



Hyperglycemia, Reduced Hematopoietic Stem Cells, and Outcome of COVID-19

Benedetta Maria Bonora,^{1,2} Paola Fogar,¹ Jenny Zuin,¹ Daniele Falaguasta,¹ Roberta Cappellari,¹ Annamaria Cattelan,¹ Serena Marinello,¹ Anna Ferrari,¹ Angelo Avogaro,¹ Mario Plebani,¹ Daniela Basso,¹ and Gian Paolo Fadini^{1,2}

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Admission hyperglycemia has emerged worldwide as a predictor of poor coronavirus disease 2019 (COVID-19) outcome. Hyperglycemia leads to a defect in circulating hematopoietic stem/progenitor cells (HSPCs), which, in turn, predicts diabetic complications. Here, we explored whether reduced HSPCs mediated at least part of the prognostic effect of hyperglycemia on COVID-19 outcome. We found that patients with COVID-19 ($n = 100$) hospitalized in a nonintensive setting displayed dramatically (50–60%) reduced levels of HSPCs measured by flow cytometry as $CD34^+$, $CD34^+CD45^{dim}$, or $CD34^+CD133^+$ cells, compared with control subjects ($n = 595$). This finding was highly significant (all $P < 10^{-10}$) after multivariable adjustment, or manual 1:1 patient match, or propensity score matching. Admission hyperglycemia (≥ 7.0 mmol/L) was present in 45% of patients, was associated with a significant further $\sim 30\%$ HSPCs reduction, and predicted a 2.6-fold increased risk of the primary outcome of adverse COVID-19 course (admittance to the intensive care unit or death). Low HSPCs were also associated with advanced age, higher peak C-reactive protein, and neutrophil-to-lymphocyte ratio. Independently from confounders, 1 SD lower $CD34^+$ HSPCs was associated with a more than three-fold higher risk of adverse outcome. Upon formal analysis, reduction of HSPCs was a significant mediator of the admission hyperglycemia on COVID-19 outcome, being responsible for 28% of its prognostic effect.

Diabetes is a major determinant of poor coronavirus disease 2019 (COVID-19) outcomes, including admittance to

the intensive care unit (ICU) and death (1). Despite the prevalence of diabetes among people with COVID-19 may not be higher than expected (2), admission hyperglycemia has been reported in up to 50% of patients (3). Hyperglycemia results from the hyperinflammatory state of COVID-19 (4) in conjunction with possible β -cell infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (5). Admission hyperglycemia, even in individuals without a history of diabetes, predicts an adverse COVID-19 course (6,7), but the reasons for this association are unclear. Hyperglycemia may reflect a more severe inflammatory process or a preexisting propensity to metabolic dysregulation. On the other side, hyperglycemia can compromise the function of immune cells and affect hematopoietic responses. Indeed, diabetes impacts bone marrow (BM) function, leading to a shortage of circulating hematopoietic stem/progenitor cells (HSPCs) (8). In humans and rodents with diabetes, remodeling of the BM niche hampers the physiologic mobilization of HSPCs into the bloodstream (9). In turn, low circulating HSPCs predict adverse outcomes, including diabetic complications (10,11) cardiovascular events, and death (12). The mechanistic link between hyperglycemia and shortage of circulating HSPCs relies on excess myelopoiesis (13). Although COVID-19 is characterized by exaggerated myelopoiesis (14), little is known about HSPC levels and their clinical meaning in COVID-19.

Here, we hypothesize that hyperglycemia in COVID-19 affects circulating HSPCs and that pauperization of HSPCs in turn mediates the adverse effect of hyperglycemia on COVID-19 outcomes.

¹Department of Medicine, University of Padova, Padua, Italy

²Veneto Institute of Molecular Medicine, Padua, Italy

Corresponding author: Gian Paolo Fadini, gianpaolo.fadini@unipd.it

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RESEARCH DESIGN AND METHODS

Study Participants

This prospective observational study was conducted according to the principles of the Declaration of Helsinki, and the protocol was approved by the University Hospital of Padua Ethical Committee (No. 4930/Ao/20). Patients were admitted between December 2020 and March 2021 to the infectious disease ward of the same hospital and signed informed consent. Inclusion criteria were age ≥ 18 and symptomatic PCR-confirmed SARS-CoV-2 infection. Exclusion criteria were age > 100 , severe renal or liver disease, advanced cancer, short life expectancy, pregnancy or lactation, or inability to provide informed consent. We recorded the following information: age, sex, cardiovascular risk factors (diabetes, obesity, hypertension, smoking), comorbidities (cardiovascular disease, chronic kidney disease [CKD], cancer), prehospital medications, and laboratory data.

The control population was composed of individuals not affected by COVID-19, selected among those attending the same hospital in prior years and who had the same measure of circulating HSPCs.

Measures and Outcomes

HSPCs were defined by expression of CD34 with/without CD45-diminished (dim) criterion and CD133 coexpression. Total CD34⁺, CD34⁺CD45^{dim}, and CD34⁺CD133⁺ HSPCs were quantified in fresh peripheral blood as previously described (10) and reported as relative (/10⁶ blood cells) or absolute (/mL of blood) count (Supplementary Fig. 1).

The primary end point of the outcome analysis was the composite of ICU admittance or in-hospital death. The secondary outcome was death at 6 months. Outcomes were ascertained by accessing the patients' electronic medical records and the local death registry.

Statistical Analysis

Continuous data are presented as mean (SD) and categorical variables as percentages. Comparisons between two groups were performed using the Student *t* test for continuous variables or χ^2 for categorical variables. Linear correlations were analyzed with the Pearson *r* coefficient. Outcome analysis was performed using logistic regression.

We used three approaches to compare COVID-19 patients with control subjects: 1) retained the entire population and adjusted the differences with multiple linear regression; 2) manually matched 100 patients for age, sex, and metabolic status (obesity and diabetes), further adjusting for residual confounders, as above; or 3) performed a 1:1 propensity score matching with the nearest neighbor method without replacement and 0.5 SD caliber. Missing variables were handled with multiple imputation by chained equation using the decision tree regressor method and the most frequent value as the starting point. The between-group balance was

good in the absence of significant differences at $P < 0.05$ or absolute standardized mean difference < 0.10 .

To evaluate whether HSPCs mediated the association between hyperglycemia and adverse outcome, we used the SPSS macro PROCESS (model 4) with 95% CI from 5,000 bootstrap replicates.

RESULTS

Patients and Control Subjects

We included 100 patients with COVID-19 initially hospitalized in a nonintensive care setting (Table 1). They were on average 67.8 years old, 59% were men, and 75% had at least one comorbid condition. Despite only 18% of patients had preexisting diabetes, 45% had admission hyperglycemia defined as a first fasting plasma glucose (FPG) ≥ 126 mg/dL (7 mmol/L). Of those without a history of diabetes but with admission hyperglycemia, only 17% had HbA_{1c} $\geq 6.5\%$ (48 mmol/mol).

Profoundly Reduced HSPCs in Patients With COVID-19

COVID-19 patients were compared with 595 control subjects (Supplementary Table 1). After adjusting for confounders (age, sex, smoking, hypertension, cardiovascular disease, CKD, and medications), levels of all HSPC phenotypes were significantly ~ 50 – 60% lower in COVID-19 patients compared with control subjects. Results were similar when comparing COVID-19 patients with 100 manually matched control subjects (Fig. 1A) and comparing 87 COVID-19 patients with 87 control subjects matched using propensity score matching (Fig. 1B). A profound and significant (always $P < 0.001$) reduction of circulating HSPCs was found based on expression of CD34 with/without the CD45-diminished criterion and CD133 coexpression and based on absolute or relative cell count. For further analyses, we focused on CD34⁺ cells as the most reliable HSPC phenotype (10).

HSPCs and Features of COVID-19 Patients

Levels of CD34⁺ HSPCs inversely correlated with age ($r = -0.23$; $P = 0.02$), peak C-creative protein ($r = -0.21$; $P = 0.035$), and admission FPG ($r = -0.21$; $P = 0.036$), but not with diabetes history or HbA_{1c}. Patients with admission hyperglycemia had significantly lower HSPCs using any antigenic definition and cell count (Fig. 1C and Supplementary Fig. 2). Among other hematological parameters, CD34⁺ HSPCs were inversely correlated with white blood cell count ($r = -0.23$; $P = 0.018$) and with the neutrophil-to-lymphocyte ratio (N/L; $r = -0.44$; $P < 0.001$), a marker of myeloid-biased hematopoiesis (Fig. 2A). Age and FPG were the nonhematologic features most consistently correlated with absolute and relative levels of all HSPC phenotypes (Fig. 2B).

HSPCs and COVID-19 Outcomes

Most patients (87%) had pneumonia, and the standard in-hospital treatment included glucocorticoids and low-molecular-weight heparin. FPG and HSPCs measured upon

Table 1—Clinical characteristics of COVID-19 patients

Variable	All N = 100	Good outcome n = 72	Poor outcome n = 28	P
Demographics and anthropometrics				
Age, years	67.8 (17.7)	66.9 (18.6)	70.3 (15.3)	0.393
Male sex (%)	59.0	59.7	57.1	0.816
Comorbidities				
Diabetes (%)	18.0	13.9	28.6	0.088
Hypertension (%)	54.0	50.0	64.3	0.202
Current smoking (%)	8.0	9.7	3.6	0.418
Obesity (%)	18.0	15.3	25.0	0.260
CHD (%)	13.0	6.9	28.6	0.004
Atrial fibrillation (%)	12.0	12.5	10.7	0.807
CKD (%)	13.0	5.6	32.1	<0.001
Chronic obstructive pulmonary disease (%)	6.0	6.9	3.6	0.528
Stroke (%)	8.0	6.9	10.7	0.537
COVID pneumonia (%)	87.0	83.3	96.4	0.082
Gastrointestinal symptoms (%)	11.0	8.3	17.9	0.175
COVID-19 therapies				
Low-flow oxygen (%)	46.0	59.7	10.7	<0.001
High-flow oxygen (%)	43.0	25.0	89.3	<0.001
Noninvasive ventilation (%)	28.0	13.9	64.3	<0.001
Invasive ventilation (%)	21.0	0.0	44.0	<0.001
Remdesivir (%)	43.0	41.7	46.4	0.670
Glucocorticoids (%)	87.0	84.7	92.9	0.282
Tocilizumab (%)	2.0	1.4	3.6	0.489
Low-molecular-weight heparin (%)	95.0	93.1	100.0	0.156
Convalescent plasma (%)	35.0	36.1	32.1	0.712
Medication before hospitalization				
ACE inhibitors (%)	24.0	26.4	17.9	0.375
Angiotensin receptor blockers (%)	16.0	13.9	21.4	0.361
Calcium channel blockers (%)	19.0	18.1	21.4	0.703
Antiplatelet agents (%)	23.0	18.1	35.7	0.060
Statins (%)	27.0	23.6	35.7	0.225
Warfarin (%)	7.0	6.9	7.1	0.972
New anticoagulants (%)	8.0	5.6	3.6	0.686
Insulin (%)	8.0	1.4	25.0	<0.001
Other diabetes medications (%)	10.0	11.1	10.7	0.955
Laboratory				
FPG, mmol/mol	7.7 (3.7)	7.0 (2.9)	9.7 (4.5)	<0.001
FPG, mg/dL	139.1 (66.1)	125.8 (52.7)	175.4 (81.1)	
HbA _{1c} , mmol/mol	44.4 (11.6)	43.0 (9.3)	47.6 (16.0)	0.086
Serum creatinine, μ mol/L	104.8 (122.4)	90.8 (114.4)	141.4 (136.1)	0.063
eGFR, mL/min/1.73 m ²	76.6 (29.1)	82.7 (24.9)	60.9 (33.5)	0.001
C-reactive protein, mg/L	93.8 (7.7)	73.8 (60.7)	146.0 (88.9)	<0.001
AST, units/L	40.0 (24.6)	38.7 (24.0)	44.3 (26.3)	0.307
ALT, units/L	41.1 (51.3)	35.5 (32.5)	45.0 (63.3)	0.329
Lactate dehydrogenase, units/L	356 (448.7)	334.6 (508.7)	424.2 (218.2)	0.371
Outcomes				
Primary outcome (%)	28.0	0.0	100	—
Death (%)	13.0	0.0	46.4	—
ICU admittance (%)	21.0	0.0	75.0	—
Hospitalization, days	15.6 (12.8)	12.3 (8.3)	24.7 (17.3)	<0.001

Patients were divided according to the occurrence of the primary outcome during hospitalization. Data are expressed as mean (SD) or as indicated. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

hospitalization did not differ between patients who had started glucocorticoids at home (29%) compared with those who were not on glucocorticoids upon admission (FPG 129.4 ± 39.8 vs. 143.8 ± 73.3 mg/dL; $P = 0.317$;

CD34⁺ HSPCs 138.2 ± 104.7 vs. $167.8 \pm 113.0/10^6$; $P = 0.229$).

During the hospital stay (mean duration 15.7 days), 28 patients were admitted to the ICU or died. Patients with

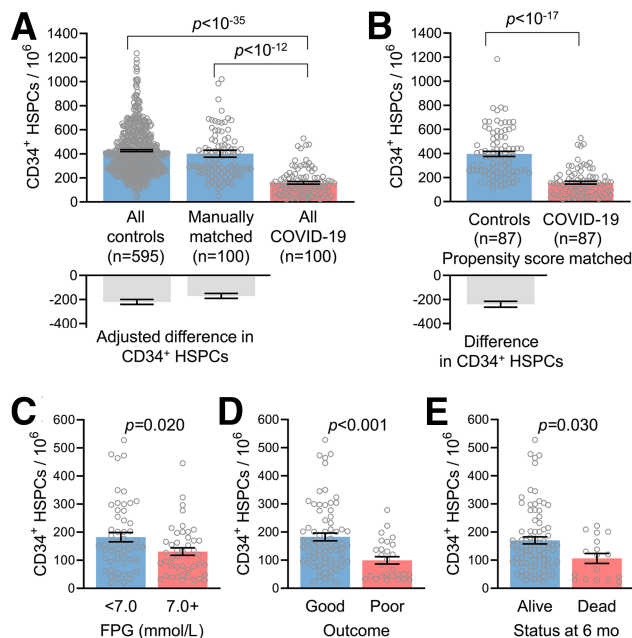


Figure 1—Levels of circulating HSPCs in COVID-19 and clinical outcomes. **A:** Comparison of the levels of CD34⁺ circulating HSPCs in patients with COVID-19 and in control individuals. All control subjects are shown along with a subset of control subjects manually matched for age, sex, and metabolic status (see text). The bottom part of panel **A** shows the adjusted differences in HSPC levels between COVID-19 and the two groups of control individuals (for adjusted covariates see text and tables). **B:** Comparison of the levels of circulating HSPCs in propensity score-matched cohorts of patients with COVID-19 and control subjects. The bottom part of panel **B** shows the difference in HSPC levels between COVID-19 patients and matched control individuals (no adjustment). **C:** Levels of CD34⁺ HSPCs in COVID-19 patients, with and without hyperglycemia defined using the standard 7.0 mmol/L threshold for FPG. **D:** Levels of CD34⁺ HSPCs in COVID-19 patients experiencing poor (admittance to the ICU or death) or good outcome during hospitalization. **E:** Levels of CD34⁺ HSPCs in COVID-19 patients according to their status (live/dead) at 6 months after hospitalization. Column heights represent the mean and bars represent the SE. Superimposed data points are referred to individual patients. *P* values are shown for the between-group comparisons.

such a poor outcome (Table 1) had a higher prevalence of preexisting coronary heart disease (CHD) and CKD (reflected by lower admission estimated glomerular filtration rate [eGFR]). They also exhibited higher admission FPG (175.4 ± 81.1 vs. 125.8 ± 52.7 mg/dL; $P < 0.001$). HSPC levels were significantly and further reduced in patients with poor compared with those with good COVID-19 outcome (CD34⁺ 99.1 ± 13.1 vs. 182.6 ± 115.6 cells/ 10^6 ; $P < 0.001$) (Fig. 1D and Supplementary Fig. 3). The hospital stay was longer for patients with poor outcome, who showed higher peak C-reactive protein and more often required high-flow oxygen.

In logistic multivariable analyses (Supplementary Table 2), CD34⁺ HSPC levels remained significantly associated with adverse outcome in model 1 (adjusted for age and sex), model 2 (further adjusted for confounders at baseline; i.e., CHD, eGFR and FPG), and model 3 (further adjusted for

peak C-reactive protein, N/L, and high-flow oxygen). In the fully adjusted model, a 1 SD decrease in CD34⁺ HSPCs had an odds ratio for poor outcome of 3.1 (95% CI 1.08–8.92; $P = 0.036$). Results were similar when HSPCs were defined as CD34⁺CD45^{dim} cells in place of total CD34⁺ cells (odds ratio 3.1; 95% CI 1.10–8.77; $P = 0.033$).

At 6 months after hospitalization, 17 patients had died. Relative counts of CD34⁺, CD34⁺CD45^{dim}, or CD34⁺CD133⁺ HSPCs were significantly lower in those who died than in those who were alive at 6 months (Fig. 1E and Supplementary Fig. 4).

Hyperglycemia, HSPCs, and COVID-19 Outcomes

Patients with admission hyperglycemia had a 2.58-times higher rate of adverse outcome compared with those with FPG <7.0 mmol/L (42.2% vs. 16.4%; $P = 0.004$). Admission FPG was a predictor of poor COVID-19 outcome after adjusting for age, sex, and baseline covariates (CHD and eGFR). However, when the CD34⁺ HSPC level was entered in the model, the predictive value of FPG was diminished and no longer significant (Supplementary Table 3). According to a mediation analysis, the indirect effect of FPG on COVID-19 outcome mediated by CD34⁺ HSPCs was 27.9% of the total effect (bootstrapped 95% CI 6.3–72.1; $P = 0.01$) (Fig. 3).

Data and Resource Availability

Original data associated with this article are available from the corresponding author upon reasonable request.

DISCUSSION

Building from our previous studies on diabetes, we show that reduced HSPC levels are significant mediators of the negative prognostic effect of hyperglycemia on COVID-19 outcome.

Recently, HSPCs from COVID-19 patients have been found stuck in the G1 phase and prone to apoptosis (14). Furthermore, binding of the spike protein to ACE2 impaired HSPC survival and fostered myeloid differentiation (15). We now show that COVID-19 leads to a dramatic pauperization of circulating HSPCs, which is strongly and independently associated with an adverse outcome.

Diabetes is a predictor of death from COVID-19 (2), but hyperglycemia is often observed even in individuals without diabetes with severe COVID-19 (6). Hyperglycemia exerts negative effects on innate immunity, favoring severe infections and increasing mortality from infectious diseases (16). Mechanistically, high glucose modifies the activation of monocyte-macrophages, facilitating SARS-CoV-2 replication, suppressing T-cell responses, and exacerbating lung damage in COVID-19 (17). Hyperglycemia also causes exaggerated myelopoiesis (13) that typically elevates N/L, a feature of severe COVID-19 (16). Such excess myelopoiesis hampers mobilization of HSPCs from the BM to peripheral blood (9), reducing circulating HSPCs (18). Indeed, we found that hyperglycemia was a

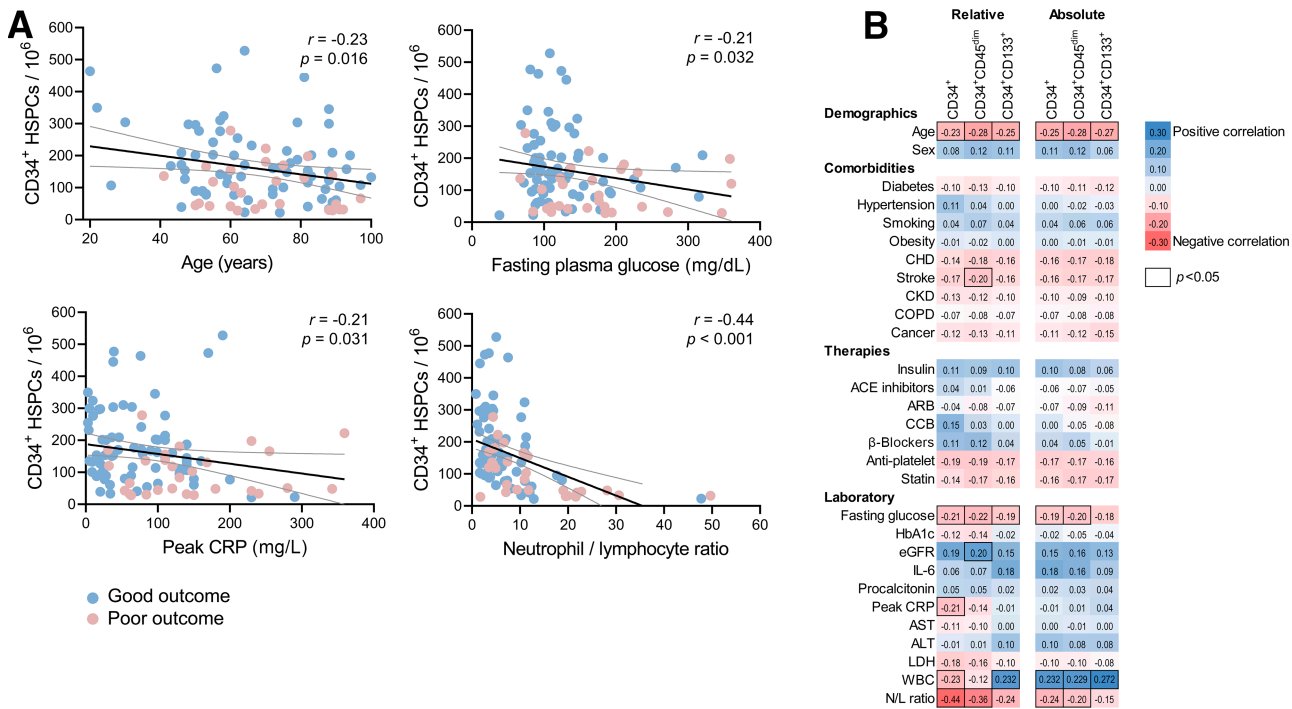


Figure 2—Clinical correlates of HSPC levels in COVID-19. **A:** The strongest correlations for CD34⁺ HSPCs are shown as scatter plots. Patients are divided according to good or poor outcome (admittance to the ICU or death) using the color code described in the legend. Pearson *r* coefficients and the respective *P* values are shown. **B:** The heat map shows values of the Pearson *r* coefficients for each antigenic definition of HSPCs and their relative and absolute cell count in peripheral blood. The code color allows easy interpretation: intense blue represents strong direct correlation, intense red represents strong inverse correlation, and white represents no correlation. Cell boxing indicates statistical significance at *P* < 0.05. ARB, angiotensin receptor blocker; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; IL, interleukin; LDH, lactate dehydrogenase; WBC, white blood count.

significant determinant of HSPC levels among COVID-19 patients. Despite the correlation of HSPCs with glucose levels being relatively weak, it was similar to that with age, which is well established. On the other side, the lack of correlation with HbA_{1c} is consistent with the transient nature of COVID-19–associated hyperglycemia (19). The stronger association of HSPCs with inflammatory markers than with organ-damage markers supports that hyperinflammation was responsible for reducing HSPCs. Remarkably, entering HSPCs in the outcome model nullified the prognostic value of N/L, suggesting that the link between N/L and severe COVID-19 may be ascribed to reduced HSPCs.

The strong link between low HSPCs and adverse outcomes relies on their multifaceted role in optimizing hematopoiesis, modulating immune-inflammation, as well as maintaining vascular homeostasis (8). It is therefore not surprising that HSPC derangement contributes to COVID-19 worsening, which has prominent immune-inflammatory and vascular manifestations (20). Our new data are consistent with the interpretation that HSPC reduction mediates part of the effect of hyperglycemia on COVID-19 outcome. The statistical mediation analysis formally supports such a concept, providing a quantitative estimate of the direct and indirect effects.

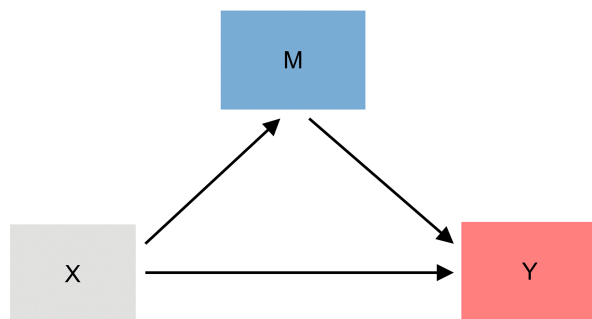
Although glucocorticoid therapy may confound the association between hyperglycemia and COVID-19 outcomes

(21), in-hospital use of glucocorticoids was unlikely to affect our results because we measured FPG and HSPCs upon admission. Additionally, we observed no difference in FPG and HSPC levels between patients who initiated glucocorticoids at home or at the time of hospitalization, ruling out a meaningful confounding.

As a therapeutic implication of our findings, we speculate that the observed benefit of dipeptidyl peptidase 4 inhibitors against COVID-19 progression (22) may rely on their well-known stimulatory effect on circulating progenitors (23).

We finally report that low HSPCs at time of hospitalization for COVID-19 were associated with mortality at 6 months. While the study was underpowered to show an independent effect, we anticipate that reduced HSPCs may play a role in long-COVID. The immune checkpoint PD-L1 appears to be deficient in HSPCs from patients with diabetes (24), and PD-1 overexpression has been related to long-COVID (25). Future studies should therefore evaluate whether the PD-1/PD-L1 axis links HSPC defects to the development of long-COVID.

We acknowledge that we only measured HSPC levels but not their function, including differentiation capacity and skewness. While reduced HSPC levels can reflect alterations in survival and traffic, functional assays would enable a better understanding of HSPCs in COVID-19. In addition, while we quantified HSPC only upon hospitalization, a

A Model 4 of mediation in PROCESS

X: admission FPG
Y: adverse COVID-19 outcome
M: levels of HSPCs (mediator)

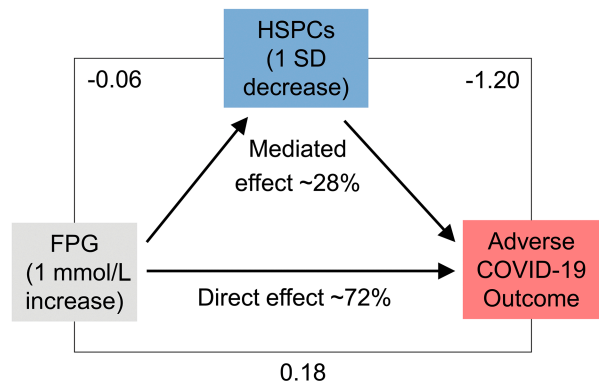
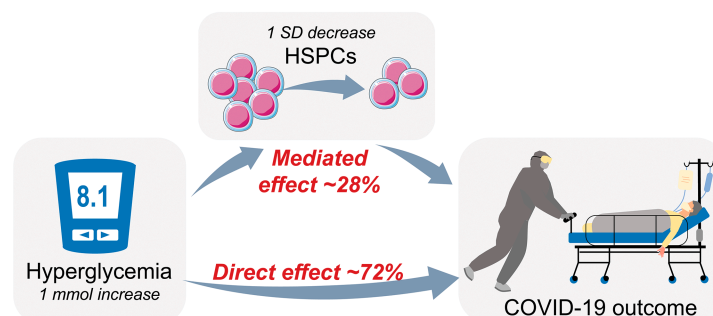
B Result of the analysis**C** Graphical representation

Figure 3—Results of the mediation analysis. Panel A shows the standard model 4 for mediation analysis using the PROCESS macro, which was implemented in SPSS: the effect of X onto Y is analyzed through the mediating effect of M. Panel B shows results of the analysis, where X is 1 mmol/L increase in admission FPG, Y is adverse COVID-19 outcome (admittance to the ICU or death), and M is 1 SD decrease in circulating CD34⁺ HSPCs. Coefficients are shown for each connection in the model along with calculation of the percentage mediated effect over the total effect. C: Graphical representation of the mediation effect.

time-course analysis may reveal more insight along the disease development and progression. Finally, although backed by prior mechanistic studies, a causal relationship cannot be biologically proven with mediation analysis and will require further investigation in vitro and in vivo.

In conclusion, we describe a new pathway whereby metabolic dysregulation reflected by admission hyperglycemia is associated with low circulating HSPCs among COVID-19 patients. Along with other culprits, such a shortage of circulating HSPCs may contribute to the prognostic effect of hyperglycemia on COVID-19 outcome.

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