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BRAIN DEATH AND ORGAN DONATION DURING THE COVID-19 PANDEMIC: A RETROSPECTIVE OBSERVATIONAL STUDY

COVID-19 PANDEMİSİNDE BEYİN ÖLÜMÜ VE ORGAN BAĞIŞI: RETROSPEKTİF GÖZLEMSEL ÇALIŞMA

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Abstract

Aim: Transplantation processes were impacted worldwide due to the COVID-19 pandemic. The present study investigates brain death and cadaveric organ donation during the pandemic at a large referral hospital in Turkey.

Methods: All brain death cases diagnosed between 11.3.2020 and 11.3.2021 in our center were retrospectively evaluated. Patient data were analyzed, including demographic characteristics, family consent rates, and additional COVID-19 tests for donor eligibility. In addition, declaration and donation times, the number of donors, and the usability of organs were studied. Furthermore, the patients whose organs could not be used despite family consent were considered regarding the medical reasons for that outcome.

Results: 26 adult brain death cases were included in the study. Family consents were granted in seven (26.9%) patients. The organs of three of the seven cases with family consent were transplanted. In one of the remaining four, the second RT-PCR test was positive. In the other ones, both RT-PCR tests were negative, but COVID-19 could not be ruled out through laboratory tests and chest tomography, and bacteremia were evident in blood cultures. The non-donor's lymphocyte count (0.665 $\times 10^9$/L [0.340-0.770]) was significantly lower than that of donor (1.182 $\times 10^9$/L [1.050-1.780]) ($p < 0.05$). Besides, procalcitonin levels were significantly higher among non-donors (10.48 µg/L [3.19-26.68]) ($p < 0.05$).

Conclusions: The COVID-19 pandemic has drastically affected transplantation processes. Prolonged stays due to additional evaluations for COVID-19 may pose the risk of intensive care acquired infections in donors and should be careful in terms of donor loss due to infections.

Keywords: COVID-19, brain death, organ transplantation

Öz

Amaç: COVİD-19 pandemisi dünya genelinde olduğu gibi ülkemizde de organ nakli süreçlerini etkilemiştir. Bu çalışma ile pandemi döneminde bölgedeki en büyük referans pandemi hastanesindeki beyin ölümü ve kadaverik organ donasyonu olgularının değerlendirilmesi amaçlanmıştır.

Yöntemler: 11.3.2020-11.3.2021 tarihleri arasında hastanemizde tanı koyulan tüm beyin ölümü olguları retrospektif olarak değerlendirilmiştir. Demografik özellikler, aile onay oranları ve COVID-19 ekartasyonu açısından yapılan ek değerlendirmeler dahil olmak üzere hasta verileri analiz edildi. Deklarasyon ve donasyon süreleri, donor sayısı ve organların kullanılabilirlik oranları incelenmiştir. Ayrıca, aile onayı olmasına rağmen tıbbi nedenlerle organları kullanılamayan olgular, bu sonucun altta yatan nedenleri açısından değerlendirildi.

Bulgular: Çalışmaya 26 erişkin beyin ölümü olgusu dahil edilmiştir. Yedi (%26,9) hastada aile onayı mevcuttu. Aile onamı olan 7 olgunun 3'ünün organları transplante edilmiştir. Geri kalan olgulardan bir olgunun alınan ikinci RT-PCR testi pozitifti. Diğer olgularda her iki RT-PCR negatif olmasına rağmen laboratuar tetkikleri ve donasyon öncesi çekilen toraks tomografilerinde COVID-19 ekarte edilememişti, ayrıca kan kültürlerinde bakteriyemi mevcuttu. Donor olmayanların medyan lenfosit sayısı (0,665 × 109/L [0,340-0,770]), donorlere göre (1,182 ×109/L [1,050-1,780]) anlamı olarak düşüktü ($p < 0,05$). Ayrıca prokalsitonin düzeyleri donor olmayanlarda (10.48 µg/L [3.19-26.68]) anlamlı olarak daha yüksek saptandı ($p < 0,05$).

Sonuç: COVID-19 pandemisi transplantasyon süreçlerini büyük oranda etkilemiştir. Bu dönemde COVID-19 ekartasyonu açısından yapılan ek değerlendirmelere bağlı uzamış yoğun bakım yatış süreleri ve beraberinde gelişebilecek yoğun bakım kaynaklı enfeksiyonların, donor kaybı oranlarını artırabileceği göz önünde bulundurulmalıdır.

Anahtar Kelimeler: COVID-19, beyin ölümü, organ nakli

Introduction

Ongoing developments in transplantation present a life-saving treatment option for end-stage organ failures. However, donor pools for cadaveric organ transplantation remain limited. Accurate detection of brain death (BD) cases is critical for expanding organ donations and, hence, ensuring the continuity of transplantation processes, particularly those of heart and lung that can be performed via cadaveric donors.

The COVID-19 pandemic has impacted organ transplant processes worldwide. Similar situations had arisen during past viral disease outbreaks such as Ebola, West Nile Virus, SARS-CoV, and influenza A/H1N1, necessitating a series of arrangements to minimize setbacks in transplantation procedures. These include measures taken to screen donors for infectious diseases and avoid the risk of transmission to recipients, as well as healthcare professionals[1,2].

The COVID-19 pandemic has affected the whole world, resulting in the infection of more than 270 million people and the death of 5 million people as of December 2021[3]. The first COVID-19 case in Turkey was reported in March 2020; since then, healthcare resources and workforce have mainly been assigned to pandemic units to treat COVID-19 cases. In a similar vein, most intensive care unit (ICU) beds have been allocated for COVID-19 treatment, resulting in a lower overall number of BD cases that typically constitute the main supply of cadaveric donors. Besides, factors such as the necessity of immunosuppressant use after transplantation and the risk of asymptomatic COVID-19 in donors or recipients have also influenced transplantation processes negatively.

Current literature on COVID-19 is vast; however, there are limited studies on BD during the pandemic. The present study investigates BD cases and cadaveric organ donation during the pandemic at Ankara City Hospital, a large regional referral center. Accordingly, the study analyzes the relevant BD diagnosis rates, additional COVID-19 tests and consultations required for donor eligibility, the effect of these evaluations on declaration and donation times, and the resulting number of donors and usable organs.

Materials and Methods

This single-center, retrospective, observational study was conducted at a tertiary training and research hospital in Ankara, Turkey. Local ethics committee approval was obtained for the investigation (approval number: 2021/E2-21-391). All patient data were accessed through electronic medical records and files.

All BD cases diagnosed between 11.3.2020 and 11.3.2021 were retrospectively evaluated. Pediatric cases were excluded (age <18). Patient data were analyzed, including demographic characteristics, comorbidities, acute physiology and chronic health evaluation II (APACHE II) and Glasgow Coma Scale (GCS) scores at ICU admission, BD etiologies, clinical testing and radiological imaging, and laboratory findings.

In our center, BD diagnoses are made by the BD commission as per the criteria specified in the Organ and Tissue Transplantation Services Regulation, the Ministry of Health, Turkey (Official Gazette 01.02.2012, 28191)[4]. All patients having the preconditions for BD diagnosis undergo an apnea test (AT). If this is not feasible, computed tomography (CT) cerebral angiography is performed to assess cerebral blood circulation according to the Turkish Neurological Society, Diagnostic Guidelines for Brain Death[5]. After the diagnosis of BD, family interviews for donation consent are conducted by our hospital's organ and tissue transplantation coordinators. Then, the results of the interviews and patient data are submitted by the coordinators to the National Coordination Center for Organ Transplantation for further consideration. The present study covers the final outcomes of these assessments and the rates of donation and usable organs.

In Turkey, potential donors are evaluated during the COVID-19 pandemic as per the recommendations of the Ministry of Health, The Coronavirus Scientific Advisory Board. The Department of Tissue, Organ Transplantation Services requires from the donors at least two consecutive negative results for COVID-19 reverse transcription-polymerase chain reaction (RT-PCR) test from endotracheal aspirate with a minimum interval of 24 hours. Besides, the donors are inquired about disease symptoms and history of contact and travel. Furthermore, all donors are required chest CT and pulmonary diseases and infectious diseases consultations[6].

The analysis for the present study included all laboratory tests, chest CT imaging results, and additional evaluations for COVID-19 required from the donors, as mentioned above. The patients whose organs could not be used despite family consent, i.e., non-donors, were evaluated regarding the medical reasons for that outcome, laboratory values were compared. The investigation also covers the time from ICU admission to BD diagnosis and the time from family consent for donation to organ procurement.

• *Statistical analysis*

All statistical analyses were performed via the IBM SPSS Statistics 25.0 software package. The Shapiro-Wilk test, skewness and kurtosis values, and histograms were used to determine the conformity of variables to the normal distribution. Numerical variables with normal distribution are expressed as mean±standard deviation, and those without normal distribution as median (minimum-maximum [min-max]).

Categorical variables are presented as numbers and percentages. The Mann-Whitney U test was used to compare the medians of donor and non-donor laboratory values. A p-value <0.05 was considered statistically significant.

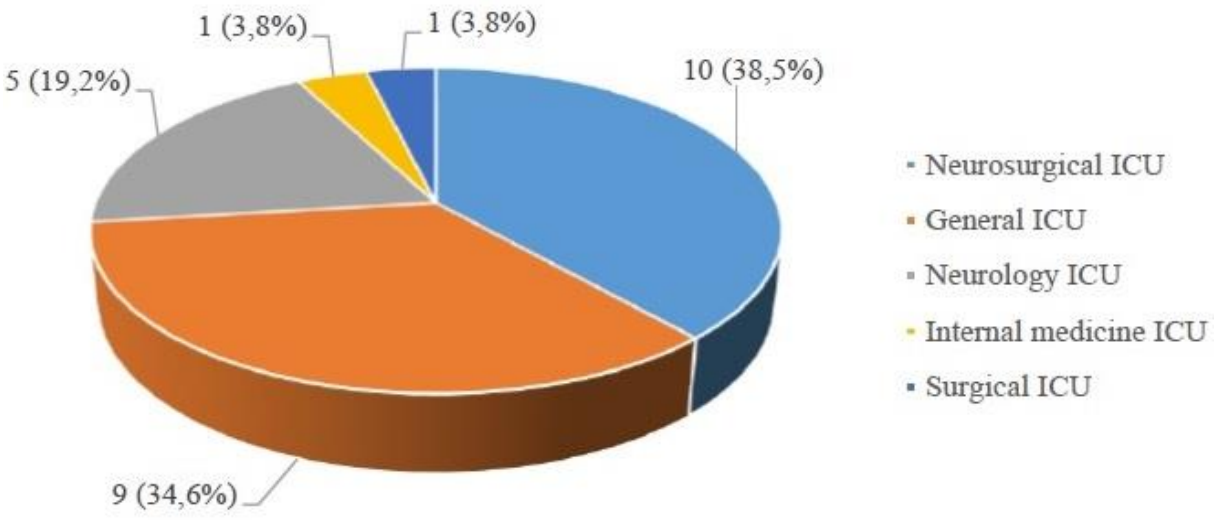

Figure 1. Intensive Care Units Where Patients Followed

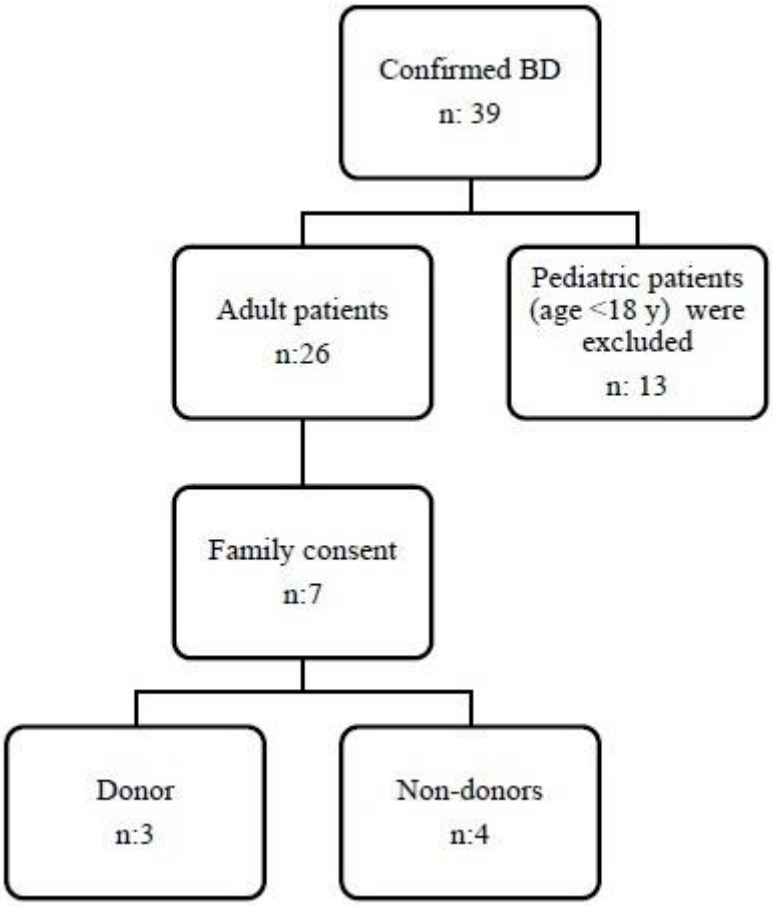

Figure 2. Brain Death, Family Consent and Donors in the First Year of the Pandemic

Results

There were 39 cases of confirmed BD in our center between 11.3.2020 and 11.3.2021, the initial year of the COVID-19 pandemic. 13 patients of age <18 were excluded. The median age of the remaining 26 BD cases was 46 (min-max, 20-78). 13 (50%) of these were male. Regarding ICUs and their respective departments, BD diagnosis was most frequent in neurosurgical ICU with 10 (38.5%) cases and least in internal medicine ICU and surgical ICU with one case each (3.8%) (Figure 1). The median ICU length of stay was 7.5 (min-max, 2.0-37.0) days. The median APACHE II and GCS scores at ICU admission were 26.5 (min-max, 17-50) and 5 (min-max, 3-7), respectively. Hypertension was the most frequent comorbidity, seen in nine (34.6%) cases (Table 1). The most common ICU admission diagnosis among BD cases was subarachnoid hemorrhage, followed by intraparenchymal hemorrhage (Table 2).

Five (19.2%) patients had undergone neurosurgery during their ICU stay. Three (11.5%) patients had trauma history.

17 patients having the preconditions for BD diagnosis had undergone AT. The median AT duration was 10 (min-max, 8-14) minutes. AT had been terminated in five (19.2%) patients due to hemodynamic instability. The CT angiography was performed as an ancillary test in 25 (96.2%) patients and transcranial Doppler in one patient. The families of confirmed BD cases were invited by our hospital's organ and tissue transplantation coordinators for interview.

Table 1. Demographic and Clinic Characteristics and Comorbidities of Patients

Age, median (min-max), y	46 (20-78)
Male, No. (% of total)	13 (50%)
LOS ICU (days) median (min-max)	7.5 (2.0-37.0)
GCS, median (min-max)	5 (3-7)
APACHE II, median (min-max)	26.5 (17-50)
Comorbidities of Patients, No. (% of total)	
Hypertension	9 (34.6)
Diabetes mellitus	2 (7.7)
Chronic obstructive pulmonary disease	2 (7.7)
Cardiovascular disease	3 (11.5)
Chronic renal failure	2 (7.7)
Cerebrovascular disease	6 (23.1)
Others*	5 (19.2)

APACHE II: acute physiology and chronic health evaluation-II scores, GCS: Glasgow Coma Scale, ICU: intensive care unit, min-max: minimum to maximum, LOS: length of stay
*Others: Chrone diesase, chronic liver failure, hyperlipidemia, systemic lupus erythematosus

Family consent was granted in seven (26.9%) patients; one patient was excluded from donor evaluation due to being foreign national as per the decisions of the Ministry of Health, the National Coordination Center for Organ Transplantation; the families of five (19.3%) patients declined multiple invitations for interview, and those of 13 (50%) patients refused to consent to donation. None of our BD cases had an organ donation card beforehand. The most common blood group among our patients was A (42.3%). Table 3 shows patient laboratory findings at the time of BD diagnosis. The Department of Tissue, Organ Transplantation Services published instructions on 20.3.2020 to rule out COVID-19 in potential donors. Two of our cases diagnosed before this date had no COVID-19 RT-PCR tests but had not been donors either. The testing was performed in all subsequent BD cases. COVID-19 RT-PCR positivity was detected in 3 patients. 23 (88.5%) cases diagnosed with BD underwent chest CT imaging for COVID-19 screening. All donors had chest CT scans and two consecutive negative RT-PCR test results at least 24 hours apart. In the end, the organs of three of the seven cases with family consent were transplanted (Figure 2).

Table 2. Etiology of Brain Death

	No. (% of total)
Subarachnoid hemorrhage	12 (46.2)
Intracerebral hematoma	5 (19.3)
Ischemic stroke	4 (15.4)
Metanol intox	2 (7.7)
Postcardiorespiratory arrest	1 (3.8)
Meningitis	1 (3.8)
Intracranial tumor	1 (3.8)

Table 3. Laboratory Tests of Patients at Diagnosis of Brain Death

Hemoglobin, g/dL	9.7±2.6
WBC, $\times 10^9$/L	13.6±7.0
Lymphocytes, $\times 10^9$/L	1.334±0.664
Platelets, $\times 10^9$/L	187.5 (37.0-451.0)
CRP, g/L	0.18 (0.01-0.55)
PCT, μ g/L	1.24 (0.03-49.37)
Glucose, mg/dL	135.5 (65.0-292.0)
LDH, U/L	537 (227-7658)
Serum creatinine, mg/dl	1.90 (0.42-5.28)
Urea mg/dl	75 (16-201)
AST, U/L	186.5 (25.0-1046.0)
ALT, U/L	59.5 (10.0-451.0)
Sodium, mEq/L	151.1±14.5
Blood groups No. (%)	
A	11 (42.3)
B	4 (15.4)
AB	3 (11.5)
0	8 (30.8)

Abbreviations: ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, LDH: lactate dehydrogenase, PCT: procalcitonin * Numerical variables with normal distribution are expressed as mean±standard deviation, and those without normal distribution as median (minimum-maximum).

The heart and kidneys were used for transplant in the first case; the heart, liver, kidneys, and corneas in the second case; and the heart, kidneys, and corneas in the third.

The patients whose organs could not be used despite family consent, i.e., non-donors, were evaluated regarding the medical reasons for that outcome. In one of these non-donors, the second RT-PCR test was positive. In the other ones, both RT-PCR tests were negative, but COVID-19 could not be ruled out through laboratory tests and chest CT, and positive blood cultures indicated bacteremia. Therefore, these patients had been considered ineligible for organ donation by the National Coordination Center for Organ Transplantation.

Donor and non-donor some infection laboratory values measured at evaluation day were also compared. The non-donor's median absolute lymphocyte count (0.665 $\times 10^9$/L [min-max, 0.340-0.770]) was significantly lower than that of donor (1.182 $\times 10^9$/L [min-max, 1.050-1.780]) ($p < 0.05$). Besides, procalcitonin levels were significantly higher among non-donors (μg/L: 10.48 [min-max, 3.19-26.68]) ($p < 0.05$) (Table 4).

Table 4. Donor and Non-donor's Some Infection Laboratory Values

	Donor n=3	**Non-donor n=4**	**p-value***
WBC, $\times 10^9$/L	14.00 (11.00-17.57)	14.76 (4.35-16.95)	0.724
Lymphocytes, $\times 10^9$/L	1.182 (1.050-1.780)	0.665 (0.340-0.770)	0.034
LDH	620 (306-991)	743 (469-1297)	0.724
PCT, μ g/L	0.29 (0.13-0.38)	10.48 (3.19-26.68)	0.034
CRP, g/L	0.08 (0.07-0.16)	0.31 (0.13-0.40)	0.077

CRP: C-reactive protein, LDH: lactate dehydrogenase, min-max: minimum to maximum, PCT: procalcitonin, WBC: white blood cell, *Mann-Whitney U test, $P < .05$, statistically significant.

Finally, the time intervals relevant to BD diagnosis and organ procurement were considered. The median time from ICU admission to BD diagnosis was 4 (min-max, 1.0-36.0) days. In the donors, the time from family consent for donation to organ procurement was 18.5 hours in the first case, 18.2 hours in the second, and 6.2 hours in the third.

Discussion

Transplant procedures have been a drastically affected area of healthcare during the COVID-19 pandemic. The number of organ transplantations decreased worldwide, as well as in Turkey, especially in the early stages of the pandemic[7,8]. In the present study, BD was diagnosed in 26 adult patients between 11.3.2020 and 11.3.2021. As our center is the largest pandemic hospital in the region, the vast majority of ICU beds were reserved for COVID-19 treatment. BD most frequently occurred in our neurosurgical ICU. However, the number of beds in the neurosurgical ICU had decreased from 48 to 16 during pandemic. The case was similar for general ICU and neurological ICU bed capacity. This reduction seems to be the main reason for the low number of donors during the pandemic. Besides, cases of trauma, which typically constitute the primary BD etiology, were referred to other hospitals in Ankara since the trauma resuscitation area in our emergency clinic had also been allocated for COVID-19 patients. This has been another reason for the low rate of BD cases.

The appointment of healthcare professionals, such as organ and tissue transplant coordinators and transplant surgeons, in COVID-19 services has also impacted transplantation processes. There are nine transplant coordinators in our center, and they continued to work in their unit during the pandemic to maintain the processes of donor identification and transplantation and minimize the risk of viral transmission. During the pandemic, family interviews have generally been conducted via telephone worldwide[9]. However, the transplant coordinators in our center continued face-to-face interviews, observing protective measures against infection[10]. Open and effective communication is key in obtaining family consent for organ donation in BD cases. Otherwise, high refusal rates are inevitable[11]. The family consent rate for organ donation was 26.9% (n = 7/26) among our BD cases. In contrast, the Ministry of Health, Department of Tissue, Organ Transplantation Services data for 2020 indicate a family consent rate of 18.9% (n = 263/1385)[12]. This difference is most likely related to continued face-to-face family interviews in our center.

AT, the cardinal method for BD diagnosis, was performed on all cases that met the preconditions. Due to the pandemic, physicians may be reluctant to apply any technique producing aerosols that increase transmission risk, but ancillary tests are not recommended instead of AT since they can yield false positive and negative results[13]. Whenever feasible, AT should be performed for clinical confirmation of BD, even in cases with COVID-19[14]. Before the pandemic the most preferred AT approach is apneic oxygenation, which involves delivering oxygen into the trachea by placing a cannula into the endotracheal tube after weaning from ventilation[15]. In order to prevent aerosol formation and COVID-19 transmission risk, it is recommended to perform the AT either by a T-piece and attaching a filter to the expiratory limb, or via continuous positive airway pressure (CPAP)[16]. Among our cases, three had positive COVID-19 RT-PCR test results, only one of these met the preconditions for AT. Physicians wearing personal protective equipment applied the test in a negative pressure room by a T-piece and attaching a filter to the expiratory limb. In our hospital, RT-PCR tests were obtained from all cases before ICU admission. Nevertheless, as a precaution against possible false negatives, our medical staff paid utmost attention to personal protection during patient examinations, and no

COVID-19 transmission occurred among our members.

The pandemic has necessitated various arrangements for the continuity of transplantation activities. In Turkey, additional tests and consultations are requested in donor evaluation, as per the recommendations of the Ministry of Health, The Coronavirus Scientific Advisory Board[6]. In the present study, the RT-PCR test was positive in one of the four cases whose organs were unusable for medical reasons. In the other 3 cases, COVID-19 could not be ruled out by laboratory tests and chest CT, and bacteremia was evident in blood cultures. As long as the pandemic continues, further studies on organ donor evaluations are crucial. Currently, there are conflicting views regarding donor organ use in cases of suspected infections or bacteremia. Some studies advocate proceeding with transplantation under appropriate antibiotic therapy in these cases[17-19].

Prolonged ICU stays due to additional evaluations on donors potentially increase the risk of ICU-acquired infections. Physicians should be wary of complications in patients on mechanical ventilation and invasive hemodynamic monitoring, such as ventilator-associated pneumonia and catheter-related infection. Infection control measures, prompt screening of blood cultures, and, if necessary, appropriate antibiotic therapy can reduce donor loss.

In the present study, a comparison of donor and non-donor laboratory values revealed significantly lower lymphocyte counts in the non-donors. Published literature recommends referring to lymphocyte count in the haemogram test to evaluate COVID-19 suspicion, severity, or prognosis[20,21]. In a study on haematological parameters in the diagnosis of COVID-19, Peng et al.[22] found significantly lower lymphocyte count in positive cases compared to healthy individuals. The authors have indicated 88.05% specificity and 70.97% sensitivity for lymphocyte count $< 0.870\times10^9$/L in detecting acute respiratory distress syndrome due to COVID-19. COVID-19 should be diligently ruled out in cases accompanied by severe lymphopenia.

Procalcitonin, a primary inflammatory marker, was significantly higher among the non-donors in the study. However, the studies have shown that inflammatory markers can be elevated despite the absence of infection in BD cases due to increased sympathetic activity[23]. In contrast, a study on the relationship between procalcitonin level and infection in BD cases has indicated procalcitonin >9 ng/mL as a significant inflammatory marker[19]. Among our non-donors, the median procalcitonin level was 10.48 μg/L, and these cases were also bacteremic. In sum, a detailed scanning for the focus of infection can be helpful in evaluating potential donors with procalcitonin levels above a particular cutoff value.

Among our donors, the time from family consent for donation to organ procurement was median 18.25 (min-max, 6.25-18.50) hours. Concerning the same parameter, Caliskan et al.[24] reported a pre-pandemic mean of 8.5 ± 2.12 hours and a pandemic mean of 54 ± 11.53 hours. Prolonged time to organ procurement during the pandemic can be associated with protective measures, as well as additional tests and consultations required from donors.

The main limitations of this study are its single-center design and low number of cases. Besides, since our hospital is a recently established one, data is unavailable to compare pandemic and pre-pandemic statistics for BD and organ donation. On the other hand, our center is Turkey's largest pandemic hospital; therefore, the results of this study can prove valuable for future studies on BD and deceased organ donation during the COVID-19 pandemic.

Conclusion

In countries like Turkey, where cadaveric donation is only possible after BD, accurate detection of BD cases is vital for the continuity of transplantation processes. Prolonged intensive care stays due to additional evaluations for COVID-19 may pose the

risk of intensive care acquired infections in donors and should be careful in terms of donor loss due to infections. Further studies on BD detection and donor evaluation are imperative, as the end of the pandemic is still unforeseeable.

Author contributions

Author read and approved the final manuscript.

Conflict of interest

Author declares that they have no conflict of interest.

Funding

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Ethical approval

Ethics committee approval was received for this study from the University of Health Sciences, Ankara City Hospital Clinical Research Ethics Committee (Approval Date: April 7, 2021; Approval Number: 2021/E2-21-391).

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