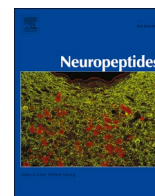




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Efficacy of Ninjin'yoeito in treating severe coronavirus disease 2019 in patients in an intensive care unit

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ABSTRACT

Coronavirus Disease-2019 (COVID-19), an infectious disease associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is a global emergency with high mortality. There are few effective treatments, and many severe patients are treated in an intensive care unit (ICU). The purpose of this study was to evaluate whether the Japanese Kampo medicine ninjin'yoeito (NYT) is effective in treating ICU patients with COVID-19. Nine patients with confirmed SARS-CoV-2 infection admitted to the ICU were enrolled in this study. All patients underwent respiratory management with invasive mechanical ventilation (IMV) and enteral nutrition. Four patients received NYT (7.5 g daily) from an elemental diet tube. We retrospectively examined the prognostic nutritional index (PNI), length of IMV, length of ICU stay, length of hospital stay, rate of tracheostomy, and mortality rate.

The median age of the enrolled participants was 60.0 years (4 men and 5 women). The median body mass index was 27.6. The most common comorbidity was diabetes (4 patients, 44%), followed by hypertension (3 patients, 33%) and chronic kidney disease (2 patients, 22%). The median length of IMV, ICU stay, and hospital stay were all shorter in the NYT group than in the non-NYT group (IMV; 4.0 days vs 14.3 days, ICU; 5.3 days vs 14.5 days, hospital stay; 19.9 days vs 28.2 days). In the NYT and non-NYT groups, the median PNI at admission was 29.0 and 31.2, respectively. One week after admission, the PNI was 30.7 in the NYT group and 24.4 in non-NYT group. PNI was significantly ($p = 0.032$) increased in the NYT group (+13.6%) than in the non-NYT group (-22.0%). The Japanese Kampo medicine NYT might be useful for treating patients with severe COVID-19 in ICU. This study was conducted in a small number of cases, and further large clinical trials are necessary.

1. Introduction

Coronavirus disease-2019 (COVID-19), first reported in Wuhan, China in December 2019, is rapidly expanding worldwide (Wang et al., 2020b). It is an infectious disease associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (Perlman, 2020; Zhang et al., 2020), and has now become a global emergency.

There are few effective treatments, and severe patients are treated in an intensive care unit (ICU). In the ICU, many patients with COVID-19 pneumonia develop severe hypoxemic respiratory failure and require invasive mechanical ventilation (IMV). Based on NIH COVID-19 Treatment Guidelines, patients in some countries may receive remdesivir and dexamethasone (Sanders et al., 2020). However, cases in ICU are invariably associated with high mortality. The ICU mortality rate reported in previous studies ranges from 16% to 78% (Arentz et al., 2020; Bhatraju et al., 2020; Huang et al., 2020; Myers et al., 2020; Wang et al., 2020a; Wang et al., 2020c; Yang et al., 2020; Zhou et al., 2020).

Globally, as of 30 August 2021, there have been 214,468,601 confirmed cases of COVID-19, including 4,470,969 deaths, reported to WHO (see, <https://covid19.who.int>). In Japan, COVID-19 has resulted in 1,388,863 confirmed cases with more than 15,797 deaths.

Ninjin'yoeito (NYT) is a Japanese Kampo medicine that improves symptoms such as anemia, anorexia, cough, and fatigue and is used to facilitate disease recovery (Amitani et al., 2015; Miyano et al., 2018). There are no reports evaluating the efficacy and safety of NYT in severe

COVID-19 patients underwent respiratory management with IMV in the ICU.

The purpose of this study was to evaluate the effectiveness of NYT in preventing the progression of COVID-19 and shortening the length of stay in the ICU or length of hospital stay. In addition, we aimed to assess the effect of NYT on the prognostic nutritional index (PNI) of patients.

2. Methods

Patients with confirmed SARS-CoV-2 infection admitted to the ICU at our hospital in May and June 2021 were enrolled in this study. All patients were diagnosed COVID-19 by a positive result for SARS-CoV-2 RNA in nasopharyngeal swabs using real-time fluorescence reverse transcription-polymerase chain reaction (RT-PCR). All patients received remdesivir and dexamethasone (Sanders et al., 2020).

All patients underwent respiratory management with IMV and circulatory management with catecholamine support as needed; enteral nutrition (20 kcal/kg/day) was performed by inserting an elemental diet tube. All patients were treated in the same manner except for NYT administration which was administered in a dose of 7.5 g daily via the elemental diet tube in some patients. Patients who received NYT were compared to those who did not receive NYT. We retrospectively examined the PNI, length of IMV, length of ICU stay, length of hospital stay, rate of tracheostomy, and mortality rate.

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Table 1
Ingredient components and pharmacological activities in Ninjin'yoeito(人參養榮湯).

Ingredient name	Component Ratio(g)	Pharmacological activities	References
Ginseng	人參 3.0	immune enhancement, anti-inflammation effects, antioxidant effects, memory enhancement, platelet-aggregation inhibitory effects, improvement of menopausal disorders, and induction of metabolic energy	(Han et al., 2018) (Kim et al., 2010) (Kim, 2012) (Kim et al., 2014) (Wang et al., 2013) (Yang et al., 2014) (MATSUDA et al., 1986) (Uto et al., 2015)
Japanese angelica root	當歸 4.0	anti-inflammatory effects	(Uto et al., 2015)
Rehmannia root	地黃 4.0	hypoglycemic effect, diuretic effect promoting effect on erythrocyte deformability and fibrinolytic activity blood coagulation inhibiting effect	(Kitagawa et al., 1971) (KUBO et al., 1994) (Matsuda, 1986)
Atractylodes rhizome	白朮 4.0	anti-inflammatory and antinociceptive effects	(Chen et al., 2016)
Poria sclerotium	茯苓 4.0	anti-inflammatory, anti-apoptotic, and anti-immunologic rejection effects.	(Lee et al., 2013) (Zhang et al., 2009) (Wang et al., 2015) (He and Dai, 2011) (Sakuragawa, 1983)
Peony Root	芍藥 2.0	anti-inflammatory and immunomodulatory effects blood coagulation inhibiting effect	(Im Ahn et al., 2017) (Kang et al., 2018)
Citrus unshiu peel	陳皮 2.0	antioxidant, anti-inflammatory, antibacterial properties, and anti-cancer activity antiobesity and lipid-improving effect	(Yuan et al., 2012) (Zhang et al., 2008) (Lee et al., 2009) (Shin et al., 2009)
Polygala root	遠志 2.0	anti-dementia, anti-aging, anti-inflammatory, and anti-oxidant	(Liu et al., 2017) (Jiangwei et al., 2011) (Ryu et al., 2008)
Astragalus root	黃耆 1.5	increase telomerase activity, anti-oxidant, anti-inflammatory, immune-regulatory, anticancer, hypolipidemic, antihyperglycemic, hepatoprotective, expectorant, and diuretic effects	(Chan et al., 2009) (Nalbantsoy et al., 2012) (Crawford and Crawford, 2018) (Olefsky, 2000) (MATSUDA et al., 1987) (Sun et al., 2018) (Zhong et al., 2016)
Cinnamon bark	桂皮 2.5	antidiabetic effects anti-thrombic activities	
Schisandra fruit	五味子 1.0	anti-hyperlipidemia effect, antiaging effect improving learning and memory impairment antitussive activity	
Glycyrrhiza	甘草 1.0	anti-inflammatory, anti-cancer and immunomodulatory effects	(Yin et al., 2018) (Menegazzi et al., 2008) (Wang et al., 2011) (Zeng et al., 2015) (Hong et al., 2009)

7.5 g of Ninjin'yoeito extract granules contains 6700 mg of a dried extract of the following mixed crude drugs.

2.1. Statistical analysis

Statistical analysis was performed using SPSS 24 statistical software (SPSS Inc., Chicago, USA). The association between NYT and non-NYT was analyzed with the chi-square test, Fisher's exact test, and Mann-Whitney *U* test. A *p* value less than 0.05 was considered to be statistically significant.

3. Results

Nine patients were enrolled in the study. The NYT group (4 patients who received NYT) and non-NYT group (5 patients who did not receive NYT) were compared.

The demographic and clinical characteristics of the patients are shown in Table 2. The median age of the enrolled patients was 60.0 (42–82) years, with 4 (44%) men and 5 (56%) women. The median body mass index (BMI) was 27.6 (20.7–38.4). The most common comorbidity was diabetes (4 patients, 44%), followed by hypertension (3 patients, 33%), and chronic kidney disease (2 patients, 22%).

The patient outcomes are shown in Table 3. The median duration of hospital stay was 23.5 (15–64) days and time exclusively in the ICU was 14.3 (4–49) days. The mortality rate was 22% (2 patients). There were no significant differences in sex, age, BMI, comorbidities, laboratory data, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and mortality rate between the NYT and non-NYT groups.

Tracheostomy was performed in 5 patients (45%), with fewer patients in the NYT group than the non-NYT group (25% vs. 80%). The

median length of IMV days was shorter in the NYT group (4.0 days) than in the non-NYT group (14.3 days). The median length of days in the ICU was shorter in the NYT group (5.3 days) than in the non-NYT group (14.5 days). The median duration of hospital stay was shorter in the NYT group (19.9 days) than in the non-NYT group (28.2 days).

The median PNI at admission was 29.0 in NYT group and 31.2 in non-NYT group. One week after admission, the PNI was 30.7 in the NYT group and 24.4 in non-NYT group. Comparing the rate of increase/decrease at the time of admission and one week after admission, PNI was significantly ($p = 0.032$) increased in the NYT group (+13.6%) compared to the non-NYT group (–22.0%).

4. Discussion

Treatment of severe COVID-19 patients tends to be prolonged, and the increase in the number of patients requiring ICU support also causes major global social and economic disruption. Longer hospital stays lead to increased medical expenses. Although effective therapeutic drugs for COVID-19 are required, currently there is no effective and specific antiviral treatment for COVID-19. Based on available evidence, remdesivir and dexamethasone have been used in Japan, but these drugs are not likely to be sufficient for successful treatment of COVID-19 (Sanders et al., 2020) (Beigel et al., 2020; Grein et al., 2020).

In this study, we investigated the use of the Japanese Kampo medicine, NYT (see <https://mpdb.nibiohn.go.jp/stork/>). Many Kampo medicines have been shown to fight viral infections, inflammation, and apoptotic or other cancers. For example, there is a report that Maoto and

Table 2
Patient characteristics.

	Total (n = 9)	NYT (n = 4)	non-NYT (n = 5)	p-value
Age, years ^a	60.0 (42–82)	58.5 (42–82)	60.0 (51–81)	0.905
Sex				
Men	4 (44)	1 (25)	3 (60)	0.294
Women	5 (56)	3 (75)	2 (40)	
Body mass index, kg/m ^{2a}	27.6 (20.7–38.4)	26.1 (20.7–38.4)	27.6 (23.6–36.3)	0.73
Time from symptom onset to admission, days ^a		8.5 (3–15)	9.0 (8–11)	1
Comorbidities				
Diabetes	4 (44)	2 (50)	2 (40)	0.764
Hypertension	3 (33)	0(0)	3 (60)	0.058
Chronic kidney disease	2 (22)	2 (50)	0 (0)	0.073
Cerebrovascular diseases	1 (11)	0 (0)	1 (20)	0.343
Liver cirrhosis	1 (11)	1 (25)	0 (0)	0.236
Laboratory data				
WBC, /μL ^a	5630 (4910–20,150)	11,195 (4980–20,150)	5630 (4910–10,330)	0.73
RBC, ×10 ⁴ /μL ^a	408 (320–496)	396 (337–427)	472 (320–496)	0.413
PLT, ×10 ⁴ /μL ^a	17.0 (5.8–26.7)	19.9 (5.8–26.7)	17.0 (11.4–22.5)	0.73
Albumin, g/dL ^a	2.80 (2.4–3.7)	2.65 (2.4–2.8)	2.90 (2.7–3.7)	0.063
Prealbumin, mg/dL ^a	8.6 (7.1–10.7)	9.55 (7.1–10.7)	7.90 (7.4–9.4)	0.556
CRP, mg/dL ^a	9.06 (1.06–15.84)	8.91 (1.06–15.44)	9.06 (2.93–15.84)	0.905
KL6, U/mL ^a	332 (124–932)	392 (124–932)	332 (186–719)	1
PNI on admission ^a	30.7 (25.2–40.3)	29.0 (25.2–32.5)	31.2 (29.6–40.3)	0.111
APACHE II score ^a	12.0 (8–16)	11.5 (8–16)	12.0 (10–13)	1

^a median (range),NYT: Ninjin'yoeito; PNI: Prognostic nutritional index; WBC: White blood cell; RBC: Red blood cell; PLT: platelet; CRP: C-reactive protein; APACHE II: Acute Physiology and Chronic Health Evaluation II.

Table 3
Patient outcomes.

	Total (n = 9)	NYT (n = 4)	non-NYT (n = 5)	p-value
Rate of tracheostomy, n (%)	5 (56)	1 (25)	4 (80)	0.099
Length of IMV, days ^a	9.4 (2–45)	4.0 (2–17)	14.3 (9–45)	0.111
Length of ICU stay, days ^a	14.3 (4–49)	5.3 (4–17)	14.5 (9–40)	0.111
Length of hospital stay, days ^a	23.5 (15–64)	19.9 (17–27)	28.2 (15–64)	0.286
Mortality, n (%)	2 (22)	1 (25)	1 (20)	0.858
PNI 1 week after admission ^a	27.0 (15.8–41.3)	30.7 (24.1–41.3)	24.4 (15.8–28.7)	0.111
Rate of change in PNI (one week), % ^a	−16.4 (−48.4 – +27.2)	+13.6 (−16.4 – +27.2)	−22.0 (−48.4–2.9)	0.032

^a median (range),NYT: Ninjin'yoeito; PNI: Prognostic nutritional index; ICU: intensive care unit; IMV: invasive mechanical ventilation.

Kakkontokasenkyushin'i might be effective in treating COVID-19-induced high fever and olfactory disorders (Nabeshima et al., 2021; Takayama et al., 2021). However, there are no reports of using NYT in the treatment of COVID-19.

Kampo medicines are inexpensive. If the ICU stay period is shortened, the medical cost benefit will be enormous. We believe that NYT should be studied for COVID-19 treatment. This report is first study to use NYT for treatment of COVID-19 infection.

NYT is composed of 12 herbal plants that are used to promote recovery from illness and improve symptoms such as general fatigue, anemia, anorexia, cough, cancer cachexia, and the side effects of anti-cancer therapies (Amitani et al., 2015; Aomatsu et al., 2021; Aomatsu et al., 2020; Miyano et al., 2018). These herbal plants include Ginseng, Japanese angelica root, Rehmannia root, Atractylodes rhizome, Poria sclerotium, Peony Root, Citrus unshiu peel, Polygala root, Astragalus root, Cinnamon bark, Schisandra fruit, and Glycyrrhiza (Table 1).

In COVID-19 patients, it is possible that NYT might improve respiratory symptoms, anxiety, nutritional status, and efficiency of rehabilitation. Especially in COVID-19 patients, NYT's antithrombotic effects and improvement of respiratory symptoms are important. Previous studies showed that Rehmannia root, Cinnamon bark, Peony Root, and Ginseng have antithrombotic effects (Matsuda, 1986; MATSUDA et al., 1987; MATSUDA et al., 1986; Sakuragawa, 1983). Therefore, NYT might be useful in treating patients with severe COVID-19.

Moreover, NYT includes Schisandra fruit and polygala root.

Schisandra fruit has been used to treat chronic cough as a prescription medication in traditional herbal medicine. *Schisandra chinensis* fruit polysaccharide-1 (SCFP-1), extracted from Schisandra fruit, has anti-tussive activity (Zhong et al., 2016). In addition, Gomisin A (G. A) is a dietary lignan compound from *Schisandra chinensis*. Gomisin suppressed colorectal lung metastasis in a lung metastasis mouse model by inducing AMPK/p38-mediated apoptosis (Kee et al., 2018). NYT inhibited the contraction of guinea pig bronchial smooth muscle induced by histamine (Inoue, 1994). In fact, NYT is an effective and promising drug with various effects in frail patients with chronic obstructive pulmonary disease, despite conventional treatment (Hirai et al., 2020).

Polygala has been widely used to improve cognitive function. NYT improves mental stress-induced anxiety in neuropeptide Y-deficient zebrafish; Schisadorina fruit was identified as the compound responsible for the anxiolytic effect of NYT (Kawabe et al., 2021).

NYT achieved good rehabilitation results in an elderly patient with hip fracture and sarcopenia; NYT improved nutritional status, such as the serum levels of retinol-binding protein and prealbumin, increased muscle mass, and improved amino acid metabolism and storage in the skeletal muscle (Morinaga et al., 2020). Recently, NYT was considered to be a novel therapeutic option for the treatment of sarcopenia and frailty (Sakisaka et al., 2018; Uto et al., 2018). Through the improvement of amino acid metabolism, NYT maintains skeletal muscle mass and might improve the loss of skeletal muscle function (Ohsawa et al., 2018).

In this study, we evaluated nutritional status using PNI. PNI is easily calculated based on the serum albumin concentration and peripheral blood lymphocyte count ($10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count } (\mu\text{L})$), and is an indicator of the nutritional and immune status (Hong et al., 2015; Ikeya et al., 2015). It has been confirmed to have prognostic value in various settings, such as infectious disease, cardiovascular disease, and various cancers (He et al., 2017; Keskin et al., 2017; Peng et al., 2017; Shirakabe et al., 2018; Sun et al., 2015; Wu et al., 2016). Recently, several reports indicated that PNI is independently associated with mortality in COVID-19 patients, and a lower PNI score is associated with a worse prognosis. (Hu et al., 2021; Wang et al., 2020b; Wang et al., 2021; Wei et al., 2021).

In this study, we compared the PNI at admission and after one week, PNI was significantly ($p = 0.032$) increased in the NYT group (+13.6%) compared to the non-NYT group (-22.0%). All patients were treated in the same manner except for NYT administration. It is possible that PNI was improved by the administration of NYT from the elemental diet tube immediately after underwent respiratory management with IMV. In addition, the NYT group had improved nutritional status and shorter length of IMV, length of ICU stay, and length of hospital stay.

This study was conducted in a small number of cases, and further large clinical trials are necessary to determine the efficacy of NYT treatment for COVID-19. In Japan, integrative randomized controlled trials of Japanese Kampo medicine for COVID-19 are underway (Namiki et al., 2021; Takayama et al., 2021; Takayama et al., 2020).

5. Conclusion

Our study suggests that the Japanese Kampo medicine NYT might be useful for treating patients with severe COVID-19 in the ICU.

Ethics statement

This study was performed in accordance with the Declaration of Helsinki and institutional guidelines. The patients/participants provided their written informed consent to participate in this study. The institutional ethics committee approval number is 2109066.

Author contributions

NA made a substantial contribution to the study conception, conducted a literature search, and drafted the manuscript. NA, KS, KM, and DK contributed to the acquisition of data. HN, and MS advised on antiviral and antibacterial agents. NA, KS, TM, JI, TY, AT, AF, KM, DK, and HR treated the patients in the ICU. KI gave advice on the Kampo medicine. NA, KS, KM, and HR reviewed the manuscript and gave final approval for publication. All authors read and approved the final manuscript.

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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