Supplemental Materials

Clonal Hematopoiesis Is Not Significantly Associated with Covid-19 Disease Severity

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Supplemental Note

Patients and Ethical Approval

The study included 568 patients with laboratory confirmed SARS-CoV2 infection between January and June 2020, whose blood samples were collected during the same time, upon informed consent and according to protocols approved by local institutional review boards (IRBs): Northshore University HealthSystem, Chicago, U.S.A (protocol EH20-170); University of Milano Bicocca-San Gerado Hospital, Monza, and Ethics Committee of the National Institute of Infectious Diseases 'Lazzaro Spallanzani', Italy (protocol 84/2020); National Institutes of Health VRC 200 (NCT00067054); ASST Spedali Civili of Brescia, Italy (Comitato Etico Provinciale: NP 4000 Studio CORONAlab and NP 4408 – Studio CORONAlabF); National Institutes of Health CALYPSO protocol (NCT04401436); International Severe Acute Respiratory Infection Consortium Clinical Characterisation Protocol UK (ISARIC4C, ethical approval was given by the South Central Oxford C Research Ethics Committee in England, 13/SC/0149, the Scotland A Research Ethics Committee, 20/SS/0028, and the WHO Ethics Review Committee, RPC571 and122RPC572, 25 April 2013). Non-hospitalized samples were collected from the Lombardy Region of Italy and centers around U.S.A. Hospitalized and ICU samples were collected throughout centers in the U.K. Research studies with these samples were conducted by protecting the rights and privacy of the study participants.

Detection of CH driver mutations

Detection of driver CH mutations was performed using target enrichment with a Twist Bioscience panel targeting exons of 56 genes capturing >97% of known CH mutations.[1-3] Library prep was performed according to the manufacturer's instructions. Paired-end

sequencing was performed on HiSeq4000 devices. All sequences were aligned to the GRCh38 version of the reference human genome using bwa 0.7.17 in alt contig aware mode as described before.[4] The generated SAM file was compressed into a BAM file and sorted by genomic position using samtools 1.9.[5] PCR duplicates were marked using picard's MarkDuplicates (version 2.17.0, http://broadinstitute.github.io/picard/). SNPs and indels were called using Shearwater (version 3.15)[6,7] and GATK's Mutect2 (version 4.0.3.0)[8] respectively, following the best practices (by default, reads with mapping quality < 30 were removed by Shearwater and < 25 by Mutect2 filtering steps). Nonsynonymous coding variants were filtered for: 1) minimal 4 reads in each direction; 2) minimal VAF of 1%; 3) maximum VAF of 40%; 4) a minor allele frequency in the SNP databases (1000 Genome global minor allele frequency, gnomAD (exomes) allele frequencies) < 0.1 % unless with a COSMIC occurrence of 100 or more.

Supplemental Tables

Supplemental Table S1. Target genes of bait capture set

ASXL1	ETV6	MPL	SF1
BCORL1	EZH2	MYD88	SF3A1
BCOR	FLT3	NOTCH1	SF3B1
BRAF	GATA2	NPM1	SMC1A
BRCC3	GNAS	NRAS	SMC3
CALR	GNB1	PHF6	SRSF2
CBL	IDH1	PIGA	STAG2
CREBBP	IDH2	PPM1D	STAT3
CREBPA	JAK2	PRPF40B	TET2
CSF1R	JAK3	PTEN	TP53
CSF3R	KDM6A	PTPN11	U2AF1
CTCF	KIT	RAD21	U2AF2
CUX1	KMT2A	RUNX1	WT1
DNMT3A	KRAS	SETBP1	ZRSR2

Supplemental Table S2. CH Driver classification

Gene name	Criteria for classification as a driver mutation	Transcript
ASXL1	Frameshift/nonsense/splice-site in exon 11-12	NM_015338
BCOR	Frameshift/nonsense/splice-site	NM_001123385
BCORL1	Frameshift/nonsense/splice-site	NM_021946
BRAF	Missense in aa range p.590-615; Missense at G469	NM_004333
BRCC3	Frameshift/nonsense/splice-site	NM_024332
CALR	Frameshift in exon 9	NM_004343
CBL	Missense in Linker/RING finger domains (p.345-434)	NM_005188
CEBPA	Frameshift/nonsense/splice-site	NM_004364
CREBBP	Frameshift/nonsense/splice-site	NM_004380
CSF1R	Missense at L301 / Y969	NM_005211
CSF3R	T615A, T618I, truncating c.741-791	NM_000760
CTCF	Frameshift/nonsense/splice-site, R377C, R377H, P378A, P378L	NM_006565
CUX1	Frameshift/nonsense/splice-site	NM_181552
DNMT3A	Frameshift/nonsense/splice-site; Missense in PWWP (p.292-350) / ADD (p.482-614) / MTase (p.634-912) domains	NM_022552
ETV6	Frameshift/nonsense/splice-site	NM_001987
EZH2	Frameshift/nonsense/splice-site; Missense in SET domain (p.617-732)	NM_001203247
FLT3	V579A, V592A, V592I, F594L, FY590-591GD, D835Y, D835H, D835E, del835	NM_004119
GATA2	Frameshift/nonsense/splice-site, R293Q, N317H, A318T, A318V, A318G, G320D, L321P, L321F, L321V, Q328P, R330Q, R361L, L359V, A372T, R384G, R384K	NM_001145661
GNAS	Missense at R201 (844)	NM_016592
GNB1	Missense at K57 / I80	NM_002074
IDH1	Missense at R132	NM_005896
IDH2	Missense at R140 / R172	NM_002168
JAK2	V617F; Missense/indel in aa range p.536-547	NM_004972
JAK3	M511T, M511I, A572V, A572T, A573V, R657Q, V715I, V715A	NM_000215

Gene	Variant description	Transcript
KDM6A	Frameshift/nonsense/splice-site	NM_021140
KIT	ins503, V559A, V559D, V559G, V559I, V560D, V560A, V560G, V560E, del560, E561K, del579, P627L, P627T, R634W, K642E, K642Q, V654A, V654E, H697Y, H697D, E761D, K807R, D816H, D816Y, D816F, D816I, D816V, D816H, del551-559	NM_000222
KMT2A	Frameshift/nonsense/splice-site	NM_005933
KRAS	Missense at G12 / G13 / Q61 / A146	NM_033360
MPL	S505G, S505N, S505C, L510P, del513, W515A, W515R, W515K, W515S, W515L, A519T, A519V, Y591D, W515-518KT	NM_005373
MYD88	L265P	NM_002468
NOTCH1	Frameshift/nonsense/splice-site/missense in exon 26-34	NM_017617
NPM1	Frameshift in exon 12	NM_002520
NRAS	Missense at G12 / G13 / Q61	NM_002524
PHF6	Frameshift/nonsense/splice-site	NM_001015877
PIGA	Frameshift/nonsense/splice-site	NM_002641
PPM1D	Frameshift/nonsense/splice-site in exon 5/6	NM_003620
PRPF40B	Frameshift/nonsense/splice-site	NM_001031698
PTEN	Frameshift/nonsense/splice-site	NM_000314
PTPN11	Missense in aa range p.58-76 and p.491-510	NM_002834
RAD21	Frameshift/nonsense/splice-site	NM_006265
RUNX1	Frameshift/nonsense/splice-site, S73F, H78Q, H78L, R80C, R80P, R80H, L85Q, P86L, P86H, S114L, D133Y, L134P, R135G, R135K, R135S, R139Q, R142S, A165V, R174Q, R177L, R177Q, A224T, D171G, D171V, D171N, R205W, R223C	NM_001001890
SETBP1	D868N, D868T, S869N, G870S, I871T, D880N, D880Q	NM_015559
SF1	Frameshift/nonsense/splice-site	NM_004630
SF3A1	Frameshift/nonsense/splice-site	NM_005877
SF3B1	Missense in terminal HEAT domains (p.529-1201)	NM_012433
SMC1A	Missense at R96 / R586	NM_006306
SMC3	Frameshift/nonsense/splice-site	NM_005445
SRSF2	Missense/deletion involving p.P95	NM_003016
STAG2	Frameshift/nonsense/splice-site	NM_006603

Gene	Mutation	Transcript
STAT3	Missense in SH2 domain (p.580-670)	NM_139276
TET2	Frameshift/nonsense/splice-site; Missense in conserved domains (p.1104-1481 and p.1843-2002)	NM_001127208
TP53	Frameshift/nonsense/splice-site; Missense in DNA-binding domain (p.95-288); Missense at P72 / R337	NM_001126112
U2AF1	Missense at S34 / R156 / Q157	NM_006758
U2AF2	Missense in RNA recognition motifs domains (p.149-231, p.259-337, p.381-462)	NM_007279
WT1	Frameshift/nonsense/splice-site	NM_024426
ZRSR2	Frameshift/nonsense/splice-site	NM_005089

Supplemental Table S3 Driver CH mutations called

ID	Covid-19 status	Gene	Chr	Pos	Ref	Alt	Variant classification	Amino Acid Change	Total coverage	Alt	VAF
H10	hospitalized	GNB1	1	1815790	T	C	missense_variant	p.K57E	1926	403	0.209
H181	hospitalized	GNB1	1	1815790	T	C	missense_variant	p.K57E	1683	399	0.237
N72	non-hospitalized	GNB1	1	1815790	T	C	missense_variant	p.K57	1370	75	0.0539
I203	ICU	NRAS	1	114716126	C	T	missense_variant	p.G12D	1878	22	0.0117
I104	ICU	CBL	11	119278182	A	G	missense_variant	p.Y371C	1122	14	0.013
H83	hospitalized	CBL	11	119278281	G	A	missense_variant	p.C404Y	1355	83	0.0613
H138	hospitalized	CBL	11	119278281	G	A	missense_variant	p.C404Y	1313	18	0.0137
H150	hospitalized	CBL	11	119278293	G	C	missense_variant	p.W408S	1479	45	0.0304
I47	ICU	ETV6	12	11839289	C	T	stop_gained	p.R105*	1169	17	0.0145
H63	hospitalized	KRAS	12	25245347	C	T	missense_variant	p.G13D	1341	28	0.0209
I77	ICU	IDH2	15	90088702	C	T	missense_variant	p.R140Q	3944	159	0.0403
H192	hospitalized	IDH2	15	90088702	C	T	missense_variant	p.R140Q	2203	881	0.4
I158	ICU	TP53	17	7670680	CT	C	frameshift_variant	p.E343X	1705	19	0.0111
H239	hospitalized	TP53	17	7673704	G	A	stop_gained	p.R306*	1669	19	0.0114
N34	non-hospitalized	TP53	17	7674221	G	A	missense_variant	p.R248	2434	25	0.01015
H50	hospitalized	TP53	17	7674872	T	C	missense_variant	p.Y220C	1478	25	0.017
N22	non-hospitalized	TP53	17	7674872	T	C	missense_variant	Y220C	1942	21	0.0106
H2	hospitalized	TP53	17	7674877	CA	C	frameshift_variant	p.V218X	1348	15	0.0111
N109	non-hospitalized	TP53	17	7674901	G	GT	frameshift_variant	TP53_p.N210	1465	30	0.017
H34	hospitalized	TP53	17	7676053	T	C	missense_variant	p.S106G	2472	45	0.0182
H218	hospitalized	STAT3	17	42322464	T	A	missense_variant	p.Y640F	1698	34	0.02
I48	ICU	STAT3	17	42323052	T	G	missense_variant	p.S614R	2072	47	0.0227
H156	hospitalized	PPM1D	17	60663019	AG	A	frameshift_variant	p.R429X	1981	23	0.0116
I26	ICU	PPM1D	17	60663083	T	A	stop_gained	p.L450*	3522	72	0.018
I103	ICU	PPM1D	17	60663095	CTGAGA	C	frameshift_variant	p.AEI454-456AX	1426	20	0.014
I32	ICU	PPM1D	17	60663164	AT	A	frameshift_variant	p.N477X	2446	30	0.012

H71	hospitalized	PPM1D	17	60663168	C	A	stop_gained	p.C478*	1627	23	0.0141
H104	hospitalized	PPM1D	17	60663181	AC	A	frameshift_variant	p.T483X	3085	56	0.019
H45	hospitalized	PPM1D	17	60663184	T	TTC	frameshift_variant	p.L484FX	2079	31	0.014
I70	ICU	PPM1D	17	60663185	T	A	stop_gained	p.L484*	2160	323	0.15
H58	hospitalized	PPM1D	17	60663262	C	CA	frameshift_variant	p.Q510QX	2170	32	0.009984
I26	ICU	PPM1D	17	60663274	A	T	stop_gained	p.K514*	2643	91	0.0344
I66	ICU	PPM1D	17	60663292	C	T	stop_gained	p.Q520*	2185	27	0.0124
H195	hospitalized	PPM1D	17	60663307	GA	G	frameshift_variant	p.E525X	1914	31	0.0162
H113	hospitalized	PPM1D	17	60663370	CT	C	frameshift_variant	p.L546X	1332	60	0.045
H109	hospitalized	PPM1D	17	60663388	C	T	stop_gained	p.R552*	1386	19	0.0137
H193	hospitalized	PPM1D	17	60663388	C	T	stop_gained	p.R552*	2020	392	0.194
I26	ICU	PPM1D	17	60663448	C	T	stop_gained	p.R572*	2944	45	0.0153
I132	ICU	PPM1D	17	60663448	C	T	stop_gained	p.R572*	1858	21	0.0113
H86	hospitalized	SRSF2	17	76736856	CGGCTGTGGTGTGAGTCCGGGG	C	inframe_deletion	p.PPDSHHSR95-102R	4260	84	0.022
I77	ICU	SRSF2	17	76736877	G	A	missense_variant	p.P95L	4043	322	0.0796
I161	ICU	SRSF2	17	76736877	G	T	missense_variant	p.P95H	2065	210	0.102
H114	hospitalized	SRSF2	17	76736877	G	A	missense_variant	p.P95L	900	58	0.0644
H192	hospitalized	SRSF2	17	76736877	G	C	missense_variant	p.P95R	2180	871	0.4
H221	hospitalized	SRSF2	17	76736877	G	T	missense_variant	p.P95H	1857	22	0.0118
I97	ICU	JAK3	19	17837197	G	A	missense_variant	p.A573V	847	12	0.0142
H45	hospitalized	DNMT3A	2	25234304	A	G	missense_variant	p.L905P	1228	18	0.0147
I187	ICU	DNMT3A	2	25234307	G	A	missense_variant	p.P904L	2748	36	0.014
H20	hospitalized	DNMT3A	2	25234307	G	A	missense_variant	p.P904L	1589	112	0.0705
H69	hospitalized	DNMT3A	2	25234307	G	A	missense_variant	p.P904L	1140	29	0.0254
H182	hospitalized	DNMT3A	2	25234307	G	A	missense_variant	p.P904L	1319	33	0.025
I154	ICU	DNMT3A	2	25234316	A	G	missense_variant	p.L901P	2081	24	0.01
I40	ICU	DNMT3A	2	25234323	G	T	missense_variant	p.R899S	1407	49	0.0348
I152	ICU	DNMT3A	2	25234325	A	G	missense_variant	p.I898T	1589	39	0.0245

I138	ICU	DNMT3A	2	25234373	C	A	missense_variant	p.R882L	1714	35	0.0204
I157	ICU	DNMT3A	2	25234373	C	T	missense_variant	p.R882H	1748	25	0.0143
H58	hospitalized	DNMT3A	2	25234373	C	T	missense_variant	p.R882H	1587	70	0.0441
H81	hospitalized	DNMT3A	2	25234373	C	T	missense_variant	p.R882H	1377	18	0.0131
H229	hospitalized	DNMT3A	2	25234373	C	T	missense_variant	p.R882H	1885	348	0.185
N41	non-hospitalized	DNMT3A	2	25234373	C	T	missense_variant	p.R882	2899	34	0.011
I4	ICU	DNMT3A	2	25234374	G	A	missense_variant	p.R882C	1912	27	0.0141
H19	hospitalized	DNMT3A	2	25234374	G	A	missense_variant	p.R882C	1670	85	0.0509
N6	non-hospitalized	DNMT3A	2	25234374	G	A	missense_variant	p.R882	2344	45	0.018
I120	ICU	DNMT3A	2	25235726	A	G	missense_variant	p.W860R	1815	33	0.021
N6	non-hospitalized	DNMT3A	2	25235726	A	G	missense_variant	W860R	1836	199	0.108
H106	hospitalized	DNMT3A	2	25235755	AC	A	frameshift_variant	p.V850X	2734	591	0.176
I128	ICU	DNMT3A	2	25235775	GC	G	frameshift_variant	p.G843X	2342	90	0.035
N9	non-hospitalized	DNMT3A	2	25235796	CCTCGTAGTAA	C	frameshift_variant	DNMT3A_p.ITTR833-836	2169	68	0.032
H106	hospitalized	DNMT3A	2	25236967	T	C	missense_variant	p.Q816R	1691	25	0.0148
I173	ICU	DNMT3A	2	25239130	C	T	missense_variant, splice_region_variant	p.R803K	1276	234	0.183
I118	ICU	DNMT3A	2	25239148	T	C	missense_variant	p.N797S	1925	42	0.0218
N13	non-hospitalized	DNMT3A	2	25239149	T	C	missense_variant	p.N797	2761	51	0.018
I93	ICU	DNMT3A	2	25239157	A	G	missense_variant	p.F794S	1312	24	0.018
I144	ICU	DNMT3A	2	25239199	A	G	missense_variant	p.I780T	2160	24	0.0111
H103	hospitalized	DNMT3A	2	25239199	A	G	missense_variant	p.I780T	2006	66	0.0329
N6	non-hospitalized	DNMT3A	2	25239209	G	A	missense_variant	p.P777	2289	49	0.019
I80	ICU	DNMT3A	2	25240313	G	A	stop_gained	p.R771*	1666	18	0.0108
I115	ICU	DNMT3A	2	25240313	G	A	stop_gained	p.R771*	1582	154	0.0973
I118	ICU	DNMT3A	2	25240313	G	A	stop_gained	p.R771*	2236	41	0.018
I190	ICU	DNMT3A	2	25240313	G	A	stop_gained	p.R771*	2119	823	0.388
I178	ICU	DNMT3A	2	25240315	G	A	missense_variant	p.S770L	2295	32	0.014
N60	non-hospitalized	DNMT3A	2	25240366	CAGA	C	inframe_deletion	DNMT3A_p.FW752-753	2385	28	0.012

N88	non-hospitalized	DNMT3A	2	25240367	AG	A	frameshift_variant	DNMT3A_p.F752	1888	29	0.015
H69	hospitalized	DNMT3A	2	25240379	G	C	missense_variant	p.R749G	1761	26	0.0148
N54	non-hospitalized	DNMT3A	2	25240379	G	C	missense_variant	p.R749	2629	50	0.018
I189	ICU	DNMT3A	2	25240417	C	T	missense_variant	p.R736H	2341	34	0.0145
I185	ICU	DNMT3A	2	25240418	G	A	missense_variant	p.R736C	1682	36	0.0214
N6	non-hospitalized	DNMT3A	2	25240418	G	A	missense_variant	p.R736	2623	109	0.0433
I51	ICU	DNMT3A	2	25240420	T	C	missense_variant	p.Y735C	1760	28	0.0159
I112	ICU	DNMT3A	2	25240420	T	C	missense_variant	p.Y735C	2058	137	0.0666
N29	non-hospitalized	DNMT3A	2	25240420	T	C	missense_variant	p.Y735	2534	77	0.0296
N62	non-hospitalized	DNMT3A	2	25240423	A	G	missense_variant	p.F734	3280	50	0.015
I27	ICU	DNMT3A	2	25240439	G	A	missense_variant	p.R729W	748	33	0.0441
H8	hospitalized	DNMT3A	2	25240439	G	A	missense_variant	p.R729W	1709	27	0.0158
H216	hospitalized	DNMT3A	2	25240439	G	C	missense_variant	p.R729G	1383	16	0.0116
N94	non-hospitalized	DNMT3A	2	25240439	G	A	missense_variant	p.R729	2245	34	0.016
H27	hospitalized	DNMT3A	2	25240690	C	A	missense_variant	p.S708I	2452	25	0.0102
I102	ICU	DNMT3A	2	25240697	C	A	missense_variant	p.G706W	1080	43	0.0398
I50	ICU	DNMT3A	2	25240729	A	T	missense_variant, splice_region_variant	p.I695N	1469	26	0.0177
I9	ICU	DNMT3A	2	25241584	ACGT	A	inframe_deletion	p.DV686-687V	2431	210	0.084
I43	ICU	DNMT3A	2	25241587	T	A	missense_variant	p.D686V	1189	70	0.0589
N7	non-hospitalized	DNMT3A	2	25241595	G	T	stop_gained	p.Y683	2832	35	0.012
I156	ICU	DNMT3A	2	25241645	C	A	stop_gained	p.E667*	2066	22	0.0106
N88	non-hospitalized	DNMT3A	2	25241654	C	G	missense_variant	p.E664	2824	39	0.013
I60	ICU	DNMT3A	2	25241666	A	G	missense_variant	p.Y660H	1861	23	0.0124
N39	non-hospitalized	DNMT3A	2	25241674	A	C	missense_variant	p.V657	3215	78	0.02415
I140	ICU	DNMT3A	2	25241678	G	A	stop_gained	p.Q656*	2052	63	0.0307
I112	ICU	DNMT3A	2	25241698	ACCAGGAGCC CTGCACCAG	A	splice_acceptor_variant,coding_sequence_variant	p.-?-649	2395	28	0.013
H106	hospitalized	DNMT3A	2	25243900	G	T	missense_variant,splice_region_variant	p.T645K	2042	33	0.0162
I175	ICU	DNMT3A	2	25243901	T	C	missense_variant	p.T645A	1743	71	0.0407

H117	hospitalized	DNMT3A	2	25243906	A	T	missense_variant	p.I643N	1754	37	0.02
I2	ICU	DNMT3A	2	25243930	C	T	missense_variant	p.R635Q	2554	27	0.0106
H168	hospitalized	DNMT3A	2	25243930	C	T	missense_variant	p.R635Q	2179	61	0.028
N5	non-hospitalized	DNMT3A	2	25243934	T	A	missense_variant	p.I634	2823	57	0.0196
I99	ICU	DNMT3A	2	25244163	G	A	stop_gained	p.Q615*	1351	27	0.016
I128	ICU	DNMT3A	2	25244163	G	A	stop_gained	p.Q615*	1434	120	0.0837
N17	non-hospitalized	DNMT3A	2	25244214	G	A	stop_gained	p.R598	3147	48	0.01505
N100	non-hospitalized	DNMT3A	2	25244214	G	A	stop_gained	p.R598	1447	29	0.0195
H26	hospitalized	DNMT3A	2	25244240	TTG	T	frameshift_variant	p.HK588-589QX	2198	427	0.168
I186	ICU	DNMT3A	2	25244248	G	C	missense_variant	p.C586W	1941	103	0.0531
H107	hospitalized	DNMT3A	2	25244250	A	AC	frameshift_variant	p.-585-586X	1967	117	0.059
H206	hospitalized	DNMT3A	2	25244265	AG	TA	missense_variant	p.PW580-581PR	3322	39	0.013
N29	non-hospitalized	DNMT3A	2	25244265	AG	A	frameshift_variant	DNMT3A_p.P580	2636	34	0.012
H133	hospitalized	DNMT3A	2	25244285	GCCTGGGCAGCCC	G	inframe_deletion	p.GAAQA570-574A	2500	46	0.019
H103	hospitalized	DNMT3A	2	25244559	C	T	missense_variant	p.G550R	3232	38	0.012
I167	ICU	DNMT3A	2	25244568	G	A	missense_variant	p.L547F	1645	52	0.0316
N82	non-hospitalized	DNMT3A	2	25244616	C	T	missense_variant	p.D531	3585	128	0.0343
H84	hospitalized	DNMT3A	2	25244622	C	T	missense_variant	p.D529N	1812	59	0.0326
H176	hospitalized	DNMT3A	2	25244625	A	ACTGGTAGCCGTCGTCGTCGTT	inframe_insertion	p.-527-528NDDDGYQ	2387	93	0.042
H167	hospitalized	DNMT3A	2	25244628	G	A	stop_gained	p.Q527*	2428	50	0.0206
N104	non-hospitalized	DNMT3A	2	25244643	GA	G	frameshift_variant	DNMT3A_p.F521	2042	42	0.019
H218	hospitalized	DNMT3A	2	25245256	G	C	missense_variant	p.C517W	2353	28	0.012
H186	hospitalized	DNMT3A	2	25245284	AG	A	frameshift_variant	p.L508X	3012	41	0.011
N27	non-hospitalized	DNMT3A	2	25246184	C	A	stop_gained	p.E469	2701	126	0.04635
H197	hospitalized	DNMT3A	2	25246208	TG	T	frameshift_variant	p.S460X	2679	49	0.018
H79	hospitalized	DNMT3A	2	25246214	TC	T	frameshift_variant	p.R458X	2442	63	0.026
I42	ICU	DNMT3A	2	25246660	GC	G	frameshift_variant	p.G413X	2547	48	0.011
N91	non-hospitalized	DNMT3A	2	25247070	G	A	missense_variant	p.A368	2648	61	0.023

I176	ICU	DNMT3A	2	25247080	A	G	missense_variant	p.Y365H	1673	45	0.0269
I15	ICU	DNMT3A	2	25247089	G	A	stop_gained	p.Q362*	2065	27	0.0131
N69	non-hospitalized	DNMT3A	2	25247105	CT	C	frameshift_variant	DNMT3A_p.Q356	2945	88	0.028
H48	hospitalized	DNMT3A	2	25247615	C	T	stop_gained	p.W330*	1100	31	0.028
H176	hospitalized	DNMT3A	2	25247624	C	T	stop_gained	p.W327*	2486	56	0.021
I176	ICU	DNMT3A	2	25247628	C	T	missense_variant	p.R326H	1633	45	0.0276
I170	ICU	DNMT3A	2	25247646	CG	C	frameshift_variant	p.R320X	1259	16	0.0127
I51	ICU	DNMT3A	2	25247647	G	A	stop_gained	p.R320*	1478	385	0.26
I195	ICU	DNMT3A	2	25247647	G	A	stop_gained	p.R320*	1836	139	0.0757
H18	hospitalized	DNMT3A	2	25247659	TC	T	frameshift_variant	p.M315X	3387	55	0.016
I140	ICU	DNMT3A	2	25247666	C	T	stop_gained	p.W313*	2445	61	0.0249
I172	ICU	DNMT3A	2	25247666	C	T	stop_gained	p.W313*	2035	73	0.0359
H66	hospitalized	DNMT3A	2	25247676	A	G	missense_variant	p.I310T	1620	459	0.283
I182	ICU	DNMT3A	2	25247677	T	G	missense_variant	p.I310L	1941	38	0.0196
H235	hospitalized	DNMT3A	2	25247691	C	T	stop_gained	p.W305*	2145	24	0.0112
H63	hospitalized	DNMT3A	2	25247742	CGG	C	frameshift_variant	p.GR287-288GX	2126	38	0.018
H63	hospitalized	DNMT3A	2	25247745	CCGTCCT	C	splice_acceptor_variant,coding_sequence_variant	p.-?-287	2150	38	0.017
I122	ICU	DNMT3A	2	25248115	AGC	A	frameshift_variant	p.A259X	2267	45	0.02
H130	hospitalized	SF3B1	2	197402110	T	C	missense_variant	p.K700E	1465	17	0.0116
H179	hospitalized	SF3B1	2	197402110	T	C	missense_variant	p.K700E	1374	77	0.056
N29	non-hospitalized	SF3B1	2	197402110	T	C	missense_variant	p.K700	1269	37	0.0289
H16	hospitalized	SF3B1	2	197402635	C	A	missense_variant	p.K666N	1549	182	0.117
I139	ICU	SF3B1	2	197402636	T	C	missense_variant	p.K666R	1600	20	0.0125
I10	ICU	SF3B1	2	197402637	T	C	missense_variant	p.K666E	1792	22	0.0123
I10	ICU	SF3B1	2	197402645	G	A	missense_variant	p.T663I	1842	64	0.0347
I97	ICU	SF3B1	2	197402654	G	A	missense_variant	p.A660V	562	10	0.0178
I10	ICU	SF3B1	2	197402655	C	A	missense_variant	p.A660S	1947	30	0.0154
N109	non-hospitalized	SF3B1	2	197402756	T	A	missense_variant	p.N626	1163	52	0.04465

I10	ICU	SF3B1	2	197402759	C	A	missense_variant	p.R625L	1929	23	0.0119
H214	hospitalized	SF3B1	2	197402760	G	A	missense_variant	p.R625C	1476	483	0.327
N109	non-hospitalized	SF3B1	2	197402765	T	C	missense_variant	p.Y623	1087	24	0.0218
I41	ICU	ASXL1	20	32433732	C	T	stop_gained	p.Q512*	2051	278	0.136
I150	ICU	ASXL1	20	32433732	C	T	stop_gained	p.Q512*	2075	79	0.0381
H183	hospitalized	ASXL1	20	32433780	G	T	stop_gained	p.E528*	3179	158	0.0497
I97	ICU	ASXL1	20	32433807	G	A	missense_variant	p.E537K	707	12	0.017
I97	ICU	ASXL1	20	32434599	TCACCACTGCCATAGAGAGGCGGC	T	frameshift_variant	p.HHCHREAA630-637X	1288	168	0.133
I118	ICU	ASXL1	20	32434745	G	GGGGAGGC	frameshift_variant	p.R678RGGX	2980	46	0.016
H18	hospitalized	ASXL1	20	32434769	AGT	A	frameshift_variant	p.KC686-687KX	2538	376	0.135
H178	hospitalized	ASXL1	20	32434841	GA	G	frameshift_variant	p.G710X	2788	69	0.026
H237	hospitalized	ASXL1	20	32434886	GA	G	frameshift_variant	p.R725X	3120	91	0.031
I31	ICU	ASXL1	20	32434940	TA	T	frameshift_variant	p.L743X	1590	148	0.086
H83	hospitalized	ASXL1	20	32434989	C	A	stop_gained	p.C759*	2012	540	0.268
H126	hospitalized	ASXL1	20	32435380	C	CT	frameshift_variant	p.L890LX	1118	87	0.071
I24	ICU	ASXL1	20	32435387	CTAACAGTTCT	C	frameshift_variant	p.SNSS892-895X	2292	26	0.012
I139	ICU	GNAS	20	58909366	G	A	missense_variant	p.R201H	1690	20	0.0118
H227	hospitalized	GNAS	20	58909366	G	A	missense_variant	p.R201H	1797	81	0.0451
H126	hospitalized	TET2	4	105234229	GCA	G	frameshift_variant	p.RT96-97RX	1046	143	0.125
H235	hospitalized	TET2	4	105234336	AATCCAGGTGAAAGCAG	A	frameshift_variant	p.NPGESS132-137X	3095	39	0.013
N27	non-hospitalized	TET2	4	105234591	TC	T	frameshift_variant	TET2_p.S217	2451	80	0.029
N54	non-hospitalized	TET2	4	105234659	CA	C	frameshift_variant	TET2_p.I240	2384	32	0.013
H131	hospitalized	TET2	4	105234763	TC	T	frameshift_variant	p.I274X	1928	24	0.0124
H161	hospitalized	TET2	4	105234763	TC	T	frameshift_variant	p.I274X	2622	184	0.062
N45	non-hospitalized	TET2	4	105234915	C	T	stop_gained	p.Q325	1947	43	0.0219
N24	non-hospitalized	TET2	4	105235097	A	AGT	frameshift_variant	TET2_p.-385-386	2200	78	0.034
H150	hospitalized	TET2	4	105235147	C	G	stop_gained	p.S402*	2505	27	0.0108
N2	non-hospitalized	TET2	4	105235172	TC	T	frameshift_variant	TET2_p.P411	1793	642	0.26

I11	ICU	TET2	4	105235178	TC	T	frameshift_variant	p.P413X	3722	191	0.048
N74	non-hospitalized	TET2	4	105235178	TC	T	frameshift_variant	TET2_p.P413	2414	98	0.039
I147	ICU	TET2	4	105235203	GA	G	frameshift_variant	p.E421X	2536	573	0.19
H99	hospitalized	TET2	4	105235203	GA	G	frameshift_variant	p.E421X	2477	76	0.0307
H150	hospitalized	TET2	4	105235275	C	CT	frameshift_variant	p.L445LX	3107	133	0.038
H63	hospitalized	TET2	4	105235547	C	CA	frameshift_variant	p.-535-536X	2016	478	0.192
I121	ICU	TET2	4	105235662	C	T	stop_gained	p.Q574*	2179	254	0.117
H173	hospitalized	TET2	4	105235778	TG	T	frameshift_variant	p.G613X	1780	57	0.032
H96	hospitalized	TET2	4	105235966	C	G	stop_gained	p.S675*	2443	32	0.0131
I6	ICU	TET2	4	105236172	C	T	stop_gained	p.Q744*	1895	321	0.169
I42	ICU	TET2	4	105236172	C	T	stop_gained	p.Q744*	2484	33	0.014
I97	ICU	TET2	4	105236315	T	A	stop_gained	p.Y791*	1414	129	0.0912
I147	ICU	TET2	4	105236559	A	AT	frameshift_variant	p.I873IX	2330	288	0.107
N74	non-hospitalized	TET2	4	105236563	CA	C	frameshift_variant	TET2_p.P874	2002	49	0.021
H84	hospitalized	TET2	4	105236781	C	T	stop_gained	p.Q947*	2156	62	0.0288
N109	non-hospitalized	TET2	4	105237058	C	A	stop_gained	p.S1039	1200	83	0.0701
I123	ICU	TET2	4	105237084	CTCAAATCACAGAAGCAAGTA	C	frameshift_variant	p.LKSQKQV1048-1054X	3577	56	0.017
I8	ICU	TET2	4	105237091	C	A	stop_gained	p.S1050*	1192	954	0.445
I50	ICU	TET2	4	105237163	TTGATAGCCACA	T	frameshift_variant	p.LDSHT1074-1078LX	2681	51	0.019
I172	ICU	TET2	4	105241425	G	T	stop_gained	p.E1166*	1408	70	0.0497
H113	hospitalized	TET2	4	105241429	G	A	missense_variant,splice_region_variant	p.R1167K	698	23	0.033
I179	ICU	TET2	4	105242863	T	G	missense_variant	p.I1177S	1922	34	0.0177
I66	ICU	TET2	4	105242882	TG	T	frameshift_variant	p.G1184X	2677	38	0.015
I157	ICU	TET2	4	105242904	C	T	stop_gained	p.Q1191*	1681	354	0.211
H6	hospitalized	TET2	4	105243633	AC	A	frameshift_variant	p.T1220X	3146	45	0.013
H4	hospitalized	TET2	4	105243714	GA	G	frameshift_variant	p.E1247X	1804	148	0.082
N6	non-hospitalized	TET2	4	105243760	G	A	missense_variant	p.R1262	1627	23	0.0134
N90	non-hospitalized	TET2	4	105243763	G	A	missense_variant	p.C1263	1458	125	0.0872

I29	ICU	TET2	4	105259636	A	AG	frameshift_variant	p.Q1274QX	1317	22	0.016
I147	ICU	TET2	4	105259665	T	G	missense_variant	p.S1284A	1963	64	0.0326
I147	ICU	TET2	4	105259669	T	C	missense_variant	p.F1285S	1981	72	0.0363
H29	hospitalized	TET2	4	105259683	T	TC	frameshift_variant	p.S1290SX	3031	64	0.021
H128	hospitalized	TET2	4	105261761	AG	A	frameshift_variant	p.E1320X	1042	23	0.0221
H215	hospitalized	TET2	4	105269684	A	AT	frameshift_variant	p.-1373-1374X	2793	124	0.043
H176	hospitalized	TET2	4	105272591	C	T	stop_gained	p.R1404*	2024	39	0.019
H99	hospitalized	TET2	4	105272741	GT	G	frameshift_variant	p.V1454X	3130	123	0.038
I77	ICU	TET2	4	105272742	T	A	missense_variant	p.V1454D	3967	53	0.0134
I97	ICU	TET2	4	105272775	G	A	missense_variant	p.R1465Q	772	9	0.0117
H66	hospitalized	TET2	4	105272838	CAAAT	C	frameshift_variant	p.SN1486-1487X	2062	169	0.078
I135	ICU	TET2	4	105272871	C	G	stop_gained	p.S1497*	1952	22	0.0113
I23	ICU	TET2	4	105275080	C	T	stop_gained	p.Q1524*	1695	200	0.118
N84	non-hospitalized	TET2	4	105275110	C	CA	frameshift_variant	TET2_p.Q1534	1328	20	0.013
I120	ICU	TET2	4	105275190	T	A	stop_gained	p.Y1560*	1724	430	0.249
I64	ICU	TET2	4	105275338	AATTCTTCTAATCCC	A	frameshift_variant	p.NSSNP1610-1614X	2812	254	0.088
N66	non-hospitalized	TET2	4	105275614	C	T	stop_gained	p.Q1702	2923	823	0.2825
H34	hospitalized	TET2	4	105275992	C	T	stop_gained	p.Q1828*	2415	31	0.0128
H113	hospitalized	TET2	4	105276029	C	CAG	frameshift_variant	p.A1840AX	1454	62	0.039
H211	hospitalized	TET2	4	105276088	G	A	missense_variant	p.G1860R	1971	105	0.0533
I105	ICU	TET2	4	105276092	G	A	missense_variant	p.G1861E	1097	30	0.0273
I134	ICU	TET2	4	105276092	G	T	missense_variant	p.G1861V	2217	34	0.0153
H140	hospitalized	TET2	4	105276092	G	A	missense_variant	p.G1861E	2476	79	0.0319
N73	non-hospitalized	TET2	4	105276092	G	A	missense_variant	p.G1861	3176	50	0.014
H66	hospitalized	TET2	4	105276113	AT	A	frameshift_variant	p.H1868X	2187	30	0.012
H173	hospitalized	TET2	4	105276114	TG	T	frameshift_variant	p.G1869X	3014	229	0.096
H214	hospitalized	TET2	4	105276128	T	C	missense_variant	p.I1873T	1752	39	0.0223
I126	ICU	TET2	4	105276151	C	T	missense_variant	p.H1881Y	2041	32	0.0157

I140	ICU	TET2	4	105276160	A	G	missense_variant	p.T1884A	2228	47	0.0211
N59	non-hospitalized	TET2	4	105276177	CAATAGG	C	inframe_deletion	TET2_p.NR1890-1891	2678	269	0.089
H6	hospitalized	TET2	4	105276248	G	A	missense_variant	p.G1913D	2334	34	0.0146
N83	non-hospitalized	TET2	4	105276391	G	GA	frameshift_variant	TET2_p.E1961	2390	35	0.014
H229	hospitalized	TET2	4	105276395	C	T	missense_variant	p.P1962L	2409	586	0.243
I147	ICU	RAD21	8	116854454	CT	C	frameshift_variant	p.K317X	1754	358	0.171
H140	hospitalized	RAD21	8	116866697	TC	T	frameshift_variant	p.R11X	2339	24	0.012
H11	hospitalized	JAK2	9	5073770	G	T	missense_variant	p.V617F	1217	17	0.014
H126	hospitalized	JAK2	9	5073770	G	T	missense_variant	p.V617F	494	104	0.211
H128	hospitalized	JAK2	9	5073770	G	T	missense_variant	p.V617F	829	75	0.0905
N19	non-hospitalized	JAK2	9	5073770	G	T	missense_variant	p.V617	1359	110	0.072
N70	non-hospitalized	JAK2	9	5073770	G	T	missense_variant	p.V617	1489	146	0.086
H115	hospitalized	BCOR	X	40052205	T	TA	frameshift_variant	p.L1724FX	885	21	0.025
H115	hospitalized	BCOR	X	40053925	A	AG	frameshift_variant	p.L1646PX	755	214	0.214
N1	non-hospitalized	SMC1A	X	53405077	G	A	missense_variant	p.R711	1823	21	0.012
I34	ICU	BRCC3	X	155077239	C	T	stop_gained	p.R89*	754	20	0.0265

Supplemental Table S4 Proportional odds model results for Covid-19 covariates with the 3 different hospitalization status as outcome

Multivariable Proportional Odds Model for Hospitalization Outcome						
Variable	**Coef**	**SE**	**OR**	**2.5% CI**	**97.5% CI**	**P-val**
Age	-0.005	0.010	0.995	0.975	1.015	0.617
Sex						
Male	1.042	0.203	2.836	1.910	4.240	0***
Female	--	--	--	--	--	--
Ethnicity						
White	--	--	--	--	--	--
Non-white	0.483	0.290	1.622	0.922	2.881	0.095
Diabetes						
Yes	0.447	0.226	1.563	1.006	2.442	0.048*
No	--	--	--	--	--	--
COPD/Asthma						
Yes	-0.261	0.271	0.770	0.452	1.310	0.334
No	--	--	--	--	--	--
CV						
Yes	0.491	0.247	1.634	1.009	2.662	0.047*
No	--	--	--	--	--	--
Cancer/neoplasm/hem dz						
Yes	-0.296	0.376	0.744	0.355	1.561	0.431
No	--	--	--	--	--	--
Immunodeficiency						
Yes	0.744	0.330	2.105	1.111	4.067	0.024*
No	--	--	--	--	--	--
Smoking						
Ever-smoker	-0.068	0.173	0.934	0.666	1.312	0.694
Never-smoker	--	--	--	--	--	--
Coef = coefficient; SE = standard error; OR = odds ratio; CI = confidence interval						

* *p* value < 0.05, *** *p* value < 0.001

Supplemental Table S5 Blood count information at admission

		Data available subjects	Data missing subjects	Min	2.5% CI	Median	Mean	Std	97.5% CI	Max
Hgb [g/L]	Hospitalized + ICU	419	29	10.6	115.7	120.0	118.3	27.5	120.9	173.0
	non-cancer	388	26	10.6	117.2	121.5	120.0	27.5	122.7	173.0
	cancer	31	3	78.0	107.7	112.0	113.7	19.4	121.3	157.0
WBC [10^9/L]	Hospitalized + ICU	419	29	1.6	8.4	7.9	8.8	4.5	9.2	30.7
	non-cancer	388	26	1.8	8.5	8.0	9.0	4.5	9.4	30.7
	cancer	31	3	1.6	5.3	6.4	6.7	4.0	8.2	18.6
Lymphocyte [10^9/L]	Hospitalized + ICU	410	38	0.1	1.0	1.0	1.1	0.7	1.2	7.7
	non-cancer	379	35	0.1	1.1	1.0	1.1	0.7	1.2	7.7
	cancer	31	3	0.2	0.7	0.9	0.9	0.5	1.1	2.2
Neutrophil [10^9/L]	Hospitalized + ICU	409	39	0.8	6.6	6.1	7.0	4.1	7.4	26.8
	non-cancer	379	35	1.0	6.7	6.3	7.1	4.1	7.6	26.8
	cancer	30	4	0.8	4.0	4.7	5.2	3.4	6.4	15.5
Platelets [10^9/L]	Hospitalized + ICU	414	34	26.0	267.1	253.5	280.5	139.1	293.9	878.0
	non-cancer	384	30	26.0	272.2	257.5	286.0	137.6	299.7	878.0
	cancer	30	4	32.0	160.0	196.0	210.1	141.4	260.7	583.0

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Appendix A: The ISARIC4C Investigators

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