An Autonomous Treatment Platform for COVID-19, Long COVID and Influenza with Machine Learning

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Abstract

The persistent impact of COVID-19 on global health remains a critical concern, calling for ongoing vigilance and response [1]. We propose ACT-ML, an autonomous machine learning platform rooted in Traditional Chinese Medicine (TCM) principles, to address this challenge by providing scalable personalized antiviral treatment for COVID-19, long COVID, and influenza in outpatient settings. The system transforms the clinical triage process into a machine learning task, utilizing TCM formulas predefined by experienced physicians as predictable labels for classification. The platform leverages 340 million synthetic patient records, focusing on 44 symptoms and categorizing patients into three age groups: 14-40, 41-60, and 60-80+. To validate the system, we conducted a 49-patient retrospective simulation study. In addition, we conducted a clinical feasibility trial among 27 patients from June to August 2023. The platform demonstrated 100% alignment with TCM experts in both the simulation study and the clinical feasibility trial. In the trail, there was no COVID-19 or influenza related hospitalization or death from any cause and no cases of SARS-CoV-2 infection recurrence (rebound cases) through day 28. ACT-ML offers continuous accessibility, scalability, and enables contactless operations and swift medication delivery. We believe that the platform has the potential to alleviate clinician shortages during ongoing health crises by administering personalized antiviral treatment at scale.

Introduction

Despite progress in public health measures and vaccination efforts, COVID-19 remains a formidable challenge to global health due to its mutable nature [1], the observed waning immunity post-vaccination and subsequent to natural infections [2, 3], and a risk profile markedly graver than that of influenza [4]. As we enter the next phase of the endemic, it's crucial to effectively treat mild cases to prevent their progression to severe stages and alleviate the strain on our healthcare system. The convergence of COVID-19, long COVID, and influenza during winter seasons introduces a new layer of complexity and risk [5]. This necessitates the development of a universal treatment platform for COVID-19, long COVID, and influenza.

Persistent waves of COVID-19 infection create a relentless strain on healthcare systems. The possibility of reinfection occurring as frequently as every 3.7 months [6] adds complexity, placing an ongoing burden on healthcare providers to handle a persistent increase in cases. For example, in China, between December 2022 and March 2023 (121 days), an estimated 85% of the population, or approximately 1.1 to 1.2 billion people, were infected [7]. This translates to daily case counts ranging from approximately 9.09 million to 9.92 million. Previous studies have shown that early antiviral intervention is preferred for managing mild COVID-19 cases and preventing “long COVID” symptoms [8,9,10]. However, the vast scale of infections poses a challenge to this approach.

Precision medicine is essential in tailoring antiviral therapies. While prevailing antiviral treatment regimens have demonstrated efficacy in reducing hospitalizations and mortality, protocols involving drugs such as Plaxvoid (nirmatrelvir and ritonavir) [11] and Azvudine [12]

do not allow for dosage adjustments based on patient age, symptoms, and associated risk factors. This limitation may compromise their effectiveness in real-world applications. Notably, a study reported a decline in Plaxvoid's efficacy from 86% in initial clinical trials to 37% in subsequent evaluations [13]. By tailoring the dosages based on individual patient characteristics including age, pre-existing health conditions, and severity of symptoms, we can create an optimal treatment plan that is personalized and effective. Such an approach not only enhances the effectiveness of antiviral medications but also reduces the likelihood of adverse side effects.

As indicated in the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia" from China [14], Traditional Chinese Medicines (TCM) have been recommended for COVID-19 management and have yielded favorable outcomes in clinical practice [15,16]. TCM uniquely allows for the customization of antiviral therapies based on individual patient parameters such as age, symptoms, and comorbidities. Its guiding philosophy, “Yi Bing Tong Zhi” (or “Treating different diseases with the same principle”), strikes a balance between personalized and standardized treatments. The concept of "Yi Bing Tong Zhi" promotes a symptom-based approach over a test-based one, broadening the treatment scope from just COVID-19 to include influenza. We suggest that COVID-19 can be viewed as a type of influenza with a distinct capability to compromise the immune system. One of the fundamental distinctions between influenza and COVID-19 lies in the latter’s aggressive assault on the patient’s immune defenses [17]. However, the wide-scale application of TCM is challenged due to the scarcity of experts and varied practitioner expertise.

Following the emergence of COVID-19 in late 2019, the AI (artificial intelligence) community swiftly responded by developing solutions to address the challenges posed by the virus. Between 2020 and 2021, hundreds of AI applications were created specifically for this purpose. However, subsequent evaluations have indicated that these applications struggle to demonstrate effectiveness in the clinical management of the disease. [18, 19]. Given this gap, there is a need for innovative solutions that can address both the scale and complexity of the disease.

In this study, we propose a machine learning-based autonomous treatment system, specifically designed for the management of COVID-19, long COVID (post-acute sequelae of COVID-19), and influenza. This system, deeply rooted in Traditional Chinese Medicine (TCM) principles, offers home-based treatment plans. A principal aspect of our approach is the utilization of a substantial dataset comprising 340 million synthetic patient records aligned with clinical knowledge. This extensive synthetic data, central to our model's development, enables a robust and comprehensive understanding of diverse patient profiles. The system reformulates the clinical triage process into a machine learning classification problem, stratifying classification into 9 classes, each corresponding to a specific prescription. To ensure practical implementation in a pharmacy setting, these classes have been condensed into five categories. These categories are defined based on a combination of the patient's age, symptoms, and pre-existing comorbidities. Prescriptions are formulated under the guidance of a senior physician with a 40-year tenure in respiratory diseases and influenza, focusing on 44 distinct symptoms and three patient age groups. Our model categorizes adult patients into three age groups: 14-40, 41-60, and 61-80+. The cornerstone of our methodology is the leverage of synthetic data, which not only enhances the model’s accuracy but also ensures its relevance across diverse patient

demographics. To mitigate medical uncertainties in the treatment of COVID-19, we have developed a framework named 'Rubik Challenge.' Furthermore, to validate our machine learning model, we conducted a validation during the development phase, as well as a retrospective simulation study and a clinical feasibility trial. This system aims to mitigate the ongoing pressure on healthcare systems and provide scalable, personalized antiviral treatment. Its primary goal is to efficiently prevent the progression of mild and moderate cases into more severe stages, thereby filling a critical gap in current healthcare strategies.

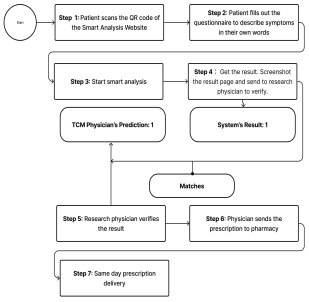
Results

Dataset and system overview

In the development of ACT-ML, we generated a synthetic dataset including 340 million patient records with COVID-19, long COVID and influenza in the development phase. To attest the model's robustness and validity, an independent test dataset consisting of 36 million patient records was designated for the testing phase. To ensure the testing dataset accurately mirrors real-world patient profiles, it is constructed in three parts: initially, a randomly selected subset constituting 5% of the total dataset; followed by patients exhibiting the 11 prevalent symptoms and symptom combinations as identified by the CDC [20]; and finally, clinically significant cases featuring patients with high risk health conditions such as asthma, heart disease, and hypertension [21].

Our proposed machine learning framework focuses on 44 unique symptoms and categorizing the population into three age brackets: 14-40, 41-60 and 60+. Patient's age, presented symptoms and pre-existing conditions serve as input variables, for each age group, while the model outputs one of 54 predictive labels, each corresponding to a specific, pre-established TCM prescription. The 54 categories are further subdivided into three age groups (14-40, 41-60, and 60+) and two severity levels (mild/moderate and severe). Each severity level and age group has nine classes. After consultation with the pharmacy, the number of predictive labels was reduced to 5 to ensure feasibility for deployment in clinical settings. To balance accuracy with performance on mobile devices, we favor decision trees over random forests due to their lower computational requirements, smaller model size, and faster build times, despite the potentially higher accuracy of random forests. Furthermore, we introduce a control system to guarantee the optimization of model performance in mimicking the physician's clinical decision-making process. Our proposed machine learning model has two components: (1) inputs from patients, using a binary-response questionnaire, to assess the patient's age, the presence of symptoms, and pre-existing comorbidities and (2) a prescription recommendation denoted by a numerical identifier generated by the machine learning system. Each identifier represents a TCM prescription.

a.



b.

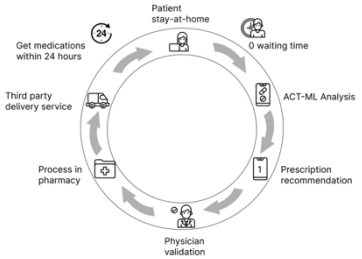


Figure 1: a. Workflow of the machine learning based treatment system. b. We streamline the services to make it possible for patients to get medication within 24 hours after symptom onset.

Figure 1 displays the workflow of the system. In the clinical study, participants interact with an online application to receive a prescription suggestion from the AI, which is then validated by a senior physician. After validation, the prescription number is sent to the pharmacy for processing. Relying on delivery services, the patient can receive medications within 24 hours. Participants are asked to take the online assessment every three days, or earlier if changes in symptoms are noted. A research physician will follow up with patients every three days through phone calls. Treatments participants might receive one of the traditional Chinese medicine formulas: LizCOVIDCure-1, LizCOVIDCure-2, LizCOVIDCure-3, LizoCOVIDCure-4 and LizCOVID-5.

Retrospective simulation study of performance of AI versus physicians

To further validate the ACT-ML system, we conducted a retrospective simulation study on real-world patient data. We tested the model on 49 patients diagnosed with COVID-19 between late December 2022 and February 2023 in a clinic at Sheng'Ai Hospital, China. In the development phase, the model achieved an average accuracy of 87%. However, this may pose clinical risks if deployed in the real world. To address this, we deployed a control system on top of the decision tree model, inspired by control systems in autonomous driving systems [22, 23]. This control system ensures that the model is fully aligned with the decision-making process of senior physicians. We simulated patient scenarios by entering the patient's age, symptoms, and pre-existing comorbidities into the ACT-ML system and compared the generated recommendations to the actual traditional Chinese medicine (TCM) formulations prescribed by a human physician. The ACT-ML system achieved 100% accuracy and was fully aligned with the physicians' predictions.

Proof-of-concept feasibility clinical trail of the AI system

Patient Population

Table 1 shows the characteristics of the outpatient population. In this feasibility study, we assessed the clinical feasibility and safety of an artificial intelligence system in managing outpatients diagnosed with COVID-19, post-COVID-19 syndrome, and influenza. Between June 16 and August 16, 2023, a total of 27 patients were enrolled. Among the 27 participants in the study, 26 of them were outpatients, and one was hospitalized during the initiation of the study. The baseline attributes of all participants were documented, including factors such as age, sex, severity of disease at initial admission, vaccination status, comorbidity, and initial symptoms. Across all participants, there were no COVID-19 and influenza related hospitalization or death from any cause (0 hospitalization, 0 death) through day 28.

Participants went through a total of 52 ACT-ML sessions. When we evaluated the ACT-ML system, we compared its recommendations to the traditional Chinese medicine (TCM) prescriptions given by a senior doctor. The system's suggestions matched the doctor's decisions 100% of the time.

The outpatients were categorized into three groups based on their diagnoses: 1) Active SARS-CoV-2 infection (14 individuals) - these individuals tested positive for SARS-CoV-2 using a

Table 1: Baseline clinical characteristics of outpatients.

Characteristics	Total （26）	Active Infection (14)	Long Covid (10)	Influenza (2)
Age				
14-40 y	9 (34.62%)	5 (35.71%)	3 (30.00%)	1 (50.00%)
41-60 y	9 (34.62%)	3 (21.43%)	6 (60.00%)	0
61-80 y	6 (23.08%)	4 (28.57%)	1 (10.00%)	1 (50.00%)
> 80 y	2 (7.69%)	2 (14.29%)	0 (0.00%)	0
Average age	50.9	53.5	48.5	42.5
Sex				
Male	7 (26.92%)	5 (35.71%)	0	2 (100%)
Female	19 (73.08%)	9 (64.29%)	10 (100.00%)	0
Vaccine status[b]				
Vaccinated and boosted (>= 3 doses)	14 (58.33%)	9 (64.29%)	5 (50.00%)	N/A
Vaccinated (2 doses)	7 (29.17%)	4 (28.57%)	3 (30.00%)	N/A
Partially vaccinated (1 dose)	1 (4.17%)	0	1 (10.00%)	N/A
Unvaccinated	2 (8.33%)	1 (7.14%)	1 (10.00%)	N/A
Pre-existing Comorbidity				
High blood sugar	1 (3.85%)	1 (7.14%)	0	0
High uric acid	1 (3.85%)	1 (7.14%)	0	0
Hypertension	2 (7.69%)	1 (7.14%)	1 (10%)	0
Chronic bronchitis	1 (3.85%)	1 (7.14%)	0	0
Diabetes	1 (3.85%)	1 (7.14%)	0	0
Pulmonary emphysema	1 (3.85%)	1 (7.14%)	0	0
Endometrial cancer	1 (3.85%)	0	1 (10%)	0
Ovarian cancer	1 (3.85%)	0	1 (10%)	0
Lung cancer	1 (3.85%)	0	1 (10%)	0
Thyroid Nodules	3 (11.54%)	1 (7.14%)	2 (20%)	0
Patient with at least one pre-existing comorbidity	8 (30.77%)	3 (21.43%)	5 (50%)	0
Symptoms on admission				
Fever	6 (23.08%)	5 (35.71%)	0	1 (50.00%)
Fatigue	8 (30.77%)	5 (35.71%)	2 (20.00%)	1 (50.00%)
Cough	20 (76.92%)	10 (71.43%)	10 (100%)	1 (50.00%)
Expectoration	8 (30.77%)	5 (35.71%)	2 (20.00%)	2 (100.00%)
Sore throat	6 (23.08%)	4 (28.57%)	0	2 (100.00%)
Headache	6 (23.08%)	5 (35.71%)	0	0
Muscle ache	4 (15.38%)	3 (21.43%)	0	1 (50.00%)
Running nose	4 (15.38%)	4 (28.57%)	0	0
Swollen tonsils	2 (7.69%)	0	1 (10.00%)	1 (50.00%)
Loss of smell/taste	4 (15.38%)	4 (28.57%)	0	0
Swollen hands and feet	1 (3.85%)	1 (7.14%)	0	0
Other Covid-19 Medication				
Antiviral (Azvudine)[c]	1 (3.85%)	1 (7.14%)	0	0

a. The ICU case was excluded from this analysis. Detailed information about the ICU case can be found in the severe cases' case study.
b. The vaccine status of the two influenza cases were not recorded.
c. One patient completed Azvudine treatment before joining the study, tested negative at the beginning of the study, and was not considered in the rapid test conversion time data.

rapid antigen test within 30 days before starting treatment; 2) Long COVID (Post-Acute Sequelae of SARS-CoV-2 infection) (10 individuals) - these individuals had a positive rapid antigen test result for SARS-CoV-2 that was taken more than 30 days before treatment; and 3) Influenza (2 individuals) - these patients tested negative for SARS-CoV-2 but were diagnosed with influenza. In the outpatients, the age range spanned from 20 to 92 years. In terms of age distribution, the mean age across all cohorts was 50.9 years. For active SARS-CoV-2 infection, the average age was slightly higher at 53.5 years, whereas it was 48.5 years on average for the long COVID (Post-Acute Sequelae of SARS-CoV-2 infection) group and 42.5 years for the Influenza group. In terms of gender, a significant majority of the patients were female (73.08%), especially evident in the long COVID group where 100% patients were female. Excluding those in the influenza group, 58.33% of individuals had received at least three vaccine doses (indicating they were boosted), while 8.33% had not been vaccinated at all. In all outpatients, a significant proportion (30.77%) exhibited the presence of one or more risk factors. This percentage was lower in the active SARS-CoV-2 infection group at 21.43% but notably higher in the long COVID group at 50%. Among the long COVID group, 30% of them had cancer. In terms of symptoms for active SARS-CoV-2 infection, coughing was most prevalent at 71.43%. Other common symptoms included fatigue, evident in 35.71% of active SARS-CoV-2 infection patients, 20% among long COVID patients and 50% of Influenza patients, and fever, present in 35.71% of active SARS-CoV-2 infection and 50% of Influenza patients.

Clinical Result For Active SARS-CoV-2 Infection: Outpatient

Table 2 shows clinical results for patients with active SARS-CoV-2 infection. In our study, we assessed 14 patients presenting with active SARS-CoV-2 infection in outpatient settings, as confirmed by positive antigen tests within 30 days preceding the treatment initiation, and observed a range of symptom severities. We assessed the conversion time for a SARS-CoV-2 rapid antigen test to change from a positive to a negative result, the number of days until symptom disappearance, and the occurrence of recurrent infections (rebound cases). 13 patients exhibited symptoms aligned with the mild-to-moderate categorization, while 1 case presented with severe clinical manifestations, according to the WHO criteria [24]. Among all participants, there was no COVID-19-related hospitalization or death from any cause through day 28. None of the participants with active SARS-CoV-2 infection experienced a recurrence of infection (rebound cases) within 28 days post-treatment. There was no adverse events emerging during or after the treatment period (up to day 28).

Clinical Result For Active SARS-CoV-2 Infection (Mild and Moderate)

For mild and moderate patients, their rapid antigen tests typically converted from positive to negative at an average of 7 (SD 1.41) days after enrollment. Patients in this group took an average of 1.79 ACT-ML sessions, for a total of 25 sessions for this group. Regarding the alleviation of symptoms, fever generally subsided within an average of 2 (SD 1.41) days, while coughs took an average of 7.44 days (SD 3 days) to subside. Loss of smell or taste was reported by 23.08% of patients, and on average, this symptom improved within 6.50 (SD 1.73) days.

Table 2 : Outcomes in patients with active SARS-CoV-2 infection.

Characteristics	Active Infection - mild and moderate condition (13)	Active Infection - severe condition (1)
Antigen test conversion time after enrollment, mean (SD), day[a]	7.00 (1.41)	N/A
Symptoms, n (%)		
Fever	4 (30.77%)	1(100%)
Fatigue	4 (30.77%)	1(100%)
Cough	9 (69.23%)	1(100%)
Expectoration	5 (38.46%)	1(100%)
Sore throat	4 (30.77%)	0.00
Headache	5 (38.46%)	0.00
Muscle ache	3 (23.08%)	1(100%)
Running nose	4 (30.77%)	0.00
Loss of smell/taste	3 (23.08%)	0.00
Swollen hands and feet	0	1(100%)
Symptom alleviation - Time from ACT-ML to symptom disappearance, mean (SD), day		
Fever	2 (1.41)	4
Fatigue	6 (2.94)	56
Cough	7.44 (3)	56
Expectoration	7.8 (6.38)	56
Sore throat	3 (2.16)	0
Headache	7.6 (2.07)	0
Muscle ache	6.67 (2.08)	0
Running nose	7 (1.83)	0
Loss of smell/taste	6.5 (1.73)	0
Swollen hands and feet	0	41.00
Death after enrollment, n (%)	0	0
Conversion to severe case after enrollment, n (%)	0	0
Rebound of infection (28 days after completion of treatment）	0	0
Reappearance of symptoms (28 days after finish of treatment）	0	0
Adverse events emerging during or after the treatment period (up to day 28)	0	0
ACT-ML		
Total ACT-ML sessions	25	6
Average ACT-ML session/person	1.79	6

a. The patient with severe condition who presented a negative rapid test result prior to their inclusion in the study were excluded from the analysis of antigen test conversion time.

Table 3: Outcomes in patients with Long COVID (Post-Acute Sequelae of SARS-CoV-2 infection).

Characteristics	Long COVID (10)
Time from initial infection to start of treatment, mean (SD), day	221
Symptom, n (%)	
Cough	10 (100%)
Fatigue	2 (20%)
Expectoration	2 (20%)
Swollen tonsils	1 (10%)
Symptom alleviation - Time from ACT-ML to symptom disappearance, mean (SD), day	
Cough	11.2 (4.66)
Fatigue	10.5 (0.71)
Expectoration	7.5 (2.12)
Swollen tonsils	5
Death after enrollment, n(%)	0
Conversion to severe case after enrollment, n (%)	0
Adverse events emerging during or after the treatment period (up to day 28)	0
ACT-ML	
Total ACT-ML sessions	14
Average ACT-ML session/person	1.4

Table 4 : Outcomes in patients infected with influenza.

Characteristics	Influenza (2)
SARS-CoV-2 Antigen Test	Negative
Symptom, n (%)	
Fever	1
Cough	1
Fatigue	1
Expectoration	2
Sore throat	2
Muscle ache	1
Swollen tonsils	1
Symptom alleviation - Time from ACT-ML to symptom disappearance, mean (SD), day	
Fever	4.00
Cough	7.00
Fatigue	3.00
Expectoration	5 (2.83)
Sore throat	6.5 (0.71)
Muscle ache	3.00
Swollen tonsils	9.00
Death after enrollment, n (%)	0
Hospitalization after enrollment, n (%)	0
Conversion to severe case after enrollment, n (%)	0
Adverse events emerging during or after the treatment period (up to day 28)	0
ACT-ML	
Total ACT-ML sessions	4
Average ACT-ML session	2

Clinical Result For Active SARS-CoV-2 Infection (Severe)

Extended Data Table 1 displays the clinical events and characteristics of the patients. A 92-year-old patient with multiple comorbidities, including hypertension, high uric acid levels, high blood sugar, and diabetes, developed severe COVID-19 symptoms. Prior to enrolling in the study, the patient had been hospitalized for 15 days and spent 10 days in the intensive care unit (ICU). After being discharged from the hospital upon the request of the patient and their family, the patient joined our study to receive stay-at-home treatment. During this phase, the patient underwent six ACT-ML sessions over 56 days. Initial symptoms upon enrollment included the fever, cough, pleural effusion in the lung, swelling in hands and feet, shortness of breath, low blood-oxygen levels (80%) and the presence of white mucus.

Over the following weeks, their temperature regulation, oxygen saturation levels, mobility and symptoms, such as coughing, improved. The patient suffered from high fever (fluctuating between 37.5°C and 38.7°C) for 6 days before the treatment. The patient's fever subsided after four days of treatment, but their cough persisted for 56 days. Their SpO2 (peripheral capillary oxygen saturation), measured by a portable pulse oximeter, improved significantly, increasing from 80% to 91%. Notably, their dependency on supplemental oxygen decreased over time. By the end of the study, the patient had recovered significantly, no longer required oxygen support at night and could walk independently with a walking stick. A comprehensive analysis of this severe case can be found in the "Severe COVID-19 Case Analysis -1" section in the extended data.

Clinical Result For Active SARS-CoV-2 Infection (Severe): Inpatient

Extended Data Table 2 displays the clinical events and characteristics of the patients. An 81-year-old patient with multiple comorbidities, such as diabetes, nephrolithiasis, and cholelithiasis, was diagnosed with COVID-19. Prior to enrolling to the study, the patients stayed in hospital for 7 days. Given the severity of the patient's symptoms and the presence of 11 complications, including systemic sepsis, advanced pneumonia, SARS-CoV-2 infection, electrolyte imbalances, hypoproteinemia, clinical anemia, left-sided minimal pleural effusion, pericardial effusion, pulmonary bullae, radiological 'white lung' on CT imaging, and fever, the patient was admitted to the ICU (Intensive Care Unit). The patient was hospitalized throughout the study. The patient joined the study on the same day they were admitted to the ICU. The patient participated in 3 ACT-ML sessions. The initial symptoms upon admission to the study were fever, difficulty breathing, sore throat, headaches, body aches, dry nasal passages, abdominal pain, and full-body myalgia. Although the patient was initially outside the intended scope of our outpatient study, we considered that it would be unethical to deny the treatment. Despite undergoing a range of conventional treatments, the patient experienced a persistent fever and other symptoms. The patient experienced persistent fever with fluctuating intensity, spiking to 39.5 degrees Celsius after 4 p.m. daily for seven days. After undergoing ACT-ML sessions in our study, the patient showed significant improvements. The fever subsided within five days of treatment. The abdominal pain resolved after 4 days of treatment. After 10 days of treatment, the patient's condition had improved significantly, allowing for a transfer from the ICU to a general medical ward. The detailed analysis of this patient's case can be found in the “Severe COVID-19 Case Analysis-2” section in the extended data. There was no adverse events emerging during or after the treatment period (up to day 28).

Clinical Result For Long COVID (Post-Acute Sequelae of SARS-CoV-2 Infection)

Table 3 displays clinical outcomes for patients diagnosed with long COVID. In our evaluation of these 10 patients, each participated in an average of 1.4 ACT-ML sessions, totaling 14 sessions across the group. All patients consistently reported persistent cough and fatigue, and one patient exhibited swollen tonsils. The average time since their initial SARS-Cov-2 infection is 221 days. There was no COVID-19-related hospitalization or death from any cause through day 28. There was no adverse events emerging during or after the treatment period (up to day 28). There was no adverse events emerging during or after the treatment period (up to day 28).

In terms of symptom relief, patients with a cough began to experience improvement on average at 11.2 days (SD 4.7) after starting treatment. All patients in this group had been experiencing a persistent cough since their initial infection. Fatigue showed improvement at an average of approximately 10.5 days (SD 0.71), and for those experiencing expectoration, relief was observed around 7.5 days (SD 2.12) after treatment initiation.

Clinical Result For Influenza

Table 4 displays clinical outcomes for patients diagnosed with influenza. In our study, two patients diagnosed with influenza were enrolled, both presented with negative SARS-CoV-2 rapid antigen test. Participants took an average of 2 ACT-ML sessions and a total 4. There was no influenza-related hospitalization or death from any cause through day 28. There was no adverse events emerging during or after the treatment period (up to day 28).

Before starting the treatment, one patient had a fever of a temperature of 39.00 degrees Celsius. The fever subsided within 4.00 days of treatment. All patients presented with sore throat symptoms, which alleviated after an average of 6.50 (SD 0.71) days. One patient presented with swollen tonsils, and this symptom showed relief on the ninth day.

Discussion

In outpatient settings, the study attests the effectiveness and safety of a machine learning-driven system we developed, called ACT-ML, in autonomously managing diverse clinical presentations of COVID-19, spanning from mild to severe cases, while also competently treating patients with long COVID (post-acute sequelae of SARS-CoV-2) and those diagnosed with influenza. We conducted a simulation test in the development phase and implemented a feasibility clinical trail to assess the machine learning system. Collectively, our findings indicate that the ACT-ML system offers a promising solution to autonomously offer treatment solutions for outpatients with mild and moderate COVID-19, long COVID, and influenza without intervention from human physicians and offers support for those with severe COVID-19 conditions.

Despite significant progress in medical research, COVID-19 remains a persistent challenge to public health globally [25]. Further complicating matters is the brief intervals between reinfections [4], which consistently stress healthcare systems. In this stage of the endemic, it's vital to treat a large number of mild cases promptly to prevent overburdening our healthcare system and to prevent these cases from worsening. Offering personalized and adaptive care to patients for these mild cases is key. To address this, we developed an AI-driven system to mimic senior TCM physician’s decision process regarding case management and triage. We

transformed the traditional clinical triage process into a classification problem in machine learning, with patients' symptoms and age as input and the outcome variable being one of five prescriptions, pre-established by senior medical professionals. This AI framework leverages a substantial dataset of 340 million synthetic patient data, focusing on 44 unique symptoms and categorizing the population into three age brackets. The machine learning system provides a balanced approach to deliver standardized care and offer antiviral treatment tailored to a patient's age, health risk factors, and symptoms, while ensuring cost efficiency at scale.

Another strength of our study is that we conducted a comprehensive early-stage clinical feasibility validation of the AI-based clinical decision-making system across various clinical scenarios. This study presents four key findings. First, the machine learning system proved effective in autonomously treating mild and moderate COVID-19 cases. Patients with mild to moderate COVID-19 experienced a relief in symptoms such as fever, which subsided within an average of two days (SD 1.41). Furthermore, the system facilitated the transition of patients from positive to negative on rapid antigen tests within an average of seven days (SD 1.41). Secondly, beyond managing mild and moderate cases, the ACT-ML system has shown its efficacy in managing severe COVID-19 cases. This was evident from two distinct case studies—an outpatient and an ICU case—which pointed to ACT-ML's significant potential in enhancing outcomes, especially in improving oxygen saturation levels and rapid abatement of fever. However, more extensive research is necessary for broader validation. In addition, the system showed promise in addressing long COVID. The underlying mechanisms of long COVID remain unclear to the medical community. Nonetheless, we hypothesized that the prolonged presence of the SARS-CoV-2 virus may contribute to this condition [26]. This theoretical stance aligns with

the foundational scenarios presented in our “Rubric Cube Challenge”, which underpins the architecture of our AI system. In our study, notably, improvements in persistent cough, common among long COVID patients, were observed within an average of 11.2 (SD 4.66) days after treatment began. Lastly, the versatility of the ACT-ML platform extends to the management of influenza. Given the inherent challenges in distinguishing between symptoms of COVID-19 and influenza in real world clinical settings, the system effectively addressed both conditions. The ACT-ML system effectively treated typical influenza symptoms, including fever and sore throat, which were alleviated in an average of 4 days and 6.5 days, respectively. This suggests that ACT-ML could serve as a comprehensive solution for managing a range of viral infections, optimizing treatment strategies for COVID-19, long COVID and influenza.

The web-based application "ACT-ML" offers more than just clinical effectiveness. Its inherent advantages include continuous availability (24/7), scalability, and a user-friendly, contactless interface for seamless interactions. This 24/7 functionality becomes particularly invaluable in pandemic scenarios or in winter seasons, where the volume and unpredictability of cases can strain traditional healthcare infrastructures. Its scalable digital architecture allows it to handle numerous cases simultaneously, providing standardized care during large-scale outbreaks. By offering timely interventions, "ACT-ML" reduces waiting times for patients, which can negatively impact their health outcomes. Furthermore, it broadens healthcare access by providing consistent, high-quality care regardless of geographical or infrastructural challenges. Given its features, the platform can complement the current healthcare system and potentially address clinician shortage during peak medical demands. In addition, the user-friendlily interface, designed for a contactless procedure and seamlessly integrated with pharmacy logistics and

third-party delivery systems, ensures that patients obtain their medication within a 24-hour timeframe. This optimization not only mitigates potential infection exposure for both medical professionals and patients but also expedites the initiation of treatment post-exposure.

To improve clinical feasibility, our approach focuses on mitigating the inherent uncertainties of machine learning models in real-world clinical settings. Since the onset of the pandemic in 2020, a variety of AI solutions have been developed to tackle its multifaceted challenges. However, studies indicate these tools have yet to yield proven clinical benefits [17,18]. This can be attributed to the uncertainties inherent in machine learning model deployments and the prevailing medical ambiguities associated with COVID-19 management. To mitigate uncertainties inherent to machine learning, we employed a substantial volume of 340 million synthetic patient data aligned with medical knowledge, integrated a control system and explainable algorithms like decision trees for system robustness. To safeguard patient data privacy and expedite processing time, we modified the model to a more compact size, enabling on-device data processing. In response to medical uncertainties, we employed the "Rubric Challenges" framework and integrated principles from Traditional Chinese Medicine (TCM) to balance heterogeneous and homogeneous treatment approaches. We focused on 44 symptoms, identified from a knowledge graph based on real-world clinical data of influenza, and categorized patients into three age groups. Altogether, through the implementation of these strategies, we have designed an AI system that is feasible for integration into real-world clinical environments and offers user-friendly interaction for patients.

Although our ACT-ML system has achieved good performance, some challenges remain. First, our study lacked a control group. Ideally, a comparison of our system's outcomes with standardized antiviral treatments prescribed by human physicians in outpatient settings would offer more comprehensive insights. Second, the scope of our study was limited by the number of participants. A broader participant base would not only enhance the statistical power and generalizability of our findings but also provide a more diverse representation, ensuring that the system's effectiveness is tested across a wider range of individual variations. Extended studies with larger patient groups are necessary to provide a more granular understanding and to refine treatment methodologies especially for individuals grappling with long COVID.

In conclusion, we developed a machine-learning based clinical decision-making system rooted in traditional Chinese medicine principles for autonomously managing diverse COVID-19 conditions, as well as long COVID (post-acute Sequelae of SARS-CoV-2 infection) and influenza cases. The system, which integrates a substantial volume of synthetic data aligned with clinical knowledge and a clinical rule-based control layer, matches the performance of senior TCM physicians. Furthermore, to validate this approach, we conducted a two-step validation process: a simulation study and a proof-of-concept feasibility trial in real-world clinical settings. These validations demonstrate the system's potential as a tool to administer personalized antiviral treatment plans tailored to patients' age, symptoms, and pre-existing health risk factors at scale, offering a solution to alleviate clinician shortages. Extensive studies are needed to ensure findings are widely applicable and representative across diverse contexts.

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Methods

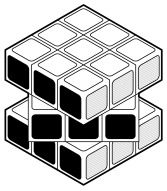
Medical uncertainty framework

The treatment of COVID-19 presents a significant challenge due to several factors. These include the heterogeneity of symptoms among individuals [27,28,29], the clinical similarities between COVID-19 and influenza [30] and the rapid progression from mild to severe disease in specific population subgroups [31]. To address these uncertainties, in our TCM cocktail formula, we implement “The Rubric Challenge”, a mathematical formula, to determine an optimal combination of herbs from Traditional Chinese Medicine (TCM). This formula is specifically designed with dual objectives in mind: the reduction of viral load and the alleviation of symptoms.

Drawing inspiration from Rubik's cubes as shown in **Figure 2(a**), we can understand that despite the numerous possible permutations, there are only three major sides to the puzzle. By focusing on these three essential layers, we can similarly address the uncertainty in the treatment. The Rubik's Cube's complexity comes from its three-dimensional structure with three independent

rotating layers on each axis (X, Y, and Z). This allows for a staggering 43,252,003,274,489,856,000 possible permutations, arising from the different arrangements of its 26 movable pieces [32]. The cube's intricate mechanism and the interaction of these layers account for its immense variety of configurations, making it a highly complex puzzle despite having "three sides" in terms of layers per axis. Just as solving the three layers of the Rubik's cube allows us to solve the entire puzzle, addressing the key components in treatment helps us manage the overall uncertainty. As illustrated in **Figure 2(b)**, an effective treatment for COVID-19, long Covid and influenza can be represented by the formula "X = F[V + S + Min(T)]". In this formula:

a.



b.

$$X = f[\, V + S + \mathrm{Min}(T)]$$

Figure 2 : a. The Rubik's Cube's complexity stems from its three-dimensional design, featuring three rotating layers on each axis (X, Y, Z), leading to 43,252,003,274,489,856,000 potential permutations [30]. This vast number is due to the various arrangements of its 26 movable pieces. Despite seemingly having only "three sides" per axis, its intricate design and layer interactions create a deeply complex puzzle. b. The Rubik's Cube Challenge metaphorically illustrates the complex strategy required to treat COVID-19, long COVID, and influenza. Solving the puzzle's three layers, despite its myriad combinations, mirrors the intricate approach required to manage these multifaceted viral infections.

- "X" stands for an effective treatment of COVID-19, long COVID and influenza.
- "f" represents the individual's immune strength, indicating how their immune system responds to the disease.

- “V” refers to the incorporation of antiviral medical herbs in treatment protocols aimed at reducing the viral load.
- “S” signifies the use of specific herbs to treat the patient's particular symptoms.
- “T” is the minimum time elapsed between infection and initiation of treatment, emphasizing that the success of the treatment is crucially dependent on minimizing this time.

In conclusion, an effective treatment plan for COVID-19, long COVID, and influenza combines the individual's immune response, the application of antiviral herbs, symptom-specific herbal treatments, and the initiation of treatment as soon as possible after infection.

Datasets. Synthetic data aligned with clinical knowledge.

The quality and size of the dataset are fundamental to the performance of machine learning models. To mitigate the issue of overfitting and to diversify our dataset, we leveraged synthetic data as a solution. This approach draws inspiration from the successful implementation of synthetic data in the control systems of autonomous vehicles [33,34], demonstrating the potential of synthetic data in novel applications. However, it is important to note that the use of synthetic data in the medical field is still in its early stages [35]. For ACT-ML, we used an extensive dataset comprising 340 million patient records for the training phase. To evaluate the robustness and validity of our model, a separate dataset of 36 million patient records was employed for the testing phase.

In our study, we introduce a structured methodology, grounded in the mathematical method of combinations, specifically designed to generate synthetic data suitable for clinical use. This synthetic dataset is constructed using a three-stage structure.

A combination, in mathematics, is the selection of items without consideration for the order in which they are chosen, often denoted as nCr or 'n choose r'. The formula for calculating a combination is as follows:

C(n, r) = n! / r!(n-r)!

where '!' represents the factorial operator, signifying the product of an integer and all the integers below it (e.g., 4! = 4*3*2*1 = 24). In our case, we target 44 symptoms, Given a set of 44 elements (or symptoms, in this context), the total number of possible combinations is 2^44. This value is approximately 17.592 trillion (17,592,186,044,416 to be exact). The task of generating or processing all of these combinations presents a significant computational challenge due to the immense volume of data involved. Therefore, in practical applications, specific strategies are commonly implemented to either sample a subset of these combinations or reduce the overall space of combinations, making the data more manageable to work with. We implemented a three-stage process to generate the synthetic data, which consists of the following steps:

1. Commonly observed symptoms

For computational feasibility, our methodology heavily weights symptom combinations most frequently observed in prior studies [27,36,37]. This tactic ensures that our synthetic dataset closely mirrors the empirical symptom distributions found in actual patient cases. This close

alignment enhances the model's predictive power and its applicability to real-world clinical scenarios.

2. Data with clinical significance

Our synthetic dataset incorporates clinically significant symptoms to ensure that vital indicators are not overlooked. From prior research, certain symptoms and comorbidities carry substantial clinical significance, influencing the severity and progression of the disease [38]. These include a high fever, persistent cough, and comorbidities such as asthma, hypertension, cardiovascular disease, and diabetes [39, 40]. The inclusion of these pertinent factors within our synthetic dataset enables a more comprehensive and clinically relevant disease modeling approach.

3. Post training dataset adjustment

After training our model, we make necessary adjustments to the dataset to improve its effectiveness. This fine-tuning process is especially crucial in dealing with issues like data imbalance, overfitting, and underfitting, which are common challenges in machine learning models. We use a technique known as resampling to handle data imbalance [41]. Resampling is a simple but effective approach where we either increase the instances of underrepresented data (oversampling) or reduce the instances of overrepresented data (undersampling). This step helps in achieving better prediction accuracy in our model.

The concept of combinations plays a vital role in understanding the wide range of symptom presentations in diseases like COVID-19. It allows us to generate a more expansive set of potential patient symptom scenarios, which is particularly useful when training machine learning

models or attempting to capture the extensive variability in symptom presentations in infectious diseases.

System Overview

Figure 3 (a) shows the user interface of the application. There are two main components in our proposed machine learning-based web application: binary inputs from patients to identify age, symptoms, and pre-existing comorbidities, and a prediction process to recommend predefined prescriptions. Depending on the complexity of a patient's symptoms, the process of entering these symptoms can take between 2 to 7 minutes. After entering their

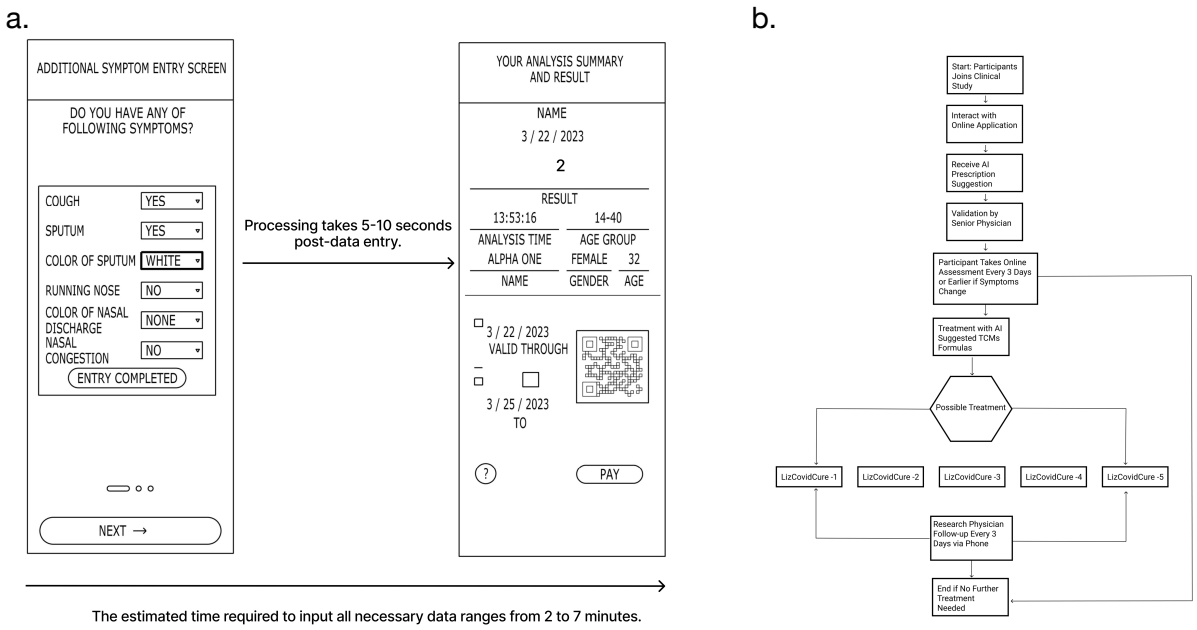


Figure 3: a. User interface of the ACT-ML web application. Our web application features a binary symptom input system and a predictive prescribing algorithm. Symptom entry takes 2 to 7 minutes, with results delivered in 5 to 10 seconds. b. The workflow of the ACT-ML from the patient's perspective.

symptoms, patients receive their results within 5 to 10 seconds. **Figure 3 (b)** shows the

workflow of the process from patient's perspective. Participants took the ACT-ML assessment every three days, or earlier if new symptoms developed. The ACT-ML system adopts a dynamic treatment strategy to adjust patients' prescriptions dynamically as they progress through different stages of the disease.

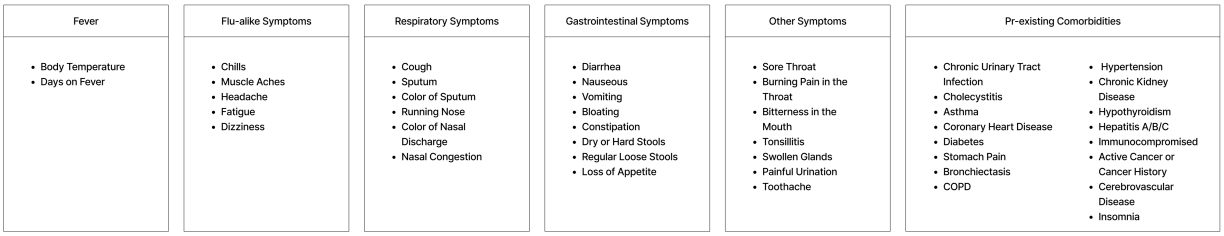


Figure 5: For each age group, the ACT-ML system targeted 44 specific symptoms, which were categorized into six groups: body temperature, flu-like symptoms, respiratory symptoms, gastrointestinal symptoms, other symptoms, and pre-existing comorbidities.

Targeted Symptom

Figure 5 shows 44 symptoms we identified as focus of our study. In the context of Traditional Chinese Medicine (TCM), the critical difference between influenza and COVID-19 is that the latter aggressively targets patients' immune systems. This direct assault heightens the probability of multi-organ dysfunction, a phenomenon observed in severe COVID-19 cases [17]. We categorized these symptoms into seven groups using a knowledge graph that we constructed. This knowledge graph is derived from a comprehensive analysis of 150 typical cases selected from 3600 influenza patients. These cases, treated in an outpatient setting between the years 2011 and 2014, were carefully selected due to their distinctive symptoms, making them representative of a wider population of influenza patients.

Training algorithm

Recognizing potential uncertainties and vulnerabilities inherent in deep learning models, we strategically selected our machine learning methodologies to alleviate these concerns, guided by the insights from Goodfellow [42] and Breiman [43]. Specifically, we opted to employ the Decision Tree and Random Forest algorithms, allowing us to ensure the robustness of our data analysis while simultaneously mitigating potential security vulnerabilities.

A Decision Tree is a flowchart-like structure, where each internal node denotes a test on an attribute, each branch represents an outcome of the test, and leaf nodes correspond to class labels or decision results [44]. It is one of the simplest and yet most effective forms of machine learning, often used for classification and regression tasks. Decision Trees are interpretable and easily understood, even by those without a background in machine learning.

On the other hand, a Random Forest is an ensemble machine learning method that involves constructing multiple decision trees during training and outputting the class that is the mode of the classes (classification) or mean prediction (regression) of the individual trees [43]. By utilizing both these algorithms, we aimed to not only capitalize on their individual strengths but also to garner a more comprehensive and nuanced understanding of the dataset.

Edge Learning Consideration

To safeguard patient data privacy and facilitate the local processing of models on edge devices across various operating systems, including Android and IOS system, we opted for a web-based application approach rather than utilizing native software [45]. However, implementing edge

learning on mobile devices poses distinct challenges due to hardware limitations, battery constraints, and memory restrictions [46]. Consequently, there is a need to design a lightweight model that balances a small footprint with high performance to ensure optimal user experience on mobile devices.

Given edge learning's computational constraints, our study favors decision tree algorithms over random forest models. Although random forests often provide higher predictive accuracy, they demand more computational resources and yield larger models. Our decision tree approach, with its compact model size, effectively balances computational efficiency and mobile user experience.

In contrast, our decision tree model, which is a mere 6 kilobytes (KB), is only 0.000095% the size of the random forest model at 6 gigabytes (GB). Despite this significant difference in size, the decision tree achieves an accuracy rate of 87%, compared to the random forest's 92% — a marginal 5% discrepancy in performance. Therefore, the decision tree is the more efficient choice for our needs. These smaller models enhance web application performance by loading and processing faster than larger ones, improving user experience and response times. Additionally, the reduced resource requirements lower operational costs and boost sustainability. Therefore, when viable, opting for smaller models significantly optimizes web application performance and sustainability.

Control System

Even a minimal error rate in the predictions of machine learning models can have critical, potentially fatal consequences in real-world clinical applications. Drawing upon the principles of integration between rule-based control systems and machine learning systems, as observed in autonomous driving vehicles [22], we introduced an additional layer of control to the existing machine learning models. This enhancement was strategically implemented to improve the feasibility and precision of applications within real-world clinical contexts.

Evaluation of machine learning model

	precision	recall	f1-score	support
class 38	0.80	1.00	0.89	664159
class 40	1.00	1.00	1.00	1276182
class 42	1.00	0.75	0.86	671416
class 44	0.70	0.61	0.65	670204
class 46	0.88	1.00	0.94	2151861
class 48	1.00	0.79	0.88	873496
class 50	0.59	1.00	0.74	1267887
class 52	1.00	0.79	0.88	3090174
class 54	1.00	0.84	0.91	1496110
accuracy			0.87	12161489
macro avg	0.89	0.86	0.86	12161489
weighted avg	0.91	0.87	0.88	12161489

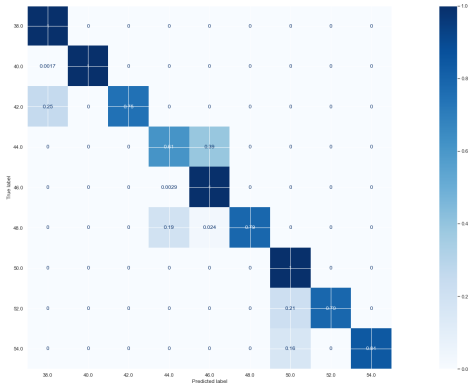


Figure 5: a. A classification report was generated employing precision, recall, and the F1-score and average accuracy rate as the evaluation criteria for the assessment of the model's performance. The report demonstrated the results among age group 41-60. In the development stage, the average precision, recall, f1-score and accuracy is 88.6%, 86.4%, 86.1% and 87.0% respectively. A confusion matrix was generated to visualize the results. b. A confusion matrix was generated for the age group 41-60 using a decision tree model.

In evaluating the performance of our decision tree models, we employed a set of metrics including the precision, F1 score, recall, and average accuracy rate. **Figure 5 (a)** shows the classification report. Precision refers to the ratio of correctly predicted positive observations to the total predicted positives, reflecting how many of the predicted positive instances are relevant [47]. The F1 score is a harmonic mean of precision and recall, providing a balance between

these two metrics [48]. Recall, also known as sensitivity or true positive rate, is the ratio of correctly predicted positive observations to all actual positive class observations, representing the ability of the model to identify all relevant instances [47]. The average accuracy rate measures the proportion of both true positives and true negatives in the entire dataset, providing a general indication of the model's performance across all classes [48,49]. The formula of precision, recall, F1 score and accuracy is as follows:

Precision = True Positives / (True Positives + False Positives)

Recall = True Positives / (True Positives + False Negatives)

F1 score = 2* (precision * recall)/(precision +recall)

Accuracy= True Positives + True Negatives / True Positives + True Negatives + False Positives + False Negatives

- **True Positives (TP)**: Cases where both the model's prediction and the actual truth are positive.
- **True Negatives (TN)**: Cases where both the model's prediction and the actual truth are negative.
- **False Positives (FP)**: Cases where the model predicts positive, but the actual truth is negative. This is commonly referred to as a "Type I error."
- **False Negatives (FN)**: Cases where the model predicts negative, but the actual truth is positive, known as a "Type II error."

The following is an explanation of the concepts of true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN) in the context of comparing machine learning model predictions with Traditional Chinese Medicine (TCM) practitioners' recommendations for prescriptions.

True Positives (TP):

In this context, a true positive (TP) occurs when both the machine learning model's prediction and the TCM practitioner's recommendation agree on the specific prescription for a patient. This represents a successful case where the model is able to accurately identify the appropriate prescription based on the patient's symptoms and condition.

True Negatives (TN):

A TN occurs when both the model's prediction and the TCM practitioner's recommendation agree that a particular prescription is not suitable for a patient. This represents another successful case where the model is able to correctly rule out the need for the specific prescription.

False Positives (FP):

An FP occurs when the machine learning model suggests a particular prescription for a patient, but the TCM practitioner's recommendation disagrees, indicating that the prescription is not suitable for the patient's condition. This represents an error where the model incorrectly identifies the need for the specific prescription, potentially leading to inappropriate treatment or medication.

False Negatives (FN):

An FN occurs when the machine learning model recommends against a particular prescription for a patient, but the TCM practitioner's recommendation disagrees, indicating that the prescription would be beneficial for the patient's condition. This represents an error where the model fails to identify the need for the specific prescription, potentially delaying or preventing appropriate treatment.

In the context of comparing machine learning model predictions with TCM practitioners' prescription recommendations, these four metrics provide valuable insights into the model's ability to effectively suggest appropriate treatments for patients. By evaluating the TP, TN, FP, and FN rates, it is possible to assess the model's accuracy, sensitivity, and specificity, which are crucial for determining its suitability for real-world applications in TCM practice.

Figure 5(b) presents a confusion matrix for the 41-60 age group, demonstrating the decision tree model's performance. This matrix not only identifies misclassifications but also emphasizes the recall score, a key metric for evaluating the model's success in correctly identifying positive cases. Particularly vital in areas like medical applications, where missing a positive case can be critical, the recall score is essential for balancing precision, especially useful in imbalanced datasets, and crucial for reducing false negatives. This metric significantly aids in refining model performance.

Proof-of-concept Clinical Feasibility Trial Settings

The study is a single-center, open-label, intervention study conducted from June 16th to August 16th 2023, in outpatient settings at a TCM clinic in Sheng'ai TCM Hospital, Kunming, Yunnan, China, during the outbreak of COVID-19 from May 2023 to August 2023. Sheng'ai TCM Hospital Network operates 37 clinics spread across five provinces in China. They employ over 1,000 traditional Chinese medicine physicians and serve a patient base of 1.6 million members. This period marked the second wave of infection since China downgraded COVID-19 from class A to class B [50]. This wave was mainly caused by SARS-CoV-2 (Omicron XBB) [51].

In contrast to studies such as the EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) conducted on Pfizer's Paxlovid (nirmatrelvir and ritonavir), our study did not require a treatment initiation window of within 5 days post-confirmation of a positive SARS-CoV-2 test result [52].

Clinical Study Inclusion and Exclusion Criteria

Extended Data Figure 1 shows the flow diagram of the proof-of-concept feasibility trial. The participants represent a diverse range of patients. The inclusion criteria were defined as follows: 1) either male or female (14 years or older), and their COVID-19 vaccination status was not a factor for inclusion; 2) individuals with any high-risk conditions that could lead to severe manifestations of the disease were also included; 3) evidence of COVID-19 testing was not required to initiate treatment to reflect real-world complexities [53]; 4) the cohort was extended to include patients diagnosed with influenza [54]; 5) participation was made entirely voluntary, providing an opt-out option and digital consent through a web-application. Participants in the study did not receive any financial compensation; 6) individuals with post-acute sequelae of SARS-CoV-2 infection, commonly referred to as 'long COVID' [55]; 7) Non hospitalized adults in outpatient settings. This wide-ranging patient base enables a more accurate representation of the heterogeneity encountered in regular clinical practice.

Note: Only one hospitalized case was included, involving a patient who was hospitalized and admitted to the ICU (intensive care unit) before the enrollment in the study. We considered it unethical to deny our treatment to this patient. A detailed analysis of this particular case is available in the extended data.

Certain demographics were exempted from the study in an effort to uphold ethical standards and circumvent potential adverse effects. This included pregnant individuals [56] and those with

known histories of allergic reactions to medical herbs commonly used in Traditional Chinese Medicine (TCM) [57].

Clinical Study Outcome and follow-up

In this study, we've set four objetives. 1) Our primary objective is to evaluate the reliability of our machine learning system by comparing its classifications to those made by human physicians. 2) The secondary goal is to assess COVID-19-related hospitalization or death from any cause through day 28. 3) Thirdly, we evaluate if the machine learning system's recommended prescription alleviates COVID-19, long COVID and Influenza symptoms. 4) Finally, for participants who tested positive within 30 days on the SARS-CoV-2 rapid antigen test, we conduct a 28-day monitoring period following the start of treatment to identify any "rebound" cases, a concern that emerged from prior experiences with Plaxvoid (Nirmatrelvir/Ritonavir) treatment [56]. This is to ensure detection of any potential recurrence of SARS-Cov-2 infection. This multifaceted analysis of outcomes allowed us to gain a comprehensive understanding of the disease progression patterns within our study cohort.

The initiation of patient follow-ups commenced on the date the ACT-ML was undertaken. Subsequent follow-ups were scheduled every 3 days from the start date until the end of treatment, death, follow-up of 28 days or the end of follow-up on September 16th 2023, whichever came first.

Safety

Safety endpoints included adverse events emerging during or after the treatment period (up to day 28), serious adverse events, and adverse events leading to discontinuation of the trial formula, all of which were recorded. Investigators actively collected safety information through day 28.

Conclusion

This study found that the use of an autonomous treatment system with machine learning, named "ACT-ML", was effective in treating patients infected with Omicron XBB, long COVID, and influenza, irrespective of age, vaccination status, or pre-existing comorbidities. This machine learning system can assist non-hospitalized patients and also provide clinical support to those who are hospitalized.

Dataset Availability

The datasets generated and analyzed in this study are not publicly available, primarily due to concerns surrounding privacy and confidentiality. The nature of the data, which includes sensitive information potentially identifying participants, necessitates strict control over its access and distribution to protect participant privacy. Accordingly, in line with ethical research practices, these datasets are securely stored and their access is tightly restricted.

Code Availability

The computational methods and analyses presented in this study are primarily based on custom-written code, complemented by open-source libraries. The codebase is written in Python 3.7,

utilizing libraries such as NumPy for numerical operations, Pandas for data manipulation, scikit-learn for machine learning models, and Matplotlib for data visualization. The code developed for this research is not publicly available due to proprietary concerns. It encompasses unique algorithms and methodologies that are critical for our ongoing and future projects. The paper provides detailed descriptions of the methodologies to offer insights into our approach. We encourage direct contact with our research group for collaborations or inquiries regarding the code, subject to agreements that respect its proprietary nature. We appreciate the scientific community's understanding of the necessity to maintain confidentiality in this aspect of our work.

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Author Contributions

Jia Le Xian contributed to the study design, data collection, data cleaning, data processing, statistical analysis, machine learning, interpretation of results, and drafted and revised the paper. Si Kai Xian contributed to patient monitoring and evaluation, validation of machine learning results, ensuring their comparability with human doctor decision-making, and interpretation of the results. Ruan Sheng Xiang contributed to coordination with the pharmacy and management of the study site.

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Declaration of Competing Interest

Jia le Xian is the founder of Lizora Technologies, a company that may potentially benefit from the findings of this research. Lizora Technologies also provided funding for the study. Ruan Sheng Xiang holds the position of vice president at the Shang'Ai Traditional Chinese Medicine Hospital. The hospital has no direct financial involvement in this study, but the position may be perceived as a potential conflict of interest given the subject matter of the research.

The authors affirm that these roles have not influenced the study design, data collection, analysis, interpretation, or the decision to submit the results for publication. All procedures and methodologies were conducted objectively and adhere to the academic and ethical standards.

Appendix A. Extended Data

Detailed analysis of two severe COVID-19 cases and flow diagram of the proof-of-concept feasibility trial can be found in the extended data.

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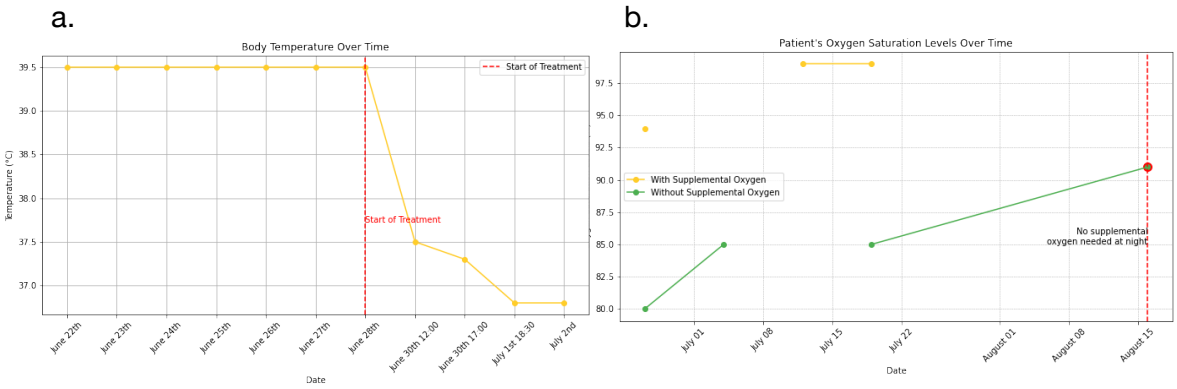
Appendix 1. Extended Data

Severe COVID-19 Case Analysis -1

Extended Data Table 1 shows the patient's characteristics and clinical information. The patient under evaluation is aged 92 years. The patient presented multiple comorbidities, including hypertension, high uric acid levels, high blood sugar, and diabetes. In the study, the patient



Extended Data Figure 1: Clinical outcome of severe case 1. **a.** Graphical representation of the body temperature variations. The patient was initially admitted to the Intensive Care Unit (ICU) and subsequently released from the ICU as per the informed consent of the patient and the patient's family. From June 16th to June 21st, the patient experienced a fluctuating fever with temperatures ranging between 37.5°C and 38.7°C over 6 days. After 4 days' treatment, the patient's fever abated. **b.** Visualization of improvement of oxygen saturation levels of an outpatient severe COVID-19 case. The patient's oxygen saturation levels improved from below 80% to 91%.

underwent a total of 6 ACT-ML sessions. From June 21st (start of treatment) to August 16th, the only medication the patient took was the prescriptions from ACT-ML.

On May 31st, the patient exhibited initial symptoms and was subsequently admitted to the hospital on June 1st after testing positive for SARS-CoV-2 via PCR (Polymerase Chain Reaction). During the hospitalization, the patient was admitted to the ICU (Intensive Care Unit) from June 5th to June 15th. The patient had a negative PCR test on June 10th. On June 15th, the patient was discharged home upon the request of both the patient and their family.

On June 21st, the patient was enrolled in the study, during which they undertook the first ACT-ML session and began the prescribed treatment regimen. Initial symptoms upon enrollment included the fever, cough, pleural effusion in the lung, swelling in hands and feet, shortness of breath, low blood-oxygen levels (80%), and the presence of white mucus.

From June 16th to June 21st, the patient experienced a fluctuating fever with temperatures ranging between 37.5°C and 38.7°C over 6 days. The patient depended on an oxygen concentrator at home, and without it, their oxygen saturation level fell below 80%. Following four days of treatment based on ACT-ML recommendations, their body temperature stabilized at 37°C by June 24th.

On June 26th, the body temperature was normal, but the patient still depended on the oxygen concentrator. Without supplemental oxygen, the oxygen saturation level dropped below 80%. The cough slightly improved on June 26th.

On July 4th, it was observed that, in the absence of supplemental oxygen, the patient's oxygen saturation levels elevated to 85%, a notable improvement from previous readings below 80%.

On July 12th, the swelling in the hands had subsided. However, the left foot remained swollen. With an oxygen supply of 3 liters per minute(oxygen production rate), the oxygen saturation level was 99%.

On July 19th, the swelling in the foot showed improvement. With an oxygen supply of 2 liters per minute (oxygen production rate), the oxygen saturation was between 98%-99%. When supplied with 1 liter of oxygen per minute, the oxygen saturation was 80%. The patient's mobility improved. There was no need for a walking stick, and the patient could walk independently.

On July 31st, swelling in the foot improved.

On August 16th, during the follow-up, the patient required supplemental oxygen occasionally during the day and not at all at night. When not using supplemental oxygen, their oxygen saturation levels improved to 91%.

Timeline of the Patient's Medical Events:

- May 31st:

  Initial symptoms manifested.

- June 1st:

  Admitted to the hospital after testing positive for SARS-CoV-2 via PCR.

- June 5th to June 15th:

Admitted to ICU due to the severity of symptoms.

- June 10th:

Tested negative for SARS-CoV-2 through PCR.

- June 15th:

Patient discharged upon mutual request of the patient and their family.

- June 16th-21st:

Fever episodes with temperature fluctuating between 37.5°C and 38.7°C.

Consistently low oxygen saturation levels below 80%.

Pleural effusion in the lung observed.

- June 21st:

Enrolled in ACT-ML study.

Commencement of ACT-ML-prescribed treatment regimen.

Initial symptoms upon enrollment included the fever, cough, pleural effusion in the lung, swelling in hands and feet, shortness of breath, low blood-oxygen levels (80%), and the presence of white mucus.

- June 24th:

After four days on the medication recommended by ACT-ML, temperature stabilized to a normal 37°C.

- June 26th:

Maintained a normal body temperature.

Required oxygen concentrator to sustain an oxygen saturation of 94%. Without the concentrator, levels plummeted below 80%.

Notable improvement in coughing symptoms.

- July 4th:

Oxygen saturation showed a marked improvement, reaching 85% in the absence of supplemental oxygen.

- July 12th:

Hand swelling completely subsided, though left foot swelling remained.

Achieved an oxygen saturation level of 99% when provided with 3 liters/min of supplemental oxygen.

- July 19th:

Foot swelling showed signs of improvement.

Oxygen saturation was between 98%-99% when given 2 liters/min of oxygen and 80% when given 1 liter/min.

Patient exhibited improved mobility, being able to walk without the aid of a walking stick.

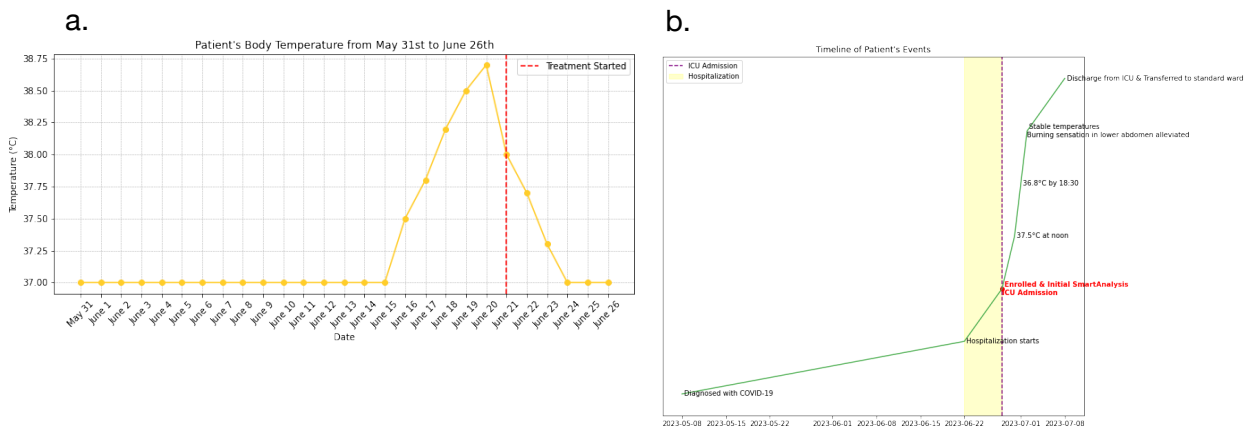
- July 31st:

Slight swelling in the foot was observed but deemed non-severe.

- August 16th:

During the follow-up, it was observed that the patient needed supplemental oxygen only occasionally during the day and not at all during the night. Without supplemental oxygen, the oxygen saturation levels were a stable 91%.

Severe COVID-19 Case Analysis - 2



Extended Data Figure 2: a. The provided graphic illustrates the body temperature changes of a patient with severe COVID-19 who was admitted to the hospital. The administration of medication by the hospital did not result in a reduction of the patient's fever. The patient consistently exhibited elevated body temperatures exceeding 39.5°C, typically around 4 p.m. daily. The patient experienced fever for seven days prior to initiating treatment. Following the commencement of a four-day treatment regimen as advised by the ACT-ML system, the patient's fever resolved. b. Chronological outline of the patient's significant medical events, from admission into the hospital to the Intensive Care Unit (ICU), followed by the subsequent transfer to a standard hospital ward.

Background: Extended Data Table 2 shows patient's characteristics and clinical information. The patient is 81 years old. While our study was designed exclusively for outpatients, we were approached by the patient and their family expressing an interest in participating the study. Upon thorough assessment, we determined that denying treatment would be unethical. The patient remained hospitalized throughout the study and participated in three ACT-ML sessions. It's important to note that this particular case was excluded from the main study's analysis, as detailed in Table 1. The patient presents with several comorbidities, namely 1) type 2 diabetes, 2) nephrolithiasis, and 3) cholelithiasis.

Medications administered during hospitalization:

1. Doxycycline (reduce the fever)

2. Ambroxol (nebulization to expectorate phlegm)

3. Dexamethasone,

4. Sodium Phosphate

5. Nebulization therapy

6. Vitamin C

7. Xuebijing (a traditional Chinese medicine injection used for Systemic inflammatory response syndrome)

8. Budesonide Sulfate and Terbutaline (relieve bronchospasm)

The patient had been diagnosed with COVID-19 on May 8th via a PCR test. A follow-up PCR test on June 28th converted to be negative.

The patient was admitted to hospital A from June 22nd to June 28th with symptoms of fever, chest tightness, cough, expectoration for 7 days. During this period, they consistently had a fever that fluctuated, reaching up to 39.5°C after 4 p.m. daily. Due to the deterioration of symptoms on June 28th, the patient was transferred to the ICU at Hospital B.

Upon transfer from Hospital A to the Intensive Care Unit (ICU) at Hospital B on June 28th, the discharge diagnostic findings from Hospital A encompassed the following conditions:

1. Systemic sepsis

2. Advanced pneumonia

3. Infection with SARS-CoV-2

4. Electrolytic imbalances

5. Hypoproteinemia

6. Clinical anemia

7. Left-sided minimal pleural effusion

8. Pericardial effusion

9. Pulmonary bullae

10. Radiological evidence of "white lung" as detected on computed tomography (CT) imaging.

11. Fever

On June 28th, the patient was enrolled in the study and underwent the first ACT-ML. The initial symptoms upon admission to the study were fever, difficulty breathing, sore throat, headaches, body aches, dry nasal passages, abdominal pain, and full-body myalgia.

When using hospital administrated medicine alone, the fever did not subside. Every day around 4 p.m., the patient had a fever, with high temperatures exceeding 39.5°C. It was only after taking prescriptions generated by the ACT-ML that the fever subsided. On the June 30th, recorded body temperatures were 37.5°C at midday and 37.3°C by 17:00 hours. By 18:30 hours on the 1st of July (Day 5 of treatment), the fever had abated, and the body temperature returned to a normal 36.8°C, and the previously observed sore throat symptom was no longer present.

Between the 1st and 2nd of July, the patient's body temperature consistently registered within the normal range. Prior to this period, the individual reported a sensation akin to burning in the abdominal region. Post-medication administered, by the 2nd of July, this abdominal discomfort

had subsided. The patient showed improvement in muscle pain (myalgia) and had normal bowel movements. However, the patient still faced significant respiratory challenges.

On the 8th of July, the patient exhibited clinical improvement and was consequently transitioned from the Intensive Care Unit (ICU) to a standard medical ward.

Timeline of the Patient's Medical Events:

- May 8th:
  -First COVID-19 symptom onset
  -PCR COVID-19 test positive
- June 22nd- June 28th (Hospital A)
  - Admitted to Hospital A
  - Despite the administration of hospital-prescribed medications, the patient's fever persisted, spiking daily around 4 p.m. and often exceeding 39.5°C
  - 11 complications diagnosed (Extended Table 2)
- June 28th:
  - Patient enrolled in the study and underwent the initial ACT-ML.
  - The initial symptoms upon admission to the study were fever, difficulty breathing, sore throat, headaches, body aches, dry nasal passages, abdominal pain, and full-body myalgia.
  - A PCR test for COVID-19 yielded negative results.
  - Due to symptom exacerbation, the patient was transitioned to Hospital B's ICU (Intensive Care Unite).
- June 30th:

- Day 3 of the study. Temperatures recorded were 37.5°C at noon and 37.3°C by 17:00 hours

• July 1st:

- On the fifth day of the ACT-ML intervention, by 18:30 hours, the fever had normalized to 36.8°C.

- The patient no longer experienced throat discomfort.

• July 1st - 2nd:

- Stable temperatures within the normal range were observed.

- Previously reported burning sensation in lower abdomen alleviated post-medication.

- Generalized myalgia showed improvement, but respiratory challenges persisted.

• July 8th:

- Significant clinical improvement observed.

- Patient transferred from the ICU to a standard medical ward.

Extended Data Table 1: Clinical events and characteristics of severe COVID-19, case number 1.

Patient Information	
Age	92
Comorbidities	
1	Hypertension
2	High uric acid levels
3	High blood sugar
4	Diabetes
5	Swelling of the feet and hands
Treatment & Testing	
PCR Test Result	Positive for SARS-CoV-2
PCR Test Date	June 1st
Start of ACT-ML	June 21st
ACT-ML Sessions	6
Treatment Period	June 21st to August 16th
Prescriptions	Prescriptions from ACT-ML only
Hospitalization	
Hospital Admission Date	June 1st
ICU Admission	Yes
ICU Days	10
Discharge Date	June 15th
Negative PCR Test	June 10th
Symptoms & Observations Before Study (Up to June 21st)	
First Symptom Onset Date	May 31st
Initial Symptoms upon Admission to the Study (June 21st)	Fever, cough, swelling in hands and feet, shortness of breath, white mucus.
Body Temperature	Varied between 37.5°C and 38.7°C (June 16th-21st)
Oxygen Saturation	Below 80% (June 16th-21st);
Respiratory Symptoms	There was evidence of pleural effusion in the lung.
Symptoms & Observations In Study (Starting from June 21st)	
Oxygen Saturation	94% with oxygen concentrator, bellow 80% without concentrator (June 26th);
	85% without oxygen concentrator (July 4th);
	99% with 3 liters/min (July 12th);
	98%-99% with 2 liters/min (July 19th);
	80% with 1 liter/min (July 19th);
	91% without oxygen concentrator (August 16th)
Swelling	Hand swelling subsided (July 12th);
	Foot swelling improved (July 31st)
Mobility	Improved (July 19th, without walking stick)
Oxygen Concentrator Dependency	Occasionally during day, not at night (August 16th)

Extended Data Table 2: Clinical events and characteristics of severe COVID-19, case number 2.

Patient Information	
Age	81
Study Design	Exclusively for outpatients, but this case was treated as an exception.
Study Participation	Hospitalized throughout, underwent three ACT-ML sessions.
Exclusion from Main Study	Yes, as detailed in Table 1.
Comorbidities	
1	Type 2 diabetes
2	Nephrolithiasis
3	Cholelithiasis
Medications During Hospitalization	
1	Doxycycline
2	Ambroxol
3	Dexamethasone
4	Sodium Phosphate
5	Nebulization therapy
6	Vitamin C
7	Xuebijing (Traditional Chinese Medicine injection)
8	Budesonide Sulfate and Terbutaline
Treatment & Testing	
PCR Test Result	Positive
PCR Test Date	May 8th
Negative PCR Test	June 28th
ACT-ML Sessions	3
Start of ACT-ML	June 28th
Treatment Period	June 28th - July 8th (9 days)
Prescriptions	Hospital medications and prescriptions recommended by ACT-ML
Hospitalization	
Admission Date Hospital A	June 22nd to June 28th
ICU Admission	Yes
ICU Days	Transferred to ICU at Hospital B on June 28th due to symptom deterioration
Diagnostic Findings from Hospital A	
1	Systemic sepsis
2	Advanced pneumonia
3	Infection with SARS-CoV-2
4	Electrolytic imbalances
5	Hypoproteinemia
6	Clinical anemia
7	Left-sided minimal pleural effusion
8	Pericardial effusion
9	Pulmonary bullae

10	Radiological "white lung" (CT imaging)
11	Fever
Symptoms & Observations Before Study (Up to June 28th)	
First Symptom Onset Date	May 8th
Initial Symptoms upon Admission to the Study	Fever, chest tightness, cough, expectoration
Body Temperature	Persistent fever, fluctuating in intensity, rising to 39.5°C after 4 p.m daily (June 22th to June 28 th)
Symptoms & Observations In Study (Starting from June 28th)	
Body Temperature	37.5°C at midday; 37.3°C by 17:00 (June 30th);
	36.8°C by 18:30; (July 1st)
	Normal body temperatures; (July 1st-July 2nd)
Sore throat	Sore throat symptom disappeared (July 1st)
Abdominal Pain	Abdominal discomfort subsided, (July 1st -July 2nd)
Full body Myalgia	Improved (July 1st -July 2nd)
Progression	
Transfer out from ICU	Stabilized condition and transferred from ICU to standard medical ward (July 8th)

Extended Data Figure 1: Flow diagram of the proof-of-concept feasibility trial.