Assessment of the Efficacy of Spironolactone for COVID-19 ARDS Patients[*]

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ABSTRACT

INTRODUCTION AND AIM

The aim of our study is to compare patients monitored for ARDS diagnosis linked to COVID-19 treated with spironolactone with patients who did not use spironolactone and to retrospectively identify whether there was any positive effect on mortality using clinical and laboratory data from patients.

MATERIAL AND METHOD

Two groups were created of patients treated due to severe ARDS diagnosis linked to COVID-19. One group administered spironolactone (Group S, n=30) and the other group was not (Group F, n=30). Groups were compared in terms of demographic characteristics, presence of comorbidity, inotropic agent requirements, (intensive care unit) ICU length of stay', days of mechanical ventilation and mortality. Additionally, fever, PO2/FIO2 (Horowitz ratio), lymphocyte count, CRP value, SOFA scorer, and d-dimer levels on the ICU length of stay, 1st day, 3rd day, 5th day, 8th day, 12th day, day of discharge or day of exitus were compared between the groups and statistically analyzed.

RESULTS

Group S was found to have a higher ICU length of stay and days of mechanical ventilation compared to Group F. ($p<0.05$). Group F had significantly a higher mortality rate compared to Group S. ($p<0.05$). The final Horowitz value in Group F was found to be significantly lower compared to Group S. ($p<0.05$). The lymphocyte values in Group F were significantly lower than Group S on the 1st, 3rd, 5th, 8th and 12th day and at the final measurement. ($p<0.05$). The CRP values in Group F were significantly higher than Group S on the 3rd, 5th, 8th and 12th day and at the final measurement. ($p<0.05$). The SOFA scores on the 8th and 12th days and at the final measurement in Group F were found to be significantly higher than GroupS. ($p<0.05$).

CONCLUSION

In our study, parameters for disease severity regressed, patients survived for longer and mortality was identified to be lower in the group using spironolactone.

Key words: *Spironolactone, Covid19ARDS, Treatment, SARSCov-2.*

Covid-19 ARDS Olgularında Spironolaktonun Etkinliğinin Değerlendirilmesi

ÖZ

GİRİŞ ve AMAÇ

Çalışmamızın amacı, spironolakton ile tedavi edilen COVID-19 ile bağlantılı ARDS tanısı alan hastaları spironolakton kullanmayan hastalarla karşılaştırmak ve hastalardan alınan klinik ve laboratuvar verilerini kullanarak geriye dönük olarak mortalite üzerinde herhangi bir olumlu etki olup olmadığını belirlemektir.

MATERYAL VE METOD

Hastalar spironolakton kullanılan (Grup S n=30) ve spironolakton kullanılmayan (Grup F n=30) olmak üzere iki gruba ayrıldı. Gruplar demografik özellikleri, komorbidite varlığı, inotropik ajan gereksinimleri, yoğun bakım yatış günleri, mekanik ventilasyon günleri ve mortalite açısından karşılaştırıldı. Ayrıca yoğun bakım yatışı, 1. gün, 3. gün, 5. gün, 8. gün ve 12. gün, taburculuk günü; ateş, PO2/FIO2 (Horowitz oranı), lenfosit sayısı, CRP değeri, SOFA skorları ve d-dimer seviyeleri gruplar arasında karşılaştırıldı ve istatistiksel olarak analiz edildi.

BULGULAR

Grup S'nin Grup F'ye göre daha yüksek yoğun bakım yatış ve mekanik ventilasyon gününe sahip olduğu bulundu ($p<0.05$). Grup F'de ölüm oranı Grup S'ye göre anlamlı derecede yüksekti. ($p<0.05$) Grup F'de nihai Horowitz değeri Grup S'ye göre anlamlı derecede düşük bulundu ($p<0.05$). Grup F'deki lenfosit değerleri 1., 3., 5., 8. ve 12. günlerde ve son ölçümde Grup S'ye göre anlamlı derecede düşüktü. ($p<0.05$). Grup F'deki CRP değerleri 3., 5., 8. ve 12. günlerde ve son ölçümde Grup S'ye göre anlamlı derecede yüksekti ($p<0.05$). Grup F'de 8. ve 12. gün ve son ölçümde SOFA skorları GrupS'ye göre anlamlı derecede yüksek bulundu ($p<0.05$).

SONUÇ

Çalışmamızda spironolakton kullanan grupta hastalık şiddeti parametreleri geriledi, hastalar daha uzun yaşadı ve mortalitenin daha düşük olduğu belirlendi.

Anahtar Kelimeler: *Spironolakton, Covid19ARDS, Tedavi, SarsCov 2.*

INTRODUCTION

Since the end of 2019, the Severe Acute Respiratory Coronavirus-2 (SARS-CoV-2) virus and the COVID-19 infection which it causes have spread rapidly around the whole world and continue to cause life-threatening respiratory failure. More than three millions people were identified to be affected by the virus with clinical symptoms varying from asymptomatic to acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome (ARDS) tableau developing linked to COVID-19 is the most important reason for intensive care admission and death. Each day these numbers and mortality are rapidly increasing (Alhazzani W et al. 2020, Guan WJ et al. 2019).

SARS-CoV-2 is an enveloped positive single-strand RNA virus that may cause a range of symptoms like fever, fatigue, dry cough, muscle pain and respiratory failure (He F et al. 2020). There is still antiviral treatment not found which is effective against this virus, which has very high mortality and morbidity due to this clinical tableau. As a result, finding medications which will ensure a reduction in mortality of critical cases especially carries great importance in order to cope with this pandemic (Lu H et al. 2020). Mostly the disease causes intensive care requirements with increasing respiratory distress on the 9^{th} or 10^{th} day, while the prognosis includes increased mortality for cases with ARDS and septic shock in the clinic (Murthy S et al. 2020).

The host cell for SARS-CoV-2 are type 2 pneumocytes. The virus has its own spike receptor binding protein and uses angiotensin converting enzyme-II (ACE-II) receptors to enter type II pneumocytes. Downregulation of this receptor causes a relative increase in angiotensin-II.

In the lungs, downregulation of ACE-II activity eases first neutrophil infiltration (Sodhi CP et al. 2018). This increase in alveolar angiotensin-II (AT-II) levels with many regional or systemic effects cause increased pulmonary vasoconstriction, capillary permeability, fibrosis stimulation and finally cytokine storm. The first reports from China stated that 40% of cases with severe disease had ARDS tableau and that low ACE-I activity may trigger this tableau (Guan WJ et al. 2019). AT-II is also a strong systemic vasoconstrictor and the most important trigger for aldosterone production. In this way it negatively affects the renin-angiotensin-aldosterone system (RAAS) disrupting blood pressure regulation, homeostasis and electrolyte balance (Busse LW et al. 2020). Increasing angiotensin-II levels in COVID-19 ARDS cases increases aldosterone synthesis and may cause a secondary hyperaldosteronism tableau with hypoxia accompanied by hypernatremia and hypokalemia.

Spironolactone is an aldosterone antagonist. Its success in exceeding diuretic resistance by natriuresis of mineralocorticoid antagonists, especially when a restrictive fluid regime is administered to hypernatremic ARDS patients, makes

spironolactone a relatively good alternative to furosemide. The use of loop diuretics is reported to worsen the secondary hyperaldosteronism tableau (Butler J et al. 2017).

The aim of our study is to compare patients monitored for ARDS diagnosis linked to COVID-19 treated with spironolactone with patients who did not use spironolactone and to retrospectively identify whether there was any positive effect on mortality using clinical and laboratory data from patients.

MATERIAL-METHOD

Our study was completed in the COVID-19 intensive care unit in the Anesthesiology and Reanimation Clinic in İstanbul Sultan Abdülhamit Han Education and Research Hospital after receiving ethics committee permission.

Ethical approval was obtained from the local ethical committee of University of Health Sciences, Hamidiye Clinical Research Ethics committee (Ethic Committee: 15/09/2020- 31665 document no) and the study was completed at University of Health Sciences Sultan 2. Abdülhamid Han Training And Research Hospital, Department of Anesthesiology Intensive Care Unit.

Two groups were created of patients aged 33-88 years treated due to severe ARDS diagnosis. Spironolactone was administered to do first group (Group S, N=30) and was not given to the second group (Group F, n=30). A total of 60 patient files were retrospectively screened and included in the study. Patients whose real-time PCR test was not positive and who had any organ failure before hospitalization (chronic kidney failure, decompensated heart failure, etc.) were excluded from the study.

All patients monitored with ARDS diagnosis had the determined COVID-19 ARDS monitoring and treatment protocol applied in our clinic. Within the framework of this protocol, patients had SARS-CoV-2 infection diagnosis made with real-time PCR test and the antiviral treatment determined by our country's science council was administered. Patients with respiratory failure, disrupted mental status, hypoxia, hemodynamic instability, disrupted tissue oxygenation, and organ failure findings continuing in spite of high-flow oxygen therapy (HFOT) or non-invasive ventilation (NIV) had orotracheal intubation performed and were connected to a mechanical ventilator in line with lung-protective ventilator strategies. PEEP values were set according to the ARDSnet lower PEEP/higher FiO_2 table. Patients with PaO2/FiO2 (Horowitz) values below 150 in spite of this were placed in prone position for 18-24 hours. Routine diuretic treatment for patients used furosemide, while spironolactone (75 mg/day, divided into 3 equal doses) (ALDACTONE® 25mg, Istanbul) was chosen for patients with hypernatremia ($\geq$158 mmol/L) and/or hypokalemia ($\leq$ 3.5 mmol/L)

tendencies. Electrolyte inbalances of all patients developed during treatment were intervened. All patients received the same treatment and care for antiviral therapy and all other intensive care approaches.

When collecting study data, laboratory parameters, clinical findings and treatments were retrospectively obtained from the hospital database for both groups. In line with the data obtained, the group using spironolactone during intensive care treatment (Group S, n=30) and the group not using spironolactone (Group F, n=30), a total of 60 COVID19 ARDS patients, were compared in terms of demographic characteristics, presence of comorbidity, inotropic agent requirements, length of stay in intensive care unit (ICU), days of mechanical ventilation and mortality rate. Additionally, fever, PO2/FIO2 (Horowitz ratio), lymphocyte count, CRP value, SOFA scorer, and d-dimer levels measured on the 1st day, 3rd day, 5th day, 8th day and 12th day, day of discharge or day of exitus were compared between the groups and statistically analyzed.

STATISTICAL METHOD:

Descriptive statistics for data used mean, standard deviation, median, minimum, maximum, frequency and percentage values. Distribution of variables was tested with the Kolmogorov Smirnov test and quantitative independent data were examined with the Mann-Whitney U test. Analysis of qualitative independent data used the chi-square test and the Fisher test if chi-square conditions were not met. Analyses used the SPSS 26.0 program.

RESULTS

There were no significant differences for the ages, sex distribution and comorbidity rates among patients in Group F and Group S ($p>0.05$). There was no significant difference in inotrope rates in Group F and Group S ($p>0.05$), while Group S had significantly higher ICU length of stay and mechanical ventilation days compared to Group F ($p<0.05$). Group F had significantly higher exitus rate compared to Group S ($p<0.05$). These values indicate the correlated lower mortality in Group S may be explained by patients have longer stay in intensive care and more mechanical ventilation days (Table 1).

Table 1. Comparison of demographic characteristics, inotrope requirements, ICU length of stay, days of mechanical ventilation and mortality rate in the groups

		Group F		Group S		p	
		Mean±sd/n-%	Median	Mean±sd/n-%	Median		
Age		58,5 ± 15,4	59,0	59,1 ± 14,2	60,0	0,967	m
Gender	Male	26 86.6%		22 73.3%		0,361	x^2
	Female	4 13.4%		8 26.7%			
Comorbidity	(-)	10 33.3%		10 33.3%		1,000	x^2
	(+)	20 66.7%		20 66.7%			
İnotrope	(-)	16 53.3%		16 53.3%		1,000	x^2
	(+)	14 46.6%		14 46.6%			
ICU length of stay		11,8 ± 6,3	9,0	29,6 ± 20,0	27,0	***0,003***	m
Days of Mec Vent		10,6 ± 5,5	9,0	23,2 ± 15,6	22,0	***0,008***	m
	Exitus	26 86.6%		14 46.6%		***0,005***	x^2
	Discharge	4 13.4%		16 53.3%			

m Mann-whitney u test/ x^2 Ki-kare test Chi- square test

The laboratory and clinical findings in the groups were compared initially, on the 1st, 3rd, 5th, 8th and 12th days and on discharge or when exitus with data obtained explained individually.

There were no significant differences for fever initially, on the 1st, 5th, 8th and 12th day in Group F and Group S ($p>0.05$). Group F had significantly higher values on the 3rd day and final measurement compared to Group S ($p<0.05$) (Table 2).

Table 2. Comparison of fever data in groups

	Group F		Group S		p
	Mean±sd	Median	Mean±sd	Median	
Fever					
İnitial	37,9 ± 0,8	37,8	37,9 ± 0,6	38,1	0,835 m
1st day	38,1 ± 0,6	38,1	37,6 ± 0,9	37,8	0,146 m
3rd day	38,2 ± 0,5	38,0	37,4 ± 0,5	37,5	***0,000*** m
5th day	37,6 ± 0,5	37,6	37,5 ± 0,9	37,4	0,738 m
8th day	37,6 ± 0,7	37,8	37,3 ± 0,3	37,4	0,167 m
12th day	37,2 ± 0,6	37,4	37,2 ± 0,5	37,3	0,586 m
Final measur.	37,9 ± 0,8	37,8	36,8 ± 0,5	36,8	***0,001*** m

m Mann-whitney u test

Group F and Group S did not have significant differences for Horowitz value initially, and on the 1st, 3rd, 5th, 8th and 12th days ($p>0.05$). The final measurement Horowitz value in Group F was significantly lower compared to Group S ($p<0.05$) (Table 3).

Table 3. Comparison of Horowitz values in groups

	Group F		Group S		p	
	Mean±sd	Median	Mean±sd	Median		
Horowitz						
Initial	130,3 ± 49,5	150,0	102,7 ± 28,1	100,0	0,065	m
1st day	129,3 ± 46,5	120,0	99,3 ± 36,3	100,0	0,050	m
3rd day	117,3 ± 37,7	100,0	112,7 ± 37,6	110,0	0,983	m
5th day	117,5 ± 46,3	105,0	127,9 ± 49,5	110,0	0,510	m
8th day	127,5 ± 45,0	110,0	160,0 ± 52,9	165,0	0,152	m
12th day	125,0 ± 77,9	100,0	181,0 ± 58,8	200,0	0,100	m
Final Meas.	77,0 ± 64,6	60,0	191,5 ± 116,4	280,0	***0,010***	m

[m] Mann-whitney u test

The initial lymphocyte values in Group F and Group S were not significantly different ($p>0.05$). Group F had lower lymphocyte values on the 1st, 3rd, 5th, 8th, 12th day and final measurement compared to Group S ($p<0.05$). In spite of the lack of difference initially, the higher lymphocyte value in Group S is correlated with lower mortality (Table 4).

Table 4. Comparison of lymphocyte values in groups

	Group F		Group S		p	
	Mean±sd	Median	Mean±sd	Median		
Lymphocyte						
Initial	561,3 ± 257,7	560,0	774,7 ± 370,4	690,0	0,158	m
1st day	541,3 ± 215,0	590,0	884,7 ± 502,4	750,0	***0,049***	m
3rd day	589,3 ± 247,9	610,0	1019,3 ± 645,9	950,0	***0,031***	m
5th day	576,9 ± 199,1	660,0	1226,9 ± 762,5	1130,0	***0,017***	m
8th day	632,9 ± 264,7	520,0	1416,4 ± 890,1	1270,0	***0,049***	m
12th day	590,0 ± 506,1	390,0	1647,3 ± 969,6	1510,0	***0,014***	m
Final meas.	647,8 ± 458,3	430,0	1962,9 ± 1501,5	1550,0	***0,006***	m

[m] Mann-whitney u test

Group F and Group S did not have significant differences in CRP values initially and on the 1st day ($p>0.05$). Group F had higher CRP values on the 3rd, 5th, 8th and 12th days and for the final measurement compared to Group S ($p<0.05$) (Table 5). Assessed as a parameter for disease severity, lower CRP values in Group S is assessed as significant with the lower value for mortality.

Table 5. Comparison of CRP values in groups

	Group F		Group S		p	
	Mean±sd	Median	Mean±sd	Median		
CRP						
Initial	171,1 ± 66,9	179,0	166,7 ± 54,3	170,0	0,901	m
1st day	183,5 ± 49,8	184,0	146,1 ± 52,8	152,0	0,085	m
3rd day	175,6 ± 48,8	182,0	132,4 ± 57,3	135,0	***0,040***	m
5th day	168,6 ± 54,2	178,0	115,9 ± 54,3	131,0	***0,048***	m
8th day	174,9 ± 54,2	182,5	84,4 ± 42,0	80,0	***0,002***	m
12th day	153,7 ± 65,6	153,0	63,1 ± 31,6	60,0	***0,009***	m
Final meas.	177,8 ± 63,9	170,0	68,1 ± 67,0	40,0	***0,001***	m

[m] Mann-whitney u test

There were no differences in SOFA score between Group F and Group S, initially, on the 1st, 3rd and 5th days ($p>0.05$). Group F had significantly higher SOFA score on the 8th and 12th days and for the final measurement ($p<0.05$) (Figure 1). A marker of disease severity, the SOFA score was found to be significantly lower in Group S, especially on progressive days of the disease.

There were no significant differences in D-Dimer values between Group F and Group S on the 1st, 3rd and 5th day and for the final measurement ($p>0.05$) (Figure 1).

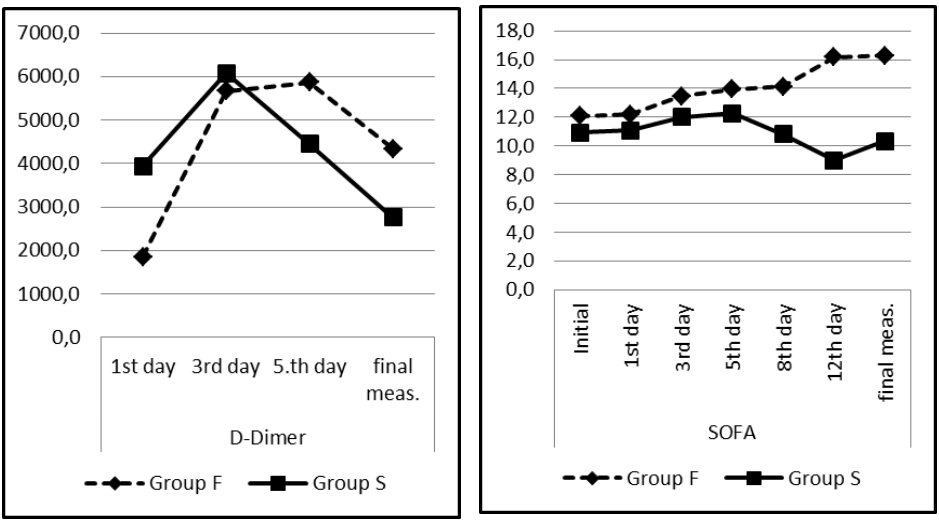

Figure 1. Comparison of SOFA scores and D-dimer levels in groups

DISCUSSION

COVID-19 disease caused by the single-strand RNA virus of SARS-CoV-2 has led to many question marks related to treatment since its emergence. Antiviral agents used in the first plan targeted DNA viruses, not the RNA virus. As a result, efficacy was debatable. As immune modulatory medications may suppress protective acute inflammation, there were doubts about indications. There was no proven information found about the antiviral activity of antimalarial medications like chloroquine and hydroxychloroquine. Additionally, they involved serious side effects. When benefit and harm from corticosteroids were compared, it appeared they may cause serious problems (Stockman LJ et al. 2016). Different medication combinations are still used for COVID-19 treatment and none have efficacy fully revealed.

In order to identify medications that can be used for COVID-19 treatment and assess efficacy, it is necessary to review the effect mechanism and physiopathology of the virus.

The renin-angiotensin (RA) system includes 2 key enzymes ensuring control of angiotensin-I and angiotensin-II; angiotensin converting enzyme-I (ACE-I) and ACE-II. These vasoactive peptides have deep effects in many organ systems. Both ACE inhibitors and aldosterone receptor blockers (ARB) increase the ACE-II activity in cardiac myocytes. ACE-II is found in the respiratory system and gastrointestinal tract (Ferrario CM et al. 2005).

SARS-CoV-2 has a viral envelope containing sharp spikes with glycoprotein structure. This viral envelope has two subunits called S1 and S2. Subunit S1 binds to ACE-II on the cell surface, while subunit S2 binds to the cell membrane (Hoffmann M et al., 2020). The increase in angiotensin-II will reduce anti-inflammatory processes (Heneghan C et al. 2020). It was reported there was a need to prove the positive or negative contributions of this to COVID-19 treatment with scientific studies (Aronson J et al. 2020).

In China, patients with COVID-19 diagnosis were reported to have mild symptoms at rates of 81%; more severe symptoms and findings like dyspnea, respiratory rate ≥30/min, blood oxygen saturation ≤93%, arterial oxygen to inspired oxygen rate <300 and more than 50% infiltration in the lungs at rates of 14%; and critical disease like respiratory failure, septic shock or multiple organ function disorder or failure at rates of 5% (Zhang H et al. 2020). COVID-19 has the potential to cause disease progressing over a broad spectrum from simple upper respiratory tract infection to severe ARDS. Severe ARDS cases leading to increased mortality form the focal point in our study.

There are publications stating that the etiology of cases developing COVID-19 pneumonia or COVID-19 ARDs is the same and that all patients have various degrees of hypoxemia, while initial symptoms and clinic may vary. These may be classified as patients with normal breathing ("silent" hypoxemia) to those with notable degrees of dyspnea; those responding to nitric oxide or not; with deep hypocapnia or normo/hypercapnia; and patients benefitting from prone position or not (Gattinoni L et al. 2020). The severity of the infection, host response, physiological reserves and comorbid diseases, ventilator sensitivity of hypoxia and duration from onset of disease to treatment in hospital are held responsible for development of these clinical differences (Gattinoni L et al 2020). In accordance with the literature, our clinical experience in intensive care shows that hypoxemia is the main element; however, we see different clinical progressions and treatment responses in our patients. This process has caused us to update our monitoring and treatment protocols in intensive care and increased our knowledge and experience of COVID-19 treatment.

It was revealed that the increase in angiotensin-II formation based on ACE activation plays an important role in the pathophysiology of ARDS with vasoconstrictor and proinflammatory effects. SARS-CoV-2 disrupts the lungs by using ACE-II cellular receptors, with ACE-I/ACE-II imbalance triggering angiotensin-II-mediated vascular inflammation and causing pulmonary injury observed in COVID-19 disease. Additionally, angiotensin-II induces aldosterone release and with excessive mineralocorticoid release increases vascular injury and pulmonary injury. Along with this, aldosterone may negatively affect lung injury through immune cells with mineralocorticoid receptors (South AM et al. 2020). This physiological mechanism made it probable that the aldosterone

antagonist of spironolactone would contribute to treatment of COVID-19 ARDS cases and made research definitely necessary.

Many studies have reported that COVID-19-linked ARDS cases are different to classic ARDS cases defined by the Berlin criteria in terms of some clinical features and treatment response. Equivalent to this, it was reported that there may be differences in treatment to be applied (Sodhi CP et al. 2018). ARDS occurs when the lungs are directly or indirectly affected by acute systemic inflammation. In the early exudative stage, widespread epithelial destruction of endothelial cells and alveolar injury occurs (Xu L et al. 2020). The alveolar epithelial injury is greater in COVID-19 ARDS and endothelial exudation is observed relatively less. CT screening of patients generally observes multifocal bilateral irregular shadows or ground glass opacity, while some patients may have mixed ground glass opacity and consolidation pattern (Chung M et al. 2020). Patients with severe pulmonary lesions may not have any clinical complaint and lactate levels, an important parameter showing tissue perfusion, may be normal. These patients with good clinical status incompatible with widespread infiltration identified radiologically in the lungs are observed to worsen rapidly and require mechanical ventilation. It is reported that ARDS tableau symptoms in COVID-19 cases are equivalent to the 8^{th}-12^{th} day since onset of symptoms. This duration, which is incompatible with classic ARDS, complies with our cases (Zhou F et al. 2020). The clinical onset, lung findings and physiopathology of COVID-19 ARDS cases appear to be very different from classic ARDS.

These differences lead to consideration that other treatment methods may be attempted in addition to classic ARDS treatment. In our study, patients using spironolactone had lower mortality and patients survived longer. Linked to this, the ICU length of stay and mechanical ventilation duration were longer in these patients. In our study, it seems contradictory that mortality was lower and the intensive care unit stay was longer in the Spironolactone group. This is due to the fact that intensive care treatment in Covid19 takes longer in patients who survived.

While ARDS is characterized by reduced pulmonary compliance and severe hypoxemia, cases with normal pulmonary compliance are reported among COVID-19 ARDS cases. According to the oxygenation index in the Berlin criteria, cases which can be assessed as severe ARDS are not reported to have diffuse alveolar injury (Thille AW et al. 2013). In ARDS associated with COVID-19, the oxygenation index (PaO_2/FiO_2) can be divided into 3 groups; with PEEP $\geq$ 5 cmH_2O as mild (200 mmHg $\leq$ PaO_2/FiO_2 <300mmHg), mild-moderate (150mmHg $\leq$ PaO_2/FiO_2 <200mmHg) and moderate-severe (PaO_2/FiO_2 <150 mmHg).(21) In our study, all cases in the moderate-severe group comprised COVID-19 ARDS cases. All cases had PaO_2/FiO_2 rates <150 mmHg. A dramatic

elevation was observed in Horowitz rates in patients using spironolactone and in correlation with this, mortality was lower.

The irregular RAAS signal occurring with the SARS-CoV-2/ACE-II interaction and resulting increased aldosterone-mediated mineralocorticoid receptor (MR) activation forms an important connection between SARS-CoV-2 and inflammatory pulmonary injury. This shows that RAAS inhibitors and especially MR antagonists like spironolactone may play an effective role in treatment (South AM et al. 2020). Contrary to other RAAS antagonists, spironolactone has antiandrogenic effects which is among indicators that it may be more effective for treatment (Wang X et al. 2020). This antiandrogenic effect has great importance for SARS-CoV-2 because it inhibits expression of TMPRSS2, a transmembrane protease required for entry of the androgen-dependent virus. Thus, the primary duty of spironolactone is the reducing effect on pulmonary edema, in addition to both MR antagonist and antiandrogenic effects, and it was reported to have an important place in COVID-19 ARDS treatment (Liaduet L et al. 2020). In our study, higher rates for males were observed most in both groups, in accordance with the literature. Parameters correlated with disease severity like fever, lymphocyte count and SOFA score were lower in the spironolactone group compared to the other group.

Our study has some limitations. The most important limitation of our study is that it is a retrospective study and does not include randomization. Another limitation is the low number of cases compared. Despite these, we think that it is valuable in terms of its great contribution to Covid19 treatment and in terms of guiding prospective randomized studies based on our clinical observation.

CONCLUSION

It is definitely necessary to consider different treatments for COVID-19 ARDS. Illuminating the causative elements and physiopathology will provide great contribution to treatment of COVID-19 ARDS. Classic treatments were revealed to have less efficacy in severe cases in mortality studies. When the disease-inducing effect of SARS-CoV-2 on systems is investigated in terms of physiopathology, it is considered that an aldosterone antagonist will contribute to treatment. In our study, parameters for disease severity regressed, patients survived for longer and the mortality rate was lower in the group using spironolactone. Proving the effect of spironolactone with large-scale randomized controlled studies will offer great contribution to COVID-19 ARDS treatment.

AUTHOR CONTRIBUTIONS

Study conception and design: A.E., B.B.G. / Acquisition of data: F.Y., O.K., T.G., Z.K. / Analysis and interpretation of data: B.B.G, T.E / Drafting of

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Acknowledgments/disclaimers/conflict of interest

All authors declare no conflict of interest that may have influenced either the conduct or the presentation of the research.

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Informed consent

Ethical approval was obtained from the local ethical committee of University of Health Sciences, Hamidiye Clinical Research Ethics committee (Ethic Committee: 15/09/2020- 31665 document no) and study was completed at University of Health Sciences Sultan 2. Abdülhamid Han Training And Research Hospital, Department of Anesthesiology Intensive Care Unit.

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