

Supplementary Material

Appendix 1: Summary of balance for the “HCQ-AZ” and “AZ” subsets, respectively, using propensity score matching with Optimal Full Matching.

1a. Summary of balance subset “HCQ-AZ”

Summary of Balance for Matched Data:										
	Means	Treated	Means	Control	Std. Mean Diff.	Var.	Ratio	eCDF Mean	eCDF Max	Std. Pair Dist.
distance	0.9306	0.9306		0.0004	0.9863	0.0004	0.0077	0.0019		
SEX	0.5220	0.5189		0.0061	.	0.0030	0.0030	0.1598		
AGE1	0.5602	0.5603		-0.0003	.	0.0001	0.0001	0.1507		
AGE2	0.3519	0.3428		0.0190	.	0.0091	0.0091	0.1379		
AGE3	0.0835	0.0914		-0.0286	.	0.0079	0.0079	0.2080		
AGE4	0.0044	0.0055		-0.0156	.	0.0010	0.0010	0.0350		
INPATIENT	0.1092	0.1263		-0.0547	.	0.0171	0.0171	0.2103		
VARIANT1	0.1553	0.1609		-0.0155	.	0.0056	0.0056	0.0155		
VARIANT2	0.1371	0.1304		0.0195	.	0.0067	0.0067	0.0701		
VARIANT3	0.1721	0.1743		-0.0057	.	0.0022	0.0022	0.0841		
VARIANT4	0.1844	0.1863		-0.0048	.	0.0019	0.0019	0.0549		
VARIANT5	0.0863	0.0831		0.0113	.	0.0032	0.0032	0.0891		
VARIANTNA	0.2648	0.2651		-0.0005	.	0.0002	0.0002	0.0597		
VACCINATION	0.1230	0.1167		0.0256	1.1430	0.0110	0.0226	0.2169		
DIABETE	0.0524	0.0492		0.0190	1.1770	0.0110	0.0281	0.2627		
HBP	0.1116	0.1042		0.0317	1.1813	0.0110	0.0218	0.2627		
OBESITY	0.1971	0.1941		0.0101	1.0708	0.0110	0.0235	0.2648		
ASTHMA	0.0757	0.0579		0.0903	1.8033	0.0110	0.0204	0.1965		
COPD	0.0112	0.0169		-0.0722	0.5364	0.0145	0.0382	0.2099		
CANCER	0.0398	0.0279		0.0813	2.3272	0.0110	0.0198	0.1880		
IMMUNODEFICIENCY	0.0177	0.0154		0.0234	1.3884	0.0110	0.0301	0.1571		
AutoImmuneDiseases	0.0526	0.0531		-0.0031	1.0288	0.0110	0.0318	0.2502		
ChronicCardiacDiseases	0.0178	0.0187		-0.0088	0.9600	0.0112	0.0333	0.1974		
Sample Sizes:										
	Control	Treated								
All	1771.	23172								
Matched (ESS)	69.06	23172								
Matched	1771.	23172								
Unmatched	0.	0								
Discarded	0.	0								

1b. Summary of balance for subset “AZ”

Summary of Balance for Matched Data:										
	Means	Treated	Means	Control	Std. Mean Diff.	Var.	Ratio	eCDF Mean	eCDF Max	Std. Pair Dist.
distance	0.7612	0.7612		0.0004	0.9947	0.0007	0.0079	0.0016		
SEX	0.5291	0.5420		-0.0260	.	0.0130	0.0130	0.2643		
AGE1	0.3126	0.3289		-0.0351	.	0.0163	0.0163	0.1081		
AGE2	0.3917	0.3742		0.0358	.	0.0175	0.0175	0.2255		
AGE3	0.2612	0.2595		0.0040	.	0.0017	0.0017	0.2102		
AGE4	0.0345	0.0375		-0.0162	.	0.0029	0.0029	0.1023		
INPATIENT	0.3421	0.3581		-0.0338	.	0.0161	0.0161	0.1790		
VARIANT1	0.0334	0.0402		-0.0377	.	0.0068	0.0068	0.0447		
VARIANT2	0.1835	0.1903		-0.0175	.	0.0068	0.0068	0.1145		
VARIANT3	0.1586	0.1612		-0.0072	.	0.0026	0.0026	0.2280		
VARIANT4	0.1752	0.1839		-0.0230	.	0.0087	0.0087	0.1659		
VARIANT5	0.1068	0.0912		0.0506	.	0.0156	0.0156	0.1689		
VARIANTNA	0.3425	0.3332		0.0196	.	0.0093	0.0093	0.1403		
VACCINATION	0.1854	0.1778		0.0273	1.1764	0.0162	0.0324	0.3063		
DIABETE	0.1250	0.1071		0.0758	1.5038	0.0162	0.0249	0.3410		
HBP	0.2694	0.2388		0.0971	1.3181	0.0162	0.0431	0.3824		
OBESITY	0.2277	0.2053		0.0759	1.3135	0.0162	0.0333	0.3419		
ASTHMA	0.0711	0.0717		-0.0037	1.0797	0.0162	0.0459	0.2694		
COPD	0.0263	0.0232		0.0275	1.4798	0.0162	0.0442	0.1885		
CANCER	0.0610	0.0520		0.0523	1.5554	0.0162	0.0368	0.2598		
IMMUNODEFICIENCY	0.0259	0.0217		0.0377	1.7050	0.0162	0.0431	0.1878		
AutoImmuneDiseases	0.0599	0.0598		0.0007	1.1026	0.0162	0.0457	0.2719		
ChronicCardiacDiseases	0.0740	0.0522		0.1150	2.6037	0.0162	0.0251	0.2491		
Sample Sizes:										
	Control	Treated								
All	1771.	4578								
Matched (ESS)	178.73	4578								
Matched	1771.	4578								
Unmatched	0.	0								
Discarded	0.	0								

Appendix 2: Multivariate logistic regression for the “HCQ-AZ” subset with ivermectin excluded from treatment**Table 7c:** Multivariate logistic regression for the HCQ-AZ* subset(ivermectin excluded from treatment) at 56 days cutoff (PSM with Optimal Full Matching)

	“HCQ-AZ” subset (N = 24614)		
Treatment factor	OR*	95%CI	p-value
HCQ-AZ	0.409	[0.313 ; 0.537]	< 0.001
Demography			
Sex (female/male)	0.425	[0.351 ; 0.514]	< 0.001
Age < 50 yrs (reference)			
Age 50-69 (vs ref.)	2.439	[1.862 ; 3.223]	< 0.001
Age 70-89 (vs ref.)	4.646	[3.486 ; 6.249]	< 0.001
Age > 89 (vs ref.)	8.941	[5.554 ; 14.330]	< 0.001
Disease severity			
Inpatient	72.858	[54.238 ; 100.081]	< 0.001
Variant			
A (Wuhan) (reference)			
B.1.160 (Mars 4) (vs ref.)	1.366	[1.033 ; 1.809]	0.029
B.1.7.7 (UK) (vs ref.)	1.289	[0.941 ; 1.761]	0.112
B.1.617.2 (Delta) (vs ref.)	1.093	[0.774 ; 1.535]	0.61
Others (vs ref.)	1.457	[1.054 ; 2.009]	0.022
Null (vs ref.)	0.998	[0.756 ; 1.321]	0.987
Vaccination			
Vaccinated	0.799	[0.425 ; 1.418]	0.465
Comorbidities			
Diabetes	1.021	[0.652 ; 1.566]	0.924
Obesity	1.835	[1.327 ; 2.518]	< 0.001
High blood pressure	0.931	[0.640 ; 1.332]	0.699
Asthma	0.801	[0.401 ; 1.477]	0.502
COPD	1.499	[0.603 ; 3.311]	0.346
Cancer	0.753	[0.378 ; 1.389]	0.387
Immunodeficiency	2.16	[0.885 ; 4.911]	0.077
Auto-immune diseases	0.941	[0.440 ; 1.830]	0.865
Chronic cardiac diseases	1.201	[0.581 ; 2.340]	0.603

*ivermectin excluded from the subset

Table 8b: Logistic regression for the “HCQ-AZ” subset (ivermectin excluded from treatment) – treatment:covariate interactions detected (PSM with Optimal Full Matching).

Interaction ¹	OR	95%CI	p-value
HCQ-AZ subset²			
HCQ:SEX (men/women)	0.196	[0.058 0.573]	0.005
HCQ:AGE3	0.033	[0.005 0.174]	< 0.001
HCQ:AGE4	0.033	[0.003 0.299]	0.004

HCQ:INPATIENT	0.095	[0.011 0.479]	0.012
HCQ:VARIANT3	0.106	[0.016 0.626]	0.016
HCQ:VARIANT6	0.012	[0.002 0.057]	< 0.001

¹calculations performed at 56 days cutoff; HCQ = hydroxychloroquine, HCQ:SEX interaction value calculated for men with respect to women; AGE3 = age in the interval [70 – 89] years; AGE4 = age ≥ 90 years; COPD = Chronic Obstructive Pulmonary Diseases ; VARIANT3 = UK ; VARIANT6 = Null.

²ivermectin excluded from the subset.

Appendix 3: Sensitivity analysis

3a. “HCQ-AZ” subset model (b)

```
glm(formula = Status_56.EFS ~ HCQ + SEX + AGE + INPATIENT + VARIANT +
  VACCINATION + DIABETE + OBESITY + HBP, family = quasibinomial(),
  data = m.data, weights = weights)
```

Coefficients:

	OR	2.5 %	97.5 %	Pr(> t)
(Intercept)	0.0028	0.0018	0.0043	< 2e-16 ***
HCQ	0.3925	0.3007	0.5156	1.03e-11 ***
SEX	0.4454	0.3711	0.5329	< 2e-16 ***
AGE2	2.3989	1.8494	3.1403	9.00e-11 ***
AGE3	4.8823	3.7106	6.4816	< 2e-16 ***
AGE4	9.9734	6.3537	15.6173	< 2e-16 ***
INPATIENT	68.0729	51.4821	91.7830	< 2e-16 ***
VARIANT2	1.3135	1.0005	1.7276	0.050172 *
VARIANT3	1.2463	0.9270	1.6750	0.144302
VARIANT4	1.3748	1.0031	1.8799	0.046798 *
VARIANT5	1.4205	1.0370	1.9412	0.028054 *
VARIANTNA	0.9426	0.7163	1.2419	0.673355
VACCINATION	0.7464	0.4227	1.2554	0.290334
DIABETE	1.0787	0.7143	1.5974	0.711616
OBESITY	1.7974	1.3321	2.4101	0.000105 ***
HBP	0.9761	0.6918	1.3604	0.888250

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for quasibinomial family taken to be 0.7517078)

```
Null deviance: 5188.9 on 24942 degrees of freedom
Residual deviance: 2955.7 on 24927 degrees of freedom
AIC: NA
```

Call:

```
glm(formula = Status_56.EFS ~ HCQ * (SEX + AGE + INPATIENT +
  VARIANT + VACCINATION + DIABETE + OBESITY + HBP), family = quasibinomial(),
  data = m.data, weights = weights)
```

Coefficients:

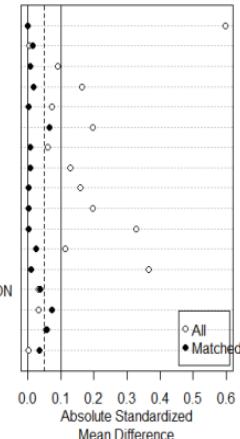
	OR	2.5 %	97.5 %	Pr(> t)
HCQ:SEX	1.7009	0.8131	3.7286	0.169932
HCQ:AGE2	0.4058	0.1181	1.2248	0.126719
HCQ:AGE3	0.0390	0.0092	0.1360	2.02e-06 ***
HCQ:AGE4	0.0324	0.0049	0.1811	0.000184 ***
HCQ:INPATIENT	0.2991	0.0843	0.8630	0.039802 *
HCQ:VARIANT2	1.3931	0.3870	5.0310	0.609949
HCQ:VARIANT3	0.2759	0.0736	0.9906	0.050827 .
HCQ:VARIANT4	0.2081	0.0504	0.8064	0.025645 *
HCQ:VARIANT5	0.9116	0.1879	4.3970	0.907471
HCQ:VARIANTNA	0.0299	0.0079	0.0995	5.09e-08 ***
HCQ:VACCINATION	2.0850	0.1824	91.8549	0.619091
HCQ:DIABETE	0.7698	0.0812	14.0197	0.831797
HCQ:OBESITY	0.3502	0.0752	1.8020	0.188547
HCQ:HBP	11.4762	1.0860	388.1810	0.087079 .

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for quasibinomial family taken to be 0.8207921)

```
Null deviance: 5188.9 on 24942 degrees of freedom
Residual deviance: 2881.6 on 24913 degrees of freedom
AIC: NA
```

Number of Fisher Scoring iterations: 9



3b. “HCQ-AZ” subset model (c)

Call:

```
glm(formula = Status_56.EFS ~ HCQ + SEX + AGE + INPATIENT + VARIANT +
    VACCINATION, family = quasibinomial(), data = m.data, weights = weights)
```

Coefficients:

	OR	2.5 %	97.5 %	Pr(> t)
(Intercept)	0.0030	0.0019	0.0046	< 2e-16 ***
HCQ	0.4332	0.3305	0.5720	2.21e-09 ***
SEX	0.4572	0.3811	0.5467	< 2e-16 ***
AGE2	2.4871	1.9168	3.2600	1.70e-11 ***
AGE3	4.8564	3.6984	6.4388	< 2e-16 ***
AGE4	8.8672	5.5786	14.0249	< 2e-16 ***
INPATIENT	65.6848	49.8886	88.1052	< 2e-16 ***
VARIANT2	1.3062	0.9966	1.7149	0.05356 .
VARIANT3	1.2383	0.9211	1.6633	0.15588
VARIANT4	1.3906	1.0156	1.8992	0.03874 *
VARIANT5	1.5329	1.1282	2.0797	0.00614 **
VARIANTNA	0.9395	0.7149	1.2361	0.65459
VACCINATION	0.5629	0.3163	0.9505	0.03984 *

Signif. codes:	0	****	0.001	***
	0.01	**	0.05	.*
	0.1	'	1	

(Dispersion parameter for quasibinomial family taken to be 0.7504333)

Null deviance: 5146.3 on 24942 degrees of freedom

Residual deviance: 2970.6 on 24930 degrees of freedom

AIC: NA

Number of Fisher Scoring iterations: 9

Call:

```
glm(formula = Status_56.EFS ~ HCQ * (SEX + AGE + INPATIENT +
    VARIANT + VACCINATION), family = quasibinomial(), data = m.data,
    weights = weights)
```

Coefficients:

	OR	2.5 %	97.5 %	Pr(> t)
HCQ:SEX	1.2682	0.6370	2.6058	0.506956
HCQ:AGE2	0.1557	0.0272	0.5515	0.011433 *
HCQ:AGE3	0.0311	0.0052	0.1167	5.53e-06 ***
HCQ:AGE4	0.0328	0.0036	0.2214	0.000876 ***
HCQ:INPATIENT	0.6965	0.2641	1.6388	0.433613
HCQ:VARIANT2	1.5553	0.4906	4.9208	0.449369
HCQ:VARIANT3	0.7663	0.2103	2.8273	0.685846
HCQ:VARIANT4	0.3768	0.1008	1.3858	0.141672
HCQ:VARIANT5	0.2173	0.0578	0.7710	0.020443 *
HCQ:VARIANTNA	0.0574	0.0185	0.1623	2.21e-07 ***
HCQ:VACCINATION	4.3157	0.4940	123.6460	0.271702

Signif. codes:	0	****	0.001	***
	0.01	**	0.05	.*
	0.1	'	1	

(Dispersion parameter for quasibinomial family taken to be 0.7359688)

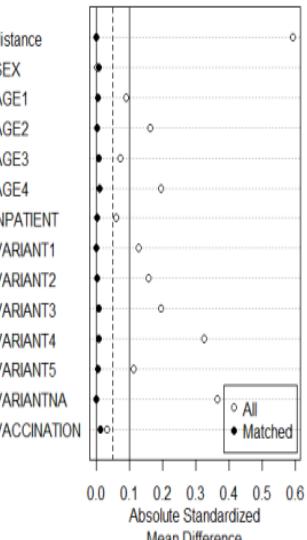
Null deviance: 5146.3 on 24942 degrees of freedom

Residual deviance: 2901.3 on 24919 degrees of freedom

AIC: NA

Number of Fisher Scoring iterations: 9

3c. "HCQ-AZ" subset reduced to men only.



```
Call:
glm(formula = Status_56.EFS ~ HCQ + AGE + INPATIENT + VARIANT +
    VACCINATION + DIABETE + OBESITY + HBP + ASTHMA + COPD + CANCER +
    IMMUNODEFICIENCY + AutoImmuneDiseases + ChronicCardiacDiseases,
    family = quasibinomial(), data = m.data, weights = weights)
```

Coefficients:

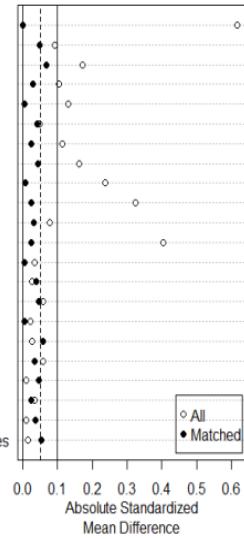
	OR	2.5 %	97.5 %	Pr(> t)	distance
(Intercept)	0.0029	0.0017	0.0048	< 2e-16 ***	AGE1
HCQ	0.3898	0.2811	0.5421	1.67e-08 ***	AGE2
AGE2	2.5743	1.9010	3.5296	2.05e-09 ***	AGE3
AGE3	5.1529	3.7222	7.2170	< 2e-16 ***	AGE4
AGE4	9.8590	4.9738	19.4656	4.14e-11 ***	INPATIENT
INPATIENT	58.2485	42.4845	81.8766	< 2e-16 ***	VARIANT1
VARIANT2	1.3761	0.9943	1.9118	0.0554 .	VARIANT2
VARIANT3	1.1883	0.8280	1.7050	0.3496	VARIANT3
VARIANT4	0.9481	0.6365	1.4045	0.7915	VARIANT4
VARIANT5	1.4266	0.9766	2.0801	0.0652 .	VARIANT5
VARIANTNA	0.9014	0.6507	1.2525	0.5340	VARIANTNA
VACCINATION	0.8758	0.4483	1.6130	0.6834	VACCINATION
DIABETE	1.1993	0.7387	1.9051	0.4511	DIABETE
OBESITY	2.1115	1.4850	2.9824	2.62e-05 ***	HBP
HBP	1.0064	0.6727	1.4831	0.9749	OBESITY
ASTHMA	0.7697	0.3231	1.6266	0.5214	ASTHMA
COPD	2.5741	0.9854	6.1599	0.0411 *	COPD
CANCER	0.9498	0.4372	1.9105	0.8882	CANCER
IMMUNODEFICIENCY	2.6687	1.0349	6.3474	0.0328 *	IMMUNODEFICIENCY
AutoImmuneDiseases	0.6423	0.2087	1.6339	0.3916	AutoImmuneDiseases
ChronicCardiacDiseases	1.0831	0.5463	2.0500	0.8121	ChronicCardiacDiseases

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for quasibinomial family taken to be 0.7134203)

Null deviance: 3322.0 on 11919 degrees of freedom
 Residual deviance: 1924.8 on 11899 degrees of freedom
 AIC: NA

Number of Fisher Scoring iterations: 8



3d. "HCQ-AZ" subset reduced to women only.

```
Call:
glm(formula = Status_56.EFS ~ HCQ + AGE + INPATIENT + VARIANT +
    VACCINATION + DIABETE + OBESITY + HBP + ASTHMA + COPD + CANCER +
    IMMUNODEFICIENCY + AutoImmuneDiseases + ChronicCardiacDiseases,
    family = quasibinomial(), data = m.data, weights = weights)
```

Coefficients:

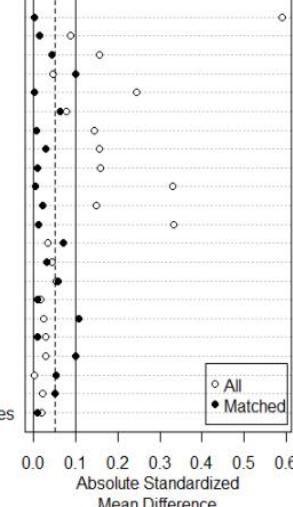
	OR	2.5 %	97.5 %	Pr(> t)	distance
(Intercept)	0.0010	0.0004	0.0024	< 2e-16 ***	AGE1
HCQ	0.4995	0.2780	0.7499	0.00153 **	AGE2
AGE2	2.4163	1.4112	4.3281	0.00192 **	AGE3
AGE3	4.5257	2.5964	8.2517	2.76e-07 ***	AGE4
AGE4	7.3639	3.3318	16.2248	6.69e-07 ***	INPATIENT
INPATIENT	89.1950	50.3117	172.7725	< 2e-16 ***	VARIANT1
VARIANT2	1.1012	0.6428	1.8788	0.72360	VARIANT2
VARIANT3	1.2107	0.6647	2.1737	0.52535	VARIANT3
VARIANT4	1.6063	0.8982	2.8449	0.10578	VARIANT4
VARIANT5	1.2742	0.6848	2.3169	0.43347	VARIANT5
VARIANTNA	1.1341	0.6723	1.9134	0.63605	VARIANTNA
VACCINATION	0.6769	0.1805	1.9374	0.51078	VACCINATION
DIABETE	0.5396	0.1816	1.3698	0.22560	DIABETE
OBESITY	1.4204	0.7429	2.6197	0.27333	HBP
HBP	0.9044	0.4267	1.8005	0.78323	OBESITY
ASTHMA	1.3110	0.4896	3.0623	0.55761	ASTHMA
COPD	1.1487	0.2130	4.1121	0.84870	COPD
CANCER	0.9996	0.3219	2.5783	0.99936	CANCER
IMMUNODEFICIENCY	0.1652	0.0000	2.7862	0.41282	IMMUNODEFICIENCY
AutoImmuneDiseases	0.8314	0.2315	2.2965	0.74724	AutoImmuneDiseases
ChronicCardiacDiseases	2.4798	0.3952	11.4363	0.27524	ChronicCardiacDiseases

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for quasibinomial family taken to be 0.9763696)

Null deviance: 1766.3 on 13022 degrees of freedom
 Residual deviance: 1048.1 on 13002 degrees of freedom
 AIC: NA

Number of Fisher Scoring iterations: 9



3e. Subset AZ only (IVM excluded) vs "no AZ no HCQ no IVM"

```

glm(formula = Status_56.EFS ~ AZ + SEX + AGE + INPATIENT + VARIANT +
  VACCINATION + DIABETE + OBESITY + HBP + ASTHMA + COPD + CANCER +
  IMMUNODEFICIENCY + AutoImmuneDiseases + ChronicCardiacDiseases,
  family = quasibinomial(), data = m.data, weights = weights)

Coefficients:
            OR    2.5 %   97.5 % Pr(>|t|)    
(Intercept) 0.0032  0.0014  0.0069 < 2e-16 ***
AZ           0.6089  0.4895  0.7572 8.38e-06 ***
SEX          0.3106  0.2474  0.3883 < 2e-16 ***
AGE2         2.2948  1.4764  3.6758 0.000346 ***
AGE3         7.2612  4.7372 11.5122 < 2e-16 ***
AGE4         8.1541  4.8358 14.0657 1.38e-14 ***
INPATIENT    58.8594 35.2921 106.7959 < 2e-16 ***
VARIANT2     1.5039  0.9769  2.3556 0.068639 .  
VARIANT3     1.7877  1.0399  3.0922 0.036372 *  
VARIANT4     1.9132  1.1387  3.2457 0.015052 *  
VARIANT5     1.4667  0.8897  2.4426 0.136496  
VARIANTNA    2.0430  1.3228  3.2125 0.001575 ** 
VACCINATION   0.5670  0.1993  1.4464 0.258083  
DIABETE       0.6396  0.2644  1.4552 0.301375  
OBESITY       2.0839  1.0729  3.9602 0.027181 *  
HBP          0.4789  0.2379  0.9388 0.035151 *  
ASTHMA        0.4066  0.0735  1.5100 0.230304  
COPD          3.5236  1.0007 10.8995 0.036076 *  
CANCER        0.5459  0.1405  1.6738 0.328982  
IMMUNODEFICIENCY 6.7062  1.4852 25.8342 0.008778 ** 
AutoImmuneDiseases 0.6228  0.0813  2.8703 0.588528  
ChronicCardiacDiseases 0.1880  0.0511  0.5552 0.005096 ** 
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

(Dispersion parameter for quasibinomial family taken to be 1.077491)

Null deviance: 3756.6 on 4914 degrees of freedom
 Residual deviance: 2294.6 on 4893 degrees of freedom
 AIC: NA

Number of Fisher Scoring iterations: 8

```

Call:
glm(formula = Status_56.EFS ~ AZ * (SEX + INPATIENT + VARIANT +
  VACCINATION + DIABETE + OBESITY + HBP + ASTHMA + COPD + CANCER +
  IMMUNODEFICIENCY + AutoImmuneDiseases + ChronicCardiacDiseases),
  family = quasibinomial(), data = m.data, weights = weights)

```

```

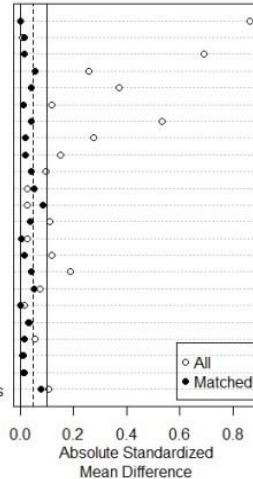
Coefficients:
            OR    2.5 %   97.5 % Pr(>|t|)    
.AZ:SEX      6.1759  3.7108 10.4503 5.77e-12 ***
.AZ:INPATIENT 0.1603  0.0290  0.6337 0.016338 *  
.AZ:VARIANT2  3.6543  1.4321  9.3928 0.006769 ** 
.AZ:VARIANT3  1.3639  0.4095  4.6033 0.614313  
.AZ:VARIANT4  1.4244  0.4785  4.2467 0.524469  
.AZ:VARIANT5  0.9507  0.3177  2.8513 0.927826  
.AZ:VARIANTNA 0.2774  0.1072  0.7165 0.007987 ** 
.AZ:VACCINATION 0.1839  0.0170  2.5603 0.178775  
.AZ:DIABETE    9.8631  0.9127 124.0031 0.067064 .  
.AZ:OBESITY    0.4672  0.0833  2.9555 0.400581  
.AZ:HBP        0.2061  0.0226  1.8882 0.160710  
.AZ:ASTHMA     13.0902  0.4765 504.7077 0.136121  
.AZ:COPD       0.0424  0.0016  1.8136 0.070076 .  
.AZ:CANCER      0.0108  0.0005  0.1842 0.001865 ** 
.AZ:IMMUNODEFICIENCY 1.0067  0.0142  47.2424 0.997535  
.AZ:AutoImmuneDiseases 0.7560  0.0227  61.2304 0.879364  
.AZ:ChronicCardiacDiseases 2.7550  0.2339  70.5359 0.454860  
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

(Dispersion parameter for quasibinomial family taken to be 1.175363)

Null deviance: 3756.6 on 4914 degrees of freedom
 Residual deviance: 2300.6 on 4879 degrees of freedom
 AIC: NA

Number of Fisher Scoring iterations: 8



Appendix 4: R version 4.3.1 line commands to run the multivariate logistic regression with Propensity Score Matching

(0) download the publically available IHU-Méditerranée dataset from : [Dryad | Data -- Monocentric retrospective cohort of 30,423 COVID-19 patients \(datadryad.org\)](#)

(1) transform the dataset in a .csv (coma separated variable) file and add 4 binary variables that list for every patient whether an event (ICU transfer or DEATH) occurred at 42,56,90 and 640 days after presentation (here we have named these additional variables Status_42.EFS, Status_56.EFS, Status_90.EFS and Status_640.EFS).

- (2) launch the R software (version 4.3.1) interactive windows
- (3) install package from a selected CRAN mirror using the interactive menu “Packages” and then “Install packages”
- (4) activate interactively at the prompt the packages needed:

```
> library(survival)
> library(MatchIt)
> library(optmatch)
> library(survey)
> library(quickmatch)
> library(marginaleffects)
> cohort_entry_status_2_ok <- read.csv (file="cohort_entry_status_ok_2_mod.csv", header=TRUE, sep=',')
> nrow(cohort_entry_status_2_ok)
> wrk_hcq_az_cohort <- subset (cohort_entry_status_2_ok, (HCQ == 1 & AZ == 1) | (HCQ == 0 & AZ == 0 & IVM == 0))
> nrow(wrk_hcq_az_cohort)
> str(wrk_hcq_az_cohort)
> wrk_hcq_az_cohort[wrk_hcq_az_cohort == 'NULL'] <- 'NA'
```

Make variables numerical

```
> wrk_hcq_az_cohort$VACCINATION <- as.numeric(as.character(wrk_hcq_az_cohort$VACCINATION))
> wrk_hcq_az_cohort$DIABETE <- as.numeric(as.character(wrk_hcq_az_cohort$DIABETE))
> wrk_hcq_az_cohort$HBP <- as.numeric(as.character(wrk_hcq_az_cohort$HBP))
> wrk_hcq_az_cohort$OBESITY <- as.numeric(as.character(wrk_hcq_az_cohort$OBESITY))
> wrk_hcq_az_cohort$ASTHMA <- as.numeric(as.character(wrk_hcq_az_cohort$ASTHMA))
> wrk_hcq_az_cohort$COPD <- as.numeric(as.character(wrk_hcq_az_cohort$COPD))
> wrk_hcq_az_cohort$CANCER <- as.numeric(as.character(wrk_hcq_az_cohort$CANCER))
> wrk_hcq_az_cohort$IMMUNODEFICIENCY <- as.numeric(as.character(wrk_hcq_az_cohort$IMMUNODEFICIENCY))
> wrk_hcq_az_cohort$AutoImmuneDiseases <- as.numeric(as.character(wrk_hcq_az_cohort$AutoImmuneDiseases))
> wrk_hcq_az_cohort$ChronicCardiacDiseases <- as.numeric(as.character(wrk_hcq_az_cohort$ChronicCardiacDiseases))
```

For each covariate replace NA values by the mean values for each covariate

```
> wrk_hcq_az_cohort$VACCINATION[is.na(wrk_hcq_az_cohort$VACCINATION)] <- mean(wrk_hcq_az_cohort$VACCINATION, na.rm=TRUE)
> wrk_hcq_az_cohort$DIABETE[is.na(wrk_hcq_az_cohort$DIABETE)] <- mean(wrk_hcq_az_cohort$DIABETE, na.rm=TRUE)
> wrk_hcq_az_cohort$HBP[is.na(wrk_hcq_az_cohort$HBP)] <- mean(wrk_hcq_az_cohort$HBP, na.rm=TRUE)
```

```

> wrk_hcq_az_cohort$OBESITY[is.na(wrk_hcq_az_cohort$OBESITY)] <- mean(wrk_hcq_az_cohort$OBESITY,
na.rm=TRUE)
> wrk_hcq_az_cohort$ASTHMA[is.na(wrk_hcq_az_cohort$ASTHMA)] <- mean(wrk_hcq_az_cohort$ASTHMA,
na.rm=TRUE)
> wrk_hcq_az_cohort$COPD[is.na(wrk_hcq_az_cohort$COPD)] <- mean(wrk_hcq_az_cohort$COPD,
na.rm=TRUE)
> wrk_hcq_az_cohort$CANCER[is.na(wrk_hcq_az_cohort$CANCER)] <- mean(wrk_hcq_az_cohort$CANCER,
na.rm=TRUE)
> wrk_hcq_az_cohort$IMMUNODEFICIENCY[is.na(wrk_hcq_az_cohort$IMMUNODEFICIENCY)] <-
mean(wrk_hcq_az_cohort$IMMUNODEFICIENCY, na.rm=TRUE)
> wrk_hcq_az_cohort$ChronicCardiacDiseases[is.na(wrk_hcq_az_cohort$ChronicCardiacDiseases)] <-
mean(wrk_hcq_az_cohort$ChronicCardiacDiseases, na.rm=TRUE)
> wrk_hcq_az_cohort$AutoImmuneDiseases[is.na(wrk_hcq_az_cohort$AutoImmuneDiseases)] <-
mean(wrk_hcq_az_cohort$AutoImmuneDiseases, na.rm=TRUE)

> str(wrk_hcq_az_cohort)

> wrk_hcq_az_cohort$SEX <- ifelse(wrk_hcq_az_cohort$SEX == "1", "0", wrk_hcq_az_cohort$SEX)

> wrk_hcq_az_cohort$SEX <- ifelse(wrk_hcq_az_cohort$SEX == "2", "1", wrk_hcq_az_cohort$SEX)

> wrk_matchit <- subset (wrk_hcq_az_cohort,
select=c(HCQ,SEX,AGE,INPATIENT,PERIOD,VARIANT,VACCINATION,DIABETE,HBP,OBESITY,ASTHM
A,COPD,CANCER,IMMUNODEFICIENCY,AutoImmuneDiseases,ChronicCardiacDiseases,Status_42.EFS,Status
_56.EFS,Status_90.EFS,Status_700.EFS))
> wrk_matchit$HCQ <- as.numeric(as.character(wrk_matchit$HCQ))
> wrk_matchit$AGE <- as.character(as.integer(wrk_matchit$AGE))
> wrk_matchit$SEX <- as.numeric(as.character(wrk_matchit$SEX))
> str(wrk_matchit)
> m.check_balance <- matchit(HCQ ~ SEX + AGE + INPATIENT + VARIANT + VACCINATION + DIABETE +
HBP + OBESITY + ASTHMA + COPD + CANCER + IMMUNODEFICIENCY + AutoImmuneDiseases +
ChronicCardiacDiseases, data = wrk_matchit, method = NULL, distance = "glm")
summary(m.check_balance)

```

Matching with the 'quick' option (Fast Full Generalized Matching)

```

> m.get_balance <- matchit(HCQ ~ SEX + AGE + INPATIENT + VARIANT + VACCINATION + DIABETE +
HBP + OBESITY + ASTHMA + COPD + CANCER + IMMUNODEFICIENCY + AutoImmuneDiseases +
ChronicCardiacDiseases, data = wrk_matchit, method = "quick", distance = "glm", link = "logit")

```

Matching with the 'full' option (Optimal Full Matching)

```
> m.get_balance <- matchit(HCQ ~ SEX + AGE + INPATIENT + VARIANT + VACCINATION + DIABETE +
  HBP + OBESITY + ASTHMA + COPD + CANCER + IMMUNODEFICIENCY + AutoImmuneDiseases +
  ChronicCardiacDiseases, data = wrk_matchit, method = "full", distance = "glm", link = "logit")
> summary(m.get_balance)
```

Love plot and density plots

```
> plot(summary(m.get_balance))
> plot(m.get_balance, type = "density", interactive = FALSE, which.xs = "VARIANT")
> plot(m.get_balance, type = "density", interactive = FALSE, which.xs = "AGE")
> m.data <- match.data(m.get_balance)
```

Check interactions between treatment and covariates

```
> m.fit.logis <- glm(Status_56.EFS ~ HCQ *(SEX + AGE + INPATIENT + VARIANT + VACCINATION +
  DIABETE + OBESITY + HBP + ASTHMA + COPD + CANCER + IMMUNODEFICIENCY +
  AutoImmuneDiseases + ChronicCardiacDiseases), data = m.data, weights = weights, family =
  quasibinomial(link=logit))
> summary(m.fit.logis)
```

Unadjusted Risk Ratio :

```
> avg_comparisons(m.fit.logis, variables = "HCQ", vcov = ~subclass, newdata = subset(m.data, HCQ == 1), wts =
  "weights", comparison = "lnratioavg", transform = "exp")
```

Unadjusted Odds Ratio :

```
> avg_comparisons(m.fit.logis, variables = "HCQ", vcov = ~subclass, newdata = subset(m.data, HCQ == 1), wts =
  "weights", comparison = "lnoravg", transform = "exp")
> lreg.or <- exp(cbind(OR = coef(m.fit.logis), confint(m.fit.logis)))
> round(lreg.or, digits=4)
```

Calculate adjusted Odds Ratios for treatment effect

```
> m.fit.logis <- glm(Status_56.EFS ~ HCQ + SEX + AGE + INPATIENT + VARIANT + VACCINATION +
  DIABETE + OBESITY + HBP + ASTHMA + COPD + CANCER + IMMUNODEFICIENCY +
  AutoImmuneDiseases + ChronicCardiacDiseases, data = m.data, weights = weights, family = quasibinomial())
> lreg.or <- exp(cbind(OR = coef(m.fit.logis), confint(m.fit.logis)))
> round(lreg.or, digits=4)
```