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SARS-CoV-2 vakcinācija iedzimto
imunitātes traucējumu pacientiem Latvijā:
imūnās atbildes reakcija un
iemesli atteikumam no
rekomendētas vakcinācijas

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Anotācija

Iedzimti imūnsistēmas traucējumi (IIT) ir heterogēna reto slimību grupa, kurai raksturīga imūnsistēmas disregulācija. Visbiežāk sastopamais IIT veids ir pārsvarā antivielu deficīti (PAD), no tiem biežāk izplatītie – selektīvs IgA deficīts (SIgAD) un parasts mainīgs imūndeficīts (PMID). Vakcinācija PAD pacientiem ir īpaši nozīmīga saistībā ar paaugstinātu infekciju risku, tomēr pēcvakcinācijas humorālā atbildes reakcija PAD pacientiem var būt traucēta. Savukārt T-šūnu atbildes reakcija var sniegt aizsardzību arī tad, ja antivielu veidošanās ir ierobežota.

Šī pētījuma mērķis ir analizēt humorālo un T-šūnu imūno atbildi pret SARS-CoV-2 antigēnu PAD pacientiem un imūnās atbildes saistību ar slimības fenotipu un smagumu, kā arī izpētīt iemeslus atteikumam no rekomendētas SARS-CoV-2 vakcinācijas IIT pacientiem Latvijā.

Promocijas darbs ir veidots kā četru secīgu publikāciju kopa. Pirmajā daļā analizēta IIT izplatība Latvijā, raksturojot pacientu medicīnisko dokumentāciju. Otrajā un trešajā pētījuma daļā tika novērtēta PAD (PMID un SIgAD) pacientu humorālā un T-šūnu SARS-CoV-2 specifiskā atbilde, kā arī citokīnu profils pēc SARS-CoV-2 antigēna stimulācijas, izmantojot enzīmu saistītu imūnsorbijas testu, interferona- γ izdalīšanās testu un xMAP tehnoloģiju. Ceturtajā pētījuma daļā, izmantojot daļēji strukturētu interviju un tematisko analīzi, tika pētīti IIT pacientu iemesli atteikumam no rekomendētās SARS-CoV-2 vakcinācijas.

IIT punkta prevalence Latvijā 2020. gada decembrī bija 7,1 uz 100 000 iedzīvotāju. SARS-CoV-2 specifisko IgG klases antivielu līmenis PMID pacientiem bija zemāks (5,47 (IQR = 4,08)) nekā veseliem kontrolgrupas indivīdiem (9,43 koeficients (IQR = 2,13)) ($p < 0,05$). Mūsu pētījumā netika konstatētas statistiski nozīmīgas atšķirības SARS-CoV-2 specifiskajā T-šūnu un citokīnu atbildes reakcijā starp PMID, SIgAD pacientu grupu vai kontroles grupu ($p > 0,05$). Pēc SARS-CoV-2 antigēna stimulācijas pacientiem ar autoantivielām serumā tika novērots IL-4 līmeņa pieaugums, kā arī sākotnēji augstāks IL-4 un TNF- α līmenis ($p < 0,05$), savukārt IL-10 līmenis statistiski nozīmīgi atšķīrās pacientiem ar limfadenopātiju ($p < 0,05$), hepatomegāliju ($p < 0,01$) un splenomegāliju ($p < 0,01$), bet pacientiem ar zemu pārslēgto atmiņas B šūnu īpatsvaru bija izteiktāks TNF- α līmeņa pieaugums salīdzinājumā ar citām grupām ($p < 0,01$). Kā piecas galvenās tēmas, kas ietekmēja IIT pacientu lēmumu nevakcinēties, tika identificētas: (1) bailes un nenoteiktība, (2) riska un ieguvumu vērtējums, (3) ārējā ietekme no apkārtējiem cilvēkiem, (4) neuzticēšanās un nevēlēšanās pakļauties, (5) pārliecība par Covid-19 vakcīnu un vakcināciju kopumā.

Iedzimto imunitātes traucējumu izplatība Latvijā ir līdzīga citu Eiropas valstu rādītājiem, tomēr Latvijā ir mazāks diagnosticēto PAD īpatsvars. T-šūnu atbilde pret

SARS-CoV-2 antigēnu PMID un SIgAD pacientiem neatšķīrās no kontroles grupas pacientiem, bet humorālā atbilde PMID pacientiem bija samazināta. Vairāku citokīnu (IL-4, IL-10, IL-21, TNF- α) līmeņu izmaiņas pēc SARS-CoV-2 antigēna stimulācijas ir saistītas ar slimības klīniskajiem vai imunoloģiskajiem fenotipiem. Lai gan lielākā daļa IIT pacientu atteikšanās iemesli no SARS-CoV-2 vakcinācijas bija līdzīgi tiem, kas novēroti vispārējā populācijā, pastāv arī slimībai specifiski faktori: uzskats, ka vakcinācija imūndeficīta pacientiem ir kontrindicēta, kā arī uzskats, ka imūnglobulīnu aizstājterapijas saņemšanas gadījumā SARS-CoV-2 vakcinācija nav nepieciešama.

Atslēgvārdi: iedzimti imunitātes traucējumi, pārsvarā antivielu deficīti; parasts mainīgs imūndeficīts; selektīvs IgA deficīts; iedzimtu imunitātes traucējumu prevalence; SARS-CoV-2 imūnā atbilde; vilcināšanās vakcinēties.

Abstract

SARS-CoV-2 Vaccination in Patients with Inborn Errors of Immunity in Latvia: Immune Response and Reasons for Refusal of Recommended Vaccination

Inborn errors of immunity (IEI) are a heterogeneous group of rare diseases characterized by immune system dysregulation. The most common type of IEI is predominantly antibody deficiencies (PAD), with selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID) being the most frequently observed. Vaccination is particularly important for PAD patients due to their increased risk of infections; however, their humoral immune response to vaccines may be impaired. Nevertheless, T-cell responses can provide protection even when antibody production is limited.

The aim of this study is to investigate the humoral and T-cell immune response to the SARS-CoV-2 antigen in PAD patients, as well as the association of immune responses with disease phenotype and severity. Additionally, the study examines the reasons for refusal of recommended SARS-CoV-2 vaccination among IEI patients in Latvia.

This dissertation is structured as a series of four sequential publications. In the first part, the prevalence of IEI in Latvia was analyzed using patient medical records. The second and third parts assessed the humoral and T-cell SARS-CoV-2-specific response in PAD (CVID and SIgAD) patients, as well as cytokine profile following SARS-CoV-2 antigen stimulation, using enzyme-linked immunosorbent assay, interferon- γ release assay, and xMAP technology. In the fourth part, semi-structured interviews and thematic analysis were used to explore the reasons why IEI patients refused recommended SARS-CoV-2 vaccination.

The point prevalence of IEI in Latvia in December 2020 was 7.1 per 100 000 inhabitants. The level of SARS-CoV-2-specific IgG antibodies in CVID patients was lower (5.47 ratio, IQR = 4.08) compared to healthy controls (9.43 ratio, IQR = 2.13) ($p < 0.05$). No statistically significant difference was found in SARS-CoV-2-specific T-cell and cytokine responses between patients with CVID, SIgAD, or the control group ($p > 0.05$). After SARS-CoV-2 antigen stimulation, patients with serum autoantibodies exhibited an increase in IL-4 levels, as well as initially higher IL-4 and TNF- α levels ($p < 0.05$). Moreover, IL-10 levels differed significantly in patients with lymphadenopathy ($p < 0.05$), hepatomegaly ($p < 0.01$), and splenomegaly ($p < 0.01$). Patients with a low proportion of switched memory B cells exhibited a more pronounced increase in TNF- α levels compared to other groups ($p < 0.01$). Five key themes influencing IEI patients' decision to avoid vaccination were identified: (1) Fear

and uncertainty, (2) Risk–benefit assessment, (3) External influence from others, (4) Distrust and unwillingness to comply, (5) Beliefs about COVID-19 vaccines and vaccination in general.

The prevalence of IEI in Latvia is similar to other European countries, but Latvia has a lower proportion of PAD. The T-cell response to the SARS-CoV-2 antigen in CVID and SIgAD patients did not differ from that of the control group, but the humoral response in CVID patients was reduced. Changes in the levels of several cytokines (IL-4, IL-10, IL-21, TNF- α) following SARS-CoV-2 antigen stimulation were associated with clinical or immunological disease phenotypes. While most reasons for vaccine hesitancy among IEI patients were similar to those observed in the general population, disease-specific factors were also identified: the belief that vaccination is contraindicated in patients with immunodeficiency, as well as the perception that SARS-CoV-2 vaccination is unnecessary for those receiving immunoglobulin replacement therapy.

Keywords: inborn errors of immunity; predominantly antibody deficiencies; common variable immunodeficiency; selective IgA deficiency; prevalence of inborn errors of immunity; SARS-CoV-2 immune response; vaccine hesitancy.

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Darbā izmantotie saīsinājumi

Saīsinājums	Skaidrojums latviešu valodā	Skaidrojums angļu valodā
BAFF	B šūnu aktivācijas faktors	<i>B-cell activating factor</i>
CD	Diferenciācijas kopa	<i>Cluster of Differentiation</i>
Covid-19	2019. gada koronavīrusa slimība	<i>Coronavirus Disease 2019</i>
CXCL13	CXC motīva hemokīna ligands 13	<i>CXC Motif Chemokine Ligand 13</i>
ELISA	Enzīmu saistīts imūnsorbcijas tests	<i>Enzyme-Linked Immunosorbent Assay</i>
ESID	Eiropas Imūndeficītu biedrība	<i>European Society for Immunodeficiencies</i>
ICOS	Inducējams kostimulators	<i>Inducible Co-Stimulator</i>
Ig	Imūnglobulīns	<i>Immunoglobulin</i>
IGRA	Interferona- γ izdalīšanās tests	<i>Interferon- γ Release Assay</i>
IIT	Iedzimti imunitātes traucējumi	<i>Inborn Errors of Immunity</i>
IL	Interleikīns	<i>Interleukin</i>
IFN	Interferons	<i>Interferon</i>
LTBR	Limfotoksīna beta receptors	<i>Lymphotoxin Beta Receptor</i>
mRNA	Informatīvā ribonukleīnskābe	<i>Messenger Ribonucleic Acid</i>
NFKB2	Kodola faktora kapa B apakšvienība 2	<i>Nuclear Factor Kappa B Subunit 2</i>
NK	Dabiskās galējās šūnas	<i>Natural killer cells</i>
NRAS	Neirolblastomas RAS vīrusa onkogēna homologs	<i>Neuroblastoma RAS Viral Oncogene Homolog</i>
PAD	Pārsvarā antivielu deficīts	<i>Predominantly Antibody Deficiency</i>
PMID	Parasts mainīgs imūndeficīts	<i>Common Variable Immunodeficiency</i>
PTEN	Fosfatāzes un tensīna homologs	<i>Phosphatase and Tensin Homolog</i>
SARS-CoV-2	Smaga akūta respiratorā sindroma koronavīruss 2	<i>Severe Acute Respiratory Syndrome Coronavirus 2</i>
SigAD	Selektīvs IgA deficīts	<i>Selective IgA Deficiency</i>
SKID	Smags kombinēts imūndeficīts	<i>Severe Combined Immunodeficiency</i>
SMAD7	Drozofilu proteīna Mad homologs 7	<i>Drosophila protein Mothers against decapentaplegic homolog 7</i>
TGF- β 1	Tumora augšanas faktors β 1	<i>Tumour Growth Factor β1</i>
TFH	T folikulārā līdzētājšūna	<i>T Follicular Helper</i>
TFR	T folikulārā regulatorā šūna	<i>T Follicular Regulatory cell</i>
TNF- α	Tumora nekrozes faktors α	<i>Tumour necrosis factor α</i>
Treg	T regulatorās šūnas	<i>Regulatory T cell</i>

Ievads

Iedzimti imūnsistēmas traucējumi (IIT) ir heterogēna reto slimību grupa, kurai raksturīga imūnsistēmas disregulācija (Bousfiha et al., 2020). Klīniski šīs slimības izpaužas ar atkārtotām vai neparastām infekcijām, autoimunitāti, autoiekaisīgiem sindromiem, atopiju un/vai ļaundabīgām slimībām (Poli et al., 2025). IIT diagnoze tiek noteikta atbilstoši klīniskajiem un laboratorajiem slimības kritērijiem un ģenētiskās testēšanas rezultātiem (Costagliola & Consolini, 2023). IIT ārstēšana ir atkarīga no diagnozes un traucējumu smaguma pakāpes un var ietvert allogēnu cilmes šūnu transplantāciju, imūnglobulīnu aizstājterapiju, bioloģisko medikamentu lietošanu, profilaktisku antibiotiku lietošanu un cita veida infekciju profilaksi, tai skaitā vakcināciju, kā arī komplikāciju ārstēšanu (Fevang, 2023; Hanitsch et al., 2020). Vakcinācija tiek uzskatīta par vienu no efektīvākajiem infekciju profilakses veidiem. Tiek pieņemts, ka vakcīnas iedarbojas, izraisot patogēnam specifiskas imūnās atbildes reakcijas, kuru rezultātā veidojas aizsargājošas antivielas un atmiņas imūnšūnas (Shoja Doost et al., 2024), tomēr pacientiem ar dažiem IIT traucējumu veidiem šis mehānisms var būt defektīvs (Paris, 2023; Tangye et al., 2022).

Visbiežāk sastopamais IIT veids, kura gadījumā arī var būt vērojami traucējumi pēcvakcinācijas atbildē, ir pārsvarā antivielu deficīts (PAD) (Poli et al., 2025). Biežākie no PAD ir selektīvs IgA deficīts (SIgAD) un parasts mainīgs imūndeficīts (PMID). Klīniski šos traucējumus raksturo paaugstināta uzņēmība pret infekcijas slimībām, kā arī ar imūnregulācijas traucējumiem saistītas neinfekciozas komplikācijas (Edwards et al., 2019). Abiem traucējumiem raksturīgi B šūnu defekti vai funkcionāli traucējumi citās imūnšūnu līnijās, kas noved pie samazinātas imūnglobulīnu sintēzes (Bagheri et al., 2023; Milito et al., 2021). Līdztekus samazinātam imūnglobulīnu daudzumam, kas raksturīgs visiem PAD pacientiem, PMID diagnostiskajos kritērijos ietilpst arī traucēta pēcvakcinācijas imūnatbilde un/vai zems pārslēgto atmiņas B šūnu skaits, kas liecina par sekundāros limfoidos orgānos esošo reaktīvo centru darbības traucējumiem (Seidel et al., 2019). Reaktīvie centri ir galvenā vieta, kur noris imūnglobulīnu klases pārslēgšanās, somatiskā hipermutācija un antivielu afinitātes nobriešana. Pacientiem ar PMID var būt disfunkcionāli un neregulāri reaktīvie centri (Schouwenburg van et al., 2022). Reaktīvo centru disfunkcijā var būt iesaistīti vairāki mehānismi, tostarp hroniska infekcija, transkripcijas faktora T-bet pastiprināta ekspresija un ar to saistīta pastiprināta CD21low atmiņas B šūnu veidošanās, CXCL13 disfunkcija (B šūnu hemoatraktants), kā arī T folikulāro līdzētājšūnu (TFH) un T folikulāro regulatoro šūnu (TFR) darbības traucējumi (Gupta et al., 2022; Romberg et al., 2019; Yang et al., 2022). TFH, izdalot interleikīnu (IL) 4 un IL-21, reaktīvo centru reakcijās limfmezglos ir būtiskas B šūnu diferenciācijai par imūnglobulīnus ražojošām plazmas šūnām un atmiņas B šūnām (Baumjohann & Fazilleau,

2021), savukārt TFR piedalās TFH regulācijā, kontrolējot imūno sinapsi starp B šūnu un TFH. Šo šūnu disfunkcija var būt saistīta ar autoimunitātes attīstību (Gupta et al., 2024; Padron & Hernandez-Trujillo, 2023). B šūnu darbības traucējumi varētu negatīvi ietekmēt arī T-šūnu atbildi PAD pacientiem, jo B šūnas kā viens no antigēnpresentējošo šūnu veidiem var piedalīties T-šūnu aktivācijā (Apostolidis et al., 2021).

Papildus B šūnu darbības traucējumiem PAD var būt saistīti arī ar traucējumiem mehānismos, kas ietekmē imūnsistēmas koordināciju un regulāciju, tai skaitā defektiem T-šūnu signālceļos, iedzimtās imunitātes šūnu, piemēram, makrofāgu, dendrītisko šūnu, dabisko galējājšūnu (NK) un iedzimto limfoīdo šūnu, darbības traucējumiem. Traucējumi var rasties arī ārpus specifiskām imūnšūnu populācijām, piemēram, primāro vai sekundāro limfoīdo orgānu mikrovīdē (Fernando et al., 2021; Ho & Cunningham-Rundles, 2020; Le Saos-Patrinis et al., 2020; Martelius et al., 2023). Šo dažādo šūnu disregulācijas sekas atspoguļojas arī izmainītos citokīnu līmeņos (Polito et al., 2019; Poto et al., 2023; Rodríguez-Ubreva et al., 2024). Tomēr PAD patoģenēzē, tostarp neinfekciozo komplikāciju attīstībā, vēl aizvien ir daudz nezināmā. Tā kā biežāk sastopamie PAD parasti attīstās pieaugušo vecumā, viens no hipotētiskajiem vides faktoriem, kas varētu ietekmēt slimības un komplikāciju attīstību, ir traucējumi imūnsistēmas reakcijā uz antigēnu, tostarp vīrusa antigēnu (Al-Hakim et al., 2024; Ameratunga et al., 2023; Strohmeier et al., 2023). 2019. gada nogalē Ķīnā tika identificēts jauns vīruss – smaga akūta respiratorā sindroma koronavīruss 2 (SARS-CoV-2), kas izraisīja pneimoniju un ātri izplatījās, sasniedzot pandēmijas apmērus (Zhou et al., 2020). Pacientu saskare ar SARS-CoV-2 antigēnu deva iespēju analizēt, kā PAD un citu IIT pacientu imunitātes defekti ietekmē imūnsistēmas reakciju uz šo jauno antigēnu (Quinti et al., 2022; Rodríguez-Ubreva et al., 2024).

Kaut arī atbildīgās institūcijas rekomendēja IIT pacientiem saņemt SARS-CoV-2 vakcināciju (ESID, 2022), daļa IIT pacientu no vakcinācijas pret SARS-CoV-2 tomēr atteicās. Ir svarīgi apzināt šo pacientu biežākās bažas vakcinācijas sakarā, lai efektīvi varētu kļiedēt nepamatotās bažas un pacienti varētu saņemt nepieciešamo vakcināciju. Arī gadījumos, kad pacientam neveidojas aizsargājošas antivielas, SARS-CoV-2 vakcīna joprojām varētu būt efektīva, jo T atmiņas šūnu klātbūtne var palīdzēt kontrolēt infekciju (Amodio et al., 2021). T-šūnu nozīmi aizsardzībā pret 2019. gada koronavīrusa slimību (Covid-19) apstiprina arī ziņojumi par to, ka Covid-19 pacientiem ar smagu slimības gaitu konstatēts vīrusam specifisko T-šūnu trūkums, savukārt pacientiem ar vieglāku slimības gaitu raksturīgas agrīni inducētas funkcionālas

SARS-CoV-2 specifiskās T-šūnas, kā arī tas, ka asimptomātiskiem cilvēkiem ar SARS-CoV-2 infekciju T-šūnu atbildes reakcijas var noritēt bez humorālas atbildes reakcijas (Sahin et al., 2021; Sekine et al., 2020; Sette & Crotty, 2021; Tan et al., 2021).

Promocijas darbs ir sadalīts trijās daļās: 1) IIT izplatības analīze Latvijas populācijā (Prokofjeva et al., 2022); 2) SARS-CoV-2 imūnās atbildes novērtējums PAD pacientiem (Lucane, Slisere, Gersone et al., 2023; Lucane, Slisere, Ozola et al., 2023); 3) faktoru, kas attur IIT pacientus no rekomendētas SARS-CoV-2 vakcinācijas, analīze (Lucane, Kursite et al., 2023).

Darba mērķis

Raksturot iedzimto imūndeficītu traucējumu (IIT) izplatību Latvijas populācijā, izvērtēt SARS-CoV-2 antigēnam specifisko humorālo un T-šūnu imūno atbildi, tās saistību ar slimības fenotipu un smagumu pacientiem ar predomanti antivielu deficītiem (PAD), kā arī identificēt faktorus, kas ietekmē atteikšanos no rekomendētas SARS-CoV-2 vakcinācijas IIT traucējumu pacientiem Latvijā.

Darba uzdevumi

1. Apkopot IIT pacientu datus izplatības noteikšanai Latvijas populācijā.
2. Noteikt SARS-CoV-2 specifisko T-šūnu un antivielu imūno atbildi pētāmajā (PMID un SIgAD pacienti) un kontroles grupā. Novērtēt atšķirības starp grupām. Izvērtēt SARS-CoV-2 specifiskās imūnās atbildes saistību ar slimības fenotipu un smagumu pētāmajā grupā.
3. Noteikt citokīnu izmaiņas pēc SARS-CoV-2 antigēna stimulācijas pētāmajā (PMID un SIgAD pacienti) un kontroles grupā. Novērtēt atšķirības starp grupām. Izvērtēt, kā citokīnu līmeņi pēc SARS-CoV-2 antigēna stimulācijas ir saistīti ar slimības fenotipu un smagumu pētāmajā grupā.
4. Izpētīt IIT pacientu iemeslus atteikumam no rekomendētas SARS-CoV-2 vakcinācijas.

Darba hipotēze

1. PMID pacientiem ir zemāks SARS-CoV-2 specifisko antivielu titrs, bet T-šūnu atbilde neatšķiras no SIgAD un kontroles grupām, savukārt SARS-CoV-2 antigēna inducētais citokīnu sekrēcijas profils atšķiras starp grupām un korelē ar slimības fenotipu un smagumu.
2. Papildus vispārējā populācijā aprakstītajiem iemesliem atteikties no rekomendētas SARS-CoV-2 vakcinācijas IIT pacientu grupā pastāv specifiski iemesli, kam ir saistība ar slimību vai tās ārstēšanu.

Darba novitāte

Pētījumā sākotnēji tika noteikta IIT izplatība Latvijas populācijā. Šis ir pirmais pētījums, kurā analizēti IIT izplatības rādītāji Latvijas populācijā. No kopējās IIT pacientu populācijas nākamā pētījuma posma veikšanai atlasīti pacienti ar PAD – specifisku IIT grupu, kurai raksturīga traucēta imūnā atbilde pēc vakcinācijas un bieži novērojamas neinfekciozas komplikācijas.

Pētījumos par SARS-CoV-2 specifisko imūno atmiņu PAD pacientiem kā surogātmarķieri visbiežāk izmantoti tieši antivielu līmeņi (Abo-helo et al., 2021; Bergman et al., 2021; Delmonte et al., 2021; Ponsford et al., 2022), savukārt par SARS-CoV-2 specifisko T-šūnu atmiņu ir pieejams mazāk pētījumu, turklāt līdz šim nevienā pētījumā nav analizēta šūnu imūnā atbilde pret SARS-CoV-2 antigēnu specifiski SIgAD pacientiem.

Ņemot vērā, ka vides faktori, tostarp saskare ar antigēniem, var ietekmēt gan PAD, gan specifiski neinfekciozo komplikāciju attīstību (Rodríguez-Ubreva et al., 2024), pētījumi par imūnās reakcijas atšķirībām pret SARS-CoV-2 antigēnu PAD pacientiem varētu sniegt jaunas atziņas par slimības patoģenēzi. Tā kā citokīniem ir svarīga loma T-šūnu izdzīvošanā un diferenciācijā, to sekrēcijas raksturojums varētu atklāt funkcionālas atšķirības ar klīnisku nozīmi (Abyazi et al., 2022). Tikai dažos pētījumos ir analizētas klīnisko fenotipu un dažādu imunoloģisko rādītāju (imūnglobulīnu, T un B šūnu subpopulāciju, bāzes citokīnu līmeņu) saistības ar imūnsistēmas atbildes reakciju pret SARS-CoV-2 antigēnu. Tāpat pētījumos lielākoties ir pētītas T-šūnu atbildes reakcijas pret SARS-CoV-2 antigēnu, nosakot IL-2 un/vai IFN- γ sekrēciju (Hagin et al., 2021; Pham et al., 2022; Leeuwen van et al., 2022). Šis ir pirmais pētījums, kurā noteikts plašāks citokīnu spektrs pēc pilnasiņu stimulācijas ar SARS-CoV-2 antigēnu PAD pacientiem.

Tā kā dažu IIT diagnožu gadījumā antivielu atbildes reakcija pret SARS-CoV-2 vakcināciju var būt samazināta un sākotnējie vakcīnu pētījumi neiekļāva pacientus ar IIT, daļai pacientu tieši datu trūkums specifiskajai populācijai kļuva par iemeslu vilcināties ar izvēli par labu vakcinācijai, tādēļ pētījumi imūnās atbildes jomā, tai skaitā izmantojot surogātmarķierus, reto imūnsistēmas slimību pacientiem ir būtiski (Aberumand et al., 2022). Tomēr pastāv arī citi iemesli atteikumam no SARS-CoV-2 vakcinācijas. Līdz šim veikti tikai trīs pētījumi par IIT pacientu iemesliem (Aberumand et al., 2022; Pergent et al., 2023; Więsik-Szewczyk et al., 2022), turklāt neviens no tiem nebija kvalitatīva dizaina pētījums. Izmantojot kvalitatīvo pētniecības pieeju, iespējams, varētu atklāt jaunus, vispārējai populācijai neraksturīgus un tieši IIT pacientiem specifiskus faktorus, kas nosaka pacientu atteikumu no vakcinācijas un kas nav bijuši paredzami, izmantojot pētnieka izstrādātus vairāku atbilžu variantu jautājumus.

Diskusija

1. Iedzimto imunitātes traucējumu izplatība Latvijas populācijā

Pirmajā pētījuma daļā no pacientu medicīniskās dokumentācijas tika iegūti dati par Latvijā diagnosticētajiem IIT pacientiem, lai novērtētu IIT izplatību Latvijas populācijā, kā arī veiktu pacientu atlasīšanu turpmākiem pētījuma posmiem. Latvijā IIT pacientu novērošana notiek Paula Stradiņa Klīniskajā universitātes slimnīcā un Bērnu klīniskajā universitātes slimnīcā, un dati tika iegūti no šīm abām slimnīcām.

Divdesmit septiņu gadu periodā no 1994. līdz 2020. gadam Latvijā tika diagnosticēti 173 pacienti ar IIT. IIT punkta prevalence Latvijā 2020. gada decembrī bija 7,1 uz 100 000 iedzīvotāju. Salīdzinot ar citām Eiropas valstīm, pēc Eiropas Imūndeficītu biedrības (ESID) reģistra datiem, kopējā IIT izplatība svārstās no 1,3 uz 100 000 iedzīvotāju Polijā līdz 8,85 uz 100 000 iedzīvotāju Īrijā (Bonilla et al., 2016; Ryan et al., 2022). Jāatzīmē, ka IIT izplatības rādītāji sākotnēji Latvijā bija ļoti zemi un ir auguši pēdējo gadu laikā: no 0,08 gadījumiem uz 100 000 iedzīvotāju 1994. gadā un 1,1 uz 100 000 iedzīvotāju 2004. gadā līdz 7,1 gadījumam uz 100 000 iedzīvotāju 2020. gadā. 2004. gadā tika uzsākts starptautiskais “J projekts” – izglītības un klīnisko pētījumu sadarbības programma imūndeficītu jomā, kas šobrīd aptver jau 32 valstis. “J projekta” mērķis ir veicināt informētību un IIT pacientu agrīnu diagnostiku un ārstēšanu. Latvijas un arī citu Austumeiropas un Centrāleiropas valstu gadījumā tas ir sekmējis IIT pacientu atpazīšanu un diagnostiku, rezultējoties pacientu skaita pieaugumā (Abolhassani et al., 2022). Tāpat IIT diagnostika ir uzlabojusies, arī ieviešot praksē jaunas diagnostikas metodes un uzlabojoties ģenētisko izmeklējumu pieejamībai.

Latvijā visbiežāk diagnosticētā IIT diagnožu grupa ir kombinēti imūndeficīti ar sindromiskām iezīmēm, savukārt citās valstīs dominējošā grupa ir PAD: no 20 % Islandē līdz 63 % Itālijā (Lougaris et al., 2020; Ludviksson et al., 2014). “J projekta” valstīs PAD īpatsvars bija 46,3 % no kopējā pacientu skaita, bet otrs biežākais IIT veids bija kombinēti imūndeficīti (14,3 %) (Abolhassani et al., 2022). Savukārt Latvijā PAD veido 21 % no kopējā IIT pacientu skaita. Mazāka PAD proporcija IIT pacientu vidū varētu būt skaidrojama ar nepietiekamu šīs slimības pacientu atpazīšanu.

Smagākās IIT formas, smaga kombinēta imūndeficīta (SKID) incidence, Latvijā no 1994. līdz 2020. gadam bija 1 no 32 963 dzīvi dzimušajiem jaundzimušajiem. Agrīna šīs slimības atklāšana ir nozīmīga, jo ļauj nekavējoties sākt izolāciju un nosūtīt pacientu allogēnai hematopoētisko cilmes šūnu transplantācijas veikšanai, turklāt ārstēšanas rezultāti ir labāki tiem bērniem, kuriem transplantācija veikta līdz 3,5 mēnešu vecumam pirms smagu infekcijas slimību pārslimošanas (Thakar et al., 2023). Agrīnai slimības diagnostikai ir izstrādāts jaundzimušo skrīnings, kas ir ticis ieviests 17 Eiropas valstīs (Blom et al., 2024). Kopš

2023. gada skrīnings ir ieviests arī Latvijā (LR Veselības ministrija, 2023). Pēc skrīninga ieviešanas SKID rādītājiem valstī ir tendence pieaugt, jo tiek diagnosticēti arī gadījumi, kad cilvēki būtu agrīni miruši no infekcijas slimībām, pirms tiktu diagnosticēts SKID, tādējādi patiesā incidence varētu būt augstāka (Ricci et al., 2024).

Šis ir pirmais pētījums par IIT izplatību Latvijas populācijā. Pētījuma galvenā priekšrocība ir ilga pētījuma periods un datu pieejamība no visiem Latvijas centriem, kuros ārstē šīs retās slimības. Potenciāls ierobežojums ir tas, ka Latvijā nav iedzimto imunitātes traucējumu pacientu reģistra, dati medicīniskajā dokumentācijā mēdz būt nepilnīgi, kā arī daži pacienti varētu nebūt diagnosticēti un novirzīti tālākai novērošanai pie imunologa, kas nozīmē, ka IIT izplatība varētu būt novērtēta kā pārāk zema.

2. PAD pacientu imunoloģiskā atbildes reakcija pret SARS-CoV-2 antigēnu

Otrajai pētījuma daļai no visiem Latvijā diagnosticētajiem IIT tika atlasīti pacienti ar biežākajiem PAD. Šajā pētījuma daļā tika iekļauti 47 dalībnieki: 17 pacienti ar PMID, 15 pacienti ar SIgAD un 15 kontroles grupas indivīdi. Atbilstoši klīniskie dati par PMID un SIgAD pacientiem tika iegūti no pacientu slimības vēsturēm un anketām. Mūsu pētījuma pacienti un kontroles grupas dalībnieki bija saņēmuši homologu vakcinācijas shēmu ar kādu no šīm vakcīnām – *Pfizer-BioNTech/BNT162b2* (divas vai trīs devas), *Spikevax mRNA-1273* (divas vai trīs devas) vai *Jcovden Ad26.COV2* (vienu devu); 50 % pacientu un 53 % kontroles grupas dalībnieku bija saņēmuši balstvakcīnas devu vismaz 6 mēnešus pēc primārās sērijas pabeigšanas. Vidējais laiks pēc pēdējās vakcīnas devas saņemšanas bija 173 dienas pacientu grupā un 215 dienas kontroles grupā. Šajā pētījuma daļā tika noteikta PAD pacientu humorālā un T-šūnu imūnā atbilde pret SARS-CoV-2 antigēnu.

Pētījuma dalībnieku asins paraugi tika iegūti no 2022. gada aprīļa līdz jūlijam. Lai noteiktu SARS-CoV-2 specifisko humorālo atbildi, tika mērīts SARS-CoV-2 specifiskais IgG antivielu līmenis pret smailes proteīna S1 domēnu, izmantojot enzīmu imūnsorbenta analīzi (ELISA). Lai noteiktu pret SARS-CoV-2 smailes proteīna S1 un S2 domēnu specifisko T-šūnu reakciju, tika izmantots interferona- γ (INF- γ) izdalīšanās tests (IGRA) *QuantiFERON SARS-CoV-2*, ar kuru mērīja INF- γ līmeņa pieaugumu pēc SARS-CoV-2 peptīdu antigēnu stimulācijas. Citokīnu izmaiņu noteikšanai pirms un pēc SARS-CoV-2 smailes proteīna antigēnu stimulācijas tika izmantota xMAP *Luminex* tehnoloģija. Tika vērtētas antivielu līmeņu, T-šūnu izdalītā INF- γ un citu citokīnu atšķirības starp pacientu un kontroles grupām un pacientu grupā – arī saistība ar slimības klīnisko ainu un smagumu.

2.1. Humorālā atbilde

Serokonversija jeb SARS-CoV-2 smailes proteīnam specifisko IgG klases antivielu līmenis, kas pārsniedza pozitivitātes sliekšni, bija vērojams 93 % PMID pacientu un visiem kontroles grupas un SIgAD pacientiem. Savukārt citos pētījumos PAD pacientu grupā ir ievērojamas seropozitivitātes līmeņa atšķirības, pieaugušo populācijā seropozitivitātes līmenim variējot no 15 līdz 100 % (Abella et al., 2022; Amodio et al., 2021; Barmettler et al., 2022; Bergman et al., 2021; Delmonte et al., 2021; Göschl et al., 2022; Hagin et al., 2021; Lin et al., 2022; Oyaert et al., 2022; Pham et al., 2022; Pulvirenti et al., 2021; Salinas et al., 2021; Shields, Faustini, Hill, Al-Taei, Walder, et al., 2022a; Squire & Joshi, 2021; Steiner et al., 2023; A. M. Zhang et al., 2024). Tomēr jāņem vērā, ka lielā daļā šo pētījumu bija salīdzinoši neliels izlases lielums. Pētījumos ar lielāku PMID pacientu izlasi seropozitivitātes līmenis variēja no 66 līdz 81 % (Shields, Faustini, Hill, Al-Taei, Tanner, et al., 2022; Leeuwen van et al., 2022). Plašo seropozitivitātes diapazonu dažādos pētījumos varētu skaidrot arī ar atšķirīgu pētījumu metodoloģiju un slimības heterogenitāti, Covid-19 pārslimošanu anamnēzē, atšķirīgu vakcinācijas shēmu lietojumu, kā arī laiku pēc pēdējās vakcīnas devas ievades (Quinti et al., 2022; Steiner et al., 2023).

Lai gan lielākajai daļai mūsu pētījuma dalībnieku specifisko antivielu titrs sasniedza pozitivitātes līmeni, SARS-CoV-2 specifisko antivielu līmenis bija zemāks PMID pacientiem, salīdzinot ar veselīgiem kontrolgrupas indivīdiem vai SIgAD pacientiem. Šis rezultāts saskan ar citiem pētījumiem, kur PMID pacientiem tika novērota gan zemāka sākotnējā specifiskā SARS-CoV-2 antivielu atbilde, gan vakcinācijas antivielu līmenis samazinājās straujāk nekā citiem IIT pacientiem vai kontroles grupas dalībniekiem Pino-Molina del et al., 2021; Shields, Faustini, Hill, Al-Taei, Tanner, et al., 2022; Leeuwen van et al., 2023). Mūsu pētījumā netika vērtēta antivielu neitralizācijas spēja, tomēr jāņem vērā, ka PMID gadījumā pat kvantitatīvi pietiekamā antivielu daudzumā var būt nepilnīga antivielu kvalitāte – aviditāte, neitralizācijas spēja un ierobežots antivielu repertuārs (Nadesalingam et al., 2023; Pham et al., 2022; Shields, Faustini, Hill, Al-Taei, Walder et al., 2022a; Steiner et al., 2023; Troelnikov et al., 2023). Pētījumos šie rezultāti skaidroti ar traucējumiem reaktīvo centru un atmiņas B šūnu veidošanā, piemēram, pacientiem ar PMID pēc vakcinācijas ar *Pfizer-BioNTech/BNT162b2* vakcīnu, salīdzinot ar veselīgiem kontrolgrupas indivīdiem, bija samazināts SARS-CoV-2 specifisko atmiņas B šūnu daudzums, kā arī tika konstatēts vairāk atipisku atmiņas B šūnu, kas varētu būt radušās ekstrapolikulārās, nevis reaktīvo centru, reakcijās, un šajā gadījumā antivielu līmenis serumā saglabājas īsāku laiku (Salinas et al., 2021). Savukārt citā pētījumā tika novērots, ka PAD pacientiem pēc primārās mRNA vakcinācijas sērijas bija samazināts IgG1+ un CD11c+

atmiņas B šūnu skaits, kas varētu liecināt par B šūnu receptoru signālceļu traucējumiem un/vai samazinātu T-šūnu palīdzību (Lin et al., 2022).

Mūsu pētījumā ne Covid-19 pārslimošana anamnēzē, ne Covid-19 smaguma pakāpe nebija saistīta ar SARS-CoV-2 specifisko antivielu līmeni vai seropozitivitāti. Tomēr jāņem vērā, ka pētījuma veikšanas brīdī, 2022. gada aprīlī, lielākā daļa pacientu (59 %) un kontroles grupas dalībnieku (53 %) jau iepriekš bija saskārušies ar SARS-CoV-2 vīrusu. Kā arī jāņem vērā šī pētījuma ierobežojums: izlases lielums bija ierobežots šo slimību retuma dēļ, kas ievērojami samazināja statistisko spēku un ierobežoja spēju noteikt nozīmīgas asociācijas. Iepriekšējos pētījumos konstatēts, ka PAD pacientiem, kuri bija pārslimojuši Covid-19, pēcvakcinācijas antivielu līmenis bija augstāks nekā tiem, kuri nekad nebija inficējušies (Shields, Faustini, Hill, Al-Taei, Walder et al., 2022). Tomēr ir arī pētījumi, kur Covid-19 pārslimošana nebija saistīta ar SARS-CoV-2 specifiskās antivielu atbildes intensitāti (Erra et al., 2022).

Tāpat mūsu pētījumā netika novērota atšķirība starp dažādiem vakcīnu veidiem un SARS-CoV-2 specifisko antivielu līmeni vai seropozitivitāti. Arī COV-AD pētījumā nebija atšķirības starp vairāku atšķirīgu homologu vakcīnu imunogenitāti PAD pacientiem (Shields, Faustini, Hill, Al-Taei, Tanner et al., 2022), savukārt citā pētījumā, kas iekļāva dažādu IIT pacientus, *Spikevax mRNA-1273* uzrādīja augstāku imunogenitāti, salīdzinot ar citām vakcīnām (*Sputnik V*, *Oxford-AstraZeneca ChAdOx1*, *Sinopharm/BIBP* un *Pfizer-BioNTech/BNT162b2*) (Erra et al., 2022). Mūsu pētījuma pacienti bija saņēmuši tikai homologus vakcīnu režīmus, savukārt citos pētījumos seropozitivitātes līmenis paaugstinājās, izmantojot heterologus vakcīnu režīmus (piemēram, *Oxford-AstraZeneca ChAdOx1* primārā shēma un revakcinācija ar *Pfizer-BioNTech/BNT162b2*) (Kamar et al., 2021; Shields, Faustini, Hill, Al-Taei, Tanner et al., 2022; Zimmerman et al., 2022). Mūsu pētījumā saņemto vakcīnas devu skaits nebija saistīts ar seropozitivitāti un nekorelēja ar SARS-CoV-2 specifisko antivielu līmeni, un mūsu pētījuma dizains neļāva novērtēt antivielu attīstības dinamiku pēc katras vakcinācijas devas saņemšanas, taču citos pētījumos daļai PMID pacientu, kuriem serokonversiju nenovēroja pēc pirmās mRNS vakcīnas devas, pozitīvs antivielu līmenis tika konstatēts pēc vairākām vakcīnu devām, kā arī uzlabojās antivielu aviditāte (Delmonte et al., 2021; Goda et al., 2022; Shin et al., 2022; Barnettler et al., 2022; Shields, Faustini, Hill, Al-Taei, Tanner et al., 2022; Tandon et al., 2023; Zimmerman et al., 2022). Tas liecina, ka vairāku SARS-CoV-2 vakcīnu devu saņemšana ir klīniski izdevīga, īpaši augsta riska PAD pacientiem (A. M. Zhang et al., 2024). Citā pētījumā secināts, ka pēc revakcinācijas PAD pacientu atmiņas B šūnās tiek novērstas IgG1 klases pārslēgšanās defekts (Lin et al., 2022). Tomēr literatūrā ir atrodamu arī pretēji ziņojumi, kuros PMID pacientiem antivielu reakcija neuzlabojas pēc trešās un/vai ceturtās mRNS vakcīnu

devas, ja sākotnēji netika novērota SARS-CoV-2 specifiskā antivielu atbilde uz pirmajām divām/trim SARS-CoV-2 mRNS vakcīnu devām (Nielsen et al., 2022; Leeuwen van et al., 2023). Kopumā jāsecina, lai gan lielai daļai PMID pacientu ir nosakāmas specifiskās SARS-CoV-2 antivielas, daļai PMID pacientu joprojām ir traucēta SARS-CoV-2 specifiskās imūnās atbildes veidošanās, un teorētiski to varētu prognozēt, ņemot vērā sākotnējo imūnsistēmas profilu un klīnisko ainu.

Iepriekš ziņots, ka pacientiem ar PAD un autoimunitāti vai citām neinfekciozām komplikācijām anamnēzē ir sliktāka atbildes reakcija uz vakcināciju (Durkee-Shock & Keller, 2022; Goda et al., 2022; Pulvirenti et al., 2021; Shin et al., 2022; Leeuwen van et al., 2023), taču ir atrodami arī pētījumi, kuros imūnā atbilde nav saistīta ar klīniskajām izpausmēm (Mizera et al., 2023; Steiner et al., 2023). Mūsu pētījumā netika konstatēta saistība starp SARS-CoV-2 specifisko IgG līmeni un slimības klīniskajām izpausmēm, taču šo datu interpretācijā jāņem vērā pētījuma izlases lielums, kas ierobežoja spēju noteikt nozīmīgas asociācijas. Lai gan mūsu pētījumā SARS-CoV-2 smailes proteīnam specifiskā IgG līmenis tieši nekorelēja ar klīniskajiem rādītājiem, tomēr tika atrasta saistība starp citokīnu līmeni, ko veido šūnas, kas iesaistītas antivielu sintēzē, un autoantivielu klātbūtni pacientu serumā. Šī saistība tiks apskatīta tālāk diskusijas sadaļā.

Starp SARS-CoV-2 specifisko antivielu un T-šūnu atbildes reakciju netika novērota statistiski nozīmīga korelācija PMID grupā, savukārt SIgAD un kontroles grupās tika novērota korelācija starp SARS-CoV-2 specifisko antivielu un T-šūnu imunitāti, un arī citos pētījumos ar veselīgiem indivīdiem ir konstatēta šī tendence – pozitīva korelācija starp SARS-CoV-2 smailes proteīnam specifisko T-šūnu (CD4⁺ un CD8⁺) daudzumu un IgG antivielu līmeni agrīni pēc vakcinācijas, kas liecina par vienlaicīgu adaptīvās humorālās un šūnu imunitātes attīstību (Boppana et al., 2021; Sahin et al., 2021). Savukārt citos pētījumos, kas iekļāva PAD pacientus, specifisko antivielu titri nekorelēja ar T-šūnu atmiņu (Göschl et al., 2022; Mizera et al., 2023). Attiecībā uz T-šūnu subpopulāciju korelāciju ar SARS-CoV-2 specifisko humorālo atbildi mūsu pētījumā tika atrasta saistība starp humorālo reakciju un centrālo atmiņas CD8⁺ šūnu daudzumu un specifiski SIgAD pacientu grupā arī ar centrālo atmiņas CD4⁺ šūnu daudzumu, līdzīgi kā iepriekš aprakstīts PAD pacientiem (Rosenthal et al., 2023; Shin et al., 2022).

Mūsu pētījumā netika konstatēta saistība starp SARS-CoV-2 specifisko antivielu atbildi un B šūnu subpopulāciju skaitu, un līdzīgi rezultāti ir arī citā pētījumā par agrīno pēcvakcinācijas atbildi IIT pacientiem (Amodio et al., 2021). Tomēr ir pētījumi, kur PAD pacientu sākotnējais IgG, IgA, kopējais B šūnu, pārslēgto atmiņas B šūnu, marginālās zonas B šūnām līdzīgo šūnu, B regulatoro šūnu vai CD21^{low} B šūnu daudzums ir saistīts ar

SARS-CoV-2 pēcvakcinācijas humorālo atbildi (Antolí et al., 2022; Barmettler et al., 2022; Gupta et al., 2024; Pham et al., 2022; Sauerwein et al., 2022; Shin et al., 2022). Mūsu pētījumā arī *EUROclass* klasifikācijas fenotipiem nebija saistības ar SARS-CoV-2 specifisko humorālo atbildi un SARS-CoV-2 vakcinācijas sakarā citi ziņojumi par šo jautājumu nav pieejami.

Jāņem vērā, ka SARS-CoV-2 specifisko antivielu daudzuma interpretāciju šajā un citos pētījumos var ietekmēt tas, ka pacienti ar PMID saņem imūnglobulīnu aizstājterapiju. Ir iespējams, ka imūnglobulīna preparāti saturēja specifiskas antivielas pret SARS-CoV-2 antigēnu asins paraugu ņemšanas brīdī, 2022. gada aprīlī (Babaha & Rezaei, 2020; Göschl et al., 2022). Lai novērstu potenciālo ietekmi, mūsu pētījumā pacientu asins paraugi tika ņemti pirms kārtējās imūnglobulīnu ievades. Laiks no donora plazmas nodošanas līdz gatava imūnglobulīnu produkta izplatīšanas sākumam parasti ilgst līdz gadam (Zimmerman et al., 2022). Arī citos pētījumos PMID pacienti, kuriem pēc vakcinācijas netika konstatēta SARS-CoV-2 specifiskā humorālā atbilde, saņēma IgG aizstājterapiju, tādēļ ir maz ticams, ka pasīvā imunizācija, ko izraisa IgG aizstājterapija, ietekmēja SARS-CoV-2 antivielu analīzes rezultātus (Arroyo-Sánchez et al., 2022; Nielsen et al., 2022; Pham et al., 2022; Sauerwein et al., 2022; Shin et al., 2022; Volk et al., 2022). Līdzīgs gadījums tika novērots arī mūsu pētījuma grupā: pacientei, kura saņem imūnglobulīnu aizstājterapiju un tādējādi tiek sasniegts normāls seruma IgG līmenis (kas pierāda līdzestību terapijai), specifisko SARS-CoV-2 antivielu titrs bija zem references intervāla pozitivitātes robežas. Tāpat vēl 2022. gada pirmajā pusē testētajiem imūnglobulīnu aizvietotājproduktiem bija zems antivielu titrs gan pret SARS-CoV-2 smailes proteīnu, gan receptorus saistošo domēnu (Farcet et al., 2022; Nielsen et al., 2022; Romero et al., 2022; Zimmerman et al., 2022).

2.2. T-šūnu atbilde

CD8⁺ T-šūnām ir izšķiroša nozīme pretvīrusu atbildes reakcijā akūtas infekcijas gadījumā, savukārt B un CD4⁺ T-šūnām ir būtiska loma vīrusu infekcijas novēršanā un galīgajā vīrusa iznīcināšanā (Wolf de et al., 2022). Ja vīruss inficē imūnkompetentu cilvēku ar iegūto imunitāti pret šo vīrusu, pēc aktivācijas CD8⁺ citotoksiskie T limfocīti ierobežo intracelulāro vīrusa komponentu izplatību, izdalot granzīmus un perforīnus, pārvadot apoptozes signālus un izdalot imūnstimulējošus citokīnus, tostarp IFN- γ un TNF- α , bet CD4⁺ T-šūnu dažādo subpopulāciju funkcija vīrusinfekciju gadījumā ir pretvīrusu imunitātes koordinēšana un regulēšana (Apostolidis et al., 2021; Piazza di et al., 2021).

Mūsu pētījumā lielākajai daļai PMID (93 %) un SIgAD (92 %) pacientu tikai konstatēta T-šūnu atbildes reakcija pret SARS-CoV-2 antigēnu, kas tika mērīta kā INF- γ sintēzes pieaugums uz SARS-CoV-2 specifisko antigēnu stimulāciju IGRA testā. Citos pētījumos

T-šūnu atbildes reakcija tika konstatēta no 53 līdz 90 % ITT pacientu (Amodio et al., 2021; Antolí et al., 2022; Delmonte et al., 2021; Gernez et al., 2022; Goda et al., 2022; Göschl et al., 2022; Hagin et al., 2021; Lin et al., 2022; Mizera et al., 2023; Oyaert et al., 2022; Salinas et al., 2021; Steiner et al., 2023).

Mūsu darbā netika konstatētas statistiski nozīmīgas atšķirības SARS-CoV-2 specifiskajā T-šūnu atbildes reakcijā starp PAD pacientu un kontroles grupām, tāpat kā citos pētījumos (Abolhassani et al., 2022; Goda et al., 2022; Göschl et al., 2022; Gupta et al., 2024; Hagin et al., 2021; Murray et al., 2023; Pham et al., 2022; Leeuwen van et al., 2023), kas atbilst slimības patogēnēzei, jo PAD pacientiem galvenokārt ir traucēta tieši antivielu sintēze, nevis T-šūnu funkcija perifērijā (Tangye et al., 2022). Vairākos pētījumos PAD pacientu grupā T-šūnu atbilde pat bija intensīvāka, salīdzinot ar kontroles grupu (Ainsua-Enrich et al., 2022; Amodio et al., 2021; Delmonte et al., 2021). Viens no skaidrojumiem varētu būt T-šūnu kompensatorā funkcija pacientiem ar primāriem B šūnu funkciju traucējumiem (Amodio et al., 2021). Tomēr PAD ir heterogēna slimību grupa, un ir pieejami pētījumi, kuros secināts, ka PMID pacientiem T-šūnu atbilde ir samazināta, salīdzinot ar kontroles grupu (Ainsua-Enrich et al., 2022; Antolí et al., 2022; Gupta et al., 2021; Sauerwein et al., 2022; Leeuwen van et al., 2023). Piemēram, pētījumā, kurā noteica SARS-CoV-2 smailes proteīnam specifisko citotoksisko T-šūnu aktivāciju, PMID pacientiem tika konstatēts mazāks smailes proteīnam specifiski aktivēto CD8+CD25+ T-šūnu skaits, salīdzinot ar kontroles grupu, kas neuzlabojās arī pēc trešās vakcīnas devas saņemšanas. Kaut gan INF- γ pozitivitātes sliekšni PMID pacientu grupā sasniedza tikpat bieži kā kontroles grupā, tomēr IFN- γ sekretējošo T-šūnu skaits bija ievērojami zemāks PMID pacientiem, salīdzinot ar kontroles grupu (Ainsua-Enrich et al., 2022). Tāpat citā nelielā pētījumā PMID pacientiem tika konstatēts samazināts SARS-CoV-2 smailes proteīnam specifisko citotoksisko T-šūnu skaits (CD8+ CD107a+ granulīms B+ perforīns+), salīdzinot ar veselīem kontrolgrupas dalībniekiem vai Brutona slimības pacientiem (Gupta et al., 2021). Rezultātu pretrunīgums varētu tikt skaidrots ar atšķirīgo pētījumu metodoloģiju un slimības heterogenitāti. Lai gan lielai daļai PAD pacientu T-šūnu imunitātē netiek novēroti primāri traucējumi, dažos gadījumos ir iespējams viegls šūnu imunitātes defekts, piemēram, daļai pacientu antivielu sintēzes defekts var būt saistīts nevis ar primāriem B šūnu darbības traucējumiem, bet ar samazinātu T folikulāro līdzētājšūnu palīdzību B šūnām sekundāro limfoido orgānu reaktīvo centru reakcijās (Amodio et al., 2021; Sepahi et al., 2024). Arī dažu specifisku patogēno gēnu variantu rezultātā varētu tikt traucēta T-šūnu imūnā atbilde, piemēram, *NFKB1* gēna patogēno variantu gadījumā ir traucēts kodola faktora κB (NF- κB) signālceļš, kas ir galvenais regulējošais transkripcijas faktors antigēnam specifisko imūnās atbildes reakciju attīstībā, kā arī proiekaisuma citokīnu (IL-1 β , TNF- α , INF- γ) pārmērīgā

ekspresijā, kas var būt saistīta ar autoimunitāti (Dieli-Crimi et al., 2018). Lai gan statistiski ticama saistība starp klīnisko ainu un T-šūnu atbildi mūsu pētījumā netika konstatēta, tomēr jāpiemin, ka vienīgajai PMID pacientei, kurai netika konstatēta pozitīva T-šūnu atbilde, klīniski izpaudās trīs autoimūnas slimības un ģenētiskajā testēšanā bija apstiprināts *NRAS* gēna patogēnais variants. Mūsu pētījuma pacientei INF- γ līmeņa pieaugums netika novērots, jo bāzes INF- γ līmenis serumā pirms antigēna stimulācijas bija līdzīgā līmenī kā citiem paraugiem pēc antigēna stimulācijas. Iepriekš pacientiem ar *NRAS* gēna patogēnajiem variantiem ir aprakstīta I tipa INF signālceļu pastiprināta aktivācija (Papa et al., 2021), bet paaugstināts II tipa INF līmenis līdz šim literatūrā nav aprakstīts. Tāpat arī imūnsupresīva terapija var būt iemesls samazinātai T-šūnu atbildei pēc vakcinācijas. Mūsu pētījumā SIgAD pacientu grupā vienīgā paciente, kurai netika novērota pozitīva T-šūnu atbilde (INF- γ līmenis serumā bija zems gan pirms, gan pēc antigēna stimulācijas), bija paciente ar reimatoīdo artrītu, kura saņēma imūnsupresējošu terapiju, tai skaitā bioloģiskos medikamentus. Arī iepriekšējos pētījumos pacienti, kuri saņēma imūnsupresējošu terapiju, uzrādīja vāju T-šūnu atbildi (Liebers et al., 2022; Oyaert et al., 2022; Sleen van et al., 2023).

Mūsu pētījumā nebija atšķirības T-šūnu atbildē starp dažādu vakcīnu saņēmējiem, un līdzīgi ziņots arī citos pētījumos IIT pacientiem (Arroyo-Sánchez et al., 2022; Erra et al., 2022; Shields, Faustini, Hill, Al-Taei, Walder et al., 2022). Mūsu pētījumā netika konstatēta saistība starp T-šūnu atbildes intensitāti un Covid-19 pārslimošanu anamnēzē vai slimības smagumu. Citos pētījumos šajā jautājumā dati ir atšķirīgi – ir pieejami pētījumi ar līdzīgiem rezultātiem (Erra et al., 2022), savukārt COV-AD pētījumā T-šūnu atbildes reakcijas pacientiem ar iepriekš pārslimotu Covid-19 bija izteiktākas, salīdzinot ar Covid-19 neskarto PAD grupu (Shields et al., 2022).

Šajā pētījumā netika konstatēta statistiski ticama saistība starp SARS-CoV-2 specifisko T-šūnu atbildi un T-šūnu apakštipiem, un līdzīgi ziņots arī citos pētījumos (Antolí et al., 2022; Goda et al., 2022; Shields et al., 2022). Arī pacientiem, kuriem neizveidojās nosakāma T-šūnu atbilde, netika novērotas statistiski nozīmīgas saistības ar T-šūnu subpopulāciju biežumu ne šajā pētījumā, ne arī citos pētījumos (Amodio et al., 2021). Mūsu pētījumā netika novērota nozīmīga korelācija starp SARS-CoV-2 specifisko T-šūnu reakciju un B šūnu apakštipiem vai kopējo IgG, IgM vai IgA līmeni, un līdzīgi ziņots arī citos pētījumos (Goda et al., 2022; Shields et al., 2022). Pašreizējā pētījumā arī *EUROclass* klasifikācijas fenotipiem nebija saistības ar T-šūnu atbildi, un SARS-CoV-2 vakcinācijas sakarā citi ziņojumi par šo jautājumu nav pieejami.

T-šūnu imūnās atbildes reakcijas atšķirības nebija saistītas ar pacienta klīniskajiem parametriem, izņemot SIgAD grupu, kurā pacientiem ar recidivējošu otītu bija statistiski

nozīmīgi zemāka T-šūnu atbildes reakcija, salīdzinot ar pacientiem bez šīs infekcijas. Tomēr citos pētījumos, tāpat kā SARS-CoV-2 specifisko antivielu atbildes trūkuma gadījumā, arī SARS-CoV-2 specifiskā T-šūnu atbilde neizveidojās pacientiem ar autoimūnām slimībām (Amodio et al., 2021; Hagin et al., 2021; Leeuwen van et al., 2022) un labdabīgu limfoproliferāciju anamnēzē (Arroyo-Sánchez et al., 2022), lai gan ir pētījumi, kuros šāda T-šūnu atbildes saistība ar klīniskajām izpausmēm nav atrodama (Goda et al., 2022). Arī šo datu interpretācijā jāņem vērā pētījuma izlases lielums, kas ierobežoja spēju noteikt nozīmīgas asociācijas.

Metodei, kas tika izmantota T-šūnu atbildes noteikšanai, ir ierobežojumi, kas jāņem vērā: T-šūnu atbildes reakcijas ir sarežģītas un var aktivizēt dažādus molekulāros ceļus, kā rezultātā var aktivēties atšķirīgi funkcionālie citokīnu ekspresijas profili. Šajā pētījumā tika izmantots komerciāli pieejams IGRA tests SARS-CoV-2 T-šūnu imūnās atbildes noteikšanai, taču pastāv liela metožu dažādība (piemēram, metodes, kas balstās uz T-šūnām raksturīgo citokīnu sekrēciju, antigēna izraisītu proliferatīvu šūnu reakciju vai noteiktu aktivācijas marķieru ekspresiju, ādas vēlīnā tipa hipersensitivitātes reakciju, un citas) un nav skaidras vienprātības par metodi, kura visprecīzāk raksturo antigēnam specifisku T-šūnu atbildes reakciju, kas apgrūtina pētījumu rezultātu savstarpējo salīdzināšanu (Barrios et al., 2022; Friedmann et al., 2020).

Kopumā, lai gan mūsu pētījumā netika konstatēta statistiski nozīmīga atšķirība SARS-CoV-2 specifiskās IFN- γ atbildes reakcijā starp PMID, SIgAD pacientu grupām un kontroles grupu, tas neizslēdz iespēju, ka dažos gadījumos PAD pacientiem varētu būt traucējumi citu citokīnu sekrēcijā (Lin et al., 2022).

3. PAD pacientu citokīnu sekrēcijas profils pēc SARS-CoV-2 antigēna stimulācijas

Šī pētījuma rezultāti atklāja, ka PAD pacientiem pēc pilnasiņu SARS-CoV-2 antigēna stimulācijas statistiski nozīmīgs pieaugums vērojams IFN- γ , TNF- α , IL-1 β , IL-10, IL-15 un IL-17A, bet ne IL-21, IL-4 un IL-6 līmenī, savukārt TGF- β 1 līmenis pēc inkubācijas ar SARS-CoV-2 antigēnu bija zemāks, nekā pirms. Citokīnu līmeņu izmaiņu dinamikā netika novērota atšķirība starp grupām (SIgAD, PMID un kontroles grupa), savukārt mērījumā bez paraugu inkubācijas ar SARS-CoV-2 antigēnu (citokīnu bāzes līmenis) tika novērotas vairāku citokīnu līmeņu atšķirības: PAD pacientiem bija raksturīgs augstāks bāzes IL-10 un IL-4 līmenis, salīdzinot ar kontroles grupu. Iepriekš ziņots, ka IL-4 signālceļu traucējumi ir saistīti ar PMID smagumu (Taraldsrud et al., 2017). Savukārt citā pētījumā ziņots, ka citokīnu līmeņa pieaugums (IL-10, IL-12, IFN- γ , IL-6, IL-8, IL-22) vienu mēnesi pēc SARS-CoV-2 vakcinācijas, salīdzinot ar līmeni pirms vakcinācijas, PMID pacientiem bija augstāks, bet citu

citokīnu līmeņu pieaugums neatšķīrās no kontroles grupas (IL-1 β , IL-4, IL-5 un TNF- α) (Rosenthal et al., 2023).

Kā minēts iepriekš, augstāks INF- γ līmenis pēc SARS-CoV-2 antigēna stimulācijas vakcinētiem PAD pacientiem bija augstāks salīdzinājumā ar nevakcinētiem pacientiem, kuri bija pārslimojuši Covid-19. Šajā pētījumā mēs neatklājām atšķirības citu citokīnu līmeņu izmaiņās pēc SARS-CoV-2 antigēna stimulācijas, salīdzinot vakcinētus un nevakcinētus pacientus, lai gan iepriekš veiktā pētījumā ar veselīgiem indivīdiem TNF- α atbildes reakcija uz stimulāciju ar SARS-CoV-2 specifisko peptīdu kopumu (smailes, nukleokapsīda un membrānas) bija ievērojami augstāka vakcinētiem indivīdiem, salīdzinot ar nevakcinētiem Covid-19 pārslimojušiem pētījuma dalībniekiem (Li et al., 2021). Šī atšķirība varētu būt saistīta ar atšķirīgu SARS-CoV-2 peptīdu kopumu, kas tika izmantots antigēna stimulācijas testā, kā arī nelielo promocijas pētījuma dalībnieku skaitu.

Tālāk darbā tika pētīts, vai SARS-CoV-2 specifiskā citokīnu reakcija ir saistīta ar PAD pacientu imunoloģiskajiem un klīniskajiem fenotipiem jeb neinfekciozajām komplikācijām. Šajā promocijas pētījumā autoantivielu esamība PAD pacientu serumā bija saistīta ar augstāku bāzes IL-4 un TNF- α līmeni, kā arī IL-4 līmeņa pieaugumu pēc SARS-CoV-2 antigēna stimulācijas. IL-4 pieaugums korelēja arī ar kopējo IgG un IgM līmeni, bet ne SARS-CoV-2 specifiskā IgG līmeni. Pētījumā tika konstatēta korelācija arī starp IL-21 līmeņa pieaugumu pēc SARS-CoV-2 antigēna stimulācijas un PMID smaguma pakāpi (punktu skaits PMID smaguma izvērtēšanas skalā pieaug, palielinoties gan infekciozo, gan neinfekciozo komplikāciju skaitam). Ir zināms, ka reaktīvajos centros TFH galvenokārt sintezē IL-21 un IL-4, atbalstot B šūnu izdzīvošanu, proliferāciju un diferenciāciju (Ueno, 2016). Savukārt TFH izdalītā IL-4 trūkums izraisa nepilnvērtīgu palīdzību B šūnām (Yusuf et al., 2010), un IL-21 defekti ir saistīti ar ilgdzīvojošo plazmas šūnu traucējumiem. Izmantojot peļu modeļus bez IL-21 receptoriem, IL-21R $^{-/-}$ pelēm sākotnējā reaktīvo centru veidošanās, imūnglobulīnu klašu pārslēgšanās un vīrusam specifiskā IgG reakcija bija normāla, tomēr šo peļu limfmezglos reaktīvie centri izzuda ātrāk un tika novēroti traucējumi ilgdzīvojošo plazmas šūnu veidošanā un ilgtermiņa antivielu līmeņa uzturēšanā (Rasheed et al., 2013). Citos pētījumos gan PMID, gan SIgAD pacientiem IL-4 un IL-21 signālceļu defekti ir saistīti ar biežāku neinfekciozo komplikāciju izplatību, tai skaitā autoimunitāti (Desjardins et al., 2018; Ho & Cunningham-Rundles, 2020; Salzer et al., 2014; Singh et al., 2014; Yazdani et al., 2019). Lai gan tieša saikne starp Covid-19 un autoimūnu slimību attīstību nav pierādīta, ir vairāki ziņojumi par autoimūno slimību attīstību pēc Covid-19 pārslimošanas (Banjongjit et al., 2024; Catriona & Paolo, 2022; Diao et al., 2020; Halpert & Shoenfeld, 2020; Kasperkiewicz & Woodley, 2023; Kouranloo et al., 2023; Laxminarayana, 2022; Lyons-Weiler, 2020; Nabizadeh et al., 2022; Shoenfeld, 2020; Stathi

et al., 2023; Y. Zhang et al., 2020). Pētījumā ar imūnkompetentiem Covid-19 pacientiem tika novērota pārmērīga plazmoblastu ekspansija, kas bija saistīta ar autoantivielu veidošanos. Šie plazmoblasti attīstījās IL-4 un B šūnu aktivācijas faktora (BAFF) ietekmē, un tika identificētas divas atšķirīgas atmiņas šūnu populācijas (CD80+/ISG15+ un CD11c+/SOX5+/T-bet+/-), kurām bija autoreaktivitātes pazīmes, kas, iespējams, kalpoja kā autoantivielu avots (Schultheiß et al., 2021). Iepriekšējos pētījumos arī ziņots, ka specifiski IL-4 un IL-10 gēnu promotera polimorfismi ir saistīti ar PMID attīstību (Rezaei et al., 2010).

Šajā promocijas darbā pacientiem ar labdabīgu poliklonālu limfoprolifērāciju, kas izpaužas kā hepatomegālija, splenomegālija un limfadenopātija, IL-10 līmeņa pieaugums pēc SARS-CoV-2 antigēna stimulācijas bija mazāks nekā pacientiem bez šīm izpausmēm vai kontroles grupā. IL-10 ražo galvenokārt T-šūnas, īpaši Treg un TFH šūnas, kā arī monocīti un B regulatorās šūnas. Tam piemīt regulatora funkcija, IL-10 ir pretiekaisuma citokīns, kas var kavēt proiekaisuma citokīnu sintēzi (Varzaneh et al., 2014). Iepriekš veiktos pētījumos splenomegālija bija saistīta ar B šūnu homeostāzes disregulāciju, tostarp samazinātu pārslēgto atmiņas B šūnu skaitu, kas varētu liecināt par reaktīvo centru attīstības traucējumiem (Wehr et al., 2008).

Interesanti, ka 2024. gadā publicētā pētījumā PMID pacientu ārstēšanā pirmo reizi tika izmantota CD4+ T-šūnu inducējamā kostimulatora (ICOS) aktivizēšana ar vopratelimabu, kas ievērojami palielināja kopējo TFH, TFH2 šūnu skaitu, kā arī normalizēja IL-4, IL-10 un IL-21 sekrēciju *in vitro*. Ārstēšana ar vopratelimabu palielināja arī plazmocītu, IgG+ B šūnu, samazināja naīvo un pārejas B šūnu skaitu un ievērojami palielināja IgG1 sekrēciju PMID pacientiem. Interesanti, ka ārstēšana ar vopratelimabu atjaunoja arī IgA sekrēciju *in vitro* vairākiem PMID pacientiem, kuriem serumā bija pilnīgs endogēnā IgA trūkums. Tādējādi arī klīniskie pētījumi apstiprina IL-4, IL-10 un IL-21 disfunkcijas nozīmi PMID patoģenēzē (Sepahi et al., 2024).

Mūsu pētījumā papildus vairāku citu jau minēto citokīnu līmeņu izmaiņām tika novērota arī TGF-β1 līmeņa samazināšanās pēc pilnasiņu stimulācijas ar SARS-CoV-2 antigēnu, turklāt šis samazinājums bija izteiktāks pacientiem, kuriem bija zemāks SARS-CoV-2 specifisko IgG antivielu titrs. TGF-β1 loma antivielu sintēzē izpaužas galvenokārt kā inducēto Treg šūnu darbības ierosināšana, lai nomāktu B šūnas (Strainic et al., 2013; Xu et al., 2016), un antivielu klases pārslēgšanās ierosināšana, galvenokārt uz IgA1 un IgA2 klases antivielām (Ferreira-Gomes et al., 2021). TGF-β1 var ražot dažādas šūnas, tai skaitā lielāko daļu imūnšūnu, reaģējot uz infekciju, un galvenokārt tas darbojas kā vairāku imūnšūnu, piemēram, Treg, NK šūnu un makrofāgu, regulators (Ramírez-Martínez et al., 2022). Jāpiemin, ka TGF-β1 sākotnēji veidojas kā latents komplekss un pirms bioloģisko funkciju veikšanas tam nepieciešama

aktivizācija, kas var notikt dažādos veidos, tostarp ar Treg starpniecību (Liénart et al., 2018). TGF- β 1 var aktivizēt NF- κ B, kas var tālāk regulēt dažādu citokīnu ekspresiju, tostarp INF- γ , TNF- α un IL-1 β (Hamidi et al., 2021; Yan et al., 2022). Mūsu pētījumā PAD pacientu grupā TGF- β 1 līmeņa izmaiņas negatīvi korelē ar IL-1 β un TNF- α līmeni. Viens no iespējamajiem skaidrojumiem TGF- β 1 līmeņa samazinājumam pēc SARS-CoV-2 antigēna stimulācijas varētu būt TNF- α un IL-1 β izraisīta SMAD7 (galvenie signālu pārnēsēji TGF- β receptoru darbībai) ekspresijas aktivācija (Bitzer et al., 2000), jo SMAD7 inhibē TGF- β 1 sintēzi (Liang et al., 2024). Mūsu pētījumā arī TNF- α līmenis bija ievērojami augstāks pacientiem ar zemu pārslēgto atmiņas B šūnu skaitu (*EUROclass* B+SmB⁻).

Pētījumam ir vairāki ierobežojumi. Pirmkārt, izlases lielums, kas bija ierobežots šo slimību retuma dēļ, kā arī kontroles grupas nelīdzsvarots apjoms attiecībā pret pētāmo grupu samazina statistisko spēku un ierobežo spēju noteikt nozīmīgas asociācijas. Otrkārt, pētījuma novērošanas plāns un plašais laika periods pēc imunizācijas shēmas pabeigšanas neļauj izvērtēt imūnās atbildes reakcijas dinamiku. Treškārt, SARS-CoV-2 infekcijas anamnēze šajā pētījumā tika noteikta, balstoties uz medicīnisko dokumentāciju un veiktajiem PCR testiem, nevis nosakot antivielas pret vīrusa nukleokapsīda proteīnu, kas var ierobežot hibrīdimunitātes noteikšanas precizitāti, īpaši vieglu vai asimptomātisku SARS-CoV-2 infekciju gadījumā. Ceturtkārt, pētījumā netika iekļauta SARS-CoV-2 specifisko atmiņas B šūnu novērtējumu vai antivielu neitralizācijas spēja. Attiecībā uz ilgtermiņa imunoloģisko atmiņu veselīem pacientiem pēc Covid-19 pārslimošanas ir novērota tendence SARS-CoV-2 specifiskās atmiņas B šūnu daudzumam pieaugt vairākus mēnešus pēc inficēšanās (Dan et al., 2021). Tāpat pilnasiņu stimulācijai ar vīrusa antigēnu ir ierobežojumi, kas jāņem vērā: T-šūnu atbildes reakcijas ir sarežģītas un var aktivizēt dažādas šūnu subpopulācijas un molekulāros ceļus, kā rezultātā var rasties atšķirīgi funkcionālie citokīnu ekspresijas profili. Tāpat ierobežojums ir tas, ka tika izmantots tikai SARS-CoV-2 smailes proteīna antigēns un netika iekļauti citi SARS-CoV-2 proteīni, piemēram, nukleokapsīda vai membrānas proteīns. Tehnisku iemeslu dēļ analizē netika iekļauts citokīns IL-2. Tāpat pastāv arī ierobežojums, salīdzinot mūsu rezultātus ar citiem pētījumiem, jo pētījumos izmantotās izmeklēšanas metodes bieži atšķiras.

4. Iemesli atteikumam no rekomendētas SARS-CoV-2 vakcinācijas

Kā minēts, IIT slimību grupas biežākā klīniskā izpausme ir paaugstināta uzņēmība pret infekcijas slimībām, kas varētu rosināt domāt, ka šie pacienti būtu īpaši ieinteresēti infekciju profilakses pasākumos. Tomēr, neraugoties uz to, ka atbildīgās institūcijas rekomendēja SARS-CoV-2 vakcināciju IIT pacientiem (ESID, 2022), kā arī to, ka vairākos pētījumos tika pierādīta vakcīnu drošība specifiski šajā pacientu grupā, kā arī tika ziņots par pozitīvu

imūnatbildes marķieru parādīšanos pēc vakcinācijas (Bergman et al., 2021; Milito et al., 2023), bija pacienti, kuri no vakcinācijas pret SARS-CoV-2 atteicās.

Šis ir pirmais pētījums, kurā tika izmantotas kvalitatīvas pētniecības metodes, lai iegūtu plašāku izpratni par motivāciju, kas ir pamatā IIT pacientu lēmumam atteikties no vakcinācijas. Promocijas darbā secināts, ka pacientu izvēli atteikties no SARS-CoV-2 vakcinācijas ietekmēja vairāki savstarpēji saistīti un pastiprinoši iemesli. Galvenās tēmas, kas tika identificētas kā iemesli atteikumam no SARS-CoV-2 vakcinācijas: (1) bailes un nenoteiktība, (2) bažas par riskiem un ieguvumu nesaskatīšana, (3) ārējās ietekmes no apkārtējiem cilvēkiem, (4) neuzticēšanās un nevēlēšanās pakļauties, (5) uzskati par vakcināciju un Covid-19.

4.1. Bailes un nenoteiktība

Pētījumā vairāki pacienti atzīmēja, ka izjūt bailes no SARS-CoV-2 vakcinācijas. Daži no šiem pacientiem spēja konkretizēt baiļu iemeslu, tomēr bija pacienti, kuru bailes bija nekonkrētas un nebija saistītas ar racionāliem apsvērumiem. Tāpat pacienti atzina, ka jūtas unikāli savas slimības dēļ un nevar uz sevi attiecināt rekomendācijas, kuras vispārējai populācijai piedāvā sabiedrības veselības speciālisti. Daži dalībnieki akcentēja arī apjukuma un nenoteiktības izjūtu, nezinot, ko uzskatīt par patiesību un ko par mītu. Tādēļ, raugoties no vakcīnu komunikācijas viedokļa, veselības aprūpes speciālistiem būtu izšķiroša loma uzticības veidošanā, informēšanā par vakcinācijas personīgajiem ieguvumiem, kā arī šo pacientu specifisko bažu un dezinformācijas novēršanā attiecībā uz SARS-CoV-2 vakcīnām (Silver et al., 2022). Uzticēšanās starp ārstiem un pacientiem ir īpaši svarīga, un ir pierādīts, ka veselības aprūpes speciālistu personīgs ieteikums saņemt vakcīnu pozitīvi ietekmē vakcinācijas izvēli (Fernandes et al., 2021; Silver et al., 2022). Šie rezultāti arī uzsver, cik svarīgi ir nodrošināt ārstu un medicīnas māsu informētību par SARS-CoV-2 vakcinācijas efektivitāti un drošību personām ar IIT (Pergent et al., 2023).

4.2. Riska un ieguvuma novērtējums

Samazināta iespējamā ieguvuma uztvere apvienojumā ar bažām par veselības pasliktināšanos pēc vakcinācijas lika dažiem dalībniekiem uzskatīt, ka ar vakcināciju saistītie riski ir lielāki par tās potenciālajiem ieguvumiem. Iepriekšējos pētījumos IIT pacienti, kas atteicās no vakcinācijas, visbiežāk izteica tieši bažas par to, ka vakcinācija nenodrošinās pietiekamu aizsardzību pret Covid-19, un tikai tad sekoja bažas par alerģiskas reakcijas, vēl nezināmas vakcīnas blakusparādības vai slimības paasinājuma iespējamību (Aberumand et al., 2022; Pergent et al., 2023), kamēr vispārējā populācijā visbiežāk minētās bija tieši bažas par iespējamām vakcīnas blaknēm. Arī mūsu pētījumā pacienti ar antivielu deficītu atzīmēja, ka iemesls atteikties no vakcinācijas bija tas, ka iepriekš pret citām vakcīnregulējamām slimībām

viņiem nebija izveidojušās antivielas. Turklāt, lai gan lielākā daļa šī pētījuma grupas cilvēku bija pārliecināti, ka Covid-19 ir smaga slimība, vakcīnas potenciāli radītos draudus daļa pacientu uztvēra kā smagākus nekā saslimšanu ar Covid-19. Pētījums Latvijas vispārējā populācijā atklāja, ka pacientu subjektīvi uztvertā uzņēmība pret Covid-19 netika identificēta kā faktors, kas ietekmētu vakcinācijas uzvedību SARS-CoV-2 sakarā (Šuriņa et al., 2021), pretēji citām valstīm (Al-Amer et al., 2022).

4.3. Ārējās ietekmes

Naratīvs par negatīvām veselības sekām pēc SARS-CoV-2 vakcinācijas ir klātesošs arī Latvijas populācijā (Šuriņa et al., 2021) un var ietekmēt IIT pacientu attieksmi pret vakcināciju. Daži dalībnieki dalījās ar negatīvas pieredzes stāstiem no ģimenes locekļiem vai tuviem draugiem, bet citi no attālākiem avotiem, tai skaitā mediķiem un likumdevējiem.

Vairāki pētījumā iesaistītie dalībnieki atzina, ka šos stāstus dzirdējuši sociālo mediju platformās. Arī pētījumos apstiprināta saistība starp mediju diskursu un iedzīvotāju vēlmi vakcinēties: valstīs, kur diskusija sociālajos plašsaziņas līdzekļos koncentrējas vairāk uz blakusparādībām vai negatīvām emocijām saistībā ar SARS-CoV-2 vakcināciju, ir zemāka vakcinācijas aptvere (Jun et al., 2022).

4.4. Neuzticēšanās un nevēlēšanās pakļauties jeb “indivīds pret sistēmu”

Iepriekšējos pētījumos lielākajai IIT pacientu daļai bažas bija saistītas specifiski ar SARS-CoV-2 vakcīnu un tikai 1,7–4,7 % pacientu pauda neuzticību vakcīnām kopumā (Aberumand et al., 2022; Pergent et al., 2023). Mūsu pētījumā dalībnieki pauda viedokli arī par tādām tēmām kā neuzticēšanās medicīnas sistēmai vai politikas veidotājiem.

Vairāki no šiem minētajiem faktoriem, kas varētu ietekmēt vilcināšanos vakcinēties, ir konstatēti arī Latvijas vispārējā populācijā, tāpēc tie nav raksturīgi tikai konkrētām iedzīvotāju grupām ar novājinātu imunitāti. Interesanti, ka citā pētījumā, kas veikts Latvijas vispārējā populācijā, tika atklāts, ka uzticēšanās valsts institūcijām un bailes no Covid-19 ir SARS-CoV-2 vakcinācijas uzvedību noteicošie faktori (Šuriņa et al., 2022). Uzticēšanos vakcinācijas kontekstā var aplūkot trijos dažādos līmeņos: uzticēšanās konkrētajam vakcīnas produktam (piemēram, SARS-CoV-2 vakcīnai un tās izstrādātājiem), uzticēšanās vakcīnas nodrošinātājam (piemēram, medicīnas darbiniekiem) un ticība politikas veidotājiem (piemēram, valdībai un veselības aprūpes sistēmas vadībai) (Maciuszek et al., 2023; Prati, 2020). Saskaņā ar mūsu pētījuma datiem pacientu uztveri par vakcīnas efektivitāti un drošību ietekmē neuzticēšanās visos trijos minētajos līmeņos. Arī pētījumi apstiprina, ka neuzticēšanās valsts iestādēm tieši ietekmē iedzīvotāju vēlmi rīkoties saskaņā ar šo iestāžu ieteikumiem, savukārt uzticēšanās un paļāvība uz valsti un veselības aprūpes sistēmu ir saistīta ar lielāku

gatavību vakcinēties pret SARS-CoV-2 (Chan et al., 2020). Tiek uzskatīts, ka neuzticēšanās politikas veidotājiem kopā ar psiholoģiskajiem un strukturālajiem faktoriem ir svarīgs aspekts, kas veido ticību sazvērestības teorijām (Kim & Kim, 2020; Simione et al., 2021; Uscinski et al., 2020; Prooijen van, 2019).

Tāpat daži dalībnieki atzīmēja izjūtu, ka vakcinācija viņiem tika uzspiesta un ir tikusi ierobežota personīgā autonomija attiecībā uz ķermeni, radot lielāku vēlmi pretoties SARS-CoV-2 vakcinācijai, un līdzīga tendence tika novērota arī pētījumā Latvijas medicīnas darbinieku vidū (Lielsvagere-Endele et al., 2022). Lai gan obligātā vakcinācija ir veiksmīga stratēģija tūlītējā perspektīvā, tā potenciāli var izraisīt pretestību un nelabvēlīgu attieksmi pret vakcināciju ilgtermiņā (Bardosh et al., 2022).

4.5. Personīgie uzskati par vakcināciju un Covid-19

Arī negatīvā personīgā pieredze saistībā ar vakcināciju un maldīgi uzskati mūsu pētījumā bija faktori, kas atturēja IIT pacientus no vakcinācijas. Lai gan daži kļūdaini uzskati bija plaši izplatīti vakcinācijas mīti, piemēram, mīts, ka vakcīnas var “pārslogot” vai “novājināt” imūnsistēmu (Geoghegan et al., 2020), citi bija raksturīgi specifiski IIT pacientiem, piemēram, pārliecība, ka vakcinācija nav nepieciešama, ja pacients saņem imūnglobulīna aizstājējterapiju. Šī būtu uzskatāma par kļūdainu pārliecību un nav atbilstoša ESID ieteikumiem (ESID, 2022). Pirmkārt, imūnglobulīna preparātu sagatavošana ir sarežģīts process, kas ilgst vairākus mēnešus (līdz pat aptuveni gadam), tāpēc sagaidāms, ka šajos preparātos pietiekams SARS-CoV-2 specifisko antivielu daudzums parādījās ar novēlošanos (Jin et al., 2021; Pham et al., 2022). Otrkārt, pat ja konkrētam pacientam neizveidojas specifiska antivielu reakcija uz vakcināciju, T-sūnu imūnā atbilde var būt normāla un kalpot kā papildu aizsardzība pret SARS-CoV-2 infekciju (Amodio et al., 2021; Bergman et al., 2021; Li et al., 2021; Moss, 2022; Shields, Faustini, Hill, Al-Taei, Tanner et al., 2022).

Arī cerība, ka vakcīnas nodrošinās pilnīgu sterilu imunitāti, apvienojumā ar tendenci novērtēt vakcīnu efektivitāti, pamatojoties nevis uz empīriskiem pierādījumiem, bet gan uz ierobežotu skaitu gadījumu, kas novēroti tuvākajā sociālajā lokā, bija papildu faktors, kas veicināja dalībnieku skepsi pret vakcīnu efektivitāti. Šie maldīgie priekšstati var būt saistīti ar Latvijas iedzīvotāju nepietiekamo veselības prātības līmeni. Iepriekš veikti pētījumi liecina, ka aptuveni 79 % Latvijas iedzīvotāju ir vājas veselības prātības kompetences, kas varētu veicināt plašāku riskantas veselības uzvedības izplatību populācijā, tai skaitā nevakcinēšanos (Gatulytė et al., 2022). Lai gan, no otras puses, iepriekšējie pētījumi rāda, ka izglītībai vispārējā populācijā ir mazāka ietekme uz vilcināšanos vakcinēties nekā uzticībai veselības aprūpei un zinātnei. Tas

liecina, ka zināšanu trūkums var nebūt tik nozīmīgs faktors kā sabiedrības uzticība veselības aprūpei un zinātnei (Rughiniš et al., 2022).

Šai pētījuma daļai ir atzīmējami vairāki ierobežojumi. Pirmkārt, intervijas notika no 2023. gada aprīļa līdz augustam, proti, ap pandēmijas stāvokļa beigām 2023. gada maijā. Ņemot vērā, ka vakcinācijas iniciatīvas galvenokārt tika veiktas 2021. un 2022. gadā, ir iespējama atcerēšanās kļūda. Tomēr šis datu vākšanas laiks ļāva arī izslēgt tos IIT pacientus, kuri bija noskaņoti vakcinēties. Otrkārt, dažas specifiskas IIT diagnožu grupas varētu būt mazāk pārstāvētas. Treškārt, pieejami vairāki modeļi, kas skaidro vilcināšanos vakcinēties. Mūsu pētījumā intervijas jautājumu izstrādāšanā tika izmantots Veselības pārliecību modelis. Taču pieejami arī citi modeļi, piemēram, 5C modelis, kurā par vakcinācijas vilcināšanos ietekmējošiem faktoriem uzskata uzticēšanos, pašefektivitāti, ierobežojumus, riska aprēķinu un kolektīvo atbildību (Gendler & Ofri, 2021). Šī pētījuma intervijas jautājumos mēs neiekļāvām jautājumus par ierobežojumiem saņemt vakcināciju (fizisko pieejamību vai cenu pieejamību), pašefektivitāti un uzskatus par kolektīvās atbildības jautājumiem, jo netika prognozēts, ka šie jautājumi varētu būt nozīmīgi, lai atturētu pacientus ar imūndeficītu no vakcinācijas (Aberumand et al., 2022; Pergent et al., 2023; Więsik-Szewczyk et al., 2022). Lai gan šie specifiskie jautājumi netika iekļauti, daļēji strukturētās intervijas formāts un atvērtie jautājumi ļāva pacientiem paust jebkāda veida bažas saistībā ar vakcināciju. Vēl jāatzīmē, ka vakcinācija bija viegli pieejama, izmantojot specializētus vakcinācijas centrus vai ģimenes ārstu prakses visā Latvijā, vakcinācija bija pieejama bez maksas, tādējādi līdz minimumam samazinot bažas par pieejamību kā vienu no būtiskiem SARS-CoV-2 vakcinācijas uzvedību ietekmējošiem faktoriem.

Nobeigumā jāpiemin, ka iemesli atteikumam no rekomendētas SARS-CoV-2 vakcinācijas IIT pacientu grupā Latvijā ir daudzšķautņaini un nozīme ir gan politiskajam kontekstam, gan sabiedrības un individuāliem psiholoģiskajiem faktoriem. Tāpat starp identificētajām tēmām, iespējams, pastāv cēloņsakarības, taču šādas teorētiskas tēmu hierarhijas struktūras izstrādei būtu nepieciešama papildu metodoloģija. Kaut gan lielākā daļa vakcinācijas vilcināšanās iemeslu šajā grupā ir līdzīgi vispārējai populācijai, iegūtie dati liecina, ka personām ar imūndeficītu ir arī unikāli uzskati un bažas, kas ietekmē viņu lēmumus attiecībā uz vakcināciju.

Secinājumi

1. IIT punkta prevalence Latvijā 2020. gada decembrī bija 7,1 uz 100 000 iedzīvotāju.
2. SARS-CoV-2 specifiskā T-šūnu atbilde PMID un SIgAD pacientiem neatšķiras no kontroles grupas pacientiem, savukārt SARS-CoV-2 humorālā atbilde PMID ir statistiski ticami zemāka, salīdzinot ar SIgAD pacientiem un kontroles grupu.
3. Humorālās atbildes reakcijas statistiski ticami neatšķiras dažādiem PAD pacientu klīniskajiem fenotipiem, savukārt vairāku citokīnu (IL-4, IL-10, IL-21, TNF- α) līmeņu izmaiņām pēc SARS-CoV-2 stimulācijas ir novērojama tendence uz saistību ar slimības klīniskajām izpausmēm vai fenotipiem.
4. IIT pacientu grupā tika konstatēti specifiski ar slimību saistīti vakcinācijas atteikuma iemesli: uzskats, ka vakcinācija imūndeficīta pacientiem ir kontrindicēta, kā arī uzskats, ka imūnglobulīnu aizstājterapijas saņemšanas gadījumā SARS-CoV-2 vakcinācija nav nepieciešama.

Priekšlikumi

1. Latvijā ir mazāks PAD īpatsvars starp diagnosticētajiem IIT pacientiem. Nepieciešams turpināt uzlabot PAD atpazīšanu un diagnostiku Latvijas populācijā, izglītojot veselības aprūpes speciālistus, kuri varētu būt iesaistīti šo pacientu aprūpē.
2. PAD pacientu SARS-CoV-2 specifiskā T-šūnu atbilde neatšķīrās no kontroles grupas, turklāt lielākā daļa pacientu uzrādīja arī pozitīvu humorālo atbildi. SARS-CoV-2 vakcinācija būtu rekomendējama šajā pacientu grupā.
3. Veselības aprūpes speciālistiem būtu izšķiroša loma uzticības veidošanā, informēšanā par vakcinācijas personīgajiem ieguvumiem, kā arī šo pacientu specifisko bažu un dezinformācijas novēršanā attiecībā uz SARS-CoV-2 vakcīnām.

Publikāciju, ziņojumu un patentu saraksts par promocijas darba tēmu

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Pielikumi



Inborn Errors of Immunity in Latvia: Analysis of Data from 1994 to 2020

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To the Editor,

Inborn errors of immunity (IEI) refer to a heterogeneous group of congenital disorders that are characterised by impaired function and dysregulation of the immune system. IEI were traditionally considered to be rare disorders (1 in 10,000–1 in 50,000 live births), but the collective prevalence is now estimated to be around 1 in 1000–1 in 5000 [1]. Prevalence is an important epidemiological indicator that is used for planning public health policies. However, the prevalence of these conditions in Latvia is unknown.

To describe the epidemiological and clinical characteristics of patients with inborn error of immunity in Latvia over a 27-year period, we conducted a retrospective study, reviewing the medical records of patients who were diagnosed with an IEI in Latvia from the 1st of January 1994 to 31st of December 2020. Data were sourced from the only tertiary centres, where immunologists consult: The Children's Clinical University Hospital and Pauls Stradins Clinical University Hospital (for adults) in Riga, Latvia, where severe patients from Latvia are treated.

Data regarding patients' demographic and clinical characteristics were collected using the computerised hospital information systems and medical records. Diagnosis of IEI was based on the diagnostic criteria of the European Society for Immunodeficiencies (ESID). We retrospectively reviewed the data of these patients and re-evaluated the compliance with the ESID diagnostic criteria.

All data were analysed using Microsoft Office Excel and IBM SPSS Statistics for Windows Version 23. Data related to demographic and clinical indicators were analysed using descriptive statistics and parametric/non-parametric analysis, as appropriate. To estimate the minimum point prevalence and incidence, we used data sourced from the Central Statistical Bureau of Latvia in March 2021 [2]. The point prevalence was expressed as alive patients per 100,000 inhabitants at a particular point in time (December 2020). Incidence was presented as the number of patients per live births.

Over a 27-year period, a total of 173 patients with IEI were identified (see Table 1), with 47% being male (male/female ratio = 1:1.1). Patients with selective IgA deficiency (183 patients, median age 7.5 (IQR: 9.2), 59% of them male) and transient hypogammaglobulinaemia of infancy (4–7 patients per year) were not included in the study population. The median age of living patient in this cohort was 14.3 years (IQR: 31.3). Most of these patients (80%) were diagnosed before the age of 18 years. The median age at the time of diagnosis was 2.9 years (IQR: 15.9), and it ranged from birth to late adulthood (0–74 years). No statistical significance was found for age at diagnosis between male and female patients ($p=0.130$). Thirty-nine (23%) patients died during the study period; the median age at death was 2.8 years (IQR: 14.4), ranging from 2 days to 51 years.

Genetic testing was performed in 52% of cases. Of these 173 patients, 31% of patients were recorded to have received IgG supplementation therapy, 10% received prophylactic antibacterial therapy, and 9% of patients received haematopoietic stem cell transplantation (HSCT), with a median age at time of HSCT of 2.1 years (IQR: 13.0). Familial cases were observed in 21% of patients.

Categories based on the International Union of Immunological Societies (IUIS) classification were distributed as shown in Table 1. The point prevalence of IEI in December 2020 in Latvia was 7.1 per 100,000 inhabitants (see Suppl. Fig. 1). The estimated 27-year incidence of severe combined

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Table 1 Patients with Inborn errors of immunity in Latvia

	Number of patients	Gender M/F	Mortalities alive/deceased	Genetic testing yes/no/no information	Prophylactic antibiotics yes/no information	Immunoglobulin replacement therapy yes/no/no information	HSCT done/not done	Family history of IEL positive/negative/no information
Immunodeficiencies affecting cellular and humoral immunity	20 (12%)	12/8	2/18	8/12	0/20/0	14/6*/0	4/16	8/12/0
Combined immunodeficiencies with associated or syndromic features	57 (33%)	21/36	52/5	54/3	4/52/1	4/52/1	1/56	3/54/0
Predominantly antibody deficiency	36 (21%)	20/16	30/6	5/31	7/23/6	32/3/1	1/35	4/19/13
Diseases of immune dysregulation	8 (5%)	6/2	4/4	5/1/2	1/5/2	1/5/2	0/8	5/1/2
Congenital defects of phagocyte number or function	18 (10%)	12/6	18/0	10/2/6	6/2/10	0/8/10	4/14	5/3/10
Defects in intrinsic and innate immunity	2 (1%)	0/2	2/0	2/0	2/0/0	2/0/0	0/2	0/2/0
Auto-inflammatory disorders	8 (5%)	3/5	8/0	5/3	0/6/3	0/6/3	0/8	2/4/2
Complement deficiencies	11 (6%)	0/11	11/0	0/11	0/11/0	0/11/0	0/11	7/4/0
Bone marrow failure	11 (6%)	6/5	5/6	0/0/11	0/0/11	0/11/0	5/6	2/9/0
Unclassified inborn error of immunity	2 (1%)	1/1	2/0	1/1	1/0/1	0/1/1	0/2	0/1/1

*Patients who died prior to 2000 (except from 1994 to 1996) did not receive immunoglobulin replacement therapy, but plasma infusions instead

immunodeficiency (SCID) in Latvia was 1 per 32,963 live births.

These data represent the first description of the epidemiology of IEL in Latvia. The prevalence of IEL in Latvia has increased tremendously, if compared to 0.08 per 100,000 in 1994 and 1.1 per 100,000 inhabitants in 2004, when Latvia joined the J project, to 7.1 per 100,000 inhabitants in 2020 (see Suppl. Fig. 1). The prevalence in other European

countries has been reported between 1.3 per 100,000 inhabitants in Russia and 18.8 per 100,000 in Iceland [3, 4].

Predominantly antibody deficiencies composed 21% of cases; however, most studies regarding the epidemiology of IEL in other European countries have reported a larger proportion of patients with predominantly antibody deficiency: ranging from 20% in Iceland to 63% in Italy [4, 5]. A smaller proportion of patients diagnosed with predominantly antibody deficiency in combination to considerably stronger

representation of paediatric patients could be due to the under-diagnosis of common variable immunodeficiencies. The rate of under-diagnosis could be high for several reasons: low availability of immunologic testing at the beginning of the study period, insufficient knowledge about IEI among non-immunologists, and low public awareness. We hypothesise that a certain number of patients with PFAPA could also be undiagnosed for this reason.

Awareness campaigns could be a solution to improve the public awareness of IEI in Latvia. In 2018, the Centre of the Rare Diseases was established in the Children Clinical University Hospital, and all IEI patients will be registered there; however, no national registries for IEI exist. Also, the availability and accessibility of immunologic testing should be improved.

The estimated incidence of SCID in Latvia was 1 per 32,963 live births. However, newborn screening for SCID is not available in Latvia; for this reason, patients with SCID that die in early infancy could be undiagnosed. The introduction of newborn screening could improve the care for these patients.

Regarding the diagnostics, genetic testing was performed in 52% of all IEI patients. Pathogenic variants were found in 18 genes (see Suppl. Table 1). The highest proportion of patients with genetically verified diagnoses was among the patients from the IUIS classification category combined immunodeficiencies with associated and syndromic features (54/57; 94.7%). Most genetically diagnosed patients had a Del 22q11.2 defect (35 patients). The diagnosis of 22q11.2 deletion was based on chromosome and fluorescence in situ hybridization (FISH) analysis. It was followed by five Familial Mediterranean fever patients with heterozygous (3) or compound heterozygous (2) *MEFV* gene mutation (three patients had Armenian; two—Slavic origin), and five patients with Nijmegen syndrome who all carried the typical Eastern Slavic mutation NM_002485.5(NBN):c.657_661del (p.Lys219fs); the origin of all five patients was Slavic. Five chronic granulomatous disease patients had a mutation in *CYBB* gene. Rare defects, with less than five patients for each gene, affected the following genes: *RAG2*, *IL2RG*, *DCLRE1C*, *CD40LG*, *WAS*, *ATM*, *SPINK5*, *KMT2D*, *KDM6A*, *PIK3CD*, *BTK*, *STAT1*, *PRF1*, *SH2D1A*, and *SBDS* (see Suppl. Table 1). The proportion of patients with a genetically confirmed diagnosis in Latvia has been increasing since 2018, when the public funding for the genetic testing abroad (Blueprint Genetics, Helsinki, Finland) became available. Before that, genetic testing was possible due to collaboration with the J project network.

Regarding the treatment, all patients who had indications for immunoglobulin replacement therapy (31% of all IEI patients) received IgG supplementation therapy. In comparison with reports from other countries, Latvia had the lowest proportion of patients receiving HSCT (9%); in other

countries, this proportion ranged up to 16% in Russia [3]. This was due to limited health care resources in Latvia at the beginning of the study period. The possibility of sending patients abroad to receive HSCT has improved within the last few years.

This is, to the best of our knowledge, the first study examining the prevalence of IEI in Latvia. The main strength of the study is the long study period. Several limitations must also be considered. There were some limitations in the clinical data available in the medical records; therefore, a prospective collection of data would have been more accurate compared to our retrospective design. Another potential limitation is that some patients could be undiagnosed or not referred to immunologists, meaning that the prevalence could be underestimated.

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Data Availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Declarations

Ethics Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Central Board of the Ethical Committee of the Health Ministry of the Republic of Latvia (No. 01–29.1/2878).

Consent to Participate (Include Appropriate Statements) Not applicable.

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Article

Long-Term Immunological Memory of SARS-CoV-2 Is Present in Patients with Primary Antibody Deficiencies for up to a Year after Vaccination

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Abstract: Some studies have found increased coronavirus disease-19 (COVID-19)-related morbidity and mortality in patients with primary antibody deficiencies. Immunization against COVID-19 may, therefore, be particularly important in these patients. However, the durability of the immune response remains unclear in such patients. In this study, we evaluated the cellular and humoral response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antigens in a cross-sectional study of 32 patients with primary antibody deficiency ($n = 17$ with common variable immunodeficiency (CVID) and $n = 15$ with selective IgA deficiency) and 15 healthy controls. Serological and cellular responses were determined using enzyme-linked immunosorbent assay and interferon-gamma release assays. The subsets of B and T lymphocytes were measured using flow cytometry. Of the 32 patients, 28 had completed the vaccination regimen with a median time after vaccination of 173 days (IQR = 142): 27 patients showed a positive spike-peptide-specific antibody response, and 26 patients showed a positive spike-peptide-specific T-cell response. The median level of antibody response in CVID patients (5.47 ratio (IQR = 4.08)) was lower compared to healthy controls (9.43 ratio (IQR = 2.13)). No difference in anti-spike T-cell response was found between the groups. The results of this study indicate that markers of the sustained SARS-CoV-2 spike-specific immune response are detectable several months after vaccination in patients with primary antibody deficiencies comparable to controls.

Keywords: inborn error of immunity; antibody deficiency; common variable immunodeficiency; selective IgA deficiency; SARS-CoV-2; immune response; T-cell response; antibody response



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1. Introduction

Primary antibody deficiencies (PAD) are a group of rare diseases that account for about 55% of all inborn errors of immunity (IEI) [1]. Selective immunoglobulin A (IgA) deficiency (sIgAD) is the most common PAD. It is characterized by diminished serum IgA levels with normal IgM and IgG levels and is often asymptomatic but may present with recurrent infections or immune dysregulation-related symptoms such as autoimmunity or atopic diseases [2]. The most common symptomatic IEI is common variable immunodeficiency (CVID), characterized by reduced serum IgG and IgA and/or IgM levels and poor vaccination responses. CVID is manifested by severe and recurrent infections, and up to 66% present with various non-infectious complications, such as autoimmunity, enteropathy, and malignancy [3].

In late 2019, a new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified [4], causing a pandemic of acute respiratory syndrome known as coronavirus disease-19 (COVID-19) with significant morbidity and mortality in the general population [5]. Early reports showed an increased risk of severe

COVID-19 disease in subjects with immunosuppression [6]. Therefore, patients with inborn errors of immunity were of special interest, as a defect in the immune system may predispose them to severe infections, including severe COVID-19, especially in patients with defects in type I interferon signaling pathways [7]. On the other hand, immunosuppression could reduce immune responses, cytokine storms, and inflammatory processes, constituting a protective factor against COVID-19 [8]. Although some studies concluded that for the majority of patients, the underlying IEI was not an independent risk factor for severe COVID-19 [9–12], some studies found increased morbidity and/or mortality, including in patients with common variable immunodeficiency [13–15]. SIgAD has also been identified as a risk factor for a more severe COVID-19 course [16,17]. Therefore, vaccination against COVID-19 may be particularly important in IEI patients. The European Society for Immunodeficiencies (ESID) recommends that patients with IEI receive any of the available COVID-19 vaccines according to the national vaccination schedule that includes a primary vaccination course and booster doses [18].

Overall, the long-term durability of the antibody response is poorly understood, with several studies showing a trend toward decreasing antibody levels over time in immunocompetent individuals [19–22] while the receptor-binding domain (RBD) of the spike protein-specific memory B-cell fraction persists [23]. This trend of decrease in antibody levels has also been observed 6 months after the vaccination in primary antibody deficiency patients [24]. Furthermore, a limited neutralizing capacity of anti-spike SARS-CoV-2 antibodies has been reported in these patients [25,26]. Therefore, since the mechanisms of somatic mutation and selection in germinal centers that lead to differentiation of mature class-switched memory B cells and antibody response may be altered in patients with specific antibody deficiencies [27], several studies have highlighted the importance of assessing cellular responses specific for the SARS-CoV-2 antigen, when evaluating vaccine-induced immunity in patients with IEI [28]. Even in cases where the patient does not develop a humoral immune response to COVID-19 at a protective level, the vaccine could still be highly effective, as the presence of memory T cells can help control the infection. The role of T cells in COVID-19 protection is supported by reports of a lack of SARS-CoV-2 responsive CD4⁺ T cells in severely infected patients, as well as a milder disease in patients with early induction of functional SARS-CoV-2-specific T cells, or the presence of T-cell responses without a humoral response in asymptomatic individuals [29–31]. The durability of SARS-CoV-2 specific T-cell responses could also be higher than the durability of humoral responses [32]; however, the long-term SARS-CoV-2-specific T-cell memory in patients with antibody deficiency remains unclear. In addition, no study to date has investigated the humoral and cellular immune response to SARS-CoV-2 vaccination, specifically in SIgAD patients. In addition, only a few studies have explored immunological correlations and predictive markers associated with higher immune responses after SARS-CoV-2 vaccination, most of them evaluating early immune responses [28,33–36].

The primary objective of this study was to evaluate a long-term SARS-CoV-2 spike-specific humoral and cellular immune response in adult patients with the most common types of primary antibody deficiency (SIgAD and CVID) compared to healthy controls of the same age. The secondary objective was to identify predictive markers that are associated with a better immune response after COVID-19 vaccination in the patient group.

2. Materials and Methods

2.1. Subjects

Patients with CVID and symptomatic SIgAD who were treated at a tertiary immunology center (Pauls Stradins Clinical University Hospital, Riga, Latvia) were invited to participate in the study from April to July 2022. A total of 47 subjects were recruited for the study, including 17 patients with CVID, 15 patients with symptomatic SIgAD, and 15 healthy controls. The diagnosis was based on diagnostic criteria of the European Society for Immunodeficiencies (ESID) clinical diagnostic criteria [37]. All patients were re-evaluated to meet

the diagnostic criteria of CVID. Relevant clinical data on CVID and sIgAD patients were obtained from patient electronic health records, including data on patient age, sex, family history of inborn error of immunity, treatment, history of SARS-CoV-2 vaccination and infection, confirmed by a positive polymerase chain reaction (PCR), clinical characteristics, including prior infections, infectious complications, such as conductive hearing loss and bronchiectasis and non-infectious complications, such as autoimmunity, polyclonal benign lymphoproliferation, granulomatous disease, enteropathy, and malignancy. A SARS-CoV-2 vaccination course was considered complete if the patient received one dose after recovery from COVID-19 or two doses if not previously infected with SARS-CoV-2. The severity of COVID-19 in the personal history was assessed using the World Health Organization (WHO) clinical progression scale [38]. Patients who were unvaccinated were excluded from association analyses. Blood samples were obtained from patients and controls. All subjects provided written consent to participate in this study. This study was performed in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Central Board of the Ethics Committee of the Health Ministry of the Republic of Latvia (No. 01-29.1/2878).

2.2. Antibody Response to SARS-CoV-2

Serum separator tubes were used to separate serum by centrifugation. Serum samples were tested using the commercial, semi-quantitative enzyme-linked immunosorbent assay (ELISA) that detects specific SARS-CoV-2 IgG antibodies against the S1 domain of the spike protein (Euroimmun Anti-SARS-CoV-2 IgG assay, Euroimmun, Lübeck, Germany), following the manufacturer's recommendations. An IgGAM ratio (optical density compared with calibrator) > 1.1 was considered a positive response.

2.3. T-Cell Response to SARS-CoV-2

To detect the response of SARS-CoV-2 spike protein-reactive T cells, an interferon-gamma release assay (IGRA) QuantiFERON SARS-CoV-2 (Qiagen, Hilden, Germany) was used. The SARS-CoV-2 spike (S) protein consists of a signal peptide, an N-terminal S1 protease fragment (also containing receptor-binding domain (RBD)), and a C-terminal S2 protease fragment [29]. Specialized QuantiFERON starter set blood collection tubes were used to collect blood: Ag1 tube, containing T-cell epitopes within the receptor-binding domain of S1 (measures CD4+ T-cell responses); Ag2 tube, containing T-cell epitopes within S1 and S2 (measures CD4+ and CD8+ T-cell responses), as well as positive and negative control tubes. The tubes were incubated at 37 °C for 20 h, then centrifuged for plasma separation and froze at −20 °C for further analysis of interferon-gamma (IFN-γ) production using an ELISA, as previously reported [39], according to the manufacturer's protocol. A value >0.15 IU/mL was considered a positive response.

2.4. Lymphocyte Isolation and Flow Cytometry

Fresh blood samples were collected in tubes containing lithium heparin. Briefly, heparinized whole blood samples were diluted and transferred to SepMate peripheral blood mononuclear cell (PBMC) isolation tubes (STEMCELL Technologies, Vancouver, Canada) containing Histopaque-1077 density gradient cell separation medium (Sigma-Aldrich, Saint Louis, MO, USA) and isolated following the manufacturer's instructions. The viability of PBMCs was detected by trypan blue staining.

After washing with phosphate-buffered saline (Thermo Fisher Scientific, Waltham, MA, USA) with 2% fetal bovine serum (Sigma Aldrich, Saint Louis, MO, USA), isolated PBMCs were incubated in 96-well plates with a fragment crystallizable region (Fc) blocking reagent (Miltenyi Biotec, Bergisch Gladbach, Germany). The PBMCs were then stained with a mixture of the following antibodies at optimal concentrations: anti-21 fluorescein isothiocyanate (FITC), anti-CD27 phycoerythrin (PE)/Dazzle594, anti-CD268 peridinin chlorophyll protein (PerCP)/Cyanine5.5 (Cy5.5), IgD-PE/Cyanine7 (Cy7), anti-IgM allophycocyanin (APC) (all from BioLegend, San Diego, CA, USA), anti-CD19 Alexa Fluor 700 (A700) (from BD

Biosciences, San Jose, CA, USA) anti-CD38 PE (from Beckman Coulter, Brea, CA, USA) for B-cell panel; anti-CD45RO electron-coupled dye (ECD), anti-CD45RO PE/Cy5.5, anti-CD8 APC/Λ700 (all from Beckman Coulter, Brea, CA, USA), anti-CD27 PE/Cyanine7, anti-CD4 APC, anti-CD3 APC/Cy7 (all from BioLegend, San Diego, CA, USA) for T-cell panel; anti-CD25 PE, anti-CD127 PE/Cy7, anti-CD4 APC, anti-CD8 APC/Λ700, anti-CD3 APC/Cy7 (all from BioLegend, San Diego, CA, USA) for T regulatory cell panel. The PBMCs were washed and then fixed with formaldehyde. For the staining of the nuclear FOXP3 antigen, anti-FOXP3-Alexa Fluor 488 (A488) (BioLegend, San Diego, CA, USA) and the Transcription Factor Staining Buffer Set (BD Biosciences, San Jose, CA, USA) were used according to the manufacturer's instructions, adjusted for 96-well staining. Data were obtained as LMD files using a Beckman Coulter Navios Ex flow cytometer and analyzed using Kaluza 2.1 software (Beckman Coulter, Brea, CA, USA). Manual gating was applied, as shown in Supplementary Material S1.

B cells were subdivided into the following subpopulations: naïve B cells (CD19+CD27−IgM+IgD+), marginal zone B cells (CD19+CD27+IgM++IgD+), switched memory B cells (CD19+CD27+IgM−IgD−), IgM-only memory B cells (CD19+CD27+IgM++IgD−), transitional B cells (CD19+IgD+CD27−IgM++CD38++), CD21low B cell (CD19+ IgM+, CD21−CD38−), plasmablasts (CD19+CD21+CD38+++IgM−), atypical memory B cells (CD19+CD21−CD27−IgD−). T cells were subdivided as follows: naïve T helper cells (CD3+CD4+CD27+CD45RA+), central/transitory memory T helper cells (CD3+CD4+CD27+CD45RA−), effector memory T helper cells (CD3+CD4+CD27−CD45RA−), terminally differentiated T helper cells (CD3+CD4+CD27−CD45RA+), recent thymic emigrant T cells (CD3+CD4+CD31+CD45RO−), naïve T cytotoxic cells (CD3+CD8+CD27+CD45RA+), central/transitory memory T cytotoxic cells (CD3+CD8+CD27+CD45RA−), effector memory T cytotoxic cells (CD3+CD8+CD27−CD45RA−), terminally differentiated T cytotoxic cells (CD3+CD8+CD27−CD45RA+). T regulatory cells were identified based on the following parameters: CD3+CD4+CD25+FOXP3+CD127dim.

2.5. Clinical and Immunologic Phenotyping of CVID Patients

Clinical phenotyping was based on the classification suggested by Chapel et al. [40] and included patients with infection-only, autoimmunity, enteropathy, polyclonal lymphocytic infiltration, malignancy, and overlapped phenotype (if the patient had more than one non-infectious complication). The severity of CVID was assessed using CVID Severity Score proposed by Ameratunga [41]. Immunological phenotyping was based on the most commonly used classifications of B-cell subtypes in CVID patients: Paris [42], Freiburg [43], EUROclass [44], and B-cell pattern classifications [45].

2.6. Data Analysis

The normality of the data was assessed using the Shapiro–Wilk test. The results indicated that the data were not normally distributed; therefore, nonparametric statistical methods were used in subsequent analysis. Differences in categorical variables were examined by using chi-square and Fisher exact tests. The Mann–Whitney U or Kruskal–Wallis tests were used to compare continuous variables by two or more groups, respectively. Spearman's rank test was used to assess the correlation between continuous variables. A *p*-value < 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics Version 23 (IBM, New York, NY, USA). Graphs were generated using GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA).

3. Results

3.1. Subjects

A total of 32 patients with primary antibody deficiencies (aged 38.5 (IQR = 21) years) and 15 healthy vaccinated controls (aged 37 (IQR = 19) years) were enrolled in the study. Table 1 summarizes the demographic and clinical data of patients and controls.

Table 1. Demographic and clinical parameters of the patients and controls.

Parameters	CVID	sIgAD	Healthy Controls	<i>p</i>
Number	17	15	15	-
Sex				
Female, <i>n</i> (%)	10 (58.8%)	12 (80%)	10 (66.6%)	0.460
Male, <i>n</i> (%)	7 (41.2%)	3 (20%)	5 (33.4%)	
Age, median (IQR)	40 (24)	37 (21)	37 (19)	0.467
Ethnicity, Caucasian, <i>n</i> (%)	17 (100%)	15 (100%)	15 (100%)	-
Age at diagnosis, median (IQR)	34 (28)	33 (45)		0.664
Positive family history, <i>n</i> (%)	1 (5.8%)	1 (6.6%)		0.755
Clinical characteristics				
Recurrent infections, <i>n</i> (%)	17 (100%)	13 (86.6%)		
Recurrent pneumonia, <i>n</i> (%)	15 (88.2%)	1 (6.6%)		
Recurrent otitis media, <i>n</i> (%)	8 (47%)	2 (13.3%)		
Recurrent sinusitis, <i>n</i> (%)	12 (70.5%)	3 (20%)		
Recurrent urinary tract infections, <i>n</i> (%)	2 (11.7%)	3 (20%)		
Sepsis in personal medical history, <i>n</i> (%)	0 (0%)	1 (6.6%)		
Bronchiectasis, <i>n</i> (%)	6 (35.3%)	0 (0%)		
Conductive hearing impairment, <i>n</i> (%)	3 (17.6%)	0 (0%)		
Autoimmunity, <i>n</i> (%)	6 (35.3%)	8 (53.3%)		0.784
Splenomegaly, <i>n</i> (%)	5 (29.4%)	1 (6.7%)		0.178
Hepatomegaly, <i>n</i> (%)	3 (17.6%)	1 (6.7%)		0.603
Enteropathy, <i>n</i> (%)	4 (23.5%)	3 (20.0%)		0.576
Malignancy, <i>n</i> (%)	2 (11.8%)	1 (6.7%)		0.548
Allergy or atopy, <i>n</i> (%)	10 (58.8%)	8 (53.3%)		0.517
CVID severity score, median	15 points (IQR = 19)			
Positive SARS-CoV-2 PCR in personal medical history, <i>n</i> (%)	10 (58.8%)	9 (60.0%)	8 (53.8%)	0.918
Severity of COVID-19 according to WHO clinical progression scale *				
Asymptomatic (score 1), <i>n</i>	1	0	0	
Mild (not hospitalized 2–3), <i>n</i>	6	8	8	
Moderate (hospitalized 4–5), <i>n</i>	2	1	0	
Severe (hospitalized 6+), <i>n</i>	1	0	0	

Abbreviation: CVID—common variable immunodeficiency; sIgAD—selective IgA deficiency; *n*—number; IQR—interquartile range; SARS-CoV-2—severe acute respiratory syndrome coronavirus 2; PCR—polymerase chain reaction; COVID-19—coronavirus disease 2019; WHO—World Health Organization. *p*-values of less than 0.05 were regarded as significant. * Ambulatory mild disease: score 1—asymptomatic, viral ribonucleic acid (RNA) detected; score 2—symptomatic—independent; score 3—symptomatic, assistance needed; Hospitalized: moderate disease: score 4—hospitalized, no oxygen therapy required; score 5—hospitalized, oxygen by mask or nasal prongs; Hospitalized: severe disease: score 6—hospitalized with non-invasive ventilation or high flow oxygen; score 7—intubation and mechanic ventilation partial pressure of oxygen/fraction of inspired oxygen ratio (pO_2/FiO_2) ≥ 150 or oxygen saturation/fraction of inspired oxygen ratio (SpO_2/FiO_2) ≥ 200 ; score 8—mechanic ventilation $pO_2/FiO_2 < 150$ or $SpO_2/FiO_2 < 200$ or vasopressors; score 9—mechanic ventilation $pO_2/FiO_2 < 150$ or $SpO_2/FiO_2 < 200$ and vasopressors, dialysis or extracorporeal membrane oxygenation (ECMO); Dead: score 10—dead.

Regarding treatment, in the CVID group, all patients except two received regular immunoglobulin replacement therapy (subcutaneously 100 mg/kg/week). A patient with sIgAD with rheumatoid arthritis was on regular immunosuppressive treatment with corticosteroids (methylprednisolone 8 mg/day), methotrexate 15 mg/week, and biological therapy with JAK inhibitor (upadacitinib 15 mg/day). Two patients had previously received chemotherapy for neoplasia, and one patient was treated with rituximab (the last dose was administered 6 months prior to vaccination).

3.2. Vaccination Status and Previous SARS-CoV-2 Infection

Of the 32 patients enrolled in this study, 28 had completed the SARS-CoV-2 immunization schedule with the messenger ribonucleic acid (mRNA) vaccine (27 patients) or the adenovirus vector vaccine (1 patient) before enrollment in a study with a median time of 173 days (IQR = 142) after the last vaccine dose, ranging from 25 to 345 days (see Table 2).

All healthy controls were vaccinated with mRNA vaccines, with days after the last dose ranging from 96 to 511 (median 215, IQR = 201).

Table 2. Vaccination-related parameters in patients and controls.

Parameter	CVID	sIgAD	Healthy Controls	<i>p</i>
Number of vaccinated individuals	15	13	15	
Vaccination				0.711
Pfizer BioNTechBNT162b2, <i>n</i>	9	9	12	
Spikevax mRNA-1273, <i>n</i>	5	4	3	
Jcovden Ad26.COV2, <i>n</i>	1	0	0	
Booster dose (3rd dose) received, <i>n</i>	10	4	8	0.118
Days after vaccination, median (IQR)	167 (77)	148 (300)	215 (201)	0.156
Positive humoral response, <i>n</i> (%)	14 (93.3%)	13 (100%)	15 (100%)	1.000
Positive T-cell response <i>n</i> /yes	14 (93.3%)	12 (92.3%)	12 (80%)	0.596
Level of anti-S IgG, ratio, median (IQR)	5.4720 (4.08)	8.6260 (5.12)	9.4350 (2.13)	0.035
CD4+ cell response (INF- γ) to S1 pool-specific protein, IU/mL, median (IQR)	0.4662 (0.86)	0.5845 (0.62)	0.2949 (0.70)	0.765
CD4+ and CD8+ cell response (INF- γ) to S1 and S2 pool-specific proteins, IU/mL, median (IQR)	0.6451 (1.28)	0.5052 (0.92)	0.5503 (0.68)	0.966

Abbreviation: CVID—common variable immunodeficiency; sIgAD—selective IgA deficiency; *n*—number; IQR—interquartile range; mRNA—messenger ribonucleic acid; anti-S IgG—anti-spike immunoglobulin G; INF- γ —interferon-gamma; S1—S1 region of the severe acute respiratory syndrome coronavirus 2 spike glycoprotein; S2—S2 region of the severe acute respiratory syndrome coronavirus 2 spike glycoprotein. *p*-values of less than 0.05 were regarded as significant.

Four patients refused the vaccination but had previously had COVID-19 in their personal medical history. None of these four patients showed a positive T-cell response to the SARS-CoV-2 S1/S2 pool antigens. Two of these patients had CVID, and two—sIgAD. Two patients with the most recent SARS-CoV-2 infection—a CVID patient 58 days after positive SARS-CoV-2 PCR and a selective IgA patient 108 days after positive PCR—showed a positive anti-spike humoral response (anti-spike IgG antibody ratio 9.91 and 2.2, respectively). The remaining two unvaccinated patients had a positive SARS-CoV-2 PCR test about a year ago, and their serum antibody levels were undetectable. We further analyzed vaccinated individuals only.

3.3. Humoral and Cellular Response to SARS-CoV-2 Vaccine

Overall, all vaccinated patients with sIgAD had anti-spike IgG antibody levels >1.1 ratios (see Table 2). Of the 15 vaccinated patients with CVID, 14 tested positive for anti-spike IgG antibodies (including the patient on rituximab), showing a wide range of antibody levels, from undetectable levels to normal or high titers. However, as can be seen in Figure 1a, the median level of antibody response in CVID patients was lower compared to the healthy controls. Overall, there was a significant but weak negative correlation between antibody levels and days after vaccination ($r_s = -0.302$; $p = 0.049$; see Figure 1b). This correlation was also observed in the sIgAD subgroup ($r_s = -0.247$, $p = 0.038$) but was not present in the CVID subgroup ($r_s = -0.247$; $p = 0.376$) and in healthy controls ($r_s = -0.182$; $p = 0.515$).

Of the 15 CVID-vaccinated patients, 14 showed a positive anti-spike T-cell response (see Table 2). The only non-responsive CVID patient had three autoimmune diseases (type 1 diabetes, celiac disease, chronic autoimmune thyroiditis) and a baseline serum INF- γ level of 3.06 IU/mL and exhibited high anti-spike IgG antibody titers (11.2 ratio). All patients with sIgAD, except for the patient on immunosuppressive therapy, had positive anti-spike T-cell response. Evaluation of T-cell responses showed no significant differences in spike-specific INF- γ production between the study groups, as well as no correlation with days after vaccination (see Figure 2).

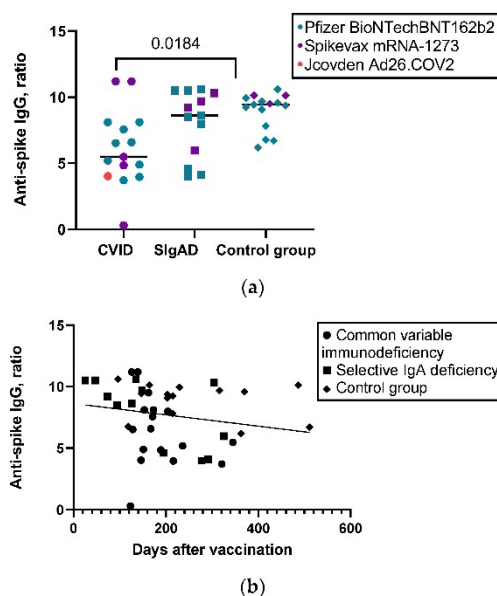


Figure 1. (a) Levels of anti-spike IgG antibody levels in different groups; (b) correlation between anti-spike IgG antibody levels and days after vaccination.

Interestingly, regarding healthy controls, three healthy controls did not exhibit an anti-spike T-cell response (on days 215; 363; 511 after the last vaccine dose) but showed a positive humoral response (anti-spike IgG antibody ratio 9.23, 6.18, and 6.69, respectively). Furthermore, we observed a positive correlation between anti-spike IgG antibody levels and T-cell response (INF- γ synthesis to the S1 and S2 pools) in the control group (S1 pool ($r_s = 0.571$; $p = 0.026$) and to the S1/S2 pool ($r_s = 0.721$; $p = 0.02$)), but we did not observe this trend in the sIgAD or CVID groups.

3.4. Immunological Memory to SARS-CoV-2 and Demographic/Clinical/Immunologic Phenotyping Markers

Age did not significantly influence the extent of humoral or cell response in any of the groups. We did not observe any differences in humoral or T-cell anti-spike responses between COVID-19-convalescent individuals and subjects naïve to infection in any of the groups.

No differences in humoral or T-cell immune responses were associated with the patient's clinical parameters, except in the sIgAD group, patients with recurrent otitis had a statistically significantly lower median T-cell response to S1/S2 antigen compared to patients without this infection ($p = 0.038$; median 0.5 (IQR = 0.8) and 0.13, respectively). In CVID patients, no correlation was found between humoral or T-cell response and the Ameratunga CVID severity score. We did not observe any difference in humoral or T-cell response between different groups of CVID Chapel phenotypes.

A significant correlation was found between the anti-spike antibody response and central memory CD8+ cell percentages ($r_s = 0.385$; $p = 0.047$), and in the selective IgA patient group also, central memory CD4+ cell percentages ($r_s = 0.635$; $p = 0.020$). We found no significant relationship between the anti-spike cellular response and the subsets of B cells. No significant correlation was observed between anti-spike IgG antibody or T-cell response and total IgG, IgM, or IgA levels.

In CVID patients, immunological classification of the patients did not reveal a difference in anti-spike humoral or T-cell response between different immunological classifications according to Paris, Freiburg, EUROclass, or B-cell pattern classifications. The only B-cell-negative CVID patient (group B- according to EUROclass classification) also exhibited a positive anti-spike IgG antibody level (11.2 ratio) and anti-spike T-cell response (0.25 IU/mL) 139 days after concluding the primary vaccination regimen with the mRNA-1273 vaccine.

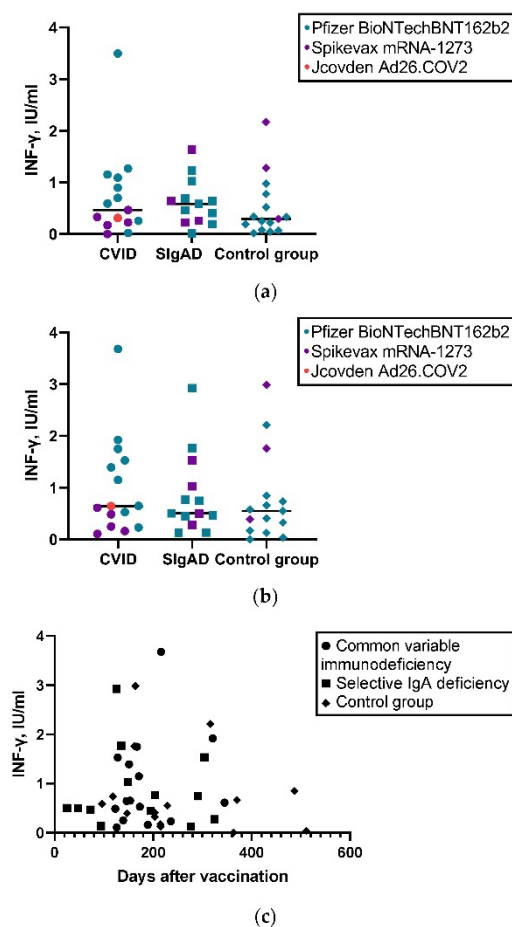


Figure 2. (a) CD4+ cell response (levels of INF-γ) to S1 pool-specific protein in different groups; (b) CD4+ and CD8+ cell response (levels of INF-γ) to S1/S2 pool-specific protein in different groups; (c) Correlation between anti-spike CD4+ and CD8+ cell response and days after vaccination.

4. Discussion

In this study, we evaluated a long-term SARS-CoV-2 spike-specific humoral and cellular immune response in a cohort of 32 adult patients with CVID (which represents 85% of patients diagnosed with CVID in Latvia [46]) or symptomatic sIgAD and 15 healthy controls. Our data suggest that CVID and sIgAD patients show a humoral and cellular immune response to the SARS-CoV-2 vaccine that is present several months after vaccination,

but the detectable anti-spike IgG antibody levels in CVID patients are lower than in healthy controls, and selective IgA patients.

A previous report examining the early response to vaccination had revealed positive anti-spike antibodies with a wide variation in seropositivity rates after vaccination, ranging between 20.6% and 90.9% [25,26,28,33–35,47,48] and cellular response in up to 85% of patients tested with IEL [35]. In our cohort, we observed comparable rates of detectable anti-spike antibodies (93% in CVID patients) and anti-spike T-cell responses (93% in CVID patients). However, almost all CVID patients received subcutaneous immunoglobulin (SCIG) replacement therapy, and this should be taken into consideration when evaluating humoral responses, as it is likely that the pool of immunoglobulin preparations contains specific antibodies to SARS-CoV-2 [49,50]. In contrast, earlier findings of Pham suggested that intravenous immune globulin (IVIG) preparations received in September 2021 did not significantly alter patient levels of SARS-CoV-2 antibodies [25]. In addition, we did not observe a correlation between total IgG and spike-specific IgG antibody levels.

We demonstrated that patients with CVID and sIgAD are capable of generating an anti-spike T-cell response at least up to almost a year (up to 345 days) after the completion of the vaccination schedule, consistent with the relatively sparing T-cell immunity of these patients. The results are in line with previously described that contrary to protein vaccines, mRNA vaccine formulations also trigger robust CD4+ T-cell responses and strong CD8+ T-cell responses, perhaps as a result of the effective presentation of endogenously generated antigens on major histocompatibility complex (MHC) class I molecules [51]. Similar to our findings, other studies that measured early vaccine responses also found no statistically significant differences in anti-spike T-cell response between healthy vaccinated controls and patients with CVID or sIgAD [33]. On the contrary, in IEL patients, a significantly higher subset of SARS-CoV-2 antigen-specific CD4 + CD40L + T cells have been described a month after vaccination, suggesting T-cell compensatory function in patients with primary B-cell impairment [28]. However, these different outcomes could be explained by differences in the methodology, as it is uncertain how much the various assays (cytokine production, antigen-induced proliferative responses, or the overexpression of certain activation markers) accurately represent the same characteristics of a T-cell response, and there is no clear consensus on methods of how to identify vaccine-specific T-cell responses [52].

Studies with healthy donors have found a positive correlation between the magnitude of anti-spike CD4+ T cells with anti-spike IgG antibody responses early after the vaccination and, consistent with the concept of intramolecular help, also anti-spike CD8+ T-cell responses, suggesting the concurrent development of adaptive humoral and cellular immunity [29]. However, studies on long-term immunological memory in healthy individuals have also found antibody titers not to be predictive of T-cell memory [53]. We found a relationship between anti-spike humoral and cellular responses in the control group; however, this link was not observed in the CVID group and, interestingly, in the selective IgA patient group who did not receive immunoglobulin replacement therapy.

Older people have been reported to be at increased risk of severe COVID-19 infection. Although there are several factors related to the increased risk, one of these risk factors could be a reduced T-cell response, partly due to a more limited repertoire of naïve T cells [31]. It has been described that the immune response to vaccination is often also weaker, with a limited duration of protection in elderly individuals [54]. This trend has also been documented by Hagin et al. in CVID patients [33]. However, we did not observe an association between the humoral or cellular immune response to vaccination and age in our cohort of primary antibody patients, similar to other reports [25,26,28].

Although it has previously been described that the humoral and T-cell response of patients with previous SARS-CoV-2 infections was significantly greater than that of patients with infection-naïve individuals after vaccination [26,34], we did not observe this in our cohort. However, these differences have been suggested to arise from constituents of the peptide pool in interferon-gamma release assays (IGRA) tests [26].

Primary antibody deficiency patients with a history of autoimmunity have previously been reported to have a poorer response to vaccination [36]. In this study, we were not able to identify an association between the magnitude of the immune response and clinical manifestations. Regarding immunological correlates with vaccine responsiveness, we found a significant correlation between the anti-spike humoral response and central memory CD8+ cell percentages and in the selective IgA patient group—also with central memory CD4+ cell percentages. The results are consistent with a previously reported expansion of the T-cell memory subsets in patients with IEL and healthy controls 28 days after vaccination with the BNT162b2 mRNA vaccine [28]. However, a recent study examining immunological predictors of impaired immune response to SARS-CoV-2 vaccination found no association to central memory CD4+ or CD8+ T cells, but a significantly higher frequency of effector memory CD8+ T cells in those of impaired humoral immune response [36], and a similar trend has also been observed with humoral response to influenzae vaccination in CVID patients [55]. We found no significant relationship between long-term anti-spike humoral response and B-cell subsets, consistent with reports on early vaccination responses in IEL patients where there was no variation in the B-cell compartment a month after vaccination was reported [28]. However, in PAD patients, lower levels of baseline IgG, IgA, total B cells, and switched memory B cells were related to poor SARS-CoV-2 vaccine anti-spike antibody response [36]. In addition, following influenza vaccination, in patients with CVID, numbers of circulating switched memory B lymphocytes (EUROClass B+ smB+) were directly correlated with a superior humoral immune response [56].

Several major limitations of this study should be considered. First, the small sample size. Second, the observational design of the study and the broad time frame within the measurements after completion of the immunization schedule does not allow us to conclude if the presence of anti-spike antibodies or anti-spike T-cell responses can confer protection against different SARS-CoV-2 or to evaluate the dynamics of the immune responses. Third, we did not include the evaluation of SARS-CoV-2-specific memory B cells in our study. Regarding long-term immunological memory in healthy patients, a trend of increased SARS-CoV-2-specific memory B cells several months after infection in healthy individuals reconvalescent from SARS-CoV-2 [53]. In patients with antibody deficiencies, Salinas et al. found an impaired spike-specific memory B-cell compartment in CVID patients, compared to healthy controls after vaccination with Pfizer/BioNTech. They also found a higher frequency of spike-specific atypical memory B-cell subsets in CVID patients compared to healthy controls after vaccination, suggesting that they retreated from extrafollicular reactions rather than germinal center reactions [34].

In conclusion, this study provides information on long-term immunological memory in patients with CVID and sIgAD. Our findings confirm that markers of the sustained SARS-CoV-2 spike-specific humoral and cellular immune response are detectable several months after vaccination. Despite the significantly lower median levels of anti-spike IgG response in CVID patients than in healthy controls, the T-cell response in CVID and sIgAD patients was comparable to that of healthy controls; therefore, vaccination should be recommended in these patients.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/vaccines11020354/s1>, Supplementation S1: Gating strategy of B and T lymphocyte subsets.

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Data Availability Statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Article

Cytokine Response Following SARS-CoV-2 Antigen Stimulation in Patients with Predominantly Antibody Deficiencies

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Abstract: Predominantly antibody deficiencies (PADs) are inborn disorders characterized by immune dysregulation and increased susceptibility to infections. Response to vaccination, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may be impaired in these patients, and studies on responsiveness correlates, including cytokine signatures to antigen stimulation, are sparse. In this study, we aimed to describe the spike-specific cytokine response following whole-blood stimulation with SARS-CoV-2 spike peptides in patients with PAD ($n = 16$ with common variable immunodeficiency and $n = 15$ with selective IgA deficiency) and its relationship with the occurrence of coronavirus disease 2019 (COVID-19) during up to 10-month follow-up period. Spike-induced antibody and cytokine production was measured using ELISA (anti-spike IgG, IFN- γ) and xMAP technology (interleukin-1 β (IL-1 β), IL-4, IL-6, IL-10, IL-15, IL-17A, IL-21, TNF- α , TGF- β 1). No difference was found in the production of cytokines between patients with PAD and controls. Anti-spike IgG and cytokine levels did not predict contraction of COVID-19. The only cytokine that distinguished between vaccinated and naturally infected unvaccinated PAD patients was IFN- γ (median 0.64 (IQR = 1.08) in vaccinated vs. 0.10 (IQR = 0.28) in unvaccinated). This study describes the spike-specific cytokine response to SARS-CoV-2 antigens, which is not predictive of contracting COVID-19 during the follow-up.

Keywords: antibody deficiency; common variable immunodeficiency; selective IgA deficiency; SARS-CoV-2; COVID-19; cytokine

1. Introduction

Predominantly antibody deficiencies (PADs) are a group of disorders characterized by impaired B cell differentiation and decreased synthesis of immunoglobulins, resulting in recurrent sinopulmonary infections and, in some cases, poor vaccine response [1]. The most common diagnoses include selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID). Patients with SIgAD have reduced serum immunoglobulin A (IgA) levels below 0.07 g/L, with normal levels of other immunoglobulins. They are often asymptomatic and do not usually have an impaired response to vaccination. Symptomatic patients may experience recurrent respiratory and gastrointestinal infections and have a higher risk of atopic or autoimmune diseases compared to the general population [2]. CVID is the most common symptomatic antibody deficiency. The European Society for Immunodeficiencies Registry working definition for CVID is decreased levels of immunoglobulins (IgG, IgA, and/or IgM) and low switched memory B cells or poor vaccine response in

individuals older than 4 years of age with no other identifiable cause or severe T cell defects [3]. Recurrent bacterial infections are the hallmark of the disease; however, the majority of patients also experience immune dysregulation-related non-infectious complications, including autoimmune diseases and malignancy [4]. Immune dysregulation, including dysregulated cytokine response, has been long known to be a part of the immunopathogenesis of predominantly antibody deficiencies, such as CVID and SIgAD [4–7].

When the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic broke out in late 2019 [8], initial reports indicated increased disease-related morbidity and mortality in immunocompromised patients [9–13], including those with PAD [14–16]. After vaccines became available, several studies have investigated both the reactogenicity and immunogenicity of SARS-CoV-2 vaccines in PAD patients, and most studies concluded that the immune response in PAD patients was inferior to that in healthy vaccine recipients [17–32].

The main SARS-CoV-2 antigen is thought to be the spike (S) protein, which binds to the human angiotensin-converting enzyme 2 receptor via the receptor-binding domain of the virus and thus enters the cell. This protein consists of three parts: a signal peptide, an N-terminal S1 protease fragment containing the receptor-binding domain, and a C-terminal S2 protease fragment [33,34]. Coordinated cellular immunity is essential for disease control in viral infections, including SARS-CoV-2, while dysregulated and exacerbated inflammatory responses play a pivotal role in the development of severe coronavirus disease-19 (COVID-19) infection [35–37]. During natural infection with SARS-CoV-2, it has been observed that along with traditional markers of inflammation, such as C-reactive protein (CRP) and serum amyloid A, there are higher levels of specific pro-inflammatory cytokines, including interleukin 6 (IL-6), IL-1 β , IL-8, IL-10, interferon gamma (IFN- γ), and tumor necrosis factor alpha (TNF- α) [38]. In addition, several other cytokines and chemokines have been shown to have altered expression in COVID-19, and the levels of some of these cytokines have been linked to the prognosis of COVID-19 [39–59]. However, some have speculated that in patients with inborn errors of immunity, immunodeficiency might act as a protective factor against the cytokine storm, which is the main trigger for the severe course of COVID-19 [60]. Therefore, the interplay between cytokine dysregulation in patients with PAD is intriguing; on the one hand, these patients may fail to mount an efficient immune response to vaccination, which could lead to a more severe course of the disease [61]. In contrast, a reduced inflammatory response could be related to a decreased risk of cytokine storms that lead to multi-organ failure [60].

In addition, attempts have been made to identify biomarkers related to efficient vaccine responses, and several associations between cytokine levels and SARS-CoV-2-specific humoral immune responses have been observed. Several studies with immunocompetent individuals have examined the correlates of SARS-CoV-2-specific humoral response and found changes in levels of M-CSF, IL-1 α , IFN- γ , IL-1 β , IL-10, IL-12p70, IL-6, IL-17A, IL-15, and IFN signaling-related cytokines (CXCL10, MCP-1, MCP-2, and MCP-3) to be correlated with SARS-CoV-2-specific antibody response in healthy volunteers [45,62–65]. Regarding PAD patients, several studies have examined the T cell response role in protection against SARS-CoV-2, showing IL-2 and/or IFN- γ secretion in response to pooled SARS-CoV-2 antigens [18,24–28]. Nonetheless, the understanding of the wider range of cytokines produced following SARS-CoV-2 antigen stimulation in individuals with predominantly antibody deficiencies is currently limited.

In this study, we aimed to describe the cytokine signatures following whole-blood stimulation with SARS-CoV-2 antigen in SARS-CoV-2 naturally infected and vaccinated PAD patients and compare these results with those of healthy controls. We also assessed whether cytokine profile or other immunological parameters were related to vaccine effectiveness for preventing coronavirus disease 2019 (COVID-19) during the follow-up period and cytokine signature relatedness with patients' clinical parameters and anti-spike antibody levels.

2. Materials and Methods

2.1. Study Population

Patients with CVID and symptomatic SIgAD who were treated at a tertiary immunology center (Pauls Stradins Clinical University Hospital, Riga, Latvia) were enrolled in the study from April to July 2022. In total, 38 adult individuals were included in the study: 31 predominantly antibody deficiency patients (16 with CVID and 15 with SIgAD) and 7 healthy controls. All 31 patients were diagnosed according to the European Society for Immunodeficiencies diagnostic criteria [3]. To gather data on the demographic and clinical characteristics of patients, a thorough medical history of the patients was compiled, and their medical records were assessed. At the onset of the study, patient medical history was collected for several clinical parameters, including the frequency and type of infections (including SARS-CoV-2 infection and SARS-CoV-2 vaccination status), autoimmune diseases, levels of autoantibodies (rheumatoid factor, anti-nuclear antibody (ANA) and extractable nuclear antigen antibody (ENA) screening, antineutrophil cytoplasmic antibodies (p-ANCA, c-ANCA, atypical ANCA), antibodies against cardiolipins and phospholipids, lupus anticoagulant, anti-double-stranded DNA, anti-histone, anti-thyroid peroxidase, anti-tissue transglutaminase, anti-gliadin, and anti-gastric parietal cell antibodies), benign polyclonal lymphoproliferation (lymphadenopathy, splenomegaly, and hepatomegaly), granulomatous disease, enteropathy, atopy, or allergy (asthma, allergic rhinitis, food allergy, and atopic dermatitis), and malignant diseases. Data regarding patient immunoglobulin levels (IgG, IgM, and IgA) and lymphocyte subpopulations on the day of blood collection were also retrieved from the patients' medical records. Lymphocytes were divided into the following subpopulations: B cells (CD19+), T cells (CD3+), T helper cells (CD3+CD4+), T cytotoxic cells (CD3+CD8+), T natural killer cells (CD3+CD56+), and activated T cells (CD3+HLADR+). The SARS-CoV-2 vaccination course was considered to be completed if the individual had received two doses if naïve to SARS-CoV-2 infection, or one dose if previously infected. The severity of COVID-19 in personal history was assessed using the World Health Organization Clinical Progress scale [66]. Immunological phenotyping was based on the EUROclass classifications [67]. CVID severity was assessed using the CVID severity score proposed by Ameratunga [68]. Following written consent to participate in this study, blood samples were obtained from patients and control participants. Four to ten months (122–317 days) after blood sample collection, the patient's medical documentation (SARS-CoV-2 PCR test results, booster vaccination status) was reviewed again, and participants were contacted to determine if they had a positive SARS-CoV-2 rapid antigen test result during this time. In cases where a patient received an additional dose of the vaccine as a booster during the follow-up period, the duration of their follow-up time was modified to account for the period leading up to the date on which they received the booster dose. This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Central Board of the Ethics Committee of the Health Ministry of the Republic of Latvia (No. 01-29.1/2878).

2.2. Blood Collection

Peripheral venous blood samples were collected from all the participants. A peripheral blood sample for SARS-CoV-2 anti-spike IgG was collected in a serum collection tube, centrifuged after 30 min, and frozen at -20°C until the day of measurement. A sample for peripheral blood mononuclear cell (PBMC) isolation and phenotyping of B and T lymphocyte subsets was collected in a lithium heparin-coated tube, and PBMCs were isolated as described previously [25]. Samples for the assessment of CD4+ and CD8+ cell cytokine responses to SARS-CoV-2 peptide stimulation and cytokine determination before/after SARS-CoV-2 peptide stimulation were collected in heparinized whole-blood QuantiFERON SARS-CoV-2 blood collection tubes (Qiagen, Hilden, Germany), incubated at 37°C for 20 h, centrifuged according to the manufacturer's protocol, and frozen at -20°C for subsequent analysis. QuantiFERON SARS-CoV-2 blood collection starter kit contains four types of blood collection tubes: negative control, Ag1 tube (contains epitopes from the

S1 fragment of the SARS-CoV-2 spike protein, measures response mediated by CD4+ cell response), Ag2 tube (contains epitopes from the S1 and S2 fragments of the SARS-CoV-2 spike protein, measures response mediated by both CD4+ and CD8+ cells), and positive control (mitogen control) [34,69]. Negative control was used to measure cytokine baseline levels and non-specific cytokine release during the incubation, while the Ag2 tube was used to measure cytokine levels after antigen stimulation.

2.3. Humoral Response to SARS-CoV-2

The humoral response to SARS-CoV-2 (IgG class antibodies to SARS-CoV-2 S1 domain of the spike protein) was assessed using the semi-quantitative enzyme-linked immunosorbent assay (ELISA) from Euroimmun (Anti-SARS-CoV-2 IgG assay, Euroimmun, Lübeck, Germany), following the manufacturer's recommendations and as described previously. An IgGAM ratio (optical density compared with the calibrator) > 1.1 was considered a positive response. SARS-CoV-2 anti-spike response was considered low if the levels were <1.1, moderate if the anti-spike IgG levels were between 1.1 and 10, and high if levels were >10.

2.4. Cytokine Detection

Cytokine levels before and after SARS-CoV-2 S1 and S2 pool peptide stimulation were determined by Luminex xMAP technology using Luminex 200 equipment (A DiaSorin Company, Austin, TX, USA) and a multiplex assay (MILLIPLEX MAP Human TH17 Magnetic Bead Panel, Cat#: HTH17MAG-14 K and MILLIPLEX MAP TGF- β 1 Magnetic Bead Single Plex Kit, Cat#: TGFBMAG-64K-01, both from Merck Millipore, Darmstadt, Germany), following the manufacturer's protocol. Levels of the following cytokines were measured: transforming growth factor beta 1 (TGF- β 1), IL-1 β , IL-4, IL-6, IL-10, IL-15, IL-17A, IL-21, and TNF- α . Antigen-specific responses were quantified as the increase or decrease in cytokine levels in SARS-CoV-2 S1 and S2 pool peptide-stimulated samples compared with paired unstimulated negative controls. For the analysis, cytokines falling below the lowest detection limit were adjusted to 0.5, and absent values were removed.

Levels of interferon gamma (IFN- γ) production before and after SARS-CoV-2 S1 and S2 pool peptide stimulation were assessed using QuantiFERON SARS-CoV-2 ELISA assay (Qiagen, Hilden, Germany), as previously reported [69], according to the manufacturer's protocol.

2.5. T and B Cell Subset Phenotyping

T and B cell subpopulations from freshly isolated PBMCs were determined by flow cytometry as described previously [25]. B cells were subdivided into the following subpopulations: naïve B cells (CD19+CD27–IgM+IgD+), marginal zone-like B cells (CD19+CD27+IgM++IgD+), switched memory B cells (CD19+CD27+IgM–IgD–), IgM-only memory B cells (CD19+CD27+IgM++IgD–), transitional B cells (CD19+IgD+CD27–IgM++CD38++), CD21low B cell (CD19+ IgM+, CD21–CD38–), plasmablasts (CD19+CD21+CD38+++IgM–), and atypical memory B cells (CD19+CD21–CD27–IgD–). T cells were subdivided as follows: naïve T helper cells (CD3+CD4+CD27+CD45RA+), central/transitory memory T helper cells (CD3+CD4+CD27+CD45RA–), effector memory T helper cells (CD3+CD4+CD27–CD45RA–), terminally differentiated T helper cells (CD3+CD4+CD27–CD45RA+), recent thymic emigrant T cells (CD3+CD4+CD31+CD45RO–), naïve T cytotoxic cells (CD3+CD8+CD27+CD45RA+), central/transitory memory T cytotoxic cells (CD3+CD8+CD27+CD45RA–), effector memory T cytotoxic cells (CD3+CD8+CD27–CD45RA–), terminally differentiated T cytotoxic cells (CD3+CD8+CD27–CD45RA+), T regulatory cells (CD3+CD4+CD25+FOXP3+CD127dim).

2.6. Statistical Analysis

The Shapiro–Wilk test was used to determine whether continuous variables were normally distributed. The results indicated that the data were not normally distributed; therefore, medians and interquartile ranges (IQRs) were used in data presentation, and

nonparametric statistical methods were used in subsequent analysis. The differences in categorical variables were examined using the chi-square and Fisher exact tests. The Mann–Whitney U or Kruskal–Wallis test was used to compare continuous variables between two or more groups, respectively. The Wilcoxon signed-rank test was used to compare two dependent samples. Spearman’s rank test was used to assess the correlation between continuous variables. A binominal regression analysis was used to predict the occurrence of COVID-19. In binominal regression analysis, the dependent variable was whether COVID-19 was present during the follow-up period, while the independent variables were measured at the beginning of this period as follows: levels of anti-spike IgG, changes in cytokine levels (IFN- γ , TGF- β , IL-1 β , IL-4, IL-6, IL-10, IL-15, IL-17A, IL-21, TNF- α) following whole-blood stimulation with SARS-CoV-2 S1 and S2 pool antigens, as well as levels of total IgG, IgA, and IgM, and different lymphocyte subpopulations as previously noted. Statistical significance was set at p value < 0.05. Statistical analysis was performed using IBM SPSS Statistics version 23 (IBM, New York, NY, USA). Graphs were generated using GraphPad Prism version 8 (GraphPad Software, San Diego, CA, USA).

3. Results

3.1. Study Population

Overall, 38 individuals were enrolled in the study: 31 patients with predominantly antibody deficiency (29.0% male, median age 40 years, IQR = 22) and seven control subjects (28.5% male, median age 50 years, IQR = 21). In the patient group, 16 and 15 patients were diagnosed with CVID and SIgAD, respectively. The clinical characteristics of the participants are presented in Table 1.

Table 1. Demographic and clinical parameters of the predominantly antibody deficiency patients.

Diagnosis	Sex	Age	Vaccination to SARS-CoV-2	Days after Vaccination	COVID-19 in Personal Medical History Prior to Blood Collection	COVID-19 during Follow-Up Period	Clinical Manifestations and Non-Infectious Complications	Infection-Related Complications
CVID	Female	30	Pfizer BioN-TechBNT162b2	153	Yes, 118 days after COVID-19, WHO score * 2	No	Recurrent pneumonia, otitis media, tonsillitis	Bronchiectasis
CVID	Female	50	Spikevax mRNA-1273	139	No	No	Recurrent pneumonia, otitis media, skin infections; viral warts; allergic rhinitis; lymphadenopathy, splenomegaly	Bronchiectasis
CVID	Female	27	Spikevax mRNA-1273	126	Yes, 55 days after COVID-19, WHO score 2	No	Recurrent pneumonia, sinusitis, osteomyelitis; allergic rhinitis; celiac disease; Hashimoto thyroiditis; type 1 diabetes mellitus	No
CVID	Female	28	Pfizer BioN-TechBNT162b2	151	No	No	Recurrent pneumonia, sinusitis, tonsillitis, skin infections; atopic dermatitis; psoriasis; lymphadenopathy, hepatosplenomegaly	No
CVID	Female	35	Jcovden Ad26.CoV2	146	Yes, 387 days after COVID-19, WHO score 2	No	Recurrent pneumonia, sinusitis, urinary tract infections; viral warts; atopic dermatitis; Hashimoto thyroiditis; lymphadenopathy	Bronchiectasis, hearing impairment due to recurrent otitis media
CVID	Male	40	Pfizer BioN-TechBNT162b2	128	No	No	Recurrent pneumonia, sinusitis, meningitis; atopic dermatitis; splenomegaly	No
CVID	Male	37	Spikevax mRNA-1273	345	Yes, 100 days after COVID-19, WHO score 2	No	Recurrent pneumonia, otitis media, sinusitis	Bronchiectasis

Table 1. Cont.

Diagnosis	Sex	Age	Vaccination to SARS-CoV-2	Days after Vaccination	COVID-19 in Personal Medical History Prior to Blood Collection	COVID-19 during Follow-Up Period	Clinical Manifestations and Non-Infectious Complications	Infection-Related Complications
CVID	Male	28	Pfizer BioN-TechBNT162b2	173	No	Yes	Recurrent pneumonia, otitis media, sinusitis, skin infections; severe EBV infection in anamnesis; lymphadenopathy	No
CVID	Female	58	Spikevax mRNA-1273	123	Yes, 41 days after COVID-19, WHO score 2	No	Recurrent pneumonia, otitis media; asthma; primary biliary cholangitis; lymphadenopathy, hepatosplenomegaly; non-infectious diarrhea	Hearing impairment due to recurrent otitis media
CVID	Female	61	Pfizer BioN-TechBNT162b2	171	Yes, 453 days after COVID-19, WHO score 6	No	Recurrent pneumonia, otitis media, tonsillitis; asthma; lymphadenopathy, hepatosplenomegaly	Bronchiectasis
CVID	Female	55	Pfizer BioN-TechBNT162b2	167	No	Yes	Recurrent pneumonia, sinusitis, tonsillitis; allergic rhinitis; non-infectious diarrhea; meningioma	No
CVID	Male	37	Pfizer BioN-TechBNT162b2	321	Yes, 86 days after COVID-19, WHO score 5	No	Recurrent pneumonia; non-infectious diarrhea	Bronchiectasis
CVID	Female	63	Spikevax mRNA-1273	189	No	No	Recurrent pneumonia, otitis media, sinusitis, tonsillitis, skin infections, meningitis	Bronchiectasis, hearing impairment due to recurrent otitis media
CVID	Male	69	Pfizer BioN-TechBNT162b2	216	Yes, 98 days after COVID-19, WHO score 5	Yes	Recurrent pneumonia, tonsillitis; asthma; chronic lymphocytic leukemia of B cell type	Bronchiectasis
CVID	Female	48	No vaccination	N/A	Yes, 73 days after COVID-19, WHO score 4	No	Recurrent pneumonia; enteropathy	No
CVID	Male	45	No vaccination	N/A	Yes, 358 days after COVID-19, WHO score 1	No	Recurrent pneumonia, otitis media, sinusitis, osteomyelitis, recurrent <i>Herpes Zoster</i> ; vitiligo	Bronchiectasis
SIgAD	Female	37	Spikevax mRNA-1273	325	Yes, 95 days after COVID-19, WHO score 2	No	Angioedema; Hashimoto thyroiditis	No
SIgAD	Female	19	Pfizer BioN-TechBNT162b2	277	No	No	Recurrent pneumonia, otitis media, urinary tract infections, tonsillitis, sepsis in anamnesis; allergic rhinitis; type 1 diabetes	No
SIgAD	Female	53	Pfizer BioN-TechBNT162b2	94	Yes, 526 days after COVID-19, WHO score 4	No	Recurrent skin infections; rheumatoid arthritis, drug-induced osteoporosis with pathological fractures	No
SIgAD	Female	30	Pfizer BioN-TechBNT162b2	47	No	No	Recurrent sinusitis, tonsillitis; atopic dermatitis asthma; lymphadenopathy, splenomegaly; non-infectious diarrhea	No
SIgAD	Female	51	No vaccination	N/A	Yes, 105 days after COVID-19, WHO score 2	No	Lichen ruber planus in oral cavity mucosa	No
SIgAD	Male	21	Pfizer BioN-TechBNT162b2	195	No	No	Atopic dermatitis; psoriasis; non-infectious diarrhea	No

Table 1. Cont.

Diagnosis	Sex	Age	Vaccination to SARS-CoV-2	Days after Vaccination	COVID-19 in Personal Medical History Prior to Blood Collection	COVID-19 during Follow-Up Period	Clinical Manifestations and Non-Infectious Complications	Infection-Related Complications
SIgAD	Female	52	Pfizer BioN-TechBNT162b2	135	No	No	Recurrent tonsillitis; allergic rhinitis; idiopathic urticaria	No
SIgAD	Female	68	Spikevax mRNA-1273	73	No	Yes	Recurrent urinary tract infections; rheumatoid arthritis; gastric cancer in anamnesis	No
SIgAD	Female	25	Pfizer BioN-TechBNT162b2	291	Yes, 345 days after COVID-19, WHO score 2	No	Recurrent urinary tract infections, tonsillitis; viral warts; atopic dermatitis; non-infectious diarrhea	No
SIgAD	Male	44	Spikevax mRNA-1273	304	Yes, 77 days after COVID-19, WHO score 2	No	Recurrent skin infections; atopic dermatitis, eosinophilic esophagitis; celiac disease, Hashimoto thyroiditis	No
SIgAD	Female	42	Pfizer BioN-TechBNT162b2	126	Yes, 59 days after COVID-19, WHO score 2	No	Recurrent tonsillitis	No
SIgAD	Female	34	Spikevax mRNA-1273	148	Yes, 35 days after COVID-19, WHO score 2	No	Recurrent tonsillitis, meningitis in anamnesis, recurrent <i>Herpes Zoster</i> ; allergic rhinitis	No
SIgAD	Female	36	No vaccination	N/A	Yes, 108 days after COVID-19, WHO score 2	Yes	Recurrent otitis media, sinusitis	No
SIgAD	Female	41	Pfizer BioN-TechBNT162b2	25	Yes, 244 days after COVID-19, WHO score 2	Yes	Recurrent tonsillitis; hepatomegaly	No
SIgAD	Male	32	Pfizer BioN-TechBNT162b2	204	No	Yes	Recurrent sinusitis, tonsillitis; atopic dermatitis	No
Control	Female	52	Pfizer BioN-TechBNT162b2	487	No	No	N/A	N/A
Control	Male	37	Pfizer BioN-TechBNT162b2	316	Yes, 140 days after COVID-19, WHO score 2	No	N/A	N/A
Control	Male	50	Spikevax mRNA-1273	147	Yes, 140 days after COVID-19, WHO score 2	No	N/A	N/A
Control	Female	50	Pfizer BioN-TechBNT162b2	96	No	No	N/A	N/A
Control	Female	31	Spikevax mRNA-1273	162	Yes, 774 days after COVID-19, WHO score 2	No	N/A	N/A
Control	Female	30	Pfizer BioN-TechBNT162b2	203	No	Yes	N/A	N/A
Control	Female	60	Pfizer BioN-TechBNT162b2	229	Yes, 113 days after COVID-19, WHO score 2	Yes	N/A	N/A

Abbreviations: CVID—common variable immunodeficiency; SIgAD—selective IgA deficiency; SARS-CoV-2—severe acute respiratory syndrome coronavirus 2; COVID-19—coronavirus disease 2019; WHO—World Health Organization. * Ambulatory mild disease: score 1—asymptomatic, viral ribonucleic acid (RNA) detected; score 2—symptomatic, independent; score 3—symptomatic, assistance needed; 1 hospitalized: moderate disease: score 4—hospitalized, no oxygen therapy required; score 5—hospitalized, oxygen by mask or nasal prongs; 1 hospitalized: severe disease: score 6—hospitalized with non-invasive ventilation or high flow oxygen; score 7—intubation and mechanic ventilation partial pressure of oxygen/fraction of inspired oxygen ratio (pO_2/FiO_2) ≥ 150 or oxygen saturation/fraction of inspired oxygen ratio (SpO_2/FiO_2) ≥ 200 ; score 8—mechanic ventilation $pO_2/FiO_2 < 150$ or $SpO_2/FiO_2 < 200$ or vasopressors; score 9—mechanic ventilation $pO_2/FiO_2 < 150$ or $SpO_2/FiO_2 < 200$ and vasopressors, dialysis, or extracorporeal membrane oxygenation (ECMO); Dead: score 10—dead.

3.2. Prior Exposure to SARS-CoV-2 Antigen and COVID-19 during the Follow-Up Period in the Study Population

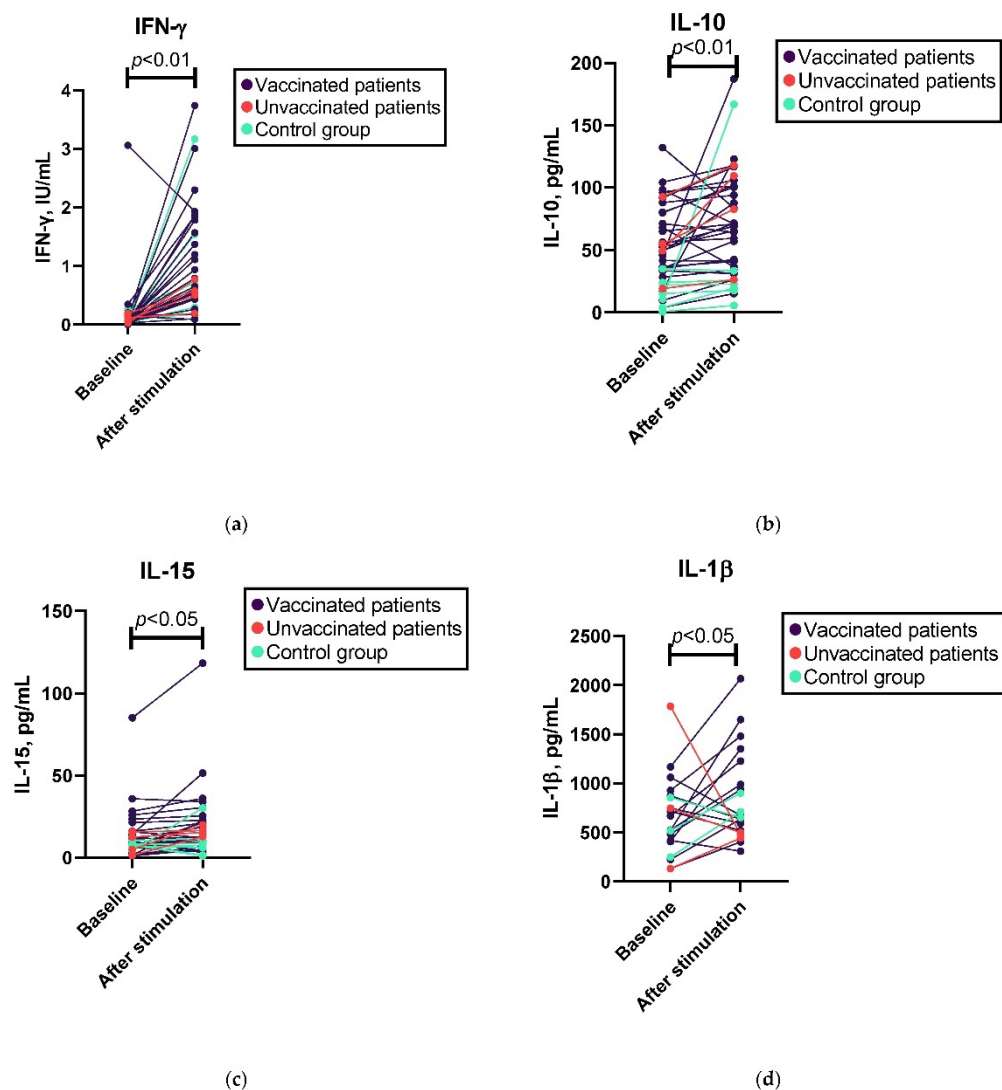
All patients and control group subjects had been previously exposed to the SARS-CoV-2 antigen at the time of blood sample collection via natural infection (4 patients, 0 controls), vaccination (12 patients, 3 controls), or both (15 patients, 4 controls). Of all vaccinated individuals (27 patients and 7 controls), the median time to completion of the vaccination regimen was 164 (IQR = 114) days: median 153 (IQR = 90) days in patients and 203 (IQR = 169) days in the healthy vaccine recipient group. The median duration between positive SARS-CoV-2 PCR test results and the date of evaluation for unvaccinated patients was 106 days (IQR = 144). Seven patients and two controls developed COVID-19 during the follow-up period, all of whom had mild disease according to the WHO classification (up to a score of 3) and were treated in an out-patient setting.

3.3. Changes in Cytokine Production Following SARS-CoV-2 Antigen Stimulation

To examine the changes in cytokine levels in response to SARS-CoV-2 antigen stimulation, we initially assessed the overall differences in cytokine production by comparing the baseline levels with those after stimulation in all study participants. Subsequently, we performed a similar analysis after excluding individuals who had not been vaccinated. Furthermore, we compared cytokine levels between the patient and control groups to determine whether significant differences existed in both baseline levels and changes in cytokine levels following antigen stimulation. Additionally, we examined the potential differences in cytokine levels and changes between patients diagnosed with common variable immunodeficiency (CVID) and selective IgA deficiency (SIgAD). All relevant statistical data are presented in Supplementary Table S1, which provides a detailed display of all pertinent statistical analyses.

Overall, we found a statistically significant increase in the levels of IFN- γ , IL-10, IL-15, IL-17A, IL-1 β , and TNF- α , but not IL-21, IL-4, and IL-6, and a decrease in TGF- β 1 following SARS-CoV-2 antigen stimulation (see Figure 1 and Supplementary Table S1a). After excluding patients who had not been vaccinated, changes were observed in the levels of the cytokines mentioned previously, except for changes in IL-15, which were not statistically significant (see Supplementary Table S1a). However, in the Mann-Whitney U test, we did not observe a significant difference between the patient and control groups regarding the increase in cytokine levels after SARS-CoV-2 antigen stimulation (see Supplementary Table S1b). In contrast, such differences were observed in the baseline cytokine levels; patients were characterized by significantly elevated baseline levels of IL-10 and IL-4 compared with the control group (see Supplementary Table S1b).

In addition, when categorizing patients based on diagnosis, we observed significant changes in IFN- γ , IL-10, IL-15, and IL-4 levels in the SIgAD subgroup, whereas only changes in the levels of IFN- γ and TGF- β 1 were observed in the CVID subgroup (see Supplementary Table S1a). We also found a statistically significant difference in the increase in IL-4 synthesis following SARS-CoV-2 antigen stimulation between different diagnosis groups: IL-4 did not increase in the CVID group (median 0 ng/mL), but we found a median 1.2 ng/mL increase in the SIgAD group (see Supplementary Table S1b).

Figure 1. *Cont.*

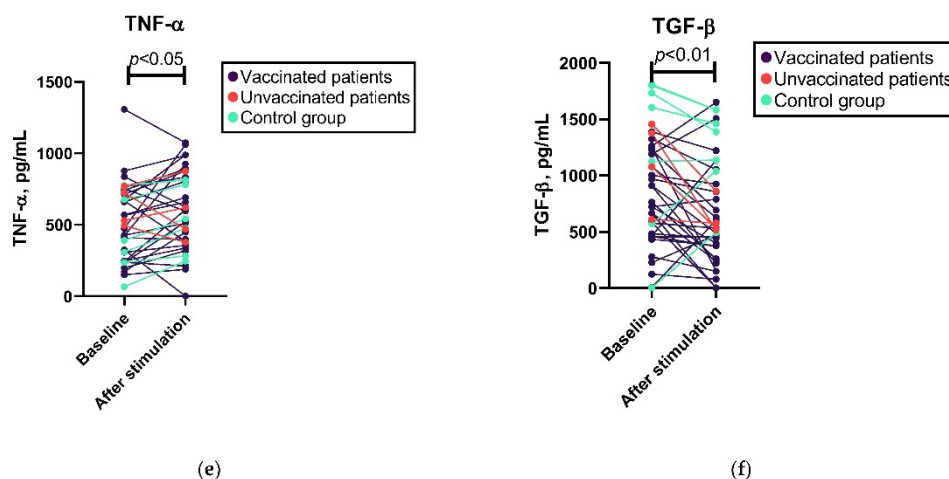


Figure 1. Wilcoxon test results for changes in cytokine levels following whole-blood SARS-CoV-2 antigen stimulation in patients and controls. (a) Levels of IFN- γ before and after SARS-CoV-2 antigen stimulation; $n = 38$. (b) Levels of IL-10 before and after SARS-CoV-2 antigen stimulation; $n = 38$. (c) Levels of IL-15 before and after SARS-CoV-2 antigen stimulation; $n = 34$. (d) Levels of IL- β before and after SARS-CoV-2 antigen stimulation; $n = 20$. (e) Levels of TNF- α before and after SARS-CoV-2 antigen stimulation; $n = 36$. (f) Levels of TGF- β 1 before and after SARS-CoV-2 antigen stimulation; $n = 38$.

3.4. Predictors of COVID-19 during the Follow-Up Period in PAD Patients

To determine potential clinical parameters that may be associated with the occurrence of COVID-19 during the follow-up period, we conducted a binomial logistic regression analysis and employed the Mann–Whitney U test. All the relevant statistical data are presented in Supplementary Table S2.

Binomial logistic regression analysis indicated that variables such as anti-spike IgG levels, cytokine levels following SARS-CoV-2 antigen stimulation, total IgG, IgM, and IgA levels, and lymphocyte subpopulations cannot be used to predict the likelihood of contracting COVID-19 (see Supplementary Table S2a). However, the Mann–Whitney U test demonstrated significant differences in cytotoxic T and NK cell subpopulations between patients who contracted COVID-19 during the follow-up period and those who did not (see Figure 2 and Supplementary Table S2b). However, the effect size of this test was moderate. After excluding patients who had not been vaccinated, significant differences in cytotoxic T cells, but not NK cells, were observed (see Supplementary Table S2b).

When categorizing patients based on their diagnosis, a consistent observation of differences in cytotoxic T cells, but not NK cells, was found in the CVID group, while in the SIgAD group, we did not find a statistically significant difference in lymphocyte subpopulations between the patients who contracted COVID-19 and those who did not.

We did not find a statistically significant relationship between the occurrence of COVID-19 during the follow-up period and anti-spike IgG or cytokine levels after the SARS-CoV-2 antigen stimulation (see Supplementary Table S2b).

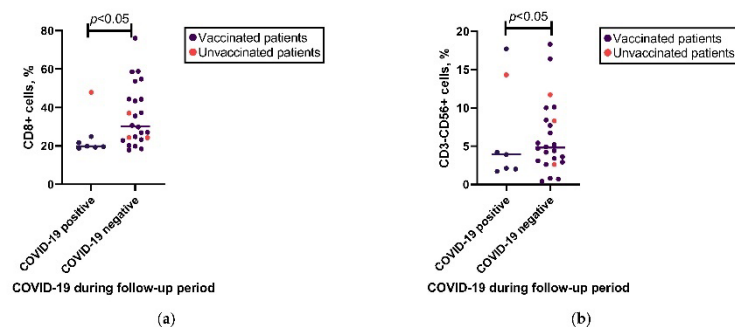


Figure 2. Associations of cytotoxic T cell and NK cell percentages with occurrence of COVID-19 in follow-up. (a) Mann–Whitney U test results for associations between cytotoxic T (CD8+) cells and occurrence of COVID-19 in follow-up in patients who did ($n = 7$) or did not ($n = 24$) have COVID-19 during the follow-up period. (b) Mann–Whitney U test results for associations between NK (CD3–CD56+) cells and occurrence of COVID-19 in follow-up in patients who did ($n = 7$) or did not ($n = 24$) have COVID-19 during the follow-up period.

3.5. Associations between the Cytokine Levels and Previous SARS-CoV-2 Vaccination

To ascertain potential differences in cytokine levels between vaccinated and unvaccinated patients and controls, the Kruskal–Wallis test was conducted. Furthermore, we assessed whether the cytokine response was correlated with the type of vaccination received within the patient group. All the relevant statistical data are presented in Supplementary Tables S3 and S6.

The Kruskal–Wallis test indicated a significant difference in the median increase in IFN- γ levels in the vaccinated, unvaccinated, and control groups (see Figure 3a and Supplementary Table S3a). When categorizing patients based on their diagnosis, a consistent observation of a difference between vaccinated and unvaccinated individuals was found in the COVID group, but not in the SIgAD group (see Supplementary Table S3b). No other significant differences were found in the increase in cytokine levels after SARS-CoV-2 antigen stimulation between the vaccinated and unvaccinated patients or vaccinated controls.

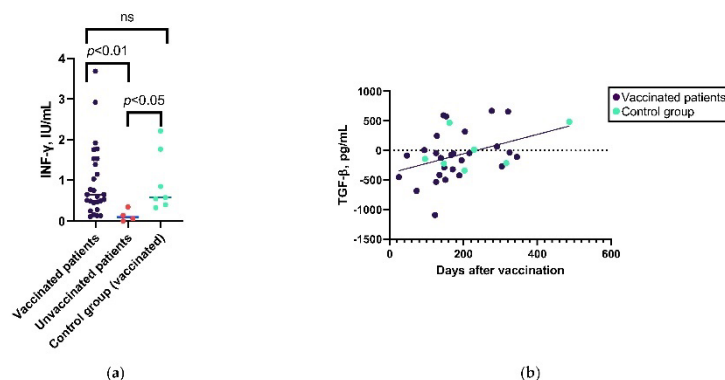


Figure 3. Associations between the cytokine levels and previous SARS-CoV-2 vaccination. (a) Mann–Whitney U test results for associations between the IFN- γ level changes after SARS-CoV-2 antigen stimulation in vaccinated patient group ($n = 28$), unvaccinated patient group ($n = 4$), and control group ($n = 7$). (b) Spearman's correlation between the increase in levels of TGF- β 1 after whole-blood stimulation with SARS-CoV-2 spike protein S1 and S2 pool peptides in vaccinated patients ($n = 27$) and control group individuals ($n = 7$). ns—non-significant.

Furthermore, there was no significant correlation between the type of vaccine administered and changes in cytokine levels (see Supplementary Table S3c).

Regarding the cytokine response correlation with time after the last vaccine dose, the only cytokine whose level changed after antigen stimulation correlated with time after vaccination was TGF- β 1 (in the patient group) (Figure 3b and Supplementary Table S6c).

3.6. Associations between the Cytokine Levels and SARS-CoV-2 Humoral Response

We also assessed whether the cytokine response to SARS-CoV-2 antigen stimulation was related to the anti-spike IgG antibody levels. All the relevant statistical data are presented in Supplementary Tables S4 and S6.

No significant correlation was observed between the levels of anti-spike IgG and the increase in cytokine levels following SARS-CoV-2 antigen stimulation in patients with PAD (see Supplementary Table S6c). However, when categorizing patients based on low, moderate, or high anti-spike antibody response, patients with low antibody response exhibited a higher median decrease in TGF- β 1 levels after stimulation with SARS-CoV-2 antigen and compared to patients with a moderate or high humoral response or control group individuals (see Figure 4 and Supplementary Table S4a).

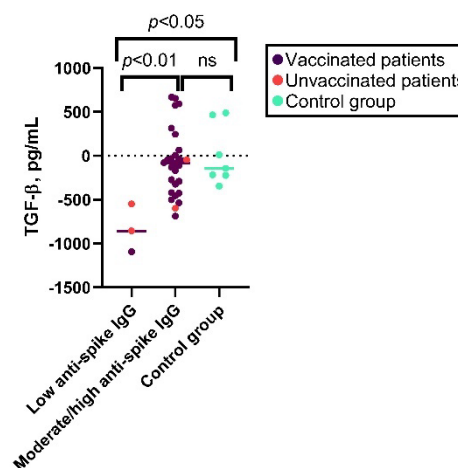


Figure 4. Kruskal–Wallis test results for associations between the levels of TGF- β 1 after SARS-CoV-2 antigen stimulation and SARS-CoV-2 humoral response. Median decrease in levels of TGF- β 1 after SARS-CoV-2 antigen stimulation in patients with low ($n = 3$), moderate, or high anti-spike IgG response ($n = 28$) and controls ($n = 7$). ns—non-significant.

3.7. Associations between the Cytokine Levels and Patient's Demographic and Clinical Characteristics

We also assessed whether there were any correlations between age and cytokine responses to SARS-CoV-2 antigen stimulation as well as any differences in cytokine responses in relation to various clinical manifestations. All relevant statistical data are presented in Supplementary Tables S5 and S6.

In the patient group, age was significantly correlated with changes in the levels of TGF- β 1 and IL-1 β following SARS-CoV-2 antigen stimulation (see Supplementary Table S6a).

Distinct variations were observed in the cytokine profiles when comparing various complications and comorbidities. The Kruskal–Wallis test indicated that there was a significant difference in the median increase in the level of IL-4 and the frequency of detected autoantibodies in personal medical history, while in the control group or patients without autoantibodies, no increase was observed; in patients who had detected autoantibodies in their personal medical history, we found a median 1.26 ng/mL increase in the levels of IL-4

following SARS-CoV-2 antigen stimulation (see Figure 5a and Supplementary Table S5a). Additionally, baseline IL-4 and TNF- α levels were higher in patients with autoantibodies. We found no association between increased cytokine levels, including IL-4, after SARS-CoV-2 antigen stimulation and clinically detectable autoimmune diseases (see Supplementary Table S5a). However, when categorizing patients according to diagnosis, in the CVID group, TGF- β 1 levels were related to the presence of autoimmune disease (see Supplementary Table S5c). An increase in the level of IL-4 following SARS-CoV-2 antigen stimulation, but not the baseline IL-4 level, was also correlated with the levels of total IgG and total IgM (see Figure 6 and Supplementary Table S6c).

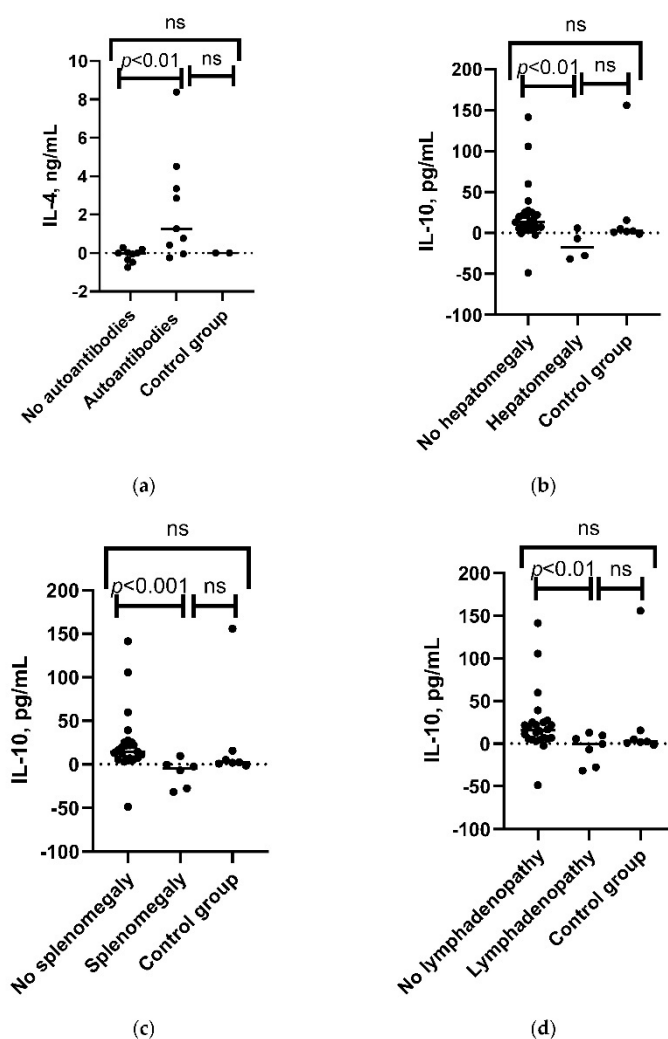


Figure 5. *Cont.*

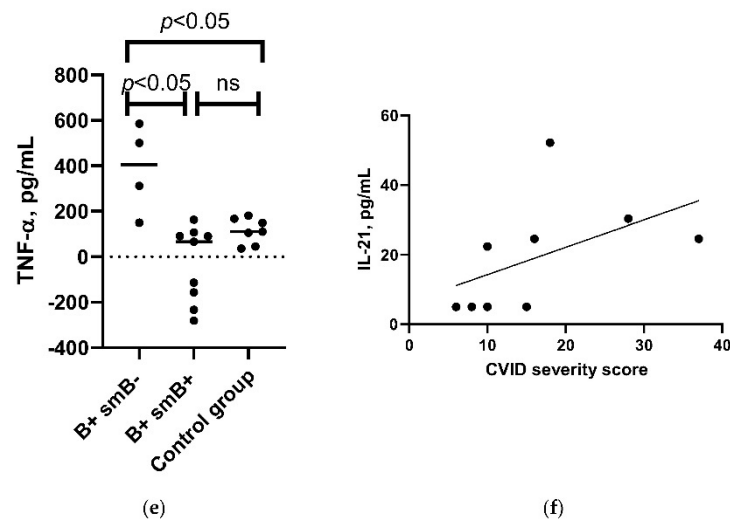


Figure 5. Associations between the IL-4, IL-10, TNF- α , and IL-21 levels and patient's clinical characteristics. (a) Mann–Whitney U test results for associations between IL-4 level changes after SARS-CoV-2 antigen stimulation in patients with detected autoantibodies ($n = 8$), patients without the condition ($n = 8$), and control group ($n = 2$). (b) Mann–Whitney U test results for associations between IL-10 level changes following SARS-CoV-2 antigen stimulation in patients with hepatomegaly ($n = 4$), patients without the condition ($n = 27$), and control group ($n = 7$). (c) Mann–Whitney U test results for associations between IL-10 level changes following SARS-CoV-2 antigen stimulation in patients with splenomegaly ($n = 5$), patients without the condition ($n = 26$), and control group ($n = 7$). (d) Mann–Whitney U test results for associations between the changes in IL-10 level following SARS-CoV-2 antigen stimulation in patients with lymphadenopathy ($n = 7$), patients without the condition ($n = 24$), and control group ($n = 7$). (e) Mann–Whitney U test results for associations between the changes in TNF- α following SARS-CoV-2 antigen stimulation in patients with B+SmB- ($n = 4$), B+SmB+ phenotype ($n = 9$), and control group individuals ($n = 7$). (f) Spearman's correlation between the CVID patients' severity score and increase in levels of IL-21 after whole-blood stimulation with SARS-CoV-2 antigen in CVID patients ($n = 9$). ns—non-significant.

Changes in IL-10 levels after SARS-CoV-2 antigen stimulation were found to be significantly associated with lymphadenopathy, splenomegaly, and hepatomegaly. IL-10 levels decreased after SARS-CoV-2 antigen stimulation in patients with lymphadenopathy, whereas an increase was observed in those without the condition and in the control group. A similar trend was observed for splenomegaly and hepatomegaly, as well as for changes in IL-15 levels and splenomegaly (see Figure 5b–d and Supplementary Table S5a). When categorizing patients based on their diagnosis, a consistent observation of changes in IL-10 levels was found in the CVID group, but not in the SIgAD group, since only one patient with each of these conditions was present in the SIgAD subgroup (see Supplementary Table S5c,d).

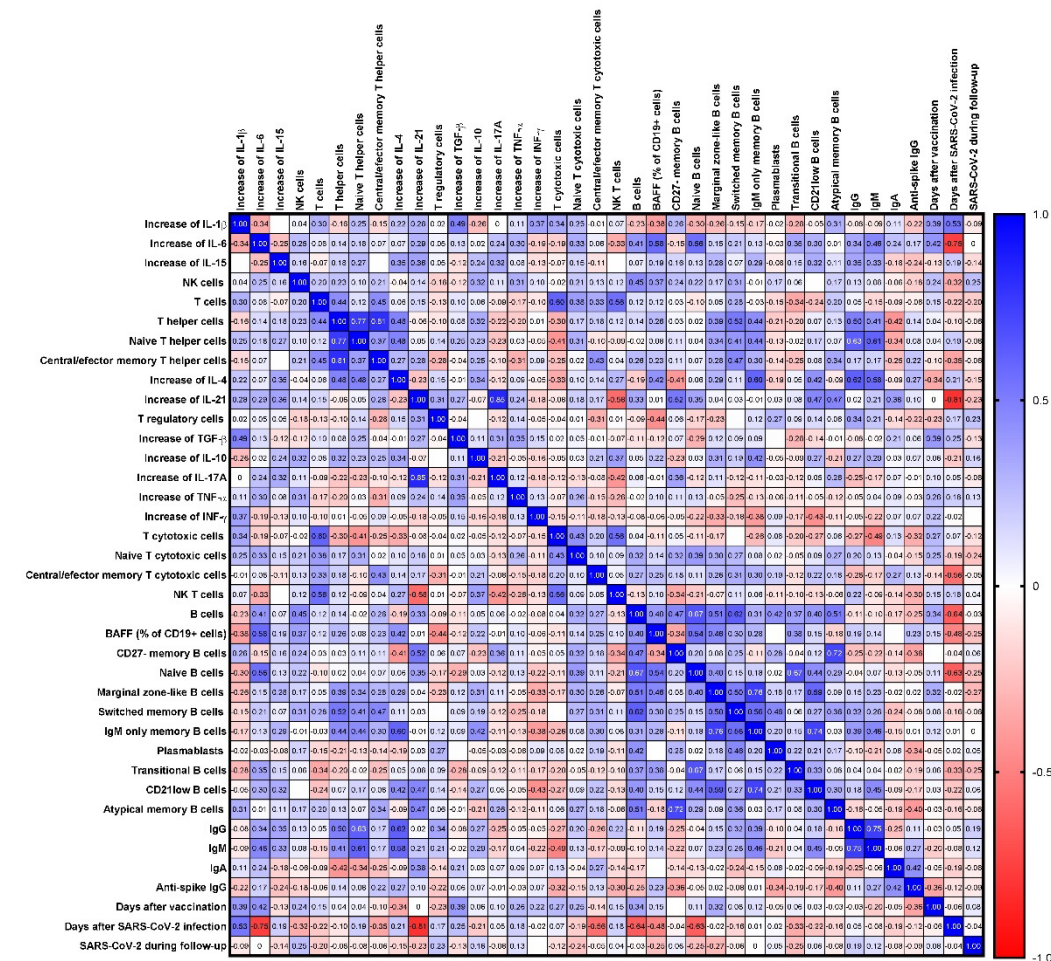


Figure 6. Correlation matrix of the changes in levels of cytokines following SARS-CoV-2 antigen stimulation and immunological parameters. Spearman r values are shown from red (−1.0) to blue (1.0). The absence of an r value in certain blank cells signifies that the corresponding Spearman's correlation coefficient (r) value is 0.

In the CVID patient subgroup, we also assessed the association with the EUROclass classification groups and found a statistically significant difference between the increase in levels of TNF- α after SARS-CoV-2 stimulation; patients with low switched memory B cell percentages (EUROclass group B+SmB-) had a higher increase in TNF- α levels compared to patients with normal switched memory B cell percentages or the control group subjects (see Figure 5e and Supplementary Table S5b). There was only one patient with B- and one patient with CD21_{low} high phenotype and two with transitional cell high phenotype; therefore, the median values for these patients have not been reported.

In the CVID patient subgroup, we assessed a correlation with the CVID severity score, and only spike-induced IL-21 response correlated with the severity of CVID ($r_s = 0.809$, $p = 0.009$, $n = 9$).

3.8. Correlation between the Cytokine Levels and Lymphocyte Subsets

Correlations between changes in cytokine levels following SARS-CoV-2 antigen stimulation and immunological parameters are shown in Figure 6 and Supplementary Table S6.

Overall, we found a significant correlation between the increase in the levels of Th17 cytokines (IL-17A and IL-21) after SARS-CoV-2 antigen stimulation, as well as TGF- β with the pro-inflammatory cytokines IL-1 β and TNF- α (see Supplementary Table S6b). We also observed a correlation between the baseline levels of pro-inflammatory cytokines: IL-1 β correlated with the levels of IL-6 and TNF- α , and IL-6 with TNF- α and IL-10 correlated with IL-4 and IL-15 (see Supplementary Table S6a).

Regarding correlations with lymphocyte subsets, several B cell subsets were correlated with changes in cytokine levels after SARS-CoV-2 antigen stimulation: marginal zone-like B cells and IgM-only memory B cells correlated with changes in IFN- γ and IL-10 levels, while IFN- γ was also correlated with CD21low B cells. Changes in IL-4 levels also correlated with IgM-only memory B cells, CD21low B cells, and T helper cells. Changes in IL-1 β levels were related to total and atypical B cells, whereas changes in IL-6 levels were related to naïve B cells. Natural killer T cells correlated with changes in IL-10, IL-17A, and IL-21 levels. Changes in IL-17A levels also correlated with total T cells and terminally differentiated T cells. Natural killer cells were correlated with changes in IL-17A and TNF- α levels (see Figure 6 and Supplementary Table S6c).

4. Discussion

In this study, we present the spike-specific cytokine response observed after whole-blood stimulation with the SARS-CoV-2 antigen in naturally infected unvaccinated and vaccinated PAD patients and explore the cytokine profile and other immunological parameters as markers for predicting the contraction of COVID-19 infection during the up to 10-month follow-up period.

Overall, we were not able to predict the occurrence of COVID-19 based on the anti-spike humoral response, baseline cytokine levels, changes in cytokine levels following whole-blood SARS-CoV-2 antigen stimulation, or other immunological parameters in patients with PAD. However, patients with higher percentages of cytotoxic T and NK cells showed a lower incidence of COVID-19 during the follow-up period. This finding is consistent with the current understanding that these specific cell types play a crucial role in the antiviral immune response, including that against SARS-CoV-2 [70]. Functional exhaustion of cytotoxic lymphocytes (such as CD8+ cytotoxic T cells and NK cells) has been associated with poor COVID-19 prognosis [33,44], whereas substantial CD8+ T cell responses have been associated with mild COVID-19 disease [71]. Cytokine levels after SARS-CoV-2 antigen stimulation did not prove to be predictive of COVID-19. To the best of our knowledge, there have been no prior studies examining the potential of cytokine levels as predictive markers of occurrence of COVID-19 in patients with PAD; however, previous research conducted on healthy individuals during an 8-month follow-up period following CoronaVac vaccination found that those who exhibited lower levels of IFN- γ in the IFN- γ release assay were at a higher risk of contracting COVID-19 [72]. Similarly, we were unable to predict the likelihood of being infected with SARS-CoV-2 through anti-spike antibody levels, which is consistent with the findings of the COV-AD study [72].

Cytokines that have previously exhibited alterations in their levels following vaccination in immunocompetent individuals include IFN- γ , IL-10, IL-15, IL-17A, IL-1 β , TNF- α , IP-10/CXCL10, IL-6, IFN- α 2, IL-12p70, IL-18, IL-23, and IL-33 [73–78]. Interestingly, in addition to several of the mentioned cytokines, we also observed a decrease in the level of TGF- β 1 following whole-blood stimulation with the SARS-CoV-2 antigen, and this decrease was more prominent in patients who showed a low anti-spike IgG response as well as in COVID patients with an autoimmune disease. The main source of TGF- β 1 is epithelial cells, but it can be produced by most immune cells in response to infection, and it mainly acts as a regulator of multiple types of immune cells, including T regulatory (Treg) cells, NK cells, and macrophages [79]. The TGF- β 1 role in antibody synthesis is mainly

induced by the induction of T regulatory cells to suppress B cells [80,81] and the induction of an isotype switch to mainly IgA1 and IgA2 class antibodies [82]. In a study on the dynamics of adaptive immune response in severe COVID-19 examining the plasmablast transcriptome changes over the course of eight weeks, plasmablasts showed a continuous immune reaction; during the first week, plasmablasts showed an immune response directed against SARS-CoV-2, characterized by the synthesis of IgG antibodies against the spike and nucleocapsid proteins, but later response switched to IgA-expressing plasmablasts, which were not specific to SARS-CoV-2 proteins and reflected continued instruction of the B lymphocytes by TGF- β 1 [82]. In addition, in the upper airways of immunocompetent patients, TGF- β 1 transcript level expression was lower in SARS-CoV-2-infected patients than in controls, and in asymptomatic individuals, TGF- β 1 correlated negatively with IFN- γ , suggesting its role in the regulation of early antiviral inflammatory response [83]. In our cohort, changes in the levels of TGF- β 1 were significantly correlated with the levels of IL-1 β and TNF- α . Indeed, TGF- β 1 can activate nuclear factor-kappa-light-chain-enhancer of activated B cells (NF- κ B), which can further upregulate various cytokines, including IFN- γ , TNF- α , and IL-1 β [84,85]. Further research is warranted to determine the function of TGF- β 1 in the adaptive immune reactions related to COVID-19 in patients with PAD.

This report confirms a higher IFN- γ response to SARS-CoV-2 antigen stimulation in vaccinated PAD patients than in unvaccinated patients who were exposed to the SARS-CoV-2 virus via natural COVID-19, similar to that previously reported in individuals in the general population [74,86], although conflicting evidence exists [87]. In our cohort, we found no difference in the changes in other cytokine levels after SARS-CoV-2 antigen stimulation when comparing vaccinated and unvaccinated patients, although previously in a study with healthy individuals, TNF- α levels in response to stimulation with peptide pools corresponding to the SARS-CoV-2 spike, nucleocapsid, or membrane protein were significantly higher in individuals who had completed a vaccination regimen than in unvaccinated individuals [74]. These differences could be because we only examined cytokine responses to S1 and S2 pools in this study.

We also examined whether the spike-specific cytokine response was associated with any specific non-infectious complications. In this study, we found an association between the magnitude of the increase in IL-4 and the presence of autoantibodies in patients' serum, as well as an increase in IL-4 correlated with total IgG and IgM levels, but not with anti-spike IgG. This finding is in line with a study of COVID-19 patients where excessive plasmablast expansion was correlated with autoantibody production, and these plasmablasts developed according to IL-4- and BAFF-driven developmental trajectories. Although they were not enriched in autoreactive B cells, two distinct memory populations (CD80+/ISG15+ and CD11c+/SOX5+/T-bet+/−) with signs of autoreactivity were identified, which were considered to be the source of COVID-19 autoantibodies [88]. Indeed, the evidence of the development of autoimmune conditions following COVID-19 has accumulated during the past few years [44,89–95]. In addition, we found a correlation between IL-21 and COVID severity score in patients with COVID. Within secondary lymphoid organs, T follicular helper (Tfh) cells are primarily engaged in ensuring B cell survival, proliferation, and differentiation by producing significant quantities of IL-21 and IL-4 [96], and the majority of inborn errors of immunity patients exhibit spike-specific circulating Tfh cells [28]. Regarding COVID and SIgAD patients, association studies suggest that defective IL-4 and IL-21 signaling has been linked to an increased prevalence of non-infectious complications, including autoimmunity [4,97–100].

IL-10 was identified as another cytokine whose increase was associated with a specific patient phenotype. IL-10 is an anti-inflammatory cytokine that is capable of inhibiting the synthesis of pro-inflammatory cytokines and is produced mainly by T cells, especially Treg and Tfh cells, as well as monocytes and B regulatory cells [7]. In our study, the extent of the spike-specific IL-10 response was significantly lower in patients with benign polyclonal lymphoproliferation, manifested as hepatomegaly, splenomegaly, and lymphadenopathy. In the EUROclass trial, splenomegaly was associated with dysregulation of B cell homeosta-

sis, including reduced switched-low memory B cells, which could indicate dysregulated germinal center development [67]. We also observed that the level of the pro-inflammatory cytokine TNF- α was significantly higher in patients with low switched memory B cell counts (EUROclass B+SmB-). Although the cytokine response to SARS-CoV-2 antigen has not been examined previously in the context of non-infectious complications of PAD, the response of circulating Tfh isolated from CVID patients to submitogenic PHA+IL-2 stimulation, as indicated by the intracellular expression of Tfh cytokines (IL-4, IL-10, IL-21), with non-infectious complications (autoimmunity and/or granulomatous disease) was lower than that in patients without these complications. In contrast, the IL-4 response was higher in patients with autoimmunity and/or granulomatous disease [101]. Studies of IL-10 levels without antigen stimulation suggest that low IL-10 production in patients with CVID-like disorders with homozygous deletion of the inducible T cell co-stimulator (ICOS), a key receptor of Tfh help to germinal center B cells, may contribute to the disturbed germinal center reaction in secondary lymphoid organs, and patients with this genetic defect can be associated with splenomegaly [102]. In addition, CVID patients have been shown to have a decreased frequency of naïve regulatory T cells, one of the major sources of IL-10, in CVID patients with splenomegaly [103].

Several major limitations should be considered. First, the sample size was limited due to the rarity of these conditions, which reduced the statistical power and limited the ability to detect significant associations; therefore, the utility of predicting factors should be studied in larger cohorts. Second, the timeframe within the measurements after completion of the immunization schedule was broad in this cohort. Third, whole-blood stimulation has limitations that should be considered: T cell responses are complex, and natural or vaccine-induced T cell stimulation can activate different cell subpopulations and molecular pathways, resulting in distinct functional cytokine expression profiles and clinical outcomes. In addition, we examined only the spike-induced cytokine response, and other SARS-CoV-2 proteins, such as the nucleocapsid or membrane proteins, were not included. The cytokine IL-2 was not included in the analysis due to technical reasons. Therefore, it is possible that predicting vaccine-induced or natural protection may be more accurate if we consider the activation of T cells that express different cytokines or activation markers in addition to those currently being examined. In addition, there is a limitation in comparing our results with those of other studies, because the methods of investigation vary significantly between studies.

5. Conclusions

No significant association was observed between spike-specific cytokine response, anti-spike IgG levels, or other relevant factors and the likelihood of contracting COVID-19. Similar to the healthy control groups, the most distinct difference between vaccinated and naturally infected unvaccinated patients with PAD was the higher increase in IFN- γ levels in the vaccinated patients.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/v15051146/s1>. Table S1. Changes in cytokine levels following SARS-CoV-2 stimulation. Table S2. Predictors of COVID-19 during the follow-up period in PAD patients. Table S3. Associations between the cytokine levels and previous SARS-CoV-2 vaccination. Table S4. Associations between the changes in cytokine levels following SARS-CoV-2 antigen stimulation and SARS-CoV-2-specific humoral response. Table S5. Associations between the cytokine levels and patient's demographic and clinical characteristics. Table S6. Spearman correlation analysis.

Author Contributions: Conceptualization Z.L., B.S. and N.K.; methodology, B.S., Z.L. and N.K.; formal analysis, Z.L.; investigation, G.G., Z.L., S.P., N.K. and B.S.; resources, N.K., G.G., P.T. and L.G.; data curation, Z.L.; writing—original draft preparation, Z.L.; writing—review and editing, B.S., G.G., S.P., L.G., P.T. and N.K.; visualization, Z.L.; supervision, N.K., L.G. and P.T.; project administration, N.K.; funding acquisition, N.K. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

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Article

COVID-19 Vaccination Coverage and Factors Influencing Vaccine Hesitancy among Patients with Inborn Errors of Immunity in Latvia: A Mixed-Methods Study

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Abstract: Background: The European Society for Immunodeficiencies recommends that all patients with inborn errors of immunity (IEI) without contraindications should receive SARS-CoV-2 vaccination. The aim of this study was to investigate the reasons that discourage IEI patients from receiving the recommended vaccination and to assess vaccination coverage among IEI patients in Latvia. Methods: In this multicenter mixed-methods study, the vaccination status of all patients with IEI within two tertiary centers in Latvia was reviewed using electronic health records. Semi-structured interviews were conducted with 16 IEI patients who did not undergo vaccination, and a thematic analysis was performed. Results: A total of 341 patients (49.3% female; median age 19.7 years (IQR:17)) were included in the quantitative part. The proportion of fully vaccinated individuals aged ≥ 12 years was 66.8%–70.9% with patients with selective IgA deficiency and 58.8% with other IEI ($\chi^2 = 14.12, p < 0.001$). The proportion of fully vaccinated individuals aged 5–11 years was 11.1%. Age was associated with vaccination status: younger patients were found to have a significantly lower likelihood of receiving vaccination ($U = 8585, p < 0.001$). The five main themes identified were as follows: (1) fear and uncertainty; (2) risk and benefit assessment: COVID-19 vaccine—is it worth it? (3) external influences: the dark horse of the decision-making—people around us; (4) individuals against the system; and (5) beliefs about vaccination and COVID-19. Under-representation of certain IEI groups and recall bias are possible limitations of this study. Conclusions: While most reasons for hesitancy were similar to those previously described in the general population, disease-specific concerns were also identified.

Keywords: vaccine hesitancy; vaccination coverage; COVID-19 vaccine; SARS-CoV-2 vaccine; inborn errors of immunity; primary immunodeficiencies; Latvia

1. Introduction

Inborn errors of immunity (IEI) encompass a diverse collection of inherited disorders characterized by defects in various parts of the immune system [1]. The defining characteristic of these disorders is immunodeficiency, which translates to increased susceptibility to infectious agents, with the specific causative agents varying depending on the particular diagnosis [2]. Although definitive treatment options, such as stem cell transplantation or gene therapy, for certain IEIs may be feasible, only supportive interventions such as lifelong immunoglobulin replacement therapy and biological or antimicrobial therapy are currently available for the majority of patients. Therefore, comprehensive management also requires a significant focus on infection prevention, where vaccination plays a pivotal role [3].

At the beginning of the coronavirus disease 2019 (COVID-19) pandemic, individuals with specific IEI were assumed to be more susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and experience more severe presentation compared to the general population [4–6]. Therefore, after vaccines became available, the European Society for Immunodeficiencies (ESID) recommended that all IEI patients devoid of contraindications should receive vaccination with any of the accessible vaccine formulations according to their national vaccination schedule to include primary courses and booster doses of vaccination, provided that they are not live vaccines for those in whom it would be contraindicated. Patients who were infected with SARS-CoV-2 and recovered were still recommended to be vaccinated against SARS-CoV-2 [7].

According to the World Health Organization's (WHO's) strategic advisory group of experts on immunization, vaccination hesitancy can be defined as a "delay in acceptance or refusal of vaccination despite availability of vaccination services" [8], and it was identified as one of the top ten global health threats already prior to the COVID-19 pandemic [9]. While vaccine hesitancy itself is a well-known phenomenon, it would be tempting to assume that patients who are aware of their defective immune system would automatically accept safe and recommended SARS-CoV-2 vaccines, since the assessment of the potential threat of COVID-19 is described as a motive for the intention to vaccinate [10]. However, an initial ambivalent attitude toward SARS-CoV-2 vaccination has been reported among some IEI patients due to limited data on vaccine efficacy and safety specific to this population [11], despite recommendations from specialists [7]. Nevertheless, when subsequent investigations were undertaken to assess the effectiveness and safety of vaccines specifically within this patient group, the reported safety data were reassuring [12–14]. Notably, although certain IEI groups have displayed diminished antibody responses against SARS-CoV-2 vaccination, the potential advantages of vaccination were deemed superior to the associated risks [15–18]. Furthermore, it is noteworthy to mention that T-cell immune responses in these patients remained largely unimpaired, highlighting the benefits of vaccination even if patients fail to mount a sufficient measurable antibody response [13,16,19–22].

Nevertheless, there have been cases in which patients declined vaccination or refrained from vaccinating their children against SARS-CoV-2, despite the inherent vulnerability of these individuals to various infectious diseases. Could the rationale underlying vaccine refusal in this patient population differ from those prevalent among the general population or patients with other chronic diseases? While several extensive studies have examined reasons for vaccination hesitancy among the general population [23–25] or other chronic diseases, such as autoimmune diseases [26–33] or cancer [34–36], data regarding reasons for the hesitancy of patients affected by inborn errors of immunity to accept vaccination against SARS-CoV-2 infection are limited. Few studies have addressed the reasons for vaccination hesitancy in this patient group, none of which had a qualitative design [11,37,38]. We hypothesized that employing a qualitative approach might uncover novel factors contributing to vaccination hesitancy, which may not have been previously documented in the general population or anticipated through researcher-designed multiple-choice queries and could be distinctive to individuals with IEI. Notably, a multinational study concluded that hesitancy to vaccinate was more prevalent in Eastern European countries than in Western Europe or North America [37]. The aim of this study was to investigate the reasons that discourage IEI patients from receiving the recommended SARS-CoV-2 vaccination and to assess vaccination coverage among IEI patients in Latvia.

2. Materials and Methods

2.1. Design

In this mixed-methods study, to assess vaccination coverage among patients with IEI and identify individuals who had not received vaccination against SARS-CoV-2, data regarding the SARS-CoV-2 vaccination status of all patients diagnosed with IEI in Latvia were extracted. Additionally, to gain insights into the reasons behind vaccination hesitancy, a qualitative approach employing thematic analysis of transcripts from semi-structured interviews was used. Qualitative methods in health care are commonly employed to

gain deeper insights into complex psycho-social phenomena, rather than ‘measure’ them. It is widely regarded as the most suitable research approach for investigating human experiences, beliefs, and perceptions [39]. In this study, quantitative and qualitative data were analyzed separately and merged in the discussion.

2.2. Quantitative Study

2.2.1. Study Population

Data were sourced from the only tertiary centers in Latvia, where immunologists consult (both children and adults): Children’s Clinical University Hospital and Pauls Stradins Clinical University Hospital. All patients diagnosed with IEI at these two facilities comprised the study population. Data were extracted from patient health records and included the following: age, gender, clinical diagnosis, treatment, and SARS-CoV-2 vaccination status. The diagnosis of IEI was based on the ESID diagnostic criteria [40]. Clinical diagnoses were classified according to the International Union of Immunological Societies (IUIS) classification [2].

2.2.2. Statistical Analysis

Data related to demographic and clinical indicators were analyzed using descriptive statistics and parametric/non-parametric analysis, as appropriate. The Shapiro–Wilk test was used to determine whether continuous variables were normally distributed. The results indicated that the age data were not normally distributed; therefore, medians and interquartile ranges (IQRs) were used in data presentation, and nonparametric statistical methods were used in subsequent analyses. The differences in categorical variables were examined using the Chi-square and Fisher exact tests. The Mann–Whitney U was used to compare continuous variables between two groups. Statistical significance was set at p value < 0.05 . Statistical analysis was performed using IBM SPSS Statistics version 29 (IBM, New York, NY, USA).

2.3. Qualitative Study

2.3.1. Study Population and Sample

A purposive maximum variation sampling strategy [41] was used to recruit patients, representing diverse demographic parameters (age group and gender) and a variety of diagnostic groups according to the IUIS classification. The sample consisted of both adult patients with IEI and parents of children with IEI who were eligible for vaccination, and none of the patients had received any SARS-CoV-2 vaccine.

2.3.2. Data Collection

Semi-structured interviews were used for qualitative data collection. The one-on-one semi-structured interview method allows the researcher to set an agenda in terms of the topics covered, while also allowing participants the freedom to express themselves openly. Therefore, it represents the optimal method for gathering data on individuals’ perspectives, beliefs, and perceptions regarding sensitive topics [39]. The semi-structured interview protocols (see Supplementation S1) were designed following a literature review and were grounded in the Health Belief Model (HBM), a theoretical model that attempts to explain why certain health behaviors are adopted, such as preventive health and vaccine use [42]. The HBM contains six constructs: encompassed perceived susceptibility (assessing the risk of becoming ill), perceived severity (evaluating the seriousness of the illness or unwanted potential consequences), perceived barriers (analyzing the influences that discourage adoption of vaccination), perceived benefits (appraising the positive outcomes associated with vaccination), cues to action (events, people, or things that trigger the behavior change), and self-efficacy (confidence and belief in the ability to perform a behavior) [42]. The main emphasis was on the “barriers” construct, and questions exploring the “self-efficacy” construct were not included, since we did not predict that this issue would be the driving force that would retrain immunodeficient patients from vaccination, as they were not

reported by previous studies in IEI patients [11,37,38]. Additionally, the input was gleaned from validated vaccine hesitancy evaluation instruments and explanatory models [43–48], as well as insights gained from a pilot interview. Interview questions were offered to participants in two languages, Latvian and Russian, to facilitate effective communication.

Eligible patients were contacted via telephone, and upon obtaining their consent to participate in the study, the interviews were conducted via telephone call. With the participants' consent, the interviews were audio-recorded and transcribed verbatim for analysis. After the transcription of the interviews, each patient was assigned a code that was used throughout the study to guarantee anonymity. Interviews were conducted from April to August 2023 by one member (Z.L.) of the authoring team at a time chosen by each participant and lasted from 7 to 55 minutes (average time—20 minutes). The interviews with these patients continued until a point of data saturation was reached, signifying that no new unique themes emerged during the final two interviews.

2.3.3. Data Analysis

The interview transcripts were analyzed using NVivo plus version 12 (Lumivero, Denver, CO, USA). A thematic inductive analysis with 'open coding' was performed on the transcripts of the interview data. The basis of thematic analysis is to reduce the complexity of the data by looking for patterns or "themes" in the data [39,49,50]. In the thematic analysis, six phases according to Braun and Clarke [49] were adopted: (1) familiarization with the data, (2) generating initial codes, (3) searching for themes, (4) reviewing themes, (5) defining and naming themes, and (6) producing the report. In the process of thematic analysis, we scrutinized the coded data and observed that certain codes exhibited a pattern, and these codes were systematically grouped into overarching themes that conveyed insights relevant to the research question. The initial themes were then reviewed, modified, and refined to "identify the 'essence' of what each theme is about" [49]. Data analysis was performed independently by two members of the authoring team, Z.L. and K.S. Both authors coded four interviews independently and then met to discuss the initial codes, overarching themes, and disparities in analysis, which were discussed until a consensus was achieved. To ensure the rigor and accuracy of the analysis, the researchers were consulted by an experienced researcher with a background in qualitative research. The authoring team engaged in a collaborative process to review and enhance the identified themes and subthemes.

2.3.4. Ethics Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was part of a study reviewed and approved by the Central Board of the Ethics Committee of the Health Ministry of the Republic of Latvia (No. 01-29.1/2878). All participants read and understood the informed consent that included information about the study, including its purpose, procedures, potential risks, and benefits, before agreeing to participate in the study; they also had an opportunity to ask any questions, which were answered by our team members. All participants provided a written form of consent prior to the interviews. They were assured of their complete anonymity and confidentiality. To safeguard their privacy, all identifiable information was carefully removed. Additionally, all data collected in this research were securely stored and accessible only to the research team. Participants were also informed that participation was completely voluntary and that they had the right to withdraw from the study at any point without facing any negative consequences.

This study adhered to the Standards for Reporting Qualitative Research guidelines (COREQ) [51].

3. Results

3.1. Quantitative Findings

3.1.1. Population Characterization

In the present study, a cohort of 341 patients was analyzed to assess vaccination rates among individuals with IEL. The median age was 19.7 years (IQR: 17; range: 0–78 years), 49.3% were female, and 44.2% were pediatric patients (see Table 1). Most of the patients living with IEL were diagnosed with predominantly antibody deficiency (64.2%), followed by combined immunodeficiency with syndromic features (17.6%). The majority of the patients (57.2%) were diagnosed with selective IgA deficiency (SIgAD). In the SIgAD group, the median age was 22 years (IQR: 15 years; range: 5–78 years), 43.1% were female, and 31.3% were pediatric patients. In the group of 146 patients with IEL other than SIgAD, the median age was 15.1 years (IQR: 19.5; range: 0–72 years), 57.5% were female, and 61.5% were pediatric patients.

Table 1. Demographic characteristics, treatment, and vaccination coverage in different IEL categories according to IUIS classification.

IEL Category	Total Number of Alive IEL Patients	Age Group Pediatric/Adult	Receives Immunoglobulin Replacement Yes/No	Vaccination Status Yes/No/Non-Eligible for Vaccination */No Information
Immunodeficiencies affecting cellular and humoral immunity	4	4/0	2/2	0/2/2/0
Combined immunodeficiencies with associated or syndromic features	60	53/7	2/58	11/33/16/0
Predominantly antibody deficiency Of those, SIgAD	219 195	65/154 61/134	21/198 0/195	131/70/0/18 115/62/0/18
Diseases of immune dysregulation	4	3/1	2/2	1/3/0/0
Congenital defects of phagocyte number or function	18	10/8	0/18	5/10/1/2
Defects in intrinsic and innate immunity	4	3/1	2/2	2/0/2/0
Autoinflammatory disorders	12	9/3	0/12	4/6/0/2
Complement deficiencies	11	1/10	0/11	6/5/0/0
Bone marrow failure	6	1/5	0/6	5/0/1/0
Phenocopies of inborn errors of immunity	1	0/1	1/0	1/0/0/0
Unclassified immunodeficiency	2	2/0	0/2	0/1/0/1
Total	341	151/190	30/311	166/149/3/23

* Patients younger than 6 months old or SCID patients with elective hematopoietic stem cell transplantation.

3.1.2. Vaccination Coverage

Of all patients with an IEL ≥ 12 years and for whom information regarding vaccination status was available ($n = 238$), 66.8% were vaccinated (see Table 2). In the age group of 5–11 years, of the 54 patients for whom the information was available, 11.1% had received the vaccination, while in the age group of 6 months to 5 years none of the patients had received the vaccination. In the patient group aged ≥ 12 years, age was significantly associated with vaccination status, and younger patients were found to have a significantly lower likelihood of receiving vaccination ($U = 8585$, $p < 0.001$). This association between vaccination status and age was not observed if analysis was conducted in the adult group separately. No association was found between the vaccination status and gender.

Data from SIgAD patients and patients with more severe IEL were also analyzed separately because of the specific characteristics and milder phenotype of SIgAD that distinguish it from other types of IELs. The results of the Chi-square test revealed a

significant association between diagnosis (SIgAD or other IEI) and vaccination status ($\chi^2 = 14.12$, $p < 0.001$). Cramer's V indicated a small effect size ($V = 0.21$) for this association.

Of the SIgAD patients ≥ 12 years of age and for whom information regarding vaccination status was available ($n = 158$), 70.9% were vaccinated, while in the age group of 5–11 years ($n = 19$), this number was 15.8%.

Of all other IEI patients aged ≥ 12 years and for whom vaccination status was available ($n = 80$), 58.8% had received SARS-CoV-2 vaccination, while in the age group of 5–11 years ($n = 35$), this number was 8.6%. After controlling for age, vaccination status was not found to be associated with immunoglobulin replacement therapy.

Table 2. Vaccination coverage comparison between the Latvian general population, SIgAD, and other IEI patients in different age groups.

Age Group, Years	Latvian General Population, % Vaccinated [52]	Selective IgA Deficiency Patients, % Vaccinated	Other IEI Patients, % Vaccinated
12–19	68	51.0	26.5
20–29	81	82.8	72.2
30–39	77	80.0	90.9
40–49	79	70.0	60.0
50–59	81	80.0	83.3
60+	71	60.0	75.0
Total	68%	70.9%	58.8%

3.2. Qualitative Study

3.2.1. Study Sample Characterization

Seventeen patients were invited to participate in the interviews, and one refused. Finally, sixteen participants were included in the qualitative study (see Table 3); nine of these were parents of children with IEI, whereas six were adult patients with IEI. Six patients were male and ten female. Four of sixteen patients were receiving immunoglobulin replacement therapy.

Table 3. Clinical and demographic characteristics of interview participants.

Code	Interviewee	Diagnosis Group	Receives Immunoglobulin Replacement	Gender of the Patient	Age Group of the Patient, Years
IEI1	Parent	Combined immunodeficiencies with associated or syndromic Features	No	F	5–11
IEI2	Parent	Predominantly antibody Deficiency	Yes	M	5–11
IEI3	Parent	Predominantly antibody Deficiency	No	M	5–11
IEI4	Parent	Diseases of immune Dysregulation	Yes	M	12–18
IEI5	Parent	Predominantly antibody Deficiency	Yes	M	5–11
IEI6	Parent	Predominantly antibody Deficiency	No	F	12–18

Table 3. *Cont.*

Code	Interviewee	Diagnosis Group	Receives Immunoglobulin Replacement	Gender of the Patient	Age Group of the Patient, Years
IEI7	Patient	Predominantly antibody Deficiency	Yes	F	40–60
IEI8	Parent	Combined immunodeficiencies	No	F	12–18
IEI9	Patient	Predominantly antibody Deficiency	No	F	>60
IEI10	Patient	Complement deficiency	No	F	19–40
IEI11	Parent	Combined immunodeficiencies with associated or syndromic Features	No	F	5–11
IEI12	Patient	Predominantly antibody Deficiency	No	F	19–40
IEI13	Parent	Autoinflammatory disease	No	F	12–18
IEI14	Patient	Predominantly antibody Deficiency	No	M	40–60
IEI15	Patient	Complement deficiency	No	F	40–60
IEI16	Parent	Combined immunodeficiencies with associated or syndromic Features	No	M	12–18

3.2.2. Findings of Thematic Analysis

Inductive thematic analysis revealed five themes and twelve subthemes for reasons that increment vaccination hesitancy or refusal (see Table 4). Identified themes (5) and subthemes (12) are described below, with participant quotations translated into English and identified by participant code. For the majority of patients, vaccination hesitancy was influenced by a combination of interconnected and mutually reinforcing reasons. Most patients reported fear and a higher perception of risks associated with vaccination (health concerns) and/or a low perception of benefits (possibly impaired immune response to vaccination) that drove them toward hesitant attitudes about vaccination. This risk/benefit evaluation was influenced by several external and internal factors, such as influences from other people's opinions, mistrust, personal beliefs about vaccination and COVID-19, and negative personal experiences.

Table 4. Themes and subthemes of factors that influence vaccination hesitancy among IEI patients in Latvia.

Themes	Subthemes
1. Fear and uncertainty	Fear Too many unknowns
2. Risk and benefit assessment: COVID-19 vaccine—is it worth it?	Concerns about negative outcomes Doubts about the positive effect Overall lack of confidence in the vaccine
3. External influences: The dark horse of the decision-making—people around us	Stories of health problems after vaccination Public figures and doctors against vaccination
4. Individuals against the system	The right to choose Mistrust General disbelief of official information
5. Beliefs about vaccines and COVID-19	Beliefs about vaccines in general Beliefs about COVID-19 and its vaccine

3.3. Theme 1. Fear and Uncertainty

Fear and uncertainty appeared to play an important role in shaping participants' decision-making about the SARS-CoV-2 vaccination, with some individuals citing these factors as the primary reasons for their refusal of the vaccine.

3.3.1. Fear

Notably, fear as a key emotion was mentioned by many participants. Mainly, participants expressed unspecified fear of vaccination.

"But even now I would not like to vaccinate him, because I am afraid, because I am afraid of some kind of reaction and that something will be bad." (IEI2)

Among those who could identify the source of their fear, predominant factors included health concerns, as well as a fear of death.

"Fear of dying. I want to live a little longer." (IEI14)

3.3.2. Too Many Unknowns

Uncertainty regarding the overarching pandemic context emerged as a recurrent theme within interviews. While not necessarily mentioned as a direct reason for vaccine refusal, it appeared as a closely linked theme alongside vaccine hesitancy. Some participants emphasized the feeling of confusion, not knowing what to consider to be true and what a myth.

"All of those horror stories somehow influence the psyche.. yes.. because the contrary information is not that much. Where is the truth—no one really knows." (IEI5)

3.4. Theme 2. Risk and Benefit Assessment: COVID-19 Vaccine—Is It Worth It?

A diminished perception of possible benefits in combination with intense health-related concerns led certain participants to perceive the risks associated with vaccination as outweighing its potential benefits.

"Well, yes, there are advantages, but there are more disadvantages than advantages." (IEI14)

3.4.1. Concerns about Negative Outcomes

The majority of participants expressed some concern regarding vaccination-associated health issues, encompassing both known adverse effects and potential long-term consequences that may still remain uncertain.

"All those listed side effects.. For example, I feel like I will get them all at once. Perhaps, it is better not to get vaccinated. For example, a blood clot formation [can occur]. I simply believe that I don't need it." (IEI12)

Concerns regarding the possibility of disease exacerbation following SARS-CoV-2 vaccination appeared to be a recurrent theme among participants.

"Well, in general, it could be that things go smoothly, but maybe something with the immunity goes wrong again, not as it should be." (IEI8)

3.4.2. Doubts about the Positive Effect

Participants, mainly in the predominantly antibody deficiency diagnosis group, had low expectations that there would be a desired effect after vaccination since they were informed that antibody responses following vaccination may be impaired.

"Well, one thing is that I may not have the antibodies after vaccination anyway." (IEI14)

Another reemerging theme was doubting the necessity of vaccination because a vaccinated person can also get infected. Several participants mentioned stories from their immediate social circles where unvaccinated people did not get infected or had milder symptoms of COVID-19 than vaccinated people.

"I had a wedding, we were 10 people, and 5 of them got sick. Of those who became sick—3 them were very ill, and all three were vaccinated three times. The other two, who were not vaccinated, were me and my husband. We did not feel anything. And we all just

got tested, and it turned out that half got sick and half didn't, and even those who were not vaccinated didn't get sick." (IEI10)

3.4.3. Overall Lack of Confidence in the Vaccine

Several participants expressed concerns and skepticism about the science behind the SARS-CoV-2 vaccination. They emphasized that SARS-CoV-2 vaccines are understudied and too novel to be used, particularly for patients with immune system diseases. Even though some participants displayed a general lack of confidence in all vaccines, the prevailing attitude among most of the participants was skepticism, which was focused primarily on SARS-CoV-2 vaccination.

"Well, there are vaccinations where you have to see what the vaccine is, because untested vaccines and vaccines that have just started to be used, if they have not yet evolved over time, they are difficult for people like me." (IEI15)

3.5. Theme 3. External Influences: The Dark Horse of the Decision-Making—People around Us

As one of the major themes, the opinions and stories of other people were mentioned as an important factor in making the decision about vaccinating against SARS-CoV-2.

3.5.1. Stories of Health Problems after Vaccination

Numerous participants recalled stories about different health problems that appeared after vaccination against SARS-CoV-2. Some participants shared stories from family members or close friends and others from distant sources. All of them, with various degrees of certainty, expressed the opinion that negative health outcomes were due to vaccination.

"My daughter's best friend's stepfather died within a month [after vaccination], he developed stomach cancer, which was not diagnosed before, right? I'm surrounded by [cases similar to these]—if you think about it, I could write a book here." (IEI15)

"And then my husband got one vaccine, and that's it. After that, he had a gout flare approximately two weeks later. It was something that he had experienced only once in the past, and now it's happening very frequently to him, for instance." (IEI10)

3.5.2. Public Figures and Doctors against Vaccination

Several participants noted that hearing public figures and doctors being against vaccination made them doubt it as well. Most commonly, polarized opinions among the medical community were mentioned. For some participants, doubts about the necessity of the SARS-CoV-2 vaccination were influenced by their attending physician or other specialists.

"And also, as government officials expressed: 'I didn't vaccinate my daughter because then she might be at risk of not having children.'" (IEI3)

"One person says one thing, another says another, and it's the same with the COVID vaccination—some say it's not necessary, even a couple of doctors told me it's better not to risk, while others say it's definitely needed, and it seems that no one really knows for sure." (IEI10)

3.6. Theme 4. Individuals against the System

Another major theme was a collision of individual thoughts and wishes and the narrative of governmental and healthcare institutions.

3.6.1. The Right to Choose

Numerous participants emphasized the feeling that the vaccination was forced on them, leaving them with a sense of their autonomy regarding their bodily choices being constrained.

"I believe that everyone is responsible for their own body. Everyone has a choice of whether to get vaccinated or not. But when they imposed all this foolish coercion, it further diminished any trust in the whole [vaccination process]." (IEI12)

"I am precautionary of the fact that, let's say, I had a colleague of mine, she had an oncological disease, by the way, she did not cope with the disease [COVID-19], but she was an anti-vaccination. Yes, she died in the end, yes, but at least she stayed with her own opinion." (IEI16)

Some reported that the compulsory vaccination campaign created more resistance to the SARS-CoV-2 vaccination and that they would have considered it if it had not been mandatory.

"I don't think people need to be forced. Here is the vaccine to do for those who want to do it, who does not want to do it should not be forced. So I think that this is what they can say so they forced it wrong. They made more resistance with this, maybe I would even go if they didn't force me so much." (IEI2)

3.6.2. Mistrust

Mistrust emerged as a prominent theme in the interviews and was manifested at different levels. Some participants expressed skepticism about the interests behind vaccines and about the vaccine developers and pharmaceutical companies. Notably, this sense of distrust extended to the healthcare system and governmental institutions, with mutual influence observed among different levels and types of mistrust.

"[I obtain the information] from the Disease Prevention and Control Centre, etc. [The information] from the government—I don't trust it." (IEI5)

"Most likely, us, ordinary people, do not have a deep understanding—is it really as the doctors say?" (IEI6)

3.6.3. General Disbelief of Official Information

Some participants expressed disbelief and doubts about the truthfulness of publicly available information about COVID-19, vaccination against it, or vaccination in general. They mentioned the pandemic and vaccination being a fraud.

"[laughs] Well, I think it was not even a real illness. Just some kind of virus. Everyone just said COVID, COVID." (IEI1)

"Now I am starting to read some publications on the Internet, that it was some kind of scam with these COVID vaccinations. They write that they are now revealing with these pharmaceutical companies and governments, they are involved in a scam" (IEI7)

3.7. Theme 5. Beliefs about Vaccines and COVID-19

Throughout interviews, different types of beliefs about vaccines or COVID-19 emerged as one of the contributing factors in the decision-making process of whether to get vaccinated both in general and particularly against SARS-CoV-2.

3.7.1. Beliefs about Vaccination in General

Different beliefs related to vaccination emerged in the interviews that were stated as some of the reasons for their unwillingness to vaccinate. Some participants mentioned that vaccines "weaken" or "overstimulate" the immune system, while others mentioned that vaccination is not necessary for treatable diseases, or might cause autism.

"My son, too, had whooping cough after being vaccinated. At the age of 14 he had whooping cough. He was treated, we managed without a hospital, but there was a strong cough, there was a very strong cough. I think that it is not necessary to be vaccinated against it, since it can be treated with medication, and those diseases that are not treatable, it seems to me that maybe it's worth getting vaccinated." (IEI7)

Also, disease-specific beliefs were mentioned, such as that vaccinations are contraindicated for rare diseases or that previous vaccinations may have been the cause of immunodeficiency itself. Some participants shared the belief that receiving immunoglobulin replacement therapy was sufficient for immunity and, therefore, did not need the vaccine.

"First and foremost, I have children for whom vaccination is not allowed at all. They have rare diseases, and they must not receive anything like that at all." (IEI11)

“Well, somehow it seems to me that vaccines are not good for him. I think they may be dangerous. And plus, if immunoglobulins give him everything he needs for protection, then why would he need it?” (IEI2)

3.7.2. Beliefs about COVID-19 or the Vaccine against It

Some participants expressed the belief that COVID-19 was not a severe disease, also mentioning examples of immunodeficient people who had mild or no symptoms.

“When my child got sick with COVID for the first time, I thought I would lose him, but during all 3 times when he was sick, he didn’t even have a fever. How can you have such a disease, if you don’t even have lungs to breathe, where the smallest thing could hurt you, and you get COVID, but you have nothing [from the clinical symptoms]?” (IEI4)

Other participants talked about different reasons why they thought that the vaccination was not necessary in their particular situation, for example, after being infected with COVID-19 or substituting vaccination with isolation from others.

“But she hasn’t been vaccinated because we didn’t make it on time, and now it doesn’t make sense. Because she was sick all the time. That period when I thought, well, let’s do it, then she got sick for the second time—she was infected with COVID without vaccination, so we thought we would wait for that period, that we didn’t need to vaccinate yet. And then there was the second episode. But this time, of course, in much milder form.” (IEI6)

4. Discussion

This study is the first to employ qualitative interviews to gain a more comprehensive understanding of the motivations underlying IEI patients’ decisions to decline vaccination, as well as access to vaccination coverage among IEI patients in Latvia. In this study, the proportion of fully primary-vaccinated individuals above 12 years of age was 66.8%, which is similar to that in the Latvian general population (68%) [52]. The main themes identified behind the vaccination hesitancy were as follows: (1) fear and uncertainty, (2) risk and benefit assessment: COVID-19 vaccine—is it worth it? (3) external influences: the dark horse of the decision-making—people around us, (4) individuals against the system, and (5) beliefs about the vaccination and COVID-19.

Previous studies in the general population have shown that sociodemographic factors, such as gender, education level, race, and ethnicity, are the most prominent factors associated with the intention to use SARS-CoV-2 vaccines [25,44]. Concerning demographic factors within the IEI group, an extensive cross-national analysis involving 40 countries revealed a linkage between female gender and greater vaccine hesitancy [37], while findings from a study conducted in Poland indicated that unvaccinated individuals were more likely to possess primary or vocational education [38]. In this study, unlike in previously mentioned IEI cohorts, age was associated with vaccination status; however, this difference can be ascribed to the predominance of pediatric cases within our cohort, where the median age was 19.7 years, contrasting with the median ages of 42–47 years in other cohorts [37,38].

While the overall vaccination rate was comparable to that in the general population, after excluding SIgAD patients, vaccine coverage in the IEI group other than SIgAD patients above 12 years of age was 58.8%, which is lower than that in the general population in Latvia. This contrasts with other studies, where the reported vaccine acceptance rate was higher in IEI patients compared to the general population [11,37,38], while the share of SIgAD patients in these cohorts was much lower (0.006%–6.9% of all included patients [37,38] vs. 57.8% in our study group). Furthermore, the qualitative analysis revealed that, in addition to universal vaccine refusal reasons, such as concerns about adverse effects, patients with IEI also had disease-specific concerns. This may have contributed to a heightened perception of vaccination as a threat, as compared to individuals in the general population. Interestingly, another study in the Latvian general population revealed that perceived vulnerability was not identified as a factor related to SARS-CoV-2 vaccination [45], unlike in other countries [24]. This is consistent with our finding that the vaccination rate in patients with the most vulnerable immune system was the lowest.

Previous studies in patients with IEI have reported uncertainty regarding whether an immune response can be mounted as the most common reason. This primary concern was then followed by concerns about allergic reactions, still unknown vaccine side effects, or post-vaccination disease flares [11,37]. Both the identified themes, namely, concern about vaccine efficacy given the immunodeficiency state, as well as concern about negative health outcomes, were also represented in our study group. In addition, although fear was a frequently mentioned theme in our study group, participants mainly expressed fear of the SARS-CoV-2 vaccination and not the virus, although the majority of patients considered COVID-19 to be a severe illness. This prioritization of fear over vaccine-related risks compared to the fear of COVID-19 has been reported previously in the general population [53], and it can be understood through the HBM constructs, including perceived susceptibility, severity, benefits, and barriers [42].

Several external and internal influences that shape IEI patient attitudes and behaviors have been described in previous studies, including advice from healthcare providers, skeptical viewpoints of the science behind the SARS-CoV-2 vaccine, and mistrust in the medical system in general [11]. In previous studies, for most patients, the concerns were SARS-CoV-2 vaccine-specific, while only 1.7–4.7% expressed mistrust in vaccines in general [11,37]. Themes such as external influence by their healthcare provider or other authorities, mistrust, as well as false beliefs were also reported by our participants. While some false beliefs were commonly reported vaccination myths, such as that vaccines might “overwhelm” or “weaken” the immune system [54], others seemed to be specific to the IEI population, such as a belief that vaccination is not necessary if the patient receives immunoglobulin replacement treatment. This belief could potentially stem from a misinterpretation of the information provided by an immunologist since this belief is true for other vaccine-regulated diseases that have sufficient vaccine coverage in the general population for which these preparations provide passive immunity [55]. However, at the beginning of the COVID-19 pandemic, this belief did not adhere to current recommendations [7]. First, immunoglobulin product preparation is a complicated process that takes several months; therefore, a delay in the appearance of sufficient levels of SARS-CoV-2 specific antibodies in these products is expected, which was especially important at the beginning of vaccination campaigns [56]. Second, even if a particular patient fails to mount a specific antibody response to vaccination, T-cell immune responses may be intact and serve as an additional defense against SARS-CoV-2 infection [57–60]. In addition, the anticipation of vaccines offering complete sterile immunity, coupled with a tendency to assess vaccine efficacy not through empirical evidence but rather through a limited number of cases observed within one’s immediate social circle, constituted an additional factor contributing to participants’ skepticism towards vaccine efficacy. These misconceptions may be associated with inadequate levels of health literacy within the Latvian population. A recent investigation indicated that approximately 79% of Latvian citizens exhibit weak health literacy competencies, potentially contributing to riskier health-related behaviors, such as vaccine hesitancy [61].

Narratives regarding the negative health consequences of the SARS-CoV-2 vaccination have been circulating around and have been reported by studies in the Latvian general population [45], as well as in our patients, including death purportedly linked to SARS-CoV-2 vaccination. In some cases, these perceptions were grounded in unsubstantiated convictions that there is a direct causal link between SARS-CoV-2 vaccination and deteriorating health conditions. Several of our participants, those who expressed concerns about negative vaccination health effects, also admitted that they had gained this information from social media platforms. Indeed, social media discourse in countries that focus more on side effects or negative emotions is correlated with a lower country’s vaccination rate [62]. In addition, vaccine skeptics frequently use online platforms to spread disinformation about vaccines [63].

Interestingly, another study in the Latvian general population revealed that, among others, institutional trust and fear of COVID-19 are predictors for SARS-CoV-2 vaccination

behaviors [64]. Trust in the context of vaccination can be conceptualized across three distinct dimensions: confidence in the vaccine product itself (e.g., SARS-CoV-2 vaccine), reliance on the vaccine provider (e.g., medical professionals), and faith in policymakers (e.g., the government and the healthcare system) [65]. According to our data, patients' perception of vaccine efficacy and safety seemed to be influenced by mistrust in all three of these levels. Interestingly, in previous studies among the general population, education was reported to have less explanatory power of vaccine hesitancy, suggesting that a deficit in scientific literacy may play a lesser role than the establishment of public trust in the health system and science [66]. Indeed, mistrust in state institutions has been reported to directly affect the population's willingness to act in accordance with the recommendations of these institutions, while trust and confidence in the state and healthcare system has been associated with greater compliance to SARS-CoV-2 vaccination in Europe [67]. Social and economic inequality has also been associated with lower SARS-CoV-2 vaccination coverage [68], as well as higher indicators of public corruption, which is believed to generate mistrust in government [69,70]. Indeed, according to the Eurobarometer, trust in political parties as well as healthcare professionals is among the lowest in the EU [71] and corruption tolerance [72], as well as the Gini coefficient, are higher than average in the EU [73], which is also reflected in data regarding vaccination hesitancy in Latvia [45]. Mistrust in policymakers is also thought to be an important aspect of formation of conspiracy beliefs, together with psychological and structural factors [74–76].

Altogether, these findings underscore the importance of providing training to physicians and nurses regarding the effectiveness and safety of SARS-CoV-2 vaccination in individuals with ICI [37]. Trust between doctors and patients is particularly important for vaccination decisions [77]. In addition, some patients expressed that they feel unique with this condition; therefore, generic information by public health professionals may not seem fully applicable to them due to their specific condition. Therefore, from the perspective of vaccine communication, healthcare professionals would play a pivotal role in building trust, communicating about the personal benefits of vaccination, and addressing misinformation and hesitancy concerns regarding SARS-CoV-2 vaccines for these specific patients with a rare disease [77]. It has been shown that healthcare professionals' recommendation to receive the vaccine has a positive effect on vaccination behavior, while the lack of confidence because the vaccine was too new showed a negative effect on vaccination intention [78]. In addition to that, initiatives that increase health literacy could be employed, including health education in schools and the provision of structured health-related information about vaccinations [61].

This study has several limitations. First, the data were gathered between April and August 2023, a period following the end of the pandemic in May 2023. Given that vaccination initiatives were predominantly conducted earlier, the potential for recall bias exists, which may lead to missing details or the inclusion of inaccurate information in participants' responses, leading to a misunderstanding of the topic. However, this time framework also enabled the exclusion of interviewees who were inclined towards vaccination, as those who harbored such intentions had enough time to proceed with vaccination. Second, there is a likelihood of under-representation of specific ICI classification categories, particularly patients with congenital neutropenia or bone marrow failure treated by hematologists in Latvia. This could potentially result in the omission of diagnoses that may have disease-specific concerns due to their unique clinical characteristics or treatment regimens (including HSCT), leading to an incomplete understanding of the issue and limited generalizability to all ICI patients. Furthermore, we used the HBM to design interview questions. However, several frameworks that could explain hesitancy have been developed, such as the 5C model of the drivers of vaccine hesitancy, which consists of five components: confidence, complacency, constraints, risk calculation, and collective responsibility [79]. In our interview questions, we did not include specific questions to explore constraints (availability or affordability), nor did we questions about confidence (or self-efficacy) and collective reasonability issues, since we did not predict that these issues would be the

driving forces that would prevent immunodeficient patients from vaccination, as they were not reported by previous studies [11,37,38]. Notably, vaccination was readily accessible through dedicated vaccination centers or local general practitioner (GP) facilities in Latvia, with no associated costs, thereby minimizing concerns about accessibility or inconvenience as substantial influential factors. In addition, some possible associations were beyond the scope of this study, as we did not incorporate information concerning the educational level of the patients or other plausible factors that have been documented as influential in vaccination decisions, and their absence might lead to an incomplete picture of the issue. Furthermore, we did not use validated vaccination hesitancy scales due to the absence of validation in the Latvian language. However, the application of such scales within this particular population could be potential fields for future research. Employing standardized scales could reduce interviewer bias and facilitate comparative analysis with patients in other populations. Moreover, the incorporation of additional factors could enhance the comprehensiveness of the insights into vaccination hesitancy.

5. Conclusions

The reasons for SARS-CoV-2 vaccine acceptance and hesitancy in the IIE patient group in Latvia are complex and multifaceted, and both specific immunity status and the geopolitical context play a role. While most reasons for vaccination hesitancy in this group are similar to those in the general population, the findings suggest that individuals with immunodeficiency have unique perceptions and concerns that influence their decisions regarding vaccination. It is important to consider these factors when consulting IIE patients about vaccination.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/vaccines11111637/s1>. Supplementary material File S1: Interview questions.

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Centrālās medicīnas ētikas komitejas atļauja

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Rīgā

Datums skatāms laika zīmogā Nr. 01-29.1/2878

Jz 03.06.2020. Nr. _____

Rīgas Stradiņa universitātes
Molekulārās ģenētikas zinātniskās
laboratorijas asoc. profesorei
Nataljai Kurjānei

Atzinums par pētījumu

*“Primāru imūndeficītu pacientu
klīniskā, imunoloģiskā un ģenētiskā
analīze Latvijas populācijā”*

Centrālā medicīnas ētikas komiteja 2020.gada 22.maijā izskatīja Rīgas Stradiņa universitātes Molekulārās ģenētikas zinātniskās laboratorijas asoc.prof. Nataljas Kurjānes 2020.gada 6.maija pieteikums atzinuma sniegšanai par pētījumu *“Primāru imūndeficītu pacientu klīniskā, imunoloģiskā un ģenētiskā analīze Latvijas populācijā”* (reģ. Veselības ministrijā 2020.gada 6.maijā Nr.5334). Pētījuma pieteikuma precizējums saņemts Veselības ministrijā 2020.gada 3.jūnijā (reģistrēts Veselības ministrijā 2020.gada 3.jūnijā Nr.6568).

Atbilstoši Centrālā medicīnas ētikas komitejas 2020.gada 22.maija sēdes protokola Nr.2020-6 I.daļas 3.punktam tiek sniegts atzinums, ka iepriekš minētais pētījums nav pretrunā bioētikas normām.

Centrālās medicīnas ētikas
komitejas priekšsēdētājs

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*Dokuments ir parakstīts ar drošu elektronisko parakstu un satur laika zīmogu

Pacientu informētas piekrišanas veidlapa

Cienītā kundze!/Godātais kungs!

Mēs aicinām Jūs piedalīties pētījumā „Primārie (pārsvārā) antivielu deficīti pieaugušajiem: meklējot slimības cēloņus un klīnisko izpausmju dažādību”, kas tiks īstenots sadarbībā ar Rīgas Stradiņa universitātes Molekulārās ģenētikas zinātnisko laboratoriju. Lūdzu, izlasiet informāciju par pētījumu, pirms parakstāt piekrišanas formu. Šo lapu Jums ir izsniedzis viens no projekta pētniekiem. Viņa/viņas pienākums ir atbildēt uz visiem jautājumiem, kas Jums varētu rasties. Pārliecinieties, ka Jums ir skaidra pētījuma būtība, saturs un paredzētās darbības, pirms parakstāt piekrišanas formu.

Pētījuma mērķis

Pētījuma mērķis ir izmeklēt primārā imūndeficīta etioloģiju, kā arī ģenētiskos, transkriptoma un imunoloģiskus faktorus, kas ietekmē primāro (pārsvārā) antivielu deficītu klīnisko dažādību.

Projekta apraksts

Primārie imūndeficīti ir iedzimto slimību grupa, kas raksturojas ar traucētu imūnās sistēmas darbību. Primārie (pārsvārā) antivielu deficīti (PAD) pieaugušajiem ir visizplatītākie primārie imūndeficīti ar specifisku balto asins šūnu - B šūnu - diferenciācijas nomākumu, traucētu antivielu ražošanu un samazinātu atbildi pret vakcināciju. Slimības klīniskās izpausmes un sākuma vecums ir ļoti mainīgs. Cēloņi, kas izraisa PAD, lielākoties nav skaidri; tikai 15–30 % gadījumu ir iespējams atrast ģenētisku (ar iedzimtību saistītu) iemeslu.

Mūsu projekta mērķis ir analizēt iedzimtību un imūnsistēmas rādītājus Latvijas iedzīvotājiem ar aizdomām par vai jau diagnosticētu primāro imūndeficītu, kā arī ģenētiskos, transkriptoma un imunoloģiskus faktorus, kas ietekmē PAD klīnisko dažādību. Iegūtie rezultāti ļaus iegūt nozīmīgu informāciju par PAD etioloģiju un klīnisko mainību, kas uzlabos slimības diagnostiku un ļaus nodrošināt pacientiem personalizēto ārstēšanu.

Pētījuma laikā Jūs tiksiet aptaujāts/aptaujāta par Jūsu veselības stāvokli un jautājumiem saistībā ar vakcināciju, kā arī saņemsiet anketu aizpildīšanai. Pētnieks, kurš Jūs aptaujās, piedāvās Jums šo anketu, kā arī sniegs papildus skaidrojumus tās aizpildīšanai, ja tas būs nepieciešams.

Jums tiks paņemts asins paraugs līdzīgi kā standarta asins analīžu veikšanai. Tāpat kā standarta asins analīžu ņemšanas gadījumā, dūriens dažiem pacientiem var šķist nepatīkams, retos gadījumos parauga ņemšanas vietā var izveidoties asins izplūdums vai iekaisums.

Iegūtais materiāls tiks izmantots, lai raksturotu imūnsistēmas stāvokli, tai skaitā imūno atbildi pret SARS-CoV-2 vīrusu, kā arī analizētu iedzimtības (ģēnu variantu DNS molekulā) un transkriptoma (RNS molekulas) faktorus, kas var veicināt dažādu slimību, tostarp arī imūndeficītu, attīstību.

Projekta ilgums

Projekta ilgums ir 3 gadi (01.01.2021. - 31.12.2023). Jūsu piekrišanas dokuments tiks saglabāts 75 gadus, Jūsu bioloģiskais materiāls (asinis, no asinīm iegūta DNS un RNS (jeb ģenētiskais materiāls)) tiks uzglabāts atbilstoši Jūsu piekrišanai. Jums būs iespēja jebkurā brīdī bez paskaidrojumiem atsaukt savu piekrišanu. Šādā gadījumā asinju paraugi, veselības stāvokļa apraksts un jebkura ar personas identifikāciju saistīta informācija tiek iznīcināta, izņemot to, kas iepriekš tikusi publicēta.

Iespējamie riski

Piedalīšanās pētījumā nav saistīta ar nopietniem riskiem Jūsu veselībai. Jums tiks paņemti asins paraugi, līdzīgi kā standarta asins analīžu veikšanai. Retos gadījumos parauga ņemšanas vietā var izveidoties asins izplūdums vai iekaisums. Asins parauga ņemšanu veiks sertificēts medicīnas speciālists.

Datu konfidencialitāte un projekta dalībnieka tiesības

Latvijas Republikas Saeimas pieņemtais „Cilvēka genoma izpētes likums”, kā arī „Fizisko personu datu apstrādes likums” un “Pacientu tiesību likums” garantē Jūsu personas datu, veselības un iedzimtības datu konfidencialitāti. Informācija tiks uzglabāta vietā ar ierobežotu pieejamību un netiks izsniegta ne Jūsu ģimenes locekļiem, ne apdrošināšanas firmām, ne darba devējam. Iegūtie dati un asinju paraugi netiks izmantoti komerciāliem mērķiem vai nelikumīgi nodoti neiesaistītām trešajām personām. Dati, kas par Jums tiks uzglabāti Rīgas Stradiņa universitātes Molekulārās ģenētikas zinātniskajā laboratorijā, tiks izsniegti tikai sekojošos gadījumos – Jums personīgi, pēc Jūsu rakstiska pieprasījuma vai arī atklājot Jums klīniski nozīmīgas variācijas, ja būsiet piekritis/piekritusi saņemt par tām informāciju.

Ziņas par Jūsu veselības stāvokli, dati no Jūsu aizpildītajām anketām un analīžu rezultāti (bet ne Jūsu personu identificējoši dati) būs pieejami arī pētniekiem, kas piedalās pētījumā. Atbilstoši Jūsu piekrišanai anonīmi dati tiks iesniegti zinātniekiem pieejamās datubāzēs, lai varētu zināšanas saistībā ar imūndeficītiem.

Tāpat ar Jūsu rakstveida piekrišanu (izņemot neatliekamās palīdzības gadījumus) Jūsu veselības stāvokļa aprakstu drīkstēs izsniegt Jūsu ārstam pēc pamatota viņa pieprasījuma. Jums ir tiesības arī

aizliegt sava veselības stāvokļa apraksta papildināšanu, atjaunošanu vai pārbaudi projekta ietvaros vai ierobežot sava iedzimtības materiāla (gēnu kopuma jeb genoma) izpēti apjomu.

Jums ir tiesības jebkurā laikā atsaukt savu piekrišanu piedalīties šajā projektā, šādā gadījumā Jūsu asiņu paraugi, aizpildītās anketas, veselības stāvokļa un iedzimtības apraksts un jebkura ar personas identificēšanu saistīta informācija tiks iznīcināta.

Ši pētījuma protokols ir apstiprināts LR Centrālajā medicīnas ētikas komitejā.

Brīvprātīga piedalīšanās

Jūsu piedalīšanās projektā ir brīvprātīga. Atteikšanās no piedalīšanās pētījumā neradīs Jums nekādas nevēlamās sekas.

Iespējamie ieguvumi

Piedalīšanās pētījumā nesniegs Jums tūlītēju labumu, taču pētījuma rezultātā iegūtie dati palīdzēs iegūt jaunas zināšanas par iedzimtības un imūnsistēmas rādītāju nozīmi primāro imūndeficītu ģenētiskajā predispozīcijā (iedzimtā nosliecē uz imūndeficītu). Tas ļaus nākotnē precīzāk paredzēt šīs slimības attīstības iespēju, uzlabot ārstēšanas efektivitāti.

Esmu iepazinies/-usies ar rakstisku informāciju par projekta mērķi, saturu un iespējamajiem riskiem. Esmu saņēmis/-usi atbildes uz visiem maniem jautājumiem. Piekrītu dalībai pētījumā un sava veselības stāvokļa apraksta papildināšanai, atjaunošanai vai pārbaudei pētījuma datu bāzē, izmantojot medicīnisko dokumentāciju. Apzinos, ka jebkurā brīdī bez paskaidrojumiem varu atsaukt savu piekrišanu un tādā gadījumā manu audu paraugi un veselības stāvokļa apraksts un jebkura ar personas identificēšanu saistīta informācija tiek iznīcināta, izņemot to, kas iepriekš publicēta.

Pētījuma dalībnieks / viņa pilnvarotā persona	Pētnieks (pilnvarotā persona)
Vārds, uzvārds (drukātiem burtiem):	Vārds, uzvārds (drukātiem burtiem):
Personas kods	Personas kods
Kontaktinformācija	Datums, paraksts
Datums, paraksts	

Epasts: mgzl@rsu.lv

Ar imūndeficītu saistītu simptomu aptauja

Vispārīgie dati

Kods (ievada pētnieks): _____

Dzimums: ☐ Vīriešu ☐ Sieviešu

Vecums: _____

Svars, kg: _____

Augums, cm: _____

Kur Jūs dzīvojāt bērnībā?

☐ Dzīvoklis pilsētā ☐ Māja pilsētā ☐ Dzīvoklis laukos ☐ Māja laukos

Cik bieži Jūs smēķējat:

☐ Nesmēķēju ☐ < 1 paciņu dienā ☐ 1 paciņu dienā ☐ > 1 paciņu dienā

Vai esat veicis vakcināciju pret:

- ☐ Pneimokoku ☐ Nē ☐ Nezinu ☐ Jā (datums) _____
- ☐ Gripu ☐ Nē ☐ Nezinu ☐ Jā (datums) _____
- ☐ Difteriju un stingumkrampjiem ☐ Nē ☐ Nezinu ☐ Jā (datums) _____
- ☐ Poliomielītu ☐ Nē ☐ Nezinu ☐ Jā (datums) _____
- ☐ Vējbakām ☐ Nē ☐ Nezinu ☐ Jā (datums) _____
- ☐ Masalām un masaliņām (MMR) ☐ Nē ☐ Nezinu ☐ Jā (datums) _____
- ☐ Ērču encefalītu ☐ Nē ☐ Nezinu ☐ Jā (datums) _____
- ☐ Citu ierosinātāju (_____) ☐ Nē ☐ Nezinu ☐ Jā (datums) _____

Vai Jums ir kāda alerģija?

☐ Nē ☐ Nezinu ☐ Jā (pret ko?) _____

Vai alerģija ir IgE-mediēta (IgE līmenis paaugstināts)?

☐ Nē ☐ Nezinu ☐ Jā

Simptomi

Kad Jums tika atklāta imūndeficīta diagnoze? (gads) _____

Kad Jums parādījās pirmie simptomi, lai aizdomātos par imūndeficītu? (gads) _____

	Pēdējo 12 mēnešu laikā?	Visas dzīves laikā?
Cik reizes slimojāt ar augšējo elpceļu infekciju?		
Cik reizes slimojāt ar gripu?		
Cik reizes slimojāt ar sēnīšu infekcijām? Kāda veida?		
Cik reizes slimojāt ar vidusauss iekaisumu?		
Cik reizes slimojāt ar tonsillītu (angīnu)?		
Cik reizes slimojāt ar plaušu karsoni?		
Cik reizes Jums ir bijusi caureja / zarnu infekcija?		
Cik reizes Jums ir bijis drudzis bez citiem simptomiem?		
Cik antibiotiku kursi Jums ir bijuši?		
Cik dienas slimības dēļ nespējāt veikt ikdienas darbus?		
Cik reizes un cik dienas esat ārstējies slimnīcā infekcijas slimību dēļ?		
Cik reizes un cik dienas esat ārstējies slimnīcā citu iemeslu dēļ?		

Vai iepriekš ārstēšanā tika lietoti sekojošie medikamenti?

- Antibiotiku profilakse ☐ Nē ☐ Nezinu ☐ Jā (cik?) _____
- Glikokortikosteroīdi (hormoni) ☐ Nē ☐ Nezinu ☐ Jā (cik?) _____
- Imūnglobulīni ☐ Nē ☐ Nezinu ☐ Jā (datums) _____

Izpausmes un blakusslimības

Vai Jums ir šobrīd vai iepriekš ir bijuši?

- Nervu sistēmas saslimšanas
☐ Meningīts ☐ Encefalīts ☐ Neiropātija ☐ Multiplā skleroze ☐ Citas _____
- Elpceļu saslimšanas
☐ Astma ☐ Bronhektāzes ☐ HOPS ☐ Citas _____
- Kuņģa-zarnu trakta saslimšanas
☐ Biežas caurejas ☐ Mutes čūlas ☐ Iekaisīga zarnu slimība ☐ Citas _____
- Kustību un balsta sistēmas saslimšanas
☐ Osteoporoze ☐ Osteomielīts ☐ Citas _____
- Autoimūnas slimības
☐ Reimatoīds artrīts ☐ Sarkanā vilkēde ☐ Celiakija ☐ Hronisks autoimūns tireoidīts
☐ Citas _____
- Endokrīnās saslimšanas
☐ Vairogdziedzera saslimšanas ☐ 1. tipa cukura diabēts ☐ Citas _____
- Ļaundabīgās saslimšanas
☐ Limfoma ☐ Leikēmija ☐ Kuņģa vēzis ☐ Krūts vēzis ☐ Citas _____
- Urīnizvadu sistēmas saslimšanas
☐ Biežas urīnceļu infekcijas ☐ Nieru mazspēja ☐ Citas _____
- Ādas saslimšanas
☐ Ekzēma ☐ Psoriāze ☐ Strutainas infekcijas ☐ Vitiligo (pigmenta zudums)
☐ Kārpas vai kondilomas ☐ Jostas roze ☐ Atkārtotās aukstumpumpas (herpes)
☐ Citas _____
- Dzirdes vai redzes problēmas
☐ Dzirdes zudums ☐ Redzes zudums ☐ Acs iekaisums (uveīts) ☐ Citas _____
- Citas slimības
☐ Palielināta liesa ☐ Palielināta akna ☐ Mazasinība ☐ Palielināti limfmezgli
☐ Citas _____

Vai Jums ir bijušas operācijas?

- Plaušu ☐ Nē ☐ Nezinu ☐ Jā (kāda?) _____
- Liesas ☐ Nē ☐ Nezinu ☐ Jā (kāda?) _____
- Citas ☐ Nē ☐ Nezinu ☐ Jā (kāda?) _____
- Izgriezti adenoīdi vai rīkles mandeles ☐ Nē ☐ Nezinu ☐ Jā

Radinieku un ģimenes dati

No kuras valsts ir Jūsu vecvecāki:

- | | |
|--------------------|---------------------------------|
| ▪ Mātes tēvs _____ | ☐ Nezinu |
| ▪ Mātes māte _____ | ☐ Nezinu |
| ▪ Tēva tēvs _____ | ☐ Nezinu |
| ▪ Tēva māte _____ | ☐ Nezinu |

Par kuriem no radiniekiem, Jums ir pieejama informācija

☐ Māte ☐ Tēvs ☐ Brāļi (Cik?) _____ ☐ Māsas _____ ☐ Dēli _____ ☐ Meitas _____

Vai kādam Jūsu ģimenē ir kāda no sekojošām slimībām?

- Imūndeficīts vai paaugstināta uzņēmība pret infekcijas slimībām: ☐ Nē ☐ Nezinu ☐ Jā
(kam? Norādiet radniecības pakāpi) _____
- Vēzis vai citas ļaundabīgas slimības:
☐ Nē ☐ Nezinu ☐ Jā (kam?) _____
- Autoimūnas slimības (piem., reimatoīds artrīts, 1. tipa cukura diabēts u. c.):
☐ Nē ☐ Nezinu ☐ Jā (kam?) _____
- Citas nozīmīgas slimības (_____)
☐ Nē ☐ Nezinu ☐ Jā (kam?) _____