

ONLINE SUPPLEMENT

Table S1. Comparison between COVID-19 and control patients. Key clinical characteristics of patients with COVID-19 are compared to those of control patients. Three groups of controls were considered as described in the text. For the propensity score matched groups, in addition to p-values, absolute standardized mean differences (SMD) are shown.

	All COVID-19	Controls				Propensity score matching			
		All	p	Manual match	p	COVID-19	Controls	p	SMD
Number	100	595		100		87	87		
Age, years	67.8 (27.6)	52.2 (16.3)	<0.001	67.3 (13.7)	0.802	64.8 (16.9)	63.0 (17.7)	0.475	0.109
Male sex, %	59.0	46.6	0.021	59.0	1.000	59.8	57.5	0.760	0.033
Diabetes, %	18.0	15.3	0.492	18.0	1.000	20.7	14.9	0.325	0.107
Smoking, %	8.0	18.0	0.015	8.0	1.000	8.0	12.6	0.376	0.107
Obesity, %	18.0	12.1	0.104	18.0	1.000	19.5	16.1	0.555	0.064
Hypertension, %	54.0	25.4	<0.001	58.6	<0.001	50.6	47.1	0.651	0.049
Cardiovascular disease, %	20.0	6.7	<0.001	26.7	0.030	18.4	16.1	0.690	0.043
Chronic kidney disease, %	13.0	7.2	0.050	18.3	0.272	13.8	13.8	1.000	0.000
Anti-platelet agents, %	23.0	12.8	0.007	37.1	<0.001	23.0	24.1	0.859	0.019
RAS blockers, %	39.0	16.1	<0.001	40.0	<0.001	35.6	35.6	1.000	0.000
Statin, %	27.0	11.8	<0.001	30.0	0.097	25.3	23.0	0.725	0.038
HSPC phenotype									
CD34 ⁺ /10 ⁶	159.2 (196.2)	426.5 (196.0)	<0.001*	400.8 (289.5)	<0.001#	156.5 (110.1)	396.1 (198.4)	<0.001	-
CD34 ⁺ CD45 ^{dim} /10 ⁶	120.3 (179.0)	284.2 (179.0)	<0.001*	319.4 (191.4)	<0.001#	120.2 (103.1)	260.0 (152.1)	<0.001	-
CD34 ⁺ CD133 ⁺ /10 ⁶	60.5 (101.6)	133.5 (101.6)	<0.001*	159.5 (110.2)	<0.001#	62.1 (66.2)	129.4 (77.7)	<0.001	-
CD34 ⁺ / ml	1045.0 (1439.7)	2855.1 (1439.7)	<0.001*	2781.9 (1500.3)	<0.001#	1062.0 (918.9)	2648.3 (1182.4)	<0.001	-
CD34 ⁺ CD45 ^{dim} / ml	807.8 (1452.4)	2277.5 (1452.4)	<0.001*	2421.3 (1451.6)	<0.001#	832.7 (860.6)	2075.2 (1145.0)	<0.001	-
CD34 ⁺ CD133 ⁺ / ml	430.1 (798.8)	1055.2 (798.8)	<0.001*	1200.2 (824.6)	<0.001#	454.6 (597.6)	1035.3 (591.8)	<0.001	-

RAS, renin angiotensin system. * Adjusted for age, sex, smoking, hypertension, cardiovascular disease, chronic kidney disease, and use of medications. # Adjusted for hypertension, cardiovascular disease, anti-platelet agents, and RAS blockers.

Table S2. Outcome analysis. The association between one standard deviation (SD) change in CD34⁺ hematopoietic stem/progenitor cells (HSPCs) with the primary outcome (poor COVID-19 course, dependent variable) was ascertained by means of logistic regression models adjusted for an increasing number of co-variates. Model 1 was adjusted for age and sex. Model 2 was further adjusted for covariates at baseline and run first without HSPCs (to show the effects of FPG) and then with HSPCs. Model 3 was fully adjusted for all confounders. Odds ratios (OR) are shown along with 95% confidence intervals (C.I.).

	Model 1		Model 2 without HSPCs		Model 2 with HSPCs		Model 3	
Variable	OR (95% C.I.)	p	OR (95% C.I.)	p	OR (95% C.I.)	p	OR (95% C.I.)	p
Age (/10 years)	1.00 (0.76-0.13)	0.978	0.78 (0.54-1.13)	0.176	0.69 (0.46-1.04)	0.077	0.98 (0.92-1.03)	0.347
Sex (male vs. female)	0.94 (0.36-2.43)	0.895	1.00 (0.36-2.78)	0.993	1.00 (0.34-2.90)	0.994	0.55 (0.12-2.58)	0.452
CHD (yes vs. no)	-	-	2.37 (0.54-10.3)	0.251	2.40 (0.50-11.5)	0.271	3.03 (0.27-34.1)	0.370
eGFR (/10 ml/min/1.73 m ²)	-	-	0.76 (0.62-0.95)	0.013	0.75 (0.59-0.75)	0.018	0.73 (0.53-1.01)	0.057
FPG (/mmol/l)	-	-	1.17 (1.01-1.35)	0.033	1.14 (0.98-1.32)	0.083	1.07 (0.86-1.34)	0.554
Peak CRP (/10 mg/l)	-	-	-	-	-	-	1.08 (0.99-1.19)	0.085
High-flow oxygen (yes vs. no)	-	-	-	-	-	-	27.7 (4.92-155)	<0.001
N/L ratio (/unit)	-	-	-	-	-	-	0.99 (0.90-1.10)	0.859
CD34 ⁺ HSPCs (/SD)	0.30 (0.14-0.63)	0.002	-	-	0.32 (0.14-0.73)	0.006	0.32 (0.11-0.93)	0.036

CHD, chronic heart disease; eGFR, estimated glomerular filtration rate, FPG, fasting plasma glucose; CRP, C-reactive protein; N/L neutrophil/lymphocyte.

Table S3. Mediation analysis. The association between one mmol/l change in fasting plasma glucose (FPG) and the primary outcome (dependent variable) was evaluated with and without

Variable	Model without HSPCs		Model with HSPCs	
	OR (95% C.I.)	p	OR (95% C.I.)	p
Age (/ year)	0.78 (0.54-1.13)	0.176	0.69 (0.46-1.04)	0.077
Sex male	1.00 (0.36-2.78)	0.993	1.00 (0.34-2.90)	0.994
CHD (yes vs no)	2.37 (0.54-10.3)	0.251	2.40 (0.50-11.5)	0.271
eGFR (/ 10 ml/min/1.73 m ²)	0.76 (0.62-0.95)	0.013	0.75 (0.59-0.95)	0.018
FPG (/ mmol/l)	1.17 (1.01-1.35)	0.033	1.14 (0.98-1.32)	0.083
HSPCs (/ SD)	-	-	0.32 (0.14-0.73)	0.006

CHD, chronic heart disease; eGFR, estimated glomerular filtration rate. HSPCs, hematopoietic stem/progenitor cells.

Figure S1. The gating strategy for quantification of HSPCs. Cells were labelled with the following monoclonal antibodies: phycoerythrin (PE)-labelled anti-human CD34 (20 μ l, BD Biosciences), allophycocyanin (APC)-labelled anti-human CD133 (5 μ l, Beckman Coulter), and Electron Coupled Dye (ECD)-labelled anti-human CD45 (10 μ l Beckman Coulter). After red blood cell lysis, the analysis was run on a Beckman Coulter analyzer (NAVIOS EX Flow Cytometer) with a target of 10^6 total cytometric events (actual average achieved 0.95×10^6). Data were analyzed by Kaluza software (Beckman Coulter). Different definitions of HSPCs were used. After selecting the mononuclear cell fraction in the morphological side scatter versus forward scatter gate, total CD34⁺ cells were quantified in the FSC vs CD34 fluorescence intensity plot for comparability with previous studies and with the literature. Identity of CD34⁺ cells as HSPC was further confirmed by low expression of CD45, thus identifying CD34⁺CD45^{dim} cells. In addition, we determined co-expression of the stem cell marker CD133 con the CD34⁺CD45^{dim} population (CD34⁺CD133⁺ HSPCs). The same trained operator performed the analysis throughout the study. Relative cell count was expressed as cells / 10^6 events (WBC), while absolute cell count was reported per ml of blood. The absolute cell count was obtained by multiplying relative cell count x WBC (white blood cell count, $\times 10^3/\text{mL}$).

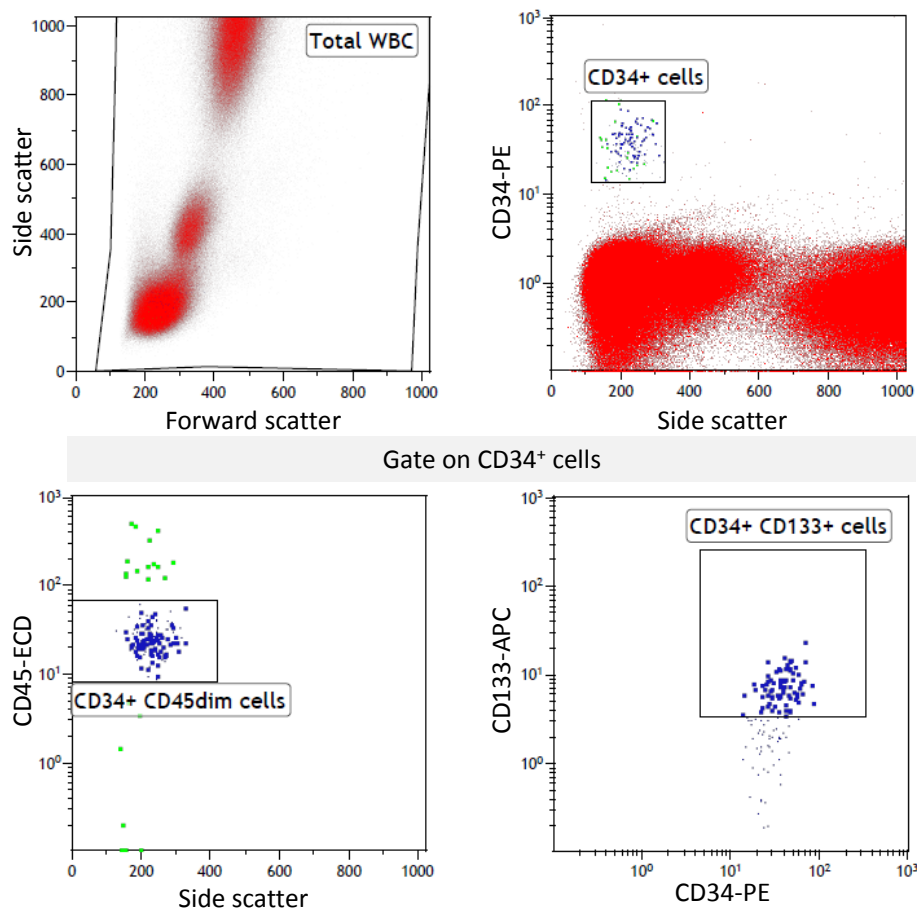


Figure S2. Hyperglycemia and HSPCs in COVID-19. Levels of hematopoietic stem/progenitor cells (HSPCs) are shown in COVID-19 patients divided between patients with and without hyperglycemia defined based on the standard 7.0 mmol/l threshold for fasting plasma glucose (FPG). Data are presented for all the three phenotypes expressed as absolute or relative cell counts in peripheral blood. Columns height represents mean and bars represent standard error. Superimposed data points are referred to individual patients. P-values are shown for the between-group comparisons.

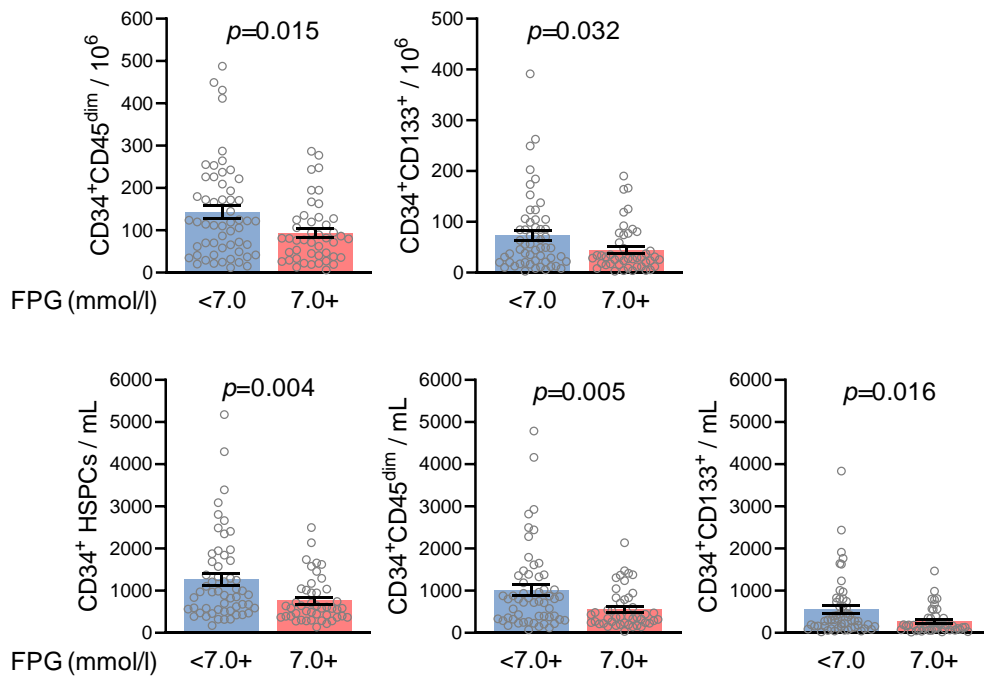


Figure S3. HSPC levels and in-hospital outcome of COVID-19. Levels of hematopoietic stem/progenitor cells (HSPCs) are shown in COVID-19 patients divided based on the occurrence or not of the primary endpoint of poor outcome, defined as admittance to the intensive care unit or death. Data are presented for all the three phenotypes expressed as absolute or relative cell counts in peripheral blood. Columns height represents mean and bars represent standard error. Superimposed data points are referred to individual patients. P-values are shown for the between-group comparisons.

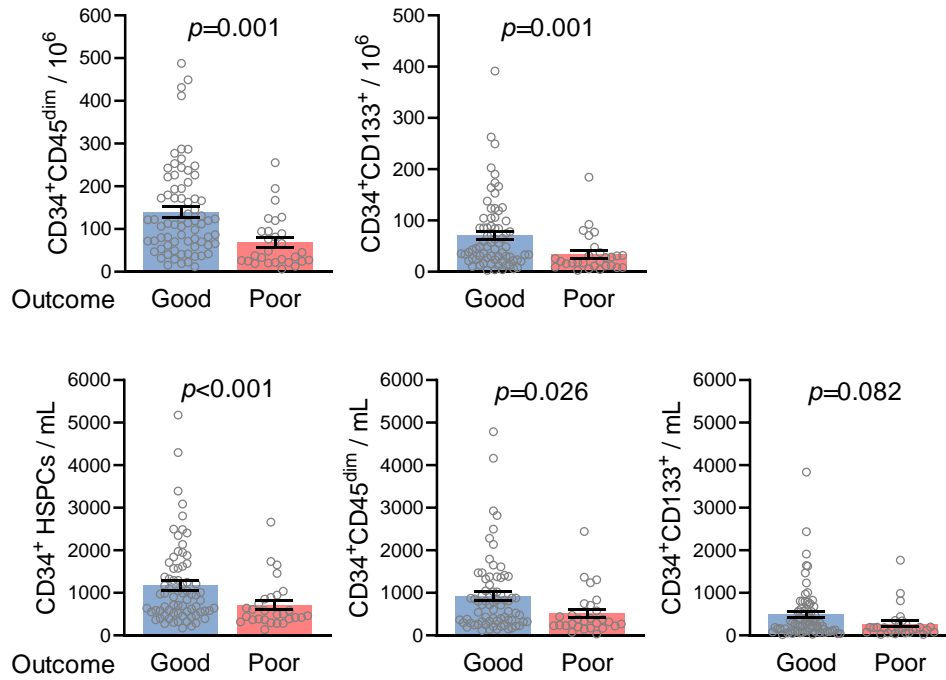


Figure S4. HSPC levels and vital status at 6 months. Levels of hematopoietic stem/progenitor cells (HSPCs) are shown in COVID-19 patients divided based on vital status at 6 months after hospitalization for COVID-19. Data are presented for all the three phenotypes expressed as absolute or relative cell counts in peripheral blood. Columns height represents mean and bars represent standard error. Superimposed data points are referred to individual patients. P-values are shown for the between-group comparisons.

