COVID-19 Vaccine Responsiveness in Patients with Multiple Myeloma and Waldenstrom's Macroglobulinemia

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Disclosures

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Disclosures:

Consultant: Adaptive Biotechnologies, BeiGene, CSL Behring, Karyopharm Therapeutics, Pharmacyclics, Sanofi-Genzyme.

Background

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- Plasma cell dyscrasias such as multiple myeloma (MM) and Waldenstrom's macroglobulinemia (WM) are associated with immunoparesis due to both hypogammaglobulinemia and various alterations of cellular immunity

- Immunodeficiency is manifested by an increased risk for infections and diminished response to routine vaccinations

- Approved and emergency use authorization COVID-19 vaccines are designed to elicit SARS-CoV-2 spike protein (S) Abs in healthy individuals. There are no established titers to determine clinical protection.

- Cancer patients particularly hematologic malignancies have higher risk of severe COVID-19 infections. Specific immune responses and degree of clinical protection following COVID-19 vaccines are unknown for MM and WM patients

COVID-19 Vaccine Response Trial

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Study of COVID-19 Vaccine Responsiveness in Patients with Multiple Myeloma and Waldenstrom's Macroglobulia

- Prospective clinical trial open and Enrolling at Massachusetts General Hospital (MGH) and Dana-Farber Cancer Institute (DFCI)
  - Clinicaltrials.gov (NCT04830046)
  - PI: Andrew Branagan, MD, PhD (MGH)
  - DFCI Site-PIs: Shayna Sarosiek, MD (WM) and Clifton Mo, MD (MM)
  - Corollary Immune Studies: Galit Alter MD and Boris Juleg, MD, PhD (Ragon Institute)

Clinical Trial Schema

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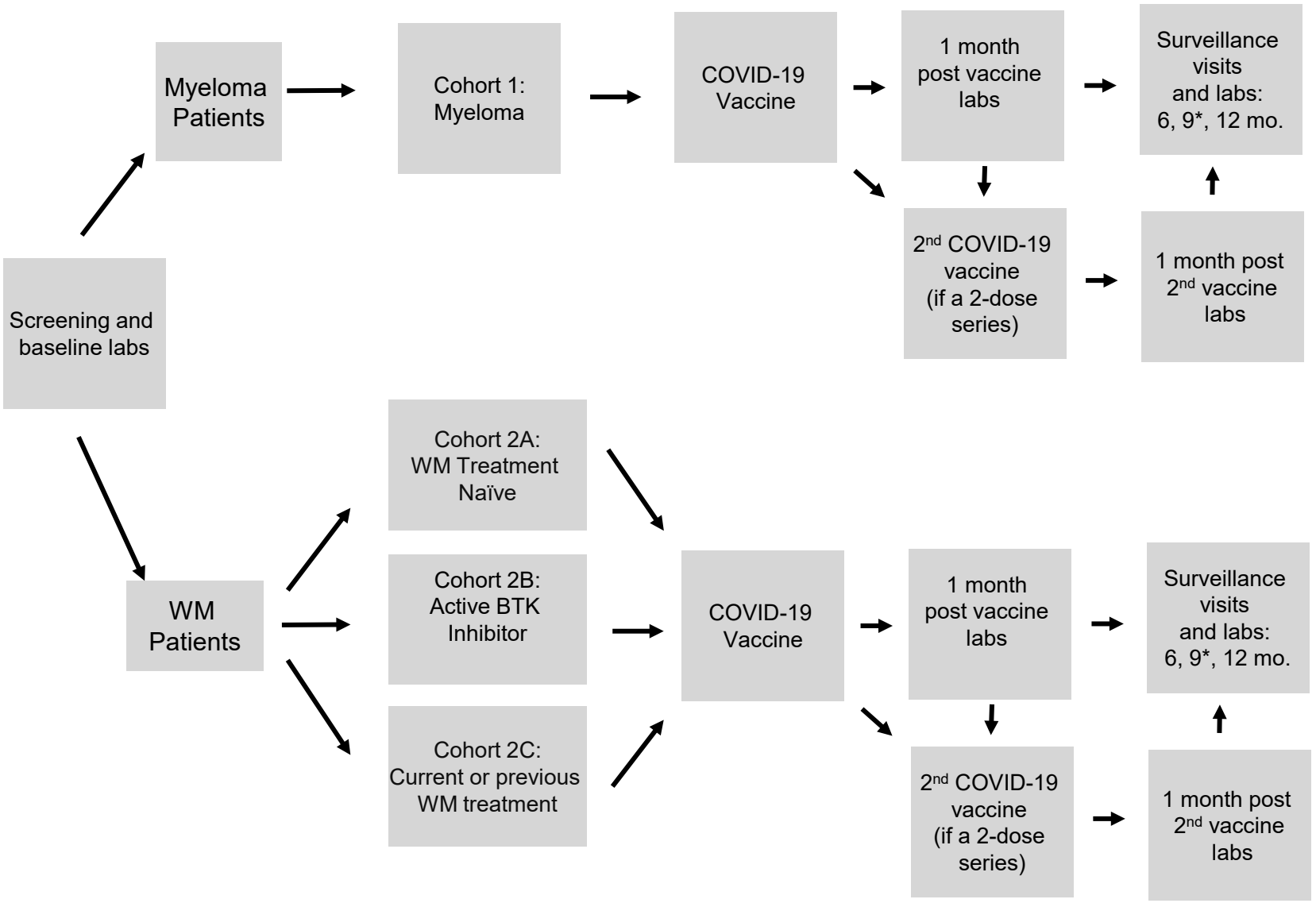

*Month 9 visit and labs are recommended

Objectives/Endpoints

Primary objective:

- *To investigate the rate of anti-spike protein* SARS-CoV-2 *antibodies 28 days following complete COVID 19 vaccination*

Secondary objectives:

- *To investigate the durability of immune responses*
- *To investigate clinical correlates of immune response*
- *To investigate rates of COVID-19 infections within the study period.*
- *To evaluate functional antibody and cell-mediated immune responses to COVID-19 vaccination; including gene expression profiling, comprehensive systems serology, and SARS-CoV-2-specific T-cell subsets.*

Methods

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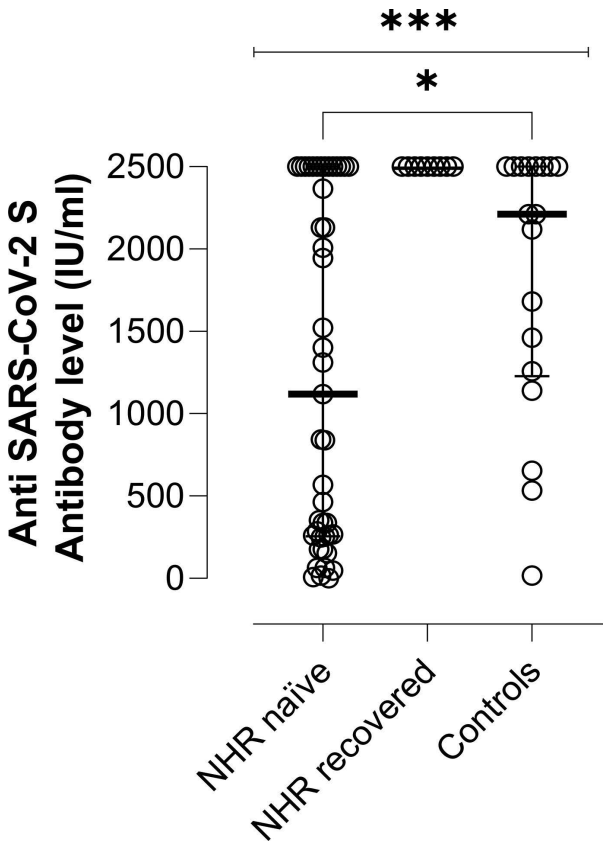
SARS-CoV-2 Spike Protein (S) Antibody Detection:

- Roche Elecsys anti-SARS-CoV-2 S Ab assay used to assess primary primary endpoint Ab responses. Range 0.08 to 2,500 U/mL.

- There are no FDA approved or established spike Ab titers to determine clinical protection. Elecsys assay titers 100-500 U/mL are most associated with neutralization of SARS-CoV-2 virus.



Torres et al. Clin Microbio and Infect. 2021

Baseline Characteristics

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	All (n=134)	MM (n=89)	WM (n=45)
Age, median (IQR)	66 (59-71)	65 (59-71)	66.5 (60-71)
Age greater than 75, n (%)	15 (11.2)	10 (11.2)	5 (11.1)
Male sex, n (%)	74 (55.2)	48 (53.9)	26 (57.8)
Race, n (%)			
White	122 (91)	79 (88.9)	43 (95.6)
Non-white	12 (9)	10 (11.2)	2 (4.4)
COVID-19 vaccine, n (%)			
BNT162b2	72 (53.7)	45 (50.6)	27 (60)
mRNA-1273	49 (36.6)	34 (38.2)	15 (33.3)
JNJ-78436735	13 (9.7)	10 (11.2)	3 (6.7)
Involved heavy chain and/or light chain			
IgG	-	42 (47.2)	-
IgA		16 (18)	
Kappa FLC		53 (60)	
Lambda FLC		22 (24.7)	
MYD88 mutational status, n (%)			
MYD88 mutant	-	-	34 (79)
MYD88 wild-type			7 (15.5)
Unknown			3 (6.7)
CXCR4 mutational status, n (%)			
CXCR4 mutant	-	-	12 (26.1)
CXCR4 wild-type			11 (24.4)
Unknown			21 (46.7)
Prior ASCT, n (%)	27 (20.1)	27 (30.3)	0 (0)
History IVIG use within 90 days, n (%)	18 (12.7)	14 (15.7)	3 (6.7)
Treatment status, n (%)			
Previously treated	115 (85.8)	83 (93.3)	32 (71.1)
Treatment naive	19 (14.2)	6 (6.7)	13 (28.9)
Current line of therapy, n (%)			
First line	60 (44.8)	43 (48.3)	17 (37.8)
Second line	32 (23.9)	25 (28.1)	7 (15.6)
Third line or greater	23 (17.2)	15 (16.9)	8 (17.8)
Hypogammaglobulinemia, n (%)*	31/129 (24)	20/87 (23)	11/42 (26.2)
IgG, median (IQR)	541 (403.5-780.5)	549.0 (406-876)	483 (348.5-741)

*IgG <400 mg/dL

Median SARS-CoV-2 Spike Ab Titers After Complete Vaccination

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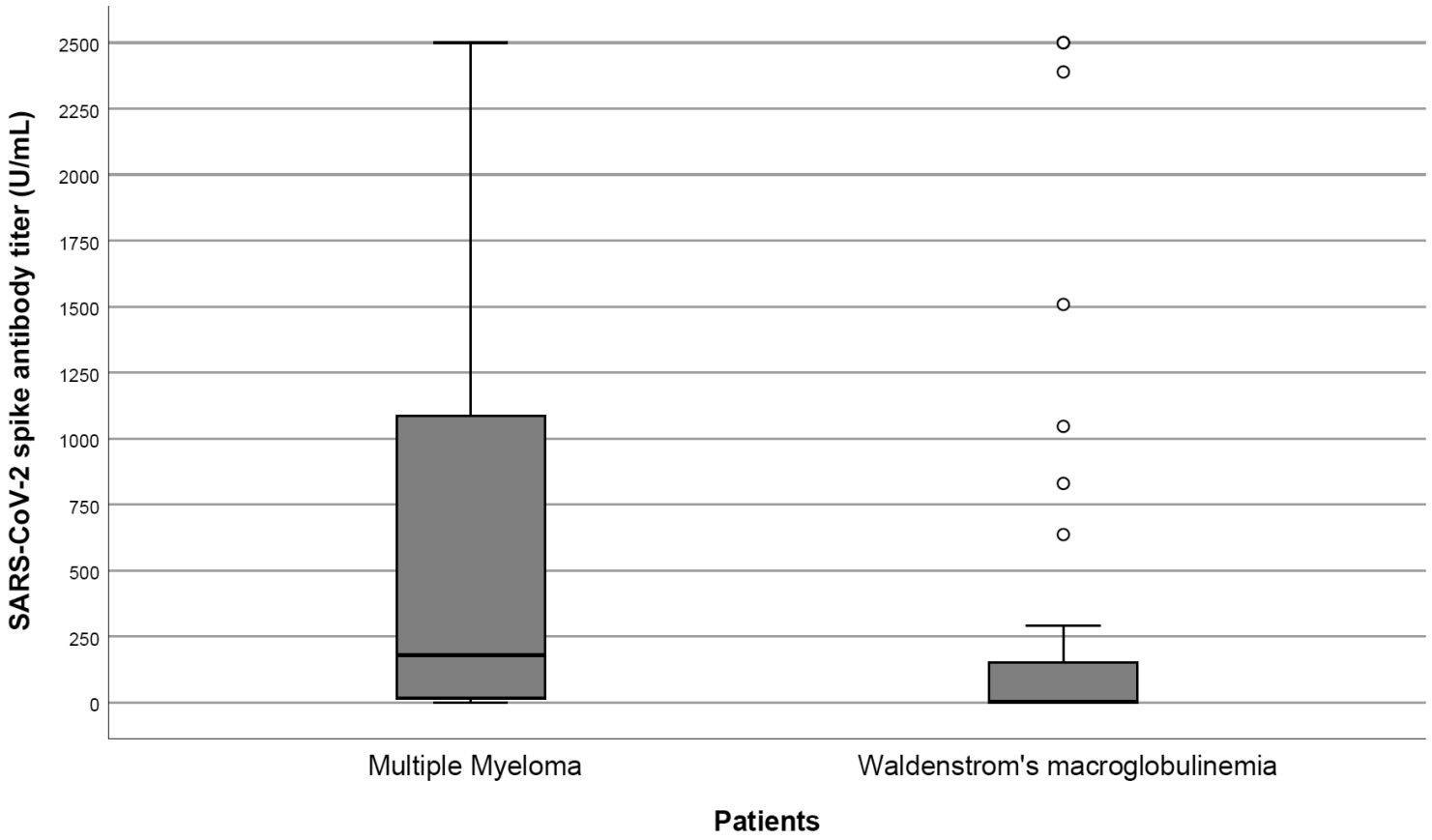

	COVID-19 spike antibody test – titer (U/mL)		
	25th Percentile	**50th Percentile**	75th Percentile
Multiple Myeloma	14.05	**178**	1097.5
Waldenstrom's macroglobulinemia	0	**3.28**	213

SARS-CoV-2 Spike Ab Responses Myeloma vs. Waldenstrom's macroglobulinema

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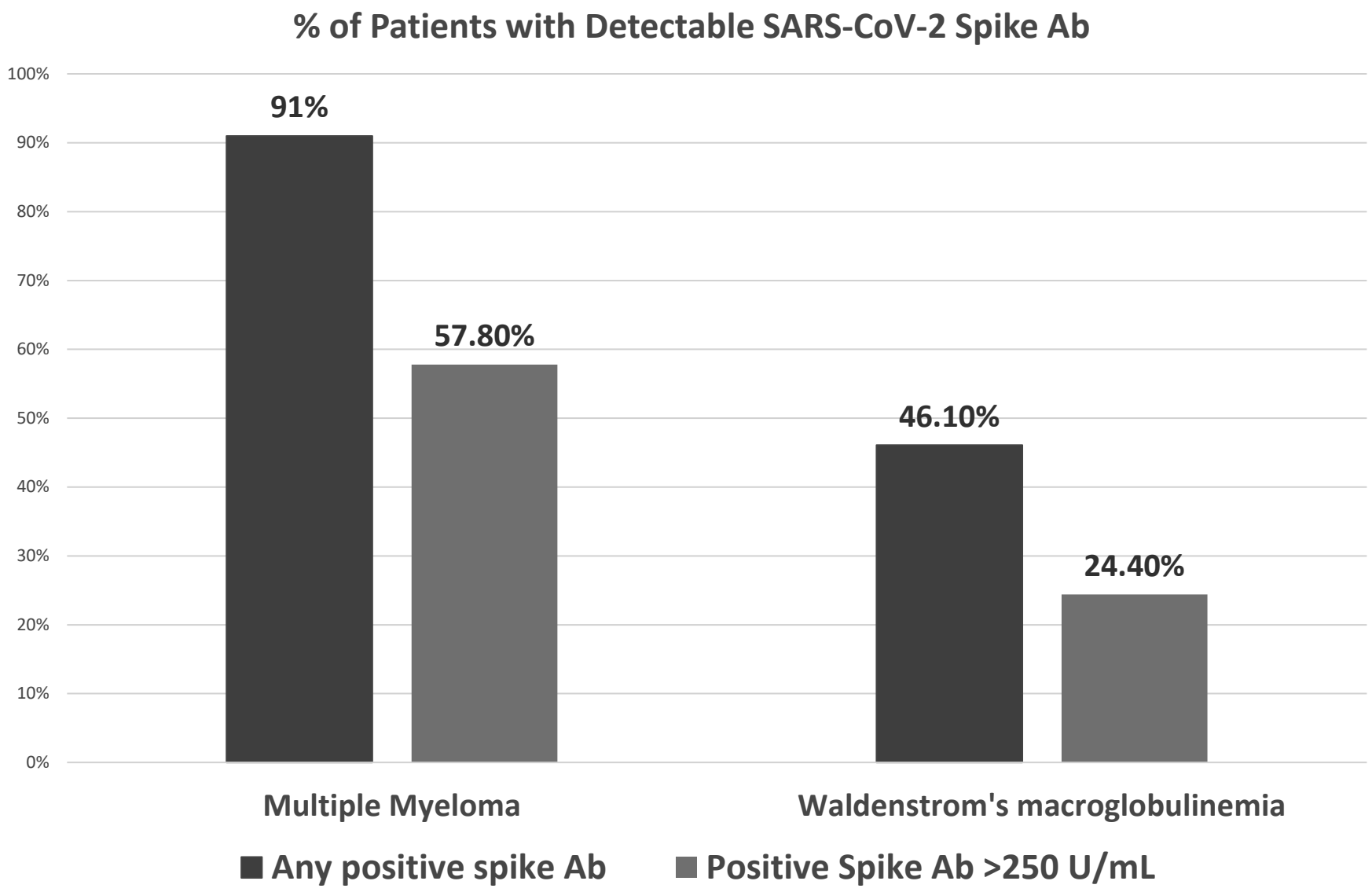

SARS-CoV-2 Spike Ab Responses in Pts Stratified Age

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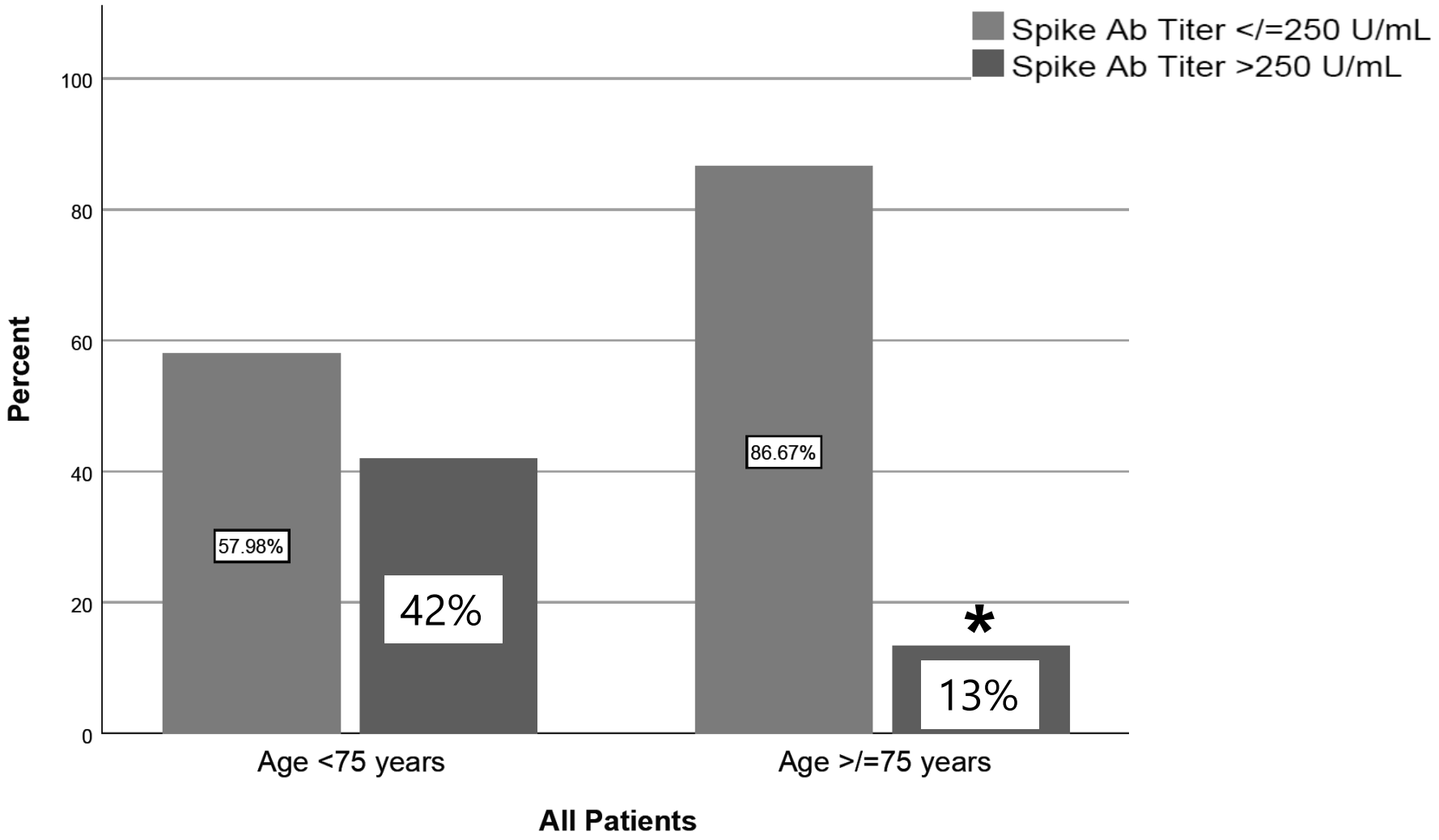

P<0.05

SARS-CoV-2 Spike Ab Response Based on Specific COVID-19 Vaccine

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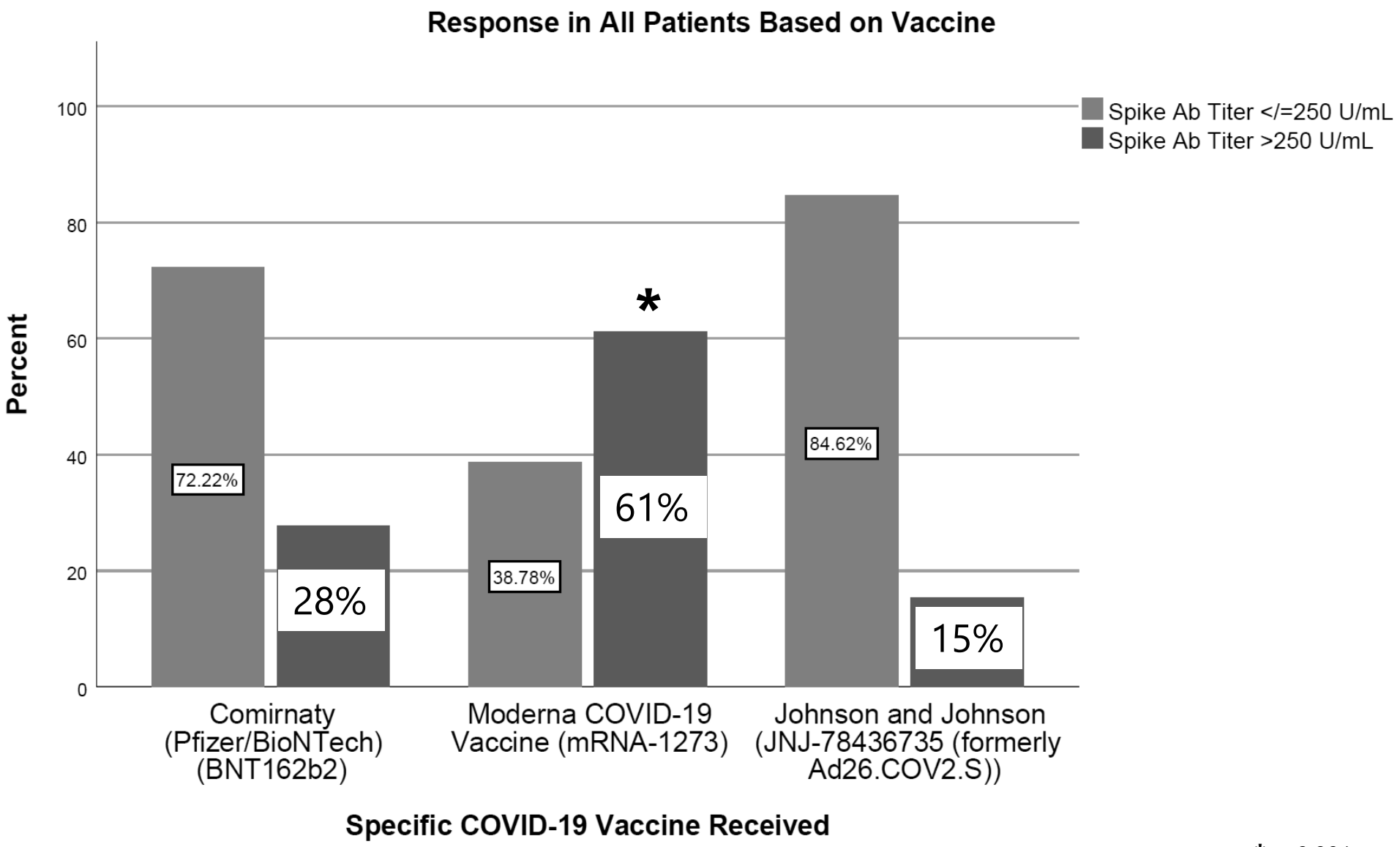

*p<0.001

SARS-CoV-2 Spike Ab Responses in WM Pts Stratified by Study Cohort

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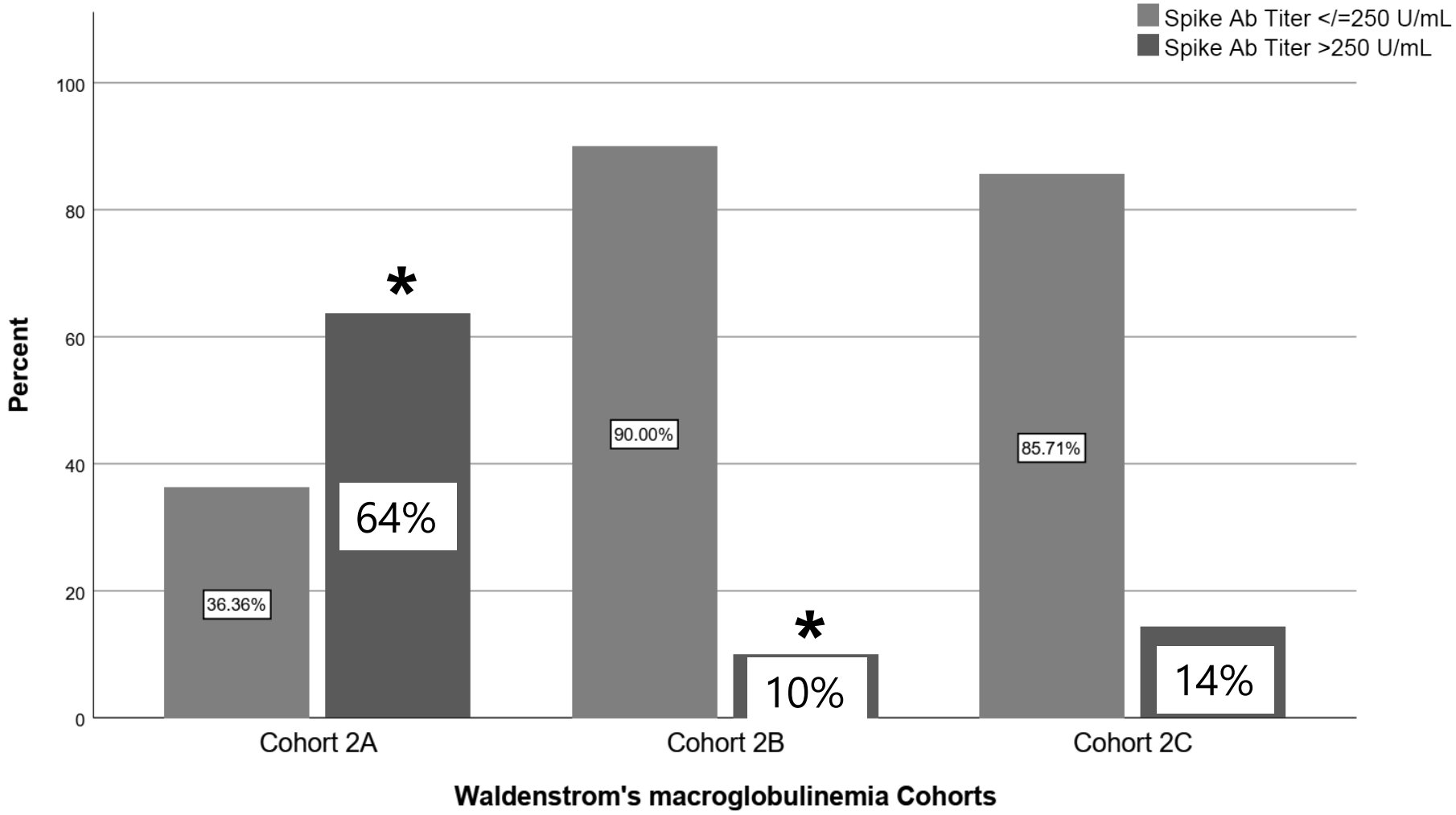

Cohort 2A	Cohort 2B	Cohort 2C
Treatment naïve WM patients	WM patients receiving BTK inhibitor	Currently or previously treated WM patients

*p<0.05

SARS-CoV-2 Spike Ab Responses in WM Pts Stratified by BTK and Rituximab Treatment Status

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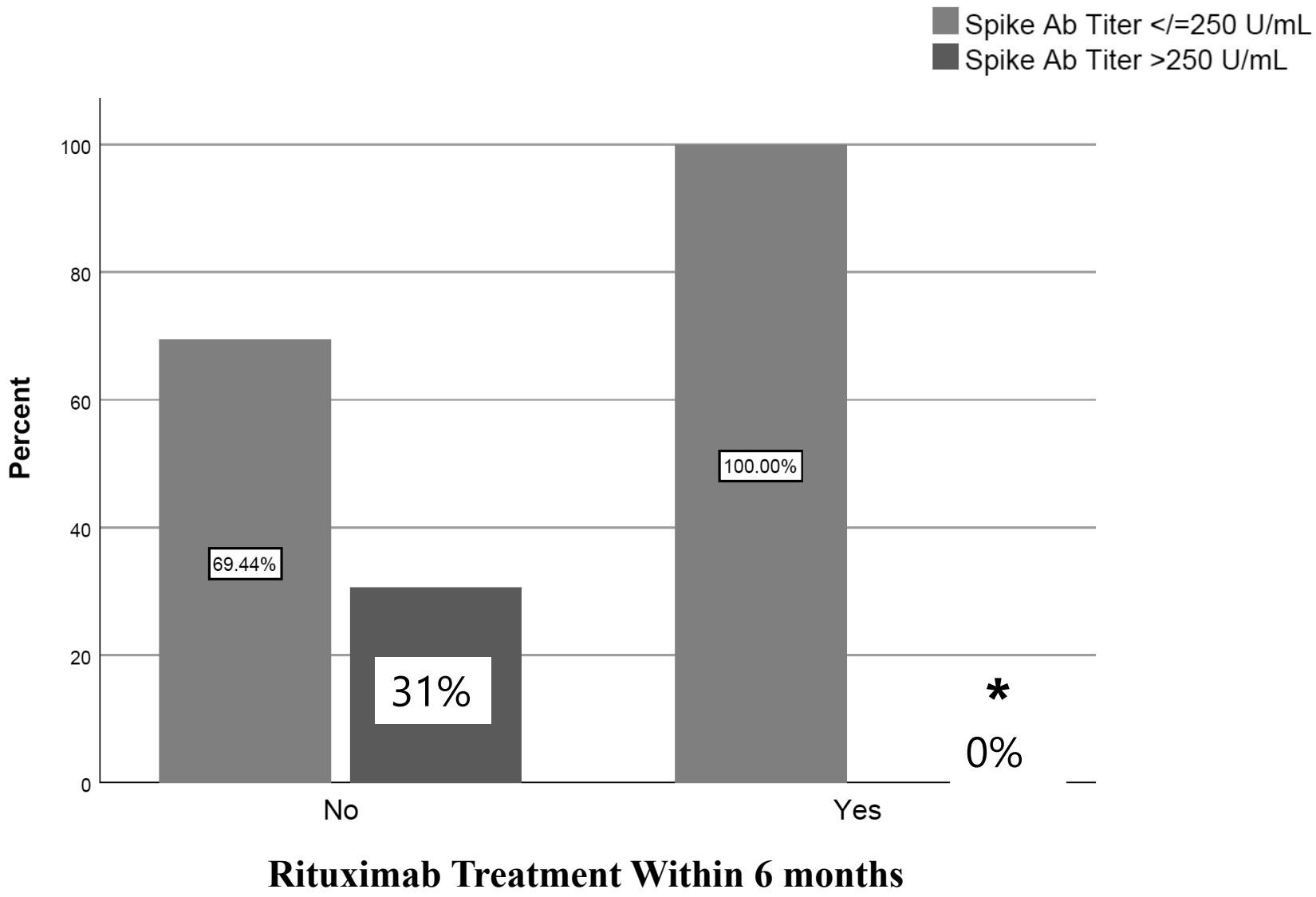

*p<0.05

SARS-CoV-2 Spike Ab Responses in MM Pts Stratified by IMiD, CD38 mAb, and PI Treatment Status

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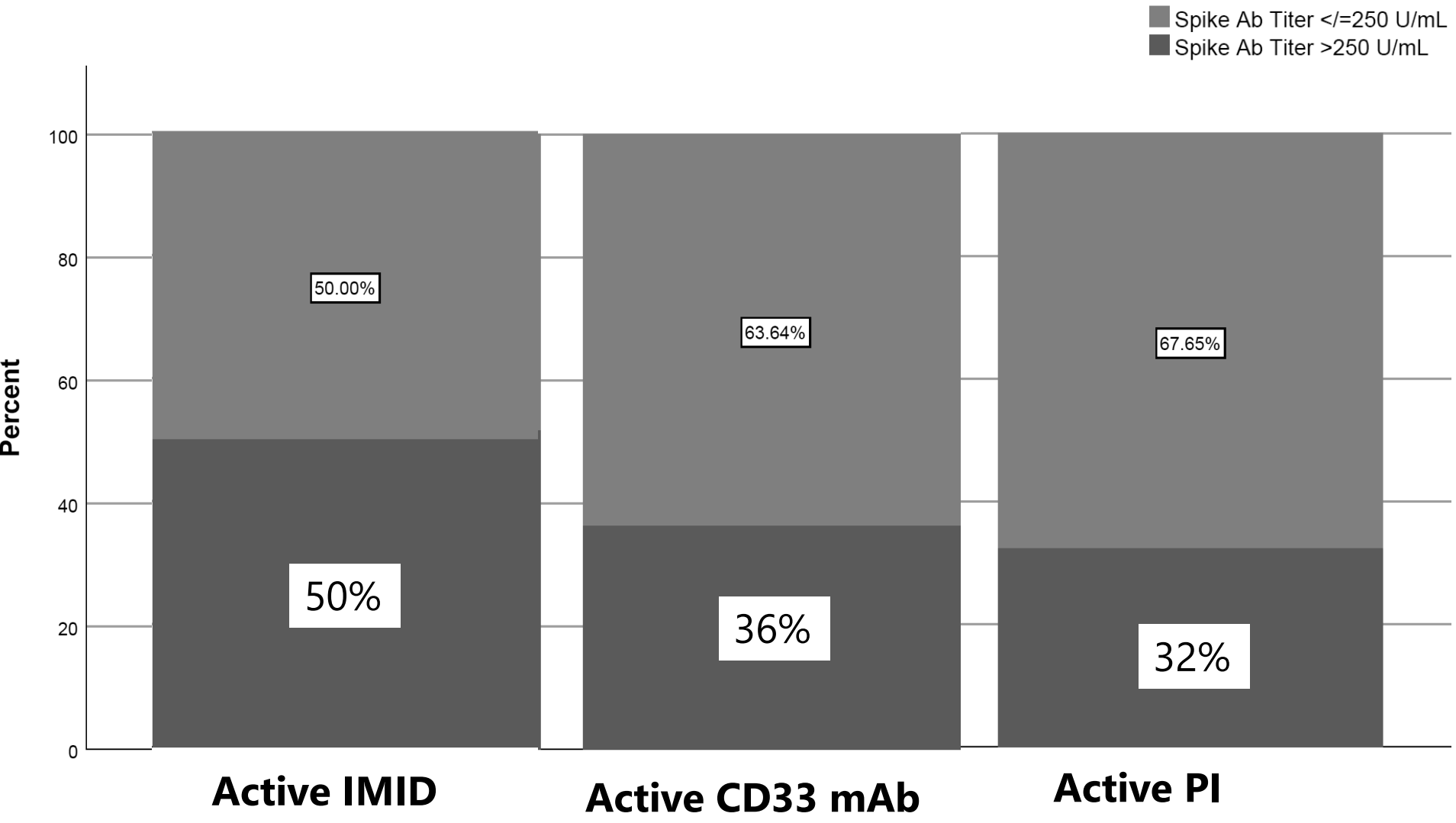

SARS-CoV-2 Spike Ab Responses in Patients with ALC less than 1000 cells/L

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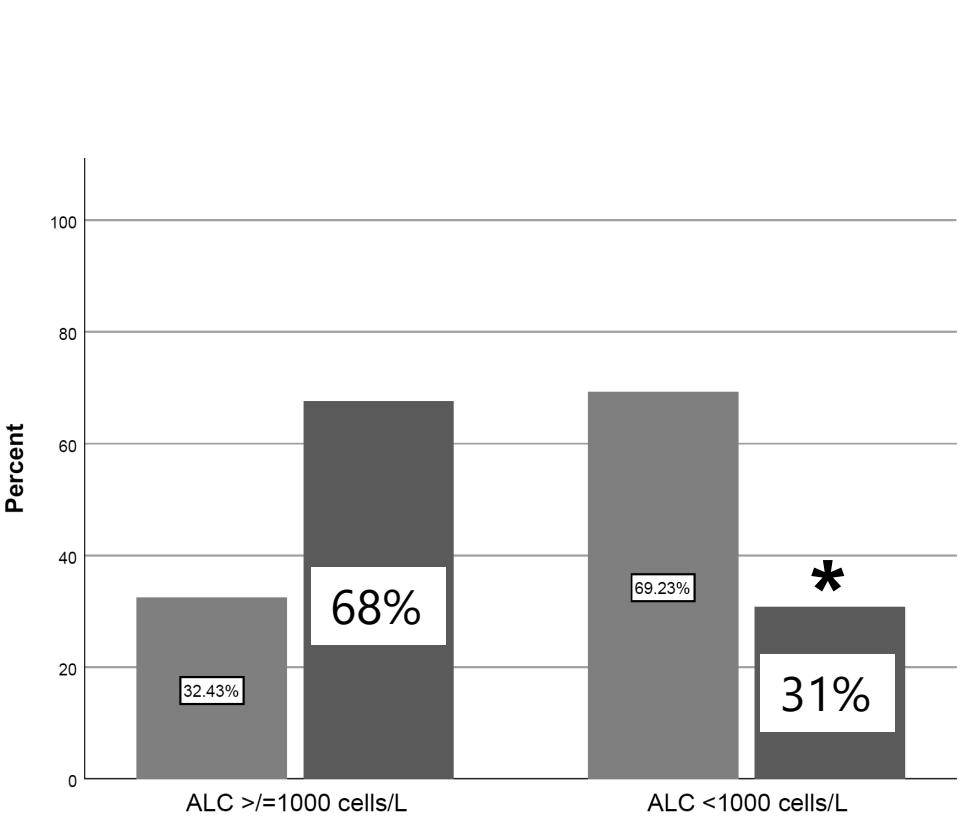
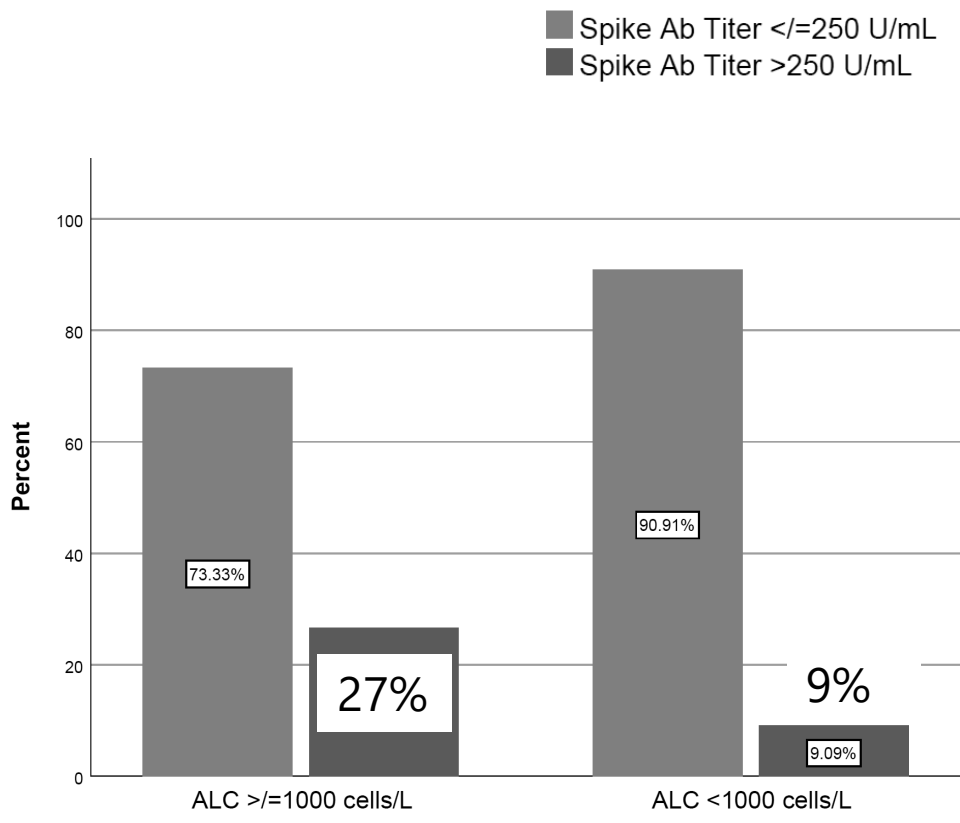


MM Patients



WM Patients

*p=0.001

SARS-CoV-2 Spike Ab Responses Stratified by Previous Lines of Treatment

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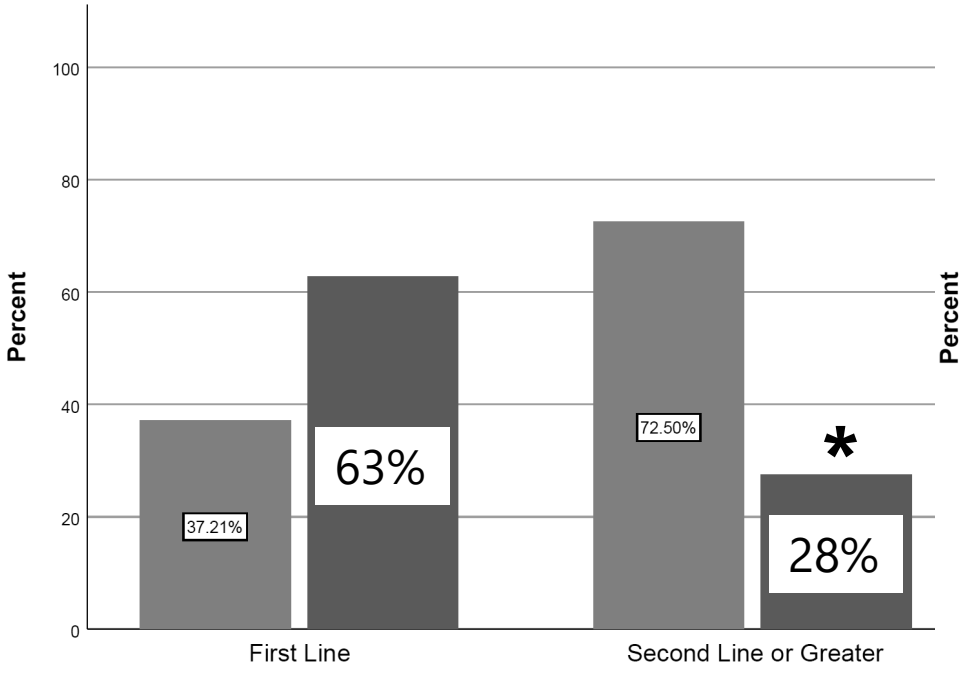
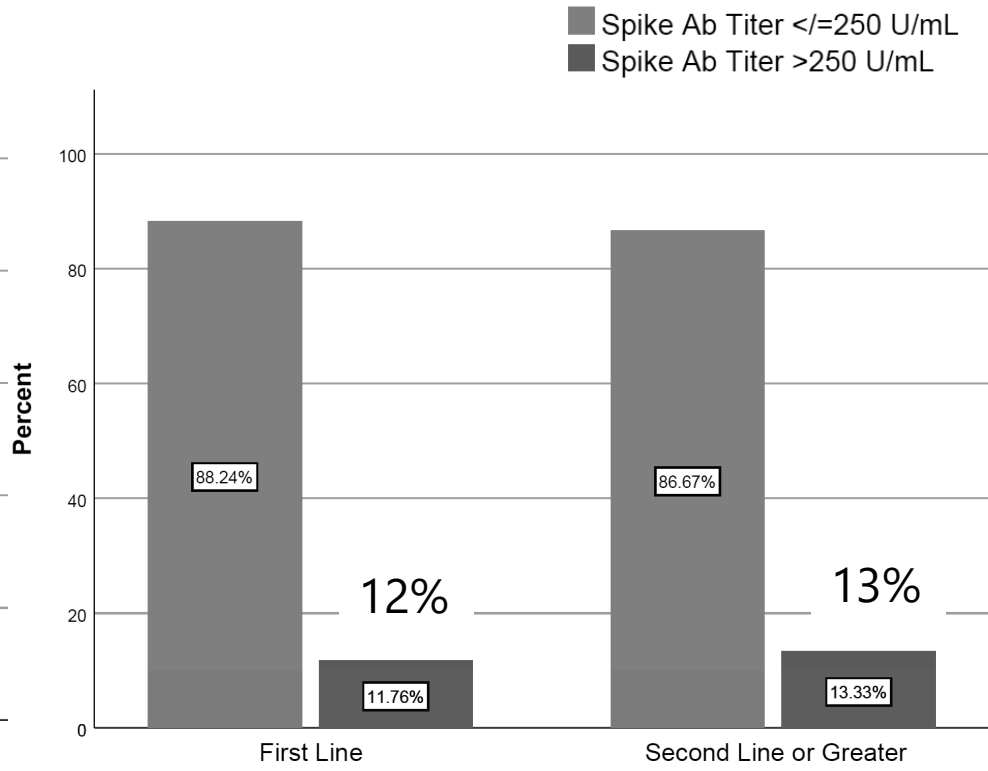


#MM Lines of Therapy



#WM Lines of Therapy

*p=0.001

SARS-CoV-2 Spike Ab Responses in MM Patients Stratified by Disease Response Status

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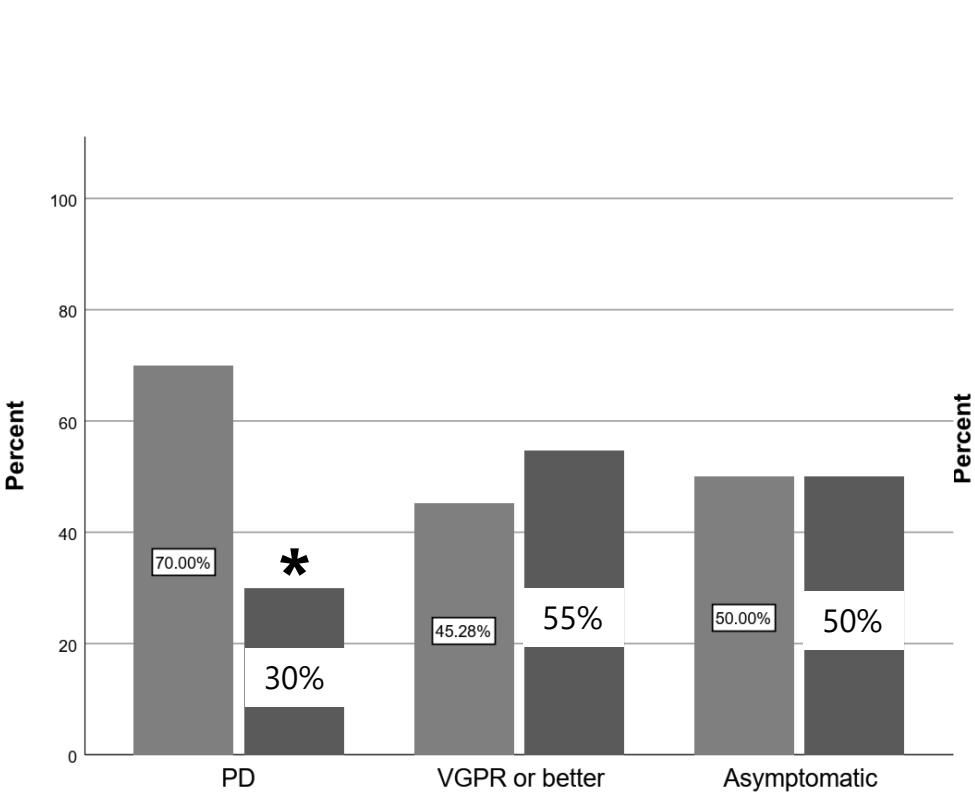
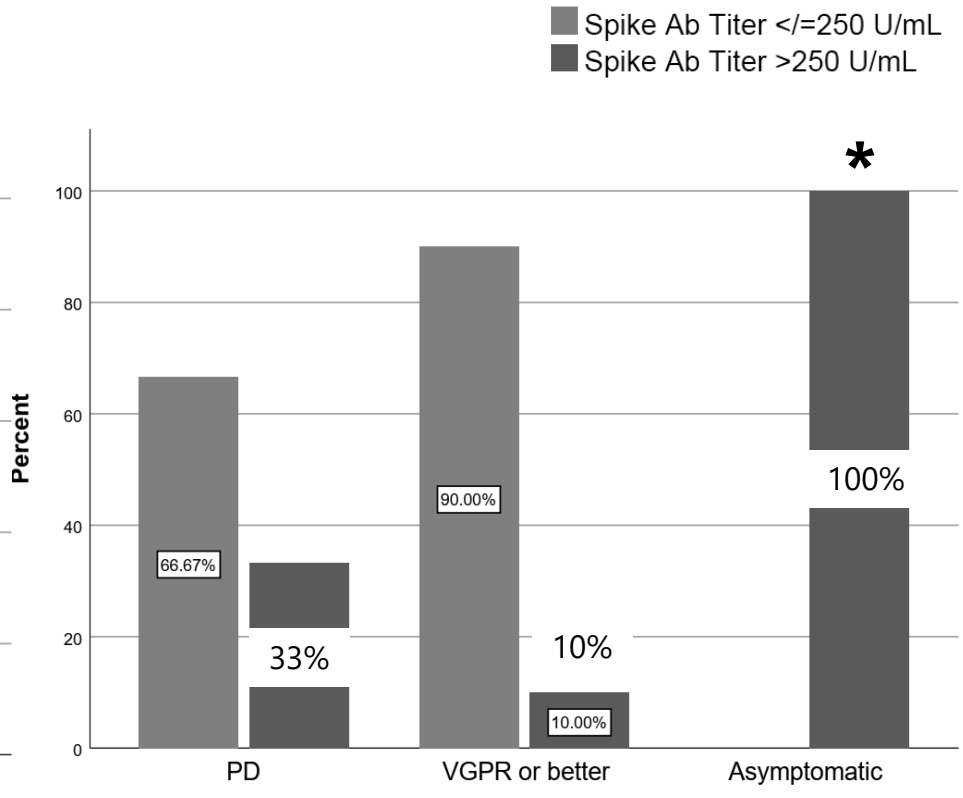


MM Disease Response



WM Disease Response

*p<0.05

Conclusions

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- Preliminary data suggest poor COVID-19 spike Ab responses in patients with MM and WM, WM patients showed more severe impairment of adequate spike Ab response compared to MM, 24% vs. 58%
- MRNA-1273 (Moderna) elicited highest spike Ab response rates followed by BNT162b2 mRNA (Pfizer/BioNTech), followed by JNJ-78436735
- Older age >75 years was associated with significantly lower spike Abs in WM and MM
- Among MM patients, progressive disease, 2+ prior lines of therapy, and ALC count <1K associated with significantly lower spike Abs
- Asymptomatic and most previously untreated WM patients achieved adequate spike Ab responses however the most significant reduction in spike Abs were seen in patients actively treated with BTK inhibitors or rituximab within 6 months
- Longitudinal spike Ab responses, comprehensive functional antibody responses, SARS-CoV-2 specific T cell responses, and COVID-19 strain-specific responses are ongoing
- Further understanding of immune responses to vaccination is needed to clarify patient risks, and need for boosters or alternative protective measures against COVID-19.

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Thank you!!

All Our Patients

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