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Autoantibody development is associated with clinical severity of COVID-19: A cohort study

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ABSTRACT

Viral infections, including respiratory diseases such as Coronavirus disease 2019 (COVID-19), are hypothesized to contribute to the onset of autoimmune disorders. Although elevated levels of autoantibodies have been observed following COVID-19, the role of specific autoantibodies linked to autoimmune diseases and their correlation with disease severity remains poorly defined.

Abbreviations: RF, Rheumatoid factor; CCP, anti-cyclic citrullinated peptide antibody; SSA, anti–Sjögren's-syndrome-related antigen A; SSB, anti–Sjögren's-syndrome-related antigen B; CEN-B, anti-centromer protein B antibody; U1RNP, anti-U1 ribonucleoprotein antibody; Scl-70, anti-topoisomerase I antibody; Sm, anti-Smith antibody; dsDNA, anti-double stranded DNA antibody; c-ANCA, anti-neutrophil cytoplasmic antibody (anti-proteinase 3); p-ANCA, anti-neutrophil cytoplasmic antibody (anti-myeloperoxidase); GBM, anti-glomerular basement membrane antibody; GAD65, anti-glutamate decarboxylase antibody; IA-2, anti-islet antigen 2 antibody; Fod IgA, anti-fodrin IgA; Fod IgG, anti-fodrin IgG; RibP IgG, anti-ribosomal P protein IgG antibody; β2-GP1 IgG, anti-beta-2 glycoprotein 1 IgG antibody; β2-GP1 IgM, anti-beta-2 glycoprotein 1 IgM antibody; β2-GP1 IgA, anti-beta-2 glycoprotein 1 IgA antibody; CL IgG, CL IgA, anti-cardiolipin IgG antibody; CL IgM, anti-cardiolipin IgM antibody; Tg, anti-thyroglobulin antibody; TPO, anti-thyroid peroxidase antibodies; TSAb, thyroid stimulating antibodies; HMGCR, anti-3-hydroxy-3-methylglutaryl-coenzym-A-reduktase antibody; cN-1A, anti-cytosolic 5′-nucleotidase 1 A antibody; Ro52, anti-Ro52 antibody; OJ, anti-OJ antibody; EJ, anti-EJ antibody; PL-12, anti-alanyl-tRNA-synthetase antibody; PL-7, anti-threonyl-tRNA-synthetase antibody; SRP, anti-signal recognition particle antibody; Jo-1, anti-histidyl-tRNA synthetase antibody; PM/ScL-75, anti-PM/Scl (Polymyositis/Scleroderma) complex (75 kDa) antibody; PM/ScL-100, anti-PM/Scl complex (100 kDa) antibody; Ku, anti-Ku antibody; SA-1, anti-SUMO-activating enzyme subunit 1 antibody; NMP2, anti-nuclear matrix protein-2 antibody; MDA5, anti-melanoma differentiation-associated gene 5 antibody; TIF1-γ, anti-transcriptional intermediary factor 1 gamma antibody; Mi-2β, anti-Mi-2β antibody; Mi-2α, anti-Mi-2α antibody; ANA, antinuclear antibodies; AMA, anti-mitochondrial antibodies; APCA, anti-parietal cell antibodies; ASMA, anti-smooth muscle antibodies; LKM, liver kidney microsomal antibody; SkM, anti-skeletal muscle antibody; CardM, anti-cardiac muscle antibody; MuSK, anti-muscle-specific kinase antibody; AdC, anti-adrenal cortex antibodies; PLA2R, anti-phospholipase A2 receptor antibody; COVID-19, Coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ICU, intensive care unit; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; aPL, anti-phospholipid; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome; GCU, general care unit..

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In this study, we used a comprehensive autoantibody panel to assess the autoantibody production across different cohorts of COVID-19 patients, categorized by disease severity. We also compared patients with severe COVID-19 to a control group with other severe, non-COVID-related diseases.

Our findings indicate that the severity of COVID-19 corresponds to the overall production of specific autoantibodies, which are particularly associated with COVID-19. This association might predispose to an increased risk for the development of autoimmune conditions after a severe course of COVID-19.

1. Introduction

The rapid global spread of Coronavirus disease 2019 (COVID-19) had a profound impact on populations worldwide. Symptoms range from mild sickness such as fever, cough, dyspnea, myalgia, or fatigue to severe cases requiring hospitalization, mechanical ventilation and death [5]. Extensive cohort studies have found an independent association between SARS-CoV-2 infection and the occurrence of autoimmune diseases [3,4]. While current data indicate an increased risk for patients after hospitalization, the exact relationship between the clinical severity of COVID-19 and the subsequent development of autoantibody production remains unclear.

Autoimmune disorders associated with autoantibodies include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), myositis, type 1 diabetes (T1D), autoimmune thyroid diseases, cardiac autoimmunity and neurological autoimmune conditions such as autoimmune encephalitis [6]. The identification of specific autoantibodies serves as a valuable biomarker and screening tool for at-risk patients and facilitates the monitoring of disease progression.

In the acute phase of COVID-19, there is a pronounced production of autoantibodies, especially those directed against immunomodulatory proteins, including cytokines, chemokines, complement components and cell surface proteins [7]. In addition, increased levels of antinuclear antibodies [8], anti-phospholipid (aPL) antibodies [9] and thyroid autoantibodies have been found in patients during the acute infection.

Since viral infections, such as the Epstein-Barr virus, are known to be environmental triggers of autoimmune diseases through mechanisms such as epitope spreading, molecular mimicry or bystander activation [1,2], it is essential to investigate how SARS-CoV-2 infection triggers autoimmunity. Chronic inflammation and elevated cytokine levels induced by a SARS-CoV-2 infection are proposed as potential promoters of self-antigens and activators of bystander T cells [10,11]. Additionally, numerous studies have documented molecular mimicry between the SARS-CoV-2 spike protein and human proteins [12,13].

However, the extent to which the production of autoantibodies is triggered by the acute infection, and particularly its relationship with the severity of the infection has not been fully elucidated so far. In the present study, we address this gap by analyzing a comprehensive autoantibody panel to evaluate autoantibody production across different cohorts of COVID-19 patients categorized in different clinical severity stages, and comparing these findings to a control group with other severe, non-COVID-related diseases.

2. Material and methods

2.1. Human subjects and ethical aspects

Human participant studies were reviewed and approved by the Ethics Committee of the Medical University of Vienna, Austria (Approval Nos. 1404/2020 and 1898/2017). The patients or legal representatives provided their written informed consent to participate in this study if possible. If this was not feasible at the time of enrollment, informed consent was obtained from patients or their legal representatives at a later timepoint.

2.2. Autoantibody detection

After collection, patient's sera were processed and stored at < -70 °C by the MedUni Wien biobank [14]. After thawing, the detection of autoantibodies was conducted following the manufacturer's protocol as outlined below:

Autoantibodies are measured according to Table 1.

2.3. Data analysis

For statistical analysis, patients were classified into seropositive or seronegative for each measured autoantibody, according to the reference range of the corresponding detection method.

Data Analysis was performed in R (version 4.2.1). Data was analyzed in a descriptive manner. For selective antibodies, titer levels between each cohort were compared groupwise, utilizing the Wilcoxon rank-sum test for pairwise comparisons between groups, with *p*-values adjusted for multiple testing using the Bonferroni correction. The overall differences between groups were assessed with the Kruskal-Wallis test.

3. Results

3.1. Patients' characteristics

In this study, we included 94 patients with COVID-19, with a male-to-female percentage of 64.9 % to 35.1 %, respectively. At the time of enrolment, the mean age was 56.7 years. Additionally, 34 % of the patients had a body mass index (BMI) over 30 and 13.8 % over 40 (Table 2).

We subdivided the cohort into three representative cohorts based on different disease courses for further analysis. The first cohort (COVID-19 ICU-ECMO) ($n = 28$), comprised COVID-19 patients admitted to an intensive care unit (ICU) who required extracorporeal membrane oxygenation (ECMO) for severe acute respiratory distress syndrome (ARDS). The second cohort (COVID-19 ICU) ($n = 37$) consisted of patients treated in the ICU with ARDS, who did not require ECMO support. The third cohort (COVID-19 GCU) ($n = 29$) included hospitalized COVID-19 patients admitted to a general care unit (GCU), who did not require ICU treatment, reflecting the mildest course of disease in this study.

No significant differences were observed between the cohorts concerning age, sex and BMI. The severity of the disease, as defined by WHO COVID-19 severity criteria (WHO-2019-nCoV-therapeutics-2022.4) as well as the need for mechanical ventilation, corresponded to the cohort stratification criteria (Table 2).

The COVID-19 ICU-ECMO cohort consists of 13 female and 15 male patients, that required invasive mechanical ventilation. This cohort represents the most severely affected patients, as they were all classified as "critical" according to the WHO COVID-19 severity criteria. 11 subjects of this cohort died during hospitalization (Fig. 1A).

In the second cohort (COVID-19 ICU), 27 patients were classified as "critical", 3 patients as "severe" and 7 patients as "moderate" according to the WHO COVID-19 severity criteria. In this cohort, 32 patients required mechanical ventilation, of whom 25 needed invasive mechanical ventilation. The cohort consisted of 10 females and 27 males. 12 patients died during hospitalization (Fig. 1B).

Out of the COVID-19 GCU cohort, 15 patients were classified as

"mild", 13 patients as "moderate" and 1 patient was classified as "severe".

10 patients were female, 19 were male. Non-invasive mechanical ventilation was required in 8 patients, and all patients in this cohort survived. (Fig. 1C).

3.2. Seropositivity of autoantibodies in COVID-19-positive patients

Based on the hypothesis that autoantibodies are more frequent in patients with a more severe disease, we analyzed the production of 54 different autoantibodies associated with diverse autoimmune diseases and compared binary antibody levels among all cohorts.

Patients in the COVID-19 ICU-ECMO and COVID-19 ICU cohort had an average of 1.6 and 1.8 positive autoantibody-testing-results, respectively. In contrast, we found a mean of 1.3 positive autoantibody-testing-results in the COVID-19 GCU cohort (Fig. 2A). We observed a similar trend by stratifying the three COVID-19 cohorts based on the WHO COVID-19 severity criteria (WHO-2019-nCoV-therapeutics-2022.4). "Critical" patients had the highest average with 1.75 positive autoantibody-testing-results, wheatear "mild" patients showed an average of 0.73 positive autoantibody-testing-results (Fig. 2B).

In the COVID-19 ICU-ECMO cohort, we observed the highest frequency for anti-TPO, −β2-GP1 IgA, -GAD65, -PL-7, -CCP and -CL IgA antibodies as compared to the COVID-19 ICU and COVID-19 GCU cohorts. We detected anti-TPO autoantibodies in 21.4 % of the COVID-19 ICU-ECMO cohort, while the percentage among the COVID-19 ICU cohort was 16.2 % and 17.2 % in the COVID-19 GCU cohort. Anti-β2-GP1 IgA autoantibodies were detected in 25 % of the COVID-19 ICU-ECMO cohort, in 16.2 % of the COVID-19 ICU cohort and in 10.3 % of the COVID-19 GCU cohort. Anti-GAD65 antibody was positive in 28.6 % of the COVID-19 ICU-ECMO, 18.9 % of the COVID-19 ICU and 3.4 % of the COVID-19 GCU cohort. For autoantibodies against PL-7, 10.7 % of patients of the COVID-19 ICU-ECMO and 2.7 % of the COVID-19 ICU cohort were positive. Anti-CCP and -CL IgA autoantibody levels were positive in the COVID-19 ICU-ECMO cohort, with 7.1 % and in the COVID-19 ICU cohort with 2.7 % positive patients. Interestingly, we did not detect autoantibodies against PL-7, CCP, CL IgA, CardM, EJ or OJ in the COVID-19 GCU cohort (Fig. 2C, **supplementary table 1**).

These results might indicate, that the severity of COVID-19 predisposes to the production of certain autoantibodies.

In particular, in this study the percentage of seropositivity for autoantibodies against TPO, β2-GP1 IgA, GAD65, PL-7, CCP and CL IgA increased with disease severity.

We stratified all seropositive patients from the three COVID-19 cohorts based on the WHO COVID-19 severity criteria (WHO-2019-nCoV-therapeutics-2022.4) (Fig. 2D). We further characterized "critical", antibody-positive patients based on survival, ventilation, and sex (Fig. 2E).

We detected the autoantibodies against GAD65, β2-GP1 IgA, TPO and ANA in over 10 % of patients, predominately among those who were classified as "critical" (Fig. 2D). Among the anti-GAD positive "critical" patients, all required mechanical ventilation and over 50 % succumbed post-infection. Among patients positive for ANA, anti-β2-GP1 IgA, and anti-SkM antibodies, over 85 % required mechanical ventilation and around 40 % died during hospitalization (Fig. 2E). Approximately 8 % of patients were positive for autoantibodies against Tg, and 5 % were categorized as "critical "(Fig. 2D). Of these "critical" patients, about 40 % died post-infection, and 75 % required invasive mechanical ventilation (Fig. 2E). We identified the existence of TSAb autoantibody in around 4 % of patients, all classified as "critical" (Fig. 2D). Of these, 50 % died post-infection, 75 % needed invasive and 25 % non-invasive mechanical ventilation. Notably, 75 % of the TSAb-positive patients were female (Fig. 2E).

In around 6 % of the patients, we detected ASMA (Fig. 2D), and over 70 % of those classified as "critical" died of COVID-19, while only 50 % "critical" patients required invasive and 25 % non-invasive mechanical ventilation. All "critical" patients who tested positive for ASMA were male (Fig. 2E). Anti-CL IgA antibody-positive patients (around 4 %) were all classified as "critical" (Fig. 2D), and all required invasive mechanical ventilation; 30 % succumbed to the infection. Notably, all anti-CL IgA-positive "critical" patients were male (Fig. 2E).

We detected anti-CCP autoantibodies in over 3 % of patients, primarily among those considered "critical" or "severe" diseased (Fig. 2D). Notably, among "critical" patients, no post-infection deaths were reported. All "critical" patients who were positive for anti-CCP required invasive respiratory support, with a gender distribution of 50 % male and 50 % female (Fig. 2E). We found autoantibodies against EJ in about 3 % of patients, all classified as "critical" (Fig. 2D). All patients required invasive mechanical ventilation and 50 % of these patients died after infection, with a gender distribution that was split evenly (Fig. 2E). We identified anti-CardM antibodies in approximately 5 % of patients, all were "critical" cases (Fig. 2D). Among these "critical" patients, around 25 % died post-infection, 75 % required invasive respiratory support, and 25 % were female.

Table 1
Detection methods for measured auto-antibodies.

Test	Method/Platform	Detection Platform	Manufacturer	Location
SSA, SSB, CEN—B, U1RNP, Scl-70, Sm, CCP	EliA Tests	Phadia 250	ThermoFisher Scientific, Thermo Fisher Diagnostics Austria GmbH	Department of Laboratory Medicine, Medical University of Vienna
RF Levels (Serum)	N Latex RF Kit	BN™ II Nephelometer	Siemens Healthcare Diagnostics	Department of Laboratory Medicine, Medical University of Vienna
ANA	Indirect Immunofluorescence Assay on HEp-2 Cells	Inova assay on Quantalyser and Novaview system	Inova Diagnostics	Department of Laboratory Medicine, Medical University of Vienna
p-ANCA, c-ANCA	Indirect Immunofluorescence Assay on human neutrophil granulocytes	Inova assay on Quantalyser and Novaview system	Inova Diagnostics	Department of Laboratory Medicine, Medical University of Vienna
ACPA, ASMA, LKM, AMA	Manual Assays	Mouse Tissue Slides	Bio-Rad Laboratories GmbH	Department of Laboratory Medicine, Medical University of Vienna
Tg, TPO, TSAb	Electrochemiluminescence Immunoassay (ECLIA)	Cobas e 801 Analyzers	Roche	Department of Laboratory Medicine, Medical University of Vienna
HMGCR, cN-1A, Ro52, OJ, EJ, PL-12, PL-7, SRP, Jo-1, PM/ScL-75, PM/ScL100, Ku, SA-1, NMP2, MDA5, TIF1-γ, Mi-2b, Mi-2a, NMP2	EUROLINE Autoimmune Inflammatory Myopathies 16 Ag (IgG)	EUROIMMUN System	EUROIMMUN Medical Laboratory Diagnostics	Division of Neuropathology and Neurochemistry, Medical University of Vienna
β2-GP1 IgA, β2-GP1 IgG, β2-GP1 IgM, CL-IgA, CL-IgG, CL-IgM, Fod IgA, Fod IgG, RibP IgG, AdC, CardM, IA-2, PLA2R, SkM, MusK	Immunoassays	Various Systems	Orgentec-Sebia, Euroimmun, IBL International GmbH, Tecan	Center for Pathophysiology, Infectiology and Immunology, Institute of Immunology, Medical University of Vienna

Table 2
Demographic and clinical data of included COVID-19-positive patients ($n = 94$). Three cohorts were compared, ICU patients with ECMO support (COVID-19 ICU-ECMO), ICU patients without EMCO support (COVID-19 ICU) and COVID-19 patients from a GCU (COVID-19 GCU). Characteristics include age (in years (y)), sex, mechanical ventilation (invasive, non-invasive, no mechanical ventilation), classification according to the WHO COVID-19 severity criteria (WHO-2019-nCoV-therapeutics-2022.4), and body mass index (BMI). *P*-value was calculated using ANOVA for numeric variables and chi-squared test for categorical variables.

	COVID-19 ICU-ECMO (N = 28)	COVID-19 ICU (N = 37)	COVID-19 GCU (N = 29)	Overall (N = 94)	P-value
Age (y)					
Mean (SD)	56.8 (8.52)	55.5 (15.5)	55.1 (17.4)	55.7 (14.3)	0.974
Median [Min, Max]	58.0 [35.0, 75.0]	57.0 [22.0, 82.0]	62.0 [26.0, 79.0]	58.5 [22.0, 82.0]	
Sex					
female	13 (46.4 %)	10 (27.0 %)	10 (34.5 %)	33 (35.1 %)	0.45
male	15 (53.6 %)	27 (73.0 %)	19 (65.5 %)	61 (64.9 %)	
Mechanical ventilation					
invasive	28 (100 %)	25 (67.6 %)	0 (0 %)	53 (56.4 %)	<0.001
non-invasive	0 (0 %)	7 (18.9 %)	8 (27.6 %)	15 (16.0 %)	
no mechanical ventilation	0 (0 %)	5 (13.5 %)	21 (72.4 %)	26 (27.7 %)	
Severity[a]					
critical	28 (100 %)	27 (73.0 %)	0 (0 %)	55 (58.5 %)	<0.001
severe	0 (0 %)	7 (18.9 %)	1 (3.4 %)	8 (8.5 %)	
moderate	0 (0 %)	3 (8.1 %)	13 (44.8 %)	16 (17.0 %)	
mild	0 (0 %)	0 (0 %)	15 (51.7 %)	15 (16.0 %)	
BMI					
over 40	0 (0 %)	9 (24.3 %)	4 (13.8 %)	13 (13.8 %)	0.0607
over 30	9 (32.1 %)	9 (24.3 %)	14 (48.3 %)	32 (34.0 %)	
under 30	19 (67.9 %)	19 (51.4 %)	11 (37.9 %)	49 (52.1 %)	

[a] Classification according to the WHO COVID-19 severity criteria (WHO-2019-nCoV-therapeutics-2022.4).

In 4 % of the patients, we detected autoantibodies against MDA5 (Fig. 2D). All "critical" patients required invasive mechanical ventilation, and 50 % succumbed to the infection. All of these " critical" patients were male (Fig. 2E). We observed autoantibodies against PL-7 in around 5 % of patients, either among "critical" or "severe" classified cases (Fig. 2D). Among "critical" patients, 25 % died. All "critical" patients required invasive mechanical ventilation. 75 % were male (Fig. 2E). We detected anti-β2-GP1 IgG, −β2-GP1 IgM, -NMP2, -OJ, and -TIF1-γ autoantibodies in 2 % of patients, all were classified as "critical" (Fig. 2D).

In summary, we observed an association between COVID-19 severity and the production of anti-GAD65, −β2-GP1 IgA and -TPO autoantibodies (Fig. 2C). Furthermore, over 50 % of ANA-positive patients were "severe" to "critical" ill (Fig. 2D). Over 80 % of "critical" ill patients who tested positive for anti-GAD65, −β2-GP1 IgA, -TPO, -CL IgA, -CCP, -MDA5 antibodies or APCA required invasive mechanical ventilation. Additionally, we observed that post-infection mortality exceeded over 50 % in "critical" ill patients who tested positive for anti-GAD65, -TPO, TSAb, ASMA, anti-EJ and -PL-7 antibodies. Notably, in the cohort of "critical" classified patients we found TSAb and APCA autoantibodies more frequently in female patients and detected ASMA and anti-CL IgA antibodies exclusively in male patients (Fig. 2E).

Our data highlights that the production of specific autoantibodies is associated with the severity of COVID-19.

3.3. Comparison of autoantibody patterns in COVID-19 ICU-ECMO vs. non-COVID ECMO cohorts

To validate whether autoantibody prevalence is indeed associated with the severity of COVID-19 rather than with a general condition of critically ill patients linked to the use of ECMO, we analyzed a control group of patients who required ECMO support for other, non-COVID-19-related conditions (non-COVID-19 ECMO), as described in **supplementary table 2**. We characterized the non-COVID-19 ECMO cohort further, based on underlying respiratory tract infections: 6 patients were diagnosed with influenza, 8 patients were diagnosed with pneumonia. For the third subgroup (non-infectious), which included 15 patients, no respiratory tract infection was reported (Fig. 3A**, supplementary table 2)**.

We observed a unique pattern of detected autoantibodies for each group. Autoantibodies against PL-7, Tg, MDA5, EJ, OJ, CardM, APCA, and ASMA were exclusively identified within the COVID-19 ICU-ECMO cohort. In contrast, anti-Ro52, -NMP2, -HMGCR, -Fod IgA, -Fod IgG, -SSA, and -AdC autoantibodies were solely detected within the non-COVID-19 ECMO cohort. Among all autoantibodies analyzed, we identified 9 distinct autoantibodies that were detected in different proportions among both groups of patients. Anti-β2-GP1 IgA antibodies and anti-TSAb, were observed more frequently in patients within the non-COVID-19 ECMO cohort.

Specifically, we detected anti-β2-GP1 IgA in 25 % of the COVID-19 ECMO cohort. In contrast, a smaller proportion of 6 % of patients within the COVID-19 ICU-ECMO cohort was positive. For anti-TSAb, 3.6 % of patients within the COVID-19 ICU-ECMO cohort were positive, compared to a substantially higher proportion of 31 % within the non-COVID-19 ECMO cohort. Anti-β2-GP1 IgA and anti-TSAb were found in the non-COVID-19 ECMO cohort in patients of all three subgroups (influenza, pneumonia, non-infectious). A similar tendency was observed for anti-SkM autoantibodies, with 3.6 % positive patients in the COVID-19 ICU-ECMO cohort and 6.9 % positive patients in the non-COVID-19 ECMO cohort, but only in those patients with influenza (16.7 % positive patients) and pneumonia (12.5 % patients).

We detected the antibodies against GAD65, TPO, CCP and CL IgA, as well as ANA, more frequently in the COVID-19 ICU-ECMO cohort. Anti-GAD65 antibodies were positive in 28.6 % of the COVID-19 ICU ECMO cohort and in 6.9 % of the non-COVID-19 ECMO cohort. We observed anti-TPO positivity in 21.4 % of the COVID-19 ICU-ECMO patients and in 6.9 % of the non-COVID-19 ECMO cohort. Anti-TPO was found in 16.6 % of the influenza patients and 6.7 % of the patients of the non-infectious subgroup. For ANA, we found positivity in 17.9 % of the COVID-19 ICU-ECMO cohort and in 10 % of the non-COVID-19 ECMO cohort. In the influenza subgroup, 16.7 % of the patients were positive, in the pneumonia subgroup 12,5 % and in 6.7 % in the non-infectious subgroup. Detection rates for autoantibodies against CCP and CL IgA were 7.1 % within the COVID-19 ICU-ECMO cohort and 3.5 % within the non-COVID-19 cohort. Out of the non-Covid-19 cohort, all anti-CCP and CL IgA positive patients were diagnosed with influenza (16.7 % positive patients) (Fig. 3B).

We conducted a detailed analysis of the titer levels for the autoantibodies positive in the COVID-19 ICU-ECMO patients. Notably, anti-GAD65 antibody titer levels displayed a diminishing trend when comparing the COVID-19 ICU-ECMO to the COVID-19 ICU, and COVID-19 GCU cohorts. The titer levels of the non-COVID-19 ECMO cohorts fell within the range between the COVID-19 GCU and ICU cohorts.

Comparatively, anti-CCP antibodies exhibited higher titers within the COVID-19 ICU-ECMO cohort than the COVID-19 ICU cohort. However, the titer levels within the non-COVID-19 ECMO cohort were comparable to those of the COVID-19 ICU-ECMO cohort. The anti-TPO

titer displayed an overall elevation across all COVID cohorts compared to the non-COVID-19 ECMO cohort. Anti-CL IgA titers demonstrated higher levels within the COVID-19 ICU-ECMO and COVID-19 ICU cohorts than the COVID-19 GCU cohort. Titer levels within the non-COVID-19 ECMO cohort were slightly elevated compared to the COVID-19 GCU cohort. The ANA titers were similar between the COVID-19 ICU ECMO and the COVID-19 ICU cohorts, as well as between the COVID-19 GCU and the non-COVID-19 ECMO cohorts. More patients with titers above the threshold were identified within the non-COVID-19 ECMO cohort. For RF, the titer levels experienced a decline between the COVID-19 ICU ECMO, COVID-19 ICU, and non-COVID-19 ECMO cohorts. However, titer levels within the non-COVID-19 ECMO cohort were higher compared to the COVID cohorts (Fig. 3C).

The data elucidates a distinct autoantibody profile present in the severely ill COVID-19 patients which differs from the pattern observed in patients with a severe illness unrelated to COVID-19. The percentage of anti-GAD65, -PL-7, -CCP, -CL IgA, -CardM, -TPO, −EJ, -OJ and ANA positive patients was higher in the COVID-19 ICU-ECMO cohort, compared to the non-COVID-19 ECMO cohort. This was underlined by elevated titer levels of anti-TPO, anti-CL IgA, and ANA. Conversely, we observed a more frequent production of anti-β2-GP1 IgA antibody and anti-TSAb in the control group.

Overall, our data indicates an association of distinct autoantibody profiles with severe COVID-19 disease.

4. Discussion

Our study elucidates that COVID-19 infection may precipitate the emergence of specific autoantibodies, suggesting a potential mechanistic link between viral infection and the development of autoimmune diseases.

We observed that the severity of COVID-19 disease corresponds to an increase in overall autoantibody production. This was evidenced by an increased detection of selective autoantibodies, associated with various autoimmune diseases, in the most severely affected COVID-19 cohort. This autoantibody profile was different from that observed in a non-COVID-19 ECMO control group of critically ill patients, thereby indicating, that the detected autoantibodies are specifically linked to COVID-19.

In line with our findings, several studies have reported an increased autoantibody production in relation to COVID-19 and correlating with disease severity [8,15–17].

We demonstrated a higher prevalence of autoantibodies against GAD65 in severe diseased COVID-19 patients, associated with acute onset of insulin-dependent diabetes (T1D). Furthermore, over 50 % of anti-GAD65 antibody positive patients with severe disease died during hospitalization. Our data suggests that T1D is a co-morbidity promoting a severe onset of COVID-19 disease, which is in line with reported literature [18–20]. Previous studies have also reported a rise in new-onset T1D cases during the COVID-19 pandemic, and a correlation between SARS-CoV-2 infection and the development of T1D [11,21–23].

ANAs, known for their association with autoimmune diseases, such as SLE Sjögren's syndrome, and myositis, and the post-COVID syndrome, were reported to be present in COVID-19 patients [24–29]. We observed similar frequencies of ANA-positive patients across the different COVID-19 cohorts, with a slight increase when comparing COVID-19 cohorts to the non-COVID-19 ECMO cohort.

Anti-CCP antibodies and RF are crucial for the diagnosis of RA [30,31]. Our study revealed a more common presence of anti-CCP in severely diseased COVID-19 patients, consistent with higher titers in the COVID vs non-COVID cohorts. These data align with post-COVID studies reporting a higher prevalence of RA in the different COVID-19 cohorts than in non-COVID-19 cohorts [3,4]. However, the frequency of RF positive patients was similar among all cohorts, COVID-19 and non-COVID-19, supporting the idea that anti-CCP antibodies might be more specific compared to RF.

While myositis cases were rarely reported in COVID-19 patients, our study demonstrated the presence of autoantibodies against PL-7, OJ, and EJ in COVID-19 patients, which were particularly elevated in severely diseased individuals, suggesting a potential risk for myositis development.

Anti-TPO antibodies are usually found in thyroid autoimmune diseases such as Hashimoto's thyroiditis [32]. In this study we detected a higher prevalence in COVID-19 ICU-ECMO patients, compared to ICU and GCU cohorts, but also compared to the non-COVID-19 ECMO cohort, which aligns with published studies [33,34]. In contrast, the thyroid autoantibody TSAb, associated with Graves-Basedow disease [35], was found most frequently in the non-COVID-19 ECMO cohort.

Our investigation of phospholipid antibodies underlines an association with the pro-thrombotic status in COVID-19 patients, as previously reported [8,9,36,37]. We found the anti-cardiolipin antibody CL IgA specifically in the COVID-19 ICU ECMO and COVID-19 ICU cohorts. Positivity rates and titer levels were increased comparing the COVID-19 ICU-ECMO cohort with the COVID-19 ICU cohort and the non-COVID-19

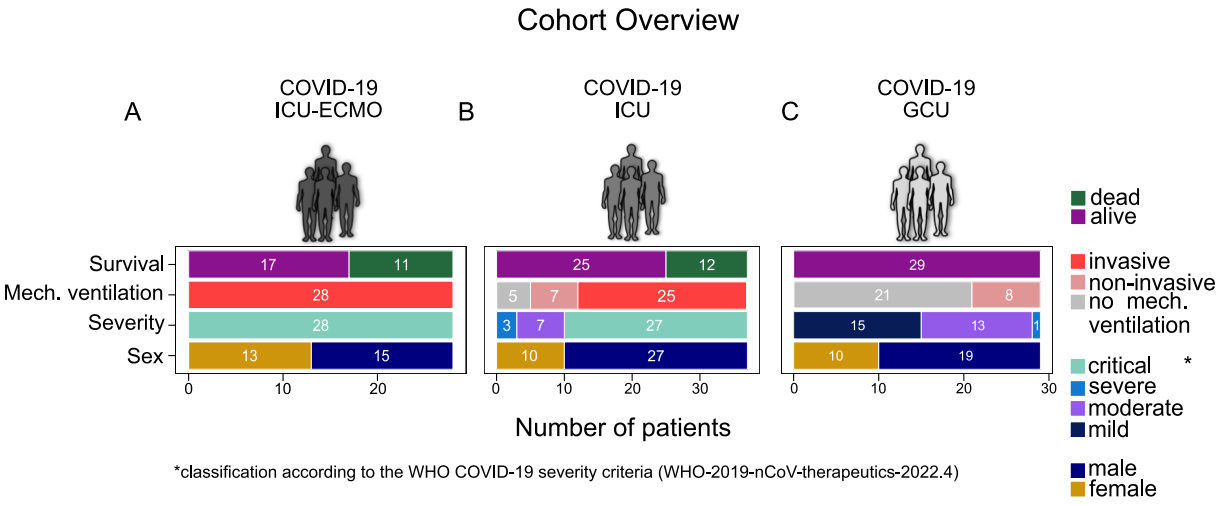

Fig. 1. Cohort overview: Characteristics of included COVID-19-positive patients ($n = 94$). Three cohorts were compared: ICU patients with ECMO support (COVID-19 ICU-ECMO), ICU patients without EMCO support (COVID-19 ICU) and COVID-19 patients from a GCU (COVID-19 GCU). Characteristics include survival, mechanical ventilation (invasive, non-invasive, no mechanical ventilation), classification according to the WHO COVID-19 severity criteria (WHO-2019-nCoV-therapeutics-2022.4) and sex. Abbreviations: mech., mechanical, ICU, intensive care unit, ECMO, extracorporeal membrane oxygenation, GCU, general care unit.

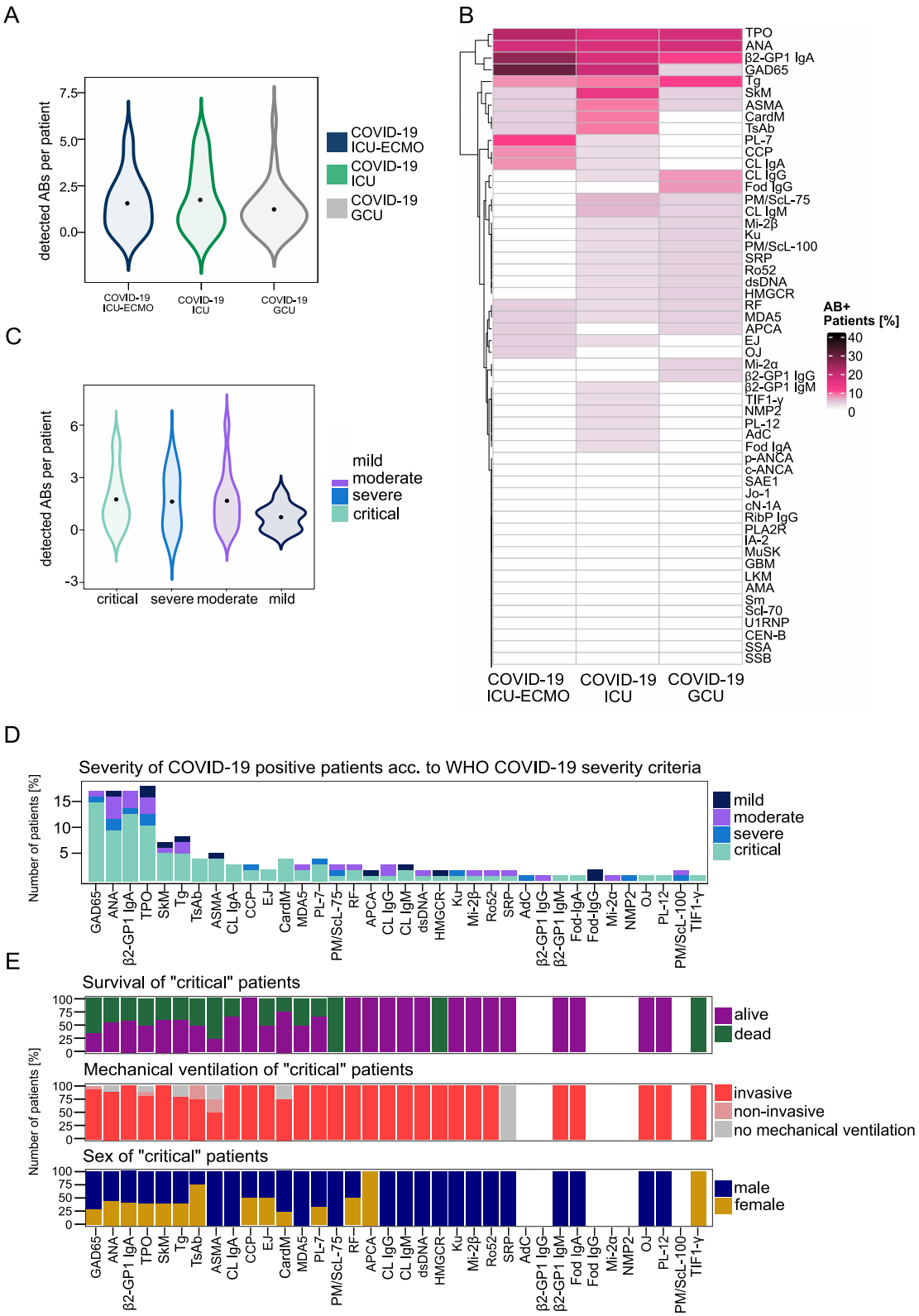

Fig. 2. A: Violin plot displaying the distribution of measured autoantibody numbers per patient across the COVID-19 ICU-ECMO, COVID-19 ICU and COVID-19 GCU cohort. B: Violin plot displaying the distribution of measured autoantibody numbers per patient across the patients stratified by the WHO COVID-19 severity criteria. C: Heatmap representing the measured autoantibodies shown in the percentage of autoantibody-positive patients per cohort. D: Stacked bar chart illustrating the distribution of autoantibody-positive patients across the WHO COVID-19 severity categories. The total height of each bar corresponds to the number of autoantibody-positive patients in percent for the indicated autoantibody. The different colors within each bar represent the proportion of patients in each WHO COVID-19 severity category. E: Stacked bar chart focusing on the subset of autoantibody-positive patients classified as "critical." The colors within each bar show the distribution of patients based on survival status, ventilation requirement, and sex. Abbreviations: AB, antibody, ICU, intensive care unit, ECMO, extracorporeal membrane oxygenation, GCU, general care unit.

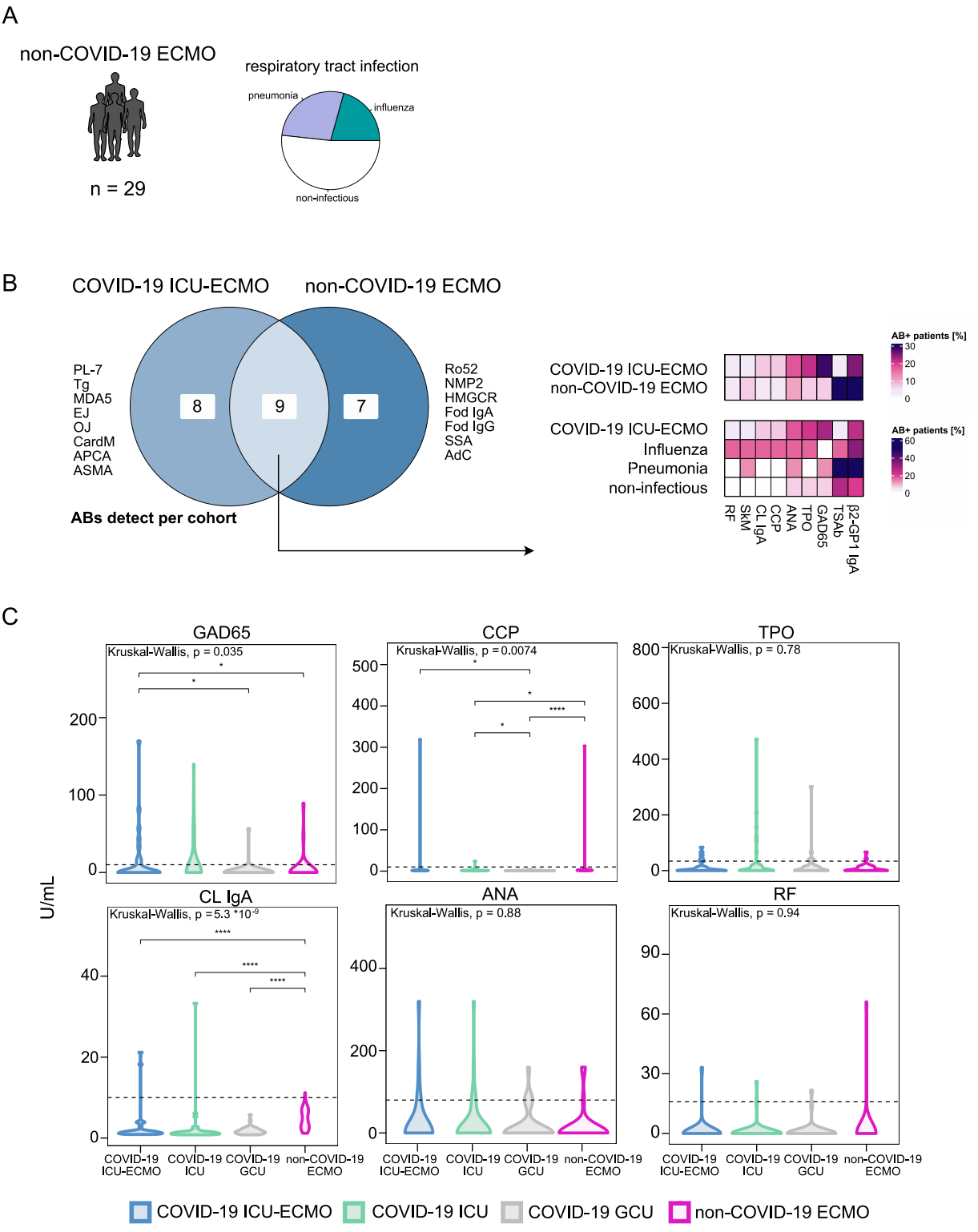

Fig. 3. A: Pie chart illustrating the classification of the non-COVID-19 ECMO cohort based on respiratory tract infections. B: Comparison of autoantibody prevalence in the COVID-19 ICU-ECMO cohort to the prevalence in a non-COVID-19 ECMO cohort ($n = 29$). Venn Diagram depicting the number of positive detected autoantibodies. Heatmap representing the percentage of autoantibody-positive patients per cohort for shared autoantibodies between the COVID-19 ICU-ECMO cohort and non-COVID-19 ECMO cohort upper panel and between COVID-19 ICU-ECMO and the influenza, pneumonia and non-infectious subgroup. C: Antibody titer of selected autoantibodies against GAD65, CCP, CL IgA, ANA and RF, for the three COVID-19 cohorts and the non-COVID-19 ECMO cohort in titer units per mL (U/mL). Line indicates threshold for positivity. Wilcoxon rank-sum test for pairwise comparisons between groups, with *p*-values adjusted for multiple testing using the Bonferroni correction. The overall differences between groups were assessed with the Kruskal-Wallis test. Significance levels: * adj. p-value <0.05, ** adj. p-value <0.01, *** adj. p-value <0.005. Abbreviations: ICU, intensive care unit, ECMO, extracorporeal membrane oxygenation, GCU, general care unit.

ECMO cohort.

Substantial evidence suggests a link between thrombotic events and severe diseases, namely cancer and conditions of chronic inflammations like SLE [38–41]. The following antibodies are further associated with SLE in the context of antiphospholipid syndrome (APS), namely Lupus anti-coagulant, anti-cardiolipin antibodies and anti-β2-GP1 [42]. Since we detected the anti-β2-GP1 IgA autoantibody, which is associated with antiphospholipid syndrome (APS) in both the COVID-19 ECMO-ICU and non-COVID-19 ECMO cohorts, follow-up analysis of autoantibodies in larger cohorts might be of further interest to investigate a potential connection between viral infections, the induction of thrombotic events and autoimmunity.

Our study identified a unique autoantibody pattern comparing the COVID-19 ECMO cohort to the non-COVID ECMO cohort. Additionally, preliminary characterization of a small subgroup of influenza patients revealed an autoantibody signature distinct from patients with pneumonia and those in the non-infectious subgroup. These findings suggest that severe viral infections, not a general condition requiring ECMO therapy, may drive autoantibody production. A follow-up study with a larger cohort of influenza patients would be valuable for validating and further exploring these observations.

While our study supports the hypothesis that autoantibody production is triggered by a severe form of COVID-19, the relatively small size of our cohorts necessitates caution. Seropositivity for autoantibodies associated with autoimmune diseases is consistent with what has been reported in post-COVID-19 cohort studies, but our study would benefit from follow-up data. Future research is crucial to understand how COVID-19 may contribute to the development of autoimmune diseases and the underlying mechanisms of autoantibody formation. It also needs to be further evaluated whether routine screening and subsequent monitoring of autoantibody levels could provide significant benefits for patient management or predict long-term outcomes. Additionally, it will be of particular interest to determine whether the production of autoantibodies is associated with viral infections beyond SARS-CoV-2.

Utilizing a comprehensive systemic autoantibody panel, our study underscores that COVID-19 stimulates the production of autoantibodies with varying targets. Our findings suggest a potential link between COVID-19 and the risk for the development of T1D, rheumatic diseases, myositis, and thyroid autoimmune diseases, corresponding to severity of the disease. This comprehensive approach provides new insights into the broader autoimmune implications of COVID-19, emphasizing the need for vigilant autoimmune monitoring in affected patients.

CRediT authorship contribution statement

Marie Brinkmann: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Ludwig Traby:** Writing – review & editing, Resources, Data curation, Conceptualization. **Manuel Kussmann:** Writing – review & editing, Resources, Data curation. **Matthias Weiss-Tessbach:** Writing – review & editing, Resources, Data curation. **Nina Buchtele:** Writing – review & editing, Resources, Data curation. **Thomas Staudinger:** Writing – review & editing, Resources, Data curation. **Elias Gaidoschik:** Formal analysis, Data curation. **Thomas Perkmann:** Writing – review & editing, Resources, Methodology. **Helmuth Haslacher:** Writing – review & editing, Resources, Methodology. **Franz Ratzinger:** Resources, Data curation. **Winfried F. Pickl:** Writing – review & editing, Resources, Methodology. **Karim El-Gedawi:** Resources, Methodology. **Melanie Feichter:** Resources, Methodology. **Ellen Gelpi:** Writing – review & editing, Resources, Methodology. **Romana Höftberger:** Resources, Methodology. **Peter Quehenberger:** Resources, Methodology. **Rodrig Marculescu:** Resources, Methodology. **Daniel Mrak:** Resources, Data curation. **Kastriot Kastrati:** Resources, Methodology. **Helga Lechner-Radner:** Writing – review & editing, Methodology. **Daniela Sieghart:** Resources, Methodology. **Daniel Aletaha:** Supervision, Resources, Project administration. **Stefan Winkler:** Supervision, Resources, Project administration. **Michael Bonelli:** Writing – original draft, Validation, Supervision, Methodology, Investigation, Conceptualization. **Lisa Göschl:** Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

MiB received grants from Galapagos. DA received grants and consulting fees from AbbVie, Amgen,Lilly, Merck, Novartis, Pfizer, Roche and Sandozand. NB received speaker fees (Mistubishi Tanabe) and investigator-initiated research grants (Mitsubishi Tanabe, CSL Behring).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clim.2025.110471.

Data availability

Data will be made available on request.

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