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Clinical study of mesenchymal stem cell treating 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 it carried out the risk of human-to-human transmission after outbreak in 2013. 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 needed to treat H7N9 induced ARDS at the time. MSCs transplant into patients with H7N9 induced ARDS were conducted in a single center and open-label clinical trial. Based on the principle of voluntariness and informed consent, 44 patients with H7N9 induced ARDS were included as a control group while 17 patients with H7N9 induced ARDS were served as an experimental group with allogeneic menstrual blood-derived MSC. Notably, MSC transplantation significantly lower the mortality compared with in control group (17.6% died in MSC group vs 54.5% died in control group). Furthermore, MSC transplantation did not result in harmful effects in human body within the 5 year follow up period with 4 patients. Collectively, these results suggest that MSCs significantly improve 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 (such as 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 belong to the H5/H7 subtype [3], but a novel avian-original influenza virus emerged at the spring of 2013 and unfortunately lead 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 the 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], human beings 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 since 2016 in mainland China, suggest that it has become more virulent [16,17]. Therefore, defending against H7N9 induced 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. Moreover, other extensive therapeutic interventions (such as extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT)) have been applied to patients with severe H7N9 infectious patients [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. The corona virus disease 2019 (COVID-19) garnered on global attention for causing infectious pneumonia in Wuhan, China [23−25]. The number of infected patients rose rapidly due to a lack of enough awareness, proximity of people, ease of mobility, and the human-to-human transmission ability of the virus [26−29]. Currently, there is no effective way to cure COVID-19. Because H7N9 and COVID-19 share similar complications (such as ARDS and lung failure) and corresponding multi-organ dysfunction with lung inflammatory lesions and structural damage [24,30]. Hence, finding a breakthrough of treatment strategy for H7N9 infection in humans will be critical for treating COVID-19 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 because of MSC's limitless self-renewal and multipotency. Furthermore, MSC-based therapies demonstrated promising effects in experimental acute respiratory distress syndrome (ARDS) via inhibition of alveolar collapse, collagen accumulation and cell apoptosis in lung tissue. Recently, Wilson et al. [31] found that by administrating allogeneic MSCs in 9 patients with ARDS, there were no prespecified adverse events including hypoxaemia, cardiac arrhythmia, and ventricular tachycardia. Currently, menstrual blood-derived MSC is attracting interest due to a source potential, a high proliferation rate, and a painless procedure free of ethical issue [32−34].

This study is the first trial to test menstrual blood-derived MSCs in patients with H7N9 induced ARDS, and we report the effects of transplantation at different stages of ARDS and assess the long-term safety, improvement of pulmonary function from H7N9 infection after MSC transplantation. Our study will not only contribute to show the function of MSCs in H7N9 induced ARDS as a pilot clinical study, but also suggest that MSCs will be 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 in a single center and open-label clinical trial. The Ethics Committee of the First Affiliated Hospital,

College of Medicine, Zhejiang University has approved the implement of this clinical research. Patients with confirmed by H7N9 infection were enrolled and admitted to our hospital from March 22, 2013 to February 10, 2014. A patient can be confirmed by clinical syndromes similar to acute influenza (including hard breath, cough, and fever), and these patients were 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 and bilateral infiltrates coherent with pulmonary edema using frontal chest radiograph; they need the application of mechanical ventilation with an endotracheal or tracheal tube [35,36]. 17 voluntary patients with H7N9 induced ARDS and informed consent formed the experimental group undergoing MSC transplantation, while 44 patients with H7N9 induced ARDS served 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

The 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 the Ethics Committee of Zhejiang University in Hangzhou, China. 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 resuspended in Plasmalyte-A by the local laboratory with specialized cell therapy center. The total usage of MSC was 100 mL for each patient in the experimental group.

2.3. Biologic measurements

Laboratory indexes of blood sample, liver function, inflammation index, renal function and myocardial enzyme were carried out at Medical Inspection Department of the First Affiliated Hospital, College of Medicine at Zhejiang University. Factors which are possible to correlate to 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; 3) Combined treatments by basic therapy, antiviral therapy, antibiotic therapy, vasoactive drugs, glucocorticoid therapy, mechanical ventilation, ECMO, 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

Only 30 patients received all the treatments mentioned above except MSC transplantation. Our MSC laboratory was alerted after informed consent, and doctors observed the hemodynamic and respiratory parameters for 1-hour period of bedside observation to ensure the status of patients was stable prior to MSC transplantation. Then the infusion was initiated using a standard blood filter tubing set. The investigators stayed at the bedside for uninterrupted observation in case any signs of an adverse reaction. 3 patients were treated with three fusions of MSCs at the early stage of H7N9 infection, while the other 6 patients were treated with three fusions of MSCs at the late stage of H7N9 infection, and only 8 patient accepted four-infusion of MSCs at the late stage of H7N9 infection. The injection dose of MSCs is determined to be 1 million per kg 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 sample, liver function, inflammation index, renal function and myocardial enzyme 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 (1−3 months), intermediate term (6 month), and long term (12 month) after MSC transplantation. Patients were evaluated for lung ventilatory function at the 6 and 12 months marks. 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 unable to perform the face-to-face interview, were called 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 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 for examining these categorical variables. One sample *t* test was applied to evaluate SF-36 scores at the 6 and 12 months follow-up visits. Statistical analysis was conducted through PASW Statistics software version 22 from SPSS (Chicago, IL, USA). $P < 0.05$ were considered statistically significant.

4. Results

4.1. MSCs and Patient characteristics

The karyotyping/G-banding of MSCs was normal by the previous study [37]. The viability ranged from 90%−95%. Additionally, the surface makers and three-line differentiation of MSCs are conducted and the detail information is referenced as previous study [37,38].

All patients in the experimental group and the control group received antiviral agents according to the standard therapy. And the CONSORT diagram of this clinical trial is shown in Fig. 1. As shown in Table 1, 17 patients were in MSC group and 44 were in control group. Average ages of patients in MSC group and control group were (62.8 ± 14.4) and (61.6 ± 11.8) a, respectively. Health condition is listed. Shock is the only complication of both groups differed from each other in our study ($P = 0.030$), which indicated that patients with H7N9 induced ARDs from MSC group underwent more severe circulatory disturbances. Eventually, 24 patients in control group died, while 3 patients died in experimental group (MSC group). The MSC group had an significantly higher survival rate than control group (82.4% in MSC group vs. 45.5% in control group; $P = 0.006$).

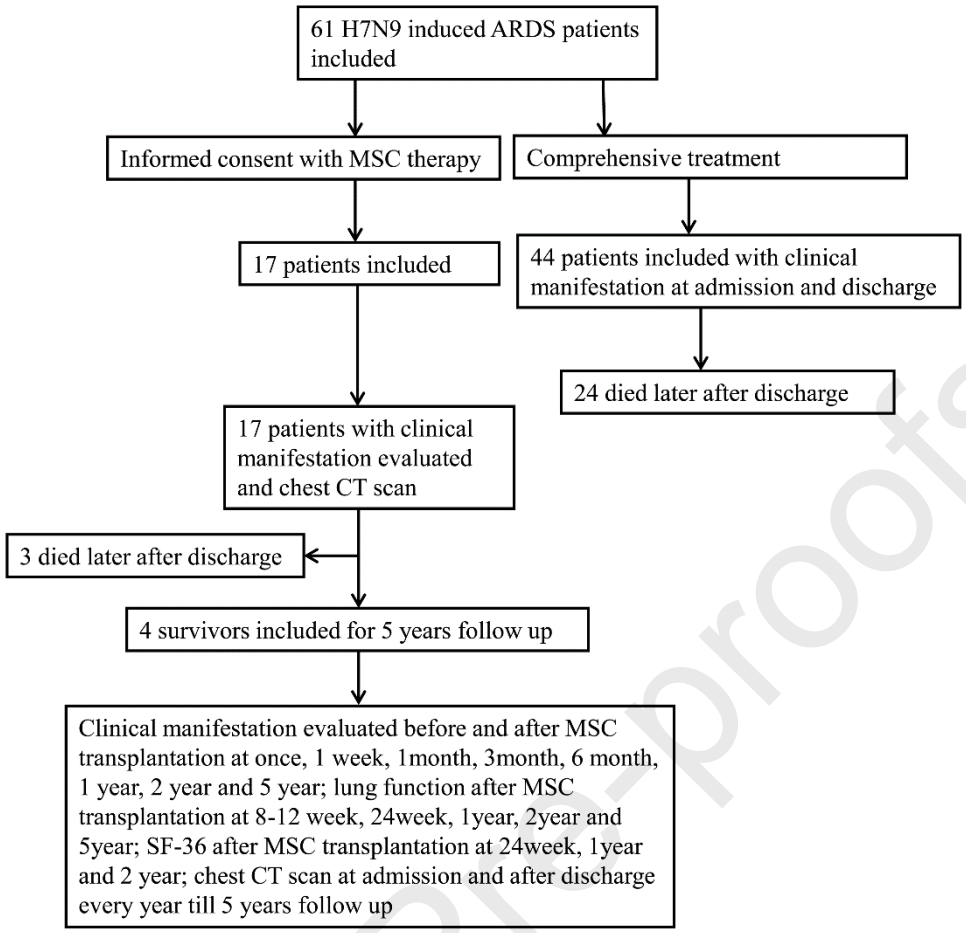

Fig. 1. The CONSORT diagram for the clinical trial of H7N9 infected patients. 44 patients with H7N9 induced ARDS were included as a control group and 17 patients with H7N9 induced ARDS were served as an experimental group with allogeneic, menstrual blood-derived MSC. MSC transplantation significantly lower the mortality compared with in control group. And laboratory tests of 4 H7N9-induced ARDS patients in MSC group in the follow-up for 5 years.

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

Baseline characteristics	Experimental group (N = 17)	Control group (N = 44)	*P*
Age	62.8 ± 14.4	61.6 ± 11.8	0.720
Underlying conditions, N (%)			
Hypertension	10(55.6)	23(52.3)	0.814
Diabetes	5(27.8)	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(5.6)	1(2.3)	0.507
Complications, N (%)			
Renal failure	1(5.6)	10(22.7)	0.152
Shock	12(66.7)	16(36.4)	0.030
Intestinal diseases	5(27.8)	5(11.4)	0.137
Double pneumonia	17(94.4)	41(93.2)	1.000

Treatment regimens, N (%)			
Antiviral agent	100(100)	100(100)	
Antibiotic therapy	14(77.8)	36(81.8)	0.732
Vasoactive drugs	12(66.7)	19(43.2)	0.093
Glucocorticoid therapy	9(50)	24(54.5)	0.745
Mechanical ventilation	14(82.4)	31(65.9)	0.207
ECMO	8(47.1)	14(31.8)	0.266
ALSS	13(72.2)	18(40.9)	0.025
CRRT	12(70.6)	16(36.4)	0.016
Death	3(16.7)	24(54.5)	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 MSC group and 19 patients in control group received vasoactive drugs attributed to the unstable circulation. The number of patients in MSC group who received glucocorticoid therapy was 9, and the number of patients in control group who received glucocorticoid therapy was 24. Fourteen patients received mechanical ventilation in MSC group, and 31 patients also received mechanical ventilation in control group. Eight patients from MSC group and 14 patients from control group were treated with ECMO. Thirty-one patients, including 13 from MSC group and 18 from control group were treated by ALSS. Twenty-eight patients including 12 from MSC group and 16 from control group received CRRT. The frequency of the standard strategies except ALSS and CRRT didn't differ from each other in our study.

4.3. Baseline clinical symptoms and laboratory features

As shown in Table 2, 58 of the H7N9 induced ARDS patients from MSC group and control group suffered from fever: 17 patients (100%) from MSC group and 41 patients from control group. A majority of patients from MSC group suffered from cough (88.9%), phlegm (72.2%), yellow sputum (27.8%), and dry cough (5.6%). Other patients from MSC group suffered from hemoptysis (16.7%), fatigue (50%), muscular soreness (33.3) and shortness of breath (77.8%). On the other hand, a majority of patients from control group suffered from cough (84.1%), phlegm (55.8%), yellow sputum (13.6%), and dry cough (0%). Other patients from control group suffered from hemoptysis (9.1%), fatigue (13.6%), muscular soreness (11.4%) and shortness of breath (31.8%).

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

Symptoms	Experimental group (N = 17)	Control group (N = 44)	Total number (N = 61)	*P*
Fever	17(100)	41(93.2)	58	0.553
Cough	16(88.9)	37(84.1)	53	1.000
Phlegm	13(72.2)	24(55.8)	37	0.232
Yellow sputum	5(27.8)	6(13.6)	11	0.271
Dry cough	1(5.6)	0(0)	1	0.290
Hemoptysis	3(16.7)	4(9.1)	7	0.404
Fatigue	9(50)	6(13.6)	15	0.007
muscular soreness	6(33.3)	5(11.4)	11	0.604
Shortness of breath	14(77.8)	14(31.8)	28	0.001

In Table 3, all the baseline of laboratory features showed no statistically significant differences in conventional blood indexes, inflammation index, liver function, serum creatinine level and creatine kinase in the two groups. Only the procalcitonin level is higher in control group than MSC

group, while the C-reactive protein level is similar in the two groups. This indicates that the patients included in the two group are comparable in our study. However, the routine blood indices between MSC group and control group are significantly different when the patients were discharged. The procalcitonin level was significantly higher in control group than MSC group (Table 4). Also, serum creatinine level was significantly higher in the control group than the MSC group (105.54 ± 96.52 vs. 63.00 ± 38.55, $P = 0.019$), showing more severe renal injury in critically ill patients. The levels of creatine kinase, prothrombin time, D-dimer are significantly higher in the control group compared to the MSC group. As the majority of the laboratory features in both groups are similar, the significant differences may attribute to the higher death rate of patients in the control group.

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

Laboratory tests	Experimental group (N = 17)	Control group (N = 44)	*P*
Blood routine			
White blood cell (10^9 L^{-1})	5.46 ± 3.2	5.54 ± 4.01	0.936
Neutrophils (10^9 L^{-1})	4.76 ± 3.01	4.60 ± 3.57	0.863
Lymphocytes (10^9 L^{-1})	0.49 ± 0.37	0.72 ± 1.40	0.498
Hemoglobin ($g \cdot L^{-1}$)	121.06 ± 22.83	124.86 ± 27.23	0.603
Platelet cell (10^9 L^{-1})	95.60 ± 52.91	131.97 ± 76.59	0.817
Inflammation index			
C-reactive protein ($mg \cdot L^{-1}$)	98.96 ± 97.03	124.56 ± 89.64	0.323
Procalcitonin	1.30 ± 2.19	7.77 ± 17.15	0.024
Liver function			
Albumin ($g \cdot L^{-1}$)	30.42 ± 5.59	29.81 ± 4.62	0.661
Alanine aminotransferase ($U \cdot L^{-1}$)	41.56 ± 25.50	61.61 ± 128.14	0.515
Aspartate aminotransferase ($U \cdot L^{-1}$)	63.17 ± 44.98	152.72 ± 416.70	0.369
TBIL	9.44 ± 4.78	12.45 ± 8.99	0.185
DBIL	5.11 ± 3.39	7.07 ± 6.80	0.251
Renal function			
Serum creatinine ($mmol \cdot L^{-1}$)	63.77 ± 24.41	106.68 ± 120.74	0.142
Myocardial enzymes ($U \cdot L^{-1}$)			
Creatine kinase	288.50 ± 285.39	818.47 ± 1671.28	0.188
LDH	515.67 ± 187.96	724.02 ± 433.25	0.055
Coagulation			
PT	12.65 ± 0.92	14.59 ± 8.92	0.364
D-dimer	7318.11 ± 5750.45	9934.19 ± 10624.10	0.330

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

Laboratory tests	Experimental group (N = 17)	Control group (N = 44)	*P*
Blood routine			
White blood cell (10^9 L^{-1})	9.62 ± 7.36	10.92 ± 11.97	0.671
Neutrophils (10^9 L^{-1})	7.34 ± 7.53	8.97 ± 10.93	0.566
Neutrophils (%)	68.53 ± 16.46	73.01 ± 20.29	0.412
Lymphocytes (10^9 L^{-1})	1.45 ± 0.73	1.29 ± 0.99	0.542
Lymphocytes (%)	20.07 ± 12.21	19.29 ± 17.97	0.868

Hemoglobin (g·L^{-1})	100.89 ± 13.10	99.44 ± 24.54	0.767
Red blood cell	3.39 ± 0.42	3.41 ± 1.09	0.915
Platelet cell (10^9 L^{-1})	201.72 ± 99.98	172.65 ± 162.89	0.486
Inflammation index			
C-reactive protein (mg·L^{-1})	44.85 ± 95.05	98.06 ± 96.82	0.054
Procalcitonin	1.47 ± 3.65	7.71 ± 12.20	0.005
Liver function			
Albumin (g·L^{-1})	36.09 ± 5.26	33.05 ± 8.68	0.174
Alanine aminotransferase (U·L^{-1})	32.28 ± 25.67	80.67 ± 84.48	0.001
Aspartate aminotransferase (U·L^{-1})	25.33 ± 16.14	158.14 ± 399.91	0.166
TBIL	22.94 ± 31.84	44.43 ± 67.64	0.204
DBIL	11.89 ± 22.07	27.50 ± 44.42	0.163
Renal function			
Serum creatinine (mmol·L^{-1})	63.00 ± 38.55	105.54 ± 96.52	0.019
Myocardial enzymes (U·L^{-1})			
Creatine kinase	52.21 ± 89.55	567.74 ± 1186.32	0.015
LDH	264.71 ± 114.35	942.20 ± 1987.96	0.212
Coagulation			
PT	11.76 ± 3.28	16.42 ± 7.66	0.002
D-dimer	4785.83 ± 4622.72	10463.00 ± 12774.32	0.015

4.4. The follow up of 4 patients with MSC transplantation

As shown in Table 5, the levels of hemoglobin were significantly upregulated after MSC transplantation, and the level of prothrombin time was downregulated according to current data. This indicated that MSC transplantation will not exert harmful effects in human body in the 5 years' follow up.

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

Blood routine	Before	After	1 week	1 month	3 months	6 months	1 year	2 years	5 years	*P*
White blood cell (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
Lymphocytes (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
Hemoglobin (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
Platelet cell (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										
C-reactive protein (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										
Albumin ($g \cdot L^{-1}$)	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
Alanine aminotransferase ($U \cdot L^{-1}$)	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
Aspartate aminotransferase ($U \cdot L^{-1}$)	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
Total bilirubin	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										
Creatine kinase	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 ($U \cdot L^{-1}$)										
Creatine kinase	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
Lactate dehydrogenase	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										
Prothrombin time	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	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

All of the patients with MSC transplantation were included in the indexes for assessing the lung function and followed up for 5 years (Table 6). Both ventilation and diffusion dysfunction persisted in the period of the acute stage, and we evaluated the lung function between year 1 to 5 of the follow up. There was no difference in the functions of FEV1, forced vital capacity (FVC), FEV1/FVC and FEF50% among the four patients during the following 5 years.

Table 6
Lung function tests of 4 H7N9-induced ARDS patients in MSC group in the further follow up for 5 years.

Lung function	8−12weeks	24 weeks	1 year	2 years	5 years	*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

Before MSC treatment, all patients showed ground-glass opacities and amalgamation at the onset of disease by chest radiography. We followed up on 4 patients with MSC treatment for 5 years, and we listed the following up data of one patient in our study. 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 they demonstrated pneumatocele and new nodes on CCT from 8−12 weeks (Fig. 2 and Fig. S1 in Appendix A). At 24 weeks and 1 year after MSC transplantation, all patients showed improvement on CCT.

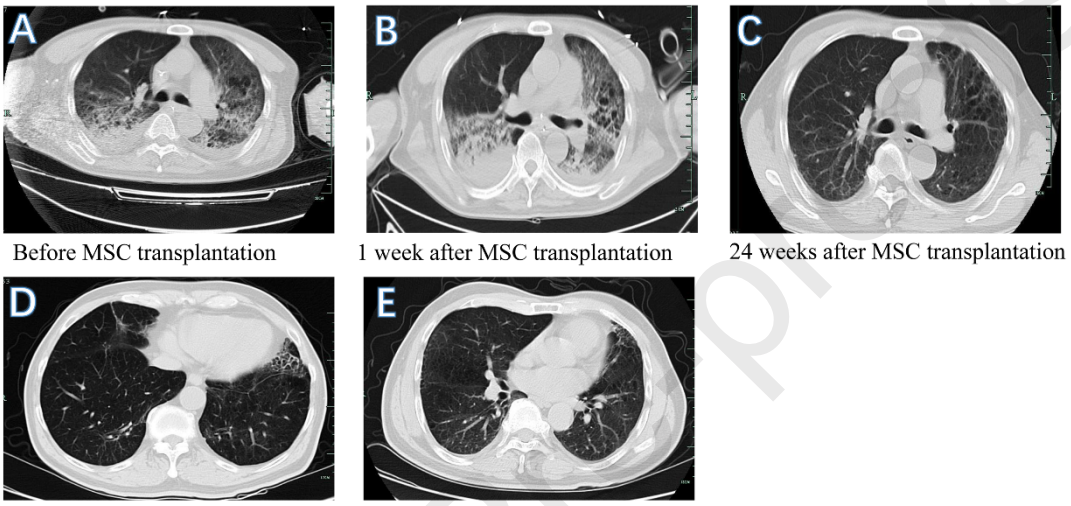

Fig. 2. Following-up of 4 patients in with MSC treatment for 5 years, and we listed the following up data of one patient in our study. Before MSC transplantation, some fibrillations were shown (A). Radiologic changes included air bronchogram, ground glass opacities, bronchiectasia, linear fibrosis, isolated areas of pleural thickening, and hydrothorax after MSC transplantation (B−E; 1 week, 24 weeks, 1 year, and 5 years). At 24 weeks and 1 year after MSC transplantation, all patients showed improvement on CCT.

All patients were lived in or near Hangzhou, Zhejiang Province, thus the SF-36 principle of these residents in Hangzhou was chosen for assessment of the patients with MSC transplantation. After following up for 2 years, we found that the scores for all elements of the SF-36 did not significantly differ (Table S1 in Appendix A). Therefore, all this data from following up with the patients indicated that MSC transplantation didn't influence the long-term survival quantity of patients.

5. Discussion

Patients suffering with H7N9 infection always produce similar symptoms including cough, fever, shortness of breath, and sputum. These patients rapidly developed 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 control group is 54.5%, however, the death rate of MSC group is 16.7%. No cases of pulmonary embolism occurred in any of the patients. This indicates that MSC therapy is a safe and effective treatment to rescue the 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 Zheng et al, the consistency regarding the tolerability and safety is encouraging to us.

Patients with ARDS had significant improvement on lung function at each follow-up. As with

the previously reported of ARDS patients [40], patient conditions between 1−6 months after discharge were significantly better than those after 6−24 months. A research on the long-term prognosis of ARDS survivors showed a mildly restrictive type of lung function tests with a moderate decrease in CO diffusion after 3 months' administration [41]. Additionally, pulmonary function in H1N1 infected patient is discovered to be almost normal, except for reducing spreading role in respiratory ability [42]. In the 1-year follow-up, fibrosis and pulmonary/ pulmonary parenchymal dysfunction are very common clinical phenomena in H1N1-associated severe ARDS infection. Over time, the imaging proved the significant improvements in lung function and fibrosis, and this improvement was particularly evident in the first 6 months after discharge from hospital [43]. Additionally, at the 3 months follow up, ground-glass opacities had significant improved over 85% patients [44]. However, there is no further significant differences about the interstitial fibrosis and ground-glass opacities after 1 year's visits [42]. These characteristics are consistent with those of survivors suffering with H7N9 infection in the current clinical trial.

In this investigation, it was found that when 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 again. After all, hundreds of people died from H7N9 in 2013. These survivors have obviously lower HRQoL than those of normal population, and it maybe a result from the deficiencies of social function and mental health. Moreover, a meta-analysis indicated that ARDS survivors can improve the function of HRQoL during the initial 6 months after discharge from hospital [45]. These reports indicated that the quality life of ARDS survivors infected with IAVs is rather worse than people who have no history of IAVs infection. Thus, we recommend that people emphasize caring for creating social interactions with these patients after recovery.

Currently, infection by COVID-19, a SARS-like virus, is widespread in Wuhan, even the rest of China [46,47]. It is surprising that COVID-19 has the ability of human-to-human transmission since the middle of December 2019 [48−50]. As of Feb 21, some 76662 cases have been reported globally, most of them in China, and the number of deaths has reached over 2230. Until now, thousands of infected patients are suffering serve ARDS without effective treatment. Lately, Xu et al. [30] have confirmed that the patient has severe pneumonia caused by COVID-19 according to pathological characteristics, and this patient died from severe infection with ARDS obtaining biopsy samples at autopsy. Which describes pathological features of COVID-19 associated ARDS that appears to be strikingly similar to H7N9-induced ARDS. Both H7N9 infected patients and COVID-19 infected patients share similar symptoms including cough, fever, shortness of breath, sputum, and dyspnea accompanied by ARDS or later pulmonary fibrosis, 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 a single-center study. With only 17 patients using MSC, we cannot guarantee every step is perfect at our phase with only one time of the clinical trial. Secondly, we should express that this is not a routine clinical trial owing to the H7N9 outbreak and no other better choice to treat these patients with severe ARDS. Therefore, they didn't want to have further visits, and some patients refused to attend, and even some did not complete follow up. Thus we are still concerned the long-term safety of MSC administration for treating H7N9 induced ARDS despite the lack of side effects observed in this clinical trial. Moreover, although some patients may have a potential lung infection in H7N9 patients, most of them are receiving other drugs without further examination, and we can't obtain the ideal comparison of lung functional indicators between the MSC group and the control group. Finally, the limitations of a small sample size are difficult to obtain the huge clinical data. Therefore, it is hard to conduct clinical studies in critically patients suffering with ARDS.

There are still some common side effects needed to be concerned before MSC application in the clinical medicine. Despite there are numerous promising results of MSC administration, long-term safety remains a matter of debate, especially hardly to managing the long-term follow up for all patients [51]. The other concern is that MSC not only has 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 GVHD), the variabilities of MSC quality from different donors and tissues are widely varies, and treatment protocols, doses and injection modes are inconsistent during experimental procedures [53]. All these factors may limit the therapeutic effect of MSC 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 ability to reduce inflammatory effects also defend against cytokine storm. Although our group has reported some clinical studies in H7N9 infected patients [6,12,15,36], understanding the detailed mechanism is still needed to reveal the potential for treating H7N9 induced ARDS. Along with our previous work [19,54,55], MSC has the ability to improve lung function through anti-inflammatory effects in acute injury lung in a mouse model. Thus, the underlying mechanism is probably that MSCs reduce the secretion of inflammatory factors. Although the clinical research of MSCs are 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 is still a problem even at 2 years after hospital discharge. Notably, MSC transplantation significantly lower the mortality. Additionally, no serious adverse effects are found after MSC administration during the periods of 5 years' visits in this study. We are currently conducting a clinical trial of 17 patients with moderate to severe ARDS, with a dominating concentration on long-term safety and a secondary concern on regulating respiratory system and improving the quality of life.

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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.

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 Tab of Animal Experimental Ethical Inspection of the First Affiliated Hospital, Collage 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).

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Highlights

1. Allogeneic menstrual blood-derived MSC transplantation significantly lower the mortality with H7N9 induced ARDS.
2. The first prospective and systematic report of H7N9 induced pneumonia to assess the health condition during the convalescent period.
3. MSC transplantation will not exert harmful effects in human body in the long-term follow up.
4. MSC-based therapy is an alternative method for treating COVID-19 induced severe ARDS.