Kastamonu Sağlık Akademisi

Araştırma Makalesi / Research Article

Does blood type have an effect on the course of COVID-19?/ *Kan Grubunun COVID-19'un Seyrine etkisi var mı?*

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Gönderim Tarihi | Recieved :29.10.2021 Kabul Tarihi | Accepted: 20.05.2022 Yayın Tarihi | Date of Publication :23.06.2022 DOI: https://www.doi.org/10.25279/sak.1014330

Atıf | Reference: YILMAZ, F.; ALBAYRAK, M.; YILDIZ, A.; OZTURK, H.B.; MARAL, S.; TIGLIOGLU, P.; ARAS, M.R.; SAĞLAM, B.; TIGLIOĞLU, M. (2022). Does blood type have an effect on the course of COVID-19?. Health Academy Kastamonu(HAK), 7(Covid-19 Additional Issue), p. 100-107

Abstract

Introduction: Predictive parameters that can affect the course of COVİD-19(Coronavirus disease 2019)infection have been the main research topic since the beginning of this pandemic. Since the discovery of blood groups, the effect of these on infectious diseases has always been of interest. Objectives: Our aim is to analyze the effect of ABO blood group on mortality, length of hospital stay and hematological and cytokine storm parameters in COVID-19 patients. Patients and methods: This retrospective study was conducted on 140 patients diagnosed with COVID-19. Demographic characteristics, laboratory parameters including ABO blood group, complete blood count (CBC) parameters, biochemical tests, cytokine storm parameters, duration of hospitalization, and final status (discharge or death) were recorded. Results: Of the 140 patients included in the analysis 72 (51.4%) were male and 68 (48.6%) were female with a mean age of 66.3±14.0 years. Age and gender, hospitalization duration and mortality rates were similar in all blood group types. Only D-dimer levels were found to be higher in blood group A compared with other blood groups. Conclusion: Although there was no difference in mortality between the groups, D-dimer level was statistically significantly higher in COVID-19 patients with A blood group. Larger studies are needed to reflect D-dimer levels on the clinical course of infection, and thus on daily practice.

Keywords: ABO Blood Group System, SARS-CoV-2, D- Dimer, Mortality

ÖZ

Giriş: COVID-19 (Koronavirüs hastalığı 2019) enfeksiyonunun seyrini etkileyebilecek öngörücü parametreler, bu pandeminin başlangıcından beri ana araştırma konusu olmuştur. Kan gruplarının keşfinden bu yana bunların bulaşıcı hastalıklar üzerindeki etkisi daima ilgi çekici olmuştur. Gereç ve yöntemler: Amacımız COVID-19 hastalarında ABO kan grubunun mortalite, hastanede kalış süresi ve hematolojik ve sitokin fırtınası parametreleri üzerindeki etkisini analiz etmektir. Bu retrospektif çalışma, COVID-19 tanısı konan 140 hasta üzerinde yapıldı. Demografik özellikler, ABO kan grubunu içeren laboratuvar parametreleri, tam kan sayımı (CBC) parametreleri, biyokimyasal testler, sitokin fırtınası parametreleri, hastanede kalış süresi ve son durum (taburculuk veya ölüm) kaydedildi. Bulgular: Analize dahil edilen 140 hastanın 72'si (%51.4) erkek ve 68'i (%48.6) kadından oluşmakta olup, ortalama yaşları 66.3±14.0 yıldır. Yaş ve cinsiyet, hastanede kalış süresi ve ölüm oranları tüm kan gruplarında benzerdi. Sadece D-dimer değerleri A kan grubunda diğer kan gruplarına göre daha yüksek bulundu. Sonuç: Gruplar arasında mortalite açısından fark saptanmamakla birlikte A kan grubuna sahip COVID-19 hastalarında D-dimer düzeyi istatistiksel olarak anlamlı derecede yüksekti. D-dimer düzeylerini enfeksiyonun klinik seyrine ve dolayısıyla günlük uygulamaya yansıtmak için daha büyük çalışmalara ihtiyaç vardır.

Anahtar kelimeler: ABO Kan Grubu Sistemi, SARS-CoV-2, D- Dimer, Ölüm

1.Introduction

The novel coronavirus SARS-CoV-2, which is a positive oriented single-stranded RNA virus, has spread rapidly around the world since it first emerged in December 2019 (Fauci, Lane, & Redfield, 2020). In March 2020, it was declared a global pandemic by the World Health Organisation (WHO). Predictive parameters that can affect the course of this infection have been the main topic of research since the beginning of the COVID-19 (Coronavirus disease 2019) pandemic.

Since the discovery of blood groups, the effect of these on infectious diseases has always been of interest. The ABO blood group consists of two antigens (A and B antigens) and four blood phenotypes (types A, B, AB, and O). Individuals with O blood group express the H antigen, which is a precursor to A and B antigens (Reid, Lomas-Francis, & Olsson, 2012; Yamamoto, 2004). The antigen gene is located on chromosome 9q34.2. The relationship between susceptibility to viral infection and ABO blood groups has been previously reported. Cheng et al. reported that blood group O individuals were less likely to be infected by SARS coronavirus (Cheng et al., 2005). B blood group has been shown to be significantly less susceptible to infection by Norwalk virus . Batool et al. reported that individuals with blood type A are more likely to get hepatitis B and HIV (Batool, Durrani, & Tariq, 2017), and Jing et al. found that blood group B was associated with a lower risk of HBV infection (Jing, Zhao, Liu, & Liu, 2020). As can be seen from the results of those studies, there are contradictory findings in the literature.

The aim of the current study was to analyze the effect of ABO blood group on mortality, hospitalization duration and hematological and cytokine storm parameters in patients with COVID-19.

2. Materials and methods

2.1 Type of research: A descriptive cross-sectional study

2.2 Research Place and Time

Diskapi Yildirim Beyazit Training and Research Hospital, 2021 April

2.3 Population, Sample and Sampling Research Method

This study was conducted on 140 patients diagnosed with RT–PCR confirmed infection of SARS-CoV-2, who were admitted in Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey, between 1 November 2020 and 1 December 2020. All participants met the case definition criteria for the clinical diagnosis based on the Republic of Turkey Health Ministry diagnosis and treatment guideline for COVID-19. A record was made of demographic characteristics, blood group (rh positive and negative subgroups were not statistically evaluated), chest computed tomography (CT) findings, laboratory parameters including complete blood count (CBC) parameters, procalcitonin, fibrinogen, ferritin, interleukin 6 (IL-6), immunoglobin A (IgA) and D-dimer values, hospitalization duration, and final status (discharge or death). All patients were followed until discharge or exitus.

2.4 Data Collection: Data was collected from patient files and Hospital Automation System**.**

2.5 Ethical approval and informed consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey (14.06.2021-113/05).

2.6 Statistical analysis

Data obtained in the study were analyzed statistically using SPSS 27.0 software. Descriptive statistics were stated as mean ± standard deviation, median (1.quantile-3.quantile), minumum and maximum values or number (n), percentage (%). The conformity of variables to normal distribution was assessed with the Kolmogorov Smirnov test. T-test, paired t-test, Anova Tukey test were used in the analysis of normally distributed data that met the parametric test usage conditions. Mann-Whitney U test, Kruskal Wallis test and Wilcoxon test were used in the analysis of non-normally distributed data. Tukey test was used for normally distributed data, mann-whitney u test with Bonferroni correction was used for pairwise comparisons. Chi-square test was used in the analysis of nominal data. A value of $p<0.05$ was accepted as statistically significant.

3. Results

The 140 patients included in the analysis comprised 72 (51.4%) males and 68 (48.6%) females with a mean age of 66.3±14.0 years, and median follow up of 11.8±8.2 days. The descriptive statistics and distribution of demographic parameters are shown in Table 1**.**

Table 1. Descriptive statistics and distribution of demographic parameters

N=140	**(Mean±SD), (n,%)**
Age (years)	66.3±14.0
Gender Female Male	 68(48.6%) 72(51.4%)
Hospitalization Time (day)	11.8±8.2
Procalcitonin (μg/L)	0.8±3.1
White blood cell ($10^3/\mu$L)	8.9±4.1
Hemoglobin (g/dL)	12.6±1.9
Hematocrit (%)	38.7±5.4
Platelet ($10^3/\mu$L)	291.9±128.6
Mean platelet volume (fL)	10.5±0.9
Plateletcrit (%)	0.3±0.1
Platelet distribution width (%)	12.3±2.2
Neutrophil ($10^3/\mu$L)	6778.6±3640.3
Lymphocyte ($10^3/\mu$L)	1289.4±728.0
Monocyte ($10^3/\mu$L)	594.5±409.3
Immunglobulin-A (g/L)	7.6±33.7
Interleukin-6 (pg/mL)	37.3±90.9
D-Dimer (μg/mL)	1.1±1.8
Fibrinogen (mg/dL)	524.2±151.1
Ferritin (ug/L)	518.5±582.7
Mortality No Yes	 116(82.9%) 24(17.1%)

Patients were classified according to blood groups and the demographic and clinical features were compared between the groups. Age and gender, hospitalization duration and mortality rates were similar in all the blood group types (Table 2).

Table 2. Bivariate analyses between the demographic and clinical parameters, and the blood groups

	Blood type				***p***
	0 (n=34)	**A** (n=59)	**B** (n=34)	**AB** (n=13)	
Age median (1.quantile 3.quantile)	68.5(50.0-73.3)	69.0(57.0-79.0)	67.5(58.8-76.3)	73(65.0-77.0)	0.602^K
Gender (n,%) Female Male	 17 (50.0%) 17 (50.0%)	 30 (50.8%) 29 (49.2%)	 14 (41.2%) 20 (58.8%)	 7 (53.8%) 6 (46.2%)	0.792^{x2}
Hospitalization Duration median (1.quantile-3.quantile)	9.0(6.0-14.3)	10(6.0-15.0)	9.5(6.0-16.3)	10(6.0-16.0)	0.960^K

Mortality (n,%) No Yes	 29 (85.3%) 5 (14.7%)	 50 (84.7%) 9 (15.3%)	 27 (79.4%) 7 (20.6%)	 10 (76.9%) 3 (23.1%)	0.826^{x2}

Hematological, biochemical and infectious parameters including white blood cell (WBC), hemoglobin (Hgb), hematocrit (Htc), platelet (Plt), mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW), neutrophil, lymphocyte, monocyte, procalcitonin, fibrinogen, ferritin, IL-6, and Ig A levels were analzyed between the groups. Only D-dimer levels were found to be higher in blood group A compared with the other blood groups (Table 3).

Table 3. The comparison of laboratory findings between the blood groups

	Blood type				***p***
	0 (n=34)	**A** (n=59)	**B** (n=34)	**AB** (n=13)	
Procalcitonin(μg/L)median(1.quantile-3.quantile)	0.1(0.0-0.1)	0.1(0.1-0.1)	0.1(0.0-0.1)	0.1(0.0-0.2)	0.875 K
WBC ($10^3/\mu L$) median(1.quantile-3.quantile)	8.64(7.22-12.37)	8.06(5.70-10.19)	8.07(5.42-10.05)	8.90(7.70-12.84)	0.294 K
HGB (g/dL) Mean±sd	12.6(12.6±2.0)	12.9(12.5±1.9)	12.6(12.6±1.5)	11.6(12.4±2.4)	0.974 A
HTC (%) Mean±sd	38.8(38.8±5.8)	39.3(38.5±5.5)	39.8(39.4±4.1)	37.8(38.0±6.6)	0.824 A
Platelet ($10^3/\mu L$) Mean±sd	296.5(315.4±149.8)	284(290.0±123.7)	281(261.9±112.6)	299(317.5±127.8)	0.321 A
MPV (fL) median(1.quantile-3.quantile)	10.3(9.9-11.0)	10.5(9.9-11.0)	10.4(9.8-11.2)	10.3(9.8-11.2)	0.896 K
PCT (%) Mean±sd	0.3(0.32±0.14)	0.3(0.30±0.12)	0.3(0.28±0.10)	0.3(0.33±0.11)	0.391 A
PDW (%) median(1.quantile-3.quantile)	11.9(10.9-13.6)	11.9(10.8-13.1)	12.1(10.7-13.5)	12.0(10.4-13.8)	0.989 K
Neutrophil ($10^3/\mu L$) median(1.quantile-3.quantile)	6840(4337-9862)	6000(3690-7530)	5640(3865-9520)	7250(4980-10650)	0.381 K
Lymphocyte ($10^3/\mu L$) median (1.quantile-3.quantile)	1375(967-1750)	1000(630-1840)	1090(710-1715)	1220(700-1560)	0.579 K
Monocyte ($10^3/\mu L$) median(1.quantile-3.quantile)	580(420-780)	590(420-750)	495(242.5-717.5)	480(270-765)	0.331 K
Ig A (g/L) median(1.quantile-3.quantile)	2.4(1.8-3.8)	2.7(2.0-3.9)	2.9(2.3-3.6)	2.4(1.6-3.5)	0.335 K
IL 6 (pg/mL) median(1.quantile-3.quantile)	23.1(10.6-43.9)	12.3(6.8-32.6)	12.8(5.9-23.9)	20.8(13.0-54.6)	0.086
D-Dimer (μg/mL) median(1.quantile-3.quantile)	0.5(0.2-0.9)	0.7(0.5-1.3)	0.5(0.3-1.0)	0.7(0.4-1.6)	***0.038 K***
Fibrinogen (mg/dL) median(1.quantile-3.quantile)	507.5(442.8-664.5)	503(426.0-594.0)	486.5(401.0-673.5)	501(350.5-527.5)	0.607 K
Ferritin (ug/L) median (1.quantile-3.quantile)	243.5(179.8-728.8)	311(181.0-680.0)	385.5(116.8-969.3)	392(169.5-696.0)	0.950 K

[A] ANOVA / [K] Kruskal-Wallis (Mann-Whitney U-test)

Mann Whitney u test with Bonferroni correction was made to determine which group the difference consisted of and it was found that there was a difference between 0 – A groups (Table 4).

Table 4. Bonferroni correction in finding intergroup difference for d-dimer

	Test Statistic	Std.Error	Std.Test Statistic	Sig.	Adj.Sig.[a]
0 -B	-3,809	9,835	-,387	,699	1,000
0 -A	-21,445	8,731	-2,456	,014	**,084**
0 -AB	-22,260	13,223	-1,683	,092	,554
B -A	17,636	8,731	2,020	,043	0,260
B -AB	-18,451	13,223	-1,395	,163	,977
A -AB	-,816	12,424	-,066	,948	1,000

4. Discussion

COVID-19 infection, which is highly transmissible human to human has caused a global pandemic threatening public health worldwide. Recent studies have reported predictive factors including demographic, clinical, immunological, hematological, biochemical, and radiographic findings that may be of use to clinicians in the prediction of COVID-19 severity. Among these factors, blood groups have also attracted the attention of researchers as SARS-CoV replicates in cells which can express ABO blood group antigens. Blood group antigens are expressed in many tissues, including erythrocyte membrane, lung epithelial cells, platelets, and endothelium etc. Spike (S) proteins of coronaviruses are associated with ACE-2 (angiotensin-converting enzyme 2) cell surface receptor in this cells and Anti-A and Anti –B antibodies can bind to the S protein and block its interaction with ACE2 (W. Li et al., 2006). Lu et al. found a structural similarity between the receptor-binding domains of SARS- CoV-2 and SARS-CoV (Lu et al., 2020). Both SARS-CoV and SARS-CoV-2 use the same receptor, which is the ACE-2 cell surface receptor on cells (Gemmati et al., 2020; Lu et al., 2020).). For all these reasons, the same mechanism applies to the SARS- CoV-2.
In Turkey, blood groups are distributed as 43.9%, 14.9%, 33.1% and 8.1% for the groups of A, B, 0, and AB respectively (Dilek et al., 1998). In a study of 2173 COVID-19 patients, Zhao et al. reported that A blood group was associated with a higher risk and O blood group was associated with a lower risk for COVID-19 infection (Zhao et al., 2020). Similar results were obtained in the study by Zietz and et al., in which the data of 1559 patients were analyzed (Zietz & Tatonetti, 2020). Li J, et al. reported that in COVID-19 patients, the ratio of blood group A was significantly higher than that of the control group, and the ratio of blood group O was significantly lower than that of the control group (J. Li et al., 2020). In the current study, the ABO blood group showed a distribution of 42.1%, 24.3%, 9.3% and 24.3% for A, B, AB and O respectively. Age and gender distribution of the patients did not differ significantly in the O, A, B and AB blood groups. In the patients with COVID-19, B blood group was seen more and O blood group was seen less. It can be interpreted from this result that the risk of COVID-19 may be higher in patients with B blood group.
Göker et al.reported that blood groups had no significantly predictive effects on the intubation requirement, admission to intensive care units, or mortality (Göker et al., 2020). Zietz et al. reported that the intubation requirement risk increased in AB and B blood groups, decreased in A blood group, and the risk of death increased in AB blood groups and decreased in A and B blood groups (Zietz & Tatonetti, 2020). In the current study, hospitalization duration and mortality rates did not differ significantly in the O, A, B and AB blood groups. Arslaner H. et all. Reported that similar data(Aslaner et al., 2021).
D-dimer, which is a fibrin degradation product, contains two D fragments. It is not normally present in human blood but is increased when the coagulation system has been activated. It has been reported that there is a relationship between increased D-dimer elevation and mortality (Fogarty et al., 2020; Tang, Li, Wang, & Sun, 2020; Zhou et al., 2020). Luo Y. et al.

reported that patients with influenza had higher concentrations of D-dimer than patients with COVID-19 (Luo et al., 2020). Shiyu Yin et al reported that D-dimer levels were found to be higher in non-COVID-19 pneumonia patients than in COVID-19 pneumonia patients (Yin, Huang, Li, & Tang, 2021). In the current study, D-dimer was statistically significantly higher in COVID-19 patients with blood group A compared to those with O, B and AB blood groups. To the best of our knowledge, this result found in the current study has been reported for the first time in the literature. With this limited finding, it can be suggested that more attention should be paid to thrombotic events in patients with A blood group who have COVID-19. Nevertheless, further studies are needed to show the underlying molecular mechanism of these findings.

5. Conclusion and Suggestions

Since the discovery of blood groups, the relationship of these with various infections has always been of interest. The COVID-19 pandemic still continues to be important and serious. The determination of predictive parameters is one of the most important steps for rapid intervention, effective treatment and decreasing mortality and hospitalization duration. The results of the current study demonstrated that hospitalization duration and mortality rates did not differ significantly among all blood types. However, D-dimer levels were statistically significantly higher in COVID-19 patients with A blood group. As no difference was determined in mortality rates between the groups, larger studies are needed to reflect D-dimer levels on the clinical course and thus on daily practice. The current study may guide more comprehensive studies on the relationship between blood group and COVID-19.

Declarations*:* The authors declare that this article is not produced from the thesis work,. The authors declared no conflict of interest. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey (14.06.2021-113/05). Author contributions: İdea: SM, BS, FY, MA. Design:SM, MT, FY, MA. İnspection: PT, MT, FY, MA. Resources:PT, AY, MT, MA. Materials:PT, AY, MA. Data collection and/or processing:MRA, AY, FY, MA. Analysis and/or interpretation:MRA, HBAÖ, FY. Literature research: MRA, HBAÖ, FY. Writing: HBAÖ, BS, FY. Critical review: SM, BS,

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