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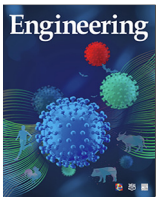

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Clinical Study of Mesenchymal Stem Cell Treatment for Acute Respiratory Distress Syndrome Induced by Epidemic Influenza A (H7N9) Infection: A Hint for COVID-19 Treatment

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ABSTRACT

H7N9 viruses quickly spread between mammalian hosts and carry the risk of human-to-human transmission, as shown by the 2013 outbreak. Acute respiratory distress syndrome (ARDS), lung failure, and fulminant pneumonia are major lung diseases in H7N9 patients. Transplantation of mesenchymal stem cells (MSCs) is a promising choice for treating virus-induced pneumonia, and was used to treat H7N9-induced ARDS in 2013. The transplant of MSCs into patients with H7N9-induced ARDS was conducted at a single center through an open-label clinical trial. Based on the principles of voluntariness and informed consent, 44 patients with H7N9-induced ARDS were included as a control group, while 17 patients with H7N9-induced ARDS acted as an experimental group with allogeneic menstrual-blood-derived MSCs. It was notable that MSC transplantation significantly lowered the mortality of the experimental group, compared with the control group (17.6% died in the experimental group while 54.5% died in the control group). Furthermore, MSC transplantation did not result in harmful effects in the bodies of four of the patients who were part of the five-year follow-up period. Collectively, these results suggest that MSCs significantly improve the survival rate of H7N9-induced ARDS and provide a theoretical basis for the treatment of H7N9-induced ARDS in both preclinical research and clinical studies. Because H7N9 and the corona virus disease 2019 (COVID-19) share similar complications (e.g., ARDS and lung failure) and corresponding multi-organ dysfunction, MSC-based therapy could be a possible alternative for treating COVID-19.

1. Introduction

Influenza A viruses (IAVs) are divided into multiple subtypes according to diversified viral surface antigens and two major pathotypes, including high and low pathogenicity for chicken [1,2]. Among these IAVs, all avian viruses with high pathogenicity have belonged to the H5/H7 subtype until recently [3]. A novel avian-original influenza virus emerged in the spring of 2013 and unfortunately led to severe and fatal respiratory disease in humans [4]. This novel virus has a similar phylogenetic genome to a virus isolated from chicken found in a live poultry market [4]. H7N9 virus is one of many reassortant viruses, which are primarily derived from the H7N3, H7N9, and H9N2 subtypes of IAVs [5–7]. Although H7N9 is pathogenically low in chickens [8], humans are much more susceptible to transmission, particularly at live poultry markets after intimate contact with H7N9-infected chickens [4,9]. H7N9 viruses are able to spread between mammalian hosts (ferrets) without losing virulence [10], and genetic mutations of H7N9 virus confer the risk of human-to-human transmission [11–13], as demonstrated in a few family clusters infected by this virus [14,15]. There have been six seasonal epidemics since the first case emerged in 2013, and the epidemic resurgence of the virus in mainland China since 2016 suggests that it has become more virulent [16,17]. Therefore, defending against H7N9-induced

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acute respiratory distress syndrome (ARDS) will be instrumental in curing H7N9 patients.

ARDS, lung failure, and fulminant pneumonia are major lung diseases in H7N9 patients, and H7N9 virus causes extrapulmonary diseases including rhabdomyolysis and encephalopathy through cytokine storms *in vivo* [4,18,19]. There is currently no vaccine available for preventing H7N9 infections. Other extensive therapeutic interventions (e.g., extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT)) have been applied to infectious patients with severe H7N9 [20–22]. However, dealing with the antiviral resistance of H7N9 and secondary-infection-induced multiple organ dysfunction in patients is still a serious concern, and there is an exigent demand to explore an effective strategy against H7N9 infection in humans. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has garnered global attention for causing the coronavirus disease 2019 (COVID-19) in Wuhan, China [23–25]. The number of infected patients has risen rapidly due to a lack of sufficient awareness, proximity between people, ease of mobility, and the human-to-human transmission ability of the virus [26–29]. At presnet, there is no effective way to cure COVID-19. H7N9 and COVID-19 share similar complications (e.g., ARDS and lung failure) and corresponding multi-organ dysfunction with lung inflammatory lesions and structural damage [24,30]. Hence, a breakthrough in treatment strategy for H7N9 infection in humans would be critical for treating COVID-19—and especially ARDS-induced severe pneumonia, which is currently causing panic around the world.

Because efforts to control lung injury via pharmacological agents have been unsuccessful, mesenchymal stem cell (MSC)-based therapy is being investigated, based on MSC's limitless self-renewal and multipotency. Furthermore, MSC-based therapies demonstrated promising effects in the experimental treatment of ARDS via inhibition of alveolar collapse, collagen accumulation, and cell apoptosis in lung tissue. Recently, Wilson et al. [31] found that administrating allogeneic MSCs in nine patients with ARDS resulted in no pre-specified adverse events, including hypoxaemia, cardiac arrhythmia, and ventricular tachycardia. Menstrual-blood-derived MSCs are currently attracting interest due to source potential, a high proliferation rate, and a painless procedure that is free of ethical issues [32–34].

This study is the first trial to test menstrual-blood-derived MSCs in patients with H7N9-induced ARDS. We report the effects of transplantation at different stages of ARDS and assess the long-term safety and the improvement of pulmonary function from H7N9 infection after MSC transplantation. Our study not only contributes to this field as a pilot clinical study showing the function of MSCs in H7N9-induced ARDS, but also suggests that MSCs are a promising tool for treating acute pneumonia in future clinical use.

2. Materials and methods

2.1. Selection of trial subjects

In our study, MSC transplantations in patients with H7N9-induced ARDS were conducted at a single center through an open-label clinical trial. The Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University, approved the implementation of this clinical study. Patients with confirmed H7N9 infection were enrolled and admitted to the hospital from 22 March 2013 to 10 February 2014. A patient can be confirmed based on clinical syndromes similar to acute influenza (including fever, cough, and shortness of breath), and the patients in this study were further confirmed via a laboratory test for the expression of the specific H7N9 genes and serum antibodies. Patients with ARDS were defined as those with PaO_2:FiO_2 less than 200 mmHg (1 mmHg = 133.3 Pa) and bilateral infiltrates coherent with pulmonary edema using a frontal chest radiograph; who require the application of mechanical ventilation with an endotracheal or tracheal tube [35,36]. Seventeen voluntary patients with H7N9-induced ARDS who had provided informed consent made up the experimental group undergoing MSC transplantation, while 44 patients with H7N9-induced ARDS acted as the control group without MSC transplantation. Unlike other studies, we infused MSCs at the acute phase or late stage of ARDS.

2.2. Source and preparation of MSCs

Allogeneic, menstrual-blood-derived MSCs were obtained from a healthy female donor (age 20–45), after signing an informed consent before the donation. As stated previously, this treatment was authorized by Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University. The mononuclear cells of the menstrual blood were examined for nucleated cells, cell differentiation, cell viability, and sterility prior to seeding for further culture. At 70%−80% confluence of the MSCs, these cells were passaged. Prior to use, MSCs were re-suspended in Plasmalyte-A (Baxter, Toronto, Canada) by a local laboratory with a specialized cell therapy center. The total usage of MSCs was 100 mL for each patient in the experimental group.

2.3. Biologic measurements

Laboratory indexes of blood samples, liver function, inflammation index, renal function, and myocardial enzymes were carried out at Laboratory Department of the First Affiliated Hospital, College of Medicine, Zhejiang University. Factors that could be correlate to the clinical features and therapeutic outcomes in H7N9 patients with ARDS were analyzed: ① baseline characteristics including age, underlying conditions, and symptoms; ② data from the laboratory examination and imaging scan; and ③ Combined treatments by basic therapy, antiviral therapy, antibiotic therapy, vasoactive drugs, glucocorticoid therapy, mechanical ventilation, ECMO, artificial liver support system (ALSS), and CRRT.

2.4. Treatments for patients

All participating patients were orally administrated the drugs (oseltamivir or peramivir) according to the standard therapy, and antibiotics were given based on positive results from blood test, throat-swab specimens or sputum tests for bacterial infections. Oxygen inhalation, non-invasive ventilation and invasive ventilation were conducted to maintain the minimum SaO_2 at 90%. In addition, ECMO were performed via femoral and internal jugular vein cannulation when PaO_2:FiO_2 < 80. Combination or monotherapy of norepinephrine, dopamine, epinephrine was also applied to patients with unstable haemodynamics. In addition, some patients also received glucocorticoid therapy including methylprednisolone and dexamethasone to control inflammatory response. Critical patients with unstable haemodynamics and multiple organ dysfunction including acute kidney injury, fluid overload, pulmonary edema, and severe electrolyte imbalance were started with the CRRT. Patients who developed acute liver failure accepted ALSS several times.

2.5. Cell transplantation and subsequent observation

Our MSC laboratory was alerted after informed consent was obtained, and doctors observed the hemodynamic and respiratory parameters over one-hour period of bedside observation to ensure that the patients' status was stable prior to MSC transplantation. The infusion was then initiated using a standard blood filter

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tubing set. The investigators stayed at the bedside for uninterrupted observation in case of any signs of an adverse reaction. Three patients were treated with three infusions of MSCs at the early stage of H7N9 infection, while the other six patients were treated with three infusions of MSCs at the late stage of H7N9 infection, and eight patients accepted four infusions of MSCs at the late stage of H7N9 infection. The injection dose of MSCs was determined to be 1 million per kilogram of body weight for each time. No MSC-infusion-related acute toxicities or seriously adverse events were found in any of these patients. A multiple intravenous infusion of MSC was tolerated in these patients with moderate to severe H7N9-induced ARDS.

2.6. Follow-up of patients with MSC transplantation

Laboratory indexes of blood samples, liver function, inflammation index, renal function, and myocardial enzymes were conducted before MSC transplantation and immediately after MSC transplantation. All of these parameters were also followed up after 1 week, 1 month, 3 months, 6 months, and 12 months. Patients were evaluated for computed tomography of the chest (CCT) at short term (Month 1–3), intermediate term (Month 6), and long term (Month 12) after MSC transplantation. Patients were evaluated for lung ventilatory function at the Month 6 and 12 follow-up. Moreover, the 36 item short-form health survey (SF-36) (Chinese version) of the medical outcome study was completed 6 and 12 months after MSC transplantation to evaluate the health-related quality of life (HRQoL). If patients were unable to perform the face-to-face interview, calls were made to obtain the survival information.

3. Calculation

Because the sample size of our study is small, univariate analysis was used. The Kolmogorov-Smirnov test was applied to check the normality of the corresponding quantitative data. Baseline data were exhibited as mean ± standard deviation (SD)/median value. To further assess the differences in this data, Student's t test was administrated, Mann–Whitney U-test analysis was utilized for these non-numeric data, and Fisher's exact test was analyzed to examine these categorical variables. One sample t test was applied to evaluate the SF-36 scores at the Month 6 and 12 follow-up. Statistical analysis was conducted through PASW Statistics software version 22 from SPSS (Chicago, IL, USA). $P < 0.05$ was considered to be statistically significant.

4. Results

4.1. MSCs and patient characteristics

The karyotyping/G-banding of MSCs was normal [37]. The viability ranged from 90% to 95%. In addition, surface marking and three-line differentiation of the MSCs were also conducted and confirmed in previous studies [37,38].

All patients in the experimental group and the control group received antiviral agents according to the standard therapy. Fig. 1 shows the CONSORT diagram of this clinical trial. As shown in Table 1, 17 patients were in the experimental group and 44 were in control group. The average ages of patients in the experimental group and control group were (62.8 ± 14.4) and (61.6 ± 11.8), respectively. Health conditions are listed in Table 1. Shock was

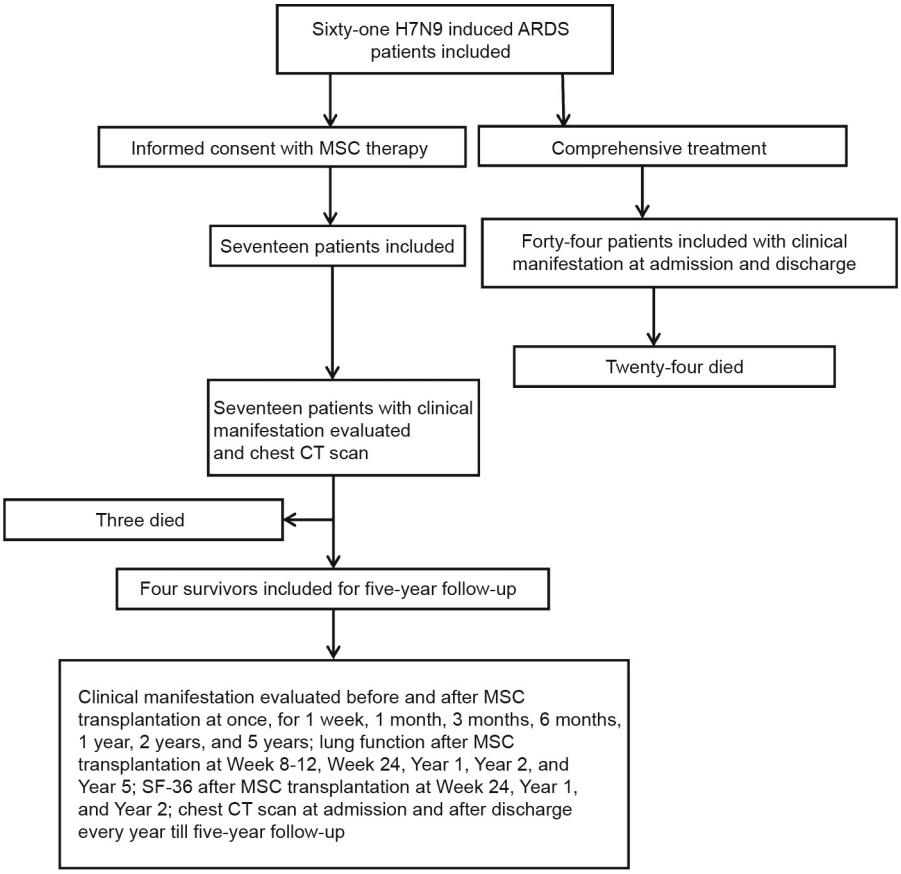

Fig. 1. The CONSORT diagram for the clinical trial of H7N9 infected patients. Forty-four patients with H7N9 induced ARDS were included as a control group and 17 patients with H7N9-induced ARDS acted as an experimental group with allogeneic, menstrual-blood-derived MSCs. MSC transplantation significantly lowered the mortality compared with the control group. Follow-up laboratory tests were taken for four H7N9-induced ARDS patients in the experimental group over five years.

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Table 1
Baseline characteristics of 61 H7N9-induced ARDS patients in the experimental group and the control group.

Baseline characteristic	Experimental group (N = 17)	Control group (N = 44)	P
Age	62.8 ± 14.4	61.6 ± 11.8	0.720
Underlying conditions			
Hypertension	10 (58.8%)	23 (52.3%)	0.814
Diabetes	5 (29.4%)	7 (15.9%)	0.305
Coronary heart diseases	0 (0%)	8 (18.2%)	0.092
COPD	0 (0%)	1 (2.3%)	1.000
CKD	0 (0%)	2 (4.5%)	1.000
Hematological diseases	0 (0%)	1 (2.3%)	1.000
Cancer	0 (0%)	4 (9.1%)	0.313
Liver diseases	1 (5.9%)	1 (2.3%)	0.507
Complications			
Renal failure	1 (9%)	10 (22.7%)	0.152
Shock	12 (70.6%)	16 (36.4%)	0.030
Intestinal diseases	5 (29.4%)	5 (11.4%)	0.137
Double pneumonia	17 (100%)	41 (93.2%)	1.000
Treatment regimens			
Antiviral agent	17 (100%)	44 (100%)	0.000
Antibiotic therapy	14 (82.4%)	36 (81.8%)	0.732
Vasoactive drugs	12 (70.6%)	19 (43.2%)	0.093
Glucocorticoid therapy	9 (52.9%)	24 (54.5%)	0.745
Mechanical ventilation	14 (82.4%)	31 (70.5%)	0.207
ECMO	8 (47.1%)	14 (31.8%)	0.266
ALSS	13 (76.5%)	18 (40.9%)	0.025
CRRT	12 (70.6%)	16 (36.4%)	0.016
Death	3 (17.6%)	24 (54.5%)	0.006

The numbers in brackets represent the proportions of the patients with corresponding characteristics. COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease.

the only complication hat was more frequent in the experimental group in our study (P = 0.030), which indicated that patients with H7N9-induced ARDs from the experimental group underwent more severe circulatory disturbances. Eventually, 24 patients in the control group died, while three patients died in the experimental group. The experimental group had a significantly higher survival rate than the control group (82.4% in the experimental group versus 45.5% in the control group; P = 0.006).

4.2. Standard therapy in two groups

Fourteen patients received antibiotic therapy in the experimental group and 36 patients received antibiotic therapy in the control group. Twelve patients in the experimental group and 19 patients in the control group received vasoactive drugs due to unstable circulation. Nine patients in the experimental group and 24 patients in the control group received glucocorticoid therapy. Fourteen patients in the experimental group and 31 patients in the control group received mechanical ventilation. Eight patients in the experimental group and 14 patients in the control group were treated with ECMO. Thirty-one patients, including 13 from the experimental group and 18 from the control group were treated by ALSS. Twenty-eight patients, including 12 from the experimental group and 16 from the control group, received CRRT. Except for ALSS and CRRT, the frequency of the standard strategies used for the two groups did not differ from each other in our study.

4.3. Baseline clinical symptoms and laboratory features

As shown in Table 2, a total of 58 of the H7N9-induced ARDS patients from the experimental group and the control group suffered from fever: 17 patients (100%) from the experimental group and 41 patients (93.2%) from the control group. A majority of patients from the experimental group suffered from cough (94.1%), phlegm (76.5%), shortness of breath (82.4%), and fatigue (52.9%). Other patients from the experimental group suffered from yellow sputum (29.4%), hemoptysis (17.6%), and muscular soreness (35.3%). In comparison, a majority of patients from the control group suffered from cough (84.1%), phlegm (54.5%), and shortness of breath (31.8%). Other patients from the control group suffered from yellow sputum (13.6%), hemoptysis (9.1%), fatigue (13.6%), and muscular soreness (11.4%). The proportions of the patients with corresponding symptoms from the experimental group were all more than those from the control group but without statistical significance.

As shown in Table 3, all the baseline of laboratory features showed no statistically significant differences in blood routine indexes, inflammation index, liver function, renal function, and coagulation in the two groups. The procalcitonin level and C-reactive protein level were both higher in the control group than in the experimental group, while the P value of the former was 0.024. This indicates that the patients in the two groups are comparable in our study. However, the blood routine indexes differed significantly between the experimental group and the control group when the patients were discharged (Table 4). The procalcitonin level was significantly higher in the control group than in the experimental group. Also, the serum creatinine level was significantly higher in the control group than in the experimental group (105.54 ± 96.52 versus 63.00 ± 38.55, P = 0.019), showing that the control group had a higher proportion of critically ill patients with more severe renal injury. The levels of creatine kinase, prothrombin time (PT), and D-dimer were significantly higher in the control group compared to the experimental group. As the majority of the laboratory features in both groups are similar, the significant differences may be associated with the higher death rate of patients in the control group.

Table 2
Symptoms of 61 H7N9-induced ARDS patients in the experimental group and the control group.

Symptom	Experimental group (N = 17)	Control group (N = 44)	Total number (N = 61)	P
Fever	17 (100%)	41 (93.2%)	58	0.553
Cough	16 (94.1%)	37 (84.1%)	53	1.000
Phlegm	13 (76.5%)	24 (54.5%)	37	0.232
Yellow sputum	5 (29.4%)	6 (13.6%)	11	0.271
Dry cough	1 (5.9%)	0 (0%)	1	0.290
Hemoptysis	3 (17.6%)	4 (9.1%)	7	0.404
Fatigue	9 (52.9%)	6 (13.6%)	15	0.007
Muscular soreness	6 (35.3%)	5 (11.4%)	11	0.604
Shortness of breath	14 (82.4%)	14 (31.8%)	28	0.001

The numbers in brackets represent the proportions of the patients with corresponding symptoms.

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Table 3
Laboratory tests of 61 H7N9-induced ARDS patients in the experimental group and the control group at admission.

Laboratory test	Experimental group (N = 17)	Control group (N = 44)	P
Blood routine index			
WBC (10^9 L^{-1})	5.46 ± 3.2	5.54 ± 4.01	0.936
N (10^9 L^{-1})	4.76 ± 3.01	4.60 ± 3.57	0.863
L (10^9 L^{-1})	0.49 ± 0.37	0.72 ± 1.40	0.498
Hb (g·L^{-1})	121.06 ± 22.83	124.86 ± 27.23	0.603
PLT (10^9 L^{-1})	95.60 ± 52.91	131.97 ± 76.59	0.817
Inflammation index			
CRP (mg·L^{-1})	98.96 ± 97.03	124.56 ± 89.64	0.323
PCT (ng·mL^{-1})	1.30 ± 2.19	7.77 ± 17.15	0.024
Liver function			
ALB (g·L^{-1})	30.42 ± 5.59	29.81 ± 4.62	0.661
ALT (U·L^{-1})	41.56 ± 25.50	61.61 ± 128.14	0.515
AST (U·L^{-1})	63.17 ± 44.98	152.72 ± 416.70	0.369
TBIL (μmol·L^{-1})	9.44 ± 4.78	12.45 ± 8.99	0.185
DBIL (μmol·L^{-1})	5.11 ± 3.39	7.07 ± 6.80	0.251
Renal function			
sCr (μmol·L^{-1})	63.77 ± 24.41	106.68 ± 120.74	0.142
Myocardial enzymes			
CK (U·L^{-1})	288.50 ± 285.39	818.47 ± 1671.28	0.188
LDH (U·L^{-1})	515.67 ± 187.96	724.02 ± 433.25	0.055
Coagulation			
PT (s)	12.65 ± 0.92	14.59 ± 8.92	0.364
D-dimer (μg·L^{-1})	7318.11 ± 5750.45	9934.19 ± 10624.10	0.330

WBC, white blood cell; N, neutrophils; L, lymphocytes; Hb, hemoglobin; PLT, platelet cell; CRP, c-reactive protein; PCT, procalcitonin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferases; TBIL, total bilirubin; DBIL, direct bilirubin; sCr, serum creatinine; CK, creatine kinase; LDH, lactate dehydrogenase; PT, prothrombin time.

Table 4
Laboratory tests of 61 H7N9-induced ARDS patients of in experimental group and control group at discharged.

Laboratory test	Experimental group (N = 17)	Control group (N = 44)	P
Blood routine index			
WBC (10^9 L^{-1})	9.62 ± 7.36	10.92 ± 11.97	0.671
N (10^9 L^{-1})	7.34 ± 7.53	8.97 ± 10.93	0.566
L (10^9 L^{-1})	1.45 ± 0.73	1.29 ± 0.99	0.542
Hb (g·L^{-1})	100.89 ± 13.10	99.44 ± 24.54	0.767
PTL (10^9 L^{-1})	201.72 ± 99.98	172.65 ± 162.89	0.486
Inflammation index			
CRP (mg·L^{-1})	44.85 ± 95.05	98.06 ± 96.82	0.054
PCT (ng·mL^{-1})	1.47 ± 3.65	7.71 ± 12.20	0.005
Liver function			
ALB (g·L^{-1})	36.09 ± 5.26	33.05 ± 8.68	0.174
ALT (U·L^{-1})	32.28 ± 25.67	80.67 ± 84.48	0.001
AST (U·L^{-1})	25.33 ± 16.14	158.14 ± 399.91	0.166
TBIL (μmol·L^{-1})	22.94 ± 31.84	44.43 ± 67.64	0.204
DBIL (μmol·L^{-1})	11.89 ± 22.07	27.50 ± 44.42	0.163
Renal function			
sCr (μmol·L^{-1})	63.00 ± 38.55	105.54 ± 96.52	0.019
Myocardial enzymes			
CK (U·L^{-1})	52.21 ± 89.55	567.74 ± 1186.32	0.015
LDH (U·L^{-1})	264.71 ± 114.35	942.20 ± 1987.96	0.212
Coagulation			
PT (s)	11.76 ± 3.28	16.42 ± 7.66	0.002
D-dimer (μg·L^{-1})	4785.83 ± 4622.72	10463.00 ± 12774.32	0.015

4.4. Follow-up with four patients with MSC transplantation

As shown in Table 5, the hemoglobin levels were significantly upregulated after MSC transplantation, and the level of PT was downregulated. This indicated that MSC transplantation did not exert harmful effects in the patients' bodies during the five-years follow-up period.

Table 5
Laboratory tests of 4 H7N9-induced ARDS patients in the experimental group during further follow-up for five years.

Laboratory tests	Time									P
Blood routine index	Before	After	Week 1	Month 1	Month 3	Month 6	Year 1	Year 2	Year 5	
WBC (10^9 L^{-1})	8.08 ± 5.14	10.33 ± 4.65	8.15 ± 1.67	6.88 ± 3.52	6.97 ± 3.37	7.00 ± 2.67	5.23 ± 1.44	6.95 ± 2.19	7.15 ± 3.60	0.820
L (10^9 L^{-1})	1.20 ± 0.64	1.23 ± 0.61	10.33 ± 9.97	8.65 ± 12.73	17.57 ± 15.10	14.93 ± 15.40	25.70 ± 3.89	1.58 ± 0.54	1.22 ± 0.30	0.380
Hb (g·L^{-1})	95.25 ± 12.82	109.00 ± 5.29	111.25 ± 11.87	126.25 ± 13.60	149.67 ± 3.06	146.00 ± 9.42	157.67 ± 7.23	157.50 ± 7.90	146.75 ± 15.44	0.000
PTL (10^9 L^{-1})	246.75 ± 62.60	281.00 ± 49.93	273.75 ± 89.72	206.75 ± 67.76	189.00 ± 57.66	168.00 ± 51.97	192.33 ± 62.17	183.00 ± 34.12	191.25 ± 37.35	0.130
Inflammation index										
CRP (mg·L^{-1})	12.60 ± 11.66	9.60 ± 11.44	4.10 ± 2.12	2.33 ± 1.33	4.77 ± 3.66	3.80 ± 4.09	6.75 ± 9.24	8.93 ± 16.12	35.19 ± 44.77	0.770
Liver function										
ALB (g·L^{-1})	35.13 ± 4.87	41.57 ± 7.13	44.43 ± 8.28	44.90 ± 8.69	46.07 ± 4.81	48.40 ± 4.76	48.30 ± 3.06	N/A	47.20 ± 7.56	0.120
ALT (U·L^{-1})	41.00 ± 30.13	39.33 ± 24.01	59.33 ± 14.01	23.75 ± 5.38	23.00 ± 17.78	34.25 ± 12.69	28.00 ± 9.66	N/A	33.33 ± 34.53	0.400
AST (U·L^{-1})	27.25 ± 13.35	24.33 ± 10.69	30.33 ± 8.02	19.50 ± 4.43	24.33 ± 11.02	23.75 ± 5.91	21.75 ± 7.63	N/A	33.00 ± 32.14	0.900
TBIL (μmol·L^{-1})	17.00 ± 7.12	17.00 ± 11.14	18.33 ± 4.93	14.00 ± 8.16	17.67 ± 7.09	17.50 ± 8.50	19.25 ± 8.88	N/A	16.97 ± 9.41	0.990
Renal function										
sCr (μmol·L^{-1})	54.50 ± 17.82	48.67 ± 20.26	64.67 ± 15.50	59.25 ± 21.72	61.33 ± 17.10	65.50 ± 11.39	68.50 ± 10.25	N/A	63.33 ± 14.57	0.800
Myocardial enzymes										
CK (U·L^{-1})	152.00 ± 142.51	84.00 ± 94.87	102.67 ± 118.15	32.50 ± 19.19	77.67 ± 37.29	79.00 ± 26.57	123.25 ± 98.44	N/A	N/A	0.270
LDH (U·L^{-1})	234.75 ± 63.33	246.67 ± 89.47	232.33 ± 21.83	182.50 ± 34.07	210.67 ± 44.23	203.00 ± 36.02	212.75 ± 45.35	N/A	N/A	0.680
Coagulation										
PT (S)	12.48 ± 0.41	11.93 ± 0.25	12.33 ± 0.61	11.30 ± 0.41	11.93 ± 0.12	10.68 ± 0.34	10.85 ± 0.52	10.90 ± 0.46	10.93 ± 0.68	0.000
D-dimer (μg·L^{-1})	4626.25 ± 3501.06	5591.33 ± 3889.10	3270.00 ± 1428.50	1090.00 ± 798.50	790.00 ± 636.40	380.00 ± 207.04	565.50 ± 394.70	1135.50 ± 1226.83	2133.33 ± 3400.59	0.161

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Table 6
Lung function tests of four H7N9-induced ARDS patients in experimental group during further follow-up for five years.

Lung function	Week 8–12	Week 24	Year 1	Year 2	Year 5	*P*
FEV1	85.65 ± 11.18	15.49 ± 7.75	87.30 ± 13.00	88.45 ± 11.78	81.67 ± 20.04	0.900
FVC	82.65 ± 11.00	79.60 ± 16.06	88.53 ± 12.03	91.53 ± 13.19	80.10 ± 14.36	0.780
FEV1/FVC	124.58 ± 46.09	101.08 ± 5.47	99.10 ± 2.22	97.10 ± 1.33	101.53 ± 9.21	0.446
FEF50%	74.88 ± 18.54	73.45 ± 22.99	74.87 ± 19.83	70.05 ± 11.27	76.73 ± 39.62	0.990

FEV1: forced expiratory volume in one second; FVC: forced vital capacity; FEF50: forced expiratory flow at 50% of vital capacity.

Four patients with MSC transplantation were included in the indexes to assess lung function and followed up for five years (Table 6). Both ventilation and diffusion dysfunction persisted during the acute stage, and we evaluated the lung function between Year 1 to 5 of the follow-up. There was no significant difference in the functions of forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, and forced expiratory flow at 50% of vital capacity (FEF50%) among the four patients during the following five years.

Before MSC treatment, all patients showed ground-glass opacities and amalgamation at the onset of disease by chest radiography. As described above, we followed up on four patients with MSC treatment for five years. We found that radiologic changes included linear fibrosis, air bronchogram, bronchiectasia, isolated areas of pleural thickening, ground -glass opacities, and hydrothorax after MSC transplantation. These changes were subsequently eliminated, while pneumatocele and new nodes were observed using CCT from Week 8–12 (Fig. 2 and Fig. S1 in Appendix A). After MSC transplantation for 24 weeks and one year, all patients showed improvement on CCT.

The SF-36 scale was chosen to assess life quality of four patients with MSC transplantation. After following up for two years, we found that the scores for all elements of the SF-36 did not significantly differ during the follow-up (Table S1 in Appendix A). Therefore, it indicated that MSC transplantation did not influence the long-term life quality of the patients.

5. Discussion

Patients suffering with H7N9 infection always produce similar symptoms, including fever, cough, shortness of breath, and sputum. These patients rapidly develop severe pneumonia, moderate-to-severe ARDS, and septic shock due to other reasons. Gao et al. [36] demonstrated that the development of refractory hypoxemia is one of the major causes of death, while the systemic inflammatory response syndrome (SIRS) may serve as the main lethal factor in the pathogenesis. According to our observation, most clinical symptoms were ameliorative from 1 to 12 months (data not shown) post standard therapy and combined therapy with MSC transplantation. The death rate of the control group was 54.5%, while the death rate of the experimental group was 17.6%. No cases of pulmonary embolism occurred in any of the patients. These findings indicate that MSC therapy is a safe and effective treatment for patients with severe lung disease induced by H7N9. There is also no evidence for MSC-associated long-term adverse events in our study. Zheng et al. [39] recently concluded that 12 patients with moderate to severe ARDS developed no infusion toxicities or MSC-related serious adverse events. Although the source and dose of MSCs in our study differ from those used by Zheng et al., we find the consistency regarding the tolerability and safety is encouraging.

Patients with ARDS had significant improvement in lung function at each follow-up. As with previously reported ARDS patients [40], the changes of the patients' conditions between 1–6 months after discharge was significantly better than those after 6–24 months. Research on the long-term prognosis of ARDS survivors showed a mildly restrictive type of lung function with a moderate decrease in carbonic oxide (CO) diffusion capacity after 3 months' MSC transplantation [41]. In addition, pulmonary function in H1N1-infected patient has been discovered to be almost normal, except for a reduced spreading role in respiratory ability [42]. In the one-year follow-up, fibrosis and pulmonary

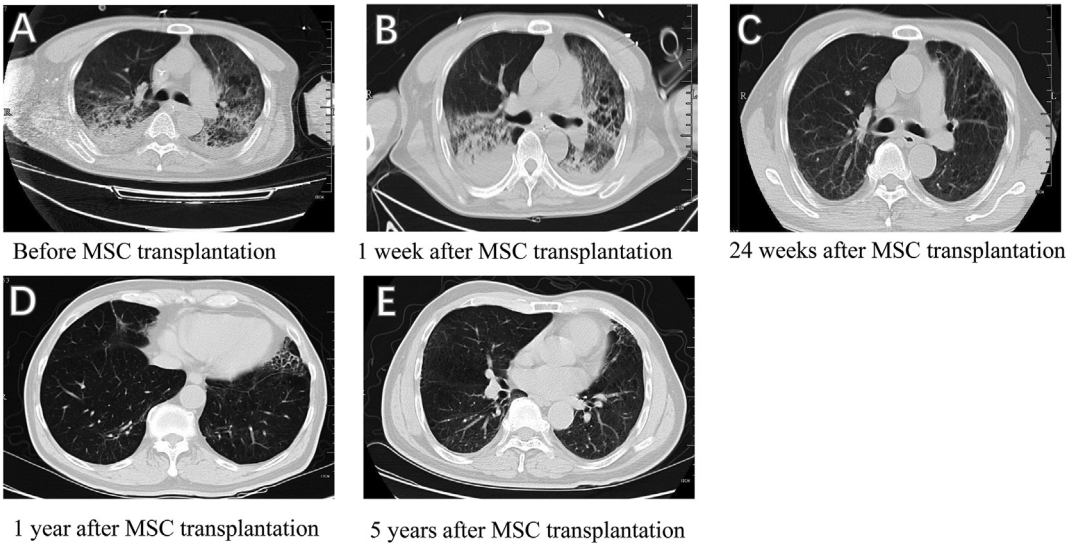

Fig. 2. Follow-up of four patients for five years after MSC treatment; images from one of these four patients are provided here. Before MSC transplantation, some fibrillations were present (a). Radiologic changes included linear fibrosis, air bronchogram, bronchiectasia, isolated areas of pleural thickening, ground-glass opacities, and hydrothorax after MSC transplantation for (b) 1 week, (c) 24 weeks, (d) 1 year, and (e) 5 years. After MSC transplantation for 24 weeks and one year, all patients showed improvement on CCT.

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parenchymal dysfunction are very common clinical phenomena in H1N1-associated severe ARDS infection. Over time, imaging reveals significant improvements in lung function and fibrosis, and this improvement is particularly evident in the first six months after discharge from hospital [43]. In addition, at the Month 3 follow-up, ground-glass opacities had significantly improved in over 85% patients [44]. However, no further significant differences were observed in the interstitial fibrosis and ground-glass opacities after the one-year follow-up [42]. These characteristics are consistent with those of survivors suffering from H7N9 infection in the current clinical trial.

In this investigation, it was found that when the patients returned home, they not only lacked basic activity, but were usually isolated from their relatives and neighbors because people were afraid of being infected with H7N9. After all, hundreds of people died from H7N9 in 2013. These survivors have obviously lower HRQoL than the normal population, which may have been a result of deficiencies in social function and mental health. Moreover, a meta-analysis indicated that ARDS survivors can improve the function of HRQoL during the initial six months after discharge from hospital [45]. These reports indicated that the quality of life of ARDS survivors infected with IAVs is rather worse than of people with no history of IAVs infection. Thus, we recommend an emphasis on care for such patients after recovery, with a focus on creating social interactions.

At present, infection by SARS-CoV-2, a SARS-like virus, is widespread in Wuhan, and even in the rest of China [46,47]. Surprisingly, COVID-19 has the ability of human-to-human transmission since the middle of December 2019 [48–50]. As of March 04, some 94 289 cases have been reported globally, most of them in China, and the number of deaths has reached over 3000. Thus far, thousands of infected patients have been suffering from serve ARDS without effective treatment. Recently, Xu et al. [30] confirmed that a COVID-19 patient caused severe pneumonia, according to pathological characteristics, died from severe infection with ARDS; biopsy samples were obtained at autopsy. This description of the pathological features of SARS-CoV-2-associated ARDS appears to be strikingly similar to that of H7N9-induced ARDS. H7N9 infected patients and SARS-CoV-2-infected patients share similar symptoms, including fever, cough, shortness of breath, sputum, and dyspnea accompanied by ARDS or later pulmonary fibrosis; thus some patients with severe symptoms with ARDS might benefit from novel methods including MSC-based therapy.

To our knowledge, this is the first prospective and systematic report of H7N9-induced ARDS to assess the health condition during the convalescent period. However, there are some limitations to this clinical trial. First and foremost, this study had a limited number of patients at a single-center study. With only 17 patients using MSC, we cannot guarantee that every step was perfect during our phase with only a one -time clinical trial. Second, we should state that this was not a routine clinical trial, owing to the H7N9 outbreak and to the lack of better options to treat patients with severe ARDS. Therefore, the patients did not want further visits; some patients refused to attend, and some did not complete follow-up. Thus, we are still concerned about the long-term safety of MSC transplantation for treating H7N9-induced ARDS, despite the lack of side effects observed in this clinical trial. Moreover, although some H7N9 patients may have had a potential lung infection, most were receiving other drugs without further examination, and it was not possible to obtain an ideal comparison of lung functional indicators between the experimental group and the control group. Finally, with the limitations of a small sample size, it is difficult to obtain huge amounts of clinical data. It is also difficult to conduct clinical studies in critically ill patients suffering with ARDS.

Some common side effects still require attention before MSC application can be part of clinical medicine. Although MSC transplantation shows numerous promising results, long-term safety remains a matter of debate, especially since it is diffcult to manage long-term follow-up for all patients [51]. The other concern is that MSC not only has the potential to inhibit tumor immune responses, but also can generate new blood vessels, which may promote tumor growth and metastasis [52]. Although MSC has shown great promise in the treatment of some immunological diseases (especially graft-versus-host disease (GVHD)), the variabilities of MSC quality from different donors and tissues is wide, and treatment protocols, doses, and injection modes are inconsistent during experimental procedures [53]. All these factors may limit the therapeutic effect of MSCs in clinical application. To overcome these obstacles, careful evaluation of appropriate cell sources, more scientific data, and a more comprehensive and systematic understanding of MSCs immunosuppression are needed.

6. Conclusions

From our clinical results, we believe that MSCs have the ability to reduce inflammatory effects and defend against cytokine storm. Although our group has reported some prior clinical studies in H7N9-infected patients [6,12,15,36], an understanding the detailed mechanism is still necessary in order to understand the potential of MSCs for treating H7N9-induced ARDS. As shown in our previous work [19,54,55], MSCs have the ability to improve lung function through anti-inflammatory effects in acute injury lung in a mouse model. Thus, the underlying mechanism is likely to be that MSCs reduce the secretion of inflammatory factors. Although the clinical study of MSCs is still in its infancy, we are optimistic that MSCs (including different sources) will be a promising tool for future clinical application.

In summary, long-term lung dysfunction in H7N9 survivors remains a problem, even two years after hospital discharge. Notably, MSC transplantation significantly lowered mortality. Furthermore, no serious adverse effects were found after MSC transplantation over a five-year follow-up period in this study. We are currently conducting a clinical trial of 17 patients with moderate to severe ARDS, with a primary focus on long-term safety and a secondary focus on regulating the respiratory system and improving the quality of life.

Conflict of Interest Statement

None.

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Authors' contribution

Lanjuan Li and Charlie Xiang conceived and designed this study; Jiajia Chen, Chenxia Hu, and Lijun Chen performed the experiments, collected and analyzed the data, and wrote the manuscript; Lingling Tang, Yixin Zhu, Xiaowei Xu, Lu Chen, Hainv Gao, Xiaoqing Lu, Liang Yu, and Xiahong Dai collected and analyzed the data. All authors have read and approved this final manuscript.

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Compliance with ethics guidelines

Jiajia Chen, Chenxia Hu, Lijun Chen, Lingling Tang, Yixin Zhu, Xiaowei Xu, Lu Chen, Hainv Gao, Xiaoqing Lu, Liang Yu, Xiahong Dai, Charlie Xiang, and Lanjuan Li declare that they have no conflict of interest or financial conflicts to disclose. This study was submitted to and approved by the Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University. MSC administration in patients with H7N9 induced ARDS was conducted in a single center and open-label clinical trial (ChiCTR-OCC-15006355) and Clinical trial registration (No. NTC02095444).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eng.2020.02.006.

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