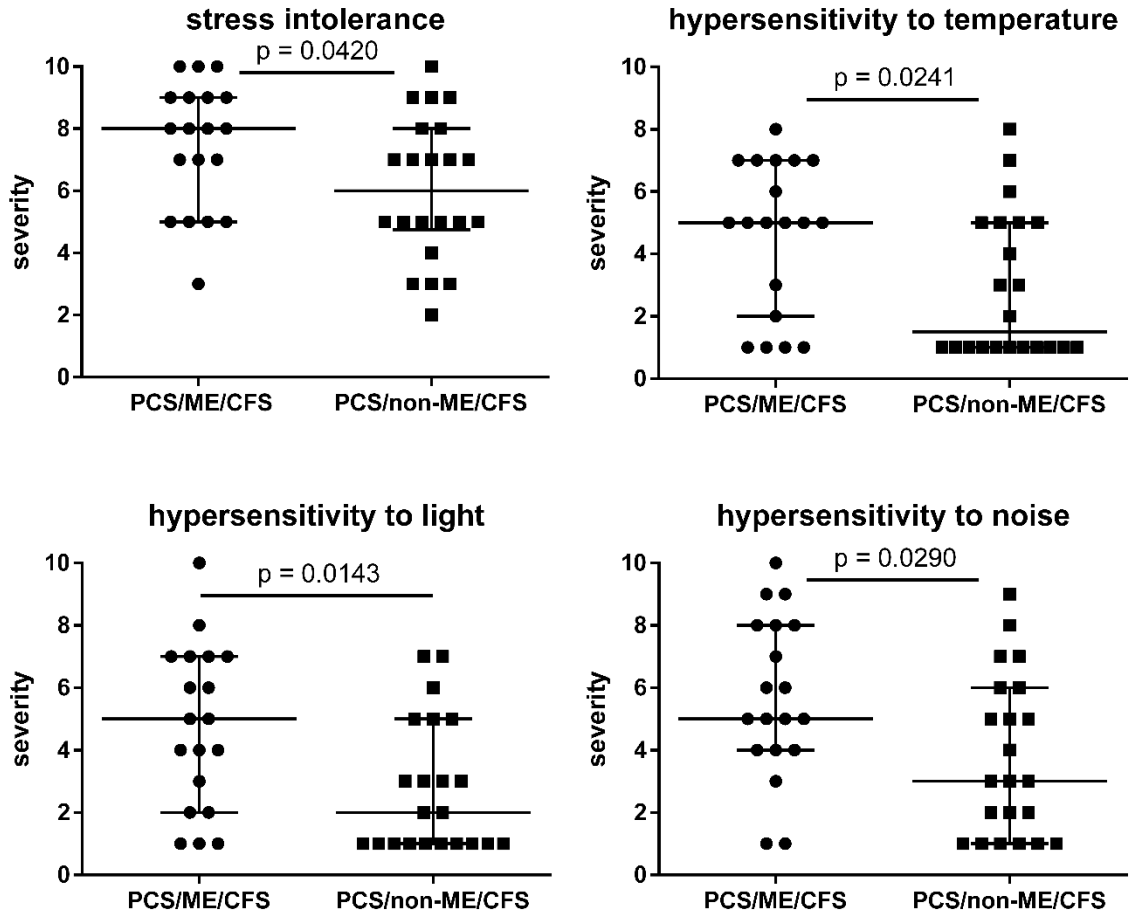
Supplementary Information for Post COVID-19 Chronic Fatigue Syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity results from a prospective observational study

List of Supplementary Information:

Supplementary Note 1: Protocol Synopsis

Questionnaires:	**CCC-Symptom Score**
	PEM Questionnaire
	Chalder Fatigue Scale
	Bell disability scale
	COMPASS31
Assessments:	**POTS**
	Hand grip strength

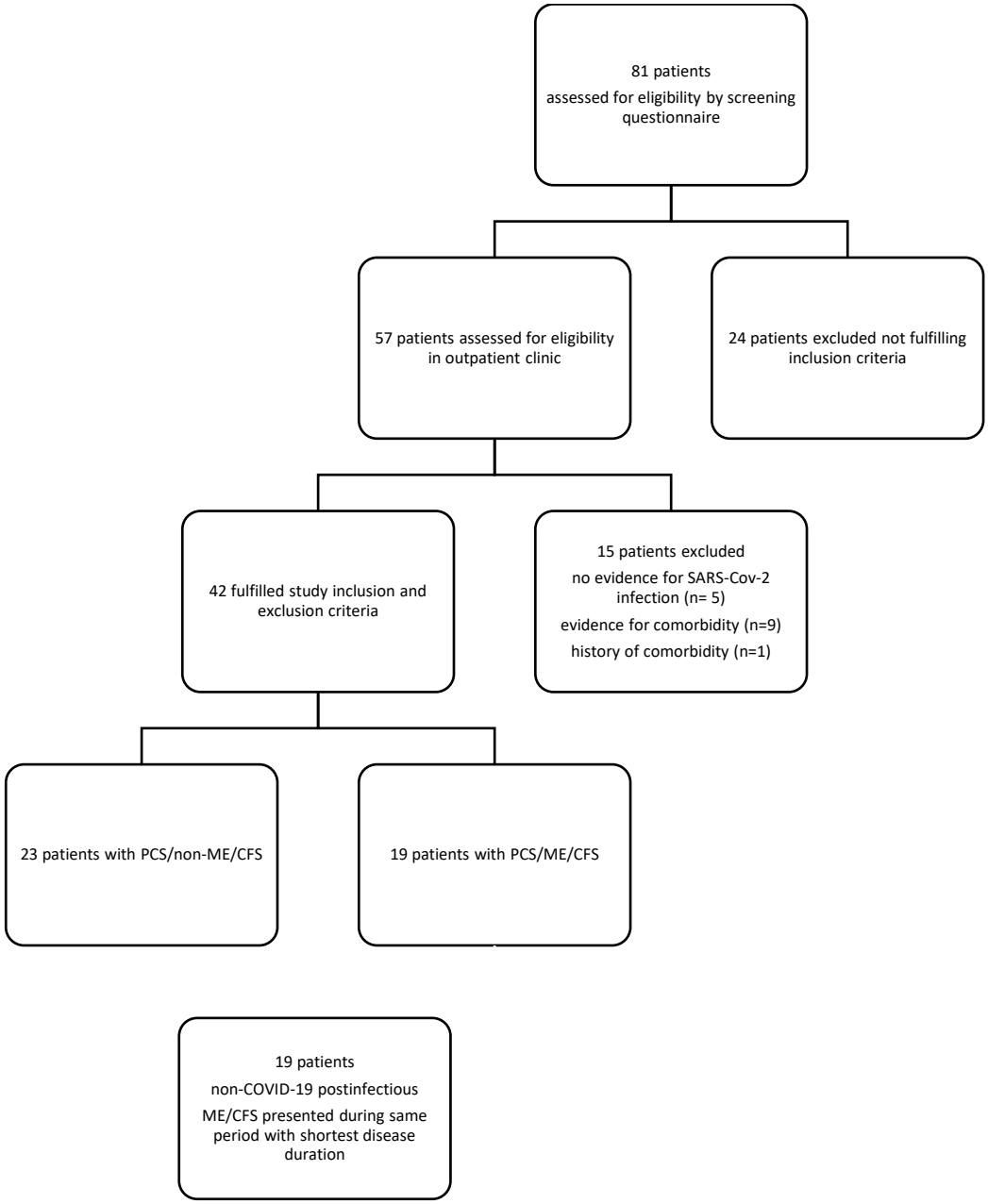
Figure S1: Severity of stress intolerance and of hypersensitivity to temperature, light, and noise in PCS/ME/CFS and PCS/non-ME/CFS patients.



PCS/non-ME/CFS: post-COVID-19 syndrome/non-myalgic encephalomyelitis/chronic fatigue syndrome; PCS/ME/CFS: post-COVID-19 syndrome/myalgic encephalomyelitis/chronic fatigue syndrome.

There is a higher symptom burden for stress intolerance, and hypersensitivity to temperature, noise and light in the PCS/ME/CFS (n=19) compared to the PCS/non-ME/CFS (n=22) cohort. Median are shown with IQR (interquartile range). The samples are compared with (two-sided) Brunner-Munzel tests. We accounted for multiplicity with the BH-correction. Source data are provided as a Source Data file.

Figure S2: Consort flow diagram



PCS/non-ME/CFS: post-COVID-19 syndrome/non-myalgic encephalomyelitis/chronic fatigue syndrome; PCS/ME/CFS: post-COVID-19 syndrome/myalgic encephalomyelitis/chronic fatigue syndrome.

All patients enrolled in this study presented at our outpatient clinics between August 2020 and November 2020. We informed patients on our website that our outpatient clinic offers a study for patients suffering from moderate to severe fatigue and exertion intolerance 3 to 6 months post COVID. Patients were selected for an appointment in our clinic based on a screening questionnaire, which specified our inclusion criteria. From a total of 81 patients, who contacted the Charité Fatigue Center during this time period, 24 were already excluded based on the screening questionnaire and 57 were assessed for eligibility in our outpatient clinic. From these, 42 fulfilled the inclusion criteria. 19 patients fulfilled the Canadian Consensus Criteria (CCC) for ME/CFS 1 (PCS/ME/CFS), the other 23 patients did not (PCS/non-ME/CFS).

From all postinfectious non-COVID-19 ME/CFS patients evaluated during the same period at our clinic (n=123) a sex- and age-matched control cohort who had the shortest duration of illness (13 months, range 7 - 19 months, n=19) was selected.

Table S1. Ten most frequent initial symptoms of COVID-19 reported by patients

	PCS/ME/CFS				PCS/non-ME/CFS				all patients	
	male	**female**	**total**	**% PCS/CFS**	**male**	**female**	**total**	**% PCS**	**total**	**% total**
n	5	14	19		8	15	23		42	
Fatigue/malaise	4	9	**13**	68	7	15	**22**	96	**35**	83
Fever/ high temperature	3	9	**12**	63	6	10	**16**	70	**28**	67
Cough	2	8	**10**	53	7	8	**15**	65	**25**	60
Resp. problems	2	8	**10**	53	5	9	**14**	61	**24**	57
Loss of smell	0	10	**10**	53	5	8	**13**	57	**23**	55
Loss of taste	0	10	**10**	53	4	8	**12**	52	**22**	52
Headache	2	9	**11**	58	2	9	**11**	48	**22**	52
Arthralgia	0	8	**8**	42	2	7	**9**	39	**17**	40
Chest pain	2	6	**8**	42	3	6	**9**	39	**17**	40
Gastrointestinal symptoms	1	8	**9**	47	1	6	**7**	30	**16**	38

This table shows the ten most frequent initial symptoms of COVID-19 reported by the 42 patients analysed in this study.

As additional information, we report the estimated effects, their standard errors, values of the test statistics and 95% simultaneous confidence intervals. The effect estimators are the contrasts (differences) of estimated relative effects (Wilcoxon-Mann-Whitney parameters).

Table S2: Effect estimators, standard errors, values of the test statistics, 95% simultaneous confidence intervals and degrees of freedom (DF) obtained from the nonparametric all-pairs Dunn-type multiple contrast tests (cf. Table 1, demographic data).

	non-COVID ME/CFS vs PCS/non-ME/CFS					non-COVID ME/CFS vs PCS/ME/CFS					PCS/non-ME/CFS vs PCS/ME/CFS					
	Effect	Std. Error	T	Lower	Upper	Effect	Std. Error	T	Lower	Upper	Effect	Std. Error	T	Lower	Upper	DF
age	-0,1066	0,0923	-1,1463	-0,3232	0,1205	0,003	0,0958	0,0308	-0,2271	0,2327	0,1096	0,0873	1,2457	-0,1054	0,3148	36
gender	-0,0423	0,0726	-0,5824	-0,216	0,134	0	0,0734	0	-0,1768	0,1768	0,0423	0,0726	0,5824	-0,134	0,216	39
bmi	0,0938	0,0883	1,0566	-0,1229	0,302	0,1854	0,0898	2,0169	-0,0396	0,3925	0,0915	0,0898	1,0139	-0,1287	0,3032	36

Table S3 Effect estimators of the relative effects, their standard errors, values of the test statistics and 95% confidence intervals obtained from the Brunner-Munzel tests (cf Table 1, PHQ9 and ESS in PCS).

	PCS/non ME/CFS vs PCS/ME/CFS				
	Effect	Std,Error	T	Lower	Upper
PHQ	0,5824	0,0908	0,9075	0,3988	0,766
ESS	0,5172	0,0912	0,1882	0,3329	0,7015

Table S4: Effect estimators, standard errors, values of the test statistics, 95% simultaneous confidence intervals and degrees of freedom (DF) obtained from the nonparametric all-pairs Dunn-type multiple contrast tests (cf Table 2, symptom score)

	non-COVID ME/CFS vs PCS/non-ME/CFS					non-COVID ME/CFS vs PCS/ME/CFS					PCS/non-ME/CFS vs PCS/ME/CFS					
	Effect	Std. Error	T	Lower	Upper	Effect	Std. Error	T	Lower	Upper	Effect	Std. Error	T	Lower	Upper	DF
sy_1 fatigue	-0,2897	0,0797	-3,4262	-0,4708	-0,0851	-0,2257	0,0763	-2,8583	-0,4022	-0,0331	0,0639	0,0845	0,7544	-0,1426	0,2651	35
sy_2 PEM	-0,401	0,0596	-5,9824	-0,5359	-0,2462	-0,1914	0,0734	-2,542	-0,3627	-0,0075	0,2096	0,0714	2,8489	0,0303	0,3759	35
sy_3 need for rest	-0,2621	0,0823	-3,036	-0,4503	-0,0515	-0,1425	0,0824	-1,707	-0,3362	0,0626	0,1195	0,0862	1,374	-0,094	0,3226	33
sy_4 imp. performance	-0,2132	0,0816	-2,5329	-0,4019	-0,0073	-0,1278	0,0895	-1,4121	-0,3375	0,094	0,0854	0,0905	0,9392	-0,1367	0,2994	34
sy_5 stress intolerance	-0,3718	0,0633	-5,317	-0,5167	-0,2062	-0,1955	0,0772	-2,4674	-0,3768	1,00E-04	0,1763	0,0836	2,0649	-0,0348	0,3723	28
sy_6 muscle pain	-0,2115	0,0901	-2,2763	-0,4189	0,017	-0,1747	0,0936	-1,8282	-0,3915	0,0605	0,0368	0,0858	0,4287	-0,1725	0,243	32
sy_7 headache	-0,2282	0,0798	-2,7598	-0,4127	-0,0258	-0,1596	0,091	-1,7235	-0,3714	0,0681	0,0687	0,0925	0,7404	-0,1578	0,2883	32
sy_8 joint pain	-0,0683	0,0975	-0,6984	-0,3001	0,1711	0,0024	0,1034	0,023	-0,247	0,2515	0,0707	0,0893	0,7893	-0,149	0,2837	30
sy_9 memory	-0,0919	0,1027	-0,8898	-0,3363	0,1641	-0,0598	0,0907	-0,6574	-0,2788	0,1652	0,0321	0,0921	0,3486	-0,1947	0,2557	25
sy_10 concentration	-0,2195	0,0902	-2,3558	-0,4271	0,01	-0,1422	0,0843	-1,6642	-0,3407	0,0685	0,0773	0,0865	0,8905	-0,1358	0,2836	31
sy_11 mental fatigue	-0,2378	0,0807	-2,8342	-0,4235	-0,0329	-0,2034	0,0835	-2,368	-0,3966	0,007	0,0344	0,0902	0,3812	-0,1846	0,2502	34
sy_12 visual disturbances	-0,0147	0,0889	-0,1657	-0,229	0,2009	0,056	0,0929	0,6013	-0,1711	0,2774	0,0707	0,0949	0,7426	-0,1619	0,2959	32
sy_15 palpitations	-0,0769	0,0948	-0,808	-0,3009	0,1552	-0,007	0,0965	-0,0729	-0,2386	0,2253	0,0699	0,0923	0,7548	-0,1557	0,2886	34
sy_16 Dizziness when standing	-0,1489	0,0914	-1,6054	-0,3632	0,0803	-0,0908	0,0998	-0,9046	-0,3269	0,156	0,0581	0,0881	0,6578	-0,1586	0,2694	29
sy_17 Dizziness when walking	-0,1967	0,0861	-2,2254	-0,3962	0,0204	-0,1021	0,0952	-1,0652	-0,3261	0,1327	0,0946	0,0912	1,0317	-0,13	0,31	33
sy_18 sleep dist	-0,1188	0,0969	-1,2146	-0,3465	0,1221	-0,1213	0,0971	-1,2377	-0,3493	0,1202	-0,0025	0,0859	-0,0292	-0,2109	0,2061	30
sy_19 hypersens. temp	-0,3629	0,0752	-4,3908	-0,5321	-0,1658	-0,189	0,0835	-2,2089	-0,3835	0,0216	0,1739	0,0737	2,3108	-0,0112	0,3475	31
sy_20 hypersens. light	-0,2752	0,0811	-3,2177	-0,4604	-0,0671	-0,0616	0,093	-0,6607	-0,2828	0,1658	0,2136	0,079	2,6192	0,0138	0,397	32
sy_21 hypersens. noise	-0,2622	0,0853	-2,931	-0,4569	-0,0436	-0,0758	0,0933	-0,8093	-0,297	0,1532	0,1865	0,0811	2,2465	-0,0175	0,3755	32
sy_22 breathing disorder	0,1992	0,0819	2,3665	-0,0073	0,3893	0,2416	0,0832	2,7884	0,0297	0,4326	0,0424	0,0896	0,4726	-0,1759	0,2567	33
sy_23 Irritable bowl	-0,1972	0,0938	-2,0473	-0,4137	0,0404	-0,0866	0,0907	-0,9502	-0,3019	0,1372	0,1106	0,0883	1,2419	-0,1086	0,3196	31
sy_24 fever	-0,0837	0,0813	-1,0247	-0,2814	0,1208	-0,0716	0,0877	-0,8129	-0,2847	0,1483	0,0122	0,0613	0,1983	-0,1405	0,1643	21
sy_25 painfull ymphnodes	-0,245	0,0788	-2,9825	-0,427	-0,0439	-0,2361	0,0836	-2,7195	-0,4286	-0,0231	0,0089	0,0744	0,1198	-0,1723	0,1895	32
sy_26 sorethroat	-0,286	0,0846	-3,1947	-0,4783	-0,0675	-0,2302	0,0863	-2,573	-0,429	-0,0102	0,0558	0,0788	0,7061	-0,1379	0,2453	31
sy_27 flu-like symptoms	-0,3815	0,0706	-4,8596	-0,54	-0,1968	-0,2541	0,0679	-3,5801	-0,4115	-0,082	0,1274	0,0862	1,4614	-0,0863	0,3298	32

Table S5: Effect estimators, standard errors, values of the test statistics, 95% simultaneous confidence intervals and degrees of freedom obtained from the nonparametric all-pairs Dunn-type multiple contrast tests (cf Table 3, autonomic dysfunction – COMPASS31)

	non-COVID ME/CFS vs PCS/non-ME/CFS					non-COVID ME/CFS vs PCS/ME/CFS					PCS/non-ME/CFS vs PCS/ME/CFS					
	Effect	Std. Error	T	Lower	Upper	Effect	Std. Error	T	Lower	Upper	Effect	Std. Error	T	Lower	Upper	DF
com_total	-0,2834	0,0781	-3,4326	-0,4618	-0,0829	-0,1068	0,0942	-1,1251	-0,3283	0,1259	0,1766	0,0839	2,0609	-0,034	0,3721	32
com_orth	-0,2164	0,0828	-2,5321	-0,4071	-0,0077	-0,053	0,0927	-0,5702	-0,2731	0,1724	0,1635	0,0853	1,8829	-0,0491	0,3618	36
com_vaso	-0,082	0,061	-1,3389	-0,2286	0,0682	8,00E-04	0,073	0,0104	-0,1764	0,1779	0,0828	0,0613	1,3445	-0,0682	0,23	32
com_secr	-0,1633	0,0835	-1,9213	-0,3582	0,0452	-0,0589	0,0967	-0,6079	-0,288	0,1766	0,1044	0,0879	1,1798	-0,1122	0,3116	34
com_gi	-0,102	0,0856	-1,1835	-0,3049	0,1096	-0,132	0,0911	-1,4317	-0,3456	0,0947	-0,0299	0,0963	-0,3107	-0,2606	0,2039	32
com_blad	-0,003	0,0774	-0,0389	-0,1918	0,186	0,0683	0,0901	0,7563	-0,1538	0,2839	0,0714	0,0907	0,7843	-0,1523	0,2881	29
com_pupil	-0,1292	0,0894	-1,4295	-0,3381	0,0919	-0,0444	0,0974	-0,4557	-0,2755	0,1915	0,0848	0,0892	0,9458	-0,1337	0,2954	36

Table S6: Standard errors of the correlation estimates of Spearman's ρ and associated test statistics (cf. Table 4) (cf Table 4, laboratory values and HGS)

		Standard Error				Test Statistic			
		Fmax1	Fmean1	Fmax2	Fmean2	Fmax1	Fmean1	Fmax2	Fmean2
Hb	PCS/non-ME/CFS	0,2033	0,1885	0,1851	0,1914	2,2795	3,0256	3,1937	2,8808
Ferritin	PCS/non-ME/CFS	0,2297	0,2319	0,234	0,2342	0,9792	0,7717	0,5076	0,4816
Bilirubin	PCS/non-ME/CFS	0,2357	0,2353	0,2351	0,2354	-0,0862	0,2397	0,3007	0,2269
Kreatinin	PCS/non-ME/CFS	0,2066	0,207	0,2147	0,2153	2,3276	2,3123	1,9203	1,8908
CRP	PCS/non-ME/CFS	0,1965	0,2071	0,1999	0,1931	-2,6255	-2,0787	-2,4547	-2,7983
IL8	PCS/non-ME/CFS	0,1895	0,2063	0,2039	0,2019	-2,9721	-2,1187	-2,2494	-2,3518
NTproBNP	PCS/non-ME/CFS	0,2313	0,2316	0,2269	0,2283	-0,8325	-0,7985	-1,1929	-1,0867
ACE1	PCS/non-ME/CFS	0,2295	0,2335	0,23	0,2325	-0,9896	-0,5795	-0,9479	-0,7116
ACE2	PCS/non-ME/CFS	0,2366	0,2201	0,2114	0,2037	1,3668	2,1543	2,527	2,8446
Hb	PCS/ME/CFS	0,1861	0,1589	0,1777	0,174	3,4448	4,7546	3,9603	4,1269
Ferritin	PCS/ME/CFS	0,2251	0,2044	0,2088	0,2084	1,652	2,6356	2,6346	2,6488
Bilirubin	PCS/ME/CFS	0,2141	0,212	0,2315	0,2245	2,4112	2,4979	1,912	2,2015
Kreatinin	PCS/ME/CFS	0,234	0,2224	0,2209	0,2248	1,5056	2,053	2,3441	2,1889
CRP	PCS/ME/CFS	0,2417	0,2425	0,2484	0,2495	-0,347	-0,0446	0,4497	0,2492
IL8	PCS/ME/CFS	0,2351	0,2412	0,2494	0,2495	-1,0447	-0,4364	-0,2856	-0,2523
NTproBNP	PCS/ME/CFS	0,1779	0,1641	0,1548	0,1617	-3,9516	-4,5969	-5,0745	-4,7162
ACE1	PCS/ME/CFS	0,2472	0,2513	0,2514	0,2523	-1,1701	-0,917	-0,9067	-0,8453
ACE2	PCS/ME/CFS	0,2464	0,2454	0,254	0,2541	-0,6833	-0,7788	-0,7102	-0,6952
Hb	non-COVID ME/CFS	0,2756	0,2746	0,2732	0,2717	0,4101	0,5095	0,6303	0,7394
Ferritin	non-COVID ME/CFS	0,2999	0,2945	0,2974	0,2921	-0,3481	-0,7276	-0,5543	-0,8463
Bilirubin	non-COVID ME/CFS	0,2489	0,2454	0,2387	0,2557	1,7709	1,8987	2,1319	1,5137
Kreatinin	non-COVID ME/CFS	0,2766	0,2746	0,2717	0,2695	0,2654	0,5152	0,738	0,877
CRP	non-COVID ME/CFS	0,2772	0,2764	0,2764	0,275	0,1232	0,2991	0,3056	0,4771
IL8	non-COVID ME/CFS	0,2389	0,2004	0,235	0,2389	-2,5524	-3,7294	-2,665	-2,5524
NTproBNP	non-COVID ME/CFS	0,2639	0,2594	0,2588	0,2592	-1,1648	-1,3642	-1,3879	-1,3721
ACE1	non-COVID ME/CFS	0,2771	0,2758	0,2773	0,2763	-0,1418	-0,3885	-0,0129	-0,3102

Table S7: Standard errors of the correlation estimates of Spearman's ρ and associated test statistics.

		Standard Error				Test statistic			
		CFQ	CFQA	CFQB	Fatigue	CFQ	CFQA	CFQB	Fatigue
fT3	PCS/non-ME/CFS	0,218	0,2174	0,2091	0,2167	0,2078	-0,3875	1,3661	-0,5431
fT4	PCS/non-ME/CFS	0,2122	0,2157	0,2102	0,1945	-1,0973	-0,697	-1,2779	-2,3335
TSH	PCS/non-ME/CFS	0,2255	0,2292	0,213	0,2257	0,8107	0,1687	1,7438	0,7994
Thromb	PCS/non-ME/CFS	0,2181	0,2182	0,2182	0,2157	-0,1653	-0,016	0,0629	0,7068
fT3	PCS/ME/CFS	0,2034	0,2486	0,2151	0,2471	-2,8574	-0,4314	-2,3702	-0,615
fT4	PCS/ME/CFS	0,2488	0,2495	0,2435	0,2453	-0,3896	0,2423	-0,9332	-0,7904
TSH	PCS/ME/CFS	0,2271	0,25	0,2105	0,2499	-1,8402	0,0272	-2,5615	0,1199
Thromb	PCS/ME/CFS	0,2415	0,2254	0,2407	0,1768	-0,3761	-1,6381	0,5084	-3,8726

Table S8: Effect estimators, standard errors, values of the test statistics, 95% simultaneous confidence intervals and degrees of freedom obtained from the nonparametric all-pairs Dunn-type multiple contrast tests (cf. Figure 1, Bell scale, Chader Fatigue Scale and SF36 physical functioning)

	non-COVID ME/CFS vs PCS/non-ME/CFS					non-COVID ME/CFS vs PCS/ME/CFS					PCS/non-ME/CFS vs PCS/ME/CFS					
	Effect	Std. Error	T	Lower	Upper	Effect	Std. Error	T	Lower	Upper	Effect	Std. Error	T	Lower	Upper	DF
Bell	0,2704	0,0703	3,6577	0,0906	0,4332	0,1341	0,0864	1,5336	-0,0812	0,3374	-0,1364	0,0886	-1,5192	-0,3447	0,0847	30
CFQ	-0,331	0,0732	-4,1868	-0,4965	-0,1423	-0,1037	0,08	-1,2867	-0,2927	0,0932	0,2273	0,079	2,7775	0,0279	0,4094	36
SF36 physical	0,2316	0,0816	2,7374	0,025	0,4193	0,1854	0,0928	1,951	-0,0477	0,3993	-0,0463	0,0897	-0,515	-0,2602	0,172	34

Table S9: Effect estimators of the relative effects, their standard errors, values of the test statistics and 95% confidence intervals obtained from the Brunner-Munzel tests (cf Figure 1, SF36 role limitation, energy and social)

	PCS vs PCS/ME/CFS				
	Effect	Std. Error	T	Lower	Upper
SF36 role limitations	0,3261	0,0508	-3,4254	0,2208	0,4314
SF36 energy	0,3318	0,0825	-2,0377	0,165	0,4986
SF36 social	0,3389	0,0883	-1,8241	0,1595	0,5183

Table S10: Effect estimators, standard errors, values of the test statistics, 95% simultaneous confidence intervals and degrees of freedom obtained from the nonparametric all-pairs Dunn-type multiple contrast tests (cf. Figure 2, PEM frequency, severity and length)

	non-COVID ME/CFS vs PCS/non-ME/CFS					non-COVID ME/CFS vs PCS/ME/CFS					PCS/non-ME/CFS vs PCS/ME/CFS					
	Effect	Std. Error	T	Lower	Upper	Effect	Std. Error	T	Lower	Upper	Effect	Std. Error	T	Lower	Upper	DF
PEM_frequency	-0,3281	0,077	-3,9468	-0,5033	-0,127	-0,1279	0,0916	-1,3817	-0,3437	0,1008	0,2002	0,076	2,5615	0,0074	0,3786	28
PEM_severity	-0,2715	0,0736	-3,5076	-0,4414	-0,0829	-0,1426	0,0898	-1,5676	-0,3533	0,0817	0,1289	0,0914	1,3942	-0,0989	0,3439	30
PEM_length	-0,4299	0,0635	-5,9004	-0,5721	-0,2625	-0,0895	0,0641	-1,389	-0,2431	0,0685	0,3404	0,0664	4,7196	0,1688	0,492	34

Table S11: Effect estimators, standard errors, values of the test statistics, 95% simultaneous confidence intervals and degrees of freedom obtained from the nonparametric all-pairs Dunn-type multiple contrast tests (cf Figure 3, HGS)

	non-COVID ME/CFS vs PCS/non-ME/CFS					non-COVID ME/CFS vs PCS/ME/CFS					PCS/non-COVID ME/CFS vs PCS/ME/CFS					
	Effect	Std. Error	T	Lower	Upper	Effect	Std. Error	T	Lower	Upper	Effect	Std. Error	T	Lower	Upper	DF
Fmax1	0,1592	0,1046	1,4963	-0,1111	0,4076	-0,0303	0,1235	-0,245	-0,3309	0,2759	-0,1895	0,1065	-1,7361	-0,4398	0,0881	19
Fmax2	0,1716	0,0988	1,7018	-0,0848	0,4067	-0,0621	0,1204	-0,5145	-0,3531	0,2398	-0,2337	0,1124	-2,0021	-0,4929	0,0635	19
Fmean1	0,1695	0,1021	1,6283	-0,0916	0,4087	-0,0664	0,1156	-0,5722	-0,3426	0,2204	-0,2358	0,1058	-2,1451	-0,4783	0,04	23
Fmean2	0,1834	0,0955	1,8776	-0,0633	0,409	-0,1006	0,1149	-0,8696	-0,3742	0,1891	-0,284	0,1126	-2,3855	-0,5373	0,0163	21

Table S12: Effect estimators of the relative effects, their standard errors, values of the test statistics and 95% confidence intervals obtained from the Brunner-Munzel tests (cf Figure 4, Pulse and arterial pressure)

		p. hat	S.E	T	Lower	Upper
PCS/non-ME/CFS	Systole	0,538	0,179	0,822	0,439	0,636
PCS/non-ME/CFS	Diastole	0,727	0,3038	2,894	0,559	0,895
PCS/non-ME/CFS	Puls	0,758	0,1805	5,536	0,658	0,858
PCS/ME/CFS	Systole	0,429	0,1718	-1,601	0,332	0,525
PCS/ME/CFS	Diastole	0,546	0,1984	0,898	0,435	0,656
PCS/ME/CFS	Puls	0,804	0,2955	3,985	0,639	0,968

Supplementary Note 1: Study Protocol

STUDY REGISTRATION FORM

1. Registration Date 22.07.2020 (dd.mm.yyyy)

2. Principal Investigator

Title	Prof. Dr. med.
First Name	Carmen
Surname	Scheibenbogen
Institute	Institut für Med. Immunologie, CVK
Research Group	AG Scheibenbogen
E-Mail address	carmen.scheibenbogen@charite.de

3. Co-Investigator (internal and/or external cooperation partners)

(Please provide: Title, Name, Email, Address, Organisation)

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4. Is industry involved? (If Yes, please provide name of cooperation or contract partners)

- (•) No
- ( ) Yes

5. Title of Project or Proposal?

Post-COVID-19 Chronic Fatigue Syndrom

6. Description of Project or Proposal

Please include rationale, central goals, main methods and impact for patients if applicable.(1.500 characters, including spaces)

Post-infectious chronic fatigue syndrome (CFS) occurs both epidemically and sporadically after infectious diseases, and this is well documented after the SARS pandemic of 2003. It is a complex, severe disease with a prevalence of 0.2 - 0.5%. Possible pathomechanisms are autoantibodies, autonomous and endothelial dysfunction and consecutive disturbed muscle metabolism.
First reports are already available from younger patients who report persistent fatigue and exercise intolerance more than 3 months after Covid-19 infection. Early characterization and treatment of post-Covid-19 syndromes is of high relevance to prevent chronification.
Patients who suffer from persistent fatigue and the cardinal symptoms of CFS (exertion/stress intolerance, cognitive disturbance according to IOM) 6 months after COVID-19 will be diagnosed in our outpatient clinic. As part of the diagnostic process, a hand strength test for muscular fatigue and a Schellong test for orthostatic intolerance are performed. Autoantibodies and soluble markers as well as gene variants associated with CFS are determined as biomarkers.

7. What type of research are you planning or conducting?

Epidemiologic work

8. If you plan a clinical study, did it already gain appropriate official approval?

- ○ No
- ◉ Yes, Charité Ethics Committee
- ○ Not applicable, because

9. What is the main goal of the project?

(Multiple choice possible)

- ☑ Diagnosis / Prediction / Stratification
- ☐ New Therapy
- ☐ Repurposed Therapy
- ☐ Vaccination
- ☐ Epidemiology
- ☑ Immunology
- ☐ Pathology
- ☑ Pathogenesis and Mechanism
- ☐ Digital Health
- ☐ Others

10. If patients are involved, is an interventional study planned?

(Multiple choice possible)

- ☐ Yes, small molecule/biologics
- ☐ Yes, ATMPs
- ☐ Yes, medical device or combinatory approach
- ☐ Yes, non-drug and non-medical device intervention
- ☑ No intervention

11. Please describe the kind of intervention. (max. 1.500 characters, including spaces)

12. Which patient material is used?

(Multiple choice possible)

- [x] Serum
- [ ] Plasma
- [x] Blood
- [ ] Smears
- [ ] Stool
- [ ] Urine
- [ ] CSF
- [ ] Biopsies
- [ ] Autopsies
- [ ] BAL
- [ ] Tissue
- [ ] Others

13. If you plan a preclinical laboratory study, are there animals involved?

- ○ Yes
- ◉ No

14. What is the status of your project?

Project running

15. When does/did the project start?

01.08.2020 (dd.mm.yyyy)

16. What is the estimated duration of the project?

6 (in months)

17. Funding of ongoing project

(Multiple choice possible)

- [x] Third Party
- [x] Intramural Funding (e. g. LOM)
- [ ] BIH
- [ ] BUA

18. If applicable, what is the total funding volume (intramural, third party) of your (planned) project.

€ 20.000 (in Euro)

19. Has a manuscript of this project already been submitted for publication?

- ○ Yes
- ◉ No

20. What do you still need to implement your project? (e.g. cooperation partner, technologies, access to research infrastructure (Core Facilities, Biosafety level laboratory ...)) (1000 characters, including spaces)

access to BIH infrastructure for data collection (Redcap) is initiated

21. General comments or suggestions (500 characters, including spaces)

22. Do you agree that general information about your project (your name, project title and project description) **will be made public on Charité's external and internal webpage outside the registry?**

- ◉ Yes
- ○ No

CSC-Number (Provided and entered by CSC!)

Synopsis Post-Covid ME/CFS
Sub-study PA-Covid-19 EA2_066-20 Charité

Date V1 20.7.20 V2 21.1.21 V3 24.09.2021

Coordinating team	Carmen Scheibenbogen, Claudia Kedor, Helma Freitag, Silvia Thiel Institute for Medical Immunology, Charité CVK
Study design and plan	Prospective observational study of patients with post COVID-19 fatigue and suspicion of ME/CFS
Background	Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex chronic disease with fatigue and post-exertional malaise (PEM) as cardinal symptoms. ME/CFS is often triggered by an infection, e.g. Epstein-Barr virus. After the SARS-CoV-1 epidemic in 2003, 27-40% of patients developed ME/CFS or similar symptoms as a result of the SARS-CoV-1 infection. Now, case reports of ME/CFS-typical long-term sequelae in the current pandemic of SARS-CoV-2 are also accumulating. The aim of this observational study is to characterise post-COVID-19 ME/CFS, to investigate the pathomechanism as basis to develop biomarkers and intervention strategies. Patients suffering from persistent fatigue and the cardinal symptoms of ME/CFS 6 months after COVID-19 (exercise intolerance, non-restorative sleep, cognitive disturbances according to IOM criteria) present to our outpatient clinic for diagnosis. The clinical data and validated questionnaires (Chalder Fatigue Score, SF36, Canadian Criteria weighted, Bell Score, COMPASS-31, ESS and PHQ9) collected during the diagnostic process, as well as routine laboratory values, are stored in REDCap. As part of the diagnostic work-up, a hand strength test is performed for muscular fatigue and a Schellong test for orthostatic dysregulation. Autoantibodies and soluble markers as well as gene variants associated with ME/CFS will be determined as biomarkers. For the assessment of biomarkers the vote EA2/067/20 is available.
Schedule of visits and assessments	**Month 6** - Routine laboratory Panel - Canadian Consensus Criteria - Canadian Criteria Scoring - Chalder Fatigue Scale - Bell Performance Status - SF-36

	- PHQ9 - ESS - COMPASS-31 - Muscle Fatigue: Hand Strength - Postural blood pressure and pulse - ECG, ECHO, if POTS further cardiologic assessment - Pulmonary function incl. O2 diffusion, chest X-ray or CT scan - Neurology examination in case of severe headache and severe cognitive impairment - Blood sampling for biomarkers - optional: Endopat, HRV **Month 9 and 18** - Follow up questionnaires via REDCap **Month 12 and 24** - Follow up questionnaires via REDCap - Muscle fatigue: hand strength - Postural blood pressure and pulse - Blood sampling for biomarkers
Criteria for inclusion	Patients suffering from persistent fatigue and cardinal symptoms of ME/CFS 6 months after COVID-19: - Fatigue (moderate to severe) - Cognitive disturbance - Exercise intolerance with increase in symptoms >2 hours - Pain (head or muscle) - Sleep not restful - Age: ≥ 18 years, ≤ 60 years - evidence of COVID-19 (PCR, serology or typical clinic with sensory disturbances or CT)
Criteria for exclusion	- organ dysfunction due to COVID-19 (pulmonology, cardiology, neurology, laboratory) - Major depression or anxiety disorder - Sleep disorder - Severe breathing difficulties - Severe COVID-19 or O2 administration - Pre-existing fatigue or disease that may be associated with chronic fatigue

CCC-Symptom Score

Date:

Name:

Skale 1-10

1= no Symptoms,…5= moderate Symptoms,…10= extreme Symptoms

	Scale 1-10	
FATIGUE		
Exhaustion		
Stress-dependent increase in		
Fatigue/exhaustion the next day		
Need for rest periods		
Performance limitations in everyday life		
Stress is not tolerated		
PAIN		
Muscle pain		
Headache (new, new type, new intensity)		
Joint pain		
COGNITIVE PERFORMANCE		
Memory/word finding disorders		
Konzentrationsstörungen		
Concentration disorders		
Visual disturbances		
Mood swings		
Reading receptivity		
CARDIOVASCULAR-CIRCULATION		
Palpitations		
Dizziness when standing up		
Dizziness when walking		
Further Symptoms		
Sleep disturbance		
Temperature sensitivity		
Sensitivity to light		
Sensitivity to noise		
Breathing disorders		
Irritable bowel with flatulence and/or diarrhea		
Fever		
Painful lymph nodes		
Sore throat		
Flu-like feeling		

PEM Questionnaire [2]

For each symptom below, please indicate number for frequency and one number for severity: Please complete the chart from left to right.

Symptoms	**Frequency:** Throughout the past 6 months, how often have you had this symptom? For each symptom listed below, circle a number from: 0 = none of the time 1 = a little of the time 2 = about half the time 3 = most of the time 4 = all of the time	**Severity:** Throughout the past 6 months, how much has this symptom bothered you? For each symptom listed below, circle a number from: 0 = symptom not present 1 = mild 2 = moderate 3 = severe 4= very severe
Dead, heavy feeling after starting to exercise		
Next day soreness or fatigue after non-strenuous, everyday activities		
Mentally tired after the slightest effort		
Minimum exercise makes you physically tired		
Physically drained or sick after mild activity		

For each question below, choose the answer which best describes your PEM symptoms.

If you were to become exhausted after actively participating in extracurricular activities, sports, or outings with friends, would you recover within an hour or two after the activity ended?						yes	no
If you were to become exhausted after actively participating in extracurricular activities, sports, or outings with friends, would you recover within an hour or two after the activity ended?						yes	no
Do you experience a worsening of your fatigue/energy related illness after engaging in minimal physical effort?						yes	no
Do you experience a worsening of your fatigue/energy related illness after engaging in mental effort?						yes	no
If you feel worse after activities, how long does this last?	≤ 1 h	2-3h	4-10h	11-13h	14-24h	≥24h	2-3 days
If you do not exercise, is it because exercise makes your symptoms worse?						yes	no

Chalder Fatigue Scale (CFQ) [3]

We would like to know more about any problems you have with feeling tired, weak or lack in energy in the last month. Please answer ALL the questions by ticking the answer which applies to you most closely. If you have been feeling tired for a long while, then compare yourself to how you felt when you were last well. Please tick only ONE box per line.

	less than usual	not more than usual	more than usual	much more than usual
1. Do you have problems with tiredness?	**0**	**1**	**2**	**3**
2. Do you need to rest more?	**0**	**1**	**2**	**3**
3. Do you feel sleepy or drowsy?	**0**	**1**	**2**	**3**
4. Do you have problems starting things?	**0**	**1**	**2**	**3**
5. Do you lack energy?	**0**	**1**	**2**	**3**
6. Do you have less strength in your muscles?	**0**	**1**	**2**	**3**
7. Do you feel weak?	**0**	**1**	**2**	**3**
8. Do you Have difficulties concentrating?	**0**	**1**	**2**	**3**
9. Do you make slips of the tongue when speaking?	**0**	**1**	**2**	**3**
10. Do you find it more difficult to find the right word?	**0**	**1**	**2**	**3**

	better than usual	no worse than usual	worse than usual	much worse than usual
11. How is your memory?	**0**	**1**	**2**	**3**

Total score : _____

Scoring: a value between 0 and 33 is possible. The higher the score, the higher the fatigue.

Bell Disability Scale (ME/CFS) [4]

100: No symptoms with exercise. Normal overall activity. Able to work or do house/home work full time with no difficulty.

90: No symptoms at rest. Mild symptoms with physical activity. Normal overall activity level. Able to work full time without difficulty.

80: Mild symptoms at rest. Symptoms worsened by exertion. Minimal activity restriction needed for activities requiring exertion only. Able to work full time with difficulty in jobs requiring exertion.

70: Mild symptoms at rest. Some daily activity limitation clearly noted. Overall functioning close to 90% of expected except for activities requiring exertion. Able to work/do housework full time with difficulty. Needs to rest in day.

60: Mild to moderate symptoms at rest. Daily activity limitation clearly noted. Overall functioning 70% to 90%. Unable to work full time in jobs requiring physical labour (including just standing), but able to work full time in light activity (sitting) if hours are flexible.

50: Moderate symptoms at rest. Moderate to severe symptoms with exercise or activity; overall activity level reduced to 70% of expected. Unable to perform strenuous duties, but able to perform light duty or deskwork 4 - 5 hours a day, but requires rest periods. Has to rest/sleep 1-2 hours daily.

40: Moderate symptoms at rest. Moderate to severe symptoms with exercise or activity. Overall activity level reduced to 50-70% of expected. Able to go out once or twice a week. Unable to perform strenuous duties. Able to work sitting down at home 3-4 hours a day, but requires rest periods.

30: Moderate to severe symptoms at rest. Severe symptoms with any exercise. Overall activity level reduced to 50% of expected. Usually confined to house. Unable to perform any strenuous tasks. Able to perform deskwork 2-3 hours a day, but requires rest periods.

20: Moderate to severe symptoms at rest. Unable to perform strenuous activity. Overall activity 30-50% of expected. Unable to leave house except rarely. Confined to bed most of day. Unable to concentrate for more than 1 hour a day.

10: Severe symptoms at rest. Bed ridden the majority of the time. No travel outside of the house. Marked cognitive symptoms preventing concentration.

0: Severe symptoms on a continuous basis. Bed ridden constantly, unable to care for self.

COMPASS 31 [5]

1. In the past year, have you ever felt faint, dizzy, “goofy”, or had difficulty thinking soon after standing up from a sitting or lying position?

1 Yes
2 No (if you marked No, please skip to question 5)

2. When standing up, how frequently do you get these feelings or symptoms?

1 Rarely
2 Occasionally
3 Frequently
4 Almost Always

3. How would you rate the severity of these feelings or symptoms?

1 Mild
2 Moderate
3 Severe

4. In the past year, have these feelings or symptoms that you have experienced:

1 Gotten much worse
2 Gotten somewhat worse
3 Stayed about the same
4 Gotten somewhat better
5 Gotten much better
6 Completely gone

5. In the past year, have you ever noticed color changes in your skin, such as red, white, or purple?

1 Yes
2 No (if you marked No, please skip to question 8)

6. What parts of your body are affected by these color changes? (Check all that apply)

1 Hands
2 Feet

7. Are these changes in your skin color:

1 Getting much worse
2 Getting somewhat worse
3 Staying about the same
4 Getting somewhat better
5 Getting much better
6 Completely gone

8. In the past 5 years, what changes, if any, have occurred in your general body sweating?

1 I sweat much more than I used to
2 I sweat somewhat more than I used to
3 I haven’t noticed any changes in my sweating
4 I sweat somewhat less than I used to
5 I sweat much less than I used to

9. Do your eyes feel excessively dry?

1 Yes
2 No

10. Does you mouth feel excessively dry?

1 Yes
2 No

11. For the symptom of dry eyes or dry mouth that you have had for the longest period of time, is this symptom:

1 I have not had any of these symptoms
2 Getting much worse
3 Getting somewhat worse
4 Staying about the same
5 Getting somewhat better
6 Getting much better
7 Completely gone

12. In the past year, have you noticed any changes in how quickly you get full when eating a meal?

1 I get full a lot more quickly now than I used to
2 I get full more quickly now than I used to
3 I haven't noticed any change
4 I get full less quickly now than I used to
5 I get full a lot less quickly now than I used to

13. In the past year, have you felt excessively full or persistently full (bloated feeling) after a meal?

1 Never
2 Sometimes
3 A lot of the time

14. In the past year, have you vomited after a meal?

1 Never
2 Sometimes
3 A lot of the time

15. In the past year, have you had a cramping or colicky abdominal pain?

1 Never
2 Sometimes
3 A lot of the time

16. In the past year, have you had any bouts of diarrhea?

1 Yes
2 No (if you marked No, please skip to question 20)

17. How frequently does this occur?

1 Rarely
2 Occasionally
3 Frequently _____ times per month
4 Constantly

18. How severe are these bouts of diarrhea?

1 Mild
2 Moderate
3 Severe

19. Are your bouts of diarrhea getting:

1 Much worse
2 Somewhat worse
3 Staying the same
4 Somewhat better
5 Much better
6 Completely gone

20. In the past year, have you been constipated?

1 Yes
2 No (if you marked No, please skip to question 24)

21. How frequently are you constipated?

1 Rarely
2 Occasionally
3 Frequently _____ times per month
4 Constantly

22. How severe are these episodes of constipation?

1 Mild
2 Moderate
3 Severe

23. Is your constipation getting:

1 Much worse
2 Somewhat worse
3 Staying the same
4 Somewhat better
5 Much better
6 Completely gone

24. In the past year, have you ever lost control of your bladder function?

1 Never
2 Occasionally
3 Frequently _____ times per month
4 Constantly

25. In the past year, have you had difficulty passing urine?

1 Never
2 Occasionally
3 Frequently _____ times per month
4 Constantly

26. In the past year, have you had trouble completely emptying your bladder?

1 Never
2 Occasionally
3 Frequently _____ times per month
4 Constantly

27. In the past year, without sunglasses or tinted glasses, has bright light bothered your eyes?

1 Never (if you marked Never, please skip to question 29)
2 Occasionally
3 Frequently
4 Constantly

28. How severe is this sensitivity to bright light?

1 Mild
2 Moderate
3 Severe

29. In the past year, have you had trouble focusing your eyes?

1 Never (if you marked Never, please skip to question 31)
2 Occasionally
3 Frequently
4 Constantly

30. How severe is this focusing problem?

1 Mild
2 Moderate
3 Severe

31. Is the most troublesome symptom with your eyes (i.e. sensitivity to bright light or trouble focusing) getting:

1 I have not had any of these symptoms
2 Much worse
3 Somewhat worse
4 Staying about the same
5 Somewhat better
6 Much better
7 Completely gone

COMPASS31-Scoring Algorithm. The raw domain scores are derived by adding the points for the questions comprising each domain. Where an answer to a question is not assigned a point, the score for that answer is zero. The final domain scores are generated by multiplying the raw score with a weight index (see Table 3). The total score is the sum of all domain scores.

Domain	Item	Answer	Points
Orthostatic Intolerance			
	1	1	1
	2	2	1
		3	2
		4	3
	3	1	1
		2	2
		3	3
	4	1	3
		2	2
		3	1
Vasomotor			
	5	1	1
	6	1	1
		2	1
	7	1	3
		2	2
		3	1
Secretomotor			
	8	1	1
		4	1
		5	2
	9	1	1
	10	1	1
	11	2	3
		3	2
		4	1
Gastrointestinal			
	12	1	2
		2	1
	13	2	1
		3	2
	14	2	1
		3	2
	15	2	1
		3	2
	16	1	1
	17	2	1
		3	2
		4	3
	18	1	1

	2	2
	3	3
19	1	3
	2	2
	3	1
20	1	1
21	2	1
	3	2
	4	3
22	1	1
	2	2
	3	3
23	1	3
	2	2
	3	1

Bladder

24	2	1
	3	2
	4	3
25	2	1
	3	2
	4	3
26	2	1
	3	2
	4	3

Pupillomotor

27	2	1
	3	2
	4	3
28	1	1
	2	2
	3	3
29	2	1
	3	2
	4	3
30	1	1
	2	2
	3	3
31	2	3
	3	2
	4	1

Assessment of POTS

Name: _____

Date: _____

Pulse and blood pressure in sitting position and standing

	Time	RR	Pulse
Sitting positin			
Standing 0’			
Standing 2’			
Standing 5’			
Standingd 10’			
Feeling after 10 minutes			

POTS is defined as an increase of heart rate pulse from the resting position to a standing position of more than 30 beats per minute or a pulse of more than 120 beats per minute accompanied by symptoms such as fainting, blurry vision, nausea etc.
Orthostatic hypotension is defined as a drop of 20mmHg in systolic or a drop of 10mmHg in diastolic blood pressure in the first three minutes of standing upright.

Hand Strength Test

Patient ID

Date:

- male
- female

- right-handed
- left-handed

Timepoint	1	2	3	4	5	6	7	8	9	10
0 (1)										
60‘ (2)										

Fmax1 maximal value of 10 pulls at timepoint 0
Fmax2 maximal value of 10 pulls at timepoint 60 minutes

Fmean1 mean value of 10 pulls at timepoint 0
Fmean2 mean value of 10 pulls at timepoint 60 minutes

Supplementary References

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