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A single center experience of intravenous immunoglobulin treatment in Covid-19

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ABSTRACT

Background: Intravenous immunoglobulins (IVIg) have been used in management of severe Covid-19. Here in this study, we report our single-center experience regarding IVIg treatment in management of severe Covid-19.

Materials and Method: Among hospitalized adult Covid-19 patients between April 1 and December 31, 2020, patients with confirmed diagnosis of Covid-19 who had Brescia-COVID respiratory severity scale score ≥ 3 , hyperinflammation and received IVIg treatment in addition to standard of care were retrospectively investigated. We grouped IVIg recipients into three according to reasons for IVIg administration: Group 1 patients requiring anti-inflammatory treatment but complicated with secondary infection and/or sepsis, group 2 patients with Covid-19 related complications including progressive disease refractory to other anti-inflammatory agents, myocarditis, adult multisystem inflammatory syndrome, hemophagocytic lymphohistiocytosis like syndrome and group 3 patients with other complications non-specific to Covid-19. Mortality and clinical data was compared among groups.

Results: A total of 46 IVIg recipients were enrolled. Group 1 comprised 17 (36.9%), group 2 comprised 18 (39.1%) and group 3 comprised 11 (23.9%) patients. No significant differences in means of age, gender and comorbidities were observed among groups. Mortality was significantly lower in group 3 when compared to group 1 (64.7% vs 18.2%, $p = 0.016$) and close to significance when compared to group 2 (50% vs 18.2% $p = 0.087$).

Conclusions: IVIg seemed to be used mostly in severe, refractory and complicated cases in our population. As a rescue agent in severe cases refractory to other anti-inflammatory strategies, 33.7% survival rate was observed with IVIg.

1. Introduction

Coronavirus disease 2019 (Covid-19) has a wide spectrum of clinical presentations with disease course varying from asymptomatic infection to severe pneumonia and mortal immunologic complications such as cytokine storm [1]. According to the reports of World Health Organization (WHO), course of Covid-19 can be classified as “mild disease” with upper respiratory tract symptoms or asymptomatic infection, “moderate disease” with lower respiratory tract involvement and “severe disease” with the need for intensive care or intubation [2].

Severe cases of Covid-19 are generally complicated by a hyper-inflammatory reaction to the viral antigens characterized by over-expression of proinflammatory cytokines. Therefore, in severe cases, in addition to antiviral treatment, management of hyperinflammation and cytokine storm with appropriate anti-inflammatory agents have been suggested as a therapeutic target [3–5]. Prompt recognition and suppression of hyperinflammation lowers the risk of Covid-19 related mortality and morbidity [1]. Considerable knowledge regarding several anti-inflammatory treatment strategies such as systemic corticosteroids, colchicine, anticytokine agents and intravenous immunoglobulins (IVIg)

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have been accumulated in the literature during the pandemic, however, precise approach for management of cytokine storm is yet to be fully clarified.

IVIg is a product containing immunoglobulins extracted from plasma of healthy donors, which have been used in management of immunodeficiencies, autoimmune and neurologic conditions, and infection related acute conditions [6]. IVIg have previously been used in infections caused by members of *coronaviridae* family (*severe acute respiratory syndrome coronavirus* (SARS - CoV) 1, *Middle East respiratory syndrome coronavirus* (MERS -CoV)) [7,8]. Likewise, IVIg have also been reported to be used in management of severe Covid-19, yet the exact mechanism of action remains to be elucidated. In addition to having potential to enhance passive immunity against the virus, IVIg treatment have been demonstrated to have promising effects on suppressing hyperinflammatory state via immunomodulatory actions such as binding to cytokines and variable regions of other antibodies [8,9].

Here in this study, we reported our single-center experience regarding IVIg treatment in management of severe Covid-19.

2. Materials and methods

This study was conducted as single-center, retrospective, cross-sectional. Ethical approval for the study was obtained from the Ethics Committee of Ankara City Hospital. Hospitalized adult Covid-19 patients between April 1 and December 31, 2020 from Ankara City Hospital Internal Medicine, Infectious Diseases and Clinical Microbiology, Critical Care clinics were retrospectively investigated. Among these, patients with confirmed diagnosis of Covid-19 (positive severe acute respiratory syndrome coronavirus 2 polymerized chain reaction test with compatible findings in chest x-ray or computed tomography) who had Brescia-COVID respiratory severity scale (BCRSS) score ≥ 3 , hyperinflammation (defined as elevation of C-reactive protein ≥ 50 mg/L or ferritin ≥ 700 ng/mL) and received IVIg treatment in addition to standard of care were enrolled [10]. Patients who were under the age of 18 or pregnant at the time of hospitalization and patients who had a history of malignant disease or psychiatric disorder were excluded.

In our center during the pandemic, hospitalization, management and discharge decisions of the Covid-19 patients were made according to the national guidelines prepared by Turkish Health Ministry [11]. In accordance with these guidelines, standard of care medical approach in our center comprised hydroxychloroquine, low molecular weight heparin, acetylsalicylic acid, favipiravir and dexamethasone. All patients in this study were managed in guidance with these regulations and received standard of care medications if not contraindicated. Likewise, administration of anti-inflammatory treatment agents including high-dose systemic glucocorticoids, tocilizumab, anakinra and IVIg were decided according to these national guidelines. The recommended IVIg dose was minimum 20 gr/day to maximum 0.4 gr/kg/day for five days.

Demographic, clinical, laboratory, imaging, treatment and outcome (length of hospital stay, intensive care unit (ICU) admission, intubation, mortality) data were collected using a standardized case report form.

Disease severity was defined as "severe" in presence of a respiratory rate ≥ 30 breaths per minute or SPO₂ $\leq 90\%$ at rest or PaO₂/FiO₂ ≤ 300 mmHg, as "critical" in presence of respiratory failure requiring mechanical ventilation or shock or multiple organ failure [12]. Patients who were neither severe nor critical were defined as non-severe/critical. All data were saved by the same physician (OK).

We grouped IVIg recipients into three according to reasons for IVIg administration: Group 1 patients requiring anti-inflammatory treatment but complicated with secondary infection and/or sepsis (positive blood, urine, sputum or deep tracheal aspiration culture with or without systemic inflammatory response syndrome defined in presence of any following two criteria; body temperature over 38°C or under 36°C, heart rate > 90 beats/minute, respiratory rate > 20 breaths per minute or partial pressure of CO₂ < 32 mmHg, leukocyte count > 12000 or < 4000 per microliters or over 10% immature forms or bands [13]), group 2

patients with Covid-19 related complications including progressive disease (need for oxygen support with a blood oxygen saturation $\leq 94\%$ or a 3% decrease in oxygen saturation in ambient air for at least 24 h and underwent positioning during hospital stay) refractory to other anti-inflammatory agents (high-dose steroids, anakinra, tocilizumab), myocarditis, adult multisystem inflammatory syndrome (MIS-A) (presence of following five criteria: a severe illness requiring hospitalization in a person aged ≥ 21 years, a positive test result for SARS-CoV-2 infection (nucleic acid, antigen, or antibody) in admission or in the previous 12 weeks, severe dysfunction of one or more extrapulmonary organ systems, laboratory evidence of severe inflammation, absence of severe respiratory illness [14]), hemophagocytic lymphohistiocytosis like syndrome (HLHS) (presence of five of the following eight criteria: fever, splenomegaly, cytopenia affecting at least two out of three series (hemoglobin < 90 g/l, platelets $< 100 \times 10^9/l$, neutrophils $< 1.0 \times 10^9/l$), hypertriglyceridemia (≥ 265 mg/dl) and/or hypofibrinogenemia (≤ 1.5 g/l), hemophagocytosis in bone marrow or spleen or lymph nodes, low or absent natural killer cell activity, ferritin ≥ 500 μ g/l, and sCD25 $\geq 2,400$ units/ml [15]), group 3 patients with other non-specific complications related to Covid-19 based on expert opinion (neurologic, hematologic, vasculitic complications). Recorded data was compared among groups. Patients regrouped according to presence of Covid-19 related mortality and data compared between survivors and non-survivors.

Data were analyzed using Statistical Package for the Social Sciences (SPSS) 22.0 software. Shapiro-Wilk's test was used to determine the distribution of the data. The distribution of continuous data was expressed as mean \pm standard deviation. Continuous variables that did not conform to normal distribution were expressed as median and interquartile range (IQR) values. Continuous variable was compared by using either student *t*-test or Mann-Whitney-*U* test according to normality. For categorical variables, χ^2 test was used for and the outcomes were expressed as number and percentages. P values below 0.05 were considered statistically significant.

3. Results

A total of 46 IVIg recipients were enrolled in the study. Group 1 comprised 17 (36.9%), group 2 comprised 18 (39.1%) and group 3 comprised 11 (23.9%) patients (Table 1). Most common reasons for IVIg administration were non-response to antiviral and other anti-inflammatory agents (12 (26.1%) patients) and secondary infection accompanying Covid-19 and/or sepsis (12 (26.1%) patients).

Demographics, comorbidities, Covid-19 disease severity and outcomes in groups were presented in Table 2. No significant differences in means of age, gender and comorbidities were observed among groups. Fifty eight point seven percent of all patients (n = 27) were defined as critical type but rates of severe and critical disease were similar among groups. Mortality was significantly lower in group 3 when compared to group 1 (64.7% vs 18.2%, p = 0.016) and close to significance when compared to group 2 (50% vs 18.2% p = 0.087) (Figure 1). Data regarding disease severity and Covid-19 outcomes in patient subgroups were presented in supplementary table 1.

Covid-19 related mortality was observed in 22 (47.8%) of all IVIg recipients. Median (IQR) age (66.5 (18) vs 56 (20); p = 0.004), number of critical patients (20 (90.9%) vs 7 (29.2%); p < 0.0001), rates of intubation (22 (100%) vs 6 (25.0%); p < 0.0001) and ICU admission (22 (100%) vs 11 (45.8%); p < 0.0001) were significantly higher in non-survivors (Table 3). Changes in laboratory parameters with treatment for patients in groups 1 and 2 were presented in supplementary table 2.

Adverse events which were suspected to be related with IVIg treatment were observed in a total of 11 (23.9%) patients with similar frequency between survivors and non-survivors (25% vs 22.7%; p = 0.857) (Table 3). Acute renal failure was the most common suspected adverse event in all patients (19.6%).

Table 1
Patient groups according to reasons for IVIg treatment.

	n (%)
Group 1: Patients requiring antiinflammatory treatment but complicated with secondary infection and/or sepsis	17 (36.9)
Secondary infection	12 (26.1)
Sepsis	5 (10.9)
Group 2: Patients with Covid-19 related complications	18 (39.1)
Progressive disease refractory to other antiinflammatory agents	12 (26.1)
Myocarditis/adult multisystem inflammatory syndrome	3 (6.5)
Hemophagocytic lymphohistiocytosis like syndrome	3 (6.5)
Group 3: Patients with other complications non-specific to Covid-19	11 (23.9)
Hematologic	5 (10.9)
Acute myelogenous leukemia	2 (4.3)
Hypogammaglobulinemia with chronic lymphocytic leukemia	2 (4.3)
Trombocytopenia	1 (2.2)
Neurologic	4 (8.6)
Postcovid myopathy	2 (4.3)
Postcovid Guillian-Barre syndrome	1 (2.2)
Myasthenia gravis	1 (2.2)
Vasculitic	2 (4.3)
Kawasaki	1 (2.2)
Granulomatosis with polyangiitis	1 (2.2)

COVID-19: coronavirus disease 2019, n: number.

4. Discussion

In our cohort, in 39.1% of the IVIg recipients treatment was administered due to Covid-19 related complications (Group 2) and in 37% due to need for anti-inflammatory treatment with concomitant secondary infection and/or sepsis (Group 1). 58.7% of the patients had critical disease. Rate of mortality detected to be 47.8% in all IVIg recipients and 74.1% in presence of critical disease. In non-survivors median age was significantly higher but gender and frequency of

comorbidities were indifferent. Mortality was observed less in patients who received IVIg for complications non-specific to Covid-19 (Group 3). Approximately one fourth of the patients had adverse events suspected to be related with IVIg treatment with acute renal failure being the most frequent, yet rate of adverse events were similar between survivors and non-survivors.

IVIg is a solution rich in pooled immunoglobulin (Ig) Gs against various antigens obtained from thousands of healthy donors [16,17]. Fab part of IgGs in IVIg modulates apoptosis and inflammatory response while Fc receptor (FcR) part inhibits phagocytosis and antibody derived cellular toxicity [18]. IVIg modulates immune response via several mechanisms including blocking various proinflammatory cytokines, leukocyte adhesion molecules and FcγR, suppressing T helper (Th) 1 and 17 subclasses and neutralizing pathogenic antibodies [19,20]. Furthermore, by inducing prostaglandin E2 in dendritic cells, IVIg may enhance regulatory T cells [21]. In addition to immunomodulation, since IVIg contains IgGs against various antigens, it may also act as an antimicrobial agent and have been used in management of viral, bacterial and fungal infections [16,22,23]. IVIg was demonstrated to reduce viral load, serum cytokine concentrations and mortality in severe H1N1 infection, in a randomized controlled, double-blind, multicenter study [24].

Clinical uses of IVIg treatment comprise several autoimmune conditions such as dermatomyositis, Kawasaki disease, lupus, multiple sclerosis and idiopathic thrombocytopenic purpura in addition to primary and secondary immunodeficiency [18,25]. Furthermore, IVIg have previously been reported to be effective in *coronaviridae* related immunogenic reactions such as myocarditis, in combination with antivirals [26,27]. Accordingly, IVIg treatment may both enhance antiviral activity and modulate hyperimmune response in Covid-19. In our patients, IVIg treatment was administered mostly (39.1%) in patients with Covid-19 related immunogenic complications such as MIS-A, HLHS like syndrome and myocarditis. Likewise, observational reports in the literature imply early administration of high-dose IVIg may improve outcomes in severe Covid-19 patients with cytokine storm [8,28]. Moreover, beneficial effects of IVIg have also been demonstrated in pediatric Covid-19 patients with cardiac involvement and MIS-C [29]. Another major reason for IVIg administration in our patient population was

Table 2
Demographics, comorbidities, disease severity and outcomes in patient groups.

	Group 1 n = 17	Group 2 n = 18	Group 3 n = 11	p Group 1 vs 2	p Group 1 vs 3	p Group 2 vs 3
Age, years, median (IQR)	63 (22)	55.5 (20)	60 (8)	0.704	0.655	0.84
Gender, male, number (%)	13 (76.5)	12 (66.7)	10 (90.9)	0.521	0.619	0.139
Patients with ≥ 1 comorbidities, number (%)	12 (70.6)	10 (55.6)	9 (81.8)	0.489	0.668	0.149
Comorbidities, number (%)						
Hypertension	5 (29.4)	6 (33.3)	5 (45.5)	0.803	0.444	0.514
Diabetes mellitus	2 (11.8)	3 (16.7)	3 (27.3)	0.679	0.353	0.646
Chronic obstructive pulmonary disease	1 (5.9)	1 (5.6)	0 (0)	1	1	1
Asthma	0 (0)	3 (16.7)	0 (0)	0.229	–	0.268
Coronary artery disease	3 (17.6)	2 (11.1)	0 (0)	0.658	0.258	0.512
End-stage renal disease	1 (5.9)	0 (0)	0 (0)	0.486	1	–
Clinical classifications, number (%)						
Non severe/critical	1 (5.9)	4 (22.2)	4 (36.4)			
Severe	6 (35.3)	2 (11.1)	2 (18.2)	0.138	0.112	0.531
Critical	10 (58.8)	12 (66.7)	5 (45.5)			
Coronavirus disease 2019 outcomes						
Length of total hospital stay (days), median (IQR)	23 (17)	22 (29)	44 (56)	0.62	0.115	0.431
Length of hospital stay after first IVIg dose(days), median (IQR)	8 (11)	14.5 (25)	11 (22)	0.258	0.286	0.804
Intubation, number (%)	11 (64.7)	12 (66.7)	5 (45.5)	0.903	0.315	0.26
Intensive care unit admission, number (%)	13 (76.5)	13 (72.2)	7 (63.6)	0.774	0.471	0.628
Death, number (%)	11 (64.7)	9 (50)	2 (18.2)	0.38	0.016	0.087

n: number, IQR: interquartile range, IVIg: intravenous immunoglobulins.

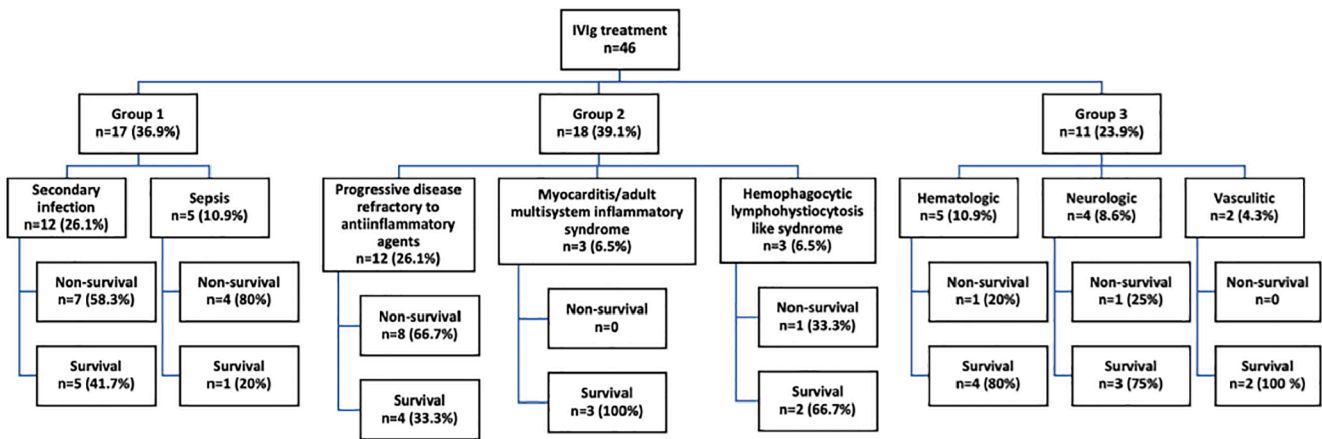


Fig. 1. Patient groups and survival rates.

Table 3

Demographics, comorbidities, disease severity, Covid-19 outcome parameters and suspected IVIg related adverse events in survivors and non-survivors.

	All patients n = 46	Survivors n = 24	Non-survivors n = 22	p
Age, years, median (IQR)	59 (19)	56 (20)	66.5 (18)	0.004
Gender, male, number (%)	35 (76.1)	18 (75)	17 (77.3)	0.857
Patients with ≥ 1 comorbidities, number (%)	31 (67.4)	14 (58.3)	17 (77.3)	0.171
Comorbidities, number (%)				
Hypertension	16 (34.8)	7 (29.2)	9 (40.9)	0.538
Diabetes mellitus	8 (17.4)	3 (12.5)	5 (22.7)	0.361
Chronic obstructive pulmonary disease	2 (4.3)	0 (0)	2 (9.1)	0.22
Asthma	3 (6.5)	2 (8.3)	1 (4.5)	1
Coronary artery disease	5 (10.9)	0 (0)	5 (22.7)	
End-stage renal disease	1 (2.2)	0 (0)	1 (4.5)	0.478
Clinical classifications, number (%)				
Non severe/critical	9 (19.6)	9 (37.5)	0 (0)	
Severe	10 (21.7)	8 (33.3)	2 (9.1)	<0.0001
Critical	27 (58.7)	7 (29.2)	20 (90.9)	
Coronavirus disease 2019 outcomes				
Length of total hospital stay (days), median (IQR)	23 (29)	23.5 (36)	23 (25)	0.733
Length of hospital stay after first IVIg dose (days), median (IQR)	11 (15)	11 (18)	11.5 (12)	0.651
Invasive mechanic ventilation, number (%)	28 (60.9)	6 (25.0)	22 (100)	<0.0001
Intensive care unit admission, number (%)	33 (71.7)	11 (45.8)	22 (100)	<0.0001
Adverse events suspected to be related with IVIg				
Total	11 (23.9)	6 (25)	5 (22.7)	0.857
Acute renal failure	9 (19.6)	4 (16.7)	5 (22.7)	0.718
Thrombosis	1 (2.2)	1 (4.2)	0 (0)	1
Skin rash	1 (2.2)	1 (4.2)	0 (0)	1

n: number, IQR: interquartile range, IVIg: intravenous immunoglobulins.

concomitant secondary infections which restrict the use of other anti-inflammatory agents such as high-dose steroids and anticytokine agents. IVIg seems to be a reasonable option in such cases due to anti-microbial activity in addition to immunomodulatory effects rather than

immunosuppression [23,24].

In a randomized controlled, double-blind study, mortality in hospitalized Covid-19 patients was significantly lower in IVIg recipients when compared to controls [30]. Our study could not demonstrate such effect since a well-matched control group was lacking. Furthermore, our population comprise rather refractory and complicated patients and rate of IVIg treatment was increased in severe and critical patients. Mortality in all IVIg recipients was 47.8% in our study while 74.1% mortality rate was observed in critical patients. Similarly, observational data in the literature reveals IVIg have been a treatment choice generally in severe cases [8,31,32]. A randomized controlled study is ongoing to further elucidate effectiveness of IVIg in severe Covid-19 (NCT 04261426).

When survivors and non-survivors were compared in our study no significant differences were observed except for median age which was significantly increased in non-survivors. An increasing trend in mortality rate was observed in patient groups 1 and 2, suggesting worse outcomes in presence of progressive disease refractory to other anti-inflammatory agents, Covid-19 related immunogenic complications and secondary infection.

In immunodeficiency, IVIg therapy is generally administered with a dose of 200–400 mg/kg every 3–4 weeks. In autoimmune and inflammatory conditions higher doses are preferred for immunomodulation (2gr/kg every 4 weeks) [33]. Likewise for management of Covid-19, high-dose regimens were reported to be preferred [34]. Accordingly, administered IVIg dose in our patient population was between 20 gr/day to 0.4 gr/kg/day for five days.

IVIg is usually a well-tolerated treatment agent [35]. Most common adverse events are reported to be mild and transient such as flushing, headache, malaise, fever, chills, fatigue and dizziness. On the other hand, on rare occasions (<5%), serious adverse events have also been reported such as kidney failure, thrombosis, arrhythmia, aseptic meningitis, hemolytic anemia and transfusion related lung injury [36,37]. Incidence of adverse events are related with properties of IVIg solutions and individual differences of patients. Risk assessment prior to treatment, slow infusion and premedication may lower the risk [35]. In our population, in 11 (23.9%) patients, serious adverse events suspected to be related with IVIg was observed, most common being acute kidney failure (19.6%) followed by thrombosis (2.2%) and skin reaction (2.2%). Thrombosis is a well-known complication of Covid-19 [38,39]. Furthermore, various other extrapulmonary manifestations including acute kidney injury and cutaneous lesions have also been reported in course of SARS-CoV 2 infection particularly in severe patients [40–42]. Due to the retrospective nature of our study, it is quite difficult to establish a causality with these events and IVIg treatment. Acute kidney injury as an adverse event was reported to be rare (<1%) in IVIg treatment, varying from asymptomatic serum creatinine elevation to acute kidney failure [43]. Nephrotoxicity is reported to be related with

high-dose regimens and spontaneously dissolve in 4–10 days with tapering [36,37]. Absence of the most common side effects of IVIg therapy in our population may be related with concomitant use of steroids for Covid-19 treatment.

There are several limitations of our study. First, this was a retrospective observational study, which might aggravate the risk of bias and causal inferences could not be drawn because of inherent known and unknown confounders. Second, there was a possibility of sampling bias since we obtained data from a convenience sample. Small sample size, heterogeneity of our patient population, particularly group 3, and lack of control group make it difficult to reach valid conclusions regarding effectiveness of IVIg.

Here in this study we reported our single center experience of IVIg in management of Covid-19. IVIg seemed to be used mostly in severe, refractory and complicated cases in our population. As a rescue agent in severe cases refractory to other anti-inflammatory strategies, 33.7% survival rate was observed with IVIg. In remaining cases survival rate was observed to be 58.8%. In addition to refractory cases, IVIg may be a treatment option in Covid-19 particularly in presence of secondary infection and various immunogenic complications. High quality studies are mandatory to further elucidate the place of IVIg treatment in management of Covid-19.

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Author contributions

All the authors made a substantial contribution to this research. All members contributed to the study design, data collection, writing the paper and approved the final form.

CRediT authorship contribution statement

AO: Conceptualization, Methodology, Project administration, Supervision, Writing - review & editing. **AE:** Conceptualization, Methodology, Project administration, Supervision, Formal analyses, Data curation, Writing - original draft, Writing - review & editing. **BA:** Conceptualization, Methodology, Formal analyses, Data curation, Writing - original draft, Writing - review & editing. **SCG:** Conceptualization, Methodology, Formal analyses, Data curation, Writing - original draft, Writing - review & editing. **ÖK:** Formal analyses, Data curation, Investigation. **ESS:** Formal analyses, Data curation, Investigation. **DE:** Conceptualization, Methodology, Project administration, Supervision. **Sİ:** Conceptualization, Methodology, Project administration, Supervision. **İA:** Conceptualization, Methodology, Project administration, Supervision. **OK:** Conceptualization, Methodology, Project administration, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.intimp.2021.107891>.

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