

Supplementary Material

The role of immune suppression in COVID-19 hospitalization: clinical and epidemiological trends over three years of SARS-CoV-2 epidemic

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Supplementary Table S1. Differences between the frequencies of females, vaccinated subjects, and co-morbidities, and between the median ages of immune suppressed patients compared to the immune competent group.

Group	Frequency (percentage)									Median	
	Co-morbidities									V	Age
	F	Resp	Card	Neph	GI/Li	Met	Neur	No	>1		
Immune competent (N=1406)	32.5	13.2	51.3	7.7	14.0	35.8	30.2	30.2	40.3	12.7	64
All tumors (N=169)	42.6	16.6	56.8	12.4	27.2	33.1	9.5	19.5	46.7	35.3	72.0
Solid tumors (N=85)	44.7	18.8	61.2	5.9	9.4	41.2	11.8	22.4	48.2	27.0	73.0
Hematologic tumors (N=94)	39.4	14.9	55.3	19.1	39.4	24.5	9.6	17.0	45.7	40.2	71.5
All immune suppressants (N=168)	47.6	19.0	51.8	17.3	33.3	36.3	8.3	19.0	50.0	44.1	66.0
Biological drugs (N=53) ¹	54.7	54.7	45.3	13.2	26.4	28.3	7.5	24.5	47.2	42.6	64.0
Chemotherapeutics (N=69) ²	43.5	15.9	52.2	11.6	31.9	31.9	13.0	17.4	47.8	45.2	72.0
Corticosteroids and other drugs (N=92) ²	47.8	21.7	53.3	23.9	37.0	41.3	8.7	18.5	59.8	45.9	63.5
Connective tissue diseases (N=56)	51.8	21.4	62.5	17.9	16.1	48.2	14.3	16.1	60.7	34.0	67.5
Rheumatoid arthritis (N=19)	42.1	21.1	63.2	21.1	10.5	52.6	21.1	15.8	68.4	47.1	69.0
Other connective tissue diseases (N=38)	55.3	21.1	60.5	15.8	18.4	44.7	10.5	18.4	55.3	29.4	67.0
Transplant recipient (N=53)	39.6	20.8	66.0	43.4	58.5	52.8	1.9	9.4	75.5	69.4	57.0
Neutropenia (N=22)	40.9	22.7	59.1	18.2	59.1	40.9	13.6	4.5	68.2	61.9	68.5
HIV/AIDS (N=18)	27.8	5.6	22.2	0.0	38.9	16.7	44.4	44.4	22.2	33.3	56.0
Asplenia (N=10)	50.0	0.0	50.0	10.0	40.0	30.0	10.0	10.0	30.0	10.0	62.0
Aplastic anemia (N=9)	44.4	0.0	66.7	33.3	55.6	22.2	11.1	11.1	55.6	22.2	71.0
Other autoimmune diseases (N=5)	66.7	0.0	20.0	0.0	0.0	20.0	0.0	60.0	20.0	20.0	71.0
A/Hypogammaglobulinemia (N=4)	50.0	25.0	0.0	0.0	25.0	0.0	0.0	50.0	0.0	12.5	41.0

Frequencies and medians that are significantly different compared to those of the group of immune competent patients are in bold. F: female; Resp: respiratory diseases; Card: cardiovascular diseases; Neph: nephropathies; GI/Li: gastrointestinal/liver diseases; Met: metabolic diseases; Neur: neurologic diseases; No: no comorbidities; >1: co-morbidities of more than 1 category; V: vaccinated.

¹during the six months prior to admission; ²during the three months prior to admission

Supplementary Table S2. Immune suppressed patients among hospitalized patients stratified by hospitalization period, age, and outcome.

Before December 2021			Since December 2021			p
	N	%		N	%	
All outcomes						
Total (N=1418)	204	14.4	Total (N=298)	115	38.6	< 0.001
18-50 (N=290)	30	10.3	18-50 (N=43)	17	39.5	< 0.001
51-70 (N=610)	86	14.1	51-70 (N=110)	47	42.7	< 0.001
>70 (N=517)	88	17.0	>70 (N=145)	51	35.2	< 0.001
Severe outcome						
Total (N=743)	132	17.7	Total (N=97)	37	38.1	< 0.001
18-50 (N=109)	13	11.9	18-50 (N=13)	5	38.5	0.024
51-70 (N=299)	58	19.4	51-70 (N=39)	15	38.5	0.012
>70 (N=334)	61	18.3	>70 (N=45)	17	37.8	0.005
Death						
Total (N=223)	51	22.9	Total (N=29)	13	44.8	0.021
18-50 (N=5)	2	40.0	18-50 (N=1)	1	100.0	1
51-70 (N=43)	18	41.9	51-70 (N=6)	4	66.7	0.39
>70 (N=175)	31	17.7	>70 (N=22)	8	36.4	0.039

P values for statistically significant differences between the two periods are highlighted in bold. N: number of immune suppressed subjects; %: percentage of immune suppressed subjects

Supplementary Table S3. Patients with co-morbidities in more than one considered category during the two time periods February 2020-November 2021 and December 2021-November 2022.

Before December 2021 (N=1418)			Since December 2021 (N=298)			p
	N	%		N	%	
Without immune suppression	578	34.4	Without immune suppression	148	49.7	0.005
Including immune suppression	632	44.6	Including immune suppression	183	61.4	< 0.001

N and %: number and percentage of subjects with co-morbidities in more than 1 category including and excluding immune suppression as co-morbidity category. P values for statistically significant differences between the two periods are highlighted in bold

Supplementary Table S4. Outcomes among immune suppressed compared to immune competent patients stratified by vaccination status in the period between the end of February 2020 and November 2021.

Outcome	Immune competent		Immune suppressed		P ^{1,2}	Non vaccinated		P ^{1,3}	Vaccinated		P ^{1,4}	P ⁵
	Non vaccinated (N=1057)	Vaccinated (N=41)	Non vaccinated (N=171)	Vaccinated (N=16)		N	%		N	%		
Favorable	506	47.9	32	78.0	< 0.001	58	33.9	< 0.001	7	43.8	0.81	0.42
Severe⁶	551	52.1	9	22.0		113	66.1		9	56.3		
Septic shock	19	1.8	0	0.0	1	1	0.6	0.34	0	0.0	1	1
Intubation	71	6.7	0	0.0	0.11	6	3.5	0.11	3	18.8	0.092	0.032
ICU admission	88	8.3	0	0.0	0.070	8	4.7	0.12	3	18.8	0.15	0.056
Death	161	15.2	5	12.2	0.82	48	28.1	< 0.001	2	12.5	1	0.24
ARDS/Pneumonia	500	47.3	8	19.5	< 0.001	98	57.3	0.015	6	37.5	0.46	0.19
Hospitalization length	Median		Median		p	Median		p	Median		p	p
	14		9		0.055	16		0.017	15.5		0.50	0.89

P values for frequencies and medians that are significantly different are in bold. N: number of subjects; %: percentage subjects; ICU: intensive care unit; ARDS: acute respiratory distress syndrome.

¹significance cut-off of 0.02 due to Bonferroni correction; ²vaccinated immune competent vs. non-vaccinated immune competent; ³non-vaccinated immune suppressed vs. non-vaccinated immune competent; ⁴vaccinated immune suppressed vs. non-vaccinated immune competent; ⁵vaccinated immune suppressed vs. non-vaccinated immune suppressed; ⁶includes septic shock, intubation, ICU admission, death, and ARDS/pneumonia

Supplementary Table S5. Outcomes among immune suppressed compared to immune competent patients stratified by vaccination status in the period between December 2021 and November 2022.

Outcome	Immune competent					Immune suppressed						
	Non vaccinated (N=49)		Vaccinated (N=99)			Non vaccinated (N=10)			Vaccinated (N=79)			
	N	%	N	%	P^{1,2}	N	%	P^{1,3}	N	%	P^{1,4}	P⁵
Favorable	26	53.1	68	68.7	0.063	5	50.0	1	53	67.1	0.14	0.31
Severe⁶	23	46.9	31	31.3		5	50.0		26	32.9		
Septic shock	1	2.0	3	3.0	1	0	0.0	1	1	1.3	1	1
Intubation	1	2.0	0	0.0	0.33	0	0.0	1	4	5.1	0.65	1
ICU admission	1	2.0	5	5.1	0.66	0	0.0	1	5	6.3	0.41	1
Death	3	6.1	11	11.1	0.39	3	30.0	0.055	8	10.1	0.53	0.11
ARDS/Pneumonia	21	42.9	27	27.3	0.062	4	40.0	1	21	26.6	0.057	0.46
Hospitalization length	Median		Median		p	Median		p	Median		p	p
	14		10		0.027	19		0.3	14		0.79	0.31

P values for frequencies and medians that are significantly different are in bold. N: number of subjects; %: percentage of subjects; ICU: intensive care unit; ARDS: acute respiratory distress syndrome.

¹significance cut-off of 0.02 due to Bonferroni correction; ²vaccinated immune competent vs. non-vaccinated immune competent; ³non-vaccinated immune suppressed vs. non-vaccinated immune competent; ⁴vaccinated immune suppressed vs. non-vaccinated immune competent; ⁵vaccinated immune suppressed vs. non-vaccinated immune suppressed; ⁶includes septic shock, intubation, ICU admission, death, and ARDS/pneumonia

Supplementary Table S6. Patients with severe outcomes among vaccinated and non-vaccinated subjects with specific immune suppression conditions in the period between the end of February 2020 and November 2021.

	Number of vaccinated (%)		Number of non-vaccinated (%)		p
	Severe outcome	Favorable outcome	Severe outcome	Favorable outcome	
All tumors	2 (40.0)	3 (60.0)	62 (68.1)	29 (31.9)	0.33
Biological Drugs	4 (66.7)	2 (33.3)	18 (72.0)	7 (28.0)	1
Chemotherapeutics	3 (100)	0 (0.0)	21 (70.0)	9 (30.0)	0.55
Other connective tissue diseases	2 (66.7)	1 (33.3)	17 (70.8)	7 (29.2)	1
HIV/AIDS	0 (0.0)	0 (0.0)	10 (90.9)	1 (9.1)	/

A / indicated that it was not possible to calculate the p-value. %: percentage of subjects

Supplementary Table S7. Patients with severe outcomes among vaccinated and non-vaccinated subjects with specific immune suppression conditions in the period between December 2021 and November 2022.

	Number of vaccinated (%)		Number of non-vaccinated (%)		p
	Severe outcome	Favorable outcome	Severe outcome	Favorable outcome	
All tumors	14 (28.6)	35 (71.4)	4 (50.0)	4 (50.0)	0.25
Biological Drugs	7 (50.0)	7 (50.0)	1 (50.0)	1 (50.0)	1
Chemotherapeutics	9 (36.0)	16 (64.0)	2 (50.0)	2 (50.0)	0.62
Other connective tissue diseases	4 (57.1)	3 (42.9)	0 (0.0)	0 (0.0)	/
HIV/AIDS	1 (16.7)	5 (83.3)	1 (100.0)	0 (0.0)	0.29

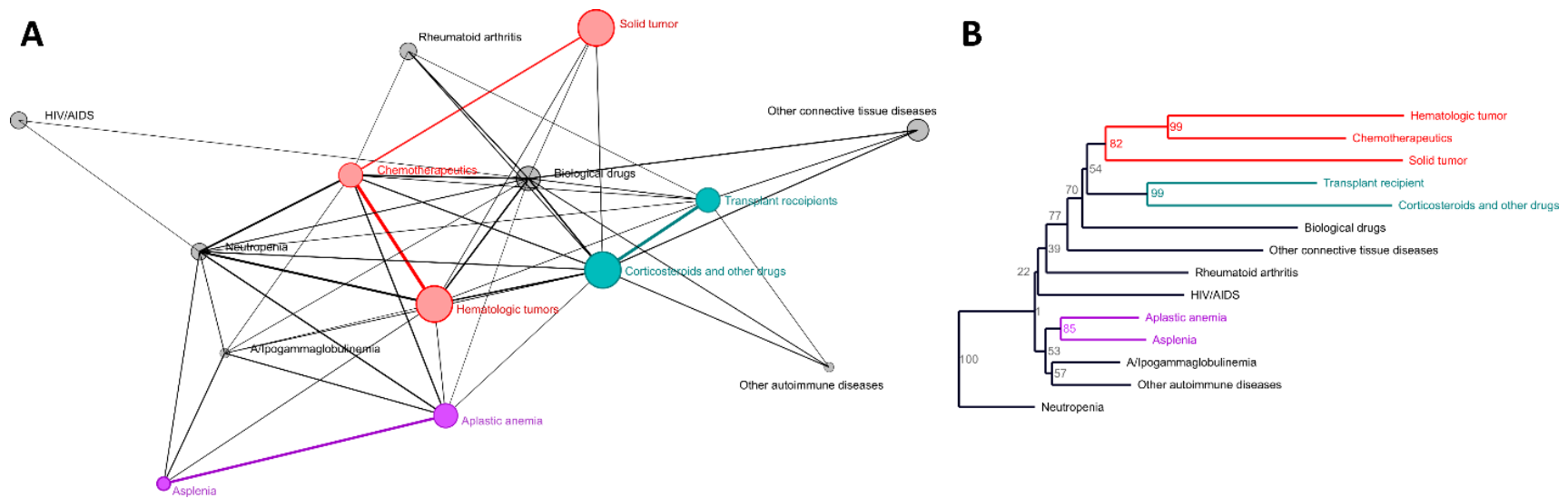
A / indicated that it was not possible to calculate the p-value. %: percentage of subjects

Supplementary Table S8. Potential predictors of severe outcomes evaluated separately (simple logistic regression) or after adjusting for the other variables (multiple logistic regression).

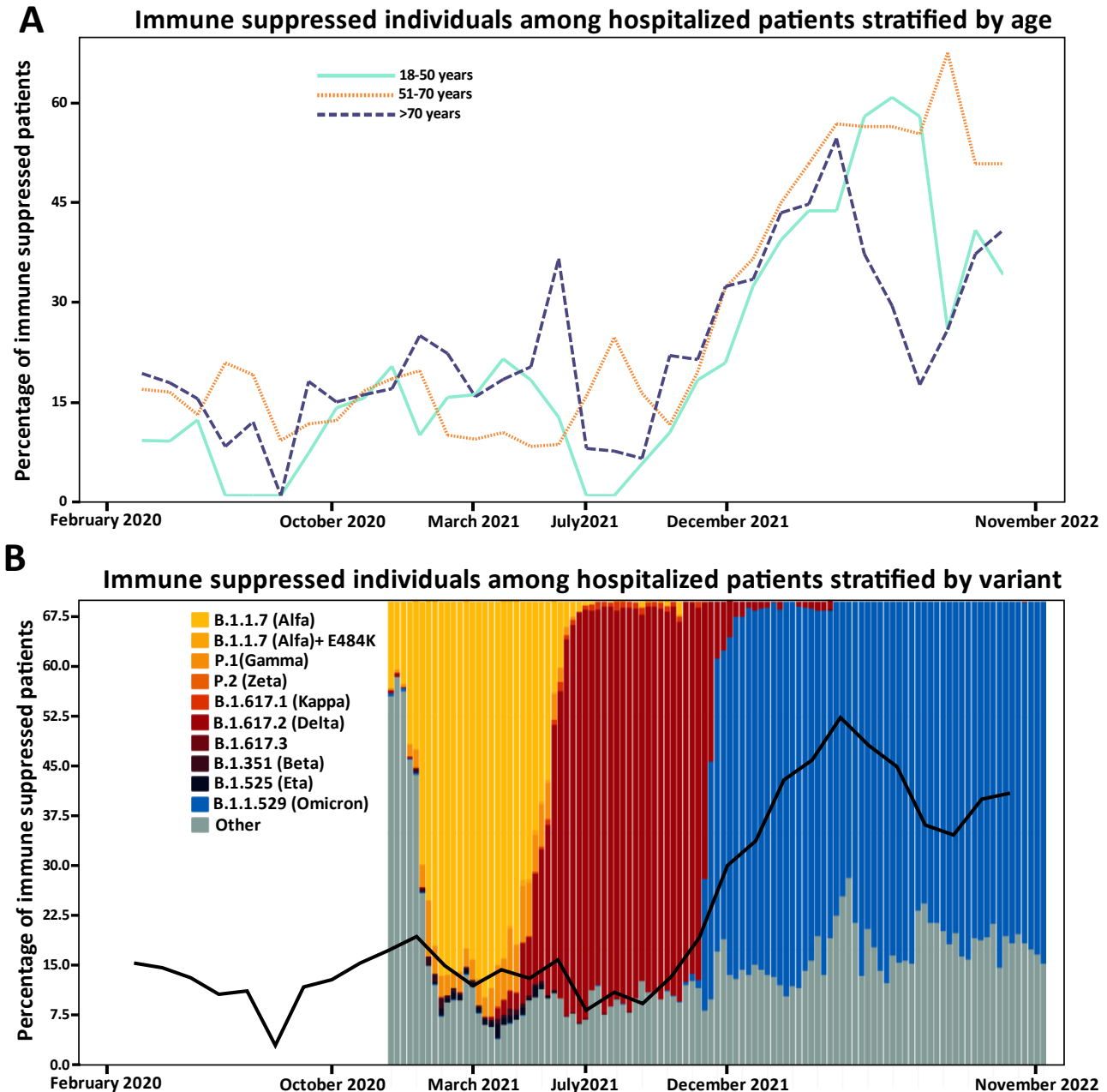
	Simple logistic regression			Multiple logistic regression		
	OR	95% CI	p	OR	95% CI	p
Immune suppression	1.21	0.95-1.54	0.13	1.64	1.23-2.19	<0.001
Age	1.02	1.02-1.03	<0.001	1.02	1.02-1.03	<0.001
Sex (male)	1.07	0.88-1.31	0.48	1.43	0.94-1.46	0.14
Co-morbidities¹	1.18	1.09-1.28	<0.001	1.14	1.03-1.26	0.011
Vaccination	0.35	0.27-0.47	<0.001	0.31	0.20-0.47	<0.001
Period (before Dec 2021)	2.28	1.75-2.97	<0.001	1.29	0.85-1.94	0.23

OR: odds ratio; CI: confidence interval

¹1, 2, 3, >3 included as continuous variables

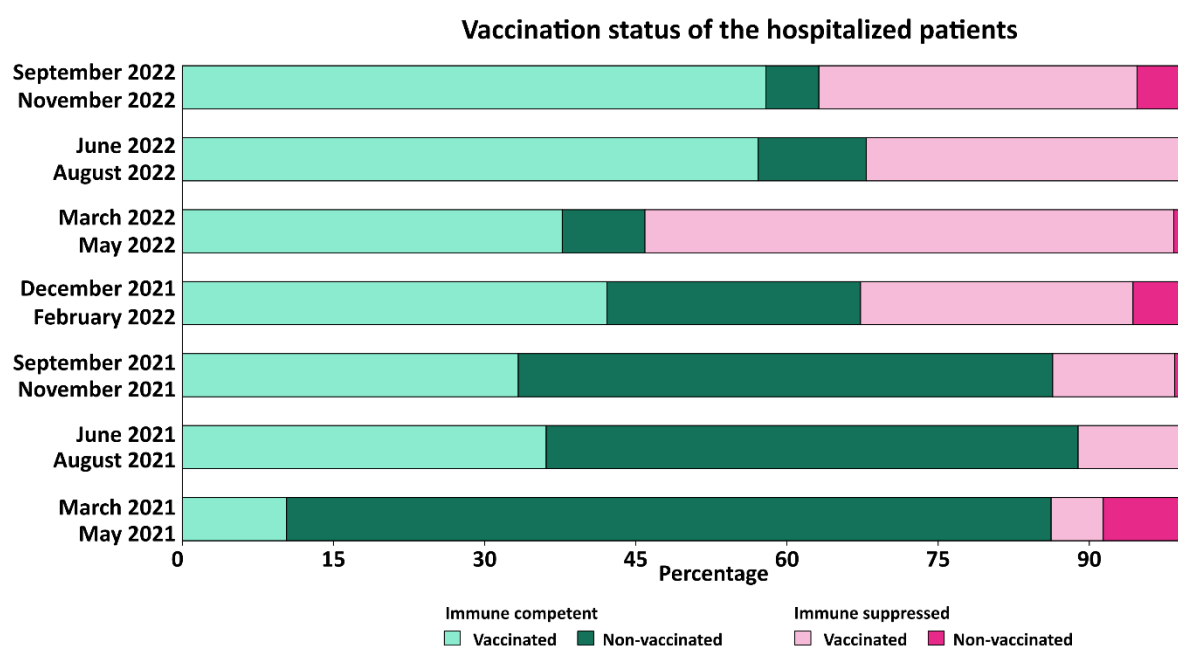


Supplementary Figure S1. Correlation between the various factors associated with immune suppression investigated in this study. In the network analysis (**A**) the size of each node is proportional to the number of patients having that condition, and the lines' thickness proportionally represents the association strength. In the clustering analysis (**B**) branch support (bootstrap) is indicated at basal nodes. Strong connections identified by both methods are highlighted with the same color.

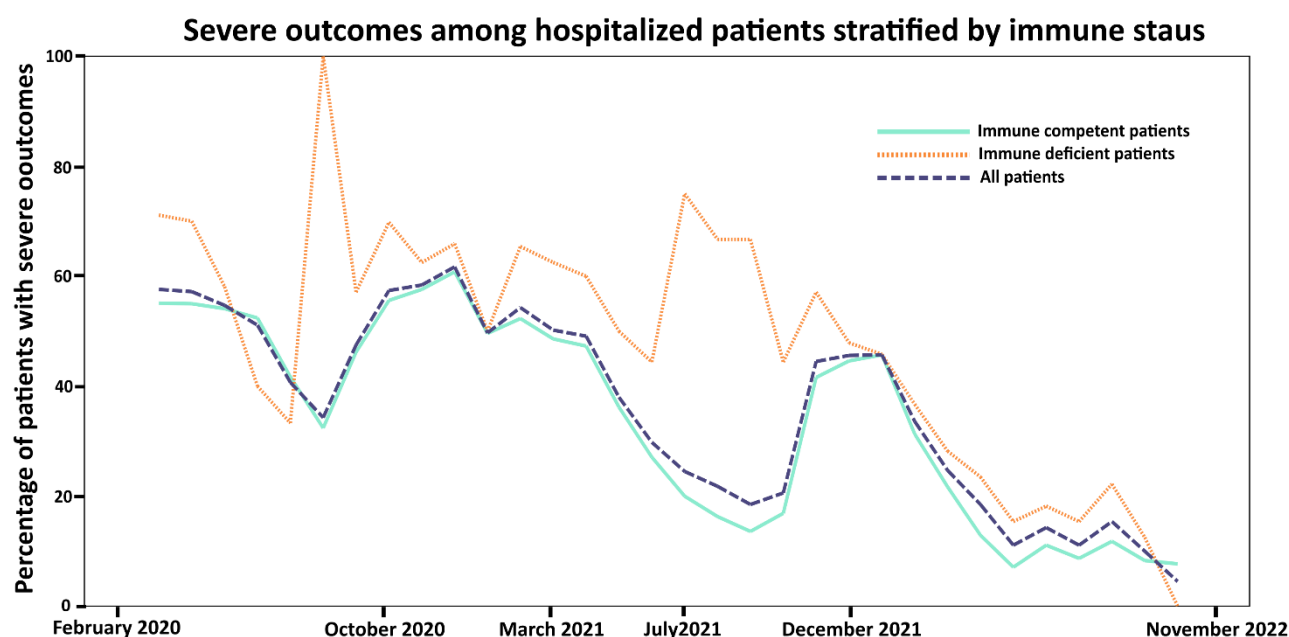


Supplementary Figure S2. Immune suppressed patients stratified by age (A) and variant (B) over time. The graphs show the proportion of immune suppressed subjects among hospitalized patients (stratified by age in A and overall in B) over time and each timepoint includes the data of 3 months – indicated timepoint +/- 1 month. In panel B, the relative frequency of variants circulating in Italy in the same period is shown as colored bars in the background (image reproduced from (1)) with each variant labeled with a different color, as indicated by the legend.

1. Istituto Superiore di Sanita'. Prevalenza e distribuzione delle varianti di SARS-CoV-2 di interesse per la sanità pubblica in Italia. Rapporto n. 28 del 3 febbraio 2023 (dati aggiornati al 30 gennaio 2023). (2023) <https://www.epicentro.iss.it/>



Supplementary Figure S3. Vaccination status of the hospitalized patients. Relative frequencies of vaccinated and non-vaccinated subjects according to their immune status are shown for three-month periods from the beginning of vaccination administration in Italy (March 2021) until the end of the study.



Supplementary Figure S4. Severe outcomes among hospitalized patients stratified by immune status. The graph shows the proportion of patients with severe outcomes among hospitalized patients stratified by immune status. Each time point includes data of 3 months – the indicated timepoint +/- 1 month.