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Wharton's jelly-mesenchymal stem cells treatment for severe COVID 19 patients: 1-year follow-up☆

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SUMMARY

Background: Recently, attention has been focused on mesenchymal stem cells (MSC) because of their unique ability to suppress inflammation induced by cytokine storms caused by COVID-19. Several patients have been successfully treated in this manner. After one year of treatment with Wharton's jelly-derived MSC injections, this study evaluated the safety and efficacy of injecting MSCs intravenously in patients with COVID-19.
Methods: This study treated four patients with severe COVID-19 with Wharton's jelly-derived mesenchymal stem cells. In this study, patients were followed up for routine tests, tumor markers, and whole-body imaging (spiral neck CT scan (with contrast), spiral chest CT scan (with & without contrast), and spiral abdominopelvic CT scan (with IV & Oral contrast)) one year after cell therapy.
Results: The results indicated that lymphocyte; lymph count significantly increased, and neutrophil, ESR, ferritin, and CRP significantly decreased. LDH showed a non-significant decrease (P-value<0.05). One year after the WJ-MSC injection, the tumor markers were normal, and no tumors were observed in patients after one year. Also, the CT scan result was normal.
Conclusions: In patients, no serious complications were observed after a one-year follow-up. After monitoring the patient via laboratory tests, tumor markers, and whole-body imaging, we concluded that the Wharton jelly-derived mesenchymal stem cells did not cause severe complications, including tumor formation, in severe COVID19 patients within a year. More clinical trials with higher sample sizes need to be performed on cell therapy with Wharton jelly-derived mesenchymal stem cells in the future.

1. Introduction

Coronavirus disease 2019 (COVID-19) has emerged as a global epidemic and has caused diverse clinical conditions, from asymptomatic carriers to severe acute respiratory distress syndrome (Huang et al., 2020; Tang et al., 2020; Xu et al., 2020). COVID-19 symptoms subside within 2 to 3 weeks, but approximately 10 % of patients experience symptoms several months after the infection. Long-term follow-up studies have been reported for severe COVID-19 patients discharged from hospitals (Huang et al., 2021; Wu et al., 2021). COVID19 is categorized into three categories based on the severity of the symptoms (Huang et al., 2020; Wu and McGoogan, 2020; Shi et al., 2020). Mild cases present symptoms such as fatigue, cough, fever, diarrhea, headache, and whether or not mild pneumonia is present. Dyspnea, decreased blood oxygen saturation, pulmonary infiltrates, acute respiratory stress, multiple peripheral ground-glass patches on both lungs, and so forth are symptoms of severe cases. Septic shock and respiratory failure are symptoms of critical cases. COVID-19 is estimated to have a

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mortality rate of 2.3 %, ranging from 6 to 41 days after the onset of symptoms (Shi et al., 2020; Wang et al., 2020).

Most cases are treated with supportive and symptomatic measures, but several antiviral agents, an antimalarial drug (chloroquine), and antibiotics have been used to treat milder and more severe cases. In addition to convalescent plasma therapy and mesenchymal stem cell therapy, other options have also been proposed to modulate the immune response in severely and critically ill patients (Shen et al., 2020; Leng et al., 2020; Orleans et al., 2020).

Mesenchymal stem cells can self-regeneration and differentiate into numerous types of cells (Meirelles et al., 2006; Chamberlain et al., 2007). Because MHC-I is not expressed to a high degree, and MHC-II is expressed in low numbers, mesenchymal stem cells are not immunogenic (Lee et al., 2014; Hass et al., 2011). That is why MSCs can be used for allogeneic cell transplantation. Several disease models have shown that MSCs can modulate the immune system and regenerate tissue (Corcione et al., 2006; Le Blanc and Davies, 2015; Wang et al., 2013; Forbes et al., 2014). There have been significant developments in stem cell technology with promising therapeutic prospects for treating various diseases, such as respiratory diseases (Fatima and Nawaz, 2015). In a previous study in 2020 conducted by our research team, Wharton Jelly-derived mesenchymal stem cells were performed in 5 patients with severe forms of COVID19. After a 1-month follow-up, Wharton's jelly-derived stem cells were safe and well-tolerated by the patient (Saleh et al., 2021).

This study examined patients for one year for routine laboratory tests, tumor markers, and whole-body imaging examinations.

2. Materials and methods

Five patients with severe COVID-19 were treated with Wharton Jelly-derived mesenchymal stem cells in a previous pilot study at Shariati Hospital. By signing the consent form, patients entered the study from July 21, 2020, to August 21, 2020. HWj-MSC cells prepared by cell Tech Pharmed were injected into patients in 150 × 106 cells via IV in 3 doses on days 0, 3, and 6 (Saleh et al., 2021). In the previous study, these patients were monitored after cell injection for 0, 3, 6, and 14 days (myocardial enzymes, hematology parameters, biochemistry, and inflammatory tests) and one year after cell therapy. In this study, patients (4 patients and one patient's information is not available) were followed up for routine tests, tumor markers, and whole-body imaging (spiral neck CT scan (with contrast), spiral chest CT scan (with & without contrast) and spiral abdominopelvic CT scan (with IV & Oral contrast)) one year after cell therapy. The Ethics Committee approved this study at the Tehran University of Medical Sciences (IR.TUMS. MEDICINE.REC.1400.035).

One year after cell therapy, all patients were evaluated for adverse events through clinical examinations, measurements of vital signs, and routine tests. One year after cell therapy, the following parameters were monitored: heart rate, respiration, blood pressure, body temperature, and oxygen saturation. Routine blood tests, biochemical indicators, myocardial enzymes, and Inflammatory Markers were performed before and after one year of cell therapy.

Beta-hCG, AFP, CEA, CA125, CA19-9, CA15-3, TPSA, and FPSA levels were measured in serum samples one year after cell therapy (ECL, HITACHI).

3. Statistical analysis

GraphPad Prism version 8.00 (GraphPad Software, Inc.) analyzed the data. We compared the means of two related groups using paired *t*-tests and one-way ANOVA for multi-group comparisons. The data were analyzed as mean ± S.D. $P < 0.05$ was considered to be statistically significant.

Table 1
Demographic data's and physical examination.

	Patient 1		Patient 2		Patient 3		Patient 4	
Gender	Female		Female		Male		Male	
Age	50–59		50–59		50–59		40–49	
Weight	94		70		88		95	
Initial vital sign	Day 0 before cell therapy	1 year after cell therapy	Day 0 before cell therapy	1 year after cell therapy	Day 0 before cell therapy	1 year after cell therapy	Day 0 before cell therapy	1 year after cell therapy
RR breaths/min	22	15	28	18	42	15	36	12
PR beats/min	71	75	92	84	89	72	66	90
Sys BP, mm Hg	141	100	103	148	124	100	139	130
Dias BP, mm Hg	76	60	71	100	89	60	90	80
So2 (without oxygen mask)	87	98	70	98	79	95	80	98
Other Physical examination	51 years old woman infected by COVID19 with severe lung involvement, she was a candidate for MSC therapy	One year after the MSC transplant, She is well with No problem. Ph/E (Lung: clear, Heart: Normal)	53 years old woman infected by COVID19 with severe lung involvement, she was a candidate for MSC therapy	One year after the MSC transplant, She is well with No problem. Ph/E (Lung: clear, Heart: Normal)	55 years old man infected by COVID19 with severe lung involvement, he was a candidate for MSC therapy	One year after the MSC transplant, He is well with No problem. Ph/E (Lung: clear, Heart: Normal)	45 years old man infected by COVID19 with severe lung involvement, he was a candidate for MSC therapy	One year after the MSC transplant, He is well with No problem. Ph/Æ (Lung: clear, Heart: Normal)
Diagnosis	COVID 19	Fully recovered	COVID 19	Fully recovered	COVID 19	Fully recovered	COVID 19	Fully recovered

Table 2
Laboratory tests (base, Day3, Day6, Day14 & 1 year).

Variables		Patient 1					Patient 2					Patient 3					Patient 4				
		Day0	Day3	Day6	Day14	Year 1	Day0	Day3	Day6	Day14	Year 1	Day0	Day3	Day6	Day14	Year 1	Day0	Day3	Day6	Day14	Year 1
Routine blood tests	Normal range																				
WBC count ($\times 10^9$/L)	3400 - 12,500	10,940	14,910	16,710	14,220	7500	9600	7560	10,620	8050	5400	10,400	11,040	10,950	11,630	6200	6100	12,740	10,050	9040	7190
Hb (g/L)	M:14–18	12.1	12.7	15.1	13.7	12.5	11.5	11	11	13.5	13	13.1	14.2	13.5	15.1	15	14.7	15.1	14.4	13.8	16.9
PLT count ($\times 10^9$/L)	F:12–16	146	195	227	218	204	233	321	428	295	220	287	243	192	205	228	307	328	183	189	226
Neutrophil (%)	150,000-450,000	NA	88	88	70	54	90	80	83	62	50	90	82	70	71	54	86	91	71	81	57
Lymphocyte (%)	45–75	NA	2	10	19	39	4	9	11	26	38	5	10	20	20	33	8	2	21	14	35
LYM count ($\times 10^9$/L)	20–40	NA	298.2	1671	2702	2925	384	680.4	1168.2	2093	2052	520	1104	2190	2326	2046	640	254.8	2110.5	1265.6	2517
ESR	M: 0 to 20 F: 0 to 25	96	73	23	26	20	104	NA	NA	51	15	74	9	25	10	6	37	5	64	17	1
Myocardial enzymes																					
LDH (U/L)	240–480	723	939	462	374	269	860	483	427	545	350	542	465	392	398	313	1458	1117	615	417	354
Biochemical indicators																					
Total Bili (mg/dl)	0.1–1.2	0.26	0.7	1	0.6	0.7	1.1	0.54	0.43	0.9	0.8	0.7	0.6	0.7	1.3	0.8	1.6	1.6	1.6	0.9	1
Direct Bili (mg/dl)	Up to 0.3	0.1	0.3	0.3	0.1	0.2	0.3	0.2	0.02	0.1	0.1	0.1	0.1	0.2	0.2	0.3	1.2	0.6	0.3	0.2	0.3
ALT (U/L)	M:up to 41	55	29	40	43	11	98	41	42	39	21	16	43	30	11	15	136	106	55	75	29
AST (U/L)	F: up to 31	23.5	20	25	20	17	68	47.5	25	18	26	19	40	15	35	18	145	50	29	27	23
BUN (mmol/L)	M:up to 38	6	23	24	16	13	23	54	43	21	14	25.2	16	21	21	16	25	14	11	11	11
Cr (μmol/L)	F: up to 31	0.8	0.8	0.7	0.8	0.6	0.5	0.9	1	1.1	0.74	0.9	0.8	1.1	0.9	0.8	0.8	0.7	0.8	0.7	1
Inflammatory markers																					
CRP	UP TO 10	60.5	6	3	0.48	2	107	101	20	3.84	2	87	53.5	24.5	4.44	3.9	45	82	35	1.47	2
Ferritin	M: 24 to 336 F: 11 to 307	1979	959	231	169	55	798	986	686	659	120	896	707	600	500	142	1087	2666	742	878	229

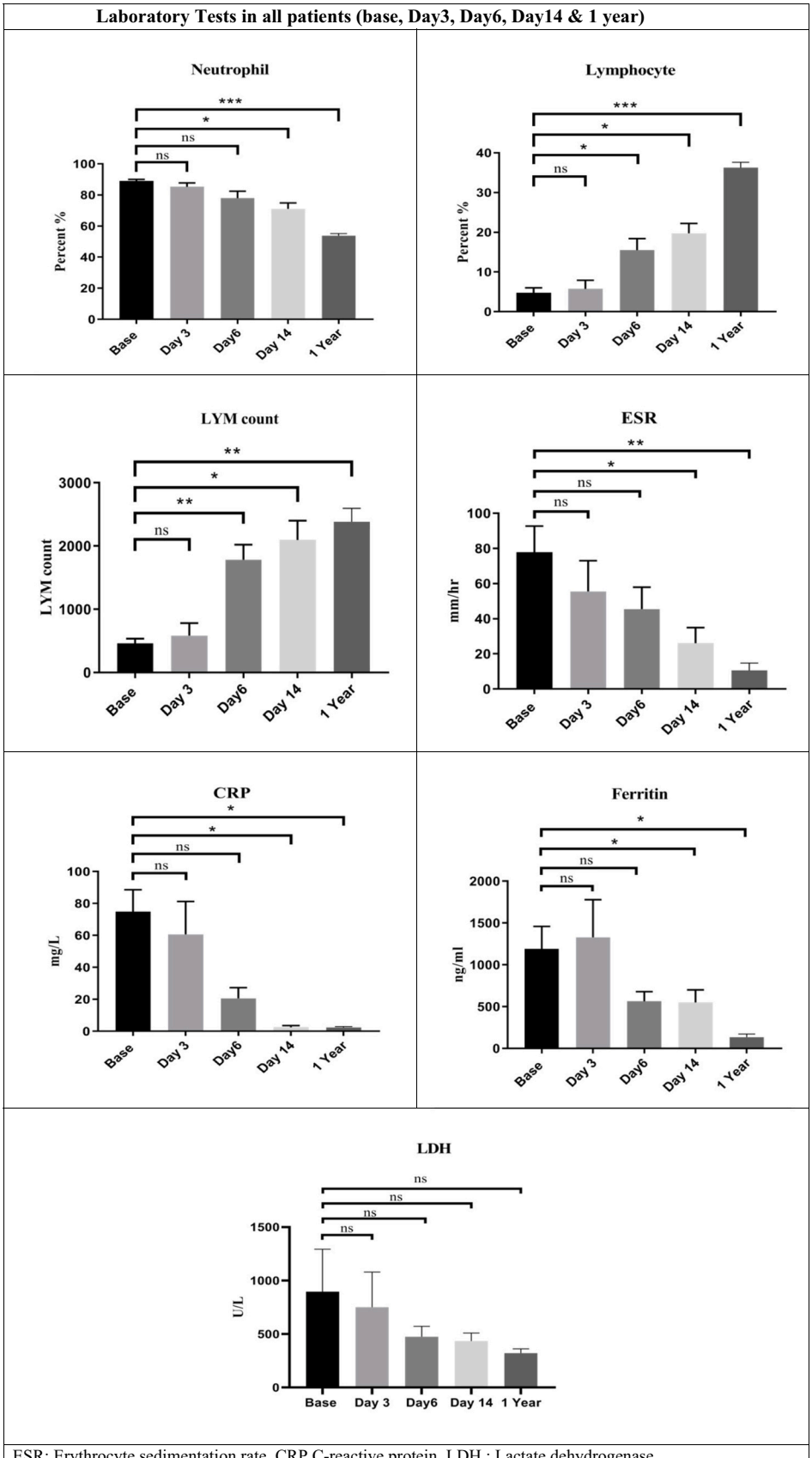


Fig. 1. Laboratory tests at day 0, 3, 6, 14, and 1 year after WJ-MSC injection.

Table 3
Tumor marker.

Variables		Patient 1	Patient2	Patient 3	Patient 4
Tumor marker	Gender Normal range	Female	Female	Male	Male
beta-hCG	F:6–24 M: up to 2 micIU/ml	<0.1	1.59	<0.1	<0.1
AFP	0.89–8.78 ng/dl	1.23	6.14	2.3	1.71
CEA	Smoker up to 10 Nonsmoker up to 5 ng/ml	1.04	2.34	2.49	3.21
CA125	<46 U/ml	7.2	8.7	17.2	13.8
CA19-9	0 and 37 U/ml	2.91	22.32	12.04	6.06
CA15-3	<30 U/ml	14.4	17.7	23.4	29.8
TPSA	0–4.0 ng/ml	0	0	0.6	0.74
FPSA	up to 2 ng/ml	0	0	1	0.6

Beta-HCG: Beta-human chorionic gonadotropin, AFP: Alpha-fetoprotein, CEA: Carcinoembryonic antigen, CA125: Cancer antigen 125, CA19-9: Cancer antigen 19-9, CA15-3: Cancer antigen 15-3, TPSA: Total prostate-specific antigen, FPSA: Free prostate-specific antigen.

4. Results

Cell therapy was administered to patients using WJ-MSC in this research. Heparin and dexamethasone were administered to all patients as common treatments. Demographic data of patients such as gender, age, weight, Initial vital signs at day 0 and 1 year after cell injection, Physical examination, and diagnosis are listed in Table 1. It was found that no serious complications were associated with WJ-MSC stem cells in this study. Wj-MSC is safe and tolerable for patients, as indicated above.

Routine laboratory tests such as hematology (WBC, PLT, Hb, neutrophil and lymphocyte percentage, absolute lymphocyte count, and ESR), myocardial enzymes (LDH), biochemical tests (Cr, BUN, ALT, AST, total and direct bilirubin), inflammation tests (ferritin, and CRP) were conducted for all patients on days base, 3, 6, 14, and 1 year after cell therapy which are shown in Table 2. Testing results have improved over time, according to the results. We statistically examined seven of these tests that are more important for COVID-19 patients of our study, including LDH, neutrophil, lymphocyte, lymph count, CRP, ESR, and ferritin, among which lymphocyte; lymph count showed a significant increase and neutrophil, ESR, ferritin, and CRP showed a significant decrease. LDH showed a non-significant decrease (P-value<0.05) (Fig. 1).

This research examined tumor markers (beta-hCG, AFP, CEA, CA125, CA19-9, CA15-3, TPSA, and FPSA) and whole-body imaging one year after cell therapy, shown in Table 3 and Fig. 2a & b, respectively. The results show 1 year after WJ-MSC injection, tumor markers were normal, and no tumors were observed in patients after one year (Table 3).

Spiral neck CT scan (with contrast), spiral chest CT scan (with & without contrast), and spiral abdominopelvic CT scan (with IV & Oral contrast) results were analyzed by an expert radiologist. One year after cell therapy, in all patients: (Fig. 2a & b).

In the spiral neck CT scan, thyroid lobes were normal. Muscular structures have normal shapes and configurations. Vascular structures were intact with smooth walls. No significant cervical LAP was depicted.

The spiral chest CT scan showed no parenchymal abnormalities in both lungs. All patients showed no signs of pulmonary fibrosis. No pleural effusions were seen. No significant mediastinal LAP was noted. Heart and great vessels size were within normal limits. Moreover, there was no abnormal post-contrast enhancement.

In the spiral abdominopelvic CT scan, the Liver was within normal limit, and no intrahepatic focal mass lesion was noted. Gall bladder, bile ducts, spleen, kidneys, and pancreas appeared normal. No obvious abdominopelvic abnormality was found.

5. Discussion

The growing evidence of MSCs' therapeutic effectiveness has been shown in preclinical and clinical studies. Many studies indicate that the short-lived viability of MSCs after the injection may also account for low engraftment (Wang et al., 2014; Von Bahr et al., 2012). MSCs have started to appear as a new treatment option for COVID-19 patients (Hashemian et al., 2021; Feng et al., 2020). After MSCs are injected, many of them are trapped in the lungs, resulting in reduced cells that reach the target site (Mäkelä et al., 2015). Since the most common infection of the COVID-19 virus is the lung, intravenous injection of these mesenchymal stem cells is beneficial in these patients.

However, new therapies, such as cell therapy, face several challenges. The tumorigenic properties of stem cells are essential to consider when using them. Several studies have evaluated the risk associated with tumorigenesis following stem cell transplantation. Both stem cells, and tumor cells can survive, proliferate, and prevent death (Bellagamba et al., 2016). After one year of cell therapy, we evaluated beta-hCG, AFP, CEA, CA125, CA19-9, CA15-3, TPSA, and FPSA. We did not include any patients with cancer diagnoses in this study. Therefore, we cannot correlate the elevation of these biomarkers with preexisting tumorigenesis conditions.

There is evidence that cancer biomarkers, such as CEA, and CA, are elevated during various inflammatory conditions of the lungs. For instance, smoking increases CEA levels, and chronic obstructive pulmonary disease increases CA125 levels (Stockley et al., 1986; Barouchos et al., 2015).

In this study, there were no complications, including tumor formation. Tumor marker results besides whole-body imaging demonstrate the safety of Wharton jelly-derived mesenchymal cells after one year.

In another study, in line with our safety results on a large scale, UC-MSC cells were used in patients with severe COVID-19. These patients were monitored for one year. They concluded that administering UC-MSCs to severe COVID-19 patients for some time could reduce lung

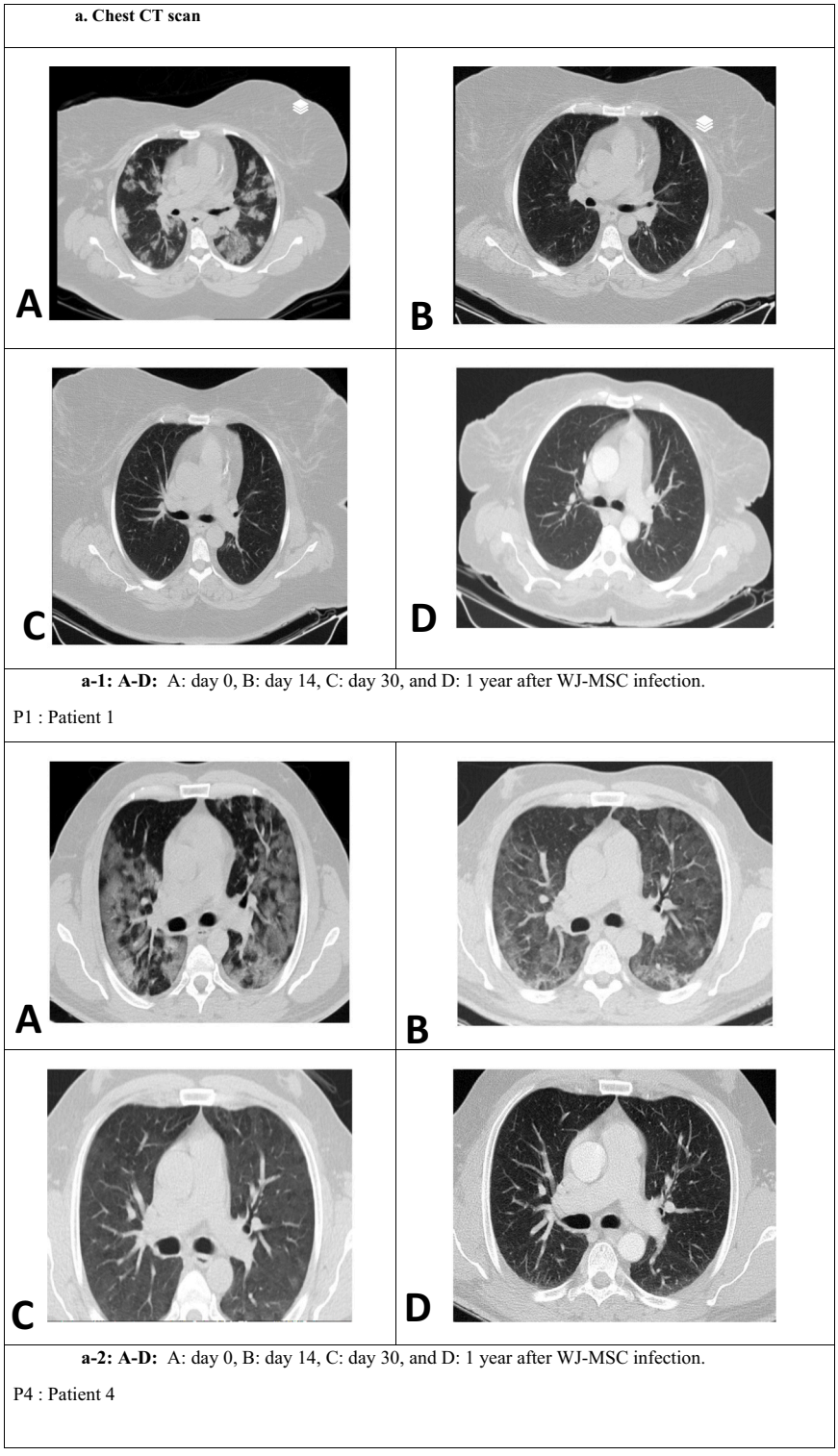
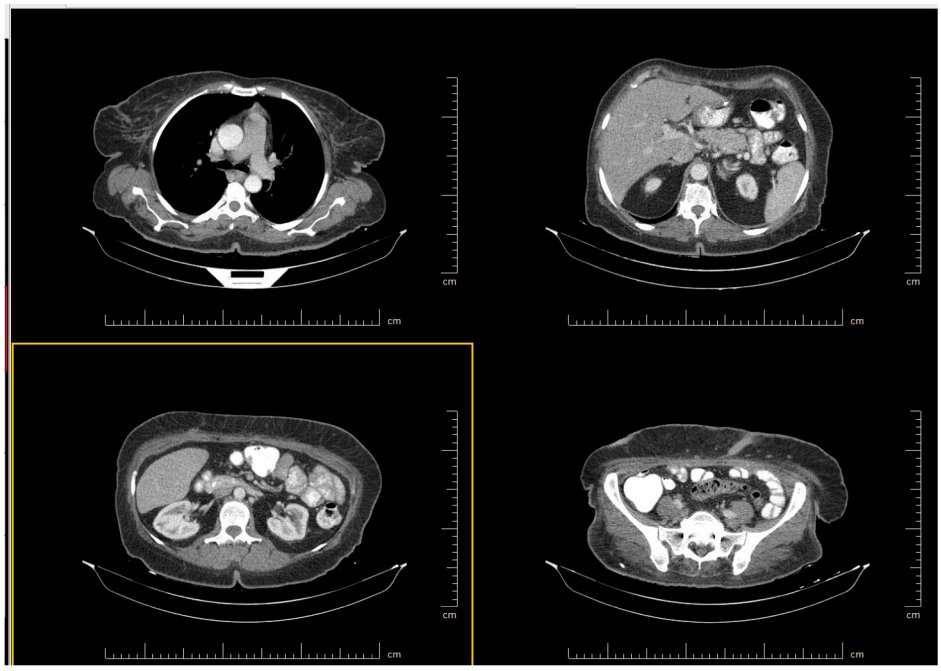


Fig. 2. a. Chest CT scan.
a-1: A-D: A: day 0, B: day 14, C: day 30, and D: 1 year after WJ-MSC infection.
P1: Patient 1.
a-2: A-D: A: day 0, B: day 14, C: day 30, and D: 1 year after WJ-MSC infection.
P4: Patient 4.
b. CT scan of thoracic and abdominopelvic with contrast.
b-1: CT scan of thoracic and abdominopelvic with contrast: No pathology is seen.
Follow up 1 year chest CT scan, revealed complete resolution of parenchymal involvement without any Sequela.
P1: Patient 1.
b-2: CT scan of thoracic and abdominopelvic with contrast: No pathology is see.
Follow up 1 year chest CT scan, revealed complete resolution of parenchymal involvement without any Sequela. P4: Patient 4.

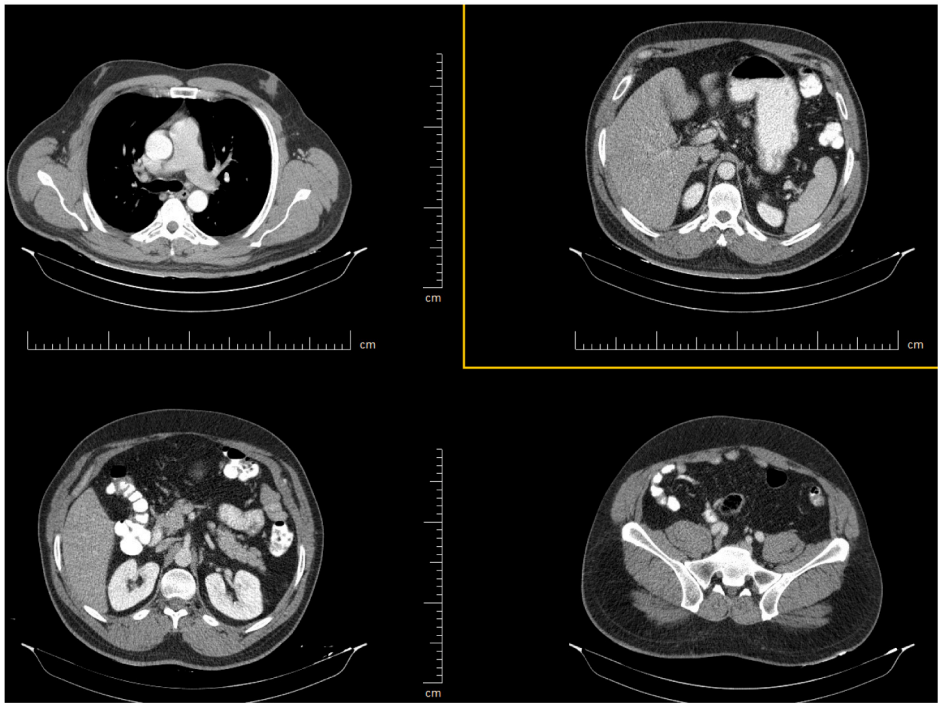
b. CT scan of thoracic and abdominopelvic with contrast



b-1: CT scan of thoracic and abdominopelvic with contrast: No pathology is seen.

Follow up 1 year chest CT scan, revealed complete resolution of parenchymal involvement without any Sequela.

P1 : Patient 1



b-2: CT scan of thoracic and abdominopelvic with contrast: No pathology is seen .

Follow up 1 year chest CT scan, revealed complete resolution of parenchymal involvement without any Sequela.P4 : Patient 4

Fig. 2. (*continued*).

lesions and offer good symptom improvement, indicating that UC-MSC administration as adjunctive therapy for COVID-19 patients is feasible (Shi et al., 2022).

6. Conclusion

This study showed that cell therapy using Wharton jelly-derived mesenchymal stem cells after one year did not have serious complications, including tumorigenesis, and the patient tolerated the patient well. It is best to do this study on a larger scale and do more research on tumor formation.

Abbreviation

WJ-MSC	Wharton's jelly derived MSCs
COVID-19	coronavirus disease 2019
ALT	alanine aminotransferase
AST	aspartate aminotransferase
Cr	creatinine
CRP	C-reactive protein
CT	computed tomography
MSCs	mesenchymal stem cells
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

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Ethics approval and consent to participate

Written informed consent was obtained from each patient or the patient's legally authorized surrogate before the conduct of study-specific procedures.

Consent for publication

Not applicable.

Code availability

Not applicable.

CRediT authorship contribution statement

MS proposed initial idea, study design and writing of the manuscript. MS, AAV, LA, NA, MB, AAS and JV were responsible for the reference selection and writing of the manuscript. MS, NA, MB, and LA took care of the patients and performed the follow-up checks. MS collected and analyzed the data. MS and LA analyzed the CT. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

All of the data generated and analyzed during this study are included in our manuscript.

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