

Supplementary data

Safety and outcomes associated with the pharmacological inhibition of the kinin-kallikrein system in severe COVID-19

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Supplementary data

Supplementary Table 1. Patients screened and excluded from study.

Excluded Patients	Age	Gender	Exclusion Criteria
E1	55	M	Symptoms >12 days
E2	63	F	Symptoms >12 days
E3	58	M	Symptoms >12 days
E4	43	M	Symptoms >12 days
E5	71	F	Symptoms >12 days
E6	56	M	Symptoms >12 days
E7	75	F	Symptoms >12 days
E8	48	M	Symptoms >12 days
E9	65	F	Symptoms >12 days
E10	55	M	Symptoms >12 days
E11	68	M	Symptoms >12 days
E12	71	F	Symptoms >12 days
E13	59	F	Symptoms >12 days
E14	40	M	Sat >94%
E15	42	M	Sat >94%
E16	41	M	Sat >94%
E17	25	M	Sat >94%
E18	56	M	Sat >94%
E19	32	F	Sat >94%
E20	66	F	Sat >94%
E21	31	M	Sat >94%
E22	37	M	Kidney transplant
E23	57	M	Kidney transplant
E24	51	M	Kidney transplant
E25	35	F	Kidney transplant
E26	19	F	Kidney transplant
E27	42	F	Kidney transplant
E28	96	M	DNPC
E29	82	M	DNPC
E30	94	M	DNPC
E31	85	M	DNPC
E32	82	F	DNPC
E33	59	M	DNPC

E34	23	M	DNPC
E35	63	M	DNPC
E36	52	M	DNPC
E37	64	M	DNPC
E38	66	M	CKD
E39	54	F	CKD
E40	67	F	CKD
E41	52	M	CKD
E42	59	F	HIV
E43	24	M	HIV
E44	58	F	HIV
E45	69	M	AMI
E46	70	M	AMI
E47	51	F	AMI
E48	54	F	AMI
E49	54	M	Hydroxycloquine use
E50	59	F	Hydroxycloquine use
E51	43	M	Hydroxycloquine use
E52	27	M	<i>Systemic sclerosis</i>
E53	62	F	<i>Systemic sclerosis</i>
E54	67	M	Stroke
E55	88	M	Stroke
E56	42	M	Thromboembolic event
E57	61	M	Pulmonary thromboembolism
E58	59	M	Hepatic cirrhosis
E59	40	M	Liver transplant
E60	45	F	Autoimmune hepatitis
E61	57	M	AML
E62	48	M	ALL
E63	63	M	Myasthenia gravis
E64	57	M	FSGS
E65	28	M	Polytrauma
E66	65	F	Expansive brain injury
E67	70	F	ND
E68	32	F	ND
E69	69	F	ND
E70	21	M	ND
E71	73	F	ND
E72	49	M	ND
E73	53	F	ND
E74	84	M	ND
E75	67	F	ND
E76	51	M	ND
E77	54	F	ND
E78	50	F	ND
E79	60	F	ND
E80	32	M	ND
E81	69	F	ND
E82	69	F	ND
E83	52	F	ND
E84	36	F	ND
E85	18	F	ND
E86	76	F	ND
E87	38	M	ND
E88	52	F	ND
E89	21	M	ND
E90	71	M	ND
E91	67	M	ND
E92	95	F	ND
E93	54	F	ND
E94	56	F	ND
E95	43	F	ND
E96	25	M	ND
E97	50	M	ND
E98	68	M	ND
E99	43	M	ND
E100	84	M	ND

E101	22	M	ND
E102	56	M	ND
E103	59	M	ND
E104	95	M	ND
E105	77	F	ND
E106	21	F	ND
E107	65	M	ND
E108	51	M	ND
E109	68	F	ND
E110	32	M	ND
E111	74	F	ND
E112	75	M	ND
E113	86	M	ND
E114	76	M	ND
E115	64	M	ND
E116	62	M	ND
E117	32	F	ND
E118	80	F	ND
E119	56	M	ND
E120	36	F	ND
E121	49	F	ND
E122	62	M	ND
E123	38	M	ND
E124	75	M	ND
E125	67	F	ND
E126	65	M	ND
E127	66	F	ND
E128	55	M	ND
E129	25	F	ND
E130	73	M	ND
E131	75	F	ND
E132	27	M	ND
E133	31	M	ND
E134	53	F	ND
E135	74	F	ND
E136	37	M	ND
E137	66	M	ND
E138	25	M	ND
E139	79	M	ND
E140	40	M	ND
E141	40	M	ND
E142	53	M	ND
E143	80	M	ND
E144	67	M	ND
E145	81	M	ND
E146	32	F	ND
E147	62	M	ND
E148	76	M	ND
E149	60	M	ND
E150	58	F	ND
E151	46	F	ND
E152	42	M	ND
E153	63	M	ND
E154	54	M	ND
E155	72	M	ND
E156	75	F	ND
E157	64	M	ND
E158	55	M	ND
E159	59	F	ND
E160	53	M	ND
E161	66	M	ND
E162	59	M	ND
E163	50	M	ND
E164	65	M	ND
E165	65	M	ND
E166	60	M	ND
E167	26	M	ND

E168	39	F	ND
E169	87	F	ND
E170	60	M	ND
E171	70	M	ND
E172	68	M	ND
E173	68	M	ND
E174	71	F	ND
E175	52	M	ND
E176	80	F	ND
E177	72	F	ND
E178	81	M	ND
E179	53	M	ND
E180	48	F	ND
E181	58	F	ND
E182	51	M	ND
E183	49	F	ND
E184	46	M	ND
E185	50	M	ND
E186	55	M	ND
E187	80	F	ND
E188	83	F	ND
E189	69	M	ND
E190	74	M	ND
E191	79	M	ND
E192	31	F	ND
E193	47	M	ND
E194	51	F	ND
E195	59	M	ND
E196	62	M	ND
E197	70	M	ND
E198	52	F	ND
E199	59	F	ND
E200	72	F	ND
E201	74	F	ND
E202	59	F	ND
E203	75	M	ND
E204	32	M	ND
E205	53	M	ND
E206	75	F	ND
E207	45	M	ND
E208	72	F	ND
E209	28	M	ND
E210	60	F	ND
E211	38	F	ND

Abbreviations: ALL, acute lymphoid leukemia; AMI, acute myocardial infarction; AML, acute myeloid leukemia; CKD, chronic kidney disease; DNPC, did not provide consent; FSGS, focal segmental glomerulosclerosis; HIV, diagnosis of HIV infection; ND, no confirmation of diagnosis by PCR.

Supplementary Table 2. Patients included in the study.

Patient Identity	Age	Gender	Inclusion date	Time since beginning of symptoms (days)	Randomization	Arm
P1	50	M	2020-04-23	7	001 YD6	SC
P2	57	M	2020-04-24	8	002 ZE3	Icatibant
P3	74	F	2020-04-29	4	003 510	iC1e/K
P4	30	M	2020-05-01	10	004 SU3	SC
P5	47	M	2020-05-01	8	005 DH1	Icatibant
P6	57	M	2020-05-04	9	006 GK4	Icatibant
P7	47	M	2020-05-07	10	007 OH1	SC
P8	47	M	2020-05-14	6	008 IE5	iC1e/K
P9	38	M	2020-05-15	4	009 ZL0	Icatibant
P10	53	M	2020-05-19	11	010 UW5	Icatibant
P11	62	F	2020-05-19	7	011 YB8	iC1e/K
P12	57	M	2020-05-20	10	012 UU6	iC1e/K
P13	63	F	2020-05-23	7	013 DU2	SC
P14	50	M	2020-05-26	12	014 KL6	SC
P15	49	F	2020-05-26	10	015 GS8	SC
P16	43	M	2020-05-27	10	016 TL8	Icatibant
P17	54	F	2020-05-27	7	017 TT4	SC
P18	46	F	2020-05-27	11	018 DC5	iC1e/K
P19	34	F	2020-05-27	11	019 MI3	SC
P20	65	M	2020-05-28	8	020 VZ9	iC1e/K
P21	40	M	2020-05-29	5	021 QR4	Icatibant
P22	38	F	2020-06-02	3	022 FM6	iC1e/K
P23	43	F	2020-06-04	7	023 WG1	SC
P24	36	M	2020-06-04	10	024 CC2	iC1e/K
P25	42	F	2020-06-08	8	025 VK0	iC1e/K
P26	65	M	2020-06-08	5	026 RL1	SC
P27	77	F	2020-06-10	10	027 ZR9	iC1e/K
P28	66	F	2020-06-12	9	028 LQ8	Icatibant
P29	57	F	2020-06-14	8	029 GG3	Icatibant
P30	58	F	2020-06-14	6	030 QT1	Icatibant

Abbreviations: iC1e/K, inhibitor of C1 esterase/kallikrein; SC, standard care.

Supplementary Table 3. Supporting medication.

Patient	Group	Supporting Medication
P1	1	None
P2	2	Dipyrrone
P3	3	Dipyrrone/Clavulanic acid/Azithromycin/Heparin/Insulin/Vasoactive drugs
P4	1	None
P5	2	Dipyrrone/Azithromycin
P6	2	Dipyrrone
P7	1	Dipyrrone/Azithromycin/Metformin
P8	3	Dipyrrone/Azithromycin
P9	2	None
P10	2	Losartan
P11	3	Losartan
P12	3	Dipyrrone/Azithromycin/Insulin/Losartan
P13	1	Dipyrrone
P14	1	Dipyrrone/Clavulanic acid/Amoxicillin/Captopril
P15	1	Insulin Dipyrrone/Clavulanic acid/Azithromycin/Heparin/Vasoactive drugs
P16	2	Dipyrrone/Clavulanic acid/Azithromycin
P17	1	Hydrochlorothiazide/Losartan
P18	3	Dipyrrone/Clavulanic acid/Azithromycin/Insulin
P19	1	Insulin
P20	3	Dipyrrone
P21	2	None
P22	3	Dipyrrone/Clavulanic acid/Azithromycin
P23	1	Amoxicillin
P24	3	Dipyrrone/Clavulanic acid/Azithromycin/Heparin
P25	3	None
P26	1	Dipyrrone/Losartan/L-thyroxin/ Clavulanic acid/Azithromycin
P27	3	None
P28	2	Enalapril/Metformin/Insulin
P29	2	Enalapril/Metformin/Insulin
P30	2	Metformin/Insulin

Group 1, standard care; group 2, icatibant; group 3, inhibitor of C1 esterase/kallikrein

Supplementary Table 4. Blood cell counts.

	Standard Care			Icatibant			iC1e/K			Total sample		
	Admission	Discharge	p	Admission	Discharge	p	Admission	Discharge	p	Admission	Discharge	p
White blood cells ($\times 10^9/\mu\text{L}$) [¥]	7.78 ± 4.38	7.27 ± 3.49	0.96	7.76 ± 4.98	7.87 ± 2.37	0.88	7.76 ± 2.76	7.79 ± 1.65	0.96	7.76 ± 4.00	7.64 ± 2.53	0.88
Segmented neutrophils ($\times 10^9/\mu\text{L}$) [¥]	5.81 ± 4.74	4.74 ± 4.00	0.16	6.60 ± 3.61	4.24 ± 1.24	0.05	5.80 ± 2.18	5.0 ± 0.82	0.85	6.08 ± 3.03	4.66 ± 2.30	0.03
Lymphocytes ($\times 10^9/\mu\text{L}$) [¥]	1.15 ± 0.20	1.92 ± 0.73	0.02	1.08 ± 0.39	2.07 ± 0.66	0.01	1.19 ± 0.43	2.16 ± 1.13	0.05	1.14 ± 0.35	2.05 ± 0.83	0.01
Monocytes ($\times 10^9/\mu\text{L}$) [¥]	0.61 ± 0.31	0.57 ± 0.19	0.62	0.50 ± 0.28	0.79 ± 0.31	0.07	0.40 ± 0.23	0.69 ± 0.30	0.03	0.51 ± 0.28	0.69 ± 0.28	0.03
Eosinophils ($\times 10^9/\mu\text{L}$) [¥]	0.05 ± 0.07	0.15 ± 0.08	0.08	0.02 ± 0.07	0.15 ± 0.08	0.01	0.02 ± 0.03	0.28 ± 0.35	0.02	0.03 ± 0.05	0.24 ± 0.28	0.01

Abbreviation: iC1e/K, inhibitor of C1 esterase/kallikrein; Paired t test or non-parametric equivalent used for comparisons between pre- and post-intervention. ¥ Non-parametric test.

Supplementary Table 5. Blood coagulation parameter values.

	Standard care			Icatibant			iC1e/K			Total sample		
	Admission	Discharge	p	Admission	Discharge	p	Admission	Discharge	p	Admission	Discharge	p
D-dimer [¥]	1070.8 ± 745.5	2345.0 ± 3928.9	0.26	834.4 ± 398.2	2429.6 ± 3181.0	0.14	8984.5 ± 24961.8	2753.4 ± 4085.7	0.72	3821.1 ± 14,942	2518.4 ± 3629.0	0.17
Platelets (x10**3/μL) [¥]	206.3 ± 66.8	382.0 ± 119.0	<0.01	215.8 ± 123.2	316.5 ± 165.8	0.02	221.4 ± 97.21	313.7 ± 107.64	<0.01	214.5 ± 95.2	337.4 ± 132	<0.01
PT (sec) [¥]	12.51 ± 0.86	12.36 ± 0.49	0.57	12.81 ± 1.73	13.40 ± 1.38	0.75	12.06 ± 0.83	12.6 ± 0.97	0.31	12.42 ± 1.11	12.69 ± 0.99	0.55
PT (%) [¥]	90.75 ± 12.88	90.87 ± 7.85	0.88	90.18 ± 18.26	80.25 ± 12.38	0.46	97.49 ± 12.57	89.37 ± 12.52	0.21	93.04 ± 14.00	87.78 ± 11.24	0.28
PT (RNI) [¥]	1.06 ± 0.07	1.06 ± 0.05	0.92	1.07 ± 0.14	1.14 ± 0.10	0.50	1.02 ± 0.07	1.06 ± 0.08	0.21	1.05 ± 0.09	1.08 ± 0.08	0.27
PTT (sec) [¥]	29.23 ± 3.57	27.39 ± 5.15	0.31	27.61 ± 5.08	28.03 ± 3.70	0.74	29.09 ± 3.28	25.56 ± 3.65	0.07	28.75 ± 3.83	26.93 ± 4.27	0.07
PTT - R [¥]	1.02 ± 0.12	0.95 ± 0.18	0.31	0.97 ± 0.19	0.99 ± 0.13	0.91	1.01 ± 0.11	0.89 ± 0.13	0.07	1.00 ± 0.13	0.94 ± 0.15	0.07

Abbreviations: iC1e/K, inhibitor of C1 esterase/kallikrein; PT, prothrombin time; PTT, partial thromboplastin time. Paired t test or non-parametric equivalent used for comparisons between pre- and post-intervention. [¥]Non-parametric test.

Supplementary Table 6. Parameters related to renal function.

	Standard care			Icatibant			iC1e/K			Total sample		
	Admission	Discharge	p	Admission	Discharge	p	Admission	Discharge	p	Admission	Discharge	p
Creatinine (mg/dL) [‡]	0.9 ± 0.3	1.0 ± 1.0	0.44	1.2 ± 1.0	1.6 ± 2.3	0.51	0.9 ± 0.3	0.8 ± 0.4	0.39	1.0 ± 0.6	1.1 ± 1.5	0.21
Urea (mg/dL) [‡]	37.6 ± 20.0	38.4 ± 33.5	0.94	40.6 ± 29.1	38.6 ± 25.4	0.62	31.4 ± 10.3	39.1 ± 38.6	0.96	34.5 ± 20.9	38.7 ± 31.7	0.68

Abbreviation: iC1e/K, inhibitor of C1 esterase/kallikrein. Paired t test or non-parametric equivalent used for comparisons between pre- and post-intervention. [‡]Non-parametric test.

Supplementary Table 7. Adverse effects during intervention.

Adverse Effect	Total	Standard care	Icatibant	iC1e/K	P
Increased ASLT/ALT, n (%)	14 (46.6)	4 (40)	5 (50)	5 (50)	0.88
Diarrhea n (%)	5 (16.6)	1 (10)	2 (20)	2 (20)	--
Nausea, n (%)	3 (10)	1 (10)	0 (0)	2 (20)	--
Vomits, n (%)	3 (10)	1 (10)	1 (10)	1 (10)	--
Hyperbilirubinemia, n (%)	3 (10)	2 (20)	1 (10)	0 (0)	--
Bradycardia, n (%)	2 (6.6)	1 (10)	0 (0)	1 (10)	--
Arrhythmia, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	--

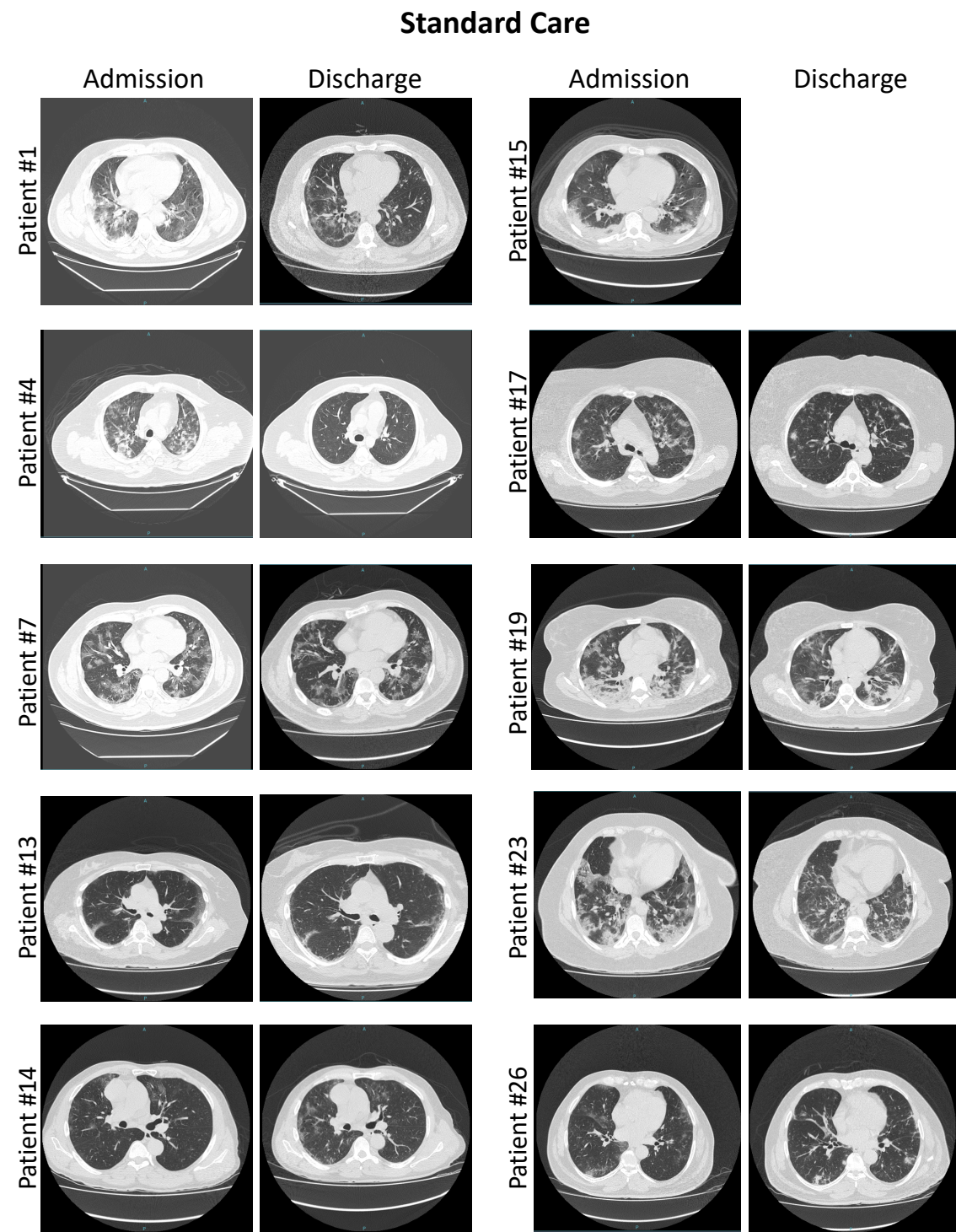
Abbreviation: iC1e/K, inhibitor of C1 esterase/kallikrein. Chi-square test (for all variables in which the expected numbers were too small no significance was calculated).

Supplementary Table 8. Clinical variables at discharge

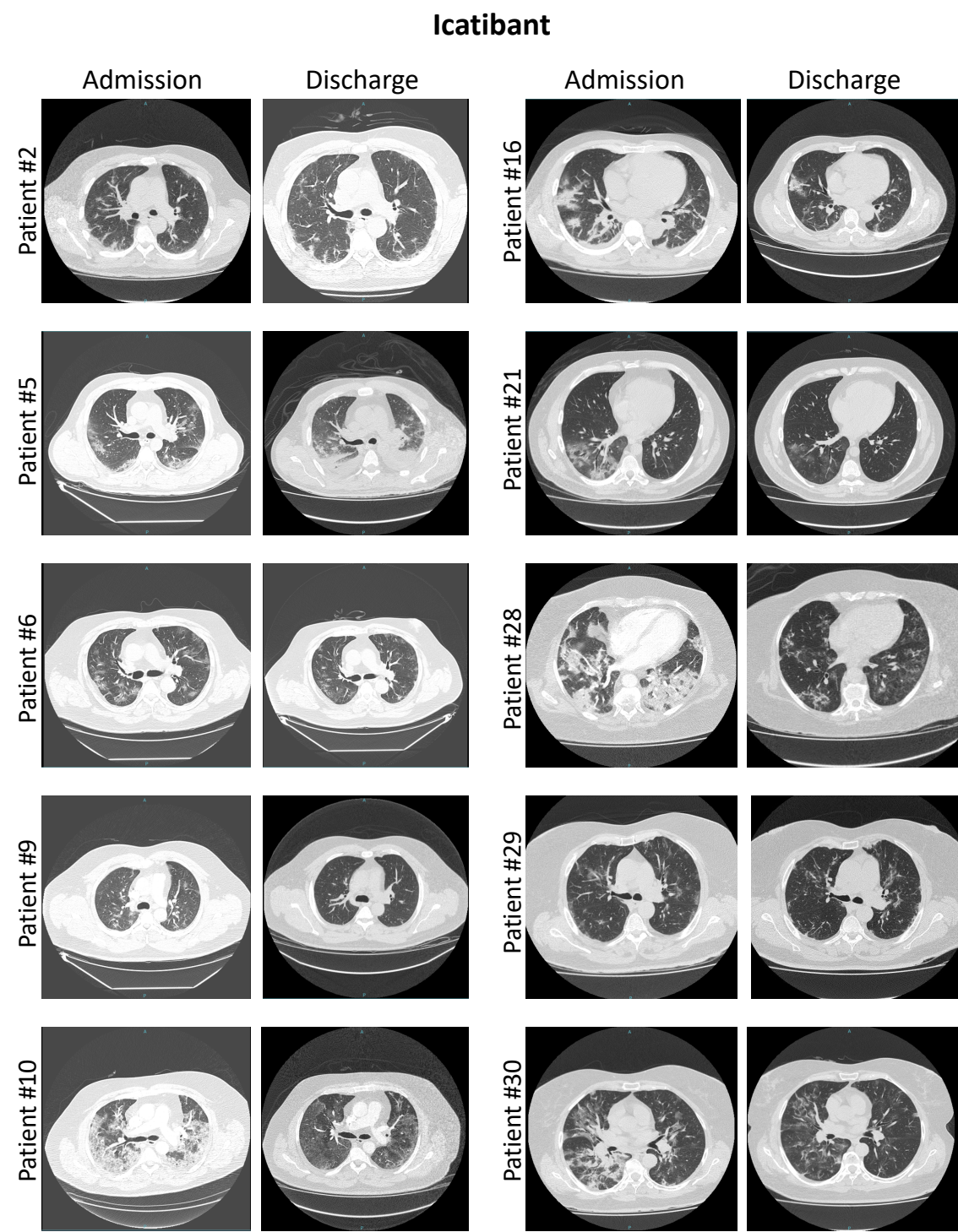
	Standard care	Icatibant	iC1e/K	p between groups
Lung CT score	10.44 ± 5.22	10.4 ± 5.34	13.4 ± 7.89	0.49
White Blood Cells (x10**3/μL) [‡]	7.38 ± 3.41	7.72 ± 2.18	8.29 ± 2.14	0.74
Lymphocytes (x10**3/μL) [‡]	1.71 ± 0.71	1.85 ± 0.62	2.2 ± 1.03	0.49
Segmented neutrophils (x10**3/μL) [‡]	5.31 ± 3.78	4.46 ± 1.46	5.39 ± 1.91	0.74
Monocytes (x10**3/μL)	0.55 ± 0.19	0.68 ± 0.24	0.62 ± 0.32	0.58
Eosinophils (x10**3/μL) [‡]	0.12 ± 0.08	0.23 ± 0.25	0.28 ± 0.31	0.40
IL-1B (pg/mL) [‡]	0.21 ± 0.16	0.24 ± 0.24	0.32 ± 0.41	0.67
IL-6 (pg/mL) [‡]	6.38 ± 3.56	10.98 ± 16.69	10.83 ± 10.2	0.63
Platelets (pg/mL [‡])	382 ± 118.99	316.5 ± 165.78	313.7 ± 107.64	0.44
Prothrombine time (RNI) [‡]	1.06 ± 0.05	1.13 ± 0.09	1.07 ± 0.08	0.10
Partial thromboplastine time (R) [‡]	0.95 ± 0.18	0.97 ± 0.12	0.89 ± 0.13	0.49

One-way ANOVA or non-parametric equivalent test was used to compare groups. [‡]Non-parametric test.

Supplementary Figure 1. Computed tomography lung scans obtained from patients randomized to standard care. Representative images were selected from the most affected region of the lungs. Scans were obtained at admission and discharge. Patient identification refers to randomization sequence as defined in Supplementary Table 2. Patient #15 missing discharge image is due to death. Each of the five lung lobes was scored 0-5 according to the following parameters: 0, no involvement; 1, <5% involvement; 2, 5-25% involvement; 3, 26-49% involvement; 4, 50-75% involvement; 5, >75% involvement.



Supplementary Figure 2. Computed tomography lung scans obtained from patients randomized to icatibant. Representative images were selected from the most affected region of the lungs. Scans were obtained at admission and discharge. Patient identification refers to randomization sequence as defined in Supplementary Table 2. Each of the five lung lobes was scored 0-5 according to the following parameters: 0, no involvement; 1, <5% involvement; 2, 5-25% involvement; 3, 26-49% involvement; 4, 50-75% involvement; 5, >75% involvement.



Supplementary Figure 3. Computed tomography lung scans obtained from patients randomized to inhibitor of C1 esterase/kallikrein (iC1e/K). Representative images were selected from the most affected region of the lungs. Scans were obtained at admission and discharge. Patient identification refers to randomization sequence as defined in Supplementary Table 2. Patient #3 missing discharge image is due to death. Each of the five lung lobes was scored 0-5 according to the following parameters: 0, no involvement; 1, <5% involvement; 2, 5-25% involvement; 3, 26-49% involvement; 4, 50-75% involvement; 5, >75% involvement.

