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CLINICAL COURSE OF COVID-19 PATIENTS UNDER MESENCHYMAL STEM CELL THERAPY

MEZENKİMAL KÖK HÜCRE TEDAVİSİ UYGULANAN COVID-19 HASTALARININ SEYRİ

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ABSTRACT

Objective: Several countries have used mesenchymal stem cells (MSCs) in clinical trials for treating Coronavirus-19 (COVID-19) patients, considering their therapeutic effects through tissue repair and anti-inflammatory mechanisms. This study aimed to investigate the early effects of MSC application in COVID-19 pneumonia patients on clinical and inflammatory parameters and life expectancy.
Material and Method: We retrospectively analyzed 164 unvaccinated patients with COVID-19 pneumonia (all age groups) who had applied to the Republic of Turkiye, Ministry of Health, Department of Tissue, Organ Transplantation, and Dialysis Services and received the MSC application from March 1, 2020 to March 1, 2021.
Results: Using the Kaplan Mayer survival analysis, the cut-off age (which significantly increased the survival risk) was found to be 61 years. Females had a 1.56 times higher risk of death than males. Sixty-eight percent (113/164) of the patients had a comorbidity, which increased the risk of death by 1.58 times compared to those without any comorbidity. The presence of coronary artery disease increased the risk of death by 1.79 times. Further, the risk of death was 7 times higher in intubated patients than in those who were not (95% CI: 3.72–13.17). Unfortunately, 64% (106/164) of the patients died. Lastly, there was a statistically significant increase in the post-MSC treatment median Sequential Organ Failure Assessment Score (SOFA) score values at the time of application, on days 3, 7, 14, and until the end (discharge/exitus).
Conclusion: This study was conducted with unvaccinated patients and MSC treatment for COVID-19-related pneumonia is not adequately effective.

Keywords: Coronavirus, COVID-19, mesenchymal stem cell, mortality, survival

ÖZ

Giriş: Birkaç ülke, doku onarımı ve anti-inflamatuar mekanizmalar yoluyla terapötik etkilerini göz önünde bulundurarak, Koronavirüs-19 (COVID-19) hastalarını tedavi etmek için klinik deneylerde mezenkimal kök hücreleri (MKH) kullanmıştır. Bu çalışma, COVID-19 pnömoni hastalarında MKH uygulamasının klinik ve inflamatuar parametreler ve yaşam beklentisi üzerindeki erken etkilerini araştırmak amaçladı.
Gereç ve Yöntem: Türkiye Cumhuriyeti Sağlık Bakanlığı Doku, Organ Nakli ve Diyaliz Hizmetleri Daire Başkanlığı'na başvuran ve 1 Mart 2020 - 1 Mart 2021 tarihleri arasında MKH uygulaması için başvurusu olan COVID-19 pnömonisi (tüm yaş grupları) olan aşılanmamış 164 hastayı geriye dönük olarak inceledik.
Bulgular: Kaplan Mayer sağkalım analizi kullanılarak, kırılım yaşı (hayatta kalma riskini önemli ölçüde artıran) 61 yıl olarak bulundu. Kadınlar erkeklere göre 1.56 kat daha fazla ölüm riskine sahipti. Hastaların %68'inde (113/164) komorbidite mevcuttu ve bu komorbiditesi olmayanlara göre ölüm riskini 1,58 kat artırıyordu. Koroner arter hastalığı varlığı ölüm riskini 1,79 kat artırdı. Ayrıca, entübe hastalarda entübe olmayanlara göre ölüm riski 7 kat daha yüksekti (%95 GA: 3.72-13.17). Maalesef hastaların %64'ü (106/164) öldü. Son olarak, MKH sonrası tedavi medyan Sıralı Organ Yetmezliği Değerlendirme Skoru (SOFA) değerlerinde uygulama sırasında, 3, 7, 14. günlerde ve sonuna kadar (taburcu/ölüm) istatistiksel olarak anlamlı bir artış oldu.
Sonuç: Bu çalışma aşılanmamış hastalarla yapılmıştır ve COVID-19 ile ilişkili pnömoni için MKH tedavisi yeterince etkili değildir.

Anahtar Kelimeler: Koronavirüs, COVID-19, mezenkimal kök hücre, mortalite, sağ kalım

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INTRODUCTION

Coronavirus-19 (COVID-19) was first identified in Wuhan, China in December 2019 and as it continued to mutate, it became a pandemic that spread globally. Initially, the disease led to extensive admissions to the emergency service with concomitantly high mortality rates, which overwhelmed the emergency clinic physicians as well as the patients and their relatives. Thus far, no COVID-19-specific drug is available for treating infected patients; meanwhile, drug, and vaccine studies have continued to look for definitive treatment (1). Different treatment strategies have been applied, especially in severe cases, but an absolute effective and safe treatment has not yet been found, and the search is ongoing due to the associated high mortality and morbidity (1).

Mesenchymal stem cells (MSCs) have reportedly strong immunomodulatory properties; accordingly, it is proposed that MSCs may be beneficial in mitigating or even preventing a cytokine storm (2). Essentially, MSCs exert a positive immunomodulatory effect and have differentiation properties (3). Most of them secrete cytokines by a paracrine effect or can cause immunomodulation by directly affecting the immune cells (4). and these effects are triggered via Toll Like Receptor (TLR) receptor activation (5,6). MSCs are powerful cells that have less immunogenicity and produce a variety of paracrine factors, including antimicrobial peptides, growth factors and anti-inflammatory proteins (6,7).

Studies conducted on MSCs over the last decade have boosted expectations for both patients and physicians regarding MSCs as a treatment modality (7). MSCs are obtained from different body tissues, with bone marrow, umbilical cord, placenta, and adipose tissue being the main sources (8,9). Bone marrow (BM)-derived MSCs are most commonly used in clinical trials; however, the number, differentiation potential, and maximum lifetime of MSCs in BM decrease as age increases (4,9,10). In recent years, oil-derived MSCs have gained significant attention due to the ease of obtaining and storing them in cell banks. (11).

In several experimental studies, intratracheally and intravenously administered BM-derived MSCs accelerated lung repair, restored alveolar fluid clearance, and improved arterial oxygenation (12-15). The aforementioned effects have ensured their extensive use in cell-centered therapeutic trials within preclinical and clinical research (12-15). The preclinical data for MSCs suggest that they are not only effective for acute lung injury caused by bacterial infections but also provide therapeutic benefits in acute traumatic lung injury (16). Although only a small proportion of MSCs were localized in the damaged lung, the administration of mouse BM-derived MSCs normalized the level of pro-inflammatory cytokines in a murine model of bleomycin-induced lung injury (17).

Many studies have demonstrated its reliability for graft versus host disease (GVHD), systemic lupus erythematosus (SLE), and other immune-mediated inflammatory diseases (18,19). All possible therapeutic agents are being tested against COVID-19 disease, and MSC application has also been used within the scope of clinical trials and research projects in Turkiye. It is critical to know the treatments and practices used in emergency services (where the patients receive their first treatments), inpatient services, and even intensive care units. Ensuring appropriate communication between different doctors working in the emergency department, who are mostly prime responders to hospital admissions, will have a significant impact on treatment compliance.

Our study was conducted to evaluate the effects of MSC application in COVID-19 pneumonia in terms of the change in clinical and laboratory parameters, and life expectancy recorded in the data system of the Republic of Turkiye, Ministry of Health, Department of Tissue, Organ Transplantation, and Dialysis Services after the application.

MATERIALS AND METHODS

Study participants and design

Between March 2020 and March 2021, patients treated for COVID-19 pneumonia, to Universities or Training and Research Hospitals in Turkiye were retrospectively analyzed. The study started after the approval from ethics committee. Patients in all age groups who received permission to have MSC application from the Department of Tissue, Organ Transplantation and Dialysis Services were selected. All patients were unvaccinated against COVID-19.

Patient selection:

COVID-19 patients who were diagnosed with reverse transcription polymerase chain reaction (RT-PCR) and received treatment with a combination of Standard medical treatment and MSCs included in this study.

Patients given MSC treatment approval by the Department of Tissue, Organ Transplantation and Dialysis Services, according to the recommendations of the Turkish Ministry of Health's Science Committee.

Pregnancy, presence of malignant tumor, history of allergy, additional treatments (ie Intravenous Immunoglobulin, Plasmapheresis, IL-6 receptor antagonists) were determined as exclusion criteria. The flow chart of the patients to be included in the study is given in Figure 1.

Applied treatments:

According to the Science Committee of the Turkish Ministry of Health, hydroxychloroquine and Favipiravir (loading dose of 1600 mg twice daily on 1st day and followed by 600 mg twice daily for 4 days) should be given to all COVID-19 patients with severe pneumonia or with persistent fever despite hydroxychloroquine therapy.

If there is no contraindication, 1x40 mg/day enoxaparin subcutaneous was started as prophylaxis in all patients. In the case of severe pneumonia, 2x40mg/day enoxaparin was

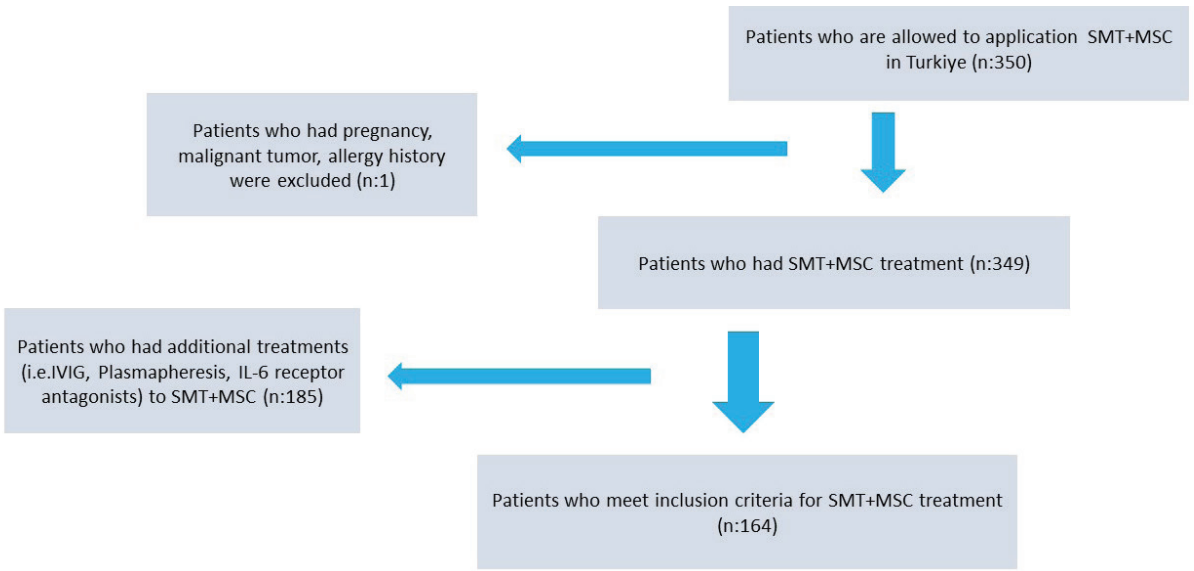

Figure 1: The flow chart of the patients who included in the study

used if the D-dimer level was above 1000 ng/mL, the body mass index was above 40 kg/m2 and there was acute venous thromboembolism.

For MSC treatment, mesenchymal stem cells were prepared from umbilical cord or adipose tissue and $1x10^6$ or $10x10^6$ cells/kg was administered each time, intratracheally or intravenously once or twice during the course of treatment according to the decision of the intensive care director.

Data collection

Patient data regarding demographic information, clinical scores, laboratory (inflammatory parameters), 75-day mortality follow-up and length of hospital stay recorded with the Ministry of Health's information systems were scanned.

Statistical analysis

We determined the age cut point that significantly discriminating survival status of the study subjects using Kaplan Meier survival analysis, and then categorized patients' ages based on the cut point. Furthermore, the effect of age category, gender, and presence of comorbidities on patients' survival were assessed using Kaplan Meier Test.

Sequential Organ Failure Assessment Score (SOFA) scores and C Reactive Protein (CRP) levels of patients at 3rd, 7th and 14th days after mesenchymal stem cell administration were compared using Friedman Test. Post hoc pairwise comparisons were conducted using Durbin-Conover Test. Results were considered statistically significant if the p value was less than 0.05. Jamovi version 1.6.18 was used for statistical analyses.

RESULTS

164 patients were included in this study. The demographic and clinical information of our study patients is presented in Table 1. The mean age of male and female patients were compared. As per the Kaplan-Meier survival analysis, the cut-off age, which significantly increases the survival risk, was also 61 years. Furthermore, the risk of death was 1.72 times higher in individuals over the age of 61 years as compared to those over the age of 61 years (hazard ratio (HR) = 1.72, 95% confidence intervals, CI: 1.17–2.54; p=0.006) (Table 2). Female patients with COVID-19-related pneumonia had a 1.56 times greater risk of death (HR =1.56, 95% CI: 1.00–2.43) than males (median survival: 20.5 years vs. 29 years) (Table 2).

Sixty-eight percent of the patients (n=113) had a comorbid disease; among these, 46% (n=76) had hypertension, 32% (n = 54) had diabetes mellitus, 14% (n=24) had coronary artery disease, and 11% (n=18) suffered from chronic obstructive pulmonary disease (Table 1). The presence of comorbidity increased the risk of death 1.58 times (HR=1.58, 95% CI: 1.03–2.44; median survival: 25 vs. 34 days) (Table 2). The presence of coronary artery disease as a comorbid disease increased the risk of death 1.79 times (HR=1.79, 95% CI: 1.10–2.92; median survival: 20 vs. 29 days) (Table 2, Figure 2).

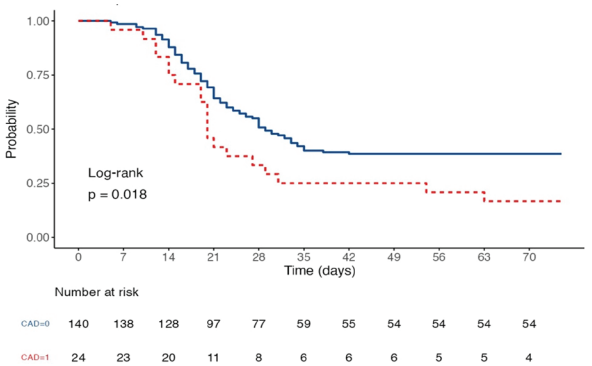

Figure 2: The correlation between Coronary Artery Disease (CAD) and survival as a result of Kaplan Meier survival analysis

Table 1: Demographic and clinical characteristics of COVID-19 pneumonia patients who underwent mesenchymal stem cell application

	Outcome	
	Death	**Alive**
Age, mean (SD)	62.7 (11.7)	58.6 (13)
Gender (Female/Male)	26/80	8/50
Admission		
Emergency service admission	67	31
External service transfer	11	6
Polyclinic admission	27	21
Number of comorbidities median (IQR)	1 (2)	1 (2)
Comorbidity status	78	35
Hypertension	51	25
DM	40	14
COPD	13	5
CAD	20	4
Intubation	95	18
Duration of intubation, mean (SD)	12.7 (8.9)	24.5 (32.9)

DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, SD: Standard deviation, IQR: Interquartile range.

The median SOFA scores changed after MSC application—Day 0: 6, Day 3: 7, Day 7: 10), Day 14: 14.5, and endpoint: 24 (Table 3). The change in median values was analyzed using the Friedman test, and we obtained that the increase was statistically significant ($p < 0.001$). Further analysis using the Durbin-Conover test revealed statistically significant correlations between the time of administration (day 0) and 7th, 14th and discharge days, between the 3rd, 14th, and discharge days, and between the 7th and discharge days ($p<0.05$) (Table 3).

After the MSC application, the baseline CRP concentrations were compared to those on the 3rd, 7th, and 14th days of application, and no statistically significant difference was observed.

Of the 164 patients, 60% (n=98) had applied for MSC therapy from the emergency department, 29% (n=48) from the outpatient clinic, and 11% (n=18) from another hospital. No statistically significant correlation was detected between the place of applying for permission and mortality.

Lastly, 64% (n=106) of our study patients died of COVID-19-related pneumonia (Table 1). The risk of death in intubated COVID-19 patients treated with MSC was found to be 7 times

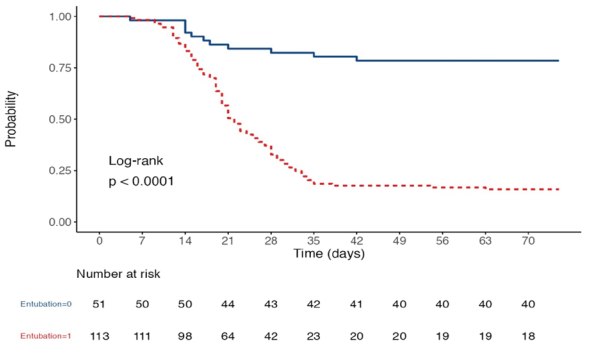

Figure 3: The risk of death in intubated COVID-19 patients who underwent MSC application was 7 times higher than those who were not intubated

Table 2: Survival analysis of COVID-19 pneumonia patients undergoing mesenchymal stem cell administration

	Median Survival		Hazard Ratio (95% CI[d20][H21])	p value
Age				
Age for cutpoint 61 (high/low)	23	32	1.72 (1.17-2.54)	0.006
Gender (Female/Male)	20.5	29	1.56 (1.00-2.43)	0.049
Admission				
Emergency service admission (Yes/No)	28	29	1.16 (0.78-1.72)	0.462
External service transfer (Yes/No)	21	28	1.09 (0.58-2.03)	0.795
Polyclinic admission (Yes/No)	29	27.5	0.78 (0.50-1.20)	0.258
Number of comorbidities				
Comorbidity status (Yes/No)	25	34	1.58 (1.03-2.44)	0.037
Hypertension (Yes/No)	27	28	1.17 (0.80-1.72)	0.408
DM (Yes/No)	23.5	28.5	1.40 (0.95-2.08)	0.090
COPD (Yes/No)	17.5	28.5	1.56 (0.87-2.79)	0.133
CAD (Yes/No)	20	29	1.79 (1.10-2.92)	0.019
Entubation (Yes/No)	22	75(N/A)	7.00 (3.72-13.17)	<0.001

DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, SD: Standard deviation, IQR: Interquartile range;
Results were considered statistically significant if the p value was less than 0.05.

Table 3: SOFA score changes after mesenchymal stem cell application

			Friedman Test	Kendall's W	Post-Hoc Pairwise Comparison (Durbin-Conover Test[d22][H23])			
SOFA Score	**Mean ± SD**	**Median (IQR)**	**p value**	**Effect size**	**SOFA Score 0 day**	**SOFA Score 3rd day**	**SOFA Score 7th day**	**SOFA Score 14th day**
0 day	6.45±3.44	6.00 (4.00)						
3rd day	8.39±6.30	7.00 (6.00)			0.247			
7th day	11.2±8.36	10.0 (12.5)	<0.001	0.131	0.021	0.247		
14th day	13.7±9.76	14.5 (20.5)			<0.001	0.006	0.110	
Discharge day	17.4±10.4	24.0 (21.0)			<0.001	<0.001	0.002	0.143

SD: Standard deviation, IQR: Interquartile range

higher than in the non-intubated patients (HR=7.00, 95% CI: 3.72–13.17; median survival: 22 days vs. > 75 days) (Table 2, Figure 3).

DISCUSSION

In our study, the life expectancy of the 164 patients was found to be lower among the patients aged above 61 years and had a comorbid disease. The correlation analysis between gender and survival rates revealed that women lived for a shorter period of time, with greater mortality than men (76% vs. 61%). We did not detect any statistically significant difference between the CRP levels, which is an inflammation marker, pre and post-MSC application. The risk of death for the intubated patients was 7 times higher than for those who were not intubated. About 64% of the patients included in the study died of COVID-19-related pneumonia.

In a study conducted on 99 patients with COVID-19 disease over a period of 25 days in January 2020 in Beijing Wuhan Hospital, China, elderly males with comorbidities were found to be likelier to be affected by COVID-19 pneumonia (20). We also observed comparable life expectancy values for elderly patients with comorbid diseases. However, when the correlation between gender and survival was considered, it was seen that women lived for a shorter period, and the mortality rates were greater than those of men (76% vs. 61%).

Both Weiss et al. and Wilson et al. have strongly claimed that MSC infusions are well-tolerated in patients with acute or chronic respiratory failure, but they were unable to provide evidence for this assertion. This is because it can be challenging to determine whether the effects of a treatment are due to the underlying critical illness or the experimental treatment being tested (6,21). Moreover, MSC applications are associated with the risk of microvascular embolization with pro-coagulant activity through tissue factor and intravenous administration, leading to pulmonary embolization by the embolus being trapped in the lung microvascular system(22,23). Also, high doses are also considered to increase the risk of death and cause mortality (22,23). One of the limitations of this research is that the coagulation status of the patients could not be evaluated, and the causes of death from the file records were determined as respiratory failure due to pneumonia.

Furthermore, it is known that MSC applications have anti-inflammatory effects (6,7). However, we couldn't find statistically significant difference regarding the levels of the inflammation marker, CRP, during the 14 days following MSC application. Despite being a retrospective analysis, we were able to verify the anti-inflammatory properties of MSCs using an important and easily measurable laboratory parameter.

Kangelaris et al. discovered that among the 457 ARDS patients who did not receive MSC treatment, those who were intubated had a higher morbidity and disease severity compared to those who were not intubated (24). Similarly, in our study, the risk of death in intubated COVID-19 patients who had MSC application was 7 times higher than in those who were not intubated (median survival: 22 days vs. >75 days) (Table 2, Figure 3). In light of these results, we think that intubation should be avoided as much as possible during intensive care treatment, and oxygenation should be provided by methods other than intubation.

Notably, the mortality rate observed in the present study (64%) is comparable to that reported in a previous study conducted in Turkiye to analyze the data of patients who were treated according to the COVID-19 diagnosis and treatment protocol published by the Ministry of Health and were not treated with MSC; they also reported 64% (53/83) mortality in patients hospitalized in the intensive care unit (25). When these results were compared, it was concluded that MSC application did not negatively affect the survival of the patients.

In conclusion, the increase in overall hospital admissions due to the COVID-19 pandemic, especially in the emergency department, has forced healthcare providers to look for newer treatment options. One such modality is MSC application, whose beneficial effects have only been demonstrated in in vitro and in vivo studies, and therapeutic efficacy by means of clinical studies has yet to be determined. The results of the present study, conducted on unvaccinated patients, suggest that MSC application is not effective enough in the treatment of COVID-19 pneumonia. Therefore, larger multicenter randomized controlled clinical studies are needed to confirm its potential therapeutic efficacy in COVID-19 pneumonia.

Ethics Committee Approval: This study was approved by Ankara City Hospital Ethics Committee (Date: 10.03.2021, No: E2-21-242).

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