NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

MEDICAL SCHOOL

PATHOPHYSIOLOGY DEPARTMENT

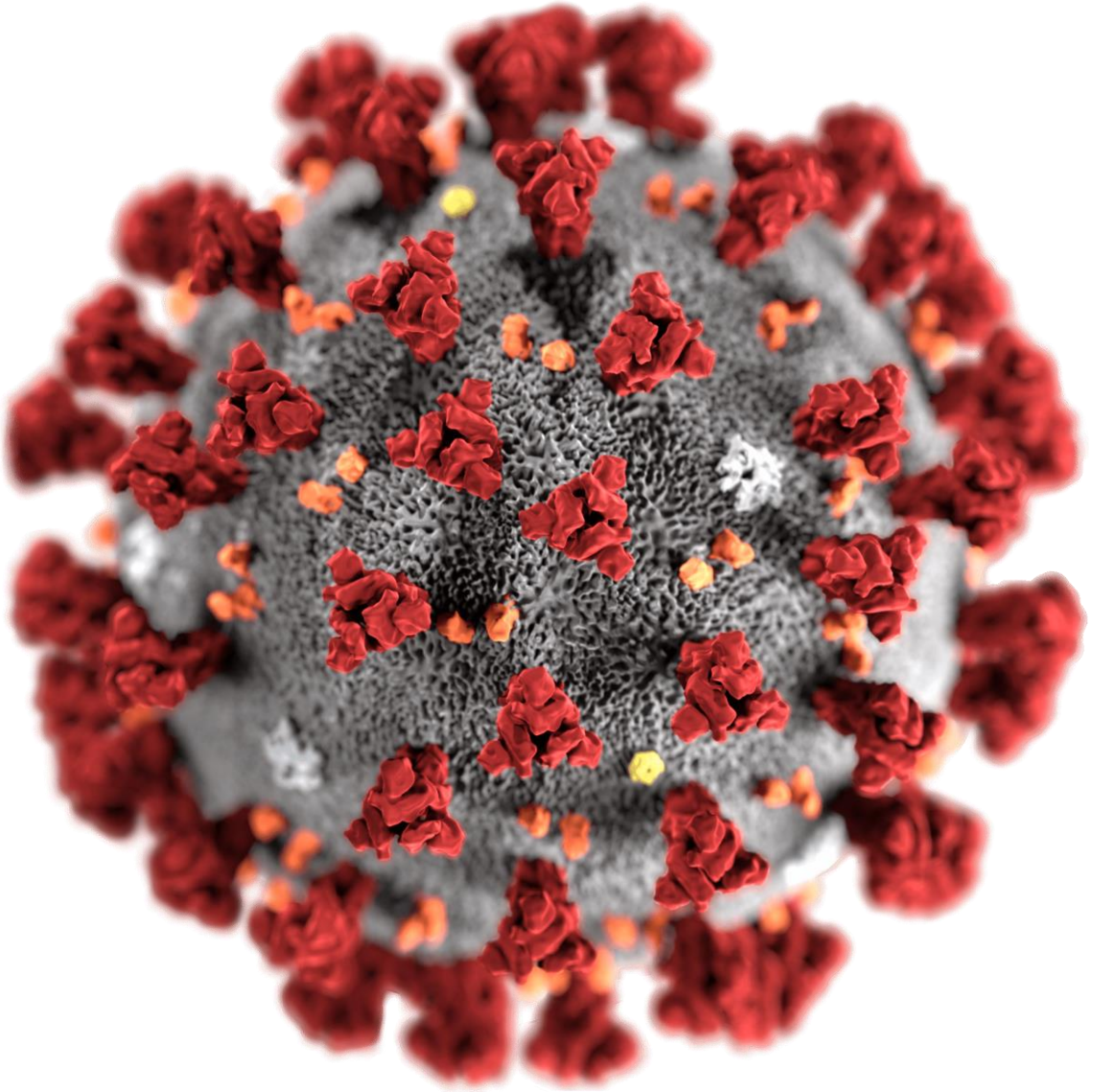
COVID-19 and vaccines against SARS-CoV-2 in patients with systemic autoimmune/autoinflammatory rheumatic diseases

Athanasios-Dimitrios Bakasis

Chalkidiki, September 2nd, 2021

Outline

- **COVID-19**
  - Classification of the clinical spectrum
  - Risk factors for severe disease
  - Immunobiological mechanisms
- **Systemic autoimmune diseases at the crossroad of COVID-19**
  - The Greek Experience
  - Existing Data
- **Vaccination against SARS-CoV-2**
  - Clinical practice guidelines and beyond
  - Data on immunogenicity, safety and efficacy
  - The role of treatment modification during vaccination period: preliminary results from a Greek multicenter prospective observational study
- **Conclusions**



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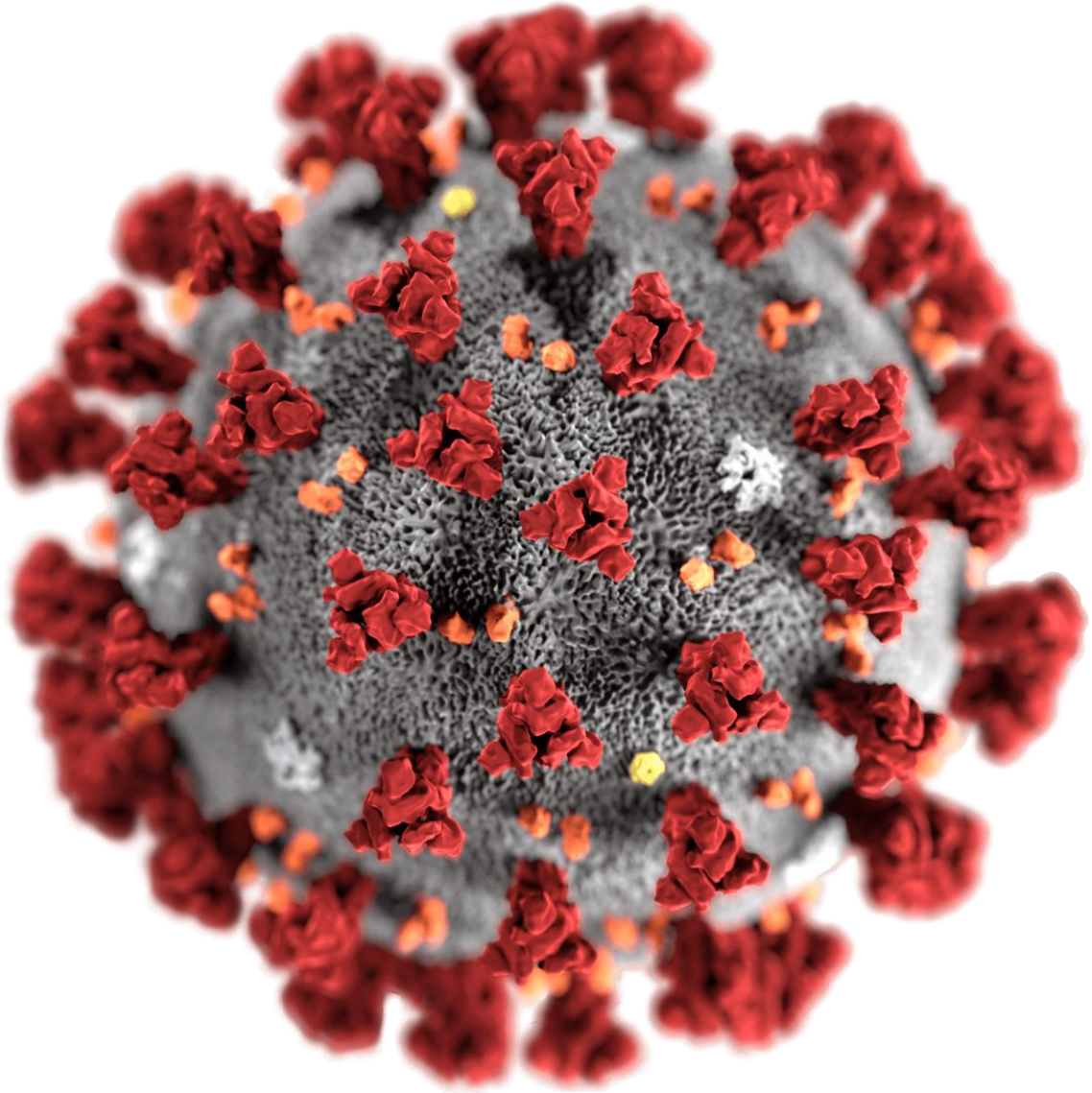

Clinical picture of COVID-19

Asymptomatic: Individuals who test positive for SARS-CoV-2 using a virologic test but who have no symptoms that are consistent with COVID-19.

***Mild Illness*:** Any of the various COVID-19 symptoms and signs BUT NOT shortness of breath or abnormal chest imaging.

Moderate Illness: Lower respiratory disease during clinical assessment or imaging and WITHOUT hypoxia (SpO2 ≥94%).

Severe Illness: Presence of hypoxia or lung infiltrates >50%.

Critical Illness: Respiratory failure, septic shock, and/or multiple organ dysfunction

NIH: COVID-19 Treatment Guidelines Panel

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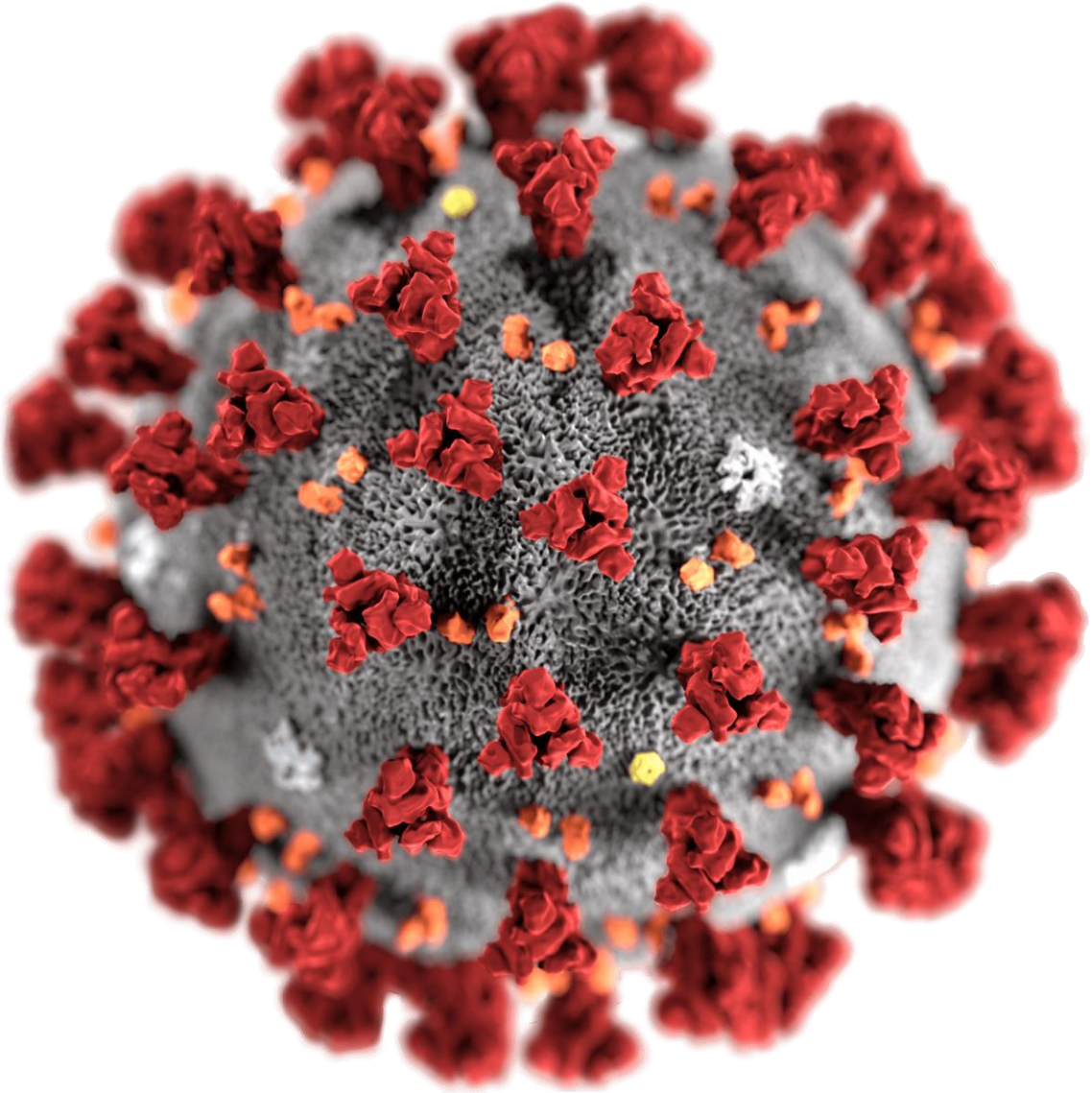

High-risk factors for severe COVID-19

- Demographics (older age, ethnicity, obesity)
- Environmental factors (smoking disorders, substance use)
- Metabolic disorders (diabetes mellitus, hyperlipidaemia)
- Heart conditions (heart failure, coronary artery disease, cardiomyopathies)
- Respiratory disease (COPD, asthma, ILD, pulmonary fibrosis, pulmonary hypertension)
- Chronic kidney disease
- Advanced liver disease
- Neurologic conditions (cerebrovascular disease, dementia)
- Haematological conditions (sickle cell disease, haematological malignancy)
- Cancer
- Other (Down s., HIV)
- Immunocompromised state (primary deficiencies, transplantation, immunosuppressive medications, autoimmune diseases)

Rosenthal N et al. JAMA Network Open. 2020
Williamson EJ et al. Nature. 2020

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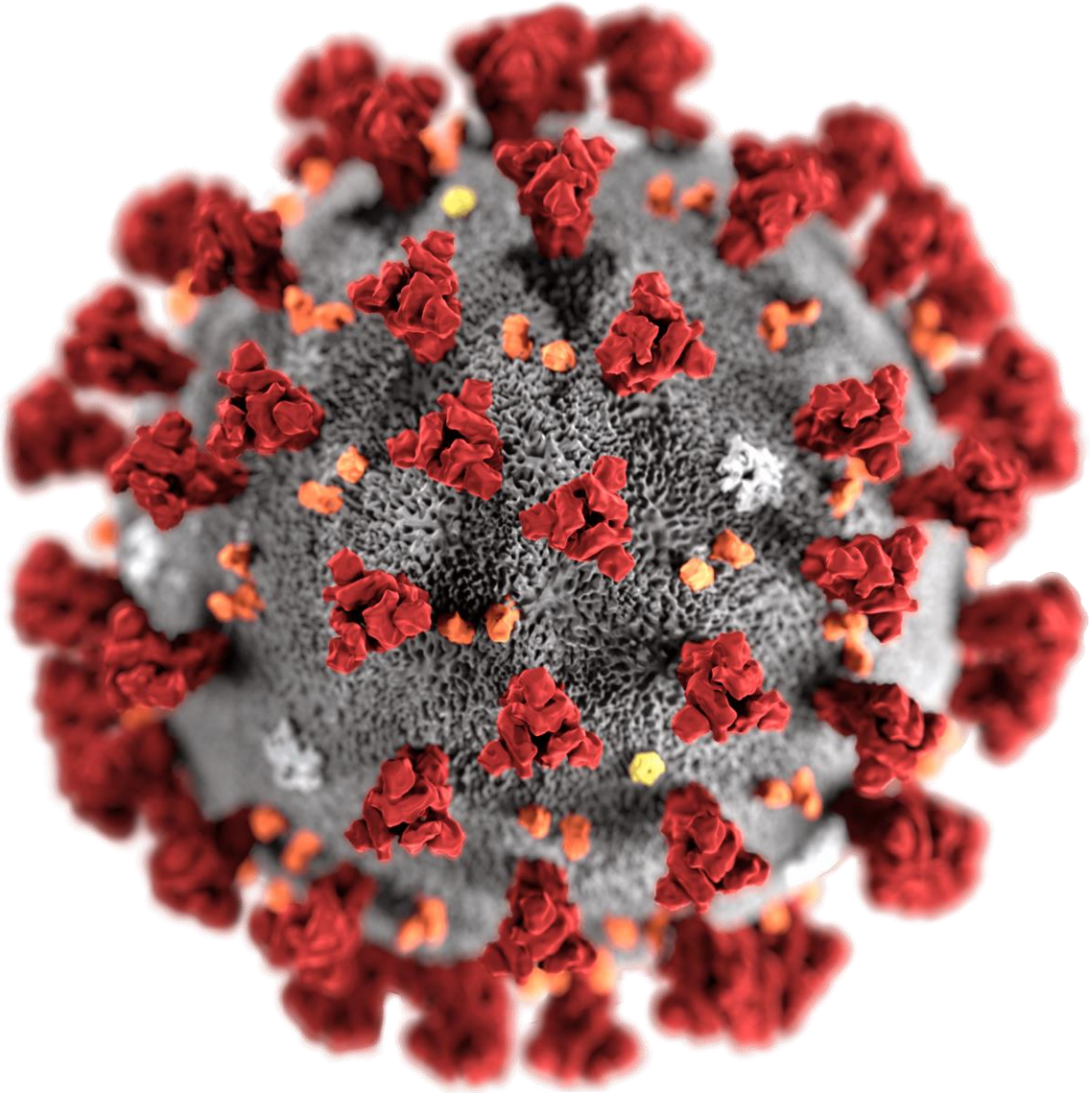
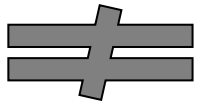


Early immunological changes in severe COVID-19

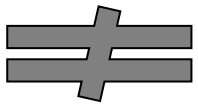
- Hyper-inflammatory state:↑ pro-inflammatory cytokines (IL-6, IL-10 και TNF-α) → hyper-inflammatory response → “cytokine storm”
- Impaired and delayed interferon type I production
- Endotheliopathy and platelet activation

Chen G, et al, J Clin Invest 2020: 130(5): 2620-2629
Goshua G, et al, Lancet Haematol 2020
Galani, IE et al. Nat Immunol 2021.

Unique characteristics of systemic autoimmune rheumatic diseases



Immunosuppressive/immunomodulatory therapy



Heightened production of interferon type I

Hooks JJ, Moutsopoulos HM et al. N Engl J Med 1979
Rodríguez Y et al. J Autoimmun 2021

Anti-inflammatory therapy may ameliorate the clinical picture of COVID-19

- ❑70-year-old woman, CAPS, canakinumab) → low-grade fever, malaise COVID-19 (+)

✓Symptoms resolved in a couple of days

- ❑57-year-old woman, SSc, DM2, obesity, tocilizumab → cough, headache, malaise, subfebrile for 1 week → relatively good general health condition, with unchanged bibasal lung crackles and no dyspnoea → she was allowed to return home with symptomatic treatment only.

✓The mild symptoms resolved in a 10 days

Moutsopoulos HM. Ann Rheum Dis. 2020
Mihai C et al. Ann Rheum Dis. 2020

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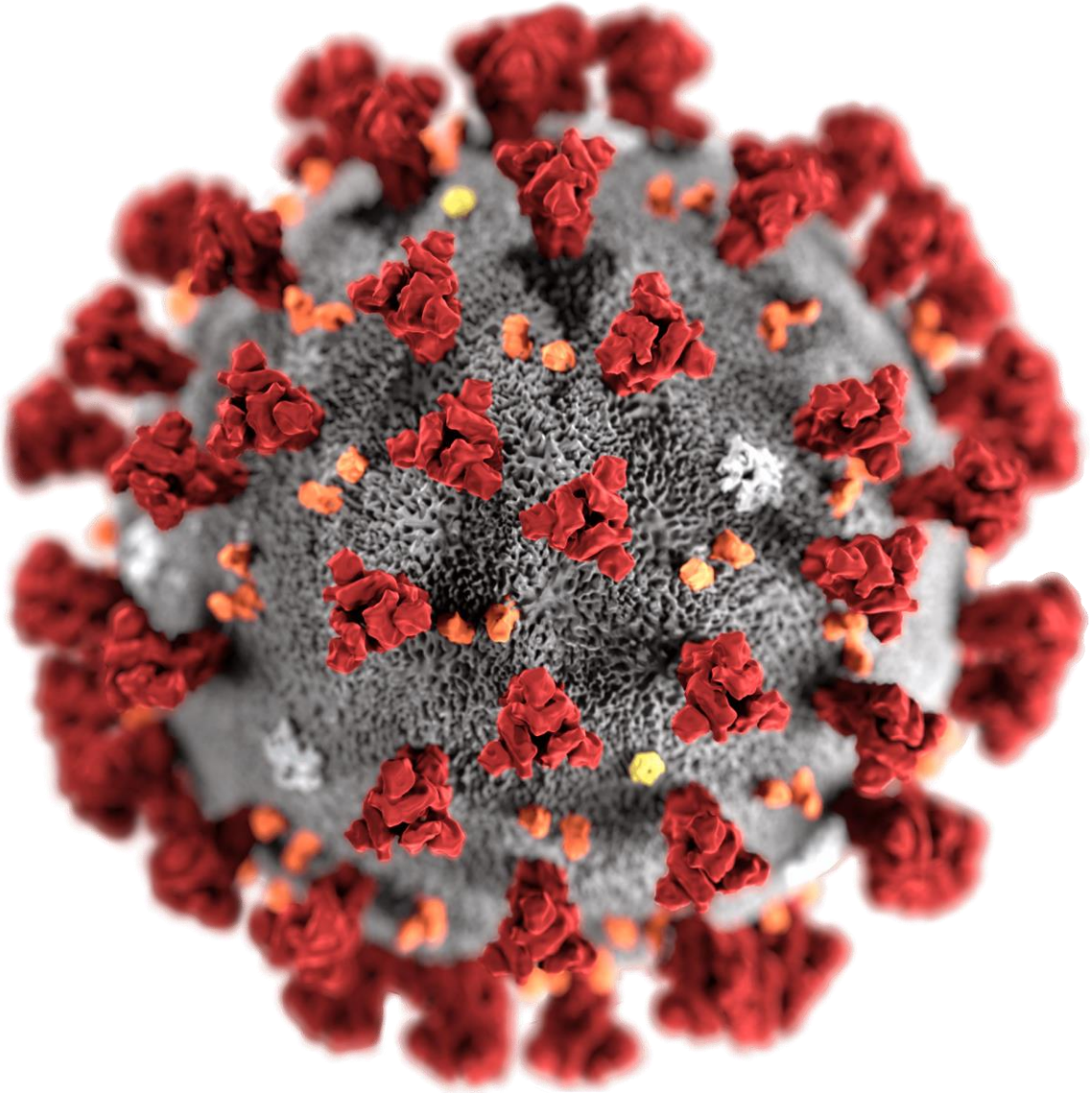


COVID-19 infection among AARD patients

- ❑ Prospective observational study: AARD patients of Greek origin infected by SARS-CoV-2
  - Clinical presentation
  - Disease course
  - Outcome

- ❑ Centers participating:
  - Department of Pathophysiology, Laikon General Hospital of Athens
  - Department of Medicine and Clinical Immunology, Euroclinic of Athens, Athens
  - Rheumatology Unit, Sismanoglio General Hospital, Athens

- ❑ Assessment of patients:
  - Telehealth
  - Physical examination
  - Laboratory examination
  - Radiological evaluation
  - Treatment management

  } Referral to hospital

- ❑ Questionnaire and data collection

Bakasis AD et al. J Autoimmun. 2021

Questionnaire

Name: **Patient Code:**

Autoimmune/auto-inflammatory disease:

Duration (years):

Disease activity:

Receiving treatment:

Date of detection of SARS-CoV-2: **Detection Method:**

Symptomatology:	Yes	No	Duration
High grade fever (>38oC)			
Low grade fever (<38^{o}C)			
Nasal congestion			
Sore throat			
Cough			
Dyspnea			
Fatigue			
Arthralgia			
Myalgia			
Anosmia			
Loss of taste			
Headache			
Vomiting			
Diarrhea			
Mental confusion			
Seizures			
Skin rash			

Recovery at home

Hospitalization

Bakasis AD et al. J Autoimmun. 2021

Questionnaire

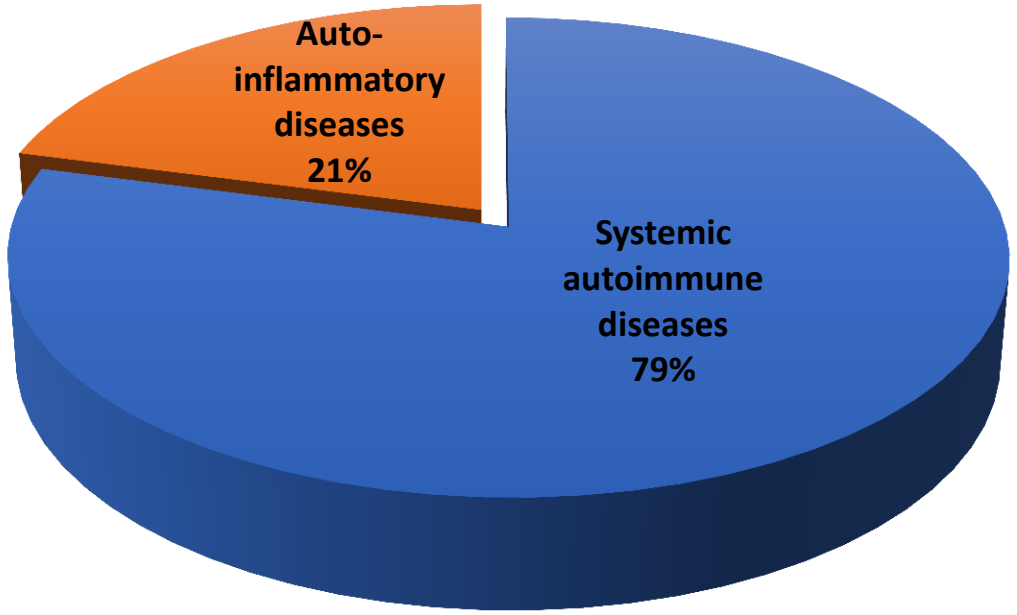
Bakasis AD et al. J Autoimmun. 2021

Filled by the attending physician

	Yes	No	Duration (days)
Σε περίπτωση ανάρρωσης στο σπίτι:			
Discontinuation of immunosuppressive/immunomodulatory treatment			
Medication:			
Vitamins and trace elements			
Low molecular weight heparin			
Corticosteroids			
Antibiotics			
In case of hospitalization:			
Discontinuation of immunosuppressive/immunomodulatory treatment			
Medication:			
Oxygen therapy			
Low molecular weight heparin			
Dexamethasone			
Remdesivir			
Antibiotics			
Comorbidities:		Describe	
Clinical examination:			
Laboratory testing:		Values	
Hemoglobin			
White blood cells/type			
Platelets			
Liver enzymes			
Cholestatic enzymes			
Lactate Dehydrogenase			
Phosphocreatine kinase			
Urea/Creatinine			
Glucose			
Sodium/Potassium			
Markers of inflammation			
D-dimers			
Ferritin			
O2 saturation			
Radiological examination		Περιγράψτε	
Chest X-ray			
Chest computed tomography			
Other tests (arterial blood gases, ECG, etc.)			

Population of the study

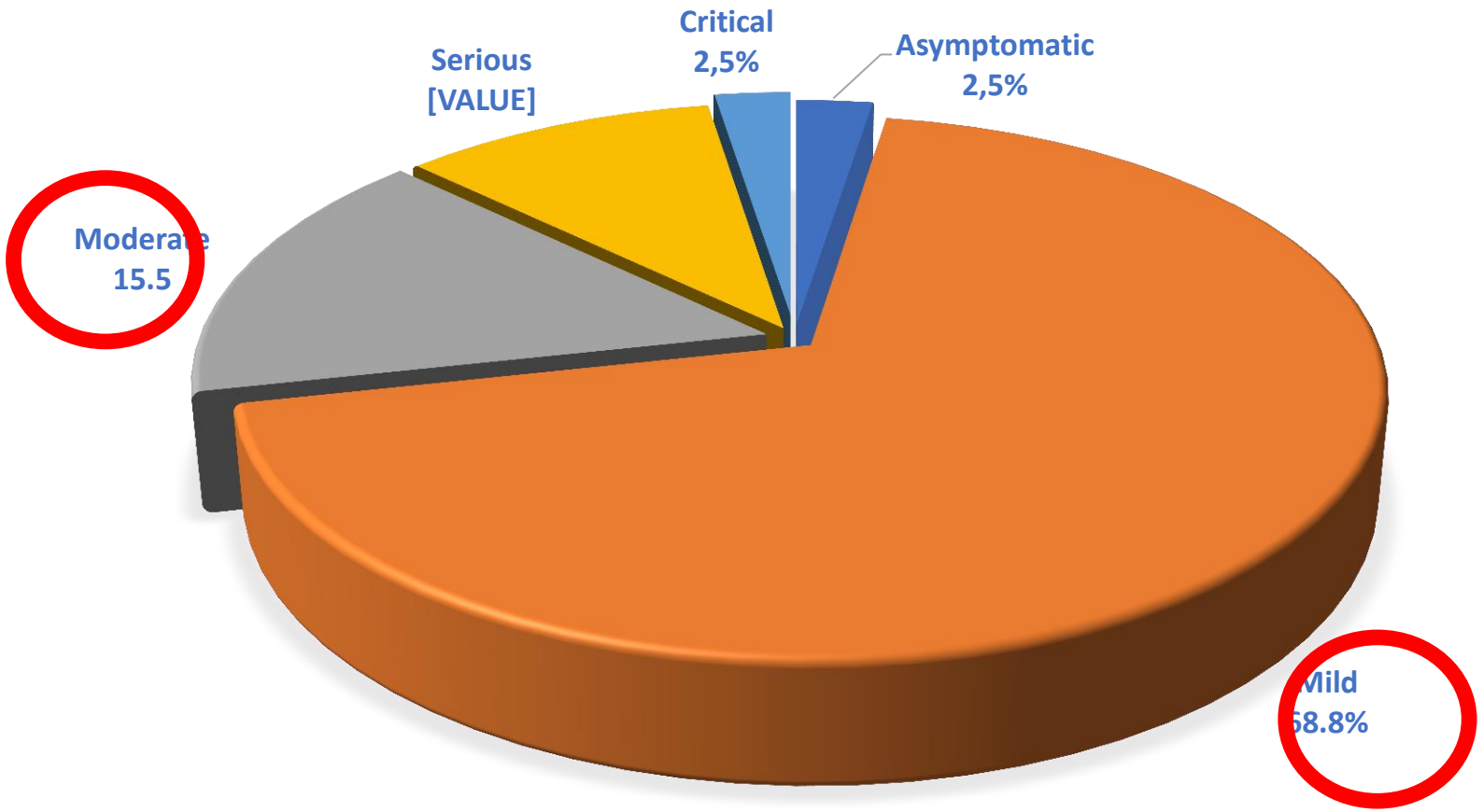
Total cases: 77



Demographics	
Female gender (%)	80.5
Age (mean ± SD, years)	49.5± 16.8
Duration of AARD (mean ± SD, years)	10.6 ± 8.5
Contact with a confirmed case (%)	75.0
Comorbidities	
Lung disease (%)	14.2
Hypertension (%)	12.5
Dyslipidaemia (%)	8.3
Other cardiovascular disease (%)	6.9
Diabetes mellitus (%)	6.9
Other (%)	3.6

Bakasis AD et al. J Autoimmun. 2021

COVID-19 disease severity



Bakasis AD et al. J Autoimmun. 2021

COVID-19 Symptomatology

Any upper respiratory (%)	**68.8**
Fatigue (%)	**58.4**
Low grade fever (%)	**45.4**
Cough (%)	**41.5**
Myalgia (%)	**37.6**
Fever (%)	**31.2**
Anosmia (%)	**29.9**
Headache (%)	**26.0**
Loss of taste (%)	**24.7**
Diarrhea (%)	**24.7**
Sore throat (%)	**22.1**
Dyspnea (%)	**14.3**
Nasal congestion (%)	**14.3**
Arthralgia (%)	**10.4**
Vomiting (%)	**3.9**
Confusion (%)	**1.3**
Seizures (%)	**1.3**
Rash (%)	**1.3**
Duration of symptomatology (mean ± SD, years)	**9.7 ± 6.4**

Bakasis AD et al. J Autoimmun. 2021

Comparison based on disease severity

	Patients with asymptomatic, mild or moderate disease (n=67)	Patients with severe or critical disease (n=10)	p-value
Demographics			
Age (mean ± SD, years)	46.6±15.4	68.9±12.8	<0.001
COVID-19 Symptoms			
Fever low grade (%)	50.7	10.0	0.016
Fever high grade (%)	25.4	70.0	0.008
Headache (%)	29.0	0.0	0.045
Shortness of breath (%)	9.0	50.0	<0.001
Seizures (%)	0.0	10.0	0.009
Medications			
Methylprednisolone (%)	29.9	60.0	0.003
Mycophenolate mofetil (%)	7.5	40.0	0.003
Rituximab (%)	0.0	10.0	0.009
Comorbidities			
Lung Disease (%)	9.0	50.0	<0.001

Bakasis AD et al. J Autoimmun. 2021

Comparison based on need for hospitalization

	Patients required hospitalization (n=18)	Patients recovered at home (n=59)	p-value
Demographics			
Age (mean ± SD, years)	63.9 ± 14.4	45.1 ± 15.0	<0.001
COVID-19 Symptoms			
Fever low grade (%)	16.7	54.2	0.005
Fever high grade (%) (> 38°C, %)	72.2	18.6	<0.001
Anosmia (%)	5.6	37.3	0.01
Shortness of breath (%)	38.9	6.8	<0.001
Confusion (%)	5.5	0.0	0.016
Medications			
Methylprednisolone (%)	61.1	25.4	0.005
Mycophenolate mofetil (%)	33.3	5.1	0.001
Comorbidities			
Lung Disease (%)	44.4	5.1	<0.001
Dyslipidemia (%)	22.2	3.7	0.014

Bakasis AD et al. J Autoimmun. 2021

Laboratory and radiological findings among hospitalized patients

	Patients required hospitalization (n=18)
LABORATORY FINDINGS	
Anemia (%)	46.7
Leukocytosis (%)	20.0
Leukopenia (%)	20.0
Lymphopenia (%)	53.3
Thrombocytosis (%)	0.0
Thrombocytopenia (%)	6.7
LFTs (%)	40.0
Number of times AST above UNL (mean ± SD)	2.1 ± 1.4
Number of times ALT above UNL (mean ± SD)	1.9 ± 1.6
CK/LDH (%)	41.7
CRP (%)	78.6
Number of times CRP above UNL (mean ± SD)	8.9 ± 8.5
ESR (%)	40.0
Ferritin (%)	25.0
Number of times Ferritin above UNL (mean ± SD)	2.7 ± 0.3
D-Dimers (%)	55.5
Number of times D-Dimers above UNL (mean ± SD)	2.8 ± 1.2
Hypoxia (%)	52.9
O_2 Saturation (mean ± SD)	89.6 ± 4.6

Bakasis AD et al. J Autoimmun. 2021

Disease flares

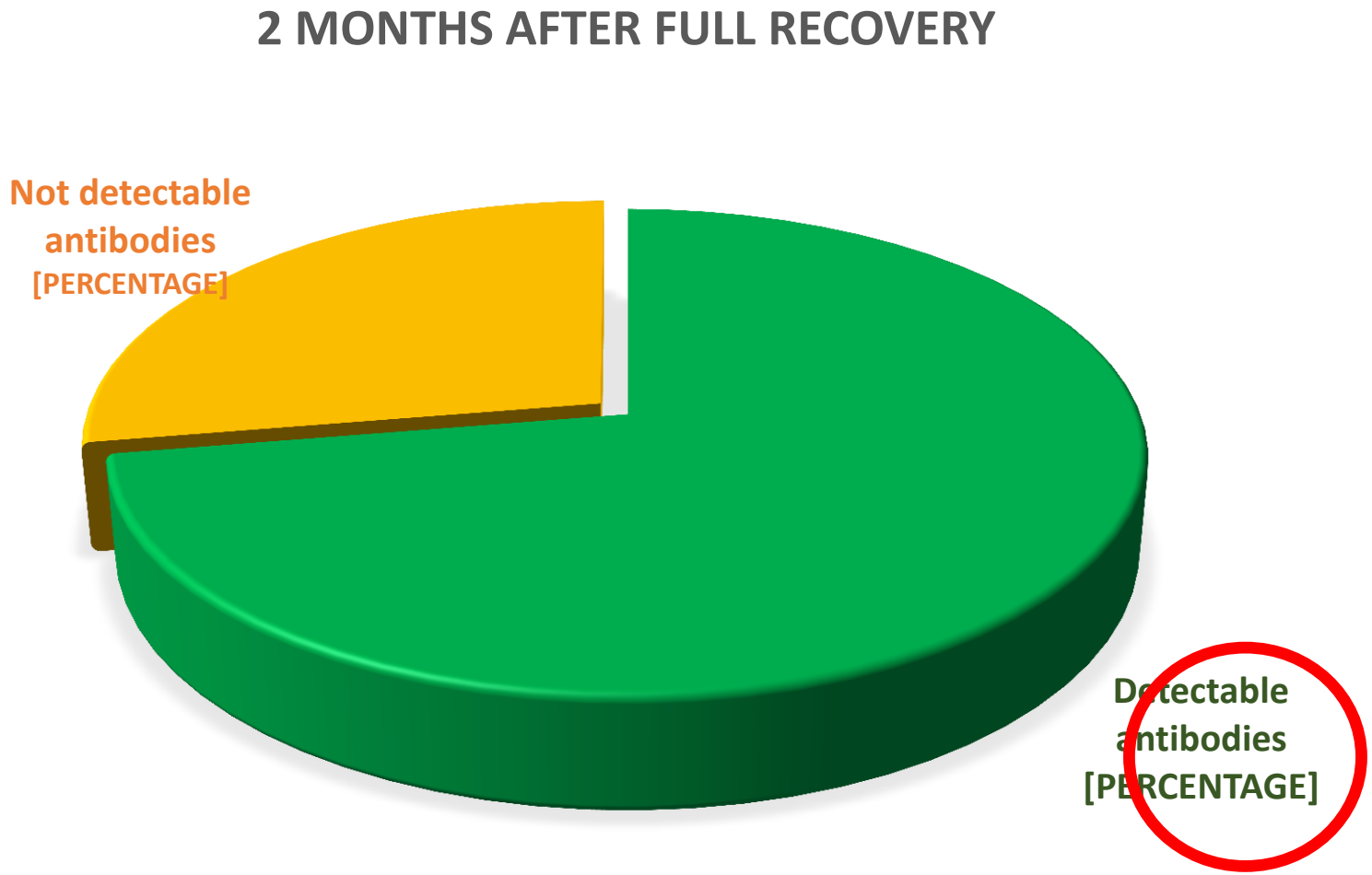
1 disesase exacerbation was observed:

- male, 17yo, TRAPS, in remission on colchicine.
- generalized skin rash accompanied + arthralgias + fever, a

✓ subsided following an increase in colchicine dose

Bakasis AD et al. J Autoimmun. 2021

Anti-SARS-CoV-2 antibodies



Bakasis AD et al. J Autoimmun. 2021

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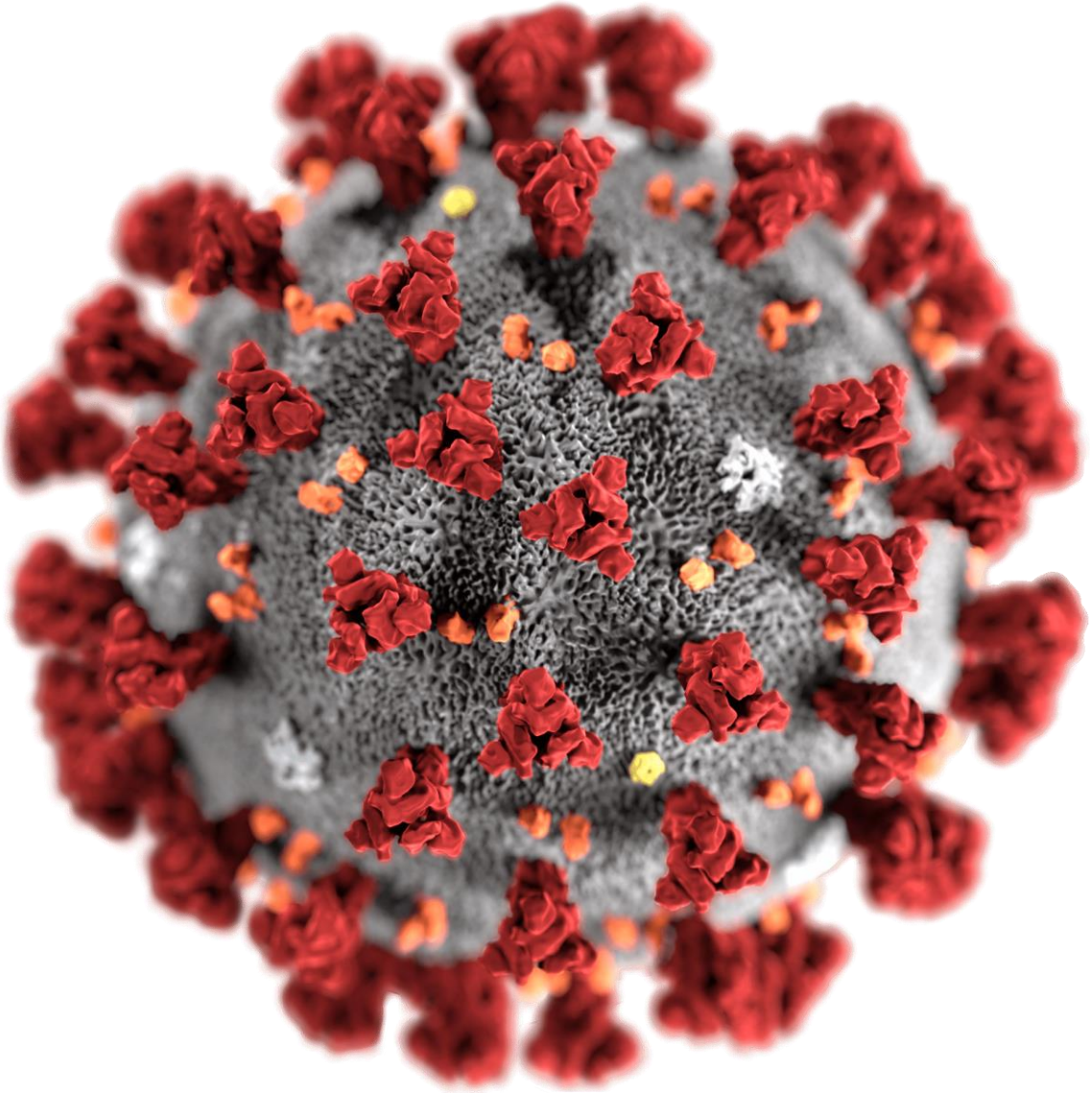


COVID-19 among AARD patients

- ✓ Similar incidence of COVID-19 and hospitalization AARD patients and the general population
- ✓ No differences in prevalence of severe pneumonia in ICU between AARD and no-AARD patients
- ✓ 63% mild disease without hospitalization, 24% moderate hospitalization in the ward, 13% severe disease in ICU and/or death (ICU AARN patients are no different from other patients with severe disease)
- ✓ The risk of death is not significantly increased in AARD patients

Zen M et al. J Autoimmun. 2020

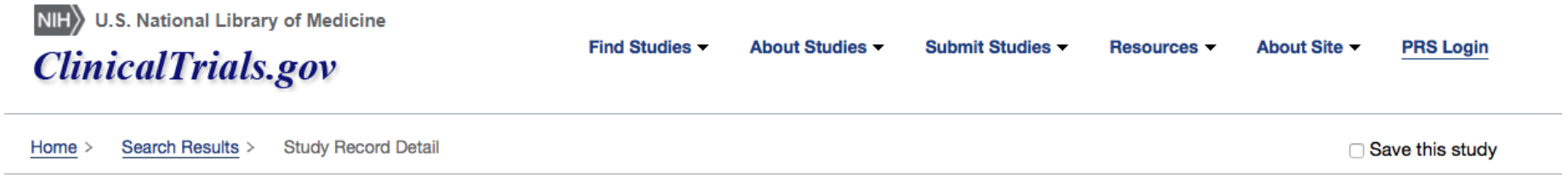
Conticini E et al. Ann Rheum Dis 2020

Haberman R et al. N Engl J Med. 2020

Moiseev S et al. Ann Rheum Dis. 2020

FAI2R /SFR/SNFMI/SOFREMIP/CRI/IMIDIATE consortium and contributors. Ann Rheum Dis. 2020

Research groups & registries were rapidly organized across the globe



Disease course, hospitalization and mortality

✕Risk factors:

- Older age,
- Male sex,
- History of lung disease, CVD, DM
- Prednisone >10mg/day, Rituximab, Mycophenolate mofetil, Cyclophosphamide
- High disease activity

✓TNF inhibitors are associated with ↓ risk of hospitalization.

Gianfrancesco M et al. Ann Rheum Dis. 2020

Strangfeld A et al. Ann Rheum Dis. 2021

FAI2R /SFR/SNFMI/SOFREMIP/CRI/IMIDIATE consortium and contributors. Ann Rheum Dis. 2020

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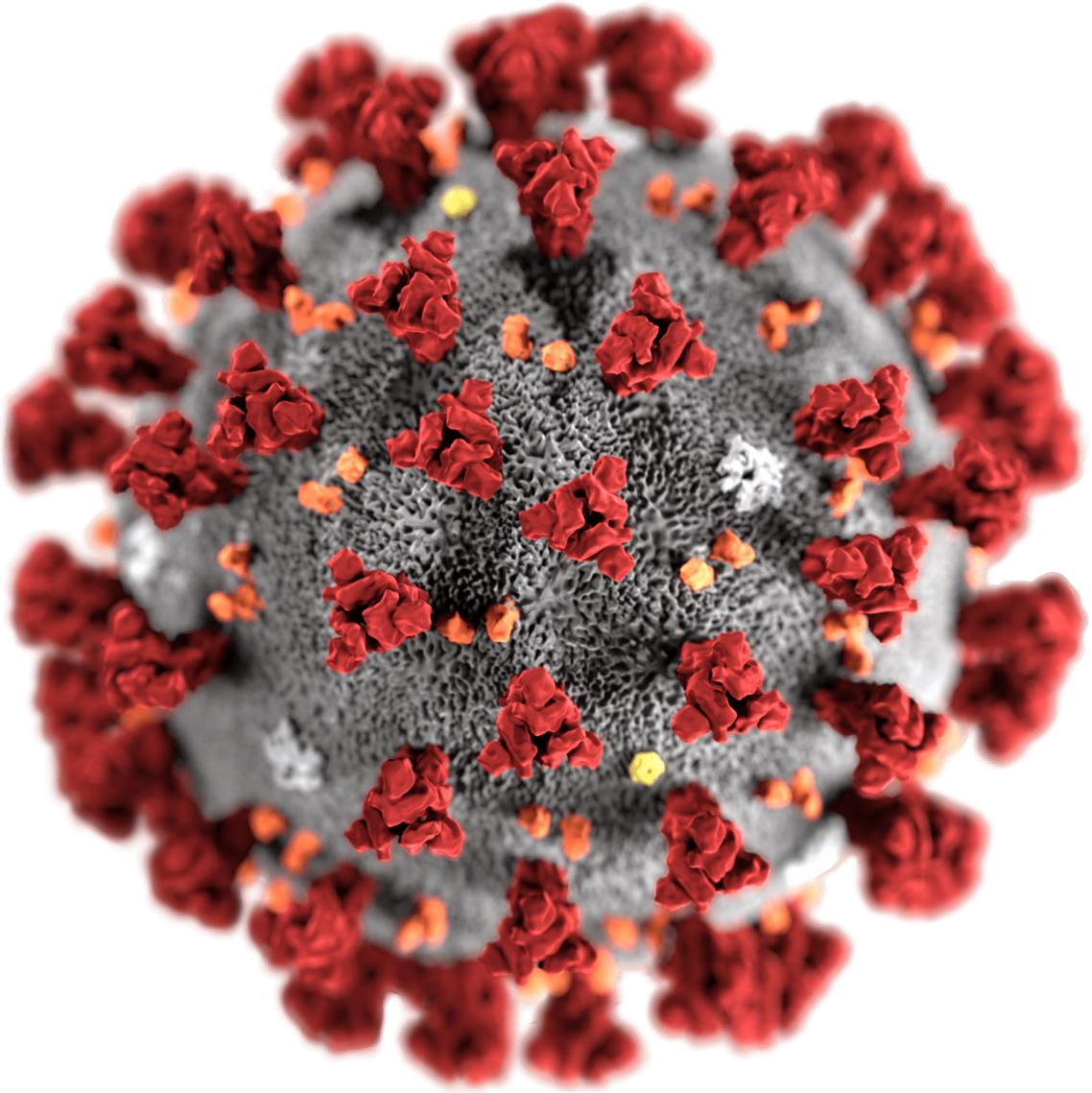
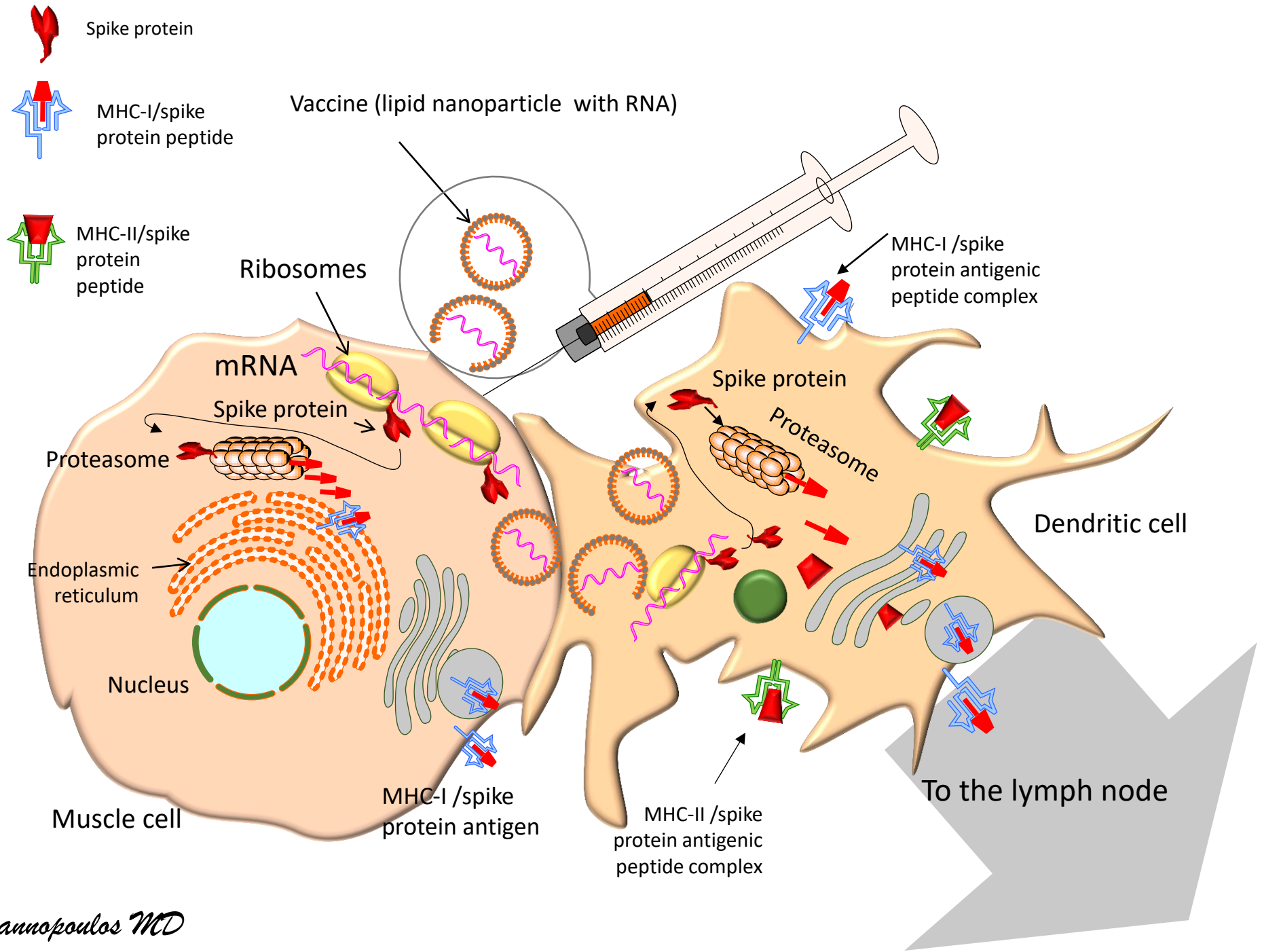
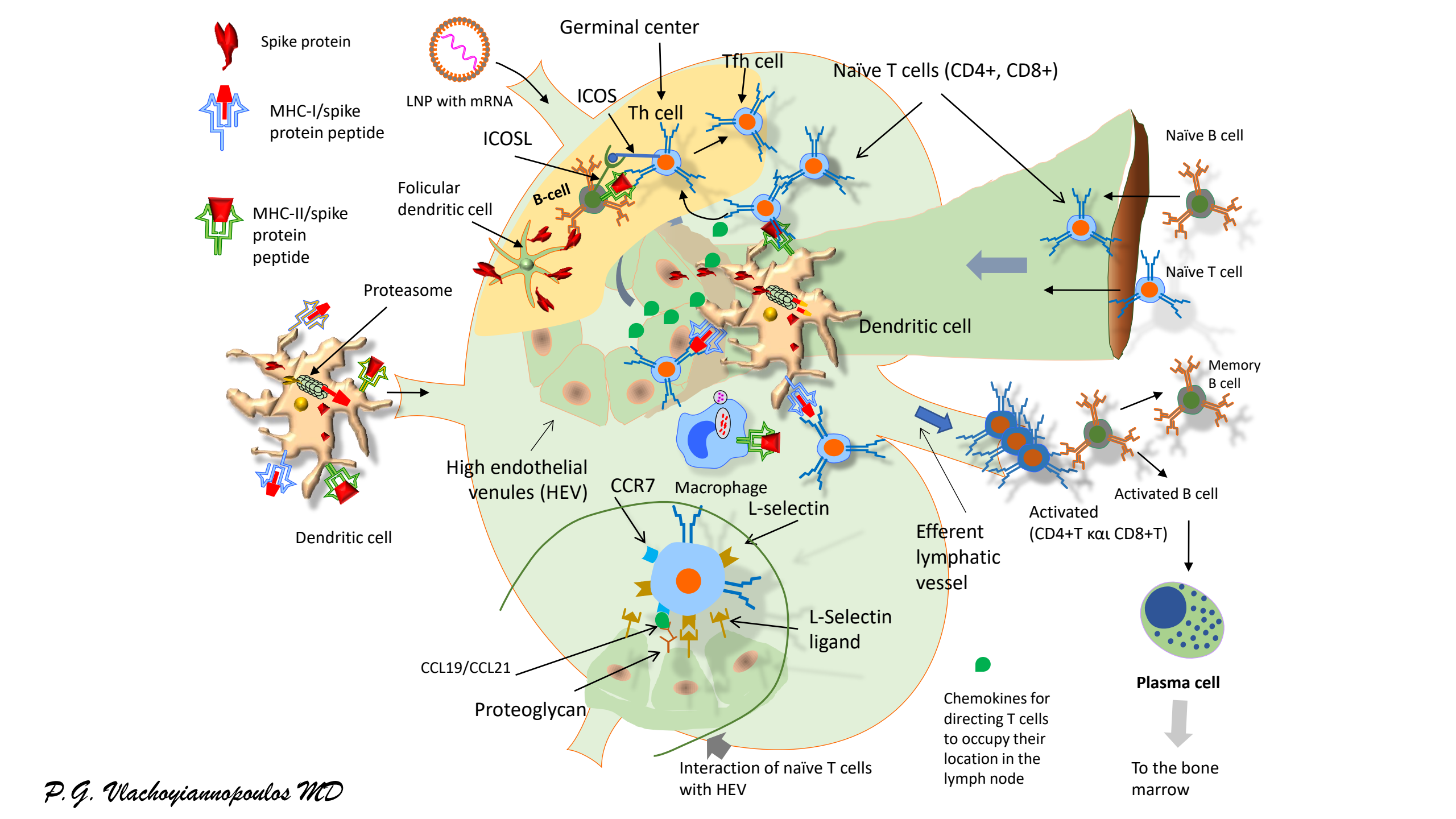




P.G. Vlachoyiannopoulos MD



P.G. Vlachoyiannopoulos MD

ACR Guidance for COVID- 19 Vaccination in Patients With Rheumatic and Musculoskeletal Diseases: Version 1

- AIIRD patients should be prioritized for vaccination before the non- prioritized general population of similar age and sex.

- Beyond known allergies to vaccine components, there are no known additional contraindications to COVID-19 vaccination for AIIRD patients.

- The expected response to COVID-19 vaccination is blunted in its magnitude and duration for many AIIRD patients on systemic immunomodulatory therapies compared to the general population.

- The benefit of COVID-19 vaccination for RMD patients outweighs the theoretical risk exists for AIIRD flare or disease worsening or the potential risk for new onset autoimmunity.

Arthritis & Rheumatology on May 2021

ACR Guidance for COVID- 19 Vaccination in Patients With Rheumatic and Musculoskeletal Diseases: Version 1

No modification

- **Strong** consensus was achieved regarding the statement to not delay COVID- 19 vaccination for patients receiving hydroxychloroquine, sulfasalazine, leflunomide, apremilast, or IVIG
- **Moderate** consensus was achieved for most of the remaining immunomodulatory therapies considered.

Modification in timing

- **One exception** was RTX for which the panel recommended to schedule vaccination such that the vaccine series would be initiated ~4 weeks prior to the next scheduled RTX dose

Arthritis & Rheumatology on May 2021

A recommended paradigm for vaccination of rheumatic disease patients with the SARS-CoV-2 vaccine

- Clinical remission prior to vaccination is desirable.
- Initiation of immunosuppressive therapy should be delayed until the vaccination is completed, if possible.
- Anti-metabolites, calcineurin and JAK inhibitors should be held 10 days before and 10 days after each vaccination dose
- Prednisone dosage (>0.5 mg/kg body weight) or an equivalent synthetic steroid dose, should be decreased to <10 mg/daily for 10 days before and after each vaccination dose (if possible).

Moutsopoulos HM. J Autoimmun. 2021.

A recommended paradigm for vaccination of rheumatic disease patients with the SARS-CoV-2 vaccine

- Patients on rituximab therapy should be vaccinated either one month prior to initiation of the therapeutic scheme or 6–8 months after the rituximab infusion.
- Patients on intravenous monthly pulse cyclophosphamide/methylprednisone therapy should be vaccinated either prior to therapeutic scheme or one month after the completion of 6 months pulse therapy.
- Immunization should be performed after the anti-cytokine drug therapy has reached baseline sera levels (if possible).

Moutsopoulos HM. J Autoimmun. 2021.

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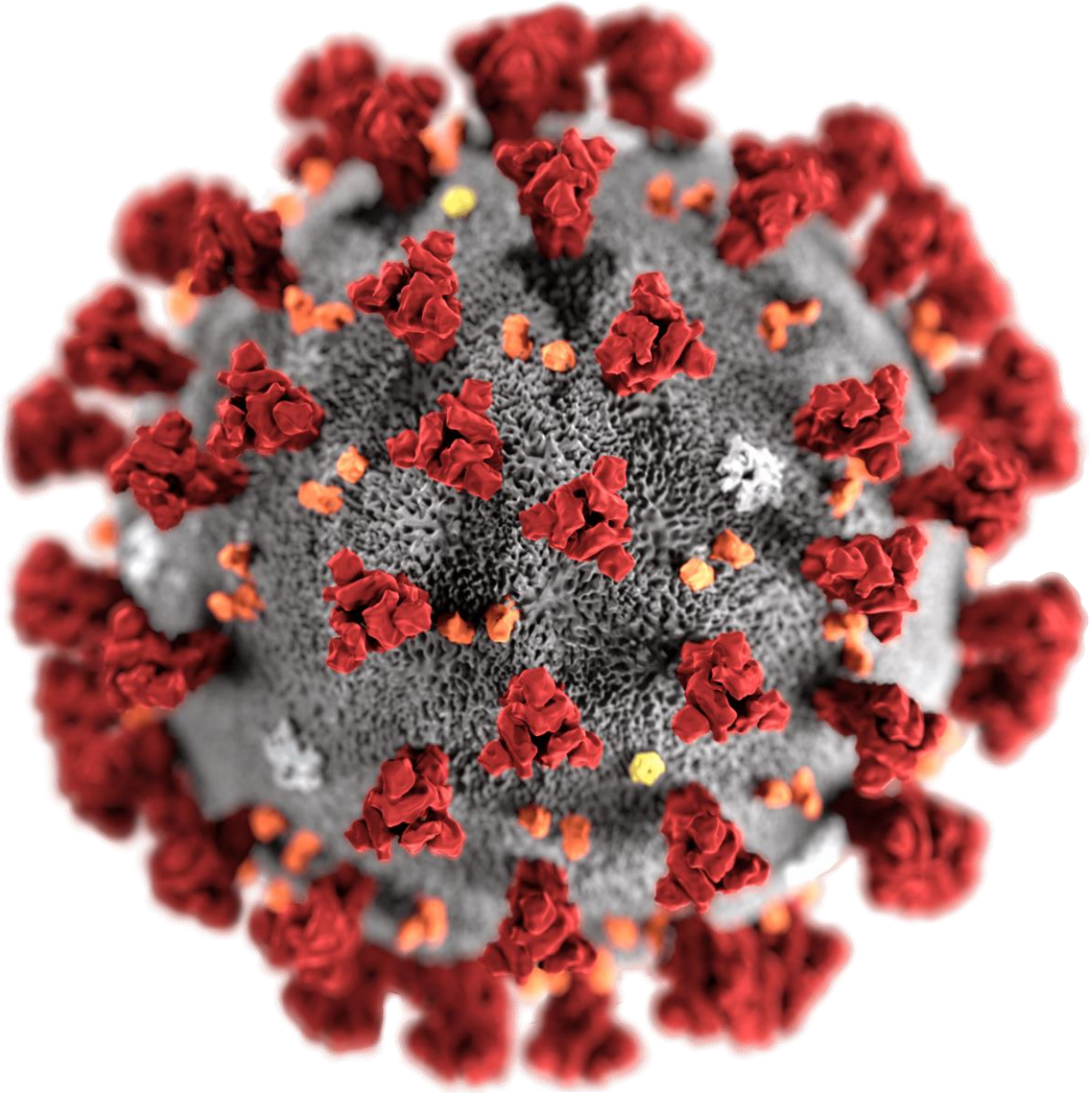

Immunogenicity, safety and eficacy of mRNA based vaccines among AARD patients

✕ Lower immunization rates compared to the control group (86% vs 100%)

✕ Negative prognostic factors: older age, steroids, mycophenolate, rituximab, methotrexate

✕ Of the patients treated with MTX only 62.2% developed antibodies, while CD8+ T lymph were not detected

✓ No change in the disease activity

✓ Comparable side effects

✓ No sympathetic COVID-19 infection

Furer et al. Ann Rheum Dis. 2021
Braun-Moscovici Y et al. Ann Rheum Dis. 2021
Haberman et al. Ann Rheum Dis. 2021
Geisen UM et al. Ann Rheum Dis. 2021

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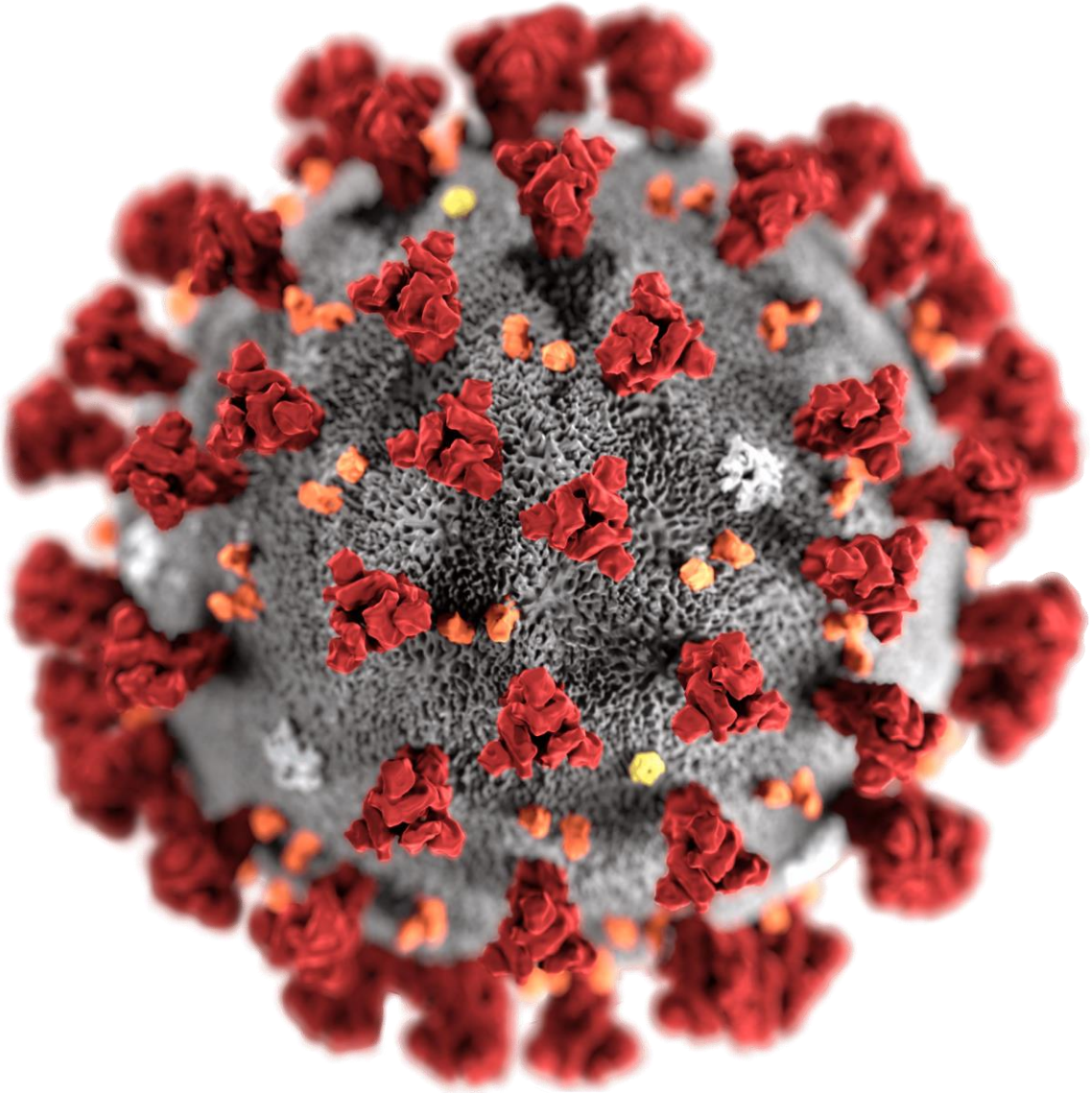
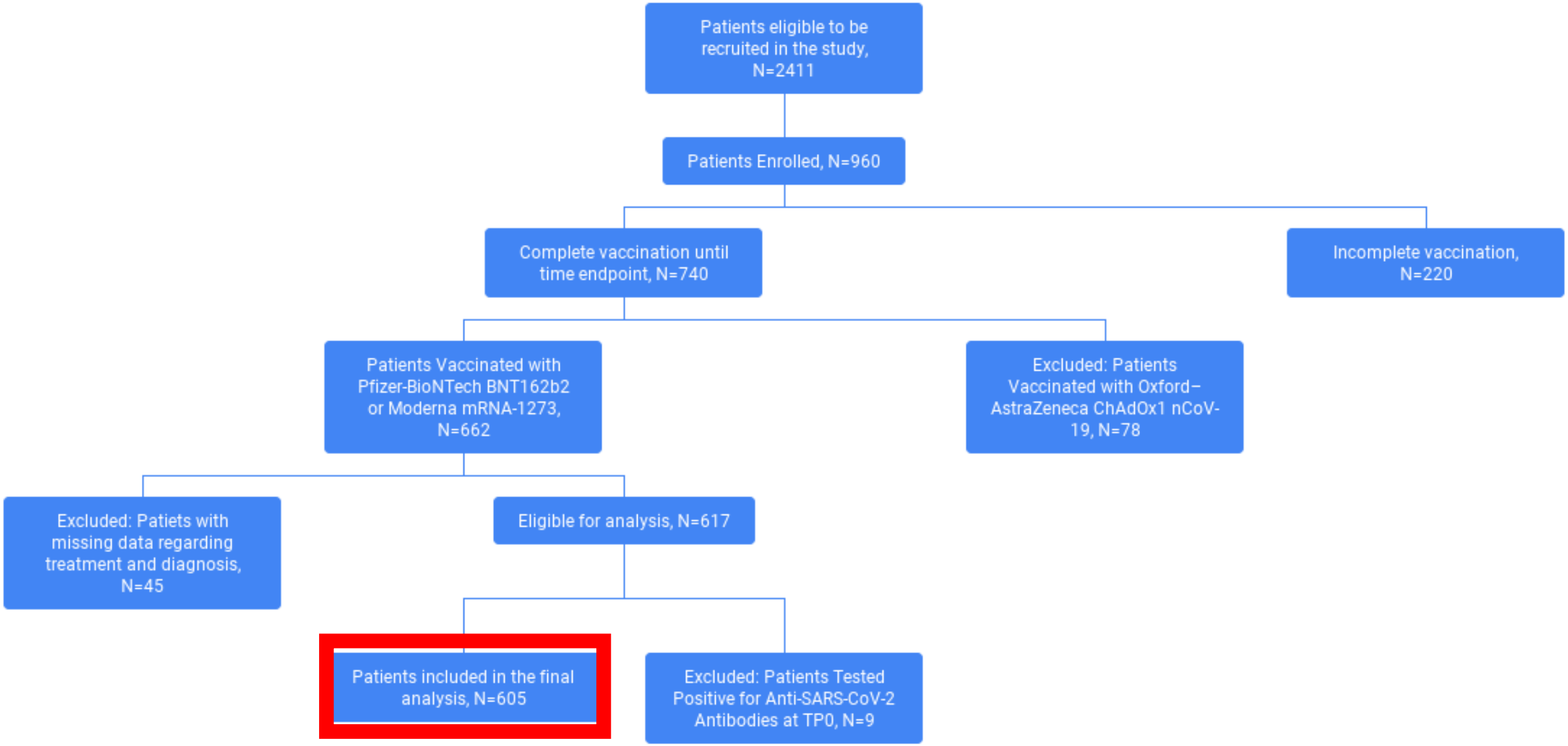


Rheumatology departments

- ❑Athens
  - Laikon general hospital
  - “Asklipieion” general hospital
  - “KAT” general hospital
  - Naval hospital of Athens
  - “Euaggelismos” general hospital
  - “G.Gennimatas” general hospital
- ❑Ioannina
- ❑Patras
- ❑Alexandroupolis

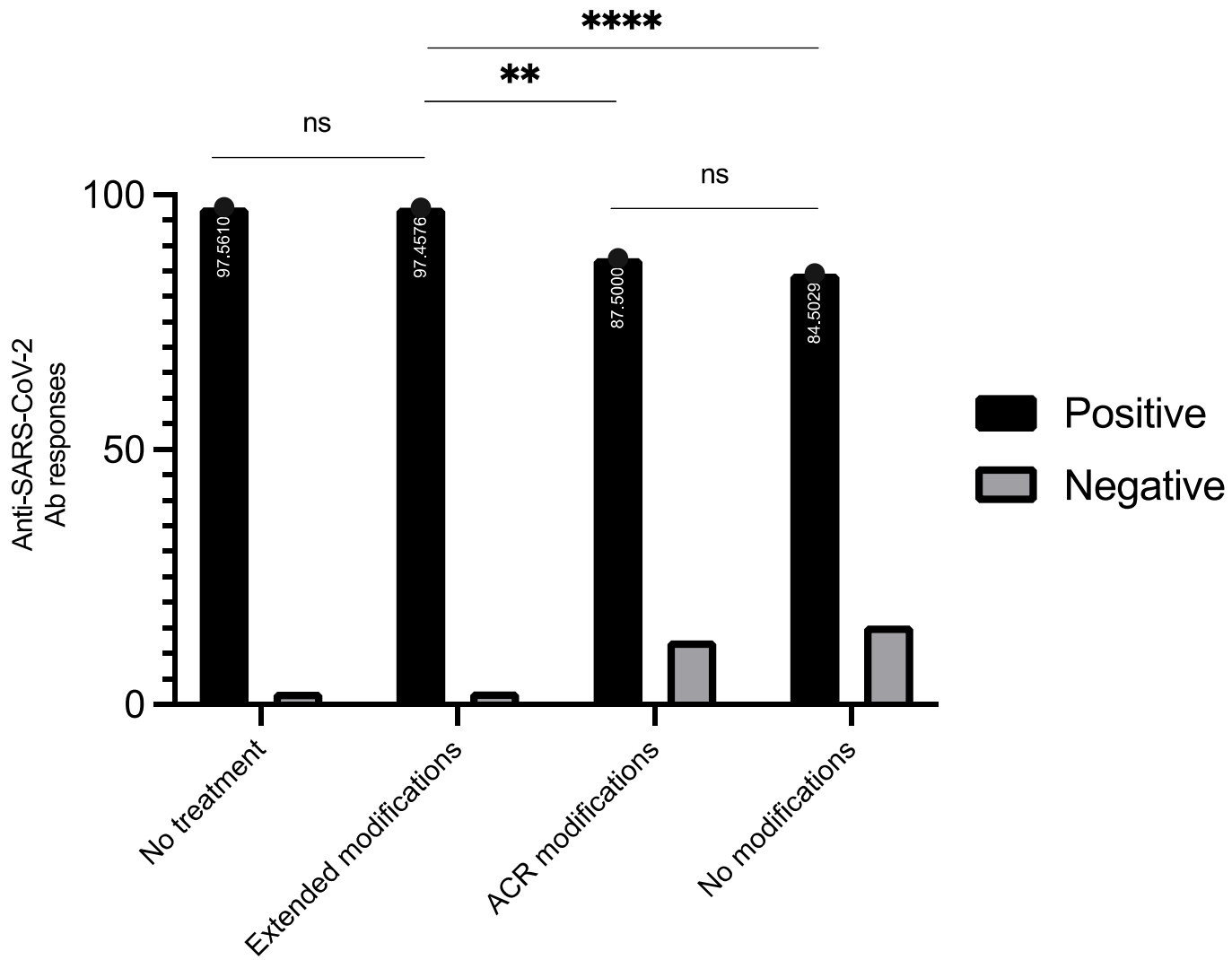
Study popupalation

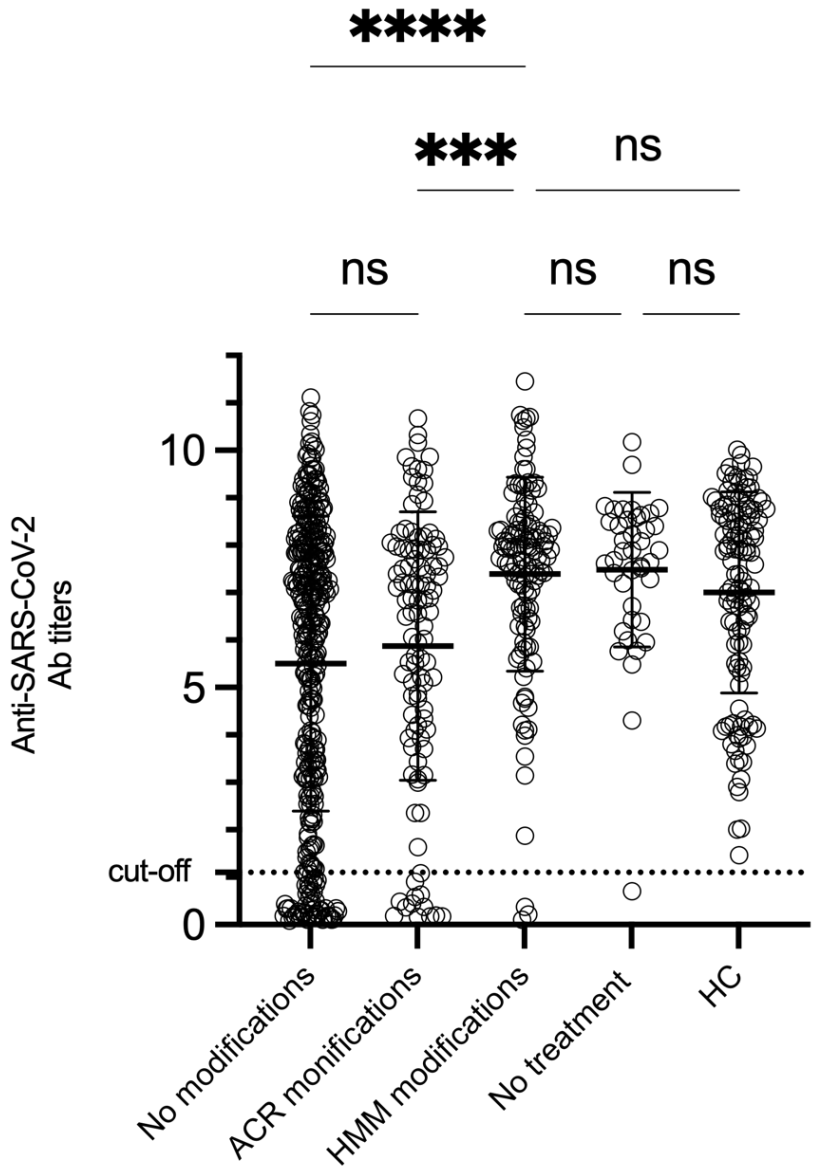


Characteristics of AARD patients and controls

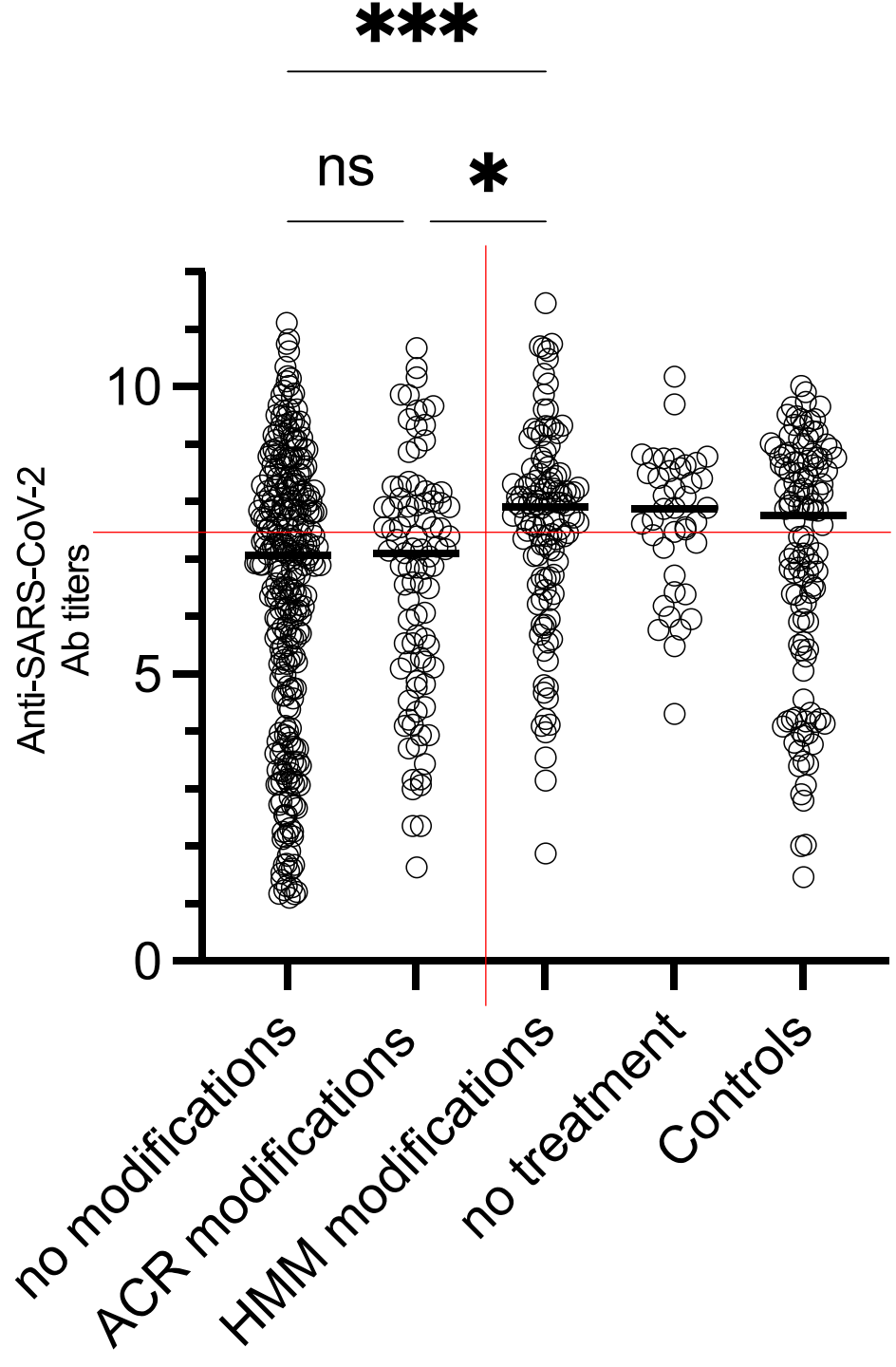
Female gender, N (%) (0=male, 1=female)	432/605 (71,40)	69/116 (59,48)
Age		
Mean±SD	57,64 ± 15,82	67,85 ± 15,43
Median (range)	58 (16-91)	72 (24-90)
Comorbidities		
Diabetes Mellitus, N (%)	58/598 (9,69)	25/116 (21,55)
Pulmonary Disease, N (%)	49/598 (8,19)	2/116 (1,72)
Cardiovascular disease, N (%)	96/598 (16,05)	51/116 (43,96)
Type of Vaccine		
Pfizer-BioNTech BNT162b2, N (%)	572/605 (94,54)	87/116 (75)
Moderna mRNA-1273 SARS-CoV-2, N (%)	33/605 (5,45)	29/116 (25)
Other vaccines		
Influenca	528/591 (89,34)	69/116 (59,48)
Pneumococcus	494/591 (83,58)	45/116 (38,79)
Immunogenicity		
Antibody responses above cut-off, N (%)	535/605 (88,42)	116/116 (100)
Spike-specific SARS-CoV-2 antibody titers		
Mean±SD	6,07 ± 2,91	7,02 ± 2,11
Median (range)	7,06 (0,08-11,45)	7,845 (1,46-10,02)

Anti-SARS-CoV-2 antibody responses

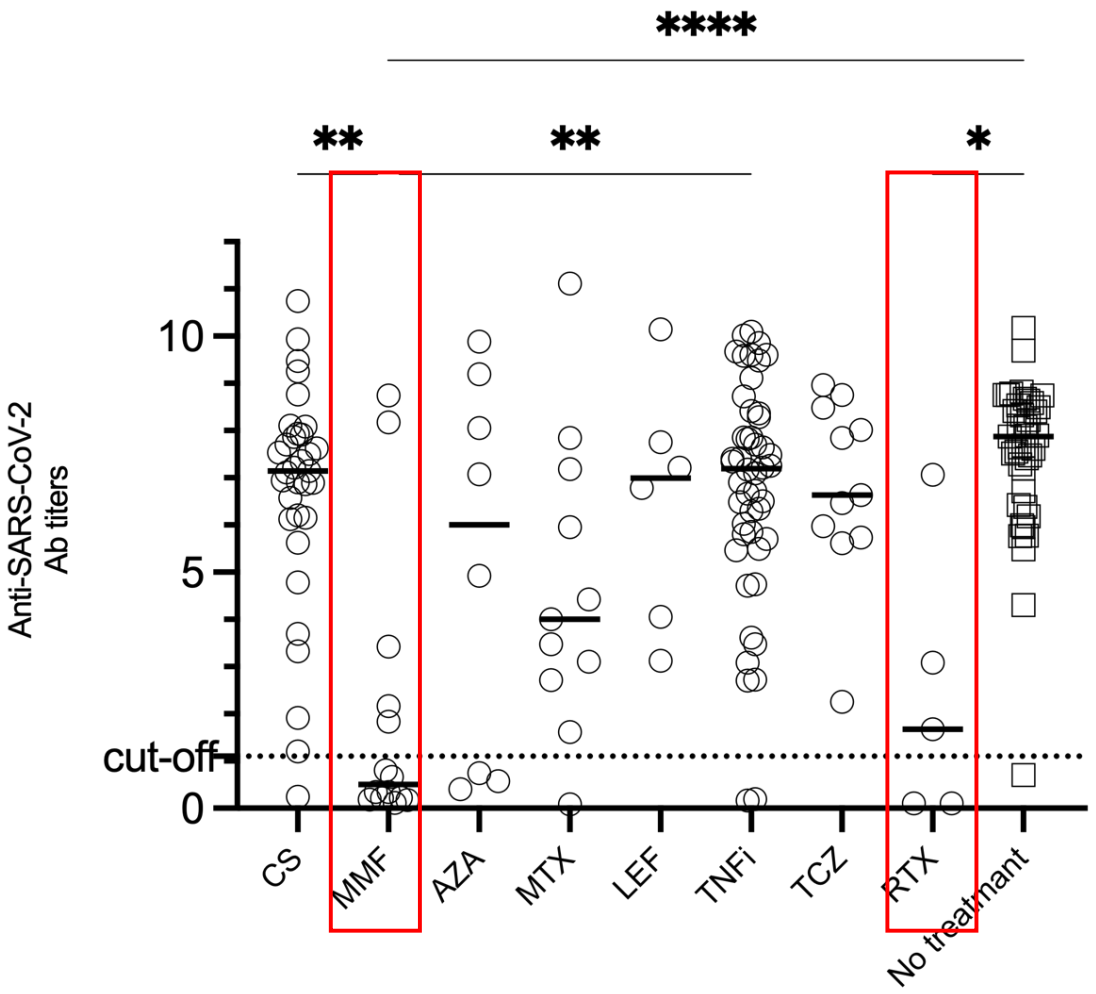




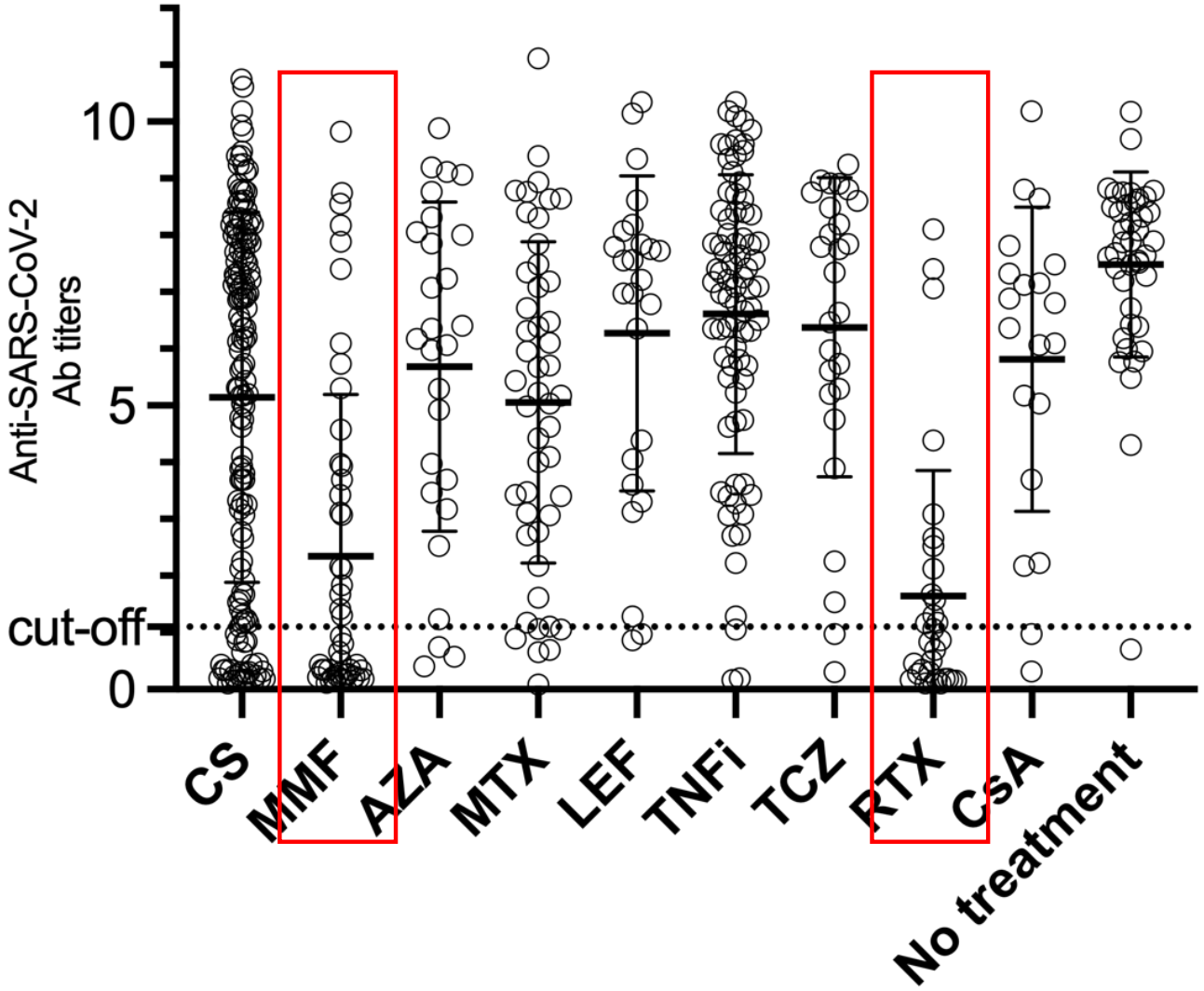
Anti-SARS-CoV-2 antibody responses



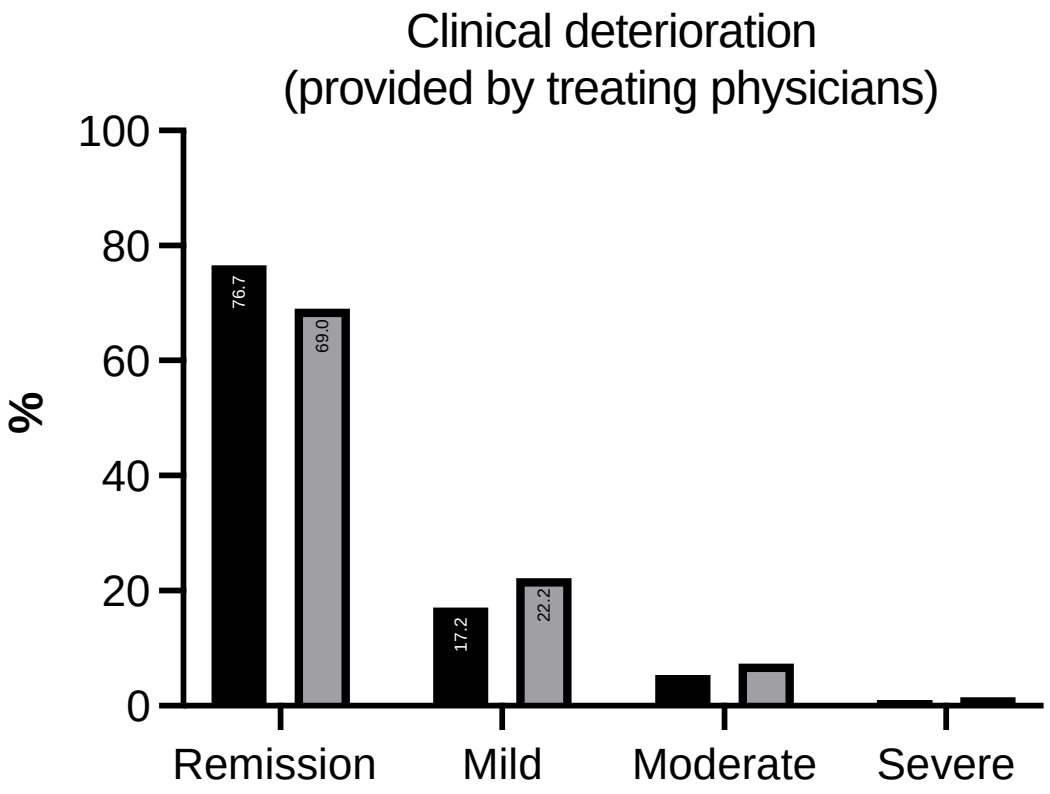
Monotherapy

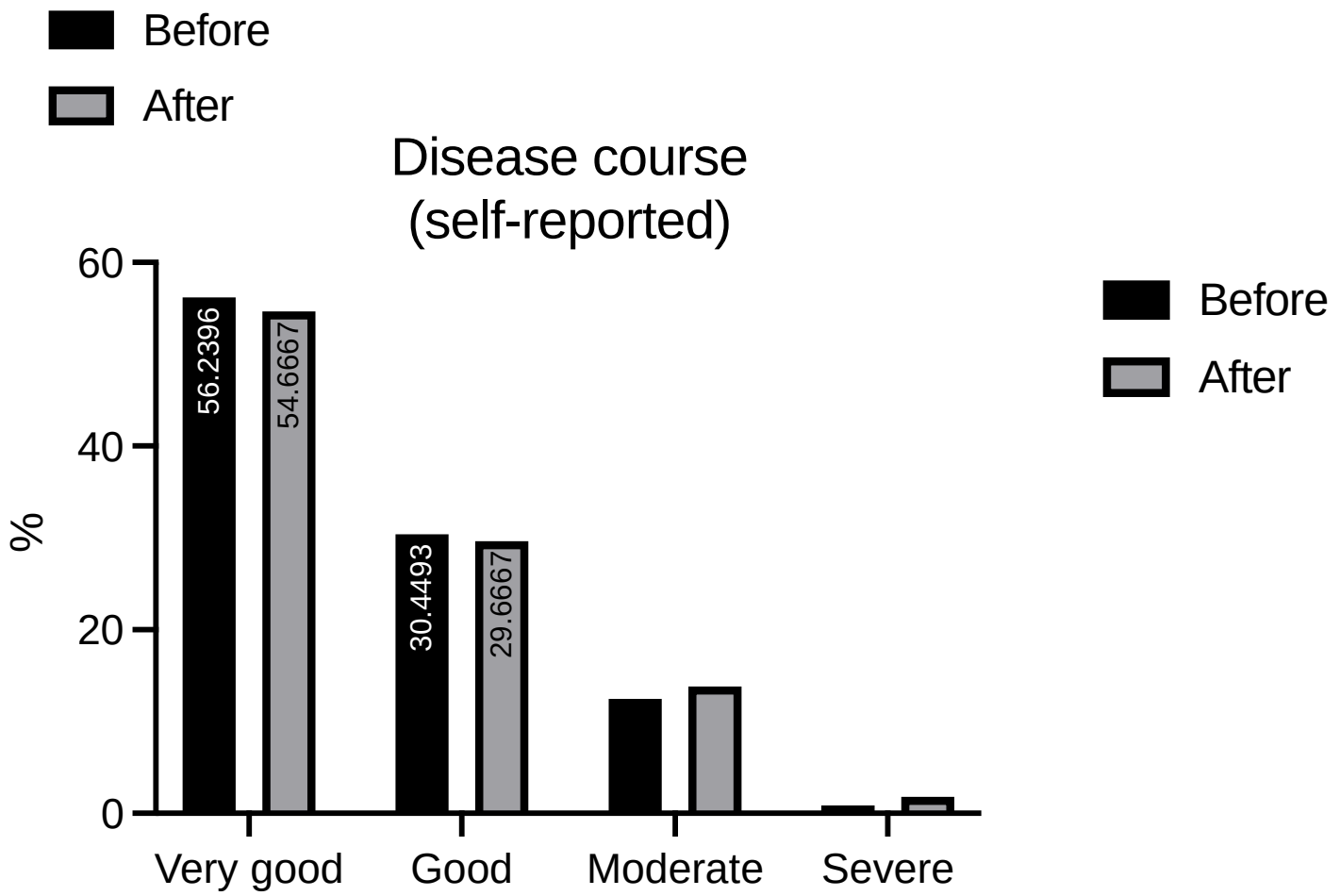


Combinational therapy

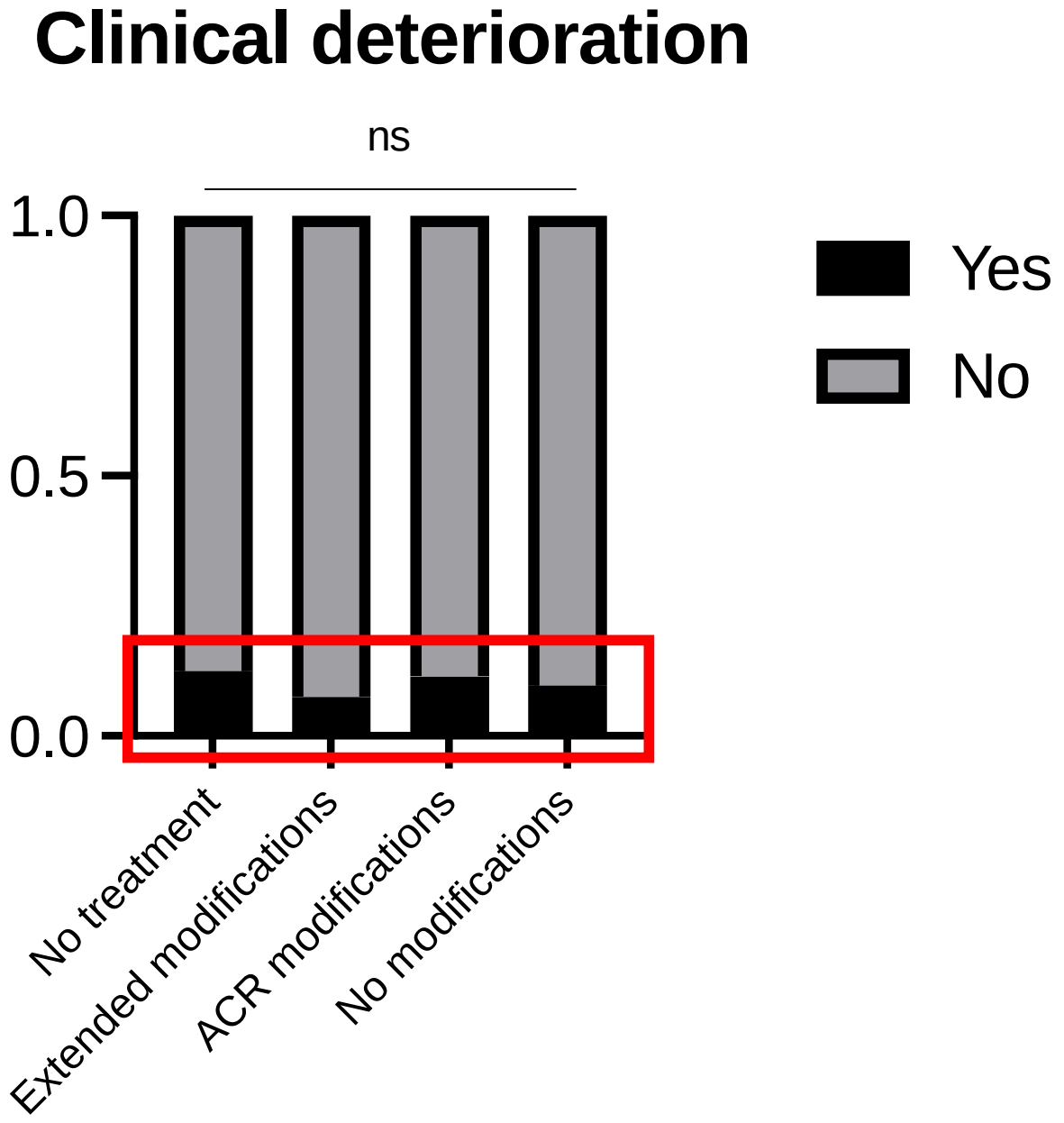


Disease activity and disease course before and after the vaccination





No sig differences in clinical deteriorations among groups



Side effects

Adverse Reactions	
No complaints, N (%)	234/600 (39,00)
Injection site pain, N (%)	263/600 (43,83)
Fatigue, N (%)	132/600 (22)
Fever, N (%)	99/600 (16,5)
Headache, N (%)	88/600 (14,66)
Diffuse pain, N (%)	62/600 (10,33)
Muskle weakness, N (%)	55/600 (9,167)

ACR Guidance for COVID- 19 Vaccination in Patients With Rheumatic and Musculoskeletal Diseases: Version 4

No modifications in immunomodulatory therapy or vaccination timing

- Hydroxychloroquine;
- Apremilast;
- IVIG;
- Glucocorticoids,
- Sulfasalazine;
- Leflunomide;
- Azathioprine;
- Cyclophosphamide (oral);
- TNFi; IL-6R; IL-1; IL-17; IL-12/23; IL-23; Belimumab;

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ACR Guidance for COVID- 19 Vaccination in Patients With Rheumatic and Musculoskeletal Diseases: Version 4

Modifications

(immunomodulatory therapy or vaccination timing)

- **Methotrexate:** 1 week after 2 dose mRNA, 2 weeks after 1 single dose vaccine
- **Mycophenolate:** 1 week after each vaccine dose
- **Oral calcineurin inhibitors:** 1 week after each vaccine dose
- **JAKi:** 1 week after each vaccine dose
- **Abatacept: (sc)** 1 week prior and after the 1st dose **(iv)** 4 weeks after abatacept infusion and postpone the subsequent infusion by 1 week (5-week gap in total)
- **Cyclophosphamide IV:** administration will occur 1 week after each vaccine dose
- **Rituximab:** vaccination 4 weeks prior to next RTX cycle; after vaccination, delay RTX 2-4 weeks after final vaccine dose

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ACR Guidance for COVID- 19 Vaccination in Patients With Rheumatic and Musculoskeletal Diseases: Version 4

Supplemental dosing-Booster dose

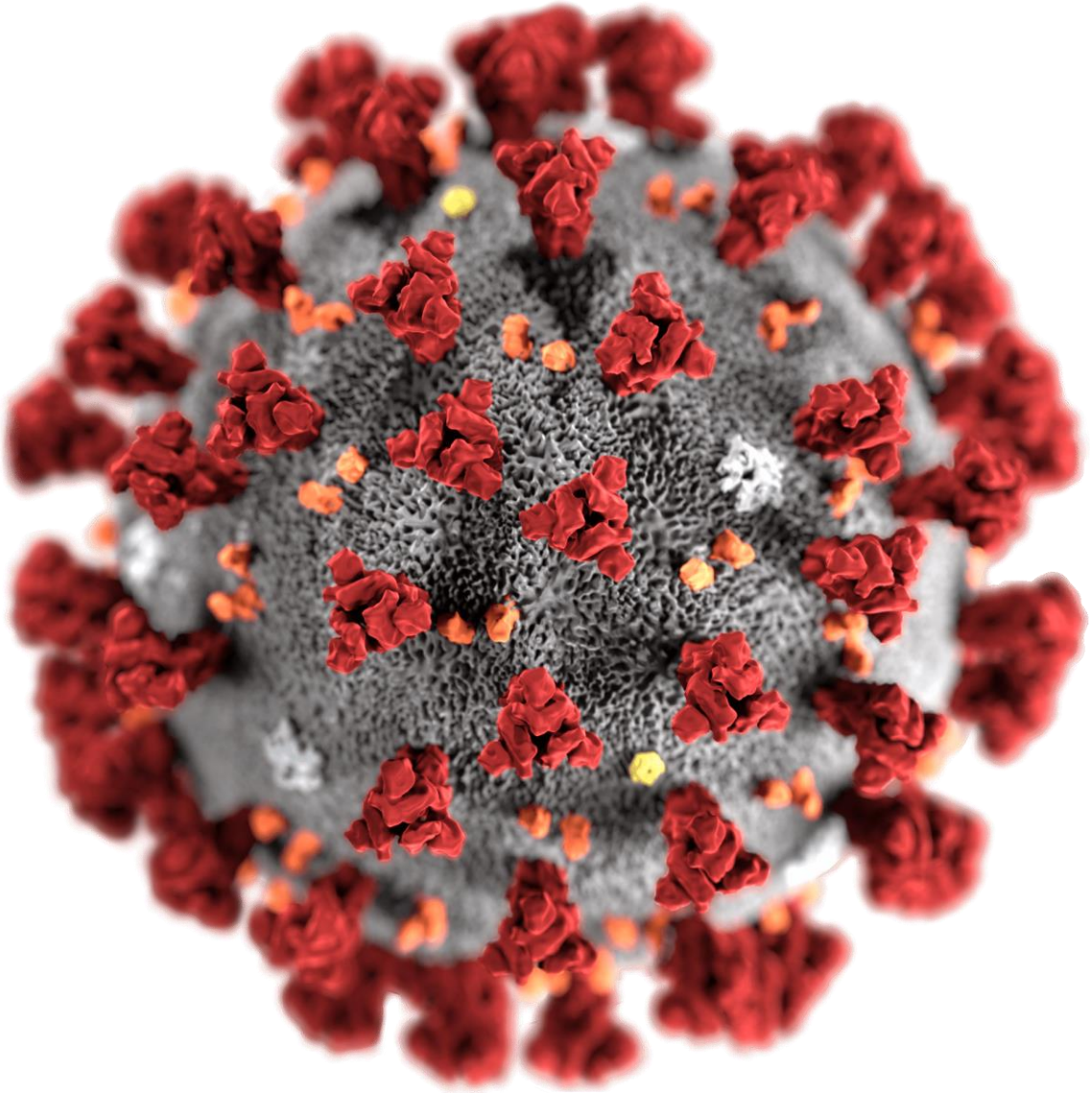
- **All immunomodulatory or immunosuppressive therapies:** Except for glucocorticoids and anti-cytokine therapies* hold all immunomodulatory or immunosuppressive medications for 1-2 weeks after booster vaccination, assuming disease activity allows.

- **Rituximab:** Patients on rituximab or other anti-CD20 medications should discuss the optimal timing with their rheumatology provider before proceeding with booster vaccination

Arthritis & Rheumatology for publication, 2021

Outline

- **COVID-19**
  - Classification of the clinical spectrum
  - Risk factors for severe disease
  - Immunobiological mechanisms
- **Systemic autoimmune diseases at the crossroad of COVID-19**
  - The Greek Experience
  - Existing Data
- **Vaccination against SARS-CoV-2**
  - Clinical practice guidelines and beyond
  - Data on immunogenicity, safety and efficacy
  - The role of treatment modification during vaccination period: preliminary results from a Greek multicenter prospective observational study
- **Conclusions**



Conclusions

- AARN patients not at high risk for severe/fatal COVID-19 disease.
- Vaccination necessary but with some precautions
- Mycophenolate mofetil, rituximab and methotrexate decrease the immunogenicity of mRNA vaccines