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ORIGINAL ARTICLE

Autoimmunity and Clinical Immunology

Adverse COVID-19 outcomes in immune deficiencies: Inequality exists between subclasses

Elif Karakoc Aydiner[1,2,3] | Sevgi Bilgic Eltan[1,2,3] | Royale Babayeva[1,2,3] | Omer Aydiner[4] | Eda Kepenekli[5] | Burcu Kolukisa[1,2,3] | Asena Pinar Sefer[1,2,3] | Ezgi Yalcin Gungoren[1,2,3] | Esra Karabiber[6] | Esra Ozek Yucel[7] | Oner Ozdemir[8] | Ayca Kiykim[9] | Hasibe Artac[10] | Nalan Yakici[11] | Koray Yalcin[12] | Haluk Cokugras[9] | Tulin Tiraje Celkan[13] | Fazil Orhan[11] | Mehmet Akif Yesilipek[12] | Safa Baris[1,2,3] | Ahmet Ozen[1,2,3]

[1]Faculty of Medicine, Division of Pediatric Allergy-Immunology, Marmara University, Istanbul, Turkey

[2]Istanbul Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies, Istanbul, Turkey

[3]The Isil Berat Barlan Center for Translational Medicine, Istanbul, Turkey

[4]Department of Interventional Radiology, Kartal Research and Training Hospital, İstanbul, Turkey

[5]Faculty of Medicine, Division of Pediatric Infectious Diseases, Marmara University, Istanbul, Turkey

[6]Faculty of Medicine, Department of Chest Diseases, Division of Adult Allergy-Immunology Marmara University, Istanbul, Turkey

[7]Faculty of Medicine, Division of Pediatric Allergy-Immunology, Istanbul University, Istanbul, Turkey

[8]Faculty of Medicine, Division of Pediatric Allergy-Immunology, Sakarya University, Sakarya, Turkey

[9]Faculty of Medicine, Division of Pediatric Allergy-Immunology, Istanbul Cerrahpasa University, Istanbul, Turkey

[10]Faculty of Medicine, Division of Pediatric Allergy-Immunology, Selcuk University, Konya, Turkey

[11]Faculty of Medicine, Division of Pediatric Allergy-Immunology, Karadeniz Teknik University, Trabzon, Turkey

[12]Pediatric Hematology/Oncology and Stem Cell Transplantation Department, Medical Park Goztepe Hospital, Istanbul, Turkey

[13]Faculty of Medicine, Division of Pediatric Hematology and Oncology, Istanbul Cerrahpasa, Istanbul, Turkey

Correspondence
Elif Karakoc Aydiner and Ahmet Ozen, Pendik Training and Research Hospital, Fevzi Cakmak Mah. Mimar Sinan Cad No:41 Ust Kaynarca Pendik, Istanbul, Turkiye.
Emails: elifaydiner@gmail.com (EKA); ahmetozen_md@yahoo.com (AO)

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Abstract

Background: Genetic deficiencies of immune system, referred to as inborn errors of immunity (IEI), serve as a valuable model to study human immune responses. In a multicenter prospective cohort, we evaluated the outcome of SARS-CoV-2 infection among IEI subjects and analyzed genetic and immune characteristics that determine adverse COVID-19 outcomes.

Methods: We studied 34 IEI patients (19M/15F, 12 [min: 0.6-max: 43] years) from six centers. We diagnosed COVID-19 infection by finding a positive SARS-CoV-2 PCR test (n = 25) and/or a lung tomography scoring (CORADS) ≥4 (n = 9). We recorded clinical and laboratory findings prospectively, fitted survival curves, and calculated fatality rates for the entire group and each IEI subclass.

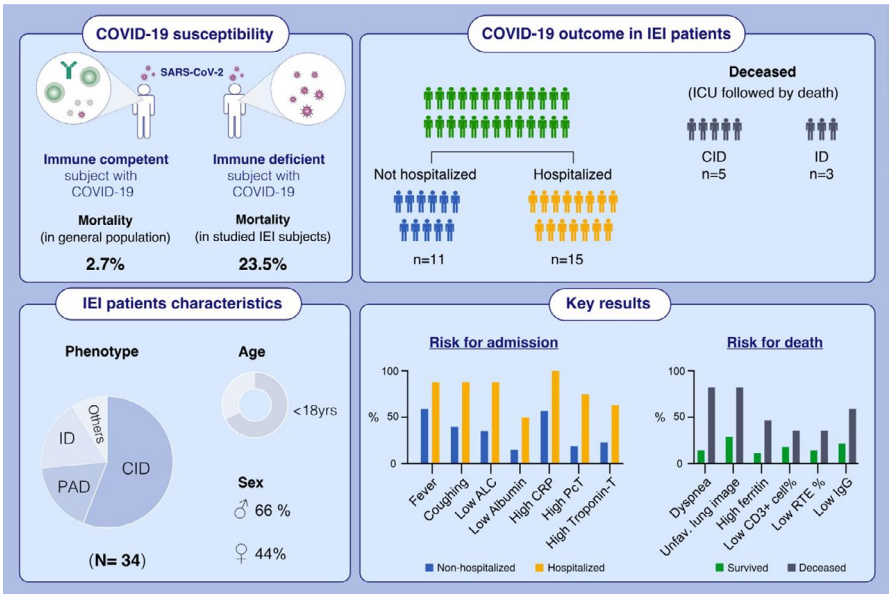
Abbreviations: ALC, absolute lymphocyte count; CID, combined immune deficiency; COVID-19, coronavirus infectious disease 2019; CRP, C-reactive protein; F, female; ICU, intensive care unit; ID, immune dysregulation; IEI, inborn errors of immunity; Ig, immunoglobulin; M, male; PAD, predominantly antibody deficiency; PcT, procalcitonin; RTE, recent thymic emigrants; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Unfav, unfavorable.

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Results: Nineteen patients had combined immune deficiency (CID), six with predominantly antibody deficiency (PAD), six immune dysregulation (ID), two innate immune defects, and one in the autoinflammatory class. Overall, 23.5% of cases died, with disproportionate fatality rates among different IEI categories. PAD group had a relatively favorable outcome at any age, but CIDs and IDs were particularly vulnerable. At admission, presence of dyspnea was an independent risk for COVID-related death (OR: 2.630, 95% CI; 1.198–5.776, $p < .001$). Concerning predictive roles of laboratory markers at admission, deceased subjects compared to survived had significantly higher CRP, procalcitonin, Troponin-T, ferritin, and total-lung-score ($p = .020$, $p = .003$, $p = .014$, $p = .013$, $p = .020$; respectively), and lower absolute lymphocyte count, albumin, and trough IgG ($p = .012$, $p = .022$, $p = .011$; respectively).

Conclusion: Our data disclose a highly vulnerable IEI subgroup particularly disadvantaged for COVID-19 despite their youth. Future studies should address this vulnerability and consider giving priority to these subjects in SARS-Cov-2 therapy trials.

KEYWORDS
COVID-19, inborn errors of immunity, outcome, SARS-Cov-2



GRAPHICAL ABSTRACT
34 IEI patients aged between 0.6 and 43 years, eight patients (23.5%) succumbed to COVID-19, indicating a highly vulnerable condition to COVID-19. Laboratory markers associated with mortality included elevated acute phase reactants, ferritin, troponin T, TLS, and reduced ALC levels, albumin, and baseline IgG. Coughing, dyspnea, CORADS category 4–6, and negative SARS-CoV-2 PCR at admission were among the predictors of lethal outcome.

1 | INTRODUCTION

In December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA virus, emerged in Hubei (China) as a novel human pathogen causing coronavirus disease 2019 (COVID-19)[1–3] with global spreading that led to a tragic pandemic. The spectrum of the infection is broad, ranging from asymptomatic illness to severe outcomes, including death. Symptomatic cases may experience diverse symptoms, including respiratory collapse, myocarditis, and thromboembolism, culminating in a fatal multiorgan failure syndrome.[4] During the time of this study, the case fatality rate of SARS-CoV-2 infection has ranged from 1% to 20%, compared to a disease fatality rate between 0.2% and 1.3% among the general population.[5] Epidemiologic data impart certain disadvantaged groups, who mainly stratified by age (each decade of life beyond age 50 years multiplying the risk), pre-existing comorbidities,

sex (male under higher risk), and genetic background.[5,6] Interestingly, the course of COVID-19 among children significantly deviates from the general population for unexplained reasons, with substantially lower mortality rates than adults.

Deficiencies of the immune system, called inborn errors of immunity (IEI), disable host defense against pathogens and cause untoward inflammatory responses that disrupt self-tissues. Over 450 gene defects, categorized under ten different functional categories, have been linked to IEIs, with each harboring distinct and overlapping features.[7,8] Whereas the most severe IEI forms profoundly impair immune protection against a diverse range of pathogens, certain IEIs create a predisposition to a narrow spectrum of pathogens, even a single microorganism. For example, defective CD27-CD70 axis produces EBV susceptibility in the affected host, and EVER1/EVER2 mutations lead to uncontrolled HPV infections; individuals with both conditions can handle broader infectious pathogens without detrimental health outcomes.[9] A recent survey showed that patients (aged 17–77 years) with immune defects affecting the TLR3- and IRF7-dependent type I interferon (IFN) production are predisposed to lethal SARS-CoV-2 infection.[6] The complexity of COVID-19 pathogenesis, that is, multiple system involvement and different inflammatory features, suggests that a breach in other signaling pathways may also create a vulnerability to this virus. Since the spread of infection across the world, researchers from different locations reported on COVID-19 outcomes among IEI individuals.[10–13] Although the accumulating evidence contributes to our understanding of COVID-19 among IEI subjects, the studies report disparate results, mainly because of an assortment bias due to the differences in these disorders' geographic distribution. For example, IEIs that follow an autosomal recessive inheritance are relatively more common in the Middle East and North African countries and Turkey than in Western

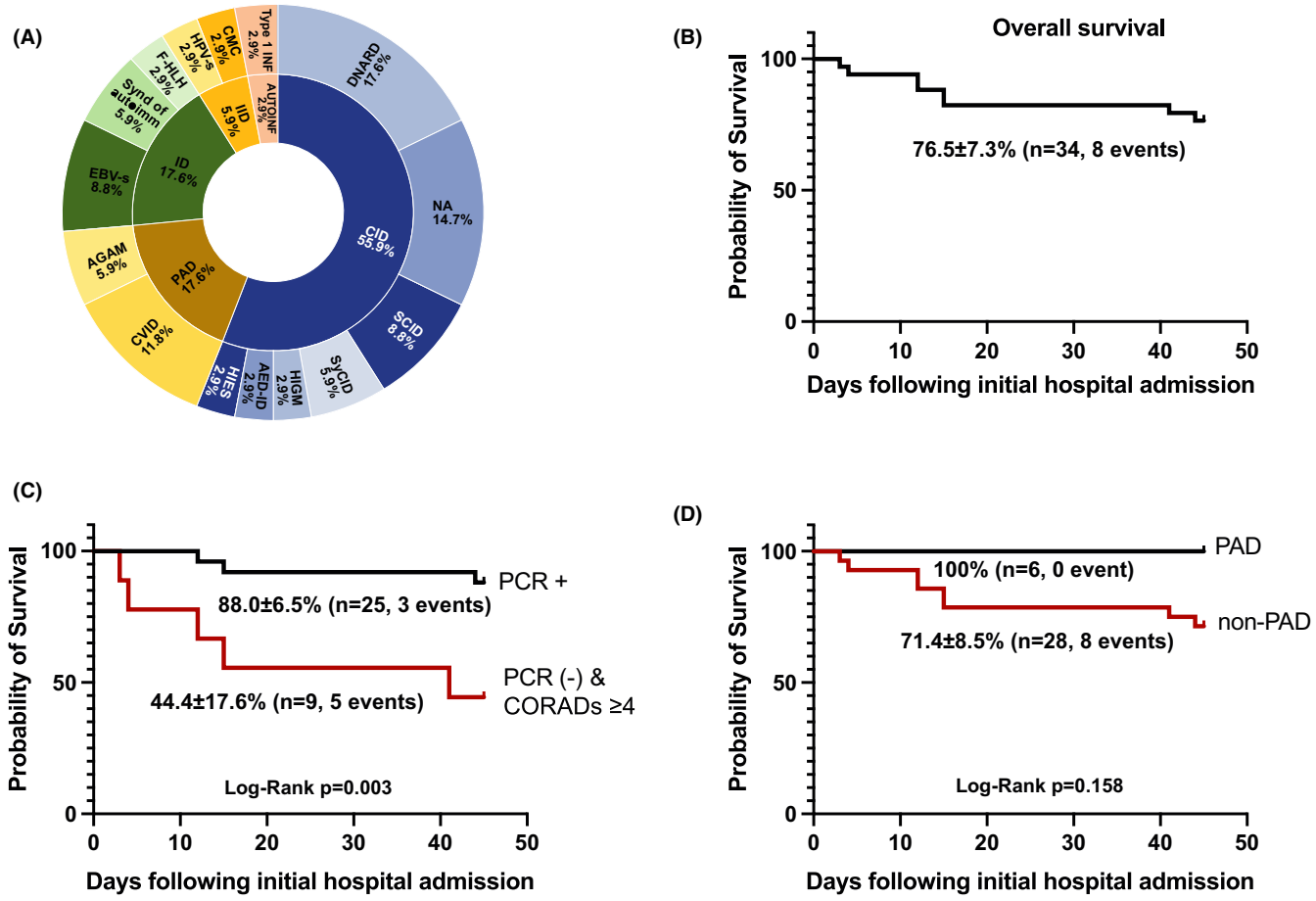


FIGURE 1 Distribution of IEI categories and the probability of survival following COVID-19. (A) A pie-chart displays of the IEI categories and corresponding subclasses of the study group. AED-ID: anhidrotic ectodermal dysplasia-immune dysregulation, AGAM, agammaglobulinemia; AUTOINF, autoinflammatory; CID, combined immunodeficiency; CMC, chronic mucocutaneous candidiasis; CVID, common variable immunodeficiency; CORADS, COVID-19 Reporting and Data System; COVID-19, coronavirus infectious disease 2019; DNARD, DNA repair defects; EBV-s, Epstein-Barr virus susceptibility; F-HLH, familial hemophagocytic lymphohistiocytosis; HIES, hyperimmunoglobulin E syndrome; HIGM, hyperimmunoglobulin M syndrome; HPV-S, human papillomavirus susceptibility; ID, immune dysregulation; IID, innate immune defect; Type I IFN, Type I interferonopathy; NA, not available; PAD, predominantly antibody deficiency; PCR, polymerase chain reaction; PID, primary immune deficiency; SCID, severe combined immunodeficiency; SCID, syndromic combined immunodeficiency; Synd of autoimm, syndromes of autoimmunity. (B–D) Kaplan-Meier curves showing the probability of survival as a function of days following hospital admission for the entire study group or the subgroups indicated in each graph

TABLE 1 Demographic, clinical, and laboratory features of COVID-19 PCR-positive patients

Patient number	P1	P22	P2	P23	P3	P4	P21	P5	P16	P8	P18
Age (years)	4.2	0.7	16.6	4.6	2.6	18.2	6.7	8.4	31.8	12.3	6.4
Gender	F	F	M	M	M	M	F	M	F	M	M
PID phenotype	SCID	SCID	CID	CID	CID	CID	CID	CID	CID	CID	CID
Sub-phenotype	SCID	SCID	SyCID	SyCID	DNARD	DNARD	DNARD	NA	NA	HIGM	AED-ID
Genotype	IL-7Ra	NA	NA	MODP1	DNMT3	NBS	ATM	NA	NA	NA	NEMO
Presenting symptom	None	Fever	Fever, cough, fatigue	Fever, diarrhea, abdominal pain	Fever, dyspnea, cough, diarrhea	Fever, cough	Fever, fatigue	Fever, cough, fatigue, sore throat	Fever, cough, chest pain, sore throat	Fever, abdominal pain, anosmia, diarrhea	Fever, cough, dyspnea, sore throat
COVID−19 contact	+	-	+	+	-	+	-	+	+	+	+
Co-morbidities	-	-	BE	AD	BE	ALL, BE	IBD	-	BE	-	IBD
Prophylaxis	-	IVIG, TMP-SMX, FLUC	IVIG, TMP-SMX	-	IVIG, TMP-SMX	IVIG, TMP-SMX	IVIG, TMP-SMX	IVIG, TMP-SMX	TMP-SMX	SCIG, TMP-SMX	TMP-SMX, AZT
Other treatments	Post HSCT 5 years	-	-	-	-	Steroid	-	-	-	-	-
Laboratory features											
ALC #/mm^3 (>1,500)	3,900	1,800	1,600	2,500	1,970	**300**	1,600	**1,400**	**1,190**	NA	2,600
ANC #/mm^3 (>1,500)	**1,100**	**1,270**	5,500	6,000	1,950	**100**	**400**	5,100	3,200	NA	2,300
ANC/ALC (high risk if>3.13)	0.28	1.4	**3.4**	2.3	0.9	0.3	0.3	**3.6**	2.6	NA	0.8
CRP (0–5 mg/L)	3	**10**	**52**	**26**	**11**	**194**	**35**	**10**	**7**	NA	**6.4**
ESR (<20 mm/h)	NA	100	NA	NA	NA	**23**	NA	NA	NA	NA	**104**
PcT (0–0.5 µg/L)	NA	0.16	0.33	0.09	NA	0.26	**3.13**	0.02	NA	NA	0.05
Ferritin (7–282 µg/L)	NA	215	79	NA	NA	**319**	**980**	NA	112	NA	119
LDH (0–248 U/L)	**274**	**295**	**272**	NA	NA	**1,265**	**353**	NA	206	NA	**532**
D-Dimer (0–0.5mg/L)	NA	**1.4**	**2.7**	**2.2.**	**0.6**	**12**	**1.13**	NA	0.17	NA	**8.4**
Fibrinogen (200–400 mg/dl)	NA	240	348	310	NA	247	143	NA	**421**	NA	**419**
Troponin T (0–14 ng/L)	NA	12.8	**15**	2.2	4.3	8	0.01	NA	0.003	NA	2.3
Albumin (3.5–5.4 g/L)	4.7	3.5	**3.3**	NA	NA	**3.4**	**1.9**	4.2	NA	NA	3.7
IL-6 (0–6.4 pg/ml)	NA	NA	6.06	NA	NA	**626**	NA	NA	NA	NA	**48.2**
Echocardiogram	Napp	Normal	Normal	Normal	NA	Pericard effusion	Normal	Napp	Napp	Napp	NA
CO-RADS (1–6)	Napp	3	**5**	Napp	NA	**6**	Napp	Napp	**4**	Napp	**6**

Abbreviations: AD, atopic dermatitis; ADA, adenosine deaminase; AED-ID, anhidrosis with ectodermal dysplasia-immune deficiency; Agam, agammaglobulinemia; AIHA, autoimmune hemolytic anemia; AIRE, autoimmune regulator; AIT, autoimmune thyroiditis; ALC, absolute lymphocyte count; ALL, acute lymphoblastic leukemia; ANC, absolute neutrophil count; ATM, ataxia telangiectasia mutation AZT, azythromycine; Autoimm, Autoimmunity; BE, bronchiectasis; beige-like anchor protein; BO, bronchiolitis obliterans; BTK, bruton's tyrosine kinase; CD, cluster of differentiation; CID, combined immunodeficiency; CMP, cardiomyopathy; CO-RADS, COVID-19 reporting and data system on chest CT images; COVID, coronavirus infectious disease; CRP, c-reactive protein; CVID, common variable immunodeficiency; CXCR5, chemokine CXC motif receptor type 5; DM, diabetes mellitus; DNARD, DNA repair defect; DNMT, de novo DNA methyltransferase; EBV-s, EBV susceptibility; ESR, erythrocyte sedimentation rate; F, female; FLUC, fluconazole; HIGM, hyper-IgM; HLH, hemophagocytic lymphohistiocytosis; HPV-S, human papilloma virus susceptibility; HSCT, hematopoietic stem cell transplant; IBD, inflammatory bowel disease; ID, immune dysregulation; IL, interleukin; IL-7Ra, interleukin-7 receptor-α; IVIG, intravenous immunoglobulin; LP, lymphoproliferation; LRBA, lipopolysaccharide-responsive; M, male; MOPD1, microcephalic osseous dysplastic primordial dwarfism; NA, not available; NBS, nijmegen breakage syndrome; NEMO, NF-kB essential modulator; PAD, predominantly antibody deficiency; PCR, polymerase chain reaction; PCT, procalcitonin; PID, primary immune deficiency; RLTPR, RGD leucine repeat tropomodulin domain and proline-rich domain containing protein; SCID, severe combined immunodeficiency; SCIG, subcutaneous immunoglobulin; SyCID, syndromic combined immune deficiency; TACI, transmembrane activator and calcium-modulator and cyclophilin-ligand interactor; TMP-SMX, trimetoprim sulfamethoxazole; Type IFN, Type I interferonopathy.

Bold indicates the values beyond the references.

P20	P9	P24	P10	P11	P12	P14	P6	P7	P13	P15	P17	P25	P19
13.6	7	27	19.3	21.1	29.1	7.8	5.1	9	15	29.7	2.6	43	12
M	M	M	M	F	F	F	M	M	M	M	F	M	F
CID	PAD	PAD	PAD	PAD	PAD	PAD	ID	ID	ID	ID	ID	IID	Auto-inflammatory
NA	Agam	Agam	CVID	CVID	CVID	IgG2 deficiency	EBV-s	EBV-s	EBV-s	Autoimm	Autoimm	HPV-s	Type I-IFN
NA	BTK	BTK	NA	NA	TACI	NA	RLTPR	RLTPR	CD137	LRBA	AIRE	CXCR4	ADA2
Sore throat	None	Anosmia, fever	None	Sneeze, anosmia	Fever, cough, fatigue, abdominal pain, diarrhea, sore throat	Headache, abdominal pain	None	Fever	Fever, cough, dyspnea, sore throat, abdominal pain	Fatigue, abdominal pain, back pain, diarrhea	Fever, dyspnea, cough	None	Fever arthralgia
+	+	+	+	+	-	+	-	-	-	+	-	-	+
Allergic rhinitis	-	-	Type I DM	BE, AIHA, AIT	BE	-	-	-	HLH, lymphoma	BE, IBD, LP, gastric cancer	BO	BE	Intracranial thrombosis
IVIG, TMP-SMX	IVIG, TMP-SMX	SCIG	IVIG	IVIG, TMP-SMX	IVIG	IVIG, TMP-SMX	IVIG, TMP-SMX	IVIG, TMP-SMX	IVIG, TMP-SMX	IVIG	IVIG, FLUC	IVIG	IVIG
-	-	-	Insulin	-	-	-	-	-	Steroid, Etoposide, Cyclosporine	Post HCST 2 years	-	-	-
2,300	3,900	NA	NA	4,400	**1,070**	1,500	6,200	4,600	**1,300**	**1,180**	**900**	**1,130**	**1,400**
740	5,300	NA	NA	8,700	4,400	1,740	5,800	4,000	3,100	1,940	2,100	**700**	**1,100**
0.3	1.3	NA	NA	1.9	**4.1**	1.1	0.9	0.8	2.3	1.6	2.3	0,6	0.7
1	**11.5**	NA	NA	1	**5**	3	1	2.5	**55**	3	**6.8**	**12**	**46**
2	NA	NA	NA	NA	NA	NA	NA	NA	**107**	5	NA	**NA**	NA
0.01	NA	NA	NA	NA	NA	0.02	0.02	NA	**5.3**	NA	**1.15**	**NA**	1.8
NA	NA	NA	NA	**285**	33	32	NA	NA	**6,200**	91	NA	**NA**	**834**
184	**360**	NA	NA	**483**	184	**388**	**318**	NA	**3,100**	156	**470**	**NA**	**335**
1	0.1	NA	NA	0.5	0.2	**1.8**	NA	NA	**2.2**	0.2	**4.1**	**NA**	**3.2**
267	NA	NA	NA	NA	NA	NA	NA	NA	**509**	NA	277	**NA**	**430**
1.2	0.1	NA	NA	NA	0.1	2.3	NA	NA	11	2.8	NA	NA	NA
4.3	4.3	NA	NA	NA	NA	4.5	4.4	4.2	**3.2**	5.2	NA	**NA**	4
NA	NA	NA	NA	NA	NA	NA	NA	NA	**321**	NA	NA	**NA**	NA
Napp	Napp	Napp	Napp	Napp	NA	Napp	Napp	Napp	CMP	Napp	NA	Napp	Napp
1	Napp	Napp	**5**	Napp	NA	Napp	Napp	Napp	**5**	2	NA	4	

nations because of higher consanguinity rates. Here, we describe a prospective multicenter survey exploring the COVID-19 performance of IEI subjects, wishing to determine risk factors for severe disease. The present study's findings differ from the reports of its kind in several fundamental ways, perhaps because of the IEI categories' distribution characteristics in the investigated population, where combined immune deficiencies (CID) predominated the studied population. Despite their youth (which is a favorable factor in the general population), we show that a vulnerable group exists among IEIs, calling out to trials of COVID-19–specific therapies in these patients.

2 | MATERIALS AND METHODS

This study is a prospective survey that examined the outcome of COVID-19 among patients with a prior diagnosis of IEI. We studied 34 patients from six different IEI centers in Turkey admitted during March 2020-December 2020. The study was approved by the Ethics Committee for Clinical Trials of the Marmara University School of Medicine with the protocol ID of 09.2020.621. We obtained written informed consent from the patients (if ≥18 years old) or their legal guardians (for those <18 years). Additionally, verbal assent was obtained from children who were >7 years of age.

We made a clinical diagnosis of IEI according to the European Society for immunodeficiencies (ESID) criteria.[14] IEI classes were determined according to the most recent International Union of Immunological Societies (IUIS) classification system, categorizing patients under ten main phenotypical groups, each group comprising numerous molecular subclasses.[7] Diagnostic investigations and the therapeutic approaches generally followed the COVID-19 guidelines of the Ministry of Health of the Republic of Turkey,[15] with patient-specific additional modifications made according to the primary physician's discretion based on the local practice and standard medical applications. We evaluated patients for COVID-19 if they described a set of clinical symptoms, suggesting COVID-19, or if they described a contact history. A COVID-19 diagnosis was made when at least one of the two criteria was satisfied: i. a positive reverse transcription-polymerase chain reaction (RT-PCR), using SARS-CoV-2 kits which were approved by the World Health Organization (WHO)[16]; ii. a radiological score between 4 and 6, assessed by chest computed tomography (COVID-19 Reporting and Data System classification system =CORADS).[17] CORADS of the Radiological Society of North America developed to score the likelihood of COVID-19 on a scale of 1 to 5, rated the images as a score of 1 corresponded to "negative" CORADS; CORADS 2 corresponded to the "atypical" category; CORADS 3 and CORADS 4 corresponded to the "indeterminate" class, with "3= lower" and "4= higher" likelihood, respectively; and CORADS 5 was deemed "typical" for COVID-19. A CORADS of 6 shows typical findings in the presence of a positive PCR test.[17] Total lung scores (TLS) were calculated according to Li et al.'s recommendation.[18] Briefly, TLS used lung tomography images to grade the overall radiologic involvement, in which percent involvement of each lobe was transformed into scores (score =1 for <5% involvement, score =2 for 5%–25%, score =3 for 26%–49%, score =4 for 50%–75%, score =5 for >75%, score 6= score 5 plus PCR positivity), and all scores summated to yield an overall lung score. The possible range for TLS was 0–25.

Patient medical charts were reviewed carefully to capture all relevant clinical data and entered in a structured questionnaire. Requested information included a contact history and the COVID-19–related symptoms: fever, cough, sore throat, dyspnea, shivering, abdominal pain, loss of smell and taste, diarrhea, arthralgia, fatigue, and presence of any additional complaints of interest. We recorded the blood test results, including a complete blood count, liver enzymes (serum glutamic-oxaloacetic transaminase: SGOT and serum glutamic pyruvic transaminase: SGPT) and renal function tests (creatinine and blood urea nitrogen), coagulation parameters (prothrombin time: PT and activated partial thromboplastin time: aPTT, INR, D-Dimer, and fibrinogen), acute phase reactants (C-reactive protein: CRP and procalcitonin: PcT), ferritin, lactate dehydrogenase (LDH), troponin T, albumin, and IL-6. An echocardiography examination report and sputum and blood culture results were noted if available. We also recorded the treatment regimens employed, duration of hospital stays, if any, and the infection outcomes.

The baseline demographics and the clinical and laboratory findings relevant to IEI were recorded: IEI category and molecular diagnosis (if known); a history of BCG and measles vaccination; comorbidities including bronchiectasis, colitis, autoimmunity, lymphoproliferation, malignancy, hypertension, and diabetes; and previous prophylactic antibiotic usage. Historical and recent immune investigations, such as lymphocyte subsets and serum trough IgG levels, were documented.

The case fatality rate (CFR) was calculated by dividing the number of deceased patients' overall symptomatic COVID-19 cases (either confirmed by SARS-CoV-2 PCR and/or with a CORADS score ≥4, as detailed above). The infection fatality rate was defined as the proportion of deceased patients among all COVID-19 cases regardless of their symptom status (COVID-19 diagnosis is detailed above).

2.1 | Statistics

We calculated the median and interquartile range values for continuous variables and frequency and percentage for the categorical variables. A Mann-Whitney *U* test compared between-group differences for continuous variables that are not normally distributed. Fisher's exact test compared the categorical variables for statistical significance. Related groups were compared using a Wilcoxon test for the nonparametric continuous variables. Overall survival (OS) was assessed for the duration between the initial admission to death or the last follow-up examination without event. Analysis of OS was done using the Kaplan-Meier method. p values <.05 were considered statistically significant. Statistical analysis was done using SPSS 20 (SPSS Inc, Chicago, Ill) and GraphPad Prism 8 (GraphPad Software Inc, San Diego, Calif).

3 | RESULTS

We found that among 34 IEI patients enrolled, the predominant category was combined immune deficiencies (CID) (19 patients), among which three were classified as severe CID (SCID). Six patients were categorized under predominantly antibody deficiency (PAD), six with immune dysregulation (ID), two with innate immune deficiency, and one with an autoinflammatory syndrome. The distribution of IEI categories and the molecular diagnoses are presented in Figure 1A and Tables 1 and 2.

Our cohort was slightly dominated by males (55.9%) with an M/F ratio of 19/15. The median age at enrollment was 12 years (min-max: 0.6–43 years). Twenty-five patients (73.5%) had a positive PCR test for the SARS-CoV-2 virus; the remaining cases received COVID-19 diagnosis based on a CORADS score ≥4 in the presence of positive contact history and/or compatible clinical symptoms. Lung CT characteristics of the latter group are shown in Figure S1. Despite the lack of microbiological evidence for SARS-CoV-2, these cases were considered probable COVID-19 and treated accordingly. It is known that the sensitivity of a PCR test ranges between 71 and 98%[19]; the combined use of clinical investigations and radiological scoring is widely accepted as a valuable diagnostic method. In the overall study population, the follow-up duration of the COVID-19 period was terminated by death in eight patients (23.5%); 26 survived the infection (Figure 1B). We analyzed if survival rates were different between patients with or without a positive PCR test; PCR-positive patients had an overall survival rate of 55.8%, whereas this figure for the subgroup of patients with negative PCR but with CORADS ≥4 was 44.4% ($p = .003$) (Figure 1C).

3.1 | Clinical characteristics of the study population

The frequencies of each presenting symptom were as follows: fever 67.5% ($n = 23$); coughing 50% ($n = 17$); dyspnea 32.4% ($n = 11$); fatigue/myalgia 41.4 ($n = 14$); diarrhea 23.8% ($n = 8$); and abdominal pain 17.6% ($n = 6$). Anosmia or taste abnormalities are well-known components of COVID-19 symptomatology, but these were rare in our study group (only three patients). None of the patients had a rash at admission; five out of 34 patients were asymptomatic at presentation to a hospital. Recent contact history with a COVID-19 case was described in 58.8% of the patients (20/34). Having dyspnea at hospital admission was found to be an independent risk factor for having a negative PCR, but CORADS score ≥4 (OR: 2.511, 95% CI; 1.137–5.543, $p = .002$) and mortality (OR: 2.630, 95% CI; 1.198–5.776, $p < .001$). The presence of fever and coughing at presentation was found to be significant risk factors for hospital admission (OR: 5.576, 95% CI; 1.827–17.013, $p = .001$ and OR: 4.500, 95% CI; 1.136–17.830, $p = .026$). Interestingly, fever was less common among CID cases than the remaining population (7/15 in CID vs. 16/19 among the rest of the group; $p = .030$).

When we evaluated patient comorbidities prior to COVID-19, 22 patients (64.7%) had significant comorbid conditions: bronchiectasis 58.8% ($n = 20$); autoimmunity 17.6% ($n = 6$); colitis 14.7% ($n = 5$); allergy 8.8% ($n = 3$); current or previous history of malignancy 8.8% ($n = 3$); lymphoproliferation 5.9% ($n = 2$); diabetes mellitus 5.9% ($n = 2$); and hypertension 2.9% ($n = 1$). Nothing the immunization history, 21 (67.7%) patients had a BCG vaccination and 21 (67.7%) had measles vaccination documented in their charts. Clinical characteristics of our study with respect to survival status is presented in Figure 2A.

3.2 | Laboratory and radiological findings

Laboratory data, including complete blood count, acute phase reactants, lactate, LDH, albumin, ferritin, d-dimer, and troponin T, are presented in Table S1. At the time of initial hospital admission, deceased patients compared to survived ones showed significantly higher levels of C-reactive protein (CRP), procalcitonin (PcT), troponin T, and ferritin ($p = .020$, $p = .003$, $p = .014$, and $p = .013$; respectively) and lower levels of absolute lymphocyte count (ALC) and albumin ($p = .012$ and $p = .022$) (Figure 2B–G). Deceased patients tended to have a higher value of ANC and lower eosinophil and monocyte counts, despite without a statistically significant difference (Figure 3A–C). The distribution of abnormal laboratory assessments concerning survival outcomes is presented in Figure 2A.

The distribution of CORADS (applicable for 58.8% patients, $n = 20$) was as follows: category-1 5% ($n = 1$), category-2 5% ($n = 1$); category-3 15% ($n = 3$); category-4 20% ($n = 4$); category-5 45% ($n = 9$); and category-6 10% ($n = 2$). Thus, 15 patients had a CORADS score of ≥4, the range considered being highly suggestive of COVID-19. The median TLS for the overall cohort was 5 (min=0 and max =20). Interestingly, TLS was significantly lower among patients who survived COVID-19 as compared to those who succumbed to the infection (Figure 2H).

We investigated the clinical parameters associated with a relatively more severe course of COVID-19; we considered "requirement for inpatient care" as a surrogate marker for this analysis. When evaluating the laboratory tests at admission, patients were cared for as inpatient vs. those followed as outpatients had comparatively lower values of ALC and albumin ($p = .010$ and $p = .019$, respectively), and higher levels of CRP, PcT, and troponin T ($p < .001$, $p = .038$, and $p = .014$, respectively) (Table S2). A similar analysis inquiring risk factors for a need for ICU care ($n = 8$) indicated that lower levels of ALC and albumin ($p = .012$ and $p = .022$, respectively) and higher values of CRP, PcT, ferritin, troponin T, and TLS ($p = .020$, $p = .003$, $p = .013$, $p = .003$, and $p = .020$, respectively) were key biomarkers (Table S3). A more detailed analysis in these cases revealed a progressive decline in ALC and eosinophil and monocyte counts and serum albumin; by contrast, there was a positive trend in the ANC, CRP, PcT, troponin T, and ferritin (Figure 4) until death.

TABLE 2 Demographic, clinical and laboratory features of CORADS ≥4 and COVID-19 PCR negative patients

Patient number	P26	P27	P28	P29	P30	P31	P32	P33	P34
Age (years)	0.6	8.6	3.2	26.3	18.8	18.3	20.1	14.1	3.5
Gender	M	F	F	M	F	F	F	M	F
PID phenotype	SCID	CID	CID	CID	CID	CID	CID	IID	ID
Sub-phenotype	SCID	DNARD	DNARD	NA	DNARD	NA	HIES	CMC	F-HLH
Genotype	NA	ATM	ATM	NA	ATM	NA	STAT3-LOF	STAT1-GOF	STXBP2
Presenting symptom	Dyspnea	Fever, cough, dyspnea, fatigue	Fever	Fever, cough, dyspnea, sore throat	Cough, fever, fatigue	Fever, cough, dyspnea, sore throat, diarrhea	Dyspnea, cough, fever, fatigue	Fever, diarrhea, cough, dyspnea	Dyspnea, cough, fever, fatigue, diarrhea
COVID−19 contact	-	+	-	-	-	-	-	+	+
Co-morbidities	None	BE, EBV associated lymphopro-liferation	None	IBD, BE	BE	Type I DM, BE, CRF	BE, Pneumatocele, Asthma	AIHA, ITP	HLH, HTN, BE, IBD
Prophylaxis	IVIG, TMP-SMX	IVIG, TMP-SMX	IVIG, TMP-SMX	IVIG	IVIG, TMP-SMX	IVIG, AZT	IVIG, TMP-SMX	IVIG, TMP-SMX	IVIG, TMP-SMX
Other treatments	Post-HSCT 40 days, tacrolimus	Rituximab	-	Infliximab	-	Insulin	-	-	Post-HSCT 40 days, tacrolimus, steroid
Laboratory features									
ALC #/mm^3 (>1,500)	9,000	900	3,000	**900**	**1,400**	**1,000**	**800**	**600**	**120**
ANC #/mm^3 (>1,500)	**720**	1,800	4,100	**30,300**	**33,400**	**17,400**	12,800	**700**	**6,800**
ANC/ALC (high risk if>3.13)	0.1	2	1.36	**33.6**	**23.8**	**17.4**	**16**	1.1	**56**
CRP (0–5 mg/L)	**7**	**116**	**12**	**179**	**211**	**54**	**148**	**73**	**299**
ESR (<20 mm/h)	NA	10	4	NA	**79**	NA	NA	NA	NA
PcT (0–0.5 µg/L)	NA	**0.98**	**0.6**	**24**	**1.7**	**3.6**	0.08	0.17	**5**
Ferritin (7–282 µg/L)	NA	**NA**	NA	**1,192**	78	**3,985**	NA	**1,238**	NA
LDH (0–248 U/L)	203	**1,158**	**270**	**2,583**	**290**	**397**	**299**	**1,540**	239
D-Dimer (0–0.5 mg/L)	NA	**1.2**	1.1	**4.48**	**0.55**	**1.3**	4.47	**5**	NA
Fibrinogen (200–400 mg/dl)	NA	330	397	**617**	**617**	310	**589**	**401**	NA
Troponin T (0–14 ng/L)	NA	9.97	5.9	6.5	4	**28.7**	3	NA	NA
Albumin (3.5–5.4 g/L)	NA	**2.2**	3.7	**1.8**	4.3	NA	3.1	**3.1**	NA
IL−6 (0–6.4 pg/ml)	NA	NA	NA	NA	**617**	NA	NA	NA	NA
Echocardiogram	NA	Napp	Napp	Pericardial effusion	Napp	Myocarditis	Napp	Napp	NA
CO-RADS (1–5)	**5**	**4**	**5**	**4**	**4**	**5**	**5**	**4**	**5**

Abbreviations: AIHA, autoimmune hemolytic anemia; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; ATM, ataxia telangiectasia mutation; AZT, azythromycine; BE, bronchiectasis; CID, combined immunodeficiency; CMC, cutaneous mucocutaneous candidiasis; CO-RADS, COVID-19 reporting and data system on chest CT images; COVID, coronavirus infectious disease; CRF, chronic renal failure; CRP, c-reactive protein; CVID, common variable immunodeficiency; DM, diabetes mellitus; DNARD, DNA repair defect; EBV-LP, Epstein-Barr virus-related lymphoproliferation; ESR, erythrocyte sedimentation rate; F, female; F-HLH, familial hemophagocytic lymphohistiocytosis; HIES, hyper-IgE syndrome; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; HTN, hypertension; IBD, inflammatory bowel disease; ID, immune dysregulation; IID, innate immune deficiency; IL, interleukin; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenesis; M, male; NA, not available; Napp, not applicable; PAD, predominantly antibody deficiency; PCR, polymerase chain reaction; PCT, procalcitonin; PID, primary immune deficiency; SCID, severe combined immunodeficiency; STAT-1 GOF, signal transducer and activator of transcription 1 gain of function; STAT3-LOF, signal transducer and activator of transcription 3 loss of function; STXBP2, syntaxin binding protein 2; TMP-SMX, trimetoprim sulfamethoxazole.

Bold indicates the values beyond the references.

3.3 | Follow-up and outcome COVID-PID cohort

Among our cohort, 67.6% of the patients were treated as inpatient and 23.5% required ICU care. Having a negative PCR test within the context of a CORADS ≥4 was found to be an independent risk for ICU admission (OR: 4.630, 95% CI; 1.378–15.552, $p = .017$) and death (OR: 4.630, 95% CI; 1.378–15.552, $p = .017$).

In the entire cohort, the infection fatality rate was 0.24 (8/34), the case fatality rate was 0.29 (8/28), as compared to an inpatient mortality rate of 0.34 (Table S4). In a subgroup analysis in which inpatient mortality was assessed, the highest mortality was observed among those with a positive CORADS (0.55), followed by the female sex (0.5). Analyzing the IEI category's effect, CID patients and the ID group had an inpatient mortality rate of 0.33 and 0.5, respectively (Table S4) In this examination, PAD patients appeared to be particularly protected from severe COVID-19; only 2 out of 6 PAD subjects were admitted to the hospital, and none died (Figure 1D). Of interest, all patients who required ICU care eventually succumbed to COVID-19. Concerning the etiology of the deceased IEI subjects, five had CID including two with DNARD and three with ID. The cause of death following COVID-19 disease was infection-related multiorgan failure in four subjects and acute respiratory distress syndrome in the remaining four patients.

Data on the treatment approaches and infection outcomes are presented in Figure S2. Fourteen patients (41.2%) received intravenous immunoglobulin (IVIG) treatment at an anti-inflammatory/immune-modulatory dose apart from the pre-existing IgRT receipt, if any, and only one patient received corticosteroid therapy. While we were unable to assess the corticosteroid response due to small sample size, we observed no meaningful impact of the immunomodulatory IVIG use on COVID-19 outcomes; the clinical, laboratory, and immunological parameters were comparable between the subjects who received this therapy with those of non-recipients. One patient (P13) receiving convalescent plasma therapy and survived the infection. One patient (P29), who is among the deceased subjects, received extracorporeal membrane oxygenation and plasmapheresis.

3.4 | Immunological investigations of the patients before COVID-19

We found that patients who succumbed to COVID-19 compared to those who survived the infection had comparatively lower serum trough IgG levels (measured before COVID) (median [IQR]: 662 [340–1,160] vs. 1,095 [775–1,639], $p = .011$) (Figure 2I). Baseline immune characteristics of the patients concerning disease outcomes are presented in Table S1 and Figure 3D–I. $CD3^+$ T-cell counts and recent thymic emigrant (RTE) percentages were significantly lower in patients who required inpatient care compared to those followed as outpatients (Table S2), and subjects who required ICU care had lower serum IgG levels compared to those who did not (Table S3).

4 | DISCUSSION

We found that among 34 IEI patients aged between 0.6 and 43 years, eight patients (23.5%) succumbed to COVID-19, indicating IEI should be considered a highly vulnerable condition to COVID-19 irrespective of age. Laboratory markers associated with mortality included elevated acute phase reactants, ferritin, troponin T, TLS, and reduced ALC levels, serum albumin, and baseline IgG. The presence of coughing and dyspnea at presentation, CORADS category between 4 and 6, and negative SARS-CoV-2 PCR at admission were among the predictors of a lethal outcome. We also noted that among those who succumbed to COVID, there were longitudinal trends in specific markers: a negative trend in ALC, eosinophil and monocyte counts, and serum albumin; and a positive trend in ANC, CRP, PcT, ferritin, and troponin T. Examining the immunologic characteristics at baseline, patients who required inpatient care had a lower $CD3^+$ T-cell count and reduced RTE percentage. Remarkably, a need for ICU care showed a lethal COVID-19 outcome.

Although it has been more than a year since the first inception of the COVID-19 pandemic, data on IEI patients' performance during this infection is scarce, with disparate reports indicating a relative mortality risk equaling to or ten times greater than the general population.[20] Our data showed a mortality rate of 23.5%, which is ×10 and ×23.5 higher than the global population[21] and the general Turkish population (1%),[22] respectively. Female gender, age less than 18 years, a negative SAR-Cov-2 PCR, and a positive radiological score appeared as risks for mortality. Among IEI categories, CIDs comprised the biggest subgroup in our study (56%), and this group had the highest mortality rate. By contrast, all six patients in the PAD category survived COVID-19.

Interestingly, some IEI subtypes, such as chronic granulomatous disease, were not represented in this cohort. The disproportional representation of various IEI subgroups may simply be due to a biased exposure of the subjects due to disparate environmental contacts. However, increased exposure to the virus may indirectly relate to the underlying disease: For example, more frequent hospital admissions in the face of a severe IEI or regular IVIG injections at a hospital may expose subjects to persons with COVID-19. Nonetheless, we show that IEI patients are at significant risk for severe COVID-19; this group needs special attention concerning developing specific management strategies.

When we inquired about the potential infection source, 41.2% of this cohort contracted the virus from an unknown person, compared to an unknown source rate of only 5.1% for the general pediatric COVID-19 cases cared for in our center. Delavari et al. reported that only 15.8% of IEI subjects with COVID-19 contracted the disease from a household member.[20] A significant proportion of IEI subjects cannot specify the source of infection indicates a significant drawback for surveillance approaches to protect these subjects at the time of contact; it is unlikely to isolate them from unknown spreaders. Thus, in our cohort, only 15% of patients were diagnosed during the asymptomatic phase through a PCR screening because of a positive history of household COVID-19 contact,

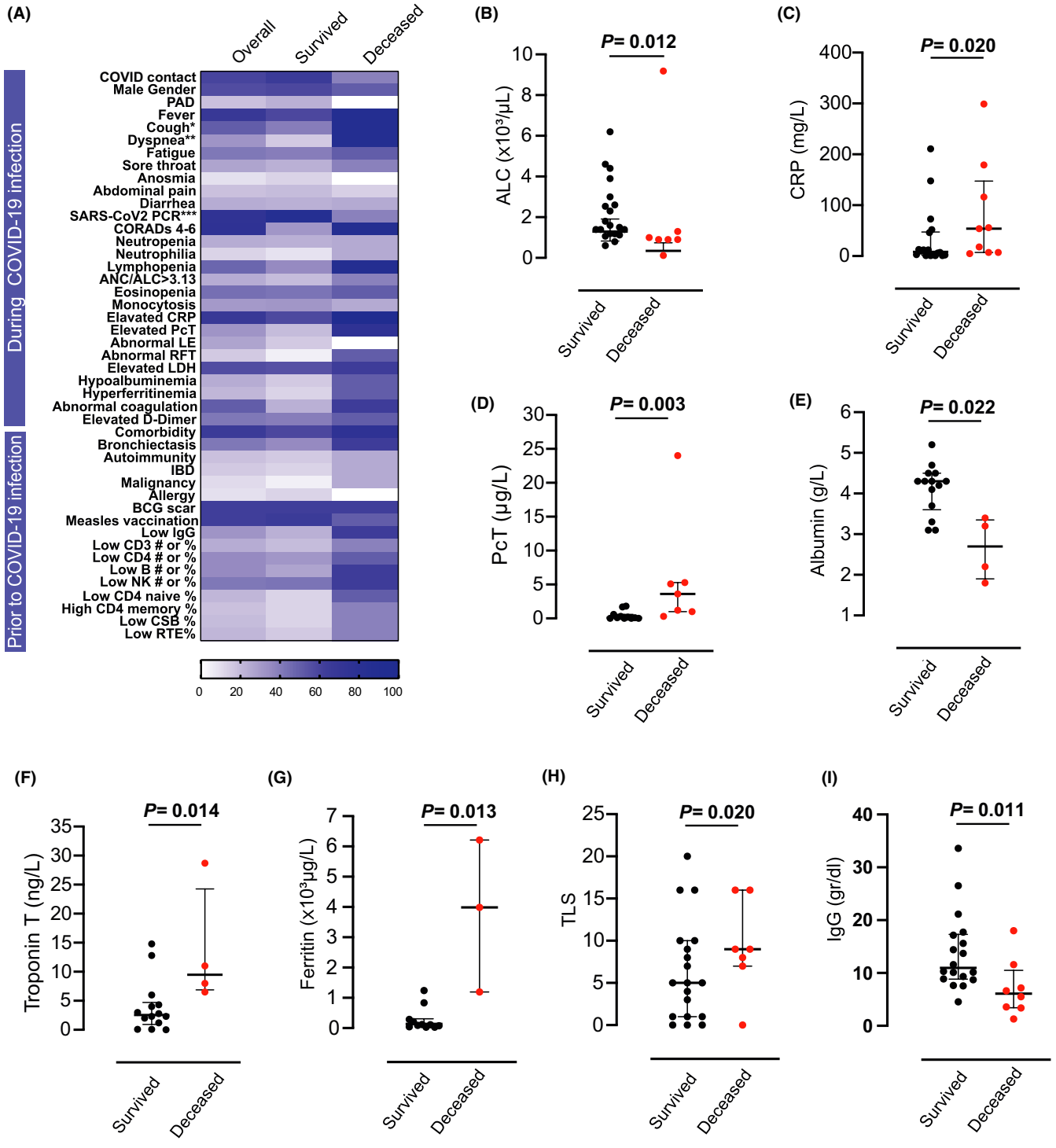


FIGURE 2 Clinical and laboratory characteristics of the study group concerning COVID-19 outcome. (A) Heatmap display of the comparative characteristics of deceased vs. survived patients. The percentage of each parameter for the overall study population, or the indicated groups, is transformed into a color according to the scale indicated at the bottom. A Fisher's exact test compared the two groups for statistical significance. *$p = .039$, **$p < .001$, ***$p = .17$, #: number, BCG, Bacilli Calmette Guerin; CSB, class-switched B cell; CD, clusters of differentiation; CORADS, COVID-19 Reporting and Data System; IBD, inflammatory bowel disease; Ig, immunoglobulin; LDH, lactate dehydrogenase; LE, liver enzymes (SGOT and SGPT); NK, natural killer; PAD; primary antibody deficiency; RFT, renal function tests (creatinine and blood urea nitrogen); RTE, recent thymic emigrants; SARS-CoV2 PCR, severe acute respiratory syndrome coronavirus 2 polymerase chain reaction, (B) Absolute lymphocyte count (ALC), (C) C reactive protein (CRP), (D) Procalcitonin (PcT), (E) Albumin, (F) Troponin-T, (G) Ferritin, (H) Total lung score (TLS), and (I) Immunoglobulin G (IgG). In B through I, the error bars represent the median and IQR values, and the statistics used the Mann-Whitney-*U* test

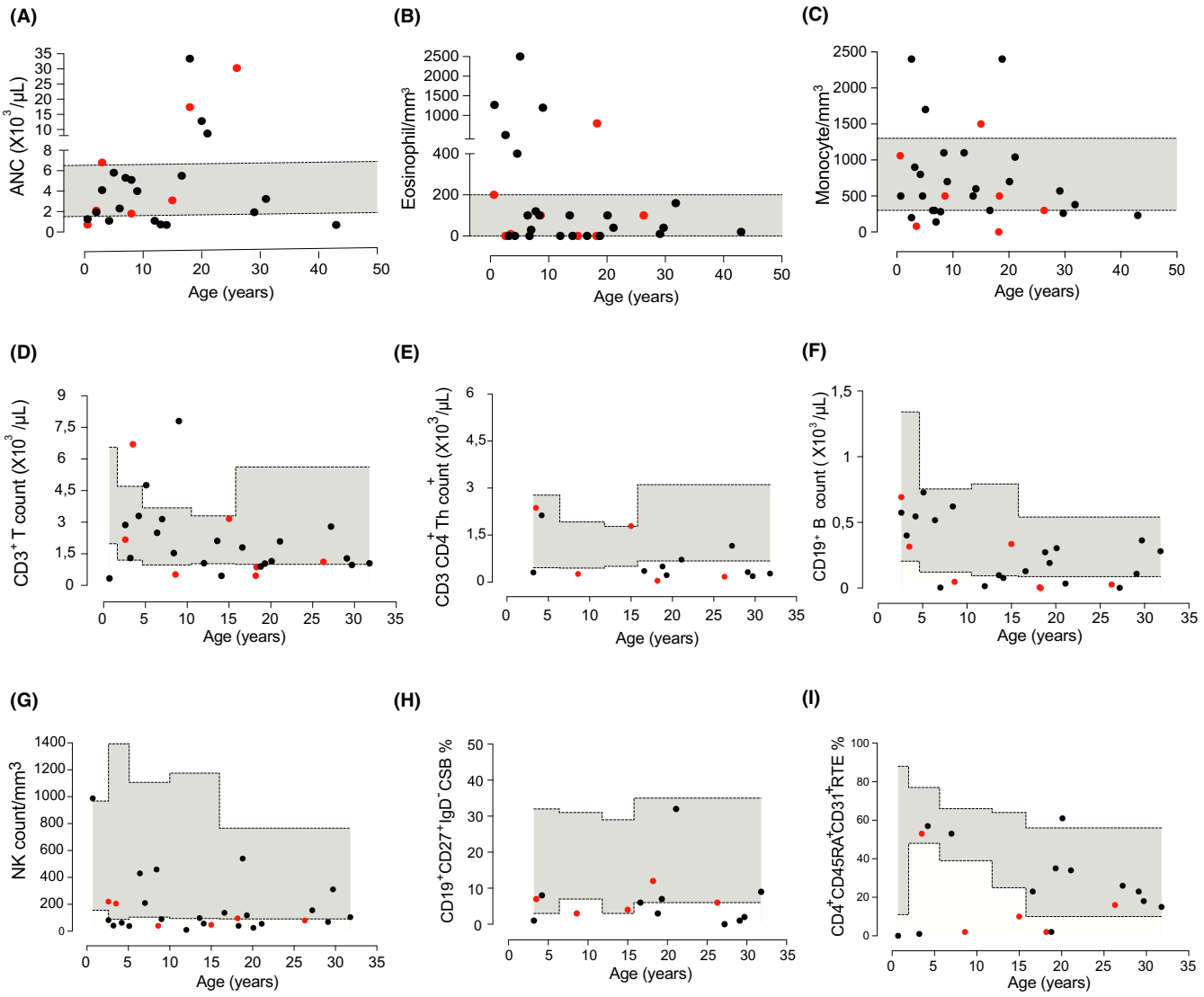


FIGURE 3 Peripheral blood counts and immune subsets of deceased vs. survived subjects. (A) Absolute neutrophil count (ANC), (B) eosinophil, (C) monocyte counts concomitant with COVID infection, (D) T-cell counts, (E) helper T-cell counts, (F) B-cell count, (G) natural killer (NK) cell count, (H) class-switched memory B cell (CSB) %, and (I) recent thymic emigrant (RTE) %. Red symbols indicate deceased subjects, and the black symbols those survived COVID. The gray shaded area demarcated by dotted lines shows the age-specific normal range

whereas 85% had already developed symptoms by the time they presented to the hospital. This figure deviates from data on the general population, where 40–80% receive COVID-19 diagnosis after developing symptoms.[23] The leading symptoms at admission in our cohort were fever, coughing, and dyspnea; these manifestations are similar to those reported in other cohorts.[11,13,24] It is interesting to note that we detected a positive SARS-CoV-2 PCR in 73.5% of cases; the remaining 26.5% received a COVID-19 diagnosis based on clinical grounds despite a negative PCR; namely, they had pneumonia and a CORADS score of ≥4. It is established that a PCR test's sensitivity for COVID-19 diagnosis is variable and subject to sample acquisition timing. Due to this limitation, clinical algorithms were developed to recognize COVID-19; a chest tomography scoring system (CORADS)[17] and TLS were proposed as valuable tests to assess the severity and extent of COVID-19 infection.[18] Hence, it is likely that those patients with a negative PCR at the time of presentation had an advanced stage of infection when the viral particles were cleared from the upper respiratory tract and localized to the lower compartments. This may explain why patients proved negative for a PCR test on nasopharyngeal swabs despite the typical clinical and radiologic findings of COVID-19. We propose that a probable COVID-19 diagnosis may be ruled in IEI subjects in the presence of clinically relevant respiratory findings, despite a lack of PCR evidence or absence of clear contact history. Serological tests for COVID-19 were assessed in a minority of IEIs patients.[12,24] However, it should be recalled that IEI subjects may not establish SARS-CoV-2 antibodies because of their inability to mount specific humoral immune responses; hence, serologic tests rely on an individual's antibody-production capacity may not be helpful in this context.

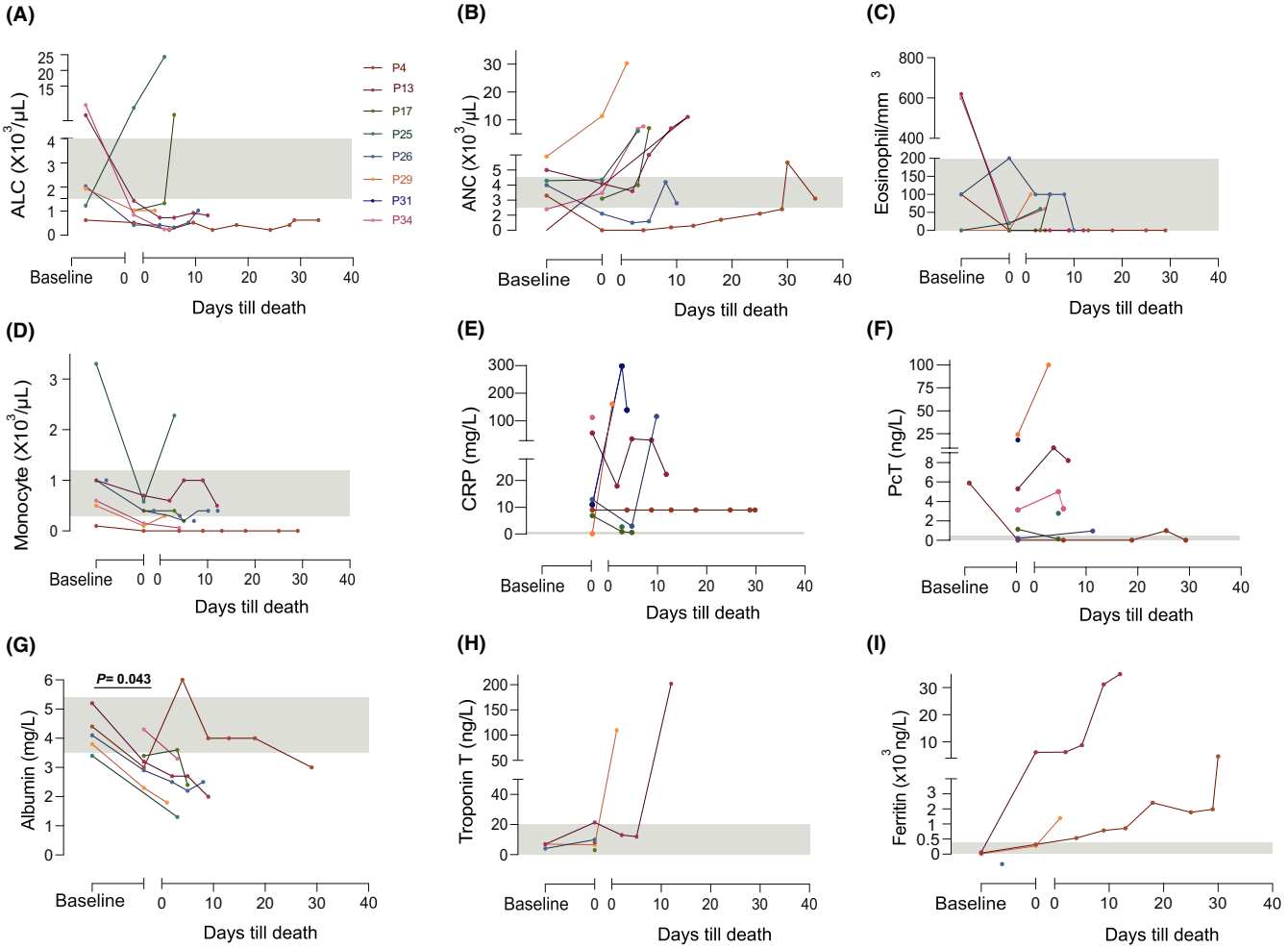


FIGURE 4 Longitudinal assessment of laboratory investigations of IEI patients who were succumbed to COVID. (A) Absolute lymphocyte count (ALC), (B) absolute neutrophil count (ANC), (C) eosinophil, (D) monocyte, (E) C reactive protein (CRP), (F) procalcitonin (PcT), (G) albumin, (H) troponin T and (I) ferritin levels. Horizontal gray bars indicate the upper and lower range. *pre-COVID vs. per-COVID albumin; $p = .043$, (Wilcoxon test)

Few studies have reported on the outcome of COVID-19 in IEIs and the factors that determine mortality, with mixed results. Marcus et al. studied 20 IEI patients from Israel, who surprisingly managed the infection uneventfully, with no patient deaths.[11] Ho et al. described a variable COVID-19 outcome among IEI patients who live in New York City, USA, with a spectrum of outcomes ranging from mild symptoms to a severe illness that resulted in inpatient mortality; baseline comorbidities and higher pro-inflammatory markers indicated a poor prognosis.[24] Delavari et al. analyzed data from the Iranian IEI registry and documented that IEI patients had a 10-fold higher COVID-19-related mortality rate than the general Iranian population.[20] A cohort from the UK showed that adults with IEI and those with symptomatic secondary immune deficiency are at a greater risk for COVID-19 related morbidity and mortality.[10] Based on the literature, certain factors predict a lethal COVID-19 outcome among IEI patients: CID (including SCID and ID), adults with secondary immune deficiency, having a previous comorbid condition, pneumonia, need for oxygen supplementation, lymphopenia, eosinopenia, neutropenia, and elevated pro-inflammatory markers at admission. Our data further suggest that elevated concentrations of acute phase reactants, ferritin, troponin T, and high TLS, and reduced ALC, hypoalbuminemia at presentation to hospital, and low trough IgG levels at baseline were indicators of mortality. Specific respiratory characteristics, namely coughing and dyspnea, a category 4 to 6 of CORADS at admission, and finding a negative SARS-CoV-2 PCR (probably indicating a shift of viral colonization has occurred from upper to lower respiratory tract), showed a high risk for mortality. Also, a prospective determination of potential markers indicated that a deadly COVID-19 in IEI was characterized by a gradually fall in ALC, eosinophil, monocyte, and albumin, and a contradictory rise in ANC, CRP, PcT, ferritin, and troponin T from the time of hospital admission until death. Baseline immune characteristics showed that a lower $CD3^+$ T-cell count and a reduced RTE percentage were characteristics of patients requiring inpatient care.

Since the inception of pandemics, different therapeutics have been trialed for COVID-19 in the general population. Our knowledge of this novel infection is still growing, as our understanding of various treatment effects. There have been no established treatment

approaches proven to be effective in COVID-19 in IEI patients; widely used medications included antibiotics, hydroxychloroquine, systemic steroids, anti-IL6R and anti-IL1R, antivirals, and enoxaparin. Supportive measures as oxygen supplementation, invasive and non-invasive ventilation, and immunoglobulins or convalescent plasma had been trialed with the variable outcome.[13,25] In our cohort, similar strategies were employed, unfortunately, with no dramatic change in the outcome.

In conclusion, IEIs patients, when contracting COVID-19, are at least ten times higher risk for the deadly outcome than the global population. We and others show that PAD has a relatively more favorable outcome at any age, but CIDs and ID are particularly vulnerable. Herein, we define a set of clinical markers that show poor COVID-19 outcomes; these predictors could be readily employed in the management of IEI subjects and further explored in future studies. We propose IEIs should be considered among COVID-19 disadvantaged groups irrespective of age. COVID-19 vaccines may protect a subgroup of IEIs, but unlikely to benefit those who cannot develop active immunity. There is an urgent need for studies exploring the role of specific therapies for IEIs, esp. those subtypes that are particularly susceptible to the infection. For example, a specific antibody cocktail may be trialed to provide passive immunity. The set of risk factors that we define can select patients who would be prioritized for preemptive therapies.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interest related to this work.

ORCID

Elif Karakoc Aydiner https://orcid.org/0000-0003-4150-5200
Sevgi Bilgic Eltan https://orcid.org/0000-0003-0561-3343
Royale Babayeva https://orcid.org/0000-0002-1044-2174
Omer Aydiner https://orcid.org/0000-0003-4895-093X
Eda Kepenekli https://orcid.org/0000-0003-1886-5224
Burcu Kolukisa https://orcid.org/0000-0002-2399-8630
Asena Pinar Sefer https://orcid.org/0000-0003-2667-0291
Ezgi Yalcin Gungoren https://orcid.org/0000-0003-0958-7824
Esra Karabiber https://orcid.org/0000-0002-8377-7637
Esra Ozek Yucel https://orcid.org/0000-0003-3712-2522
Oner Ozdemir https://orcid.org/0000-0002-5338-9561
Ayca Kiykim https://orcid.org/0000-0001-5821-3963
Hasibe Artac https://orcid.org/0000-0002-9807-2605
Nalan Yakici https://orcid.org/0000-0003-0738-4679
Koray Yalcin https://orcid.org/0000-0002-7638-9564
Haluk Cokugras https://orcid.org/0000-0002-0086-3936
Tulin Tiraje Celkan https://orcid.org/0000-0001-7287-1276
Fazil Orhan https://orcid.org/0000-0002-4850-932X
Mehmet Akif Yesilipek https://orcid.org/0000-0002-4514-8637
Safa Baris https://orcid.org/0000-0002-4730-9422
Ahmet Ozen https://orcid.org/0000-0002-9065-1901

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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