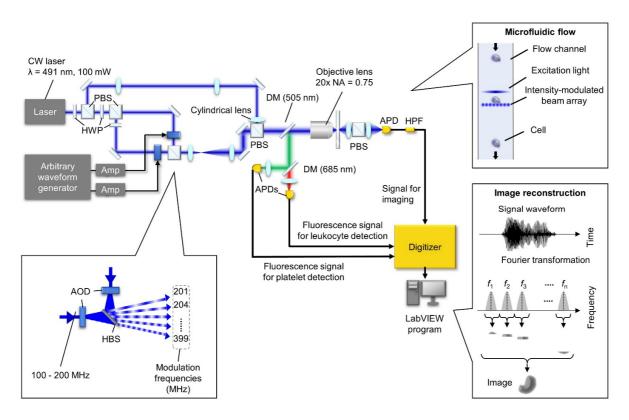
Supplementary Information

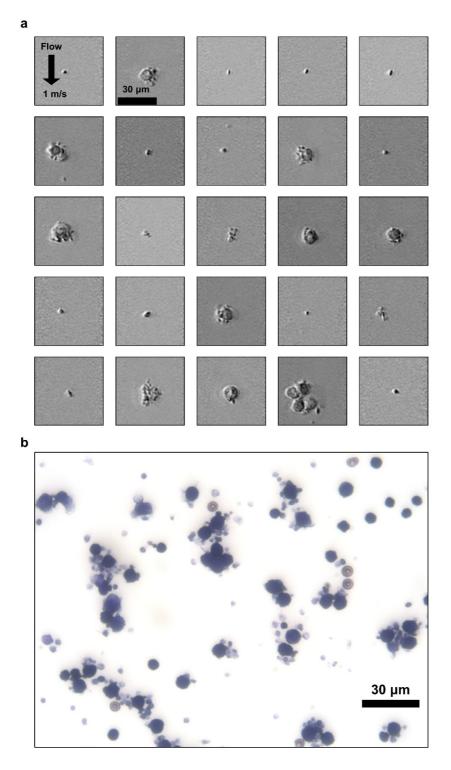
for

Massive image-based single-cell profiling reveals high levels of circulating platelet aggregates in patients with COVID-19

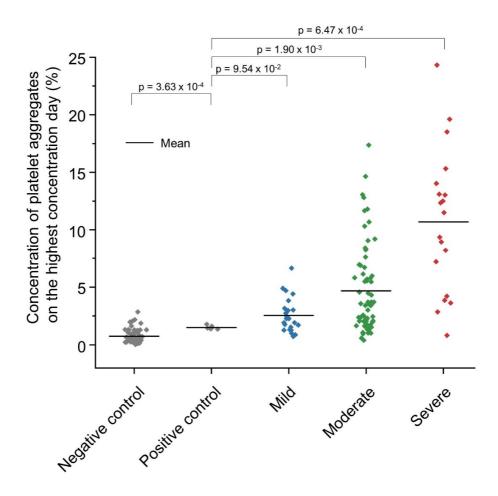
by Nishikawa et al.



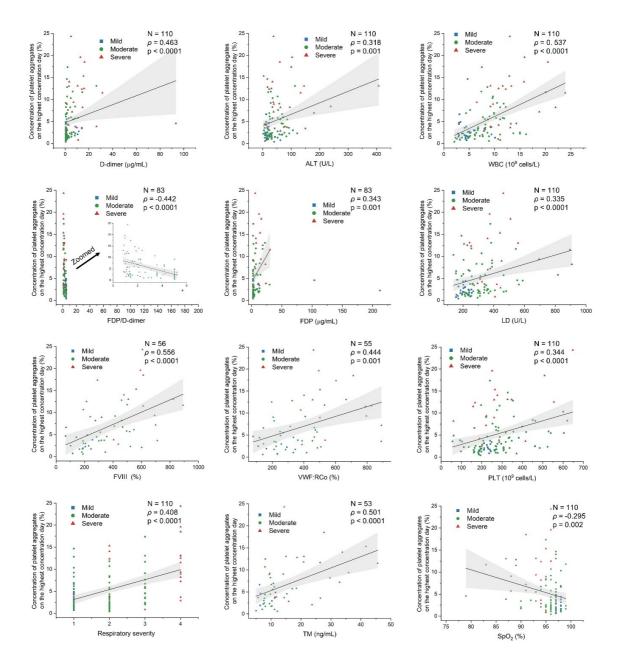
Supplementary Fig. 1 | Detailed schematic of the FDM microscope. CW: continuous wave; PBS: polarizing beamsplitter; HWP: half-wave plate; APD: avalanche photodetector; HPF: high-pass filter; DM: dichroic mirror; HBS: half beamsplitter; AOD: acousto-optic deflector; NA: numerical aperture. See "Optical frequency-division-multiplexed microscope" in the Methods section for details.



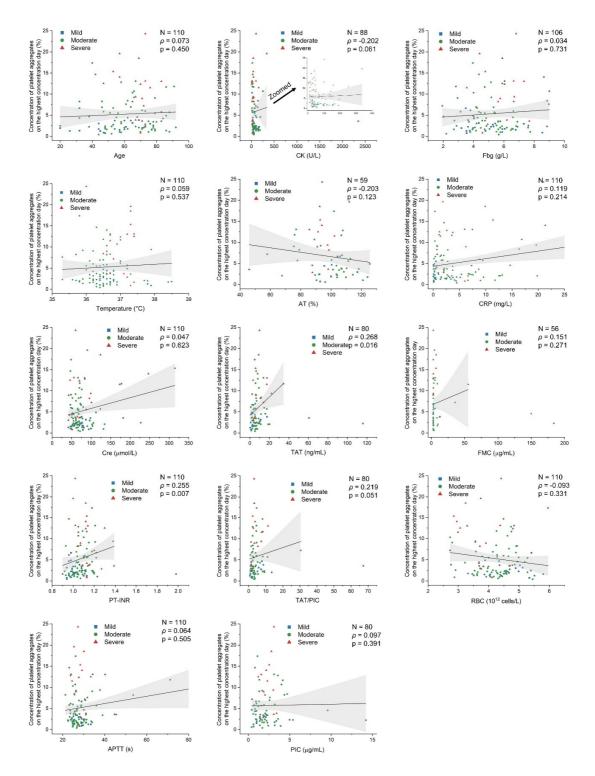
Supplementary Fig. 2 | Images of single platelets and platelet aggregates. a, Images of flowing single platelets and platelet aggregates obtained by the FDM microscope. **b,** Image of stationary single platelets, platelet aggregates, and leukocytes obtained by a conventional optical microscope. The sample was prepared using cytospin, followed by May-Giemsa staining. Both samples were obtained from a blood sample collected from a single COVID-19 patient on the same blood draw date.



Supplementary Fig. 3 | Comparison with negative and positive control groups. Negative control: healthy subjects (n = 67 biologically independent samples); positive control (n = 7 biologically independent samples): patients under no anticoagulant therapy with no abnormality confirmed by their coagulation tests (see "human subjects" in the Methods section for details); Mild: mild COVID-19 patients (n = 23 biologically independent samples); Moderate: moderate COVID-19 patients (n = 68 biologically independent samples); Severe: severe COVID-19 patients (n = 19 biologically independent samples). Samples were measured on the highest concentration day of each hospitalized patient. Exact p values were obtained using the Mann–Whitney U-test (two-sided) and shown in the figure. Source data are provided as a Source Data file.



Supplementary Fig. 4 | Strong correlations between the concentration of platelet aggregates and clinical laboratory and physical findings. Respiratory severity level 1: without oxygen administration; level 2: with oxygen administration of 0.5 - 4 L/min; level 3: with oxygen administration of ≥ 5 L/min; level 4: with tracheal intubation or VV-ECMO. Linear fits show the correlation between the concentration of platelet aggregates and each clinical parameter with a 95% confidence interval shown in gray calculated by the standard error of measured y values. P values were obtained using the two-sided ANOVA test and shown in the figure. Source data are provided as a Source Data file.

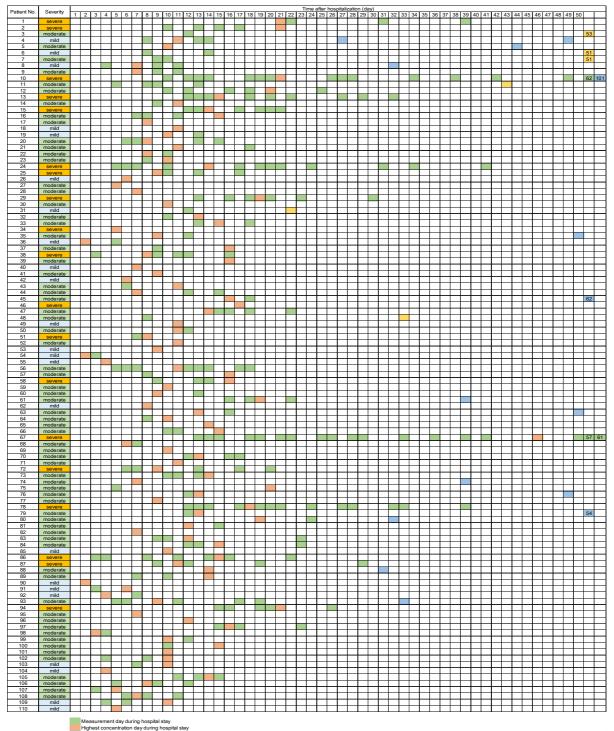


Supplementary Fig. 5 | Weak correlations between the concentration of platelet aggregates and clinical laboratory and physical findings. Linear fits show the correlation between the concentration of platelet aggregates and each clinical parameter with a 95% confidence interval shown in gray calculated by the standard error of measured y values. P values were obtained using the two-sided ANOVA test and shown in the figure. Source data are provided as a Source Data file.

Supplementary Data 1 | Demographics, clinical characteristics, and laboratory findings of patients with COVID-19. All the patients in this study were hospitalized at the University of Tokyo Hospital. Data are expressed as median values (IQR), n (%), or n/N (%). p values were calculated by the *t* test, Mann-Whitney U test, one-way ANOVA, chi-squared test, or Fisher's exact test.

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|--|--|---------------------|---------------------|---------------------|---------------------|----------|---------------------|---------------------|----------|
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| Finance37,0%h27,2%h21,2%h4,2(h)4,2(h)3,0%h3,0%h3,0%h3,0%hSmoking56,0%h10,1%h33,0%h11,0%h0.754,0%h6,60%h0.65Dadae56,0%h70,7%h27,0%h4,2%h0.236,0%h2,0%h0.0Obelas,0h 2583,0%h70,7%h27,0%h4,1%h0.236,0%h2,0%h0.0Corolay,0ha 2684,0%h03,0%h4,1%h0.82,0%h2,0%h0.0Corolay,0ha 6866,0%h0,0%h4,0%h1,0%h0.6%h4,0%h2,0%h0.0%hCorolay,0ha 689,0%h3,1%h4,0%h2,0%h0.6%h7,7%h2,0%h0.0%hCorolay,0ha 689,0%h3,1%h4,0%h1,0%h0.6%h7,7%h2,0%h0.0%hCorolay,0ha 689,0%h3,1%h4,0%h1,0%h0.6%h7,7%h2,0%h0.0%hCorolay,0ha 689,1%h4,0%h1,0%h1,0%h0.6%h7,7%h2,0%h0.0%hCorolay,0ha 689,1%h4,0%h1,0%h1,0%h0.6%h1,0%h0.0%h0.0%hCorolay,0ha 6812,1%h1,0%h4,0%h1,0%h1,0%h1,0%h0.0%h0.0%hCorolay,0ha 6612,1%h1,0%h1,0%h1,0%h1,0%h1,0%h0.0%h0.0%hCorolay,0ha 6612,1%h1,0%h1,0%h1,0%h1,0%h1,0%h0.0%h0,0%hCorolay,0ha 66< | | 73 (66%) | 11 (48%) | 47 (69%) | 15 (79%) | | 65 (66%) | 8 (73%) | |
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| Decision Decision Construction <br< td=""><td></td><td>55 (50%)</td><td>11 (48%)</td><td>33 (49%)</td><td>11 (58%)</td><td>0.75</td><td>49 (49%)</td><td>6 (55%)</td><td>0.95</td></br<> | | 55 (50%) | 11 (48%) | 33 (49%) | 11 (58%) | 0.75 | 49 (49%) | 6 (55%) | 0.95 |
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| Creatinine, µmo/L 69.4 (68.1-80.7) 64.5 (64.8-78.7) 69.4 (61.0-81.8) 69.8 (60.2-115.8) 0.42 68.1 (57.57.9) 76.0 (69.0-155.6) 0.25 Lactate dehydrogenese, UL 301.0 (220.8-379.5) 205.0 (168.0-240.0) 310.5 (238.3-358.0) 560.0 (840.0660.0) < 0.0001 | | | | | | | | | |
| Lactate delydrogenase, UL 301.0 (220.8-379.5) 205.0 (168.0-240.0) 310.5 (238.3-359.0) 560.0 (840.6660.0) < 0.0001 657.0 (320.0560.0) 664.0 (342.0-636.0) < 0.0007 C-auscive protein, mgL 4.15 (1.547.87) 0.32 (0.09-252) 5.24 (2.20-9.44) 6.66 (3.72-18.81) < 0.0001 6.37 (3.02-20.56) 3.88 (1.25-7.50) 0.0077 PT-NR 1.05 (1.00-1.13) 0.99 (0.88-1.03) 1.07 (1.02-1.13) 1.13 (107-1.22) 0.36 1.05 (1.00-1.13) 1.66 (0.98-1.22) 0.46 APTT, s 27.6 (25.4-30.9) 26.8 (25.1-28.0) 27.2 (25.1-30.7) 29.5 (27.4-36.0) 0.00075 27.2 (25.1-29.8) 3.84 (32.345.5) <0.0001 D-dimer, µg/mL - - - - - - - - - S-1 62 (65%) 4 (17%) 40 (69%) 18 (65%) 0.074 76 (77%) 8 (73%) 0.72 S-1 62 (65%) 4 (23,724.98) 4.36 (3.94-4.68) 371 (3.05-4.38) 0.0007 4.36 (3.824.70) 3.64 (2.94.28) 0.0014 D-1000000000000000000000000000000000000 | | | | . , | | | | | |
| Creactive protein, mg/L 4.15 (1.54-7.87) 0.32 (0.09-2.52) 5.24 (2.09.44) 6.66 (3.72-18.81) < 0.0001 6.37 (3.02-0.56) 3.88 (1.25-7.50) 0.0077 PT-NR 1.05 (1.00-1.13) 0.99 (9.98-1.03) 1.07 (1.02-1.13) 1.13 (1.07-1.22) 0.36 1.06 (1.00-1.13) 1.06 (0.98-1.22) 0.46 APTT, s 27.6 (55-30.9) 26.8 (25-1.29.0) 27.2 (25.1-30.7) 29.5 (27.4-36.0) 0.0075 27.2 (25.1-29.8) 3.84 (92.3-45.5) <.0001 D-dimer, µg/mL T T T T T T T T T ≤ 1 44 (4%) 19 (3%) 28 (4%) 1 (5%) <.0001 47 (47%) 1 (9%) 0.022 > 1 65 (56%) 4 (17%) 40 (95%) 18 (95%) 0.074 76 (7%) 8 (73%) 0.72 abordroty findings on the platest consentration day 44 (3 (3.2-50) 8.2 (5.4-10.5) 12 9 (9.7-159) < 0.001 7.6 (4.5-10.1) 13.3 (8.2-0.1) < 0.0001 Red cell count, x10 ⁷ /L 4.29 (3.72-468) 4.42 (3.2-2.09) 3.6 (3.894-68) | | | | | | | | | |
| PT-NR 1.05 (1.00-1.13) 0.99 (0.98-1.03) 1.07 (1.02-1.13) 1.13 (1.07-1.22) 0.36 1.05 (1.00-1.13) 1.06 (0.98-1.22) 0.46 APTT, s 27.6 (25.4-30.9) 28.8 (25.1-29.0) 27.2 (25.1-30.7) 29.5 (27.4-36.0) 0.0075 27.2 (25.1-29.8) 38.4 (32.3-45.5) < 0.0001 D-dimer, µg/mL <th< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></th<> | | | | | | | | | |
| APTT, s 27.6 (25.4-30.9) 26.8 (25.1-29.0) 27.2 (25.1-30.7) 29.5 (27.4-36.0) 0.0075 27.2 (25.1-29.8) 38.4 (32.3-45.5) < 0.0001 L-dimer, µg/mL Image: | | | | | | | | | |
| D-dimer, µg/ml. Image: Participant of the participant of the participant of the participant of the participant definition of participant definition definite definition definited efinition definited efinition def | | | | | | | | | |
| ≤1 48 (44%) 19 (83%) 28 (41%) 1 (5%) < 0.0001 47 (47%) 1 (9%) 0.022 >1 62 (56%) 4 (17%) 40 (59%) 18 (95%) 0.074 52 (53%) 10 (91%) 0.022 Anticoagulant therapy on the lighest concentration day abcrotropt findings on the lighest concentration day 84 (76%) 15 (65%) 51 (75%) 18 (95%) 0.074 76 (77%) 8 (73%) 0.72 abcrotropt findings on the lighest concentration day 84 (76%) 4.3 (3.2-5.0) 8.2 (5.410.5) 12.9 (9.7-15.9) <0.001 76 (4.5-10.1) 13.3 (8.2-20.1) <0.0001 Red cell count, ×10 ⁷ /L 4.29 (3.72-4.68) 4.42 (3.72-4.99) 4.36 (3.84-68) 3.71 (3.06-4.38) 0.0027 4.36 (3.82-4.70) 3.64 (2.994.28) 0.0046 Platelet count, ×10 ⁷ /L 263.0 (197.8327.3) 27.0 (185.0-245.0) 27.6 (0.20-337.0) 26.10 (202.0-371.0) 0.046 269.0 (200.032.0) 28.0 (28.0-28.0) 0.019 ALT, U/L 31.0 (16.0-62.0) 16.0 (12.0-25.0) 33.5 (19.3-68.0) 36.0 (22.0-37.0) 0.017 30.0 (15.6-62.0) 36.0 (28.0-26.0) | | 27.6 (25.4-30.9) | 26.8 (25.1-29.0) | 27.2 (25.1-30.7) | 29.5 (27.4-36.0) | 0.0075 | 27.2 (25.1-29.8) | 38.4 (32.3-45.5) | < 0.0001 |
| >1 62 (56%) 4 (17%) 40 (59%) 18 (95%) 52 (53%) 10 (91%) Anticoagulant therapy on the highest concentration day aboratory findings on the highest concentration day 84 (76%) 15 (65%) 51 (75%) 18 (95%) 0.074 76 (77%) 8 (73%) 0.72 aboratory findings on the highest concentration day 8.3 (04.7-10.9) 4.3 (3.2-5.0) 8.2 (5.4-10.5) 12.9 (9.7-15.9) <0.0001 | | | | | | | | | |
| Anticoagulant therapy on the tighest concentration day aboratory findings on the tighest concentration day thest concentration day 84 (76%) 15 (65%) 51 (75%) 18 (95%) 0.074 76 (77%) 8 (73%) 0.72 aboratory findings on the tighest concentration day 8.0 (4.7-10.9) 4.3 (3.2-5.0) 8.2 (5.4-10.5) 12.9 (9.7-15.9) <0.0001 | | | | | | < 0.0001 | | | 0.022 |
| highest concentration day chocatory findings on the injeast concentration day chocatory findings on the injeast concentration day check column, ×10 ¹⁷ L 64 (0%) 15 (05%) 51 (0%) 18 (95%) 0.014 76 (7%) 8 (3%) 0.72 Laboratory findings on the injeast concentration day Laboratory findings on the injeast concentration day 8.0 (4.710.9) 4.3 (3.25.0) 8.2 (5.410.5) 12.9 (9.715.9) <0.001 | | | | | | | | | |
| Red cell count, x10 ³⁷ L 4.29 (3.724.68) 4.42 (3.724.99) 4.36 (3.84.68) 3.71 (3.064.38) 0.0027 4.36 (3.824.70) 3.64 (2.994.28) 0.0046 Platelet count, x10 ³⁷ L 4.29 (3.724.68) 4.42 (3.724.99) 4.36 (3.84.68) 3.71 (3.064.38) 0.0027 4.36 (3.824.70) 3.64 (2.994.28) 0.0046 Platelet count, x10 ³⁷ L 263.0 (197.8327.3) 227.0 (165.0-245.0) 27.60 (202.0-337.0) 261.0 (202.0-371.0) 0.046 269.0 (200.0-332.0) 221.0 (158.0-261.0) 0.019 ALT, U/L 31.0 (16.0-62.0) 16.0 (12.0-25.0) 33.5 (193.48.8) 38.0 (22.0-78.0) 0.017 30.0 (15.0-62.0) 38.0 (28.0-92.0) 0.19 Creatinine, µmol/L 68.5 (65.7-83.3) 69.0 (54.8-70.7) 68.1 (57.7-91.1) 69.8 (54.8-100.8) 0.32 67.2 (54.8-77.8) 100.8 (83.1-173.3) 0.12 Lactale dehydrogenase, U/L 280.0 (215.8-374.0) 210.0 (170.0-240.0) 301.0 (229.8-363.3) 420.0 (324.0-509.0) <0.0001 257.0 (211.0-351.0) 544.0 (389.0-695.0) <0.0001 C-reactive protein, mg/L 252 (0.63-6.96) 0.39 (0.99-2.67) 2.72 (1.05-7.7) 60.1 (1 | highest concentration day Laboratory findings on the highest concentration day | 84 (76%) | 15 (65%) | 51 (75%) | 18 (95%) | 0.074 | 76 (77%) | 8 (73%) | 0.72 |
| Platelet count, ×10 ³ /L 263.0 (197.8-327.3) 27.0 (185.0-245.0) 276.0 (202.0-337.0) 261.0 (202.0-371.0) 0.046 269.0 (200.0-332.0) 221.0 (158.0-261.0) 0.019 AT, U/L 31.0 (16.0-62.0) 16.0 (12.0-25.0) 33.5 (19.3-68.0) 38.0 (22.0-78.0) 0.017 30.0 (15.0-62.0) 38.0 (28.0-92.0) 0.19 Creatinine, µmol/L 68.5 (55.7-83.3) 69.0 (54.8-78.7) 68.1 (57.7-79.1) 69.8 (54.810.0) 0.32 67.2 (54.8-77.0) 100.8 (83.1-173.3) 0.12 Lactate dehydrogenase, U/L 20.0 (215.8-37.40) 0.30 (10.0-240.0) 30.1 (228.8-36.3) 20.0 (324.0-509.0) < 0.0001 25.7 0.211.0-351.0) 54.40 (389.0-689.0) < 0.0001 C-reactive protein, mg/L 2.52 (0.63-6.90) 0.39 (0.92-257) 2.72 (1.05-7.27) 6.01 (18.3196.2) 0.0001 2.23 (0.51-6.60) 9.45 (1.11-6.31) < 0.0001 PT-NR 10.8 (1.01-1.13) 0.99 (0.88-1.60) 1.09 (1.03-1.15) 1.12 (1.05-1.16) 0.0059 1.06 (1.00-1.13) 1.14 (1.08-1.20) 0.0107 APT, s 27.2 (25-2.30.1) 2.68 (25.1-2.90) 2.68 (25.2-3.04) 2.88 (26.2-33.4) <th< td=""><td>Leukocyte count, ×10⁹/L</td><td>8.0 (4.7-10.9)</td><td>4.3 (3.2-5.0)</td><td>8.2 (5.4-10.5)</td><td>12.9 (9.7-15.9)</td><td>< 0.0001</td><td>7.6 (4.5-10.1)</td><td>13.3 (8.2-20.1)</td><td>< 0.0001</td></th<> | Leukocyte count, ×10 ⁹ /L | 8.0 (4.7-10.9) | 4.3 (3.2-5.0) | 8.2 (5.4-10.5) | 12.9 (9.7-15.9) | < 0.0001 | 7.6 (4.5-10.1) | 13.3 (8.2-20.1) | < 0.0001 |
| ALT, U/L 31.0 (16.0÷2.0) 16.0 (12.0±5.0) 33.5 (19.3+68.8) 38.0 (22.0+78.0) 0.017 30.0 (15.0÷2.0) 38.0 (28.0+20.0) 0.19 Creatinine, µm0/L 68.5 (55.78.3.3) 69.0 (54.8-77.7) 68.1 (57.7+7.9) 69.8 (64.8+10.8) 0.32 67.2 (54.8-77.8) 100.8 (83.1173.3) 0.12 Lactate dehydrogenase, U/L 280.0 (215.8-37.40) 210.0 (170.0-240.0) 30.1 (228.363.3) 420.0 (324.0-590.0) <0.0001 | Red cell count, ×10 ¹² /L | 4.29 (3.72-4.68) | 4.42 (3.72-4.99) | 4.36 (3.98-4.68) | 3.71 (3.06-4.38) | 0.0027 | 4.36 (3.82-4.70) | 3.64 (2.99-4.28) | 0.0046 |
| Creatinine, µmol/L 68.5 (55.7.83.3) 69.0 (54.8.78.7) 68.1 (57.7.91.1) 69.8 (54.8100.8) 0.32 67.2 (54.8.77.8) 100.8 (83.1-173.3) 0.12 Lactate dehydrogenase, UL 200.0 (216.8-374.0) 210.0 (170.0-240.0) 30.10 (229.8-363.3) 420.0 (324.0-509.0) < 0.0001 257.0 (211.0-351.0) 64.0 (389.0-695.0) < 0.0001 C-reactive protein, mg/L 2.52 (0.63.6.96) 0.39 (0.09.2.57) 2.72 (1.05.7.27) 6.01 (1.83·19.62) 0.0004 2.23 (0.51.660) 9.45 (1.11-26.31) < 0.0001 PT-NR 1.08 (1.01-1.13) 0.99 (0.98-1.06) 1.09 (1.03-1.15) 1.12 (1.05-1.16) 0.0059 1.06 (1.00-1.13) 1.14 (1.08-1.20) 0.017 APTT, s 27.2 (2.52-30.1) 26.8 (2.51-29.0) 26.8 (2.50-30.1) 28.8 (2.62-33.4) 0.44 26.8 (2.51-29.0) 37.8 (3.0.55.6) < 0.0001 D-dimer, µg/mL | Platelet count, ×10 ⁹ /L | 263.0 (197.8-327.3) | 227.0 (185.0-245.0) | 276.0 (202.0-337.0) | 261.0 (202.0-371.0) | 0.046 | 269.0 (200.0-332.0) | 221.0 (158.0-261.0) | 0.019 |
| Lactate dehydrogenase, UL 280.0 (215.8-37.4) 210.0 (170.0-240.0) 301.0 (229.8-363.3) 420.0 (324.0-509.0) < 0.0001 257.0 (211.0-51.0) 544.0 (389.0695.0) < 0.0001 C-reactive protein, mg/L 2.52 (0.63.6-96) 0.39 (0.09-2.57) 2.72 (1.05-7.27) 6.01 (1.83.19.62) 0.0004 2.23 (0.51.660) 9.45 (1.11-26.31) < 0.0001 PT-NR 1.08 (1.01-1.13) 0.99 (0.98-1.06) 1.09 (1.03-1.15) 1.12 (1.05-1.16) 0.0059 1.06 (1.00-1.13) 1.14 (1.08-1.20) 0.017 APTT, s 27.2 (2.52.30.1) 26.8 (25.1-29.0) 26.8 (25.0-30.1) 28.8 (26.2-33.4) 0.44 26.8 (25.1-29.0) 37.8 (30.5-5.6) < 0.0001 D-dimer, µg/mL | ALT, U/L | 31.0 (16.0-62.0) | 16.0 (12.0-25.0) | 33.5 (19.3-68.8) | 38.0 (22.0-78.0) | 0.017 | 30.0 (15.0-62.0) | 38.0 (28.0-92.0) | 0.19 |
| C-reactive protein, mg/L 2.52 (0.63.6.99) 0.39 (0.09-2.67) 2.72 (1.05-7.27) 6.01 (1.83.19.62) 0.0004 2.23 (0.51.6.60) 9.45 (1.11-26.31) < 0.0001 PT-NR 1.08 (1.01-1.13) 0.99 (0.98-1.66) 1.09 (1.03-1.15) 1.12 (1.05-1.16) 0.0059 1.06 (1.00-1.13) 1.14 (1.08-1.20) 0.017 APT. s 27.2 (25-30.1) 26.8 (25.1-29.0) 26.8 (26.2-33.4) 0.44 26.8 (25.1-29.0) 37.8 (30.553.6) <0.0001 D-dimer, µg/mL 43 (39%) 19 (83%) 23 (34%) 1 (5%) <0.0001 43 (43%) 0.0 0.0002 | Creatinine, µmol/L | 68.5 (55.7-83.3) | 69.0 (54.8-78.7) | 68.1 (57.7-79.1) | 69.8 (54.8-100.8) | 0.32 | 67.2 (54.8-77.8) | 100.8 (83.1-173.3) | 0.12 |
| PT-NR 1.08 (1.01-1.13) 0.99 (0.98-1.06) 1.09 (1.03-1.15) 1.12 (1.05-1.16) 0.0059 1.06 (1.00-1.13) 1.14 (1.08-1.20) 0.017 APT, s 27.2 (25-23.01) 26.8 (25.1-29.00) 26.8 (25.0-30.1) 28.8 (26.2-33.4) 0.44 26.8 (25.1-29.00) 37.8 (30.5-53.6) <0.0001 | Lactate dehydrogenase, U/L | 280.0 (215.8-374.0) | 210.0 (170.0-240.0) | 301.0 (229.8-363.3) | 420.0 (324.0-509.0) | < 0.0001 | 257.0 (211.0-351.0) | 544.0 (389.0-695.0) | < 0.0001 |
| APTT, s 27.2 (25.2·30.1) 26.8 (25.1·29.0) 26.8 (25.0·30.1) 28.8 (26.2·33.4) 0.44 26.8 (25.1·29.0) 37.8 (30.5·53.6) <0.0001 D-dimer, µg/mL 43 (39%) 19 (83%) 23 (34%) 1 (5%) <0.0001 43 (43%) 0 0.0002 | C-reactive protein, mg/L | 2.52 (0.63-6.96) | 0.39 (0.09-2.57) | 2.72 (1.05-7.27) | 6.01 (1.83-19.62) | 0.0004 | 2.23 (0.51-6.60) | 9.45 (1.11-26.31) | < 0.0001 |
| D-dimer, μg/mL ≤1 43 (39%) 19 (83%) 23 (34%) 1 (5%) <0.0001 43 (43%) 0 0.0002 | PT-INR | 1.08 (1.01-1.13) | 0.99 (0.98-1.06) | 1.09 (1.03-1.15) | 1.12 (1.05-1.16) | 0.0059 | 1.06 (1.00-1.13) | 1.14 (1.08-1.20) | 0.017 |
| ≤1 43 (39%) 19 (83%) 23 (34%) 1 (5%) <0.0001 43 (43%) 0 0.0002 | APTT, s | 27.2 (25.2-30.1) | 26.8 (25.1-29.0) | 26.8 (25.0-30.1) | 28.8 (26.2-33.4) | 0.44 | 26.8 (25.1-29.0) | 37.8 (30.5-53.6) | < 0.0001 |
| | D-dimer, µg/mL | | | | | | | | |
| >1 67 (61%) 4 (17%) 45 (66%) 18 (95%) 56 (57%) 11 (100%) | ≤1 | 43 (39%) | 19 (83%) | 23 (34%) | 1 (5%) | < 0.0001 | 43 (43%) | 0 | 0.0002 |
| | >1 | 67 (61%) | 4 (17%) | 45 (66%) | 18 (95%) | | 56 (57%) | 11 (100%) | |

Supplementary Data 2 | Measurement days of patients with COVID-19. Most patients were tested during their hospital stays while some patients were tested at the time of outpatient consultations after their discharge from the hospital.



Highest concentration day during hospital stay Outpatient consultation day after discharge from hospital Highest concentration day after discharge from hospital **Supplementary Data 3 | Additional laboratory findings of patients with COVID-19.** All the patients in this study were hospitalized at the University of Tokyo Hospital. p values were calculated by *t* test, Mann-Whitney U test, one-way ANOVA, chi-squared test, or Fisher's exact test.

| | All patients | Mild patients | Moderate patients | Severe patients | p value | Survivors | Non-survivors | p value |
|------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|----------|-------------------------------|-------------------------------|----------|
| FVIII, % | 329.2 (205.7-514.9) n = 56 | 189.8 (102.8-220.1) n = 11 | 342.4 (219.9-497.2) n = 30 | 563.1 (404.9-612.4) n = 15 | < 0.0001 | 311.0 (191.1-464.7) n = 45 | 517.3 (301.1-692.7) n = 11 | 0.0013 |
| TM, ng/mL | 11.2 (8.1-18.6) n = 53 | 7.7 (6.4-10.6) n = 10 | 10.8 (8.8-16.2) n = 29 | 24.4 (11.7-34.3) n = 14 | < 0.0001 | 10.2 (8.0-12.7) n = 42 | 26.4 (20.9-32.9) n = 11 | < 0.0001 |
| VWF:Rco, % | 380.9 (224.1-494.5) n = 55 | 232.1 (120.2-292.9) n = 11 | 380.9 (224.1-483.5) n = 31 | 501.4 (427.9-751.2) n = 13 | 0.0001 | 333.5 (218.0-463.7) n = 45 | 660.6 (476.3-843.4) n = 10 | < 0.0001 |
| FDP, µg/mL | 3.4 (2.5-10.9) n = 83 | 2.5 (2.5-3.5) n = 16 | 3.4 (2.5-9.2) n = 52 | 12.3 (5.9-18.6) n = 15 | 0.50 | 3.4 (2.5-8.3) n = 72 | 13.2 (7.1-22.9) n = 11 | 0.28 |
| TAT, ng/mL | 6.0 (3.5-10.2) n = 80 | 3.1 (1.5-7.9) n = 16 | 6.3 (4.3-10.4) n = 50 | 8.6 (5.3-14.8) n = 14 | 0.35 | 5.5 (3.1-8.9) n = 69 | 17.5 (10.8-22.1) n = 11 | 0.0031 |
| FMC, µg/mL | 3.0 (3.0-5.4) n = 55 | 3.0 (3.0-3.2) n = 11 | 3.0 (3.0-4.0) n = 31 | 4.8 (3.0-10.2) n = 13 | 0.70 | 3.0 (3.0-3.8) n = 45 | 6.1 (3.0-16.5) n = 10 | 0.20 |
| PIC, µg/mL | 1.9 (1.1-3.0) n = 80 | 1.0 (0.8-2.0) n = 16 | 1.9 (1.3-3.2) n = 50 | 2.2 (1.7-3.0) n = 14 | 0.16 | 1.9 (1.1-3.1) n = 69 | 1.6 (1.3-2.3) n = 11 | 0.25 |
| Fbg, g/L | 5.17 (4.03-6.20) n = 106 | 4.12 (3.55-5.55) n = 22 | 5.32 (4.19-6.33) n = 65 | 5.90 (4.59-6.69) n = 19 | 0.085 | 5.18 (4.17-6.20) n = 95 | 4.74 (2.95-5.63) n = 11 | 0.085 |
| AT, % | 100.0 (90.9-107.1) n = 59 | 100.4 (92.8-117.3) n = 11 | 103.5 (88.3-107.5) n = 33 | 93.9 (90.9-98.6) n = 15 | 0.19 | 101.6 (92.6-108.3) n = 48 | 77.8 (67.7-98.6) n = 11 | < 0.0001 |
| CK, U/L | 47.0 (28.0-97.0) n = 87 | 56.5 (35.5-87.8) n = 16 | 50.0 (28.5-104.0) n = 53 | 38.0 (24.0-97.8) n = 18 | 0.72 | 47.0 (28.0-98.0) n = 77 | 46.5 (32.0-112.5) n = 10 | 0.0044 |

Supplementary Data 4 | Multivariate regression analysis. The upper part shows the first analysis while the lower part shows the second analysis, to determine explanatory factors for predicting the concentration of platelet aggregates on the highest concentration day.

| Objective factor Explanatory factor | | | Concentration of platelet aggregates on the highest concentration day | | |
|--|----------------------|---------------------------------|--|--|--|
| | | Standardized coefficient (β) | p value | | |
| | FVIII | 0.568 | < 0.001 | | |
| Vascular endothelial | тм | | NS | | |
| disorder markers | VWF:Rco | | NS | | |
| | R ² | 0.322 (p < 0 | 0.001) | | |
| | PT-INR | 0.222 | 0.049 | | |
| | D-dimer | | NS | | |
| Coagulation / fibrinolysis markers | FDP | | NS | | |
| | TAT | | NS | | |
| | R ² | 0.049 (p = 0.049) | | | |
| | WBC | 0.265 | 0.009 | | |
| | Respiratory severity | 0.306 | 0.002 | | |
| | PLT | 0.227 | 0.006 | | |
| | LD | | NS | | |
| Other markers | ALT | | NS | | |
| | SpO ₂ | | NS | | |
| | Survival | | NS | | |
| | Gender | | NS | | |
| | R ² | 0.364 (p < 0 | 0.001) | | |

| Obje | ctive factor | Concentration of platelet aggregates on the highest concentration day | | |
|--------------------|----------------------|--|----------|--|
| Explanatory factor | | Standardized coefficient (β) | p value | |
| Selected markers | Respiratory severity | 0.355 | 0.009 | |
| | FVIII | 0.323 | 0.016 | |
| | WBC | | NS | |
| | PLT | | NS | |
| | PT-INR | | NS | |
| | R ² | 0.352 (p | < 0.001) | |

Supplementary Data 5 | Demographics, clinical characteristics, and laboratory findings of patients with other diseases. All the patients in this study were hospitalized at the University of Tokyo Hospital. Data are expressed as median values (IQR) or n/N (%).

| | Positive control |
|----------------------------|---------------------|
| | n = 7 |
| Age, years | 47.0 (17.0-70.0) |
| Sex | |
| Male | 3 (43%) |
| Female | 4 (57%) |
| Comorbidity | |
| Hypertension | 2 (29%) |
| Diabetes | 1 (14%) |
| Obesity, BMI > 25 | 1 (14%) |
| Coronary heart disease | 0 |
| Active malignancy | 0 |
| Antiplatelet therapy | 0 |
| Anticoagulant therapy | 0 |
| Laboratory findings | |
| Leukocyte count, ×109/L | 5.1 (4.7-5.2) |
| Platelet count, ×109/L | 238.0 (218.5-283.0) |
| ALT, U/L | 19.0 (15.5-29.0) |
| Creatinine, μmol/L | 64.5 (59.7-74.7) |
| Lactate dehydrogenase, U/L | 216.0 (196.0-223.0) |
| C-reactive protein, mg/L | 0.02 (0.02-0.05) |
| D-dimer, μg/mL | 0.5 (0.5-0.7) |