% predicted or FEV_1/FVC values during the study period (Supplementary Table S8).

Compliance with NPPV was good among all patients who finished the study. At 6 months, compliance for the NPPV plus IOT group was better than that for the NPPV alone group, with an adjusted between-group difference

	Total (N = 148)	NPPV plus IOT (N = 73)	NPPV alone (N = 75)
Age, years	72.70 ± 6.79	72.76 ± 6.46	72.65 ± 7.14
Male, yes	127 (85.8%)	63 (86.3%)	64 (85.3%)
BMI, Kg/m^2	22.21 ± 4.79	22.52 ± 4.74	21.90 ± 4.84
Former smoker, yes	125 (84.5%)	61 (83.6%)	64 (85.3%)
Packyears	29.06 ± 17.28	29.43 ± 17.82	28.69 ± 16.86
Family history, yes	73 (49.3%)	35 (47.9%)	38 (50.7%)
Comorbidities, yes			
Hypertension	78 (52.7%)	42 (57.5%)	36 (48.0%)
Diabetes	23 (15.5%)	10 (13.7%)	13 (17.3%)
CHD	28 (18.9%)	14 (19.2%)	14 (18.7%)
OSA	9 (6.1%)	3 (4.1%)	6 (8.0%)
COPD-related readmissions within the past year	1.00 (1.00–2.00)	1.00 (1.00–3.00)	1.00 (1.00–2.00)
FEV_1, L	0.66 ± 0.29	0.64 ± 0.20	0.67 ± 0.35
FEV_1% predicted	25.72 ± 9.12	25.59 ± 8.24	25.84 ± 9.95
FVC, L	1.47 ± 0.54	1.46 ± 0.48	1.48 ± 0.60
FEV_1/FVC (%)	46.36 ± 10.95	46.21 ± 10.85	46.50 ± 11.13
PaO_2/FiO_2 [a]	265.27 ± 74.83	263.69 ± 70.48	266.80 ± 79.28
$PaCO_2$, mmHg	66.36 ± 12.03	65.50 ± 9.94	67.21 ± 13.78
HCO_3, mmol/L	37.80 ± 5.85	38.17 ± 5.62	37.44 ± 6.08
pH	7.37 ± 0.06	7.38 ± 0.05	7.37 ± 0.06
Pulmonary hypertension, yes	76 (51.3%)	38 (50.7%)	38 (52.1%)
SRI score	51.84 ± 9.99	51.97 ± 10.04	51.71 ± 10.01
mMRC score	3.00 (3.00–4.00)	3.00 (3.00–4.00)	3.00 (3.00–4.00)
CAT score	28.81 ± 6.53	28.65 ± 6.20	28.97 ± 6.87
cNAT score	34.18 ± 10.61	33.47 ± 10.00	34.86 ± 11.20
Oxygen flow rate , L/min	2.50 (2.00–3.75)	2.50 (2.00–3.50)	2.00 (2.00–4.00)
IPAP, cm H_2O	16.00 (15.00–17.25)	16.00 (15.00–17.50)	16.00 (15.00–17.50)
EPAP, cm H_2O	5.00 (4.00–5.00)	5.00 (4.00–5.00)	4.00 (4.00–5.00)
Backup respiratory rate,/min	13.50 (12.00–15.00)	14.00 (12.00–16.00)	12.00 (12.00–15.00)

Abbreviations: BMI: Body mass index; CAT: COPD assessment test; CHD: Chronic heart disease; COPD: Chronic obstructive pulmonary disease; EPAP: Expiratory positive airway pressure; FEV1: Forced expiratory volume in 1 s; FiO_2: fraction of inspired oxygen; FVC: Forced vital capacity; HCO_3^-: bicarbonate; IOT: Internet of things; IPAP: inspiratory positive airway pressure; mMRC: Medical research council score; cNAT: COPD nocturnal symptom assessment test; NPPV: Noninvasive positive pressure ventilation; OSA: sleep apnea syndrome; $PaCO_2$, arterial carbon dioxide pressure; PaO_2, arterial oxygen pressure; SRI: Severe respiratory insufficiency questionnaire. Data presented are the mean ± standard deviation, number (%), or the median (interquartile range). [a]As some patients were unable to leave oxygen support even for a brief period, the oxygen absorption concentrations of these patients during the blood gas analysis were recorded and the oxygenation index values for these patients were calculated while they were receiving oxygen therapy.

Table 1: **Baseline characteristics.**

in usage time of 45.5 min (95% CI, 2.0–89.0; P = 0.04). However, there were no significant between-group differences in compliance thereafter (Table 4).

Regarding medical alerts based on cloud platform, 132 usage time alerts, 20 leaks alerts and 24 breaths alerts were generated during follow-up period. Alerts were followed by 176 active telephone contacts and 23 emergency home visits. 15 suspected acute exacerbations were identified and 3 acute COPD exacerbation-related readmission were confirmed by subsequent follow-up (Supplementary Table S9).

The IPAP was increased gradually over the follow-up period in the NPPV plus IOT group (mean difference from baseline to 12 months: 0.56 cm H_2O [0.15–0.96], P = 0.007; Supplementary Table S10). There was no change of ventilator settings in the control group during follow up.

Maintenance checks and repairs to the ventilation equipment during follow-up period were presented in Supplementary Table S11.

Nasal stuffiness or dryness, facial rash, and ulceration and gastric distension were reported respectively by 30 (41.1%), 7(9.6%) and 9 (12.3%) patients in the NPPV plus IOT group over the follow-up period. Among these, 50% (n = 15) of cases of nasal stuffiness or dryness, 42.8% (n = 3) of facial rash or ulceration, and 55.6% (n = 5) of gastric distension were solved by various interventions: adding humidification or adhesive dressings, readjusting the mask, or changing the ventilator settings (Supplementary Table S12). No severe adverse events were reported.

Average total 1-year stable COPD costs per patient for the intervention group were ¥9524 (95% CI ¥9012–¥10,035) compared with ¥7451 (95% CI

¥6946–¥7956) in the control group, with a between-group difference of ¥2072 (95% CI, ¥1353–¥2791; P < 0.001) (Supplementary Table S13). The average number of QALYs was 0.453 (95% CI 0.389–0.516) and 0.443 (95% CI 0.380–0.506) for the intervention group and control group, respectively. The incremental cost-effectiveness ratio (ICER) was ¥208551/QALY (95% CI ¥157,042–¥259,959), which was less than the three times the GDP per capita (Supplementary Table S14).

Similar results were obtained in the per-protocol analysis (Supplementary Tables S15–S21 and Figures S3–S4).

Discussion

This RCT performed in 148 patients with severe COPD and CHRF requiring prolonged home NPPV, found that IOT-based management, implemented for a period of 12 months, improved HRQL and prolonged the time to readmission due to COPD exacerbation. Although the trial was intended to assess the non-inferiority of IOT-based management, the findings demonstrated this novel approach was efficient and safe. Our study supports the use of IOT-based platforms to provide integrated and comprehensive remote monitoring and management of home NPPV.

Appropriate follow up, monitoring, and care are crucial for ensuring treatment effectiveness during long-term home NPPV.[5–7] Improving communication between patients, physicians, and the external companies performing the ventilator servicing is critical for monitoring compliance, allowing early detection of exacerbations, complications and comorbidities, and for improving outcomes.[5–8] There is currently a lack of consensus on the monitoring and management of home NPPV in COPD patients with CHRF. In this study, we explored the benefits of using an IOT cloud platform for monitoring of clinical information, ventilator parameters, and providing follow-up information to deliver individualized and completely integrated care management. The system allowed the team to respond rapidly to the needs of the patients, highlighting situations were adjustments to ventilator settings or therapeutic strategies were required, and identifying patients with poor adherence and adverse events. Our team performed 1052 telephone contacts (including contacts due to alerts and planned contacts) and 315 home visits (including emergency visits due to alerts and planned visits) throughout the trial in the intervention group. Our findings demonstrated that the IOT-approach provided a reliable and safe method for monitoring home NPPV and that the improved feedback pathway had a positive impact on key clinical outcomes, such as HRQL and the risk of readmission, in a population of patients with severe COPD and CHRF.

HRQL is regarded as the most significant patient-centered evaluation in COPD.[18] A recent meta-analysis

Visit	Mean (95% CI)		Treatment effect within group (95% CI)[b]		Between-group difference adjusted for baseline (95% CI)	P value	Between-group difference fully adjusted model[c] (95% CI)	P value
	NPPV plus IOT (N = 73)	NPPV alone (N = 75)	NPPV plus IOT	NPPV alone				
SRI Baseline	51.97 (49.63–54.32)	51.71 (49.41–54.02)	NA	NA	NA	NA	NA	NA
3 M	54.93 (52.40–57.47)	53.08 (50.78–55.38)	2.96 (1.39–4.52)[a]	1.36 (−0.10 to 2.83)	1.64 (−0.42 to 3.70)	0.117	1.57 (−0.45 to 3.61)	0.127
6 M	55.91 (53.33–58.50)	51.72 (49.51–53.94)	3.94 (2.16–5.71)[a]	0.01 (−1.41 to 1.44)	3.98 (1.82–6.14)	<0.001	3.97 (1.84–6.11)	<0.001
12 M	56.55 (53.92–59.17)	50.05 (47.89–52.22)	4.57 (2.42–6.72)[a]	−1.65 (−3.42 to 0.11)	6.31 (3.76–8.86)	<0.001	6.26 (3.71–8.80)	<0.001
CAT Baseline	28.65 (27.20–30.10)	28.97 (27.39–30.55)	NA	NA	NA	NA	NA	NA
3 M	26.34 (24.74–27.94)	26.80 (25.45–28.14)	−2.31 (−3.49 to −1.13)[a]	−2.17 (−3.43 to −0.91)[a]	−0.25 (−1.79 to 1.29)	0.747	−0.23 (−1.76 to 1.30)	0.766
6 M	25.15 (23.64–26.65)	27.45 (26.13–28.77)	−3.50 (−4.86 to −2.14)[a]	−1.52 (−2.86 to −0.17)[a]	−2.13 (−3.75 to −0.50)	0.010	−2.20 (−3.77 to −0.63)	0.006
12 M	24.97 (23.46–26.47)	28.32 (26.89–29.74)	−3.68 (−5.06 to −2.30)[a]	−0.65 (−2.03 to 0.72)	−3.17 (−4.86 to −1.48)	<0.001	−3.10 (−4.77 to −1.43)	<0.001
mMRC Baseline	3.15 (2.96–3.33)	3.06 (2.87–3.26)	NA	NA	NA	NA	NA	NA
3 M	2.98 (2.78–3.19)	2.86 (2.65–3.07)	−0.16 (−0.32 to −0.01)[a]	−0.20 (−0.35 to −0.04)[a]	0.05 (−0.15 to 0.26)	0.590	0.07 (−0.13 to 0.28)	0.461
6 M	2.83 (2.61–3.05)	3.08 (2.87–3.28)	−0.31 (−0.53 to −0.09)[a]	0.01 (−0.18 to 0.21)	−0.28 (−0.55 to −0.02)	0.033	−0.27 (−0.53 to −0.01)	0.044
12 M	2.93 (2.70–3.15)	3.17 (2.98–3.36)	−0.21 (−0.43 to −0.01)[a]	0.10 (−0.09 to 0.30)	−0.28 (−0.54 to −0.02)	0.075	−0.26 (−0.51 to −0.01)	0.038
cNAT Baseline	33.47 (31.14–35.81)	34.86 (32.28–37.44)	NA	NA	NA	NA	NA	NA
3 M	29.49 (27.09–31.89)	30.36 (28.21–32.50)	−3.98 (−5.84 to −2.12)[a]	−4.50 (−6.57 to −2.43)[a]	−0.02 (−2.44 to 2.39)	0.983	0.04 (−2.39 to 2.49)	0.969
6 M	26.78 (24.87–28.68)	30.84 (28.73–32.94)	−6.69 (−8.95 to −4.44)[a]	−4.02 (−6.31 to −1.73)[a]	−3.49 (−5.95 to −1.03)	0.005	−3.44 (−5.90 to −0.98)	0.006
12 M	26.58 (24.89–28.28)	32.09 (29.90–34.27)	−6.89 (−8.98 to −4.79)[a]	−2.77 (−5.09 to −0.44)[a]	−4.93 (−7.29 to −2.56)	<0.001	−4.84 (−7.22 to −2.46)	<0.001

Abbreviations: CAT: COPD assessment test; CI: confidence interval; IOT: Internet of things; M: months; mMRC: Medical research council score; NA: not applicable; cNAT: COPD nocturnal symptom assessment test; NPPV: Noninvasive positive pressure ventilation; SRI: Severe respiratory insufficiency questionnaire. [a]Adjusted P value < 0.05 for repeated measures analysis of variance with a Bonferroni correction. [b]Mean difference from baseline. [c]Adjusted for baseline values, number of COPD readmissions within the past year, age, and BMI.

Table 2: **Health-related quality of life.**

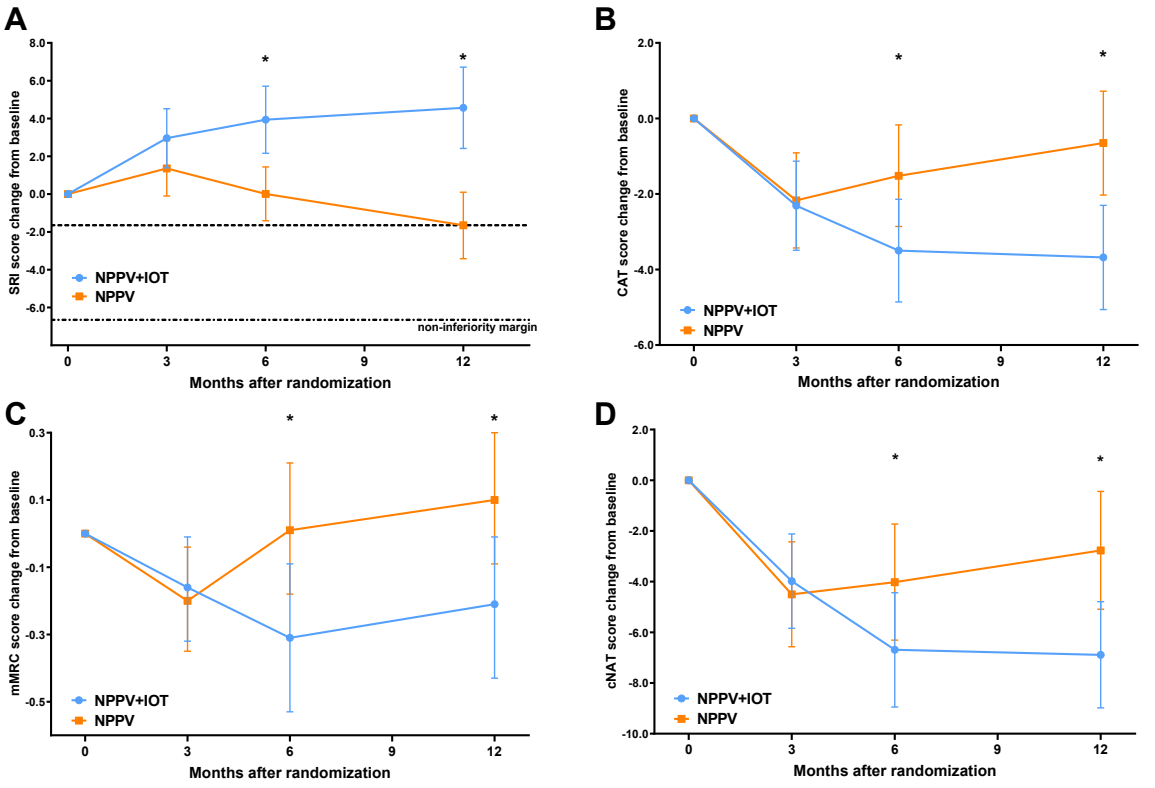

Fig. 4: Change in health-related quality of life from baseline. A: Change in SRI score from baseline; B: Change in CAT score from baseline; C: Change in mMRC score from baseline; D: Change in cNAT score from baseline. Data are shown as mean and 95% CI; * Adjusted P value < 0.05 for between-group differences using the fully adjusted model. Abbreviations: CAT, chronic obstructive pulmonary disease assessment test; mMRC score, modified Medical Research Council score; cNAT, COPD nocturnal symptom assessment test; SRI score, severe respiratory insufficiency score.

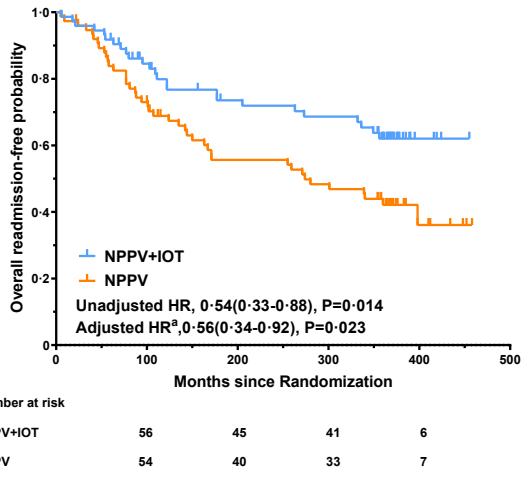

Fig. 5: Kaplan–Meier survival analysis of the time to readmission from randomization to the end of trial follow up. [a] Adjusted for the number of COPD readmissions within past year, age, and body mass index. Abbreviations: COPD, chronic obstructive pulmonary disease; HR, hazard ratio; IOT, Internet of Things; NPPV, noninvasive positive pressure ventilation.

found that the short-term use of home NPPV was associated with no significant difference in the quality of life of patients with COPD.[22] The results of the present study suggest that a lack of proper management during long-term NPPV may hamper the outcome benefits of this intervention. Indeed, patient HRQL in the control group was similar to that reported previously.[3,4,16] A significant improvement in HRQL was observed for the IOT-based management group, including domains covering respiratory complaints, physical functioning, psychological wellbeing and attendant symptoms. Based on out-of-hospital management, the reduction of acute exacerbations and adverse events, case-by-case problem-solving solutions, and maintenance checks and repairs to the ventilation equipment have the potential to improve HRQL. Notably, no between-group differences in HRQL were observed at the 3-month follow-up visit, highlighting the importance of long-term integrated management.

Readmission for a severe exacerbation of COPD has been shown to be associated with faster disease progression and increased mortality risk.[23] Previous studies

Visit	Mean (95% CI), mmHg		Treatment effect within group (95% CI)[b], mmHg		Between-group difference adjusted for baseline (95% CI)	P value	between-group difference fully adjusted model[c] (95% CI)	P value
	NPPV plus IOT (N = 73)	NPPV alone (N = 75)	NPPV plus IOT	NPPV alone				
$PaCO_2$ Baseline	65.50 (63.18–67.82)	67.21 (64.04–70.38)	NA	NA	NA	NA	NA	NA
3 M	56.70 (54.18–59.21)	58.03 (55.12–60.95)	−8.80 (−11.10 to −6.40)[a]	−9.17 (−12.64 to −5.70)[a]	−0.65 (−4.16 to 2.86)	0.714	−0.65 (−4.21 to 2.90)	0.715
6 M	57.27 (54.58–59.95)	55.43 (52.76–58.09)	−8.23 (−11.10 to −5.36)[a]	−11.78 (−15.18 to −8.37)[a]	2.38 (−1.17 to 5.94)	0.187	2.28 (−1.31 to 5.88)	0.211
12 M	56.79 (53.78–59.80)	56.86 (54.00–59.72)	−8.70 (−12.06 to −5.35)[a]	−10.34 (−13.66 to −7.03)[a]	0.50 (−3.40 to 4.42)	0.797	0.47 (−3.47 to 4.41)	0.812
PaO_2/FiO_2 [d] Baseline	263.6 (247.2–280.1)	266.8 (248.5–285.0)	NA	NA	NA	NA	NA	NA
3 M	294.9 (278.3–311.5)	318.6 (289.4–347.7)	31.22 (11.67–50.77)[a]	51.81 (20.59–83.03)[a]	−22.74 (−55.49 to 10.00)	0.171	−21.31 (−52.47 to 9.84)	0.178
6 M	307.4 (287.4–327.4)	326.0 (301.9–350.1)	43.75 (19.96–67.55)[a]	59.24 (34.91–83.57)[a]	−17.48 (−47.47 to 12.49)	0.250	−16.73 (−46.46 to 13.00)	0.267
12 M	326.1 (295.2–357.0)	334.4 (308.7–360.2)	62.42 (27.02–97.82)[a]	67.68 (40.81–94.55)[a]	−7.71 (−47.31 to 31.88)	0.700	−5.81 (−44.91 to 33.29)	0.769

Abbreviations: CI: confidence interval; FiO_2: fraction of inspired oxygen; IOT: Internet of things; M: months; NA: Not applicable; NPPV: Noninvasive positive pressure ventilation; $PaCO_2$, arterial carbon dioxide pressure; PaO_2, arterial oxygen pressure. [a]Adjusted P value < 0.05 from repeated measures analysis of variance with a Bonferroni correction. [b]Mean difference from baseline. [c]Adjusted for baseline values, number of COPD readmissions within past year, age, and BMI. [d]Since some patients cannot leave oxygen support for a short period of time, the oxygen absorption concentration of these patients during blood gas analysis were recorded and the oxygenation index of the patients were calculated.

Table 3: **Gas exchange.**

Visit	Mean (95% CI), min		Treatment effect within group (95% CI)[a], min		Between-group difference adjusted for baseline (95% CI)	P value	Between-group difference fully adjusted model[b] (95% CI)	P value
	NPPV plus IOT (N = 52)	NPPV alone (N = 47)[c]	NPPV plus IOT	NPPV alone				
3 M	369.8 (323.1–416.4)	366.8 (314.8–418.7)	NA	NA	NA	NA	NA	NA
6 M	392.6 (334.2–451.0)	345.4 (289.8–400.9)	22.8 (−7.3 to 53.1)	−21.4 (−51.3 to 8.5)	44.3 (1.8–86.7)	0.040	45.5 (2.0–89.0)	0.040
12 M	391.4 (346.1–436.7)	363.9 (314.5–413.2)	21.6 (−9.9 to 53.2)	−2.9 (−48.1 to 42.3)	25.5 (−22.7 to 73.9)	0.296	27.6 (−21.7 to 76.9)	0.269

Abbreviations: CI: confidence interval; IOT: Internet of things; M: months; NA: Not applicable; NPPV: Noninvasive positive pressure ventilation. [a]Mean difference from baseline. [b]Adjusted for baseline values, number of COPD readmissions within past year, age, and BMI. [c]Compliance analyses included patients finishing the study according to the protocol. 15 (24%) patients in the NPPV alone group were excluded because of missing data.

Table 4: **NPPV compliance.**

have demonstrated that home NPPV is associated with lower risk of rehospitalization compared with no device support.[22] In our study, IOT-based home NPPV management prolonged the time to readmission during the 12-month study period. 15 suspected acute exacerbations were identified due to medical alerts from IOT cloud platform in the intervention group, which might reduce hospitalization rate. The difference in readmission frequency between the two groups was also close to being statistically significant. These findings further demonstrate the effectiveness and safety of the IOT-based management approach.

Adherence to NPPV has been shown to be important for clinical outcomes, with 5 h of NPPV per day being recommended as a reasonable target.[6] In this study, patients in both groups achieved good compliance, with an average NPPV use of 6 h/day. Although the between-group difference in adherence was only statistically significant at 6 months, these findings show that good treatment compliance was maintained in the patients under IOT-based management.

Regarding the control group, our goal was to mimic real-world management of home NPPV in China. The IOT group had scheduled telephone contacts and home visits while the standard care group only were instructed to call the provider with problems. Paying much more attention to the IOT group might explain a substantial amount of the effects found. However, telemonitoring without out-of-hospital management might be considered as a reason for telemedicine encounter failure. Telemonitoring based on IOT program and out-of-hospital management were both important components of home NPPV treatment.

The effectiveness of IOT-based management of noninvasive ventilation has been investigated previously in patients with a range of conditions. Pinto et al.[24] showed that telemonitoring of ventilator parameters in patients with amyotrophic lateral sclerosis had a favorable impact on cost, survival, and functional status. Furthermore, Hwang et al.[13] demonstrated that telemonitoring of continuous positive airway pressure, combined with the use of automated feedback messaging, improved 90-day compliance in obstructive sleep apnea patients. Significant increases in continuous positive airway pressure adherence and improvements in patient-centered outcomes were also observed by Pépin et al.[12] in patients with obstructive sleep apnea and a high cardiovascular risk being managed by multimodal telemonitoring. Finally, Adly et al.[25] showed that telemanagement of home-isolated COVID-19 patients requiring NPPV impeded exacerbation of early-stage pneumonia. Telemedicine has also been described as holding promise for improving treatment effectiveness in COPD patients.[26] Indeed, during the COVID-19 pandemic, the need to comply with social distancing recommendations led to many healthcare professionals using IOT-based management to care for patients with COPD. However, outcome data from RCTs evaluating telemonitoring of home NPPV in patients with COPD remain limited, and there is still controversy and variability in the different interventions and applications used for the management of COPD.[27–29] The current study provided new evidence in this regard and provided valuable data for the generation of evidence-based guidelines for the monitoring and management of home NPPV in patients with COPD.

Compared to other countries, there is currently inadequate use of home NPPV in China and there is an imbalance of resources between different regions. Although more large-scale multicenter RCTs and cost-effectiveness evaluations are required, IOT-based medical platforms, such as the system used in this study, have the potential to address this imbalance and transform access to healthcare. Such interventions may well have a greater effect in low-income and middle-income countries with scarce healthcare facilities and fewer healthcare providers,[10] although challenges relating to frequent staff training and adequate access to equipment will need to be addressed.

This study has several limitations. First, although the healthcare professionals conducting the outcome assessments and the statistical analysts were blinded to the treatment assignment, blinding of investigators was not possible due to the nature of IOT-based management of NPPV. Second, the premature termination of recruitment may have induced bias. Third, the IPAP in this study was set at 16.00 (15.00–17.25) cm H_2O, rather than the IPAP settings of 21.6 and 24 cm H_2O used in the previous RCTs assessing the effectiveness of high-intensity NPPV.[3,4] However, the objective of titration in this study was to reduce $PaCO_2$ according to the maximal level tolerated by the patient. The IPAP was increased gradually over the follow-up period in the NPPV plus IOT group. Fourth, the home NPPV in this study was initiated after an episode of acute-on-chronic hypercapnic respiratory failure when judged clinically stable recommended by European Respiratory Society,[6] without the reassessment at 2–4 weeks after resolution recommended by American Thoracic Society.[7] It may reduce the generalizability of the trial results as paying more attention to a post AECOPD population probably overrates the effect that could be expected in a more chronic population. Fifth, the transcutaneous carbon dioxide tension monitoring recommended by the European Respiratory Society[6] was not be carried out during this study due to technical problems. Sixth, although the aim of the study was to assess integrated remote management of the patients, safety concerns meant that NPPV initiation and appropriate adjustment of the NPPV treatment required either a home visit or hospitalization. Finally, the overall number of patients lost to follow up was below the predicted 25%; however, the dropout rate was higher in the NPPV plus IOT group than in the control group.

In conclusion, this study was the first and largest RCT to be conducted in China to evaluate the effectiveness of IOT-based management of NPPV for patients with COPD and CHRF. Adding IOT-based management to NPPV improved HRQL and prolonged the time to readmission during the 12-month follow up.

Contributors

YS is the principal investigator of the study, with full responsibility for the contents of the manuscript, and contributed to all aspects of the manuscript. YS, CB and HL were jointly responsible for conceptualization and funding acquisition.

WJ, XJ, CD, WG and XG was responsible for the literature search, figures, data curation, data analysis, and data interpretation. WJ, CZ and HL was responsible for the cost-effectiveness analysis. WJ also wrote the original draft of this manuscript and all authors then critically reviewed it for important intellectual content.

XJ, CD, WG, XG, CT, HC, HL, YS, YZ, XG and HL contributed to the study design, and acquisition, analysis, or interpretation of data.

YS, LZ, SY, KZ, QC, XZ, CZ contributed equally to project administration.

YS and WJ have directly accessed and verified the data reported in the manuscript.

All the authors reviewed and approved the final manuscript.

Data sharing statement

De-identified enrolled patients' data collected during the study will be shared 1 year after article publication. All of the individual patient data without private information collected during the trial will be shared. In addition, the study protocol and statistical analysis plan will also be available. Researchers who provide a scientifically sound proposal will be allowed to access the individual participant data. Proposals should be sent to the corresponding author. These proposals will be reviewed and approved by the sponsor, investigator, and collaborators on the basis of scientific merit. To gain access, all individuals requesting data will need to sign a data access agreement and to confirm that data will only be used for the agreed purpose for which access was granted.

Declaration of interests

The authors declare that they have no conflicts of interest.

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Air Liquide Healthcare (Beijing) Co., Ltd. was not involved in trial design, patient recruitment, data collection, analysis or interpretation; preparation, review, or approval of the manuscript; or the decision to submit for publication.

The authors had complete independence and control over their research and findings. The authors have not been paid to write this article. The corresponding author had full access to all data in the study and was responsible for deciding when to submit the report for publication.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102518.

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