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Metabolic Regulation of SARS-CoV-2 Infection

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Abstract

Viruses are efficient metabolic engineers that actively rewire host metabolic pathways to support their lifecycle, presenting attractive metabolic targets for intervention. Here we chart the metabolic response of lung epithelial cells to SARS-CoV-2 infection in primary cultures and COVID-19 patient samples. Bulk and single-cell analyses show that viral replication induces endoplasmic stress and lipid accumulation. Protein expression screen suggests a role for viral proteins in mediating this metabolic response even in the absence of replication. Metabolism-focused drug screen showed that fenofibrate reversed lipid accumulation and blocked SARS-CoV-2 replication. Analysis of 3,233 Israeli patients hospitalized due to COVID-19 supported *in vitro* findings. Patients taking fibrates showed significantly lower markers of immunoinflammation and faster recovery. Additional corroboration was received by comparative epidemiological analysis from cohorts in Europe and the United States. A subsequent prospective interventional open-label study was carried out in 15 patients hospitalized with severe COVID-19. The patients were treated with 145 mg/day of nanocrystallized fenofibrate (TriCor[®]) in addition to standard-of-care. Patients receiving fenofibrate demonstrated a rapid reduction in inflammation and a significantly faster recovery compared to control patients admitted during the same period and treated with the standard-of-care. Taken together, our data show that elevated lipid metabolism underlies critical aspects of COVID-19 pathogenesis, suggesting that pharmacological modulation of lipid metabolism should be strongly considered for the treatment of coronavirus infection.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-strand RNA virus of the *sarbecovirus* subgenus that is related to SARS. SARS-CoV-2 infection leads to the development of coronavirus disease (COVID-19) an inflammatory lung condition resulting in acute respiratory distress and organ failure ¹. SARS-CoV-2 has infected over 165 million individuals worldwide causing nearly 3.5 million deaths since its emergence. Like other viruses, SARS-CoV-2 must rely on the host machinery to propagate, rewiring cellular metabolism to generate macromolecules needed for virion replication, assembly, and egress.

Recent work suggests that COVID-19 progression is dependent on metabolic mechanisms. Elevated blood glucose, obesity, and hyperlipidemia were found to be risk factors for SARS-CoV-2 induced acute respiratory distress, independently from diabetes ^{2,3}. In fact, metabolic risk factors are associated with a more than 3-fold increase in COVID-19 severity risk, while inflammatory lung diseases, such as chronic obstructive pulmonary disease (COPD), and asthma are associated with less than a 1.5-fold increase in risk ^{4,5}.

Metabolomics of COVID-19 patients sera showed alterations in circulating amino acids, glucose, and lipids, correlating with changes in inflammation and renal function ⁶. Work on SARS-CoV-2 infected monocytes showed changes to glycolysis ^{7,8}, while proteomics of infected kidney and colon cells showed that SARS-CoV-2 proteins interact with mitochondria, glycolysis, and lipid metabolism ^{9,10}. Other transcriptional analyses showed SARS-CoV-2 induced significant changes in similar metabolic pathways ¹¹⁻¹⁴. These results support earlier observations that the closely related SARS and MERS infections are reliant on altered lipid metabolism ¹⁵⁻¹⁷. However, recent clinical studies show conflicting results regarding the role of triglycerides in COVID-19 progression ¹⁸⁻²⁰. While these data suggest that lipid metabolic interventions should be studied in the context of COVID-19, the current reliance on animal experiments limit such efforts due to critical differences in lipid metabolism between humans and rodents ^{21,22}.

Alarming, evidence from previous coronavirus outbreaks suggests that the metabolic rewiring induced by infection has detrimental and long-term effects post-recovery. MERS infection was associated with long-term immune dysregulation and enhanced susceptibility to metabolic diseases ²³, while SARS infection was associated with long-term alterations in lipid metabolism, hyperlipidemia, and hyperglycemia even 12 years post-recovery ^{24,25}. Recent work points to similar post-sequalae effects of COVID-19 ²⁶⁻²⁸.

In this work, we charted the metabolic response of primary lung bronchiole and small airway epithelial cells to SARS-CoV-2 infection validating our results with multiple COVID-19 patient samples. We used bulk and single-cell analyses to demonstrate induction of endoplasmic stress in virus replicating cells and an associated increase in lipid accumulation, driven in part by inhibition of lipid catabolism. A comprehensive screen demonstrated a role for several viral proteins in mediating the metabolic response even in the absence of replication. Screening pharmaceutical modulators of each metabolic pathway showed that fenofibrate, a PPAR α -agonist that induces lipid catabolism, reversed metabolic changes and blocked SARS-CoV-2 replication *in vitro*. An observational study in 3,233 Israeli patients hospitalized due to COVID-19 was consistent with *in vitro* observations, showing lower inflammation and faster recovery in patients taking fibrates, while those taking thiazolidinediones that lead to increased lipid accumulation in certain tissues ²⁹⁻³¹ exhibited

sustained inflammation. Additional validation was received by comparative epidemiological analysis from cohorts in Italy and the Veteran's Health Administration in the United States.

Moreover, we performed a prospective interventional open-label study in which 15 patients hospitalized with severe COVID-19 were given 145 mg/day of nanocrystallized fenofibrate (TriCor®) added to the standard of care. These patients demonstrated a rapid reduction in inflammation and a significantly faster recovery compared to control patients admitted during the same period and treated with the same standard-of-care. Our work demonstrates that pharmacological modulations of lipid metabolism may be an effective treatment for coronavirus infection.

Results

The metabolic fingerprint of SARS-CoV-2 infection

SARS-CoV-2 and the innate immune response primarily infect epithelial cells in the nasal cavity, the bronchia, and the small airways ³². Thus, to elucidate the metabolic effects of SARS-CoV-2 we infected primary human bronchial epithelial cells with the virus (**methods**). Infected cells became noticeably smaller, showing vacuolization. RNA-Seq analysis of infected primary cells identified 535 differentially expressed genes (FDR<0.05). Enrichment analysis identified the regulation of viral transcription (FDR<3x10⁻²), immune processes (FDR<9x10⁻⁴), and cellular response to stress (FDR<5x10⁻¹¹). An analysis was also carried out on RNA-Seq data obtained from primary small airway epithelial cells infected with SARS-CoV-2 ³³, lung biopsies obtained from COVID-19 autopsies, and lung epithelial cells obtained from bronchoalveolar lavage of COVID-19 patients ³⁴. All four sample groups showed similar enrichment patterns (**Fig. 1A**).

The four sample groups showed significant enrichment in metabolic processes (FDR<4x10⁻⁴), particularly lipid (FDR<2x10⁻⁵) and carbohydrate metabolic processes (FDR<0.05; **Fig. 1A**), with 58±3% of the differentially expressed genes being metabolism-related, and 15±2% of the genes associated with lipid metabolism (**Fig. 1B**; **Supp. Fig. S1**). Analysis of aggregated metabolic categories ^{35,36} showed similar enrichment of lipid metabolism (FDR<3x10⁻¹⁷), mitochondrial function (FDR<7x10⁻⁴), and glucose metabolism (FDR<2x10⁻²) in both primary cultures and patient samples (**Fig. 1C**; **Supp. Fig. S1**).

Mapping SARS-CoV-2 induced transcriptional changes on the metabolic landscape of lung epithelial cells showed induction of a glycolytic phenotype (*i.e. Warburg-like effect*) suggested to provide nucleotides for viral replication ³⁷. Lipogenesis was also upregulated, supporting palmitoylation of viral proteins as well as lipid components of the viral replication complex ¹⁷ (**Fig. 1D**). However, in contrast to other viruses ³⁵, SARS-CoV-2 infection appears to downregulate lipid catabolism (**Fig. 1D**; **Supp. Fig. S1**).

Metabolic effects of SARS-CoV-2 replication

Metabolic changes are often linked to dysregulation of endoplasmic reticulum (ER) processes as part of the cellular response to stress. Indeed, SARS-CoV-2 infection of primary cells induced the dsRNA-activated protein kinase R (PKR/PERK) and IRE1 pathways leading to differential expression of ATF4 and splicing of XBP1 (**Fig. 2A**). ATF6 pathway of ER stress was seemingly unaffected by infection. Induction of PKR/PERK and IRE1 pathways were previously shown to lead to a Warburg-like shift to anaerobic glycolysis ³⁸, increased lipogenesis ^{39,40}, and decreased lipid catabolism ⁴¹.

Mapping differentially expressed genes on the central carbon metabolism pathway showed SARS-CoV-2 induction of key glycolysis genes (**Fig. 2B**) including rate-limiting enzymes such as hexokinase 2 (HK2) and pyruvate kinase isozyme (PKM). Metabolic analysis of SARS-CoV-2 infected cells supports these findings, showing a 50% increase (n=6, p<0.001) in lactate production (**Fig. 2C**) and a shift in the lactate over glucose ratio (glycolytic index) from 1 to 1.7 indicating a Warburg-like effect (**Fig. 2D**). Microscopic analysis confirmed a marked 85% increase in intracellular glucose in infected cells (**Fig. 2E**; *methods*). Interestingly, while core genes of the citric acid cycle did not change significantly, ATP citrate lyase (ACLY) was up-regulated suggesting a shift toward fatty acid synthesis.

Mapping of differentially expressed genes on lipid metabolism (**Fig. 2F**) showed induction of HMG-CoA synthase (HMGCS) and squalene monooxygenase (SQLE) rate-limiting steps in cholesterol synthesis⁴². Surprisingly, we found only a few significantly up-regulated lipogenesis genes, but rather significant down-regulation of lipid catabolism genes CPT1A and ACSL1 (n=3, FDR<0.01) (**Fig. 2F**). Fluorescence microscopy confirmed an increase of neutral lipids (n=3, p<0.05) and significant accumulation of phospholipids (n=3, p<0.001) in infected cells (**Fig. 2G**).

These *in vitro* data suggest that metabolic changes may be induced by SARS-CoV-2 infection separately from the immunoinflammatory disease. To validate these findings in clinically relevant data we analyzed single-cell transcriptional profiles of 2,629 lung epithelial cells obtained from 6 symptomatic COVID-19 patients (**Fig. 2H-I**; *methods*)³⁴. Our analysis identified 6 different transcriptional signatures including basal, secretory, and ciliated lung cells as well as a cluster of virus-replicating cells (**Fig. 2I**; **Supp. Fig. S2**). Gene enrichment analysis comparing virus replicating cells to uninfected epithelial cells in the same patients showed a response to endoplasmic reticulum stress (FDR<1×10⁻⁶), metabolic processes (FDR<9×10⁻⁴), and lipid metabolism (FDR<3×10⁻³; **Fig. 2J**). Our single-cell analysis showed no significant transcriptional differences in glycolysis or mitochondrial metabolism suggesting these pathways are not uniquely induced by viral replication.

SARS-CoV-2 proteins cause direct modulation of metabolic pathways

To explore the role of viral proteins in the host metabolic response to SARS-CoV-2 we expressed a large protein panel⁹ in primary bronchial epithelial cells. Gene expression analysis showed a strong up-regulation of CHOP and XBP1 splicing induced by expression of ORF9c, M, N, ORF3a, NSP7, ORF8, NSP5, and NSP12 (n=6, p<0.05; **Fig. 3A**; **Supp. Fig. S3**), supporting activation of PKR/PERK and IRE1 pathways (**Fig. 2A**). Microscopic analysis showed significant accumulation of phospholipids induced by expression of the same viral proteins (n=6, p<0.01; **Fig. 3B-C**) supporting a link between SARS-CoV-2 induced ER stress and lipid accumulation.

Microscopic analysis of intracellular glucose retention showed the involvement of a smaller subset of the same viral proteins including N, ORF3a, NSP7, ORF8, NSP5, and NSP12 in glucose accumulation (**Fig. 3D-E**). In addition, direct measurement of glucose uptake and lactate production showed a marked increase in lactate production in cells expressing the same viral protein subset (n=6, p<0.05; **Fig. 3F**) confirming a viral protein-driven shift to glycolysis (**Fig. 3G**). Independent measurement of extracellular acidification rate (ECAR), a surrogate measurement for glycolysis⁴³, confirmed the activity of the same viral proteins (**Fig. 3H**).

Finally, mitochondrial stress test analysis (*methods*) showed a marked disruption in oxidative phosphorylation, induced by expression of N, ORF3a, and NSP7 (n=6, p<0.05; **Fig. 3G-H**), which appear to play a role in the measured changes of all three metabolic pathways.

Pharmaceutical modulation of SARS-CoV-2-induced metabolic pathways

The metabolic pathways induced by SARS-CoV-2 infection can be pharmaceutically modulated at multiple points (**Fig. 4A-B**). Pharmacological modulation of host metabolism was shown to block replication of other viruses^{35,44-47}. SGLT inhibitors can block glucose absorption, while metformin can modulate mitochondrial activity potentially reversing a Warburg-like effect^{48,49}. Cholesterol synthesis can be blocked by statins, while lipid oxidation can be induced by fibrates. Telmisartan could act by decreasing ER stress through IRE1 inhibition⁵⁰. Thiazolidinediones are PPAR γ agonists that modulate lipid content in certain tissues and are thought to reduce lung inflammation^{29,51}.

Exposing SARS-CoV-2 infected primary cells to usual therapeutic concentrations (C_{max}) of these drugs produced mixed effects (**Fig. 4C-F**). Rosiglitazone, empagliflozin, and metformin showed no effect at the concentrations studied. Cloperastine, a recently identified SGLT1 inhibitor⁵², reduced viral load by 3-fold (n=3, p<0.01) without affecting cell viability but did not result in a reduction of lipid content or change in the glycolytic index. However, the PPAR α agonist fenofibrate blocked phospholipid accumulation (n=3, p<0.001) and the increase in glycolysis (**Fig. 4C-F**). A 5-day treatment with the usual therapeutic concentration of fenofibrate reduced viral load by 2-logs (n=3, p<0.001) without affecting cell viability (**Fig. 4E-F; Supp. Fig. S4**). Other PPAR α agonists, including bezafibrate, WY14643, and conjugated linoleic acid (CLA) showed a similar effect (**Supp. Fig. S4**), indicating a class effect.

To assess the clinical relevance of these findings we gathered a total of 3,233 cases of confirmed COVID-19 patients admitted to Hadassah and Ichilov Medical Centers between March 2020 to February 2021. 1,156 of these patients (35.8%) were registered with in-hospital use of different metabolic regulators (**Table S1**). Participants treated with metabolic regulators were older and had a higher prevalence of chronic medical conditions, including hypertension, diabetes mellitus, dyslipidemia, obesity, coronary heart disease, cerebrovascular diseases, and chronic kidney diseases than those without these treatments (**Table S1**) and thus were expected to be over-represented in ICU admissions and COVID-19 related deaths. Comparison between 2,806 COVID-19 patients above the age of 30 and 532,493 recent unique hospital patient records show a significant over-representation of patients taking thiazolidinediones, metformin, SGLT2 inhibitors, statins, or telmisartan (IRE1 α inhibitor) across all COVID-19 severity indicators (**Fig. 4G; Table S2**). However, patients taking fibrates (n=21) were significantly underrepresented in hospital admissions (p=0.02) and not over-represented in other severity indicators (**Fig. 4G; Table S2**). The same trends are conserved regardless of the comparison period (**Table S2**).

Metabolic regulators affect COVID-19 severity and progression

Based on our results we suggest that severe COVID-19 is characterized by early lipotoxicity-induced inflammation, marked by elevated C-reactive protein (CRP)⁵³, followed by distinct changes in neutrophils and lymphocytes marking the onset of the immunoinflammatory response^{54,55} (**Fig. 5A**). To further investigate the effect of metabolic regulators on COVID-

19 progression, we tracked a sub-cohort of high-risk COVID-19 patients above the age of 45 that were hospitalized for 3 or more days (n = 1,438; **Table S3, Supp. Fig. S7, methods**). In general, fibrates use was associated with significantly shorter hospitalization duration (p=0.03; **Fig. 5B, Table S3**). Patients taking other metabolic regulators exhibited similar or worse clinical outcomes compared to control (**Tables S3-S4**).

To track disease progression, we followed changes in CRP during the first 21-days of hospitalization. Data were fitted using locally weighted scatterplot smoothing (Lowess) comparing each drug group to all other high-risk patients that didn't take metabolic regulators (n=648; **Fig. 5C-D, Supp. Fig. S7, methods**). Both groups had similar clinical characteristics upon admission, while comorbidities were higher in patients taking metabolic regulators (**Table S3**). High CRP levels marking systemic inflammation gradually declined after admission in the control group, reaching a plateau 14-days post-admission (**Fig. 5A,C**). No significant differences were noted for patients taking statins, metformin, or SGLT-2 inhibitors compared with controls. CRP levels in patients taking thiazolidinediones, which is thought to increase lipid synthesis in certain tissues^{29,30}, failed to decline. IRE1 α inhibitor users exhibited slightly lower CRP levels than control patients throughout their hospitalization. Importantly, patients taking fibrates showed a significant decline in inflammation within 5-days post-admission (**Fig. 5C**). The neutrophil-to-lymphocyte ratio (NLR) marking immunoinflammatory stress, rose in the control group to peak around day 10 post-admission (**Fig. 5A,D; Supp. Fig. S5**). Treatment with SGLT2 inhibitors, metformin, or thiazolidinediones was associated with relatively similar responses compared to controls, albeit with higher maxima for the thiazolidinedione group. Patients taking IRE1 α inhibitors exhibited significantly elevated NLR post day 10, due to decreased lymphocyte counts during recovery (**Fig. 5D; Supp. Fig. S5**). However, patients taking fibrates showed consistently low NLR throughout their hospitalization, suggesting minimal immunoinflammatory stress. Analysis of 28-day all-cause mortality showed that no deaths were reported for the small group of patients taking fibrates (n=16, **Fig. 5E**). Mortality did not appear to differ for statins, IRE1 α inhibitors, or metformin, but was significantly higher in patients taking SGLT2 inhibitors (aHR=2.6; 95% CI, 1.1 to 6.2; p=0.034) or thiazolidinedione (aHR=3.6; 95% CI, 1.0 to 12.4; p=0.043; **Fig. 5E, Table S4, methods**).

Analysis of an additional observational cohort of 2,123 patients examined in the Outpatient Lipid Clinics of the University of Bologna and the Niguarda Hospital in Milan during the last 12 months and on adequately dosed statins, fenofibrate, or both for at least three months (**Table S5A**) indicates that fenofibrate users regardless of additional treatment had significantly less COVID-19 history and severe illness (**Table S5B-C**). Additionally, in the sub-cohort of patients reporting contact with affected people, analysis indicates that statin users are significantly more likely to develop COVID-19 (p=0.02), while fenofibrate users, regardless of additional treatment are less likely to develop COVID-19 (**Table S5D**). Parallel analysis of an observational cohort of 920,922 veterans with hypertension in the US Veteran's Health Administration, comparing fenofibrate to matched non-users, statins users, or thiazolidinediones users (VHA; **Table S6A**), showed that fenofibrate users have shorter hospitalization duration (**Table S6B**) and fairly better outcomes across several severity indicators (**Table S6C**).

Nanocrystallized fenofibrate (TriCor®) treatment reduced inflammation and sped recovery in severe hospitalized COVID-19 patients treated with standard-of-care.

To further assess the clinical relevance of our findings, we performed an interventional single-arm clinical study including severe hospitalized COVID-19 patients, who exhibited respiratory deterioration and severe pneumonia (*methods*)⁵⁶. Fifteen patients (**Table S7**) were treated with 145 mg/day of nanocrystallized fenofibrate (TriCor[®]) added to standard-of-care for 10 days or until discharge (**Fig. 6A**). Nanocrystallized fenofibrate was selected due to its improved bioavailability and short $T_{\max}$ ^{57,58} enabling rapid intervention (**Fig. 6B**).

Enrolled participants exhibited a higher prevalence of chronic medical conditions compared to other hospitalized patients admitted with severe COVID-19 during the same period and treated under the same standard-of-care, who were used as controls (**Table S7**). Despite these comorbidities, patients treated with TriCor[®] exhibited a significantly shorter hospitalization (weighted difference of 2.8 days; 95% CI, 1 to 5.7; $p < 0.001$; **Fig. 6C**), were significantly more likely to be discharged within 28 days of hospital admission (HR=3.6; 95% CI, 2.1 to 6.4; $p < 0.001$; **Fig. 6C**), and demonstrated lower rates of ICU admission and rehospitalization (**Fig. 6C, Table S7**).

Dynamic changes in serum levels of CRP and NLR, which mark the immunoinflammatory progression of the disease, also demonstrated favorable trends (**Fig. 6D-E**). Patients treated with TriCor[®] showed a rapid decline in CRP levels within 48 hours of treatment, with significantly lower CRP levels by day 3-5 post-treatment ($p < 0.001$; **Fig. 6D**). Immunoinflammatory stress, indicated by NLR remained muted throughout the treatment period, showing significantly lower stress by day 3-5 post-treatment ($p = 0.002$; **Fig. 6E**).

Patients treated with TriCor[®] also exhibited lower mortality, lower respiratory intervention rates, and significantly increased withdrawal rate from supplemental oxygen by day 7 (weighed difference of 26.1 percentage points; 95% CI, 7.0 to 45.2; $p = 0.003$; **Fig. 6F, Supp. Fig. S6, Table S7**). COVID-19 progression was investigated as a time-varying outcome using a Cox model accounting for baseline variance, which also suggests a difference in COVID-19 related risk (**Fig. 6G; methods**).

Novaplex[™] SARS-CoV-2 variant analysis showed a dominant presence of 69/70 deletion and N501Y substitution mutation correlating to the B.1.1.7 (UK) variant of the virus in the patient population (**Fig. 6H**). This relatively aggressive variant showed a similar distribution in other clinical centers in Israel during the same period (**Fig. 6I, Supp. Fig. S6**).

Discussion

Viruses are dependent on host metabolism to obtain macromolecules essential for their lifecycle. While metabolic interventions of host pathways offer promise, the current reliance on animal models and cell lines limits our ability to identify targets for intervention due to critical metabolic and genetic differences between animal models, cell lines, and patients. In this work we utilized primary human cells and clinical samples to chart SARS-CoV-2 metabolic response, to identify metabolic targets and proven therapies that could rapidly translate to effective treatment of severe COVID-19.

Glycolysis is often upregulated to supply nucleotides for virus replication^{35,44,59}, as part of a Warburg-like effect. We show that SARS-CoV-2 infection induced a Warburg-like effect in both bronchial and small airway primary cells as well as COVID-19 patient samples (**Figs. 1-2**). Interestingly, while expression of some SARS-CoV-2 proteins such as N, ORF3a, and NSP7 was sufficient to induce glycolysis (**Fig. 3**), the transcriptional response did not appear

to be specific to virus replicating cells in COVID-19 patients (**Fig. 2H-J**) and may be caused by a more general immunoinflammatory response to the infection.

Recent work in Vero and Caco-2 cell lines showed direct binding of some viral proteins to mitochondrial and glycolysis-related proteins^{9,10}, with electron microscopy studies confirming mitochondrial disruption⁶⁰, and PET/CT studies revealing increased glycolytic activity in lungs of COVID-19 patients⁶¹. These results brought several groups to assess different glucose modulators as pharmacological interventions. For example, 2-Deoxyglucose (2-DG) blocked SARS-CoV-2 replication, but at concentrations 20-fold higher than C_{max} while causing cellular damage¹⁰. Our results showed a minimal effect of the SGLT1 inhibitor cloperastine and no effect of SGLT2 inhibitor empagliflozin or metformin in blocking virus replication or affecting the patient outcome (**Figs. 4-5**). Recent observational studies support our findings^{62,63}, suggesting that while glycolysis is part of the virus lifecycle, it may not be a viable target to treat SARS-CoV-2 infection.

In contrast to glycolysis, cellular response to stress is the single most prominent transcriptional response to SARS-CoV-2 replication, dominated by the induction of PERK/PKR and IRE1 α pathways of ER stress (**Fig. 2, Supp. Fig. S2**). While induction of dsRNA-activated PERK/PKR pathway is not surprising in cells infected with RNA viruses, it is the less common induction of IRE1 α that might play a role in unique metabolic response to infection⁶⁴. IRE1 α splicing of XBP1 was previously shown to induce lipogenesis, reduce lipid catabolism, and cause mitochondrial stress in rodents^{41,65}, similar to our findings.

Our study demonstrates coordinate changes in lipid metabolism, as SARS-CoV-2 replication was associated with the upregulation of palmitoylation and cholesterol synthesis (**Fig. 1**) both critical to the virus lifecycle. SARS-CoV-2 inhibition of PPAR α -dependent lipid oxidation is surprising, as the pathway was up-regulated in other viral infections³⁵. Histological analysis of COVID-19 patient biopsies confirms our findings, showing enlarged lung epithelial cells with amphophilic granular cytoplasm⁶⁶, while electron microscopy images of infected cells showed lipid droplets accumulation^{60,67}. As lipogenesis is poorly tolerated in thin epithelial tissue⁶⁸, such accumulation is likely to lead to pulmonary lipotoxicity and severe inflammatory response. Indeed, several groups looked at lipid modulators as possible pharmaceutical interventions. Triacsin C and VPS34 inhibitors blocked viral replication at concentrations 1000-fold higher than C_{max} ⁶⁹, with similar effects shown for statins at concentrations 100-fold higher than C_{max} ⁷⁰. This gap might explain why observational studies on the effect of statins show an inconsistent reduction of 28-days all-cause-mortality and mixed effect regarding secondary outcomes⁷¹. Our study confirms these earlier observations (**Fig 5**).

Fibrates are a family of amphipathic carboxylic acids that are ligands of PPAR α , and thus up-regulate lipid oxidation, lowering serum triglycerides^{72,73}. Fenofibrate blocked viral replication *in vitro* over a 5-day period, reversing both lipid accumulation and increased glycolysis at C_{max} concentration (**Fig. 4**). An observational study in Israel confirmed these results showing patients taking bezafibrate or ciprofibrate were significantly underrepresented in COVID-19 related hospitalizations (**Fig. 4**). Compared to patients that are not treated with metabolic drugs, those taking fibrates showed a minimal inflammatory response, lower mortality, and improved disease outcomes (**Fig 5, Supp. Fig. S5, Table S2-S4**). Other observational studies in the US and Italy showed similarly improved outcomes and disease-related complications (**Table S5-S6**).

The clinical importance of understanding the role of lipid metabolism in COVID-19 is further emphasized by the diametrically opposite response induced by thiazolidinediones (TZD) in our study. Thiazolidinediones are ligands of PPAR γ that upregulate lipogenesis in certain tissues ²⁹. Our study showed that Israeli COVID-19 patients taking rosiglitazone were overrepresented in ICU admissions and death (**Fig 4**) had a worse immunoinflammatory response, and higher mortality (**Fig 5, Supp. Fig. S5, Table S2-4**). These results correlate with recent data showing that long-term thiazolidinedione use is associated with an increased risk of pneumonia in patients with type 2 diabetes ⁷⁴. Taken together, these data suggest that lipotoxicity might drive the initial inflammatory response in COVID-19 and its modulation could critically affect disease progression.

Our prospective interventional study of 15 severe hospitalized COVID-19 patients treated with 145 mg/day of nanocrystallized fenofibrate (TriCor[®]) in addition to standard-of-care showed dramatic improvement in inflammation and faster recovery compared to control patients admitted during the same period and treated with the same standard of care (**Fig 6, Table S7**). This favorable course was observed despite the presence of a higher comorbidity burden in fenofibrate-treated patients. Patients treated with TriCor[®] showed significantly decreased CRP levels 72 hours post-treatment suggesting a rapid decrease in inflammation, possibly due to PPAR α suppression of virus-induced lipotoxicity. The muted inflammatory response was further supported by the absence of elevation in NLR indicated low immunoinflammatory stress.

Our work demonstrates the importance of weaving primary human cells, with clinical samples, and observational data for the rapid clinical translation of new metabolic interventions. Additional work is needed to confirm the specific activation of biochemical pathways and validate our findings in pathology samples. Still, this mechanistic understanding allowed us to design an ad hoc prospective clinical study and show clinical significance despite a small number of patients.

Our work charts the metabolic response of human lung epithelium to SARS-CoV-2 infection, demonstrating that virus-induced lipotoxicity is a driver of immunoinflammatory stress in COVID-19 patients. Our data suggest that the up-regulation of lipid oxidation might be an effective therapeutic target in the treatment of COVID-19. These findings are supported by our non-randomized clinical study. A definitive answer regarding the efficacy of fenofibrate for the treatment of COVID-19 will require the execution of large randomized controlled clinical trials with meaningful clinical outcomes. Two randomized placebo-controlled trials are ongoing, including a large international trial in the US, Mexico, Greece, and several South American countries (FERMIN trial; NCT04517396), and a clinical trial in Israel (FENOC trial; NCT04661930).

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EXPERIMENTAL MODEL AND SUBJECT DETAILS

Human Subjects

All protocols involving human tissue were reviewed and exempted by the Hebrew University of Jerusalem and Icahn School of Medicine at Mount Sinai Institutional Review Boards.

Experiments using samples from human subjects were conducted in accordance with local regulations and with the approval of the institutional review board at the Icahn School of Medicine at Mount Sinai under protocol HS#12-00145.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

In the observational studies - the Israeli study was approved by the local institutional review board of the Hadassah Medical Center (IRB approval number no. HMO 0247-20) and the local institutional review board of the Ichilov Medical Center (IRB approval number no. 0282-20-TLV). The Italian study was reviewed by the local ethical board (AVEC) of the IRCSS S.Orsola-Malpighi University Hospital (approval number no. code LLD-RP2018).

The interventional study was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation E6 and the principles of the Declaration of Helsinki or local regulations, whichever afforded greater patient protection. The study was reviewed and approved by the Barzilai Medical Center Research Ethics Committee (0105-20-BRZ).

Cell Culture

Normal human bronchial epithelial (NHBE) cells (Lonza, CC-2540 Lot# 580580), isolated from a 79-year-old Caucasian female and were maintained at 37°C and 5% CO₂ in bronchial epithelial growth media (Lonza, CC-3171) supplemented with SingleQuots (Lonza, CC-4175) per manufacturer's instructions. Cells were maintained at the BSL3 facilities of the Icahn School of Medicine at Mount Sinai. NHBE cells (ATCC, PCS-300-010 Lot#63979089; #70002486), isolated from a 69-year-old Caucasian male and a 14-year-old Hispanic male were maintained in airway epithelial cell basal media (ATCC, PCS-300-030) supplemented with Bronchial Epithelial Growth Kit as per the manufacturer's instructions (ATCC, PCS-300-040) at 37°C and 5% CO₂. Cells were maintained at the BSL2 facilities of the Hebrew University of Jerusalem.

Viruses

SARS-related coronavirus 2 (SARS-CoV-2), Isolate USA-WA1/2020 (NR-52281) was deposited by the Center for Disease Control and Prevention and obtained through BEI Resources, NIAID, NIH. SARS-CoV-2 was propagated in Vero E6 cells in DMEM supplemented with 2% Fetal Bovine Serum (FBS), 4.5 g/L D-glucose, 4 mM L-glutamine, 10 mM Non-Essential Amino Acids (NEAA), 1 mM Sodium Pyruvate, and 10 mM HEPES. Infectious titers of SARS-CoV-2 were determined by plaque assay in Vero E6 cells in Minimum Essential Media (MEM) supplemented with 4 mM L-glutamine, 0.2% Bovine Serum Albumin (BSA), 10 mM HEPES and 0.12% NaHCO₃, and 0.7% agar.

All work involving live SARS-CoV-2 was performed in the CDC/USDA-approved BSL-3 facility of the Global Health and Emerging Pathogens Institute at the Icahn School of Medicine at Mount Sinai in accordance with institutional biosafety requirements.

METHOD DETAILS

Analysis of gene expression by RNAseq

Expression count matrices were retrieved from GEO: GSE147507-Series1 (Bronchial; culture), GSE153970 (Small airway; culture), GSE147507-Series15 (Autopsy), GSE145926 (Lavage). Differential gene expression analysis was performed using a Poisson-Tweedie distribution model using the *tweedEseq* Bioconductor package ⁷⁵. Count data from GEO were normalized using a trimmed-mean of M values (TMM) normalization with the *edgeR* Bioconductor packages ⁷⁶. Data from GSE153970 was previously normalized in GEO and was not further normalized. Genes with the following criteria were considered differentially expressed: (1) P-value adjusted by B&H method FDR < 0.05, (2) A fold change > 1.25, (3) Minimal mean expression > 20 in either condition (**Table S8**).

Bronchial culture samples are 3 independent primary normal human bronchial epithelial cultures infected apically with SARS-CoV-2 (USA-WA1/2020; MOI 2) for 24 hours, compared with 3 independent primary normal human bronchial epithelial Mock-infected with PBS for 24 hours.

Small airway culture samples are 3 independent primary human airway epithelial cultures infected apically with SARS-CoV-2 (MOI 0.25) for 48 hours, compared with 3 independent primary human airway epithelial cultures Mock-infected with PBS for 48 hours.

The autopsy samples are of two old (age > 60) unidentified COVID-19 human subjects, that died due to COVID-19, had autopsy biopsy tissue acquisition post-mortem in Weill Cornell Medicine and were provided as fixed samples for RNA extraction; the samples were compared with two old (age > 60) unidentified human biopsy lung samples, taken during lung surgery and stored at Mount Sinai Institutional Biorepository and Molecular Pathology Shared Resource Facility (SRF) in the Department of Pathology, similarly provided as fixed samples for RNA extraction.

COVID-19 patients' lung epithelial cells are bronchoalveolar lavage fluid isolates from one severe case and five critical cases. The median age of the patients was 62.5 years, and the participants included four male and two female patients. All patients had Wuhan exposure history and had a cough and/or fever as the first symptom. Diagnosis of SARS-CoV-2 was based on clinical symptoms, exposure history, chest radiography, and SARS-CoV-2 RNA-positive using commercial quantitative PCR with reverse transcription (qRT-PCR) assays. The samples were compared to three healthy controls. The median age was 24 years, and the participants included one female and three male patients. These donors were confirmed to be free of tuberculosis, tumor, and other lung diseases through CT imaging and other laboratory tests.

Analysis of Canonical Splice Variants

Reads were downloaded from SRA (GSE147507), and filtered and trimmed to remove low-quality reads and sequencing artifacts with fastp v20 ⁷⁷

(<https://github.com/OpenGene/fastp.git>). Reads were pseudoaligned to the GRCh38 genecode human transcriptome (GRCh38.p13, version 32) using Kallisto version 0.46.1⁷⁸ (<https://github.com/pachterlab/kallisto>) run with the default k-mer length of 31, in single-read, single-overhang mode, with fragment mean length of 400 and 100 SD. Differentially expressed transcripts/genes were identified using Sleuth based on a likelihood ratio test comparing the condition of interest and 100 Kallisto bootstrap samples.

Processing, Analysis, and Graphic Display of Genomic Data

Hierarchical clustering, heat maps, correlation plots, and similarity matrices were created in Morpheus. Gene ontology enrichment analyses and clustering were performed using DAVID Informatics Resources 6.7⁷⁹ and PANTHER Classification System⁸⁰. Metabolic network maps were created using McGill's Network Analyst Tool using the KEGG database⁸¹.

Quantification of Intracellular Glucose

To detect glucose uptake, we used 2-(N-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl) Amino)-2-Deoxyglucose (2-NDBG) a fluorescent analog of glucose (Invitrogen, USA; N13195). 2-NDBG is transported through SGLT-1 and GLUT-2. Increased uptake leads to 2-NDBG accumulation in the cells. Cells infected with SARS-CoV-2 for 96 hours were exposed to 6 mM of 2-NDBG for 24 hours. Cells were then fixed, counterstained with 1 µg/mL Hoechst 33258. Staining intensity was normalized to Hoechst 33258 across multiple fields of view.

Quantification of Lipids

Lipid accumulation was measured using HCS LipidTOX™ Phospholipidosis and Steatosis Detection Kit according to the manufacturer's instructions (ThermoFisher, USA; H34158). Briefly, cells were incubated in complete bronchial epithelial growth media supplemented with 1x phospholipidosis detection reagent for 48 hours. Cells were subsequently fixed in 4% PFA and stained with 1X neutral lipid detected reagent for 30 min and counterstained with 1 µg mL⁻¹ Hoechst 33258. Staining intensity was normalized to the amount of Hoechst 33258 positive nuclei across multiple fields of view.

Metabolic Analysis of Glucose, Lactate, and Glutamine

Metabolic analysis of SARS-CoV-2 infected culture media in the BSL3 facility was done using Accutrend Plus multiparameter meter (Roche Diagnostics). Culture media was collected every 48 hours and stored at -80 °C prior to analysis. Measurements were carried out using Accutrend Plus Glucose and BM-Lactate Test Strips according to the manufacturer's instructions. Each measurement was done in 3 technical measurements for each sample, validated throughout the process using calibration media. Glucose uptake, as well as lactate production, were calculated based on the difference between sample and control media.

Metabolic analysis of SARS-CoV-2 proteins expressing culture media in the BSL2 facility was done using amperometric glucose, lactate, and glutamine sensor array (IST, Switzerland) as previously described⁸². Each measurement was done in 3 technical measurements for each sample, calibrated periodically throughout the process using calibration media, according to the manufacturer's recommendations. Glucose and Glutamine uptake, as well as lactate production, were calculated based on the difference between sample and control media.

Analysis of single-cell RNAseq

Single-cell RNA sequencing data of bronchoalveolar lavage fluid from healthy and SARS-CoV-2 infected individuals was downloaded from GEO (GSE145926). We performed a reanalysis of transcript count data (UMI) of 113,683 single-cell expression profiles from this cohort. We used a permissive cell quality criterion to retain a maximum number of epithelial cells – cells were excluded from analysis if: (1) <1000 UMIs, (2) <200 genes (3) > 50% reads were from mitochondrial transcripts, (4) >50% UMIs were from transcript MALAT1, leaving a total of 75,292. Next, overdispersed genes were identified separately in each experimental batch (i.e. 10x channel) using elbow criteria applied to a median overdispersion statistic (difference of CV to median CV for genes with similar mean expression). A robust set of 1,537 genes showing high overdispersion is identified in this manner. Next, we used non-negative matrix factorization (NMF) and graph clustering to define cell types as follows. Sub-sampling 80% of genes and cells 100 times, and running NMF to reduce the dimensionality of the full dataset to between 15 and 40 dimensions as the product of two non-negative matrices⁸³. Loading matrices (i.e., activations) of these NMF components were used to calculate k-nearest neighbors (k-NN) graph (k=21) based on a cosine similarity distance. This graph was clustered using stability optimizing graph clustering⁸⁴, to identify 10 top-level cell type clusters. A cluster of 5,232 cells enriched for annotation as epithelial cells in the original study³⁴ and showing elevated expression of epithelial markers were isolated and reanalyzed in the same manner. A set of 1,737 overdispersed genes is selected, and dimensionality reduction by NMF is applied to subsamples, identifying a 6 cell type cluster by graph clustering of the k-NN network of cell cosine similarities (**Table S9**).

Differential expression analysis of single-cell RNAseq

Examining data from epithelial cells only we compare the gene expression in cells from patients with severe disease (S) to healthy controls (HC). UMI counts are depth normalized and log-transformed $\log(\text{TP10K}+1)$. To determine differential expression we use a generalized linear mixed model. We report the likelihood ratio test comparing a model with fixed effects for the disease status and the number of expressed genes per cell, and random effect for each patient sample, comparing to the same model with the disease status variable removed. 1,141 are found to be differentially expressed with B&H FDR<0.1 (**Table S8**).

Visualization of single-cell profiles

tSNE plots were generated from NMF loading matrices, with a perplexity value of 30 and the Barnes-Hut approximation method⁸⁵.

Identification of cell type and state

Epithelial cell types were primarily annotated based on the expression levels of their respective cell type markers (**Supp. Fig. S3**). All previously described major epithelial cells of the conducting airways, including basal, secretory, and ciliated cells, as well as the recently discovered FOXN4+ cells and SLC16A7, were found⁸⁶. Basal, secretory, and ciliated cells were shown by their expression levels of respective cell type markers. Notably, the FOXN4+ cells resemble the transient secretory cell type described as the most SARS-CoV-2-vulnerable bronchial cells in non-infected individuals by virtue of their function as transitional cell types differentiating from the secretory to ciliated lineage. We also

identified small clusters of cells that are predominantly derived from single patients that we call 'Virus Replicating', which have a strong expression of SARS-CoV-2 markers.

Generation Lentiviral SARS-CoV-2 Constructs

Plasmids encoding the SARS-CoV-2 open reading frames (ORFs) and eGFP control are a kind gift of Nevan Krogan (Addgene plasmid #141367-141395). Plasmids were acquired as bacterial LB-agar stabs and used per the provider's instructions. Briefly, each stab was first seeded into agar LB (Bacto Agar; BD, USA) in 10 cm plates. Then, single colonies were inoculated into flasks containing LB (BD Difco LB Broth, Lennox; BD, USA) and 100 µg/ml penicillin (BI, Israel). Transfection grade plasmid DNA was isolated from each flask using the ZymoPURE II Plasmid Maxiprep Kit (Zymo Research, USA) according to the manufacturer's instructions.

HEK 293T cells (ATCC, USA) were seeded in 10 cm cell culture plates at a density of 4×10^6 cells/plate. The cells were maintained in 293T medium composed of DMEM high glucose (4.5 g/l; Merck, USA) supplemented with 10% FBS (BI, Israel), 1x NEAA (BI, Israel), and 2 mM L-alanine-L-glutamine (BI, Israel).

The following day, cells were transfected with a SARS CoV 2 orf-expressing plasmid and the packaging plasmids using the TransIT-LT1 transfection reagent (Mirus Bio, USA) according to the provider's instructions. Briefly, 6.65 µg SARS CoV 2 lentivector plasmid, 3.3µg pVSV-G, and 5µg psPAX2 were mixed in Opti-MEM reduced serum medium (Gibco, USA), with 45µl of TransIT-LT1, kept at room temperature to complex and then added to each plate. Following 18h of incubation, the transfection medium was replaced with 293T medium and virus-rich supernatant was harvested after 48h and 96h. The supernatant was clarified by centrifugation (500×g, 5min) and filtration (0.45 µm, Millex-HV, MerckMillipore). All virus stocks were aliquoted and stored at -80°C.

The packaging plasmids (psPAX2 and pVSV-G) are a kind gift from Prof. N. Benvenisti, Stem Cell Unit at the Hebrew University, Jerusalem, Israel.

SARS-CoV-2 Proteins Lentiviral Transduction

Approximately 1×10^5 cells were infected in two consecutive sessions of 12h each. A 50% dilution of the viral stock was used in both for a final transduction efficiency of about 60%. Transduction efficiency was validated by microscopy of the eGFP transduced culture.

RNA-Seq of Viral Infections

Approximately 1×10^5 NHBE cells were infected with SARS-CoV-2 at a MOI of 2 for 24 h in complete bronchial epithelial growth media. Total RNA from infected and mock-infected cells was extracted using TRIzol Reagent (Invitrogen) and Direct-zol RNA Miniprep kit (Zymo Research) according to the manufacturer's instructions and treated with DNase I. RNA-seq libraries of polyadenylated RNA were prepared using the TruSeq RNA Library Prep Kit v2 (Illumina) according to the manufacturer's instructions. RNA-seq libraries for total ribosomal RNA-depleted RNA were prepared using the TruSeq Stranded Total RNA Library Prep Gold (Illumina) according to the manufacturer's instructions. cDNA libraries were sequenced using an Illumina NextSeq 500 platform.

Viral Load Quantitative Real-Time PCR Analysis

Genomic viral RNA was extracted from supernatants using TRIzol reagent according to the manufacturer's instructions (Thermo Fisher). RNA was reverse transcribed into cDNA using oligo d(T) primers and SuperScript II Reverse Transcriptase (Thermo Fisher). Quantitative real-time PCR was performed on a LightCycler 480 Instrument II (Roche) using KAPA SYBR FAST qPCR Master Mix Kit (KAPA biosystems) and primers specific for the SARS-CoV-2 nsp14 transcript as described previously^{87,88}. The viral load for each sample was determined using genomic viral RNA purified from viral stocks to generate a standard curve. Error bars indicate the standard error from three biological replicates.

Assembly of Metabolic Categories

Aggregate metabolic categories were created as previously described³⁵. Briefly, functional annotation gene-sets, taken from GO and KEGG, were merged into a set of glucose, lipid, mitochondrial, and amino acid gene-sets.

Metabolic Flux Quantification (Seahorse)

Mitochondrial Stress Test assay was conducted per manufacturer instructions as previously described³⁵. Briefly, cells were incubated in unbuffered DMEM supplemented with 2 mM glutamine, 1 mM sodium pyruvate, and 10 mM glucose (pH 7.4) for 1 hour at 37°C in a non-CO₂ incubator. Basal oxygen consumption rate (OCR) was measured for 30 min, followed by injection of 1.5 μM oligomycin, a mitochondrial Complex V inhibitor that blocks oxidative phosphorylation. The decrease in OCR due to oligomycin treatment is defined as the oxidative phosphorylation rate. 0.5 μM carbonyl cyanide-4 (trifluoromethoxy) phenylhydrazone (FCCP), an uncoupling agent, is added at 60 min to measure maximal mitochondrial activity followed by complete inhibition at 90 min using a mixture of 0.5 μM antimycin A and rotenone, mitochondrial Complex III and Complex I inhibitors.

Functional Annotations of Gene Expression

Differentially expressed genes were tested for enrichment overlap within functional gene sets. The general test for functional enrichment of the differentially expressed genes against various functional categories was done using the PANTHER tool⁸⁰. Enrichment P values were calculated using Fisher's exact test and corrected with familywise (Bonferroni) multiple testing correction or the Benjamini-Hochberg False discovery method as indicated.

Drug Treatments

Approximately 5×10^5 NHBE cells were infected with SARS-CoV-2 at a MOI of 2 in bronchial epithelial growth media. Culture media was supplemented with 0.1% DMSO (vehicle control), 10 μM Cloperastine (Merck; C2040), 5 μM Empagliflozin (AG-CR1-3619), 1 mM Metformin (Merck; 317240), 20 μM Fenofibrate (Merck; F6020) or 20 μM Rosiglitazone (Merck; R2408). After 24h, the media was collected and changed to bronchial epithelial growth media with the respective drug at the concentration listed above. Then, every 48 hours media was collected and replenished. The media was stored at -80°C immediately after removal. Culture viability was assessed at the end of the experiment using Hoechst staining.

Quantification and Statistical Analysis

BSL3 experiments (done with the virus) were done on NHBE from a single donor, repeated in 3 experimental repeats with 3 or more technical repeats in each experiment. BSL2 experiments (SARS-CoV-2 proteins assay) were done on NHBE from two donors, repeated in 3 experimental repeats each with 3 or more technical repeats in each experiment.

Measurements were technically repeated 3 or 4 times for each sample, images were analyzed with 5 or more fields of view; Graphs show mean $\pm$ SEM; Continuous variables were compared with a Mann-Whitney U test or a two-sample t-test or ANOVA. Categorical variables were compared with a chi-squared or Fisher's exact test, as appropriate. FDR correction was used to adjust for multiple comparisons and RNA seq comparisons; Hypergeometric testing was used to assess statistically significant enrichments. * indicates $p < 0.05$, ** indicates $p < 0.01$, *** indicates $p < 0.001$, unless denoted otherwise.

OBSERVATIONAL STUDIES

Israeli Study

A retrospective, multi-center study was conducted in Hadassah and Ichilov medical centers. A total of 150,976 participants were diagnosed positive for SARS-COV-2 following WHO interim guidance ([World Health Organization, 2020](#)). Only patients hospitalized and diagnosed with COVID-19 were included. participants with incomplete electronic medical records, aged less than 18, with pregnancy or severe medical conditions, including acute lethal organ injury (i.e., acute coronary syndrome, acute stroke, and severe acute pancreatitis) were excluded. The flowchart for patient inclusion is illustrated in Supplementary **Figure S7**. Participants were admitted between March 1st, 2020, and January 31st, 2021 to either the Hadassah Medical Center in Jerusalem or the Tel Aviv Sourasky Medical Center. The final date of the follow-up was February 28th, 2021. The study protocols were approved by the institutional ethics committee. Patient informed consent was waived by each ethics committee. Demographic and clinical characteristics, vital signs, laboratory tests, medical history and comorbidities, therapeutic interventions, and outcome data were extracted from electronic medical records using a standardized data collection method. The laboratory data included routine blood tests, blood counts, and serum biochemical markers reflecting c-reactive protein, sepsis, liver injury, kidney injury, and cardiac injury, glycemic status, and D-dimer were collected during hospitalization. In-hospital medication and respiratory intervention included the classification of the drugs, the dosage, the course of treatment, and using respiratory support were also extracted from medical records.

The retrospective study was designed to assess initial relationships between metabolic regulating drug use and COVID-19 clinical outcomes (28-day mortality and duration of hospitalization, ICU admission, mechanical ventilation, oxygen supplementation, disease severity at baseline, and inflammatory marker changes versus a control group that did not take any drug of this type.

COVID-19 poses a significant risk in older patients and patients with comorbidities ⁸⁹. Hence, to account for the fact that Metabolic drug users were older and had more comorbidities (**Table S1**), we included metabolic regulating drug users and patients over 45 in the comparative analyses, creating a more comparable control group suitable for the between treatment evaluations (**Table S3**), as previously described ⁹⁰. Propensity score

matching was avoided in this multi-drug comparison as it has been shown to increase model imbalance, inefficiency, model dependence, and bias in multiple group comparisons in small treatment groups. Significant differences in treatment group size and characteristics (Table S1) are expected to result in underestimation of treatment effect and a high level of overt bias⁹¹⁻⁹⁴.

Comparisons were conducted between hospitalized COVID-19 patients using one or more metabolic regulating drugs (fibrates, thiazolidinediones, metformin, SGLT2 inhibitors, statins, or telmisartan (IRE1 α inhibitor)) versus control patients not taking any metabolic regulating drugs. Baseline values are defined as measurements taken upon hospital admission. Statistical analyses were performed using SAS® v9.4 (SAS®, SAS Institute Cary, NC USA) software and R-3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized by a median and interquartile range (IQR) and categorical variables by a count and percentage. Statistical testing was two-sided. A p-value < 0.05 was considered statistically significant. Missing data was not imputed. Nominal p-values are presented since this was an exploratory study. Demographic and baseline clinical characteristics, comorbidities, and laboratory examinations, as well as initial univariate clinical outcomes, were compared between the groups (drugs versus no drugs) by data type using a two-sample t-test or Fisher's exact test as appropriate.

The relative risk of hospitalization, ICU admission, and 28-days all-cause-mortality of COVID-19 patients versus the general hospital population (1-year period, 5-year period, and 10-year period prior to study start date in patients 30 years and older) are presented with 95% confidence interval and level of significance (Wald test).

Dynamic changes of inflammatory markers were depicted using locally weighted scatterplot smoothing (Lowess) plotting⁹⁵ from day 1 to day 21 after admission, comparing each drug group to control patients that did not take metabolic regulators.

Time to event data is presented with Kaplan-Meier plots. Time-to-events are measured in days from the date of hospital admission to the date of in-hospital death, and release from the hospital or last follow-up or 28 days whichever sooner. Cox regression was performed to compare time-to-event data between the groups adjusting for covariates that may have been imbalanced between the groups. We did not perform matching since Cox regression models applied to the entire study cohort can effectively address confounding attributable to observed covariates and maximizes power by using all data available. Hazard ratios are presented comparing drug to control group adjusting for covariates (age, sex, current smoker, asthma, chronic obstructive pulmonary disease, cerebrovascular accident, chronic heart disease, chronic liver disease, chronic kidney disease, obesity, diabetes, hypertension, and dyslipidemia) with level of significance and 95% confidence interval. In cases of monotone likelihood (non-convergence of likelihood function), Firth's penalized maximum likelihood bias reduction method for Cox regression was implemented. Cox Regression with Firth's Penalized Likelihood has been shown to provide a solution in the case of monotone likelihood (non-convergence of likelihood function) and was shown to outperform Wald confidence intervals in these cases⁹⁶.

Italian Study

A validation study was conducted by phone interviews of the last 2,123 patients examined in the Outpatient Lipid Clinics of the University of Bologna and of the Niguarda Hospital in

Milan during the last 12 months and on adequately dosed statins, fenofibrate, or both for at least three months (**Table S5**). We excluded patients on lipid-lowering nutraceuticals (including polyunsaturated fatty acids), very low-dose or alternate-day statins, ezetimibe alone, PCSK9 inhibitors, and those on fibrates other than fenofibrate, in order to reduce the heterogeneity of the sample. Data were sampled based, comorbidities (obesity, chronic obstructive pulmonary disease, cardiovascular disease, managed as dummy variables), personal COVID history and severity, and contact with people affected by COVID. The study was carried out in adherence with the declaration of Helsinki. All participants were fully informed of the objectives of the questionnaire and gave their oral authorization to use their data for research purposes. The telephone calls were recorded. Age was compared between groups with ANOVA followed by post-hoc testing using Tukey's method. Percentages were compared by Chi-square test followed by Fisher's exact test.

US Study

A validation study was conducted using an existing observational cohort of 920,922 veterans with hypertension (defined by diagnostic codes for hypertension and at least two fills for antihypertensive medications from January 1, 2020, to October 25, 2020, and restricted to those veterans with evidence of using the Veterans Health Administration for their primary care). There were 5,144 (0.6%) veterans in the cohort who tested positive for SARS-CoV-2 between March 14, 2020, and October 25, 2020. Medication use was determined by confirmed pharmacy fills. The cohort contained a diverse, non-homogenous patient population with different disease severity. To minimize baseline differences between fenofibrate users and the three comparison groups (non-users, statin users, and TZD users), 1:5 propensity score matching was performed using Stata version 15.0. Baseline matching variables included age, sex, body mass index, race/ethnicity, and history of atherosclerotic cardiovascular disease, heart failure, diabetes mellitus, chronic lung disease, chronic liver disease, dementia, and current or former smoker. We performed nearest neighbor matching with a caliper of 0.1. We required a <10% standardized difference in each of the matched covariates between matched groups, as well as Rubin's B of $\leq 25\%$ and Rubin's R between 0.5-2 to verify sufficient matching (**Table S6A**).

INTERVENTIONAL STUDY

Design and participants

The study was conducted as an open-label, phase 3a clinical trial, in the Barzilai Medical Center, Ashkelon, Israel. The study was approved by the Barzilai Medical Center Research Ethics Committee (0105-20-BRZ). The study enrolled adults (≥ 18 years of age) with severe Covid-19 pneumonia, as confirmed by positive polymerase-chain-reaction (PCR) and evidenced by bilateral chest infiltrates on chest radiography or computed tomography. Eligible patients had a disease severity score of 4 (Hospitalized, requiring supplemental oxygen), increased oxygen requirement compared to baseline at home, a blood oxygen saturation of 93% or less on room air, or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) of less than 300 mm Hg, respiratory rate >30 breaths/min, and lung infiltrates $>50\%$ on chest CT within 72 hours of hospital admission or within 72 hours of a positive test result.

Individuals who had respiratory failure, septic shock, and/or multiple organ dysfunction, SOFA ≥ 5 or Disease Severity Score ≤ 3 (requiring noninvasive mechanical ventilation,

requiring extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation, or all) were excluded. Additionally, Individuals with known hypersensitivity to fenofibrate, patient-reported history or electronic medical record history of severe kidney disease (defined as any history of dialysis, history of chronic kidney disease stage IV or estimated Glomerular Filtration Rate (eGFR) of $< 30\text{ml/min/1.73 m}^2$ at the time of enrollment), acute pre-renal azotemia at the time of enrollment in the opinion of the investigator or bedside clinician, most recent mean arterial blood pressure prior to enrollment $< 65\text{ mmHg}$, patient-reported history or electronic medical record history of severe liver disease (defined as cirrhosis, history of hepatitis B or C or documented AST or ALT > 10 times the upper limit of normal measured within 24 hours prior to enrollment), patient-reported history or electronic medical record history of gallbladder disease, potassium > 5.0 within 24 hours prior to enrollment (unless a repeat value was ≤ 5.0), treatment with coumarin anticoagulants, immunosuppressants or bile acid resins or female subjects breastfeeding or undergoing fertility treatments were also excluded.

All participants provided written informed consent signed by the participant or legally authorized representative. Standard care according to local practice (supplemental oxygen, antiviral treatment, anticoagulants, vitamin D3, low-dose glucocorticoids, convalescent plasma, and supportive care) was provided. However, concomitant treatment with another investigational agent (except antiviral drugs) or any immunomodulatory agent was prohibited. Written informed consent was obtained from all the patients or, if written consent could not be provided, the patient's legally authorized representative could provide oral consent with appropriate documentation by the investigator. The primary analysis was performed on day 14, a follow-up was done 28 days post-admission.

Procedures

Participants who met the inclusion criteria were assigned to intervention with nanocrystallized fenofibrate (TriCor®, AbbVie Inc., North Chicago, IL USA) at a dose of 145 mg (1 tablet) once per day. Standard care for severe-hospitalized COVID-19 patients was provided according to local practice: antiviral treatment, vitamin D3, low-dose glucocorticoids, convalescent plasma, and supportive care (**Figure 6A**) as well as antipyretics for symptoms of fever (products containing paracetamol, or non-steroidal anti-inflammatories such as aspirin and ibuprofen) and dextromethorphan for symptoms of cough. Standard chronic treatments were continued unless COVID-19, clinical status, or fenofibrate treatment was a contraindication for the treatment. Control patients were collected from the observational study's database and filtered to patients that meet the inclusion criteria, admitted with low immunoinflammatory stress ($\text{NLR} < 10$ at admission), and treated according to the standard care used in the interventional study.

Valuations

For the evaluation of patients in this trial, the baseline was defined as the last observation before the administration of fenofibrate on day 0. The patients' disease severity was assessed on an ordinal scale according to the following categories: The scale is as follows: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities. Clinical status was recorded at baseline and every day during hospitalization.

Viral RNA and S-gene target failure (SGTF) Detection by Real-Time PCR

Extracted RNA (5ul) was transferred to 96 well PCR plate containing 20ul of TaqPath™ 1-step Multiplex Master Mix No ROX (Applied Bioscience, Cat number: A28523). This was followed by a one-step RT-PCR (TaqPath COVID-19 assay kit; Thermo-Fisher). Thereafter, the plate was sealed with MicroAmp clear adhesive strip (Applied Bioscience, Cat number: 4306311). The plate was loaded onto a QuantStudio™ 5 Real-Time PCR System (Applied Bioscience, Cat number: AB-A28574) and the following amplification program was used: 25°C for 2 minutes, X1 cycle 53°C for 10 minutes, X1 cycle 95°C for 2 minutes, X1 cycle 95°C for 3 seconds, followed by 60°C for 30 seconds, X40 cycles Ct threshold values were preset using the following values/parameters: MS2-15,000; by cycle 37; S gene- 20,000 by cycle 37; Orf1ab- 20,000 by cycle 37; Ngene- 20,000 by cycle 37. Samples that passed the Threshold is a Ct value >37 were re-tested or considered weak positive. Above threshold values of MS2, Orf1ab, and Ngene, but not S gene was considered S-gene target failure (SGTF). SGTF serves as a proxy for identifying B.1.1.7 cases^{97,98}.

Variant Detection by Real-Time PCR

Allplex™ SARS-CoV-2 Variants I Assay from Seegene Inc. was used according to the manufacturer protocol to perform rRT-PCR. Briefly, Extracted RNA (5ul) was transferred to 96 well PCR plate containing 15ul of the master mix were. Plates were then spun down at 2500 rpm for 5 s and analyzed on a CFX96 Touch Real-Time PCR from BioRad. Reverse Transcription reaction 1 cycle: 50 °C/20 min – 95 °C/15 min. PCR reaction 45 cycles: 94 °C/15 s – 58 °C/30 sec. Gene amplifications were analyzed by FAM (E484K mutation on S-Gene), HEX (RdRP), Cal Red 610 (N501Y mutation on S-Gene), Quasar 705 (69-70del on S-Gene), and Quasar 670 (Human Endo Internal control) fluorophores. Results were compiled and analyzed using 2019-nCoV viewer from Seegene Inc. according to the manufacturer's instructions.

Statistical analysis

Demographic data were summarized (**Table S7**), Continuous variables with non-normal distributions were expressed as median [IQR]. Categorical variables were expressed as number and percentage (%). The sample size is detailed in each display item. Comparisons between groups were performed with Mann-Whitney U test for continuous variables and Fisher's exact test or chi-squared test for categorical variables.

Analysis of weighted differences in hospitalization duration, mortality, and incidence of oxygen weaning was done using the Mantel–Haenszel test. The cumulative rates of death and hospital discharge were compared using Kaplan-Meier curves, a log-rank test, and cause-specific Cox regression analysis. The hazard ratio (HR) was calculated using the Cox proportional hazard model comparing the treatment group versus the non-treatment group as previously described^{63,71}. In the Cox regression models, individuals discharged were treated as “0-at risk” but not as censored data since individuals with COVID-19 would not be discharged unless their symptoms were significantly relieved and two continuous viral PCR negatives were achieved. Additionally, a clinic or electronic (medical records) follow-up at 28 days was conducted to register out-of-hospital death, need for supplemental oxygen, and/or rehospitalization. Since no deaths were recorded in the intervention group, Cox proportional hazards regression for mortality was performed using Firth's penalized maximum likelihood bias reduction method. Cox Regression with Firth's Penalized

Likelihood has been shown to provide a solution in the case of monotone likelihood (non-convergence of likelihood function) and was shown to outperform Wald confidence intervals in these cases ⁹⁶. Regression adjustment was applied to remove residual confounding bias where it included the covariates with a standardized difference greater than 0.10. Multi-variable adjusted residual imbalances including age, gender, clinical characteristics on admission, indicators of disease severity and organ injuries on admission, and pre-existing medical conditions were adjusted in the analysis of the association between treatment and clinical outcomes. The proportional hazard assumptions were verified using correlation testing based on the Schoenfeld residuals.

Dynamic changes of inflammatory factors tracking from day 0 to day 8 after treatment were depicted using the Lowess model ^{95,99}. A two-side α less than 0.05 was considered statistically significant. Data were analyzed in R-3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics (version 23.0, IBM, Armonk, NY, USA). Day 0 was determined to be the first day of treatment with nanocrystallized fenofibrate (TriCor[®]) in the intervention group or first-day disease severity has reached 4 (but not higher) and at least 3 MOH indicators (increased oxygen requirement compared to baseline among those on home, a blood oxygen saturation of 93% or less on room air, or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen (PaO₂/FiO₂) of less than 300 mm Hg, respiratory rate >30 breaths/min, and lung infiltrates >50% on chest CT) were recorded.

ETHICS AND OVERSIGHT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

In the observational studies - the Israeli study was approved by the local institutional review board of the Hadassah Medical Center (IRB approval number no. HMO 0247-20) and the local institutional review board of the Ichilov Medical Center (IRB approval number no. 0282-20-TLV). The Italian study was reviewed by the local ethical board (AVEC) of the IRCSS S.Orsola-Malpighi University Hospital (approval number no. code LLD-RP2018).

The American study was reviewed by the local institutional review board of the Corporal Michael J. Crescenz VA Medical Center (IRB approval number 01654).

The interventional study was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation E6 and the principles of the Declaration of Helsinki or local regulations, whichever afforded greater patient protection. The study was reviewed and approved by the Barzilai Medical Center Research Ethics Committee (0105-20-BRZ).

Statistical analysis of the Israeli studies was done by BioStats Statistical Consulting Ltd. (Maccabim, Israel), funded by the sponsor. Data management is performed in compliance with GCP and 21 CFR part 1. Statistical analyses and reporting are performed in compliance with E6 GCP, E9, and ISO 14155. Independently validated by the author. Statistical analysis of the Italian study was done by Prof. Arrigo Cicero and Dr. Chiara Pavanello. Statistical analysis of the US study was done by Prof. Jordana Cohen.

DATA AND SOFTWARE AVAILABILITY

Further information and requests for reagents may be directed to and will be fulfilled by the corresponding author Yaakov Nahmias (ynahmias@cse.huji.ac.il).

Software resources

Our custom Cell Analysis CellProfiler® Pipeline is available on <https://github.com/avnere/Single-Cell-Analysis-CellProfiler-Pipeline>.

FIGURE LEGENDS

Figure 1. Transcriptional metabolic signature of SARS-CoV-2 infection. (A) Bubble plot visualization of GO terms enriched by SARS-CoV-2 infection. Epithelial cells were isolated by bronchoalveolar lavage from 6 severe COVID-19 patients compared to 4 healthy patients (lavage). Post-mortem lung biopsies from 2 severe COVID-19 patients compared to surgical biopsies from 2 non-COVID patients (autopsy). Culture sample groups include primary small airway epithelial cells (n=3; alveoli) and primary bronchial epithelial cells (n=3; bronchial) infected with SARS-CoV-2. Enrichment analysis shows immunoinflammatory response, cellular stress ($FDR < 10^{-22}$), and lipid metabolism ($FDR < 10^{-5}$). (B) Venn diagram describing the relationship between differentially expressed genes (DEG), metabolic genes (GO:0008152), and lipid metabolism genes (GO:0006629) in SARS-CoV-2 infection of primary bronchial epithelial cells and COVID-19 patient samples. Across all four sample groups $58 \pm 3\%$ of the differentially expressed genes were metabolism-related, with $15 \pm 2\%$ of the genes associated with lipid metabolism. (C) Sunburst graph showing the coverage of composite metabolic terms³⁵ on general metabolic response induced by SARS-CoV-2 infection of primary bronchial epithelial cells and COVID-19 patient samples. Lipid and mitochondrial metabolism dominate the transcriptional metabolic signature of infection across all four sample groups (Supp. Fig. S1). (D) Schematic depicting the metabolic landscape of SARS-CoV-2 infection superimposed with a heat map of pathway-associated genes. Red and green boxes indicate gene expression changes following infection in primary bronchial epithelial cells. * marks differentially regulated genes (n=3, $FDR < 0.05$). # indicates small sample size.

Figure 2. Metabolic fingerprint of SARS-CoV-2 infection. (A) Schematic of ER stress pathways superimposed with pathway-associated genes. Red and green boxes are up and downregulated by infection, respectively. * marks differentially regulated genes (n=3, $FDR < 0.05$). Red arrows note putative activation pathways based on the transcriptional response. XBP1S/U is the ratio of IRE1-spliced over the un-spliced form of XBP1. (B) Schematic of central carbon metabolism fluxes superimposed with flux-associated genes. Differentially expressed genes (n=3, $FDR < 0.01$) are marked with *. Genes and associated fluxes are highlighted red or green for up- or down-regulation, respectively. (C) Metabolic analysis of SARS-CoV-2 and mock-infected primary bronchial epithelial cells confirms a 50% increase (n=6, $p < 0.001$) in lactate production 48 hours post-infection. (D) The ratio of lactate production to glucose uptake (glycolytic index) in SARS-CoV-2 and mock-infected primary cells. Index increases from 1.0 to 1.7 out of 2.0 indicating transition to glycolysis (i.e., Warburg effect). (E) Microscopic evaluation of primary bronchial epithelial cells infected with SARS-CoV-2 virus or mock control shows an 85% increase in the intracellular accumulation of fluorescent glucose analog (n=3; Bar = 40 μ m). (F) Schematic of lipid metabolism fluxes superimposed with flux-associated genes. Differentially expressed genes (n=3, $FDR < 0.01$) are marked with *. Genes and associated fluxes are highlighted red or

green for up- or down-regulation, respectively. (G) Microscopic evaluation of primary bronchial epithelial cells infected with SARS-CoV-2 virus or mock control. Neutral lipids (triglycerides) are dyed green while phospholipids are dyed red. Image analysis shows a 23% increase in triglycerides (n=3, p<0.05) and 41% increase in phospholipids (n=3, p<0.001) following SARS-CoV-2 infection (Bar = 10 μ m) indicating abnormal lipid accumulation in lung epithelium. (H) T-distributed stochastic neighbour embedding (tSNE) plot shows clustering of 2,629 lung epithelial cells of severe COVID-19 patients isolated by bronchoalveolar lavage (*methods*). Point coordinates were calculated based on Non-negative matrix factorization (NMF) of top over-dispersed genes (*methods*). Cell color specifies assignment to 1 of 6 clusters identified as virus replicating cells, as well as basal, secretory, FOXN4-positive, SLC16A7-positive, and ciliated cell clusters (**Supp. Fig. S2**). (I) Expression of SARS-CoV-2 (nCoV) superimposed on the tSNE plot (and associated abundance analysis showing that the virus replicating cluster is enriched with viral RNA. Proportions indicate the relative number of cells with > 1 log₂(TPX) in each group. (J) Gene enrichment analysis comparing virus replicating cells to uninfected epithelial cells showing differences in the cellular response to endoplasmic reticulum stress (FDR<1x10⁻⁶), metabolic processes (FDR<9x10⁻⁴), and lipid metabolism (FDR<3x10⁻³) in the same COVID-19 patients. * p<0.05, ** p<0.01, *** p<0.001. Error bars indicate S.E.M.

Figure 3. SARS-CoV-2 proteins modulate host metabolic pathways. Analysis of primary bronchial epithelial cells expressing different SARS-CoV-2 proteins for 72 hours using multiple independent assays. (A) Analysis of CHOP and XBP1 spliced isoform (XBP1S/U) by qRT-PCR as markers of ER stress. Expression of ORF9c, M, N, ORF3a, NSP7, ORF8, NSP5, and NSP12 significantly up-regulated both markers (n=6, p<0.05). (B-C) Microscopic analysis of triglycerides (neutral lipids) and phospholipids shows a virus protein-induced perinuclear lipid accumulation. (C) Quantification shows a significant accumulation of phospholipids in cells expressing the same panel of viral proteins that induced ER stress (n=6, p<0.01). (D-E) Microscopic analysis shows an increased abundance of fluorescent glucose analog (2-NDBG) by a smaller set of viral proteins than above. (E) Quantification shows a significant increase in intracellular glucose in bronchial cells expressing N, ORF3a, NSP7, ORF8, NSP5, and NSP12 (n=6, p<0.05). (F) Direct measurement of lactate production of bronchial epithelial cells shows significantly higher lactate production (n=6, p<0.01) in cells expressing the smaller protein subset. (G) The ratio of lactate production to glucose uptake (glycolytic index) in bronchial cells expressing viral proteins. Index significantly increases from 1.1 to 1.7 marking a shift to glycolysis (n=6, p<0.01) induced by the viral proteins. (H) Seahorse™ analysis of extracellular acidification rate (ECAR) surrogate measurement for lactate production, shows independent confirmation of increased glycolysis. (I) Seahorse™ mitochondrial stress analysis of bronchial cells expressing the viral proteins. Oxygen consumption rate (OCR) is shown as a function of time. Oligomycin, FCCP, and antimycin/rotenone were injected at 25, 55, and 85 minutes, respectively. (J) Quantification of oxidative phosphorylation (OXPHOS) shows a decrease of mitochondrial function following expression of N, ORF3a, and NSP7 (n=6, p<0.05). * p<0.05, ** p<0.01, *** p<0.001 in a 2-sided heteroscedastic student's t-test against control. Bar = 40 μ m. Error bars indicate S.E.M.

Figure 4. Therapeutic targets of SARS-CoV-2 associated host metabolic pathways. (A) Schematic depicting the metabolic landscape of SARS-CoV-2 infection. Potential drugs (white boxes) and their therapeutic targets are marked on the chart. (B) Table summarizing FDA-approved drugs that interfere with SARS-CoV-2 induced metabolic alterations. (C) Microscopic analysis of lipid accumulation in SARS-CoV-2 infected lung cells exposed to

different drugs for 5 days compared to DMSO-treated (vehicle) and mock-infected controls. Cells treated with PPAR α agonist fenofibrate showed a significant decrease in phospholipid content (n=3, p<0.001). **(D)** Lactate over glucose ratio of SARS-CoV-2 infected primary lung cells treated with various drugs. Fenofibrate significantly reduced the lactate to glucose ratio by 60% (n=3; p<0.01) normalizing the metabolic shift induced by infection. **(E)** Quantification of SARS-CoV-2 viral RNA over 5 days of treatment with a physiological concentration of various drugs or DMSO (vehicle). Treatment with 20 μ M fenofibrate reduced SARS-CoV-2 viral load by 2-logs (n=3; p<0.001). Treatment with 10 μ M cloperastine reduced viral load by 2.5 to 3-fold (n=3; p<0.05). **(F)** Cell viability 5-days post-treatment was unaffected by all drugs tested. **(G)** Comparative representation of Israeli patients above the age of 30 taking different metabolic regulators. 532,493 unique general hospital medical records were compared with 2,806 confirmed COVID-19 patients. COVID-19 patients treated with metabolic regulators were older and had a higher prevalence of chronic medical conditions and risk factors than other COVID-19 patients (**Table S1**). Patients taking thiazolidinediones (n=37; p<0.001), metformin (n=321; p<0.01), SGLT2 inhibitors (n=54; p<0.001), statins (n=924; p<0.001), or telmisartan (IRE1 α inhibitor; n = 278; p<0.001) were over-represented across all severity indicators (**Table S2**). Patients taking fibrates (n=21) were significantly underrepresented in hospital admissions (p=0.02) and were not over-represented in other severity indicators. * p<0.05, ** p<0.01, *** p<0.001 in a Wald test compared to the proportion of these drug users in medical records. Bar = 50 μ m. Error bars indicate S.E.M.

Figure 5. Observational study shows differential immunoinflammatory response to metabolic intervention. **(A)** Schematic depicting the in-hospital progression of severe COVID-19, characterized by early lipotoxicity-induced inflammation, marked by elevated C-reactive protein (CRP), followed by distinct changes in neutrophils and lymphocytes marking the immunoinflammatory response followed by recovery (**Supp. Fig. S5**). **(B)** Box and whisker plot of length of hospitalization in treatment and non-treatment groups (Control). Israeli patients taking bezafibrate or ciprofibrate (fibrates) were associated with significantly lower hospitalization duration (p=0.03). **(C-D)** Dynamic changes in the inflammation marker CRP and neutrophil-to-lymphocyte ratio (NLR) marking immunoinflammatory stress in treatment and non-treatment groups (Control) during 21-day hospitalization. The centerline shows the mean value while the 95% confidence interval is represented by the shaded region. **(C)** CRP levels gradually declined in the control group reaching a plateau by day 14 post-hospitalization. The fibrates group showed a significantly faster decline in inflammation, while the thiazolidinedione group showed marked elevation in CRP level above control. **(D)** NLR rose in the control group above normal values (dotted red line) stabilizing after 7-14 days and then declining as recovery begins. The fibrates group showed only mild stress, maintain normal levels of NLR throughout hospitalization. Patients taking statins or IRE-inhibitors showed elevated NLR post-day 10 of hospitalization. **(E)** Kaplan–Meier survival curves of 28-day in-hospital mortality for treatment and non-treatment groups (Control). The small group of patients taking fibrates did not report any deaths, while thiazolidinedione and SGLT2 inhibitor users had a significantly higher risk of mortality (HR: 3.6, 2.5; p = 0.04, 0.03 respectively, Table S4). * p<0.05, ** p<0.01, *** p<0.001. In boxplots, x is the mean; center line is median; box limits are 25th and 75th percentiles; whiskers extend to 1.5 $\times$ the interquartile range (IQR) from the 25th and 75th percentiles; dots are outliers. # indicates that the hazard ratios were calculated using Firth’s correction for monotone likelihood with profile likelihood confidence limits.

Figure 6. Nanocrystallized fenofibrate (TriCor®) reduced inflammation and sped recovery in severe COVID-19 patients treated with standard-of-care. (A) Schematic depicting interventional study design in 15 severe hospitalized COVID-19 patients receiving remdesivir, dexamethasone, and enoxaparin. Patients received 145 mg/day of TriCor® for 10 days with blood samples taken every 48-72 hours until discharge. (B) Chemical, clinical, and pharmacokinetic characteristics of nanocrystallized fenofibrate (TriCor®). Lower T_{max} compared to other fibrates enables rapid intervention in deteriorating COVID-19 patients. (C) box and whisker plot of hospitalization duration (left) and Cox accumulative estimated hospital time to discharge by day 28 analysis, plotted as 1 minus the Cox estimator (right). Patients treated with TriCor® resulted in significantly lower hospitalization duration (n=15; $p < 0.001$), and a higher likelihood of discharge (HR: 3.6, 95% CI 2.1 to 6.4; n=15; $p < 0.001$). (D-E) Dynamic changes (right) and box and whisker plots (left) of immunoinflammatory indicators CRP and neutrophil-to-lymphocyte ratio (NLR) in treatment and non-treatment groups (Control) over hospitalization duration (*methods*). The centerline shows the mean value while the 95% confidence interval is shaded. (D) High CRP levels gradually declined in the control group reaching a plateau by day 7. TriCor® treated patients showed a faster decline in inflammation, resulting in significantly lower CRP levels 3-5 days post-treatment (n=15; $p < 0.001$). (E) NLR in the control group increased during hospitalization indicating severe immunoinflammatory stress. Patients treated with TriCor® showed no increase in NLR, suggesting minimal immune response, resulting in a significantly lower NLR 3-5 days post-treatment (n=15; $p = 0.002$). (F) Withdrawal from oxygen support, plotted as cumulative incidence at day 7 (left; OR: 3.2, 95% CI 1.3 to 7.9; n=15; $p = 0.005$) Kaplan-Meier estimated time to discharge by day 28, plotted as 1 minus the survival estimator (right; HR: 2.9, 95% CI 1.7 to 5.0; n=15; $p < 0.001$). (G) Kaplan-Meier survival curves of 28-days mortality of treatment and non-treatment groups (Control) and Cox regression modeling presenting hazard ratio estimate, 95% CI and p-value. (H) Novaplex™ SARS-CoV-2 qPCR variant analysis (*methods*), showing a dominant presence of 69/70 deletion and N501Y substitution mutation correlating to the B.1.1.7 (UK) variant of the virus in the patient population. (I) Pie chart representation of variant distribution between the patient in the interventional study and other patients in other clinical centers in Israel during the same period (OR: 1.36, 0.59 to 3.1; $p = 0.44$). SGTF, S-gene target failure, serves as a proxy for identifying B.1.1.7 cases^{97,98}. Hazard ratios (HR) and the related p-values were calculated by a Cox regression model. Odds ratios (ORs) and the related p-values were calculated using Fisher's exact test (*methods*). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. In boxplots, x is the mean; center line is median; box limits are 25th and 75th percentiles; whiskers extend to 1.5× the interquartile range (IQR) from the 25th and 75th percentiles; dots are outliers. # indicates that the hazard ratios were calculated using Firth's correction for monotone likelihood with profile likelihood confidence limits.

Supporting Information

Supplementary Tables Legends

Table S1. Characteristics of COVID-19 patients in the cohort. SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, chronic obstructive pulmonary disease; SpO₂, oxygen saturation; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range. Continuous variables were compared with a two-sample t-test and categorical variables with Fisher's exact test.

Table S2. Observational comparison between unique patients' visits in Hadassah medical center taking metabolic regulators and unique patients in various hospitalization conditions in patients with COVID-19 taking metabolic regulators in different periods. Patients taking thiazolidinediones (n=37; $p<0.001$), metformin (n=321; $p<0.01$), SGLT2 inhibitors (n=54; $p<0.001$), statins (n=924; $p<0.001$), or telmisartan (IRE1 α inhibitor; n = 278; $p<0.001$) were over-represented across all severity indicators, while patients taking fibrates (n=21) were significantly underrepresented in hospital admissions ($p=0.02$) and were not over-represented in other severity indicators regardless of the period examined. Observational comparison between unique patients visits Hadassah medical center during (A) 11/2018-2019, (B) 11/2015-2020, or (C) 11/2010-2020 taking metabolic regulators and unique patients in various hospitalization conditions in patients with COVID-19 taking metabolic regulators.

Table S3. Characteristics of patients included in the study. Patients were included in the study were between the age of 45-100, that were hospitalized for more than 3 days (N=1,438). SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, chronic obstructive pulmonary disease; SpO₂, oxygen saturation; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range Continuous variables were compared with a two-sample t-test and categorical variables with Fisher's exact test.

Table S4. Cox regression model of 28-days mortality in the treatment groups versus control. Adjusted HR and p-values were calculated based using a Cox regression model adjusting for age, gender, and pre-existing comorbidities (smoking, asthma, COPD, DM, hypertension, diabetes, coronary heart disease, obesity, dyslipidemia, cerebrovascular disease, chronic liver disease, and chronic kidney disease). There were no deaths recorded in fibrate patients, resulting in monotone likelihood (non-convergence of likelihood function, a Firth's penalized maximum likelihood bias reduction method was implemented to calculate hazard ratios and confidence intervals. Thiazolidinediones and SGLT2 inhibitors users show a significantly higher risk of death within 28 days of hospitalization (adjusted risk). # indicates that the hazard ratios were calculated using Firth's correction for monotone likelihood with profile likelihood confidence limits.

Table S5. Comparative Cohort of the Outpatient Lipid Clinics of the University of Bologna and of the Niguarda Hospital in Milan. (A) Characteristics of included patients stratified by lipid-lowering treatment. Cohort of 2,123 patients (M: 48.1%, F: 51.9%) on statins (1,791, mean age 59,2 $\pm$ 15.2 years), fenofibrate (220, mean age 60,7 $\pm$ 15.4 years) or both (112, mean age 62,9 $\pm$ 16.3 years) were interviewed. Patients on statins were significantly younger than those on both drugs ($p=0.023$). 177 patients received a diagnosis of COVID by molecular swab: 9.2% of statin-treated subjects, 3.2% of fenofibrate treated ones, and 5.4% of those treated with both statins and fenofibrate ($p=0.005$) without differences in the source of exposition (family members, co-workers; $p=0.648$). (B) Disease severity stratified by lipid-lowering treatment. 134 reported mild COVID-19 symptoms and 31 patients reported severe COVID-19 symptoms, requiring hospitalization: 1.7% of statin-treated subjects, 0.5% of fenofibrate treated ones, and 0% of those treated with both statins and fenofibrate ($p=0.022$) without differences in the source of exposition (**Table S5A**). (C) Characteristics of included patients according to the personal history of COVID. Patients affected by COVID were more frequently obese, with COPD and/or cardiovascular diseases, and had strict contact with COVID affected subjects, independent of the lipid-lowering treatment. (D) Characteristics of patients exposed to contact with affected people (n=254). Out of 254 patients reporting contact with affected people, 45 became positive to COVID.

93.3% were in treatment with statins 4.4% with fenofibrate and 4.5% with both ($p=0.059$). Affected to exposed to positive contacts ratio according to background lipid-lowering was 20.5% in patients treated with statins 7.4% with fenofibrate and 4.5% with both ($p=0.059$).

Table S6. Comparative cohort in the American veteran's health administration (VHA) registry. (A) Characteristics of fenofibrate users compared with non-users before and after PSM. (B) The median duration of hospitalization among fenofibrate users vs. non-users. (C) SARS-CoV-2 infection and COVID-19 severity among fenofibrate users vs. non-users.

Table S7. Characteristics of patients compared to the patients in the interventional study. 15 Participants who met the inclusion criteria were assigned to intervention with nanocrystallized fenofibrate (TriCor®, AbbVie Inc., North Chicago, IL USA) at a dose of 145 mg (1 tablet) once per day. Standard care for severe-hospitalize COVID-19 patients was provided according to local practice: antiviral treatment, vitamin D3, low-dose glucocorticoids, convalescent plasma, and supportive care as well as antipyretic for symptoms of fever (products containing paracetamol, or non-steroidal anti-inflammatories such as aspirin and ibuprofen) and dextromethorphan for symptoms of cough. Standard chronic treatments were continued unless COVID-19, clinical status, or fenofibrate treatment was a counterindication for the treatment. Control patients were collected from the observational study's database and filtered to patients that meet the inclusion criteria, admitted with low immunoinflammatory stress ($NLR < 10$ at admission), and treated according to the standard care used in the interventional study. SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, chronic obstructive pulmonary disease; SpO₂, oxygen saturation; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range. Continuous variables were expressed as median [IQR] and were compared with a Mann-Whitney U test. Categorical variables were expressed as a count and percentage (%) and compared with a chi-squared test or Fisher's exact test. The sample size is detailed in each display item.

Table S8. Cox regression model of 28-days mortality in the treatment group versus control. Adjusted HR and p-values were calculated based using an unadjusted Cox regression model, a Cox regression model adjusting for age, gender, and pre-existing comorbidities (smoking, asthma, COPD, DM, hypertension, diabetes, coronary heart disease, obesity, dyslipidemia, cerebrovascular disease, chronic liver disease, and chronic kidney disease) or a Cox regression model adjusting for significantly different patient characteristics, obesity, chronic kidney disease, and SpO₂. (A) Cox regression model of 28-days hospital discharge. (B) Cox regression model of 28-days oxygen withdrawal. (C) Cox regression model of 28-days mortality. There were no deaths recorded in the treatment patients, resulting in monotone likelihood (non-convergence of likelihood function, a Firth's penalized maximum likelihood bias reduction method was implemented to calculate hazard ratios and confidence intervals.

Table S9. Differentially expressed genes in SARS-CoV-2 infected epithelium.

Table S10. Differentially expressed genes of different lung epithelial cell populations (methods) in severe COVID-19 patients isolated by bronchoalveolar lavage

Table S11. Primer list used for qPCR

Supplementary Figures Legends

Figure S1. Transcriptional metabolic signature of infection in COVID-19 patients' samples and SARS-CoV-2 infected primary cells. (A) Venn diagrams describing the relationship between differentially expressed genes (DEG), metabolic genes (GO:0008152), and lipid metabolism genes (GO:0006629) in COVID-19 patient sample groups including epithelial cells isolated by bronchoalveolar lavage (lavage) and post-mortem lung biopsies (autopsy), as well as primary small airway epithelial cells (alveoli) and primary bronchial epithelial cells (bronchial) infected with SARS-CoV-2. (B) Sunburst graphs showing the coverage of composite metabolic terms³⁵ on general metabolic response induced by SARS-CoV-2 infection. Lipid and mitochondrial metabolism dominate the transcriptional metabolic signature of infection across all four sample groups. (C) Heat map of metabolic and stress pathway-associated genes (**Figure 1D**) across four sample groups. Red and green boxes are up and downregulated by infection, respectively. # indicates small sample size.

Figure S2. Single-cell characterization of lung epithelial cells isolated by bronchoalveolar lavage from severe COVID-19 patients. (A) T-distributed stochastic neighbour embedding (tSNE) plot shows clustering of 5,231 lung epithelial cells (*methods*) isolated by bronchoalveolar lavage. Point coordinates were calculated based on Non-negative matrix factorization (NMF) of top over-dispersed genes (*methods*). (B) Violin graphs and tSNE plots of composite expression levels identifying the cell type and state of each of the defined clusters⁸⁶. (C) Schematic of ER stress pathways superimposed with pathway-associated genes. Red and green boxes are up and downregulated by infection, respectively. * marks differentially regulated genes (n=3, FDR<0.05). Red arrows note putative activation pathways based on the transcriptional response. XBP1S/U is the ratio of IRE1-spliced over the un-spliced form of XBP1.

Figure S3. qRT-PCR of ER stress genes induced by expression of SARS-CoV-2 proteins. Gene expression analysis of ER stress-related genes in primary bronchial epithelial cells expressing different SARS-CoV-2 proteins for 72 hours. * p<0.05, ** p<0.01, *** p<0.001 in a 2-sided heteroscedastic student's t-test against control. Error bars indicate S.E.M.

Figure S4. PPAR α agonists in SARS-CoV-2 infection *in vitro* (A) Relative viability and viral load in SARS-CoV-2 infected bronchial epithelial cells treated with different metabolic regulators for 5 days. (B) Microscopic analysis of lipid accumulation in ORF3a expressing bronchial epithelial cells treated with different PPAR α agonists. * p<0.05, ** p<0.01, *** p<0.001. Bar = 50 μ m.

Figure S5. The host-immune response in hospitalized COVID-19 patients in different metabolic interventions. (A-D) Dynamic changes in (A) neutrophils, (B) lymphocytes, (C) monocytes, and (D) platelets levels during 21-day hospitalization in treatment and non-treatment groups (Control). The centerline shows the mean value while the 95% confidence interval is represented by the shaded region.

Figure S6. Analysis of variant emergence dynamics and distribution during the study period in participants and other hospitalized patients. (A) sample distribution (left) and relative abundance (left), with and without SGTF by day from 30 November 2020 to 28 February 2021. (B) Stratified relative abundance of samples with and without SGTF of

patients in the interventional study (left) and of other hospitalized patients (right) from 16 December 2020 to 28 February 2021. (C) Distribution comparison of sample distribution with and without SGTF in stratified periods. Odds ratios (ORs) and the related p-values were calculated using Fisher's exact test (methods). SGTF, S-gene target failure, serves as a proxy for identifying B.1.1.7 cases^{97,98}.

Figure S7. Observational Study Flow Chart

References

- 1 Grasselli, G. *et al.* Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. *The Lancet Respiratory Medicine* **8**, 1201-1208, doi:10.1016/S2213-2600(20)30370-2 (2020).
- 2 Bornstein, S. R., Dalan, R., Hopkins, D., Mingrone, G. & Boehm, B. O. Endocrine and metabolic link to coronavirus infection. *Nature Reviews Endocrinology*, doi:10.1038/s41574-020-0353-9 (2020).
- 3 Zhu, L. *et al.* Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metabolism*, doi:<https://doi.org/10.1016/j.cmet.2020.04.021> (2020).
- 4 Ko, J. Y. *et al.* Risk Factors for COVID-19-associated hospitalization: COVID-19-Associated Hospitalization Surveillance Network and Behavioral Risk Factor Surveillance System. *Clin Infect Dis*, doi:10.1093/cid/ciaa1419 (2020).
- 5 Williamson, E. J. *et al.* Factors associated with COVID-19-related death using OpenSAFELY. *Nature* **584**, 430-436, doi:10.1038/s41586-020-2521-4 (2020).
- 6 Thomas, T. *et al.* COVID-19 infection alters kynurenine and fatty acid metabolism, correlating with IL-6 levels and renal status. *JCI Insight* **5**, doi:10.1172/jci.insight.140327 (2020).
- 7 Codo, A. C. *et al.* Elevated Glucose Levels Favor SARS-CoV-2 Infection and Monocyte Response through a HIF-1 α /Glycolysis-Dependent Axis. *Cell Metabolism* **32**, 437-446.e435, doi:<https://doi.org/10.1016/j.cmet.2020.07.007> (2020).
- 8 Ajaz, S. *et al.* Mitochondrial metabolic manipulation by SARS-CoV-2 in peripheral blood mononuclear cells of patients with COVID-19. *American Journal of Physiology-Cell Physiology* **320**, C57-C65, doi:10.1152/ajpcell.00426.2020 (2021).
- 9 Gordon, D. E. *et al.* A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug-Repurposing. *bioRxiv*, 2020.2003.2022.002386, doi:10.1101/2020.03.22.002386 (2020).
- 10 Bojkova, D. *et al.* Proteomics of SARS-CoV-2-infected host cells reveals therapy targets. *Nature* **583**, 469-472, doi:10.1038/s41586-020-2332-7 (2020).
- 11 Delorey, T. M. *et al.* COVID-19 tissue atlases reveal SARS-CoV-2 pathology and cellular targets. *Nature*, doi:10.1038/s41586-021-03570-8 (2021).
- 12 Melms, J. C. *et al.* A molecular single-cell lung atlas of lethal COVID-19. *Nature*, doi:10.1038/s41586-021-03569-1 (2021).
- 13 Islam, A. B. M. M. K. & Khan, M. A.-A.-K. Lung transcriptome of a COVID-19 patient and systems biology predictions suggest impaired surfactant production which may be druggable by surfactant therapy. *Scientific reports* **10**, 19395-19395, doi:10.1038/s41598-020-76404-8 (2020).

- 14 Singh, K. *et al.* Network Analysis and Transcriptome Profiling Identify Autophagic and Mitochondrial Dysfunctions in SARS-CoV-2 Infection. *Front Genet* **12**, 599261-599261, doi:10.3389/fgene.2021.599261 (2021).
- 15 Yuan, S. *et al.* SREBP-dependent lipidomic reprogramming as a broad-spectrum antiviral target. *Nature Communications* **10**, 120, doi:10.1038/s41467-018-08015-x (2019).
- 16 McBride, C. E. & Machamer, C. E. Palmitoylation of SARS-CoV S protein is necessary for partitioning into detergent-resistant membranes and cell-cell fusion but not interaction with M protein. *Virology* **405**, 139-148, doi:10.1016/j.virol.2010.05.031 (2010).
- 17 Yan, B. *et al.* Characterization of the Lipidomic Profile of Human Coronavirus-Infected Cells: Implications for Lipid Metabolism Remodeling upon Coronavirus Replication. *Viruses* **11**, 73, doi:10.3390/v11010073 (2019).
- 18 Barberis, E. *et al.* Large-Scale Plasma Analysis Revealed New Mechanisms and Molecules Associated with the Host Response to SARS-CoV-2. *Int J Mol Sci* **21**, doi:10.3390/ijms21228623 (2020).
- 19 Wang, L. *et al.* Serum triglyceride level and hypertension are highly associated with the recovery of COVID-19 patients. *Am J Transl Res* **12**, 6646-6654 (2020).
- 20 Masana, L. *et al.* Low HDL and high triglycerides predict COVID-19 severity. *Sci Rep* **11**, 7217, doi:10.1038/s41598-021-86747-5 (2021).
- 21 Bergen, W. G. & Mersmann, H. J. Comparative Aspects of Lipid Metabolism: Impact on Contemporary Research and Use of Animal Models. *The Journal of Nutrition* **135**, 2499-2502, doi:10.1093/jn/135.11.2499 (2005).
- 22 Demetrius, L. Of mice and men. When it comes to studying ageing and the means to slow it down, mice are not just small humans. *EMBO Rep* **6 Spec No**, S39-S44, doi:10.1038/sj.embor.7400422 (2005).
- 23 Kulcsar, K. A., Coleman, C. M., Beck, S. E. & Frieman, M. B. Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. *JCI insight* **4**, e131774, doi:10.1172/jci.insight.131774 (2019).
- 24 Wu, Q. *et al.* Altered Lipid Metabolism in Recovered SARS Patients Twelve Years after Infection. *Scientific Reports* **7**, 9110, doi:10.1038/s41598-017-09536-z (2017).
- 25 Yang, J. K., Lin, S. S., Ji, X. J. & Guo, L. M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol* **47**, 193-199, doi:10.1007/s00592-009-0109-4 (2010).
- 26 Akter, F. *et al.* Clinical characteristics and short term outcomes after recovery from COVID-19 in patients with and without diabetes in Bangladesh. *Diabetes Metab Syndr* **14**, 2031-2038, doi:10.1016/j.dsx.2020.10.016 (2020).
- 27 Al-Aly, Z., Xie, Y. & Bowe, B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*, doi:10.1038/s41586-021-03553-9 (2021).
- 28 Li, G. *et al.* Follow-up study on serum cholesterol profiles and potential sequelae in recovered COVID-19 patients. *BMC Infectious Diseases* **21**, 299, doi:10.1186/s12879-021-05984-1 (2021).
- 29 Ahmadian, M. *et al.* PPAR γ signaling and metabolism: the good, the bad and the future. *Nature medicine* **19**, 557-566, doi:10.1038/nm.3159 (2013).
- 30 Todd, M. K., Watt, M. J., Le, J., Hevener, A. L. & Turcotte, L. P. Thiazolidinediones enhance skeletal muscle triacylglycerol synthesis while protecting against fatty acid-

- induced inflammation and insulin resistance. *Am J Physiol Endocrinol Metab* **292**, E485-493, doi:10.1152/ajpendo.00080.2006 (2007).
- 31 Phan, A. N. H. *et al.* PPAR γ sumoylation-mediated lipid accumulation in lung cancer. *Oncotarget* **8**, 82491-82505, doi:10.18632/oncotarget.19700 (2017).
- 32 Hou, Y. J. *et al.* SARS-CoV-2 Reverse Genetics Reveals a Variable Infection Gradient in the Respiratory Tract. *Cell* **182**, 429-446.e414, doi:10.1016/j.cell.2020.05.042 (2020).
- 33 Vanderheiden, A. *et al.* Type I and Type III Interferons Restrict SARS-CoV-2 Infection of Human Airway Epithelial Cultures. *J Virol* **94**, doi:10.1128/jvi.00985-20 (2020).
- 34 Liao, M. *et al.* Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nature Medicine* **26**, 842-844, doi:10.1038/s41591-020-0901-9 (2020).
- 35 Levy, G. *et al.* Nuclear receptors control pro-viral and antiviral metabolic responses to hepatitis C virus infection. *Nature Chemical Biology* **12**, 1037-1045, doi:10.1038/nchembio.2193 (2016).
- 36 Liberzon, A. *et al.* The Molecular Signatures Database (MSigDB) hallmark gene set collection. *Cell Syst* **1**, 417-425, doi:10.1016/j.cels.2015.12.004 (2015).
- 37 Mayer, K. A., Stöckl, J., Zlabinger, G. J. & Gualdoni, G. A. Hijacking the Supplies: Metabolism as a Novel Facet of Virus-Host Interaction. *Frontiers in Immunology* **10**, doi:10.3389/fimmu.2019.01533 (2019).
- 38 Yu, Y., Maguire, T. G. & Alwine, J. C. ChREBP, a glucose-responsive transcriptional factor, enhances glucose metabolism to support biosynthesis in human cytomegalovirus-infected cells. *Proc Natl Acad Sci U S A* **111**, 1951-1956, doi:10.1073/pnas.1310779111 (2014).
- 39 Han, J. & Kaufman, R. J. The role of ER stress in lipid metabolism and lipotoxicity. *J Lipid Res* **57**, 1329-1338, doi:10.1194/jlr.R067595 (2016).
- 40 Yu, Y., Pierciey, F. J., Jr., Maguire, T. G. & Alwine, J. C. PKR-like endoplasmic reticulum kinase is necessary for lipogenic activation during HCMV infection. *PLoS Pathog* **9**, e1003266, doi:10.1371/journal.ppat.1003266 (2013).
- 41 Rutkowski, D. T. *et al.* UPR Pathways Combine to Prevent Hepatic Steatosis Caused by ER Stress-Mediated Suppression of Transcriptional Master Regulators. *Developmental Cell* **15**, 829-840, doi:<https://doi.org/10.1016/j.devcel.2008.10.015> (2008).
- 42 Sharpe, L. J. & Brown, A. J. Controlling cholesterol synthesis beyond 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR). *The Journal of biological chemistry* **288**, 18707-18715, doi:10.1074/jbc.R113.479808 (2013).
- 43 Mookerjee, S. A., Gerencser, A. A., Nicholls, D. G. & Brand, M. D. Quantifying intracellular rates of glycolytic and oxidative ATP production and consumption using extracellular flux measurements. *The Journal of biological chemistry* **292**, 7189-7207, doi:10.1074/jbc.M116.774471 (2017).
- 44 Gualdoni, G. A. *et al.* Rhinovirus induces an anabolic reprogramming in host cell metabolism essential for viral replication. *Proc Natl Acad Sci U S A* **115**, E7158-e7165, doi:10.1073/pnas.1800525115 (2018).
- 45 Kilbourne, E. D. Inhibition of influenza virus multiplication with a glucose antimetabolite (2-deoxy-D-glucose). *Nature* **183**, 271-272, doi:10.1038/183271b0 (1959).
- 46 Fujita, N. *et al.* Effects of bezafibrate in patients with chronic hepatitis C virus infection: combination with interferon and ribavirin. *J Viral Hepat* **13**, 441-448, doi:10.1111/j.1365-2893.2005.00718.x (2006).

- 47 Ikeda, M. *et al.* Different anti-HCV profiles of statins and their potential for combination therapy with interferon. *Hepatology* **44**, 117-125, doi:10.1002/hep.21232 (2006).
- 48 Andrzejewski, S., Gravel, S.-P., Pollak, M. & St-Pierre, J. Metformin directly acts on mitochondria to alter cellular bioenergetics. *Cancer Metab* **2**, 12-12, doi:10.1186/2049-3002-2-12 (2014).
- 49 Tang, D. *et al.* Metformin facilitates BG45-induced apoptosis via an anti-Warburg effect in cholangiocarcinoma cells. *Oncol Rep* **39**, 1957-1965, doi:10.3892/or.2018.6275 (2018).
- 50 Tong, Q. *et al.* Inhibition of endoplasmic reticulum stress-activated IRE1 α -TRAF2-caspase-12 apoptotic pathway is involved in the neuroprotective effects of telmisartan in the rotenone rat model of Parkinson's disease. *Eur J Pharmacol* **776**, 106-115, doi:10.1016/j.ejphar.2016.02.042 (2016).
- 51 Belvisi, M. G. & Mitchell, J. A. Targeting PPAR receptors in the airway for the treatment of inflammatory lung disease. *British Journal of Pharmacology* **158**, 994-1003, doi:<https://doi.org/10.1111/j.1476-5381.2009.00373.x> (2009).
- 52 Burggraaff, L. *et al.* Identification of novel small molecule inhibitors for solute carrier SGLT1 using proteochemometric modeling. *Journal of Cheminformatics* **11**, 15, doi:10.1186/s13321-019-0337-8 (2019).
- 53 Mueller, A. A. *et al.* Inflammatory Biomarker Trends Predict Respiratory Decline in COVID-19 Patients. *Cell Reports Medicine* **1**, 100144, doi:10.1016/j.xcrm.2020.100144 (2020).
- 54 Feng, X. *et al.* Immune-Inflammatory Parameters in COVID-19 Cases: A Systematic Review and Meta-Analysis. *Frontiers in Medicine* **7**, doi:10.3389/fmed.2020.00301 (2020).
- 55 Zhu, Z. *et al.* Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. *International Journal of Infectious Diseases* **95**, 332-339, doi:<https://doi.org/10.1016/j.ijid.2020.04.041> (2020).
- 56 World Health, O. COVID-19 clinical management: living guidance, 25 January 2021. (World Health Organization, Geneva, 2021).
- 57 Ling, H., Luoma, J. T. & Hilleman, D. A Review of Currently Available Fenofibrate and Fenofibric Acid Formulations. *Cardiol Res* **4**, 47-55, doi:10.4021/cr270w (2013).
- 58 Maciejewski, S. & Hilleman, D. Effectiveness of a fenofibrate 145-mg nanoparticle tablet formulation compared with the standard 160-mg tablet in patients with coronary heart disease and dyslipidemia. *Pharmacotherapy* **28**, 570-575, doi:10.1592/phco.28.5.570 (2008).
- 59 Smallwood, H. S. *et al.* Targeting Metabolic Reprogramming by Influenza Infection for Therapeutic Intervention. *Cell Rep* **19**, 1640-1653, doi:10.1016/j.celrep.2017.04.039 (2017).
- 60 Zhu, N. *et al.* Morphogenesis and cytopathic effect of SARS-CoV-2 infection in human airway epithelial cells. *Nature Communications* **11**, 3910, doi:10.1038/s41467-020-17796-z (2020).
- 61 Setti, L., Kirienko, M., Dalto, S. C., Bonacina, M. & Bombardieri, E. FDG-PET/CT findings highly suspicious for COVID-19 in an Italian case series of asymptomatic patients. *European Journal of Nuclear Medicine and Molecular Imaging* **47**, 1649-1656, doi:10.1007/s00259-020-04819-6 (2020).
- 62 Turabian, J. L. A Case Control-Study of Cloperastine Treatment in Covid-19. Potential

- Drug, Clinical Observation and Common Sense. *Epidemiology International Journal* **4**, 13, doi:<https://doi.org/10.23880/eij-16000S1-009> (2020).
- 63 Cheng, X. *et al.* Metformin Is Associated with Higher Incidence of Acidosis, but Not Mortality, in Individuals with COVID-19 and Pre-existing Type 2 Diabetes. *Cell metabolism* **32**, 537-547.e533, doi:10.1016/j.cmet.2020.08.013 (2020).
 - 64 Hetz, C., Zhang, K. & Kaufman, R. J. Mechanisms, regulation and functions of the unfolded protein response. *Nature Reviews Molecular Cell Biology* **21**, 421-438, doi:10.1038/s41580-020-0250-z (2020).
 - 65 Wang, N. *et al.* Impaired energy homeostasis in C/EBP alpha knockout mice. *Science* **269**, 1108-1112, doi:10.1126/science.7652557 (1995).
 - 66 Xu, Z. *et al.* Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet Respiratory Medicine* **8**, 420-422, doi:10.1016/S2213-2600(20)30076-X (2020).
 - 67 Pizzorno, A. *et al.* Characterization and treatment of SARS-CoV-2 in nasal and bronchial human airway epithelia. *bioRxiv*, 2020.2003.2031.017889, doi:10.1101/2020.03.31.017889 (2020).
 - 68 Plantier, L. *et al.* Activation of sterol-response element-binding proteins (SREBP) in alveolar type II cells enhances lipogenesis causing pulmonary lipotoxicity. *J Biol Chem* **287**, 10099-10114, doi:10.1074/jbc.M111.303669 (2012).
 - 69 Silvas, J. A., Jureka, A. S., Nicolini, A. M., Chvatal, S. A. & Basler, C. F. Inhibitors of VPS34 and lipid metabolism suppress SARS-CoV-2 replication. *bioRxiv*, 2020.2007.2018.210211, doi:10.1101/2020.07.18.210211 (2020).
 - 70 Hao Zhang, J. S., Heng Xu, Jing Sun, Wen Yin, Yu Zuo, Zhangzhao Wang, Fengmin Xiong, Yuqi Zhang, Hua Lin, Jingqiu Liu, Yiluan Ding, Naixia Zhang, Hualiang Jiang, & Kaixian Chen, W. J. Z., Kehao Zhao, Jincun Zhao, Xiangyang Xie and Cheng Luo. Activation of Peroxiredoxin 1 by Fluvastatin Effectively Protects from Inflammation and SARS-CoV-2. *SSRN Electronic Journal*, doi:<https://dx.doi.org/10.2139/ssrn.3606782> (2020).
 - 71 Zhang, X.-J. *et al.* In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19. *Cell metabolism* **32**, 176-187.e174, doi:10.1016/j.cmet.2020.06.015 (2020).
 - 72 Lalloyer, F. & Staels, B. Fibrates, glitazones, and peroxisome proliferator-activated receptors. *Arterioscler Thromb Vasc Biol* **30**, 894-899, doi:10.1161/ATVBAHA.108.179689 (2010).
 - 73 Fruchart, J. C. & Duriez, P. Mode of action of fibrates in the regulation of triglyceride and HDL-cholesterol metabolism. *Drugs Today (Barc)* **42**, 39-64, doi:10.1358/dot.2006.42.1.963528 (2006).
 - 74 Singh, S., Loke, Y. K. & Furberg, C. D. Long-term use of thiazolidinediones and the associated risk of pneumonia or lower respiratory tract infection: systematic review and meta-analysis. *Thorax* **66**, 383-388, doi:10.1136/thx.2010.152777 (2011).
 - 75 Esnaola, M., Puig, P., Gonzalez, D., Castelo, R. & Gonzalez, J. R. A flexible count data model to fit the wide diversity of expression profiles arising from extensively replicated RNA-seq experiments. *BMC Bioinformatics* **14**, 254, doi:10.1186/1471-2105-14-254 (2013).
 - 76 Robinson, M. D., McCarthy, D. J. & Smyth, G. K. edgeR: a Bioconductor package for differential expression analysis of digital gene expression data. *Bioinformatics* **26**, 139-140, doi:10.1093/bioinformatics/btp616 (2009).

- 77 Chen, S., Zhou, Y., Chen, Y. & Gu, J. fastp: an ultra-fast all-in-one FASTQ preprocessor. *Bioinformatics* **34**, i884-i890, doi:10.1093/bioinformatics/bty560 (2018).
- 78 Bray, N. L., Pimentel, H., Melsted, P. & Pachter, L. Near-optimal probabilistic RNA-seq quantification. *Nature Biotechnology* **34**, 525-527, doi:10.1038/nbt.3519 (2016).
- 79 Huang, D. W., Sherman, B. T. & Lempicki, R. A. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nature Protocols* **4**, 44-57, doi:10.1038/nprot.2008.211 (2009).
- 80 Mi, H., Muruganujan, A., Ebert, D., Huang, X. & Thomas, P. D. PANTHER version 14: more genomes, a new PANTHER GO-slim and improvements in enrichment analysis tools. *Nucleic Acids Research* **47**, D419-D426, doi:10.1093/nar/gky1038 (2018).
- 81 Xia, J., Gill, E. E. & Hancock, R. E. W. NetworkAnalyst for statistical, visual and network-based meta-analysis of gene expression data. *Nature Protocols* **10**, 823-844, doi:10.1038/nprot.2015.052 (2015).
- 82 Ehrlich, A. *et al.* Microphysiological flux balance platform unravels the dynamics of drug induced steatosis. *Lab Chip* **18**, 2510-2522, doi:10.1039/c8lc00357b (2018).
- 83 Lee, D. D. & Seung, H. S. Learning the parts of objects by non-negative matrix factorization. *Nature* **401**, 788-791, doi:10.1038/44565 (1999).
- 84 Delvenne, J.-C., Yaliraki, S. N. & Barahona, M. Stability of graph communities across time scales. *Proceedings of the National Academy of Sciences* **107**, 12755-12760, doi:10.1073/pnas.0903215107 (2010).
- 85 Maaten, L. V. D. Accelerating t-SNE using tree-based algorithms. *J. Mach. Learn. Res.* **15**, 3221-3245 (2014).
- 86 Plasschaert, L. W. *et al.* A single-cell atlas of the airway epithelium reveals the CFTR-rich pulmonary ionocyte. *Nature* **560**, 377-381, doi:10.1038/s41586-018-0394-6 (2018).
- 87 Chu, D. K. W. *et al.* Molecular Diagnosis of a Novel Coronavirus (2019-nCoV) Causing an Outbreak of Pneumonia. *Clin Chem* **66**, 549-555, doi:10.1093/clinchem/hvaa029 (2020).
- 88 Corman, V. M. *et al.* Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill* **25**, 2000045, doi:10.2807/1560-7917.ES.2020.25.3.2000045 (2020).
- 89 Rosenthal, N., Cao, Z., Gundrum, J., Sianis, J. & Safo, S. Risk Factors Associated With In-Hospital Mortality in a US National Sample of Patients With COVID-19. *JAMA Network Open* **3**, e2029058-e2029058, doi:10.1001/jamanetworkopen.2020.29058 (2020).
- 90 Cummings, M. J. *et al.* Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *The Lancet* **395**, 1763-1770, doi:10.1016/S0140-6736(20)31189-2 (2020).
- 91 King, G. & Nielsen, R. Why Propensity Scores Should Not Be Used for Matching. *Political Analysis* **27**, 435-454, doi:10.1017/pan.2019.11 (2019).
- 92 Wang, J. To use or not to use propensity score matching? *Pharmaceutical Statistics* **20**, 15-24, doi:<https://doi.org/10.1002/pst.2051> (2021).
- 93 Fullerton, B. *et al.* The Comparison of Matching Methods Using Different Measures of Balance: Benefits and Risks Exemplified within a Study to Evaluate the Effects of German Disease Management Programs on Long-Term Outcomes of Patients with

- Type 2 Diabetes. *Health Serv Res* **51**, 1960-1980, doi:10.1111/1475-6773.12452 (2016).
- 94 Ali, M. S. *et al.* Propensity Score Methods in Health Technology Assessment: Principles, Extended Applications, and Recent Advances. *Frontiers in Pharmacology* **10**, doi:10.3389/fphar.2019.00973 (2019).
- 95 Cleveland, W. S. Robust Locally Weighted Regression and Smoothing Scatterplots. *Journal of the American Statistical Association* **74**, 829-836, doi:10.1080/01621459.1979.10481038 (1979).
- 96 Heinze, G. & Schemper, M. A solution to the problem of monotone likelihood in Cox regression. *Biometrics* **57**, 114-119, doi:10.1111/j.0006-341x.2001.00114.x (2001).
- 97 Brown, K. A. *et al.* S-Gene Target Failure as a Marker of Variant B.1.1.7 Among SARS-CoV-2 Isolates in the Greater Toronto Area, December 2020 to March 2021. *JAMA*, doi:10.1001/jama.2021.5607 (2021).
- 98 Davies, N. G. *et al.* Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. *Nature* **593**, 270-274, doi:10.1038/s41586-021-03426-1 (2021).
- 99 Shyu, W. M. in *Statistical models in S* 309-376 (Routledge, 2017).

Figure 1. Transcriptional metabolic signature of SARS-CoV-2 infection. (A) Bubble plot visualization of GO terms enriched by SARS-CoV-2 infection. Epithelial cells were isolated by bronchoalveolar lavage from 6 severe COVID-19 patients compared to 4 healthy patients (lavage). Post-mortem lung biopsies from 2 severe COVID-19 patients compared to surgical biopsies from 2 non-COVID patients (autopsy). Culture sample groups include primary small airway epithelial cells (n=3; alveoli) and primary bronchial epithelial cells (n=3; bronchial) infected with SARS-CoV-2. Enrichment analysis shows immunoinflammatory response, cellular stress (FDR<10⁻²²), and lipid metabolism (FDR<10⁻⁵). (B) Venn diagram describing the relationship between differentially expressed genes (DEG), metabolic genes (GO:0008152), and lipid metabolism genes (GO:0006629) in SARS-CoV-2 infection of primary bronchial epithelial cells and COVID-19 patient samples. Across all four sample groups 58±3% of the differentially expressed genes were metabolism-related, with 15±2% of the genes associated with lipid metabolism. (C) Sunburst graph showing the coverage of composite metabolic terms {Levy, 2016 #7} on general metabolic response induced by SARS-CoV-2 infection of primary bronchial epithelial cells and COVID-19 patient samples. Lipid and mitochondrial metabolism dominate the transcriptional metabolic signature of infection across all four sample groups (Supp. Fig. S1). (D) Schematic depicting the metabolic landscape of SARS-CoV-2 infection superimposed with a heat map of pathway-associated genes. Red and green boxes indicate gene expression changes following infection in primary bronchial epithelial cells. * marks differentially regulated genes (n=3, FDR<0.05). # indicates small sample size.

Figure 2. Metabolic fingerprint of SARS-CoV-2 infection. (A) Schematic of ER stress pathways superimposed with pathway-associated genes. Red and green boxes are up and downregulated by infection, respectively. * marks differentially regulated genes (n=3, FDR<0.05). Red arrows note putative activation pathways based on the transcriptional response. XBP1S/U is the ratio of IRE1-spliced over the un-spliced form of XBP1. (B) Schematic of central carbon metabolism fluxes superimposed with flux-associated genes. Differentially expressed genes (n=3, FDR <0.01) are marked with *. Genes and associated fluxes are highlighted red or green for up- or down-regulation, respectively. (C) Metabolic analysis of SARS-CoV-2 and mock-infected primary bronchial epithelial cells confirms a 50% increase (n=6, p<0.001) in lactate production 48 hours post-infection. (D) The ratio of lactate production to glucose uptake (glycolytic index) in SARS-CoV-2 and mock-infected primary cells. Index increases from 1.0 to 1.7 out of 2.0 indicating transition to glycolysis (i.e., Warburg effect). (E) Microscopic evaluation of primary bronchial epithelial cells infected with SARS-CoV-2 virus or mock control shows an 85% increase in the intracellular accumulation of fluorescent glucose analog (n=3; Bar = 40 μ m). (F) Schematic of lipid metabolism fluxes superimposed with flux-associated genes. Differentially expressed genes (n=3, FDR <0.01) are marked with *. Genes and associated fluxes are highlighted red or green for up- or down-regulation, respectively. (G) Microscopic evaluation of primary bronchial epithelial cells infected with SARS-CoV-2 virus or mock control. Neutral lipids (triglycerides) are dyed green while phospholipids are dyed red. Image analysis shows a 23% increase in triglycerides (n=3, p<0.05) and 41% increase in phospholipids (n=3, p<0.001) following SARS-CoV-2 infection (Bar = 10 μ m) indicating abnormal lipid accumulation in lung epithelium. (H) T-distributed stochastic neighbour embedding (tSNE) plot shows clustering of 2,629 lung epithelial cells of severe COVID-19 patients isolated by bronchoalveolar lavage (methods). Point coordinates were calculated based on Non-negative matrix factorization (NMF) of top over-dispersed genes (methods). Cell color specifies assignment to 1 of 6 clusters identified as virus replicating cells, as well as basal, secretory, FOXN4-positive, SLC16A7-positive, and ciliated cell clusters (Supp. Fig. S2). (I) Expression of SARS-CoV-2 (nCoV) superimposed on the tSNE plot (and associated abundance analysis showing that the virus replicating cluster is enriched with viral RNA. Proportions indicate the relative number of cells with > 1 log₂(TPX) in each group. (J) Gene enrichment analysis comparing virus replicating cells to uninfected epithelial cells showing differences in the cellular response to endoplasmic reticulum stress (FDR<1x10⁻⁶), metabolic processes (FDR<9x10⁻⁴), and lipid metabolism (FDR<3x10⁻³) in the same COVID-19 patients. * p<0.05, ** p<0.01, *** p<0.001. Error bars indicate S.E.M.

Figure 3. SARS-CoV-2 proteins modulate host metabolic pathways. Analysis of primary bronchial epithelial cells expressing different SARS-CoV-2 proteins for 72 hours using multiple independent assays. **(A)** Analysis of CHOP and XBP1 spliced isoform (XBP1S/U) by qRT-PCR as markers of ER stress. Expression of ORF9c, M, N, ORF3a, NSP7, ORF8, NSP5, and NSP12 significantly up-regulated both markers ($n=6$, $p<0.05$). **(B-C)** Microscopic analysis of triglycerides (neutral lipids) and phospholipids shows a virus protein-induced perinuclear lipid accumulation. **(C)** Quantification shows a significant accumulation of phospholipids in cells expressing the same panel of viral proteins that induced ER stress ($n=6$, $p<0.01$). **(D-E)** Microscopic analysis shows an increased abundance of fluorescent glucose analog (2-NDBG) by a smaller set of viral proteins than above. **(E)** Quantification shows a significant increase in intracellular glucose in bronchial cells expressing N, ORF3a, NSP7, ORF8, NSP5, and NSP12 ($n=6$, $p<0.05$). **(F)** Direct measurement of lactate production of bronchial epithelial cells shows significantly higher lactate production ($n=6$, $p<0.01$) in cells expressing the smaller protein subset. **(G)** The ratio of lactate production to glucose uptake (glycolytic index) in bronchial cells expressing viral proteins. Index significantly increases from 1.1 to 1.7 marking a shift to glycolysis ($n=6$, $p<0.01$) induced by the viral proteins. **(H)** Seahorse™ analysis of extracellular acidification rate (ECAR) surrogate measurement for lactate production, shows independent confirmation of increased glycolysis. **(I)** Seahorse™ mitochondrial stress analysis of bronchial cells expressing the viral proteins. Oxygen consumption rate (OCR) is shown as a function of time. Oligomycin, FCCP, and antimycin/rotenone were injected at 25, 55, and 85 minutes, respectively. **(J)** Quantification of oxidative phosphorylation (OXPHOS) shows a decrease of mitochondrial function following expression of N, ORF3a, and NSP7 ($n=6$, $p<0.05$). * $p<0.05$, ** $p<0.01$, *** $p<0.001$ in a 2-sided heteroscedastic student's t-test against control. Bar = 40 μ m. Error bars indicate S.E.M.

Figure 4

Figure 4. Therapeutic targets of SARS-CoV-2 associated host metabolic pathways. (A) Schematic depicting the metabolic landscape of SARS-CoV-2 infection. Potential drugs (white boxes) and their therapeutic targets are marked on the chart. (B) Table summarizing FDA-approved drugs that interfere with SARS-CoV-2 induced metabolic alterations. (C) Microscopic analysis of lipid accumulation in SARS-CoV-2 infected lung cells exposed to different drugs for 5 days compared to DMSO-treated (vehicle) and mock-infected controls. Cells treated with PPAR α agonist fenofibrate showed a significant decrease in phospholipid content ($n=3$; $p<0.001$). (D) Lactate over glucose ratio of SARS-CoV-2 infected primary lung cells treated with various drugs. Fenofibrate significantly reduced the lactate to glucose ratio by 60% ($n=3$; $p<0.01$) normalizing the metabolic shift induced by infection. (E) Quantification of SARS-CoV-2 viral RNA over 5 days of treatment with a physiological concentration of various drugs or DMSO (vehicle). Treatment with 20 μ M fenofibrate reduced SARS-CoV-2 viral load by 2-logs ($n=3$; $p<0.001$). Treatment with 10 μ M cloperastine reduced viral load by 2.5 to 3-fold ($n=3$; $p<0.05$). (F) Cell viability 5-days post-treatment was unaffected by all drugs tested. (G) Comparative representation of Israeli patients above the age of 30 taking different metabolic regulators. 532,493 unique general hospital medical records were compared with 2,806 confirmed COVID-19 patients. COVID-19 patients treated with metabolic regulators were older and had a higher prevalence of chronic medical conditions and risk factors than other COVID-19 patients (Table S1). Patients taking thiazolidinediones ($n=37$; $p<0.001$), metformin ($n=321$; $p<0.01$), SGLT2 inhibitors ($n=54$; $p<0.001$), statins ($n=924$; $p<0.001$), or telmisartan (IRE1 α inhibitor; $n=278$; $p<0.001$) were over-represented across all severity indicators (Table S2). Patients taking fibrates ($n=21$) were significantly underrepresented in hospital admissions ($p=0.02$) and were not over-represented in other severity indicators. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ in a Wald test compared to the proportion of these drug users in medical records. Bar = 50 μ m. Error bars indicate S.E.M.

Figure 5. Observational study shows differential immunoinflammatory response to metabolic intervention.

(A) Schematic depicting the in-hospital progression of severe COVID-19, characterized by early lipotoxicity-induced inflammation, marked by elevated C-reactive protein (CRP), followed by distinct changes in neutrophils and lymphocytes marking the immunoinflammatory response followed by recovery (Supp. Fig. S5). (B) Box and whisker plot of length of hospitalization in treatment and non-treatment groups (Control). Israeli patients taking bezafibrate or ciprofibrate (fibrates) were associated with significantly lower hospitalization duration ($p=0.03$). (C-D) Dynamic changes in the inflammation marker CRP and neutrophil-to-lymphocyte ratio (NLR) marking immunoinflammatory stress in treatment and non-treatment groups (Control) during 21-day hospitalization. The centerline shows the mean value while the 95% confidence interval is represented by the shaded region. (C) CRP levels gradually declined in the control group reaching a plateau by day 14 post-hospitalization. The fibrates group showed a significantly faster decline in inflammation, while the thiazolidinedione group showed marked elevation in CRP level above control. (D) NLR rose in the control group above normal values (dotted red line) stabilizing after 7-14 days and then declining as recovery begins. The fibrates group showed only mild stress, maintain normal levels of NLR throughout hospitalization. Patients taking statins or IRE-inhibitors showed elevated NLR post-day 10 of hospitalization. (E) Kaplan-Meier survival curves of 28-day in-hospital mortality for treatment and non-treatment groups (Control). The small group of patients taking fibrates did not report any deaths, while thiazolidinedione and SGLT2 inhibitor users had a significantly higher risk of mortality (HR: 3.6, 2.5; $p=0.04$, 0.03 respectively, Table S4). * $p<0.05$, ** $p<0.01$, *** $p<0.001$. In boxplots, x is the mean; center line is median; box limits are 25th and 75th percentiles; whiskers extend to 1.5 $\times$ the interquartile range (IQR) from the 25th and 75th percentiles; dots are outliers. # indicates that the hazard ratios were calculated using Firth's correction for monotone likelihood with profile likelihood confidence limits.

Figure 6. Nanocrystallized fenofibrate (TriCor®) reduced inflammation and sped recovery in severe COVID-19 patients treated with standard-of-care. (A) Schematic depicting interventional study design in 15 severe hospitalized COVID-19 patients receiving remdesivir, dexamethasone, and enoxaparin. Patients received 145 mg/day of TriCor® for 10 days with blood samples taken every 48-72 hours until discharge. (B) Chemical, clinical, and pharmacokinetic characteristics of nanocrystallized fenofibrate (TriCor®). Lower T_{max} compared to other fibrates enables rapid intervention in deteriorating COVID-19 patients. (C) box and whisker plot of hospitalization duration (left) and Cox accumulative estimated hospital time to discharge by day 28 analysis, plotted as 1 minus the Cox estimator (right). Patients treated with TriCor® resulted in significantly lower hospitalization duration (n=15; p<0.001), and a higher likelihood of discharge (HR: 3.6, 95% CI 2.1 to 6.4; n=15; p < 0.001). (D-E) Dynamic changes (right) and box and whisker plots (left) of immunoinflammatory indicators CRP and neutrophil-to-lymphocyte ratio (NLR) in treatment and non-treatment groups (Control) over hospitalization duration (methods). The centerline shows the mean value while the 95% confidence interval is shaded. (D) High CRP levels gradually declined in the control group reaching a plateau by day 7. TriCor® treated patients showed a faster decline in inflammation, resulting in significantly lower CRP levels 3-5 days post-treatment (n=15; p<0.001). (E) NLR in the control group increased during hospitalization indicating severe immunoinflammatory stress. Patients treated with TriCor® showed no increase in NLR, suggesting minimal immune response, resulting in a significantly lower NLR 3-5 days post-treatment (n=15; p=0.002). (F) Withdrawal from oxygen support, plotted as cumulative incidence at day 7 (left; OR: 3.2, 95% CI 1.3 to 7.9; n=15; p = 0.005) Kaplan-Meier estimated time to discharge by day 28, plotted as 1 minus the survival estimator (right; HR: 2.9, 95% CI 1.7 to 5.0; n=15; p < 0.001). (G) Kaplan-Meier survival curves of 28-days mortality of treatment and non-treatment groups (Control) and Cox regression modeling presenting hazard ratio estimate, 95% CI and p-value. (H) Novaplex™ SARS-CoV-2 qPCR variant analysis (methods), showing a dominant presence of 69/70 deletion and N501Y substitution mutation correlating to the B.1.1.7 (UK) variant of the virus in the patient population. (I) Pie chart representation of variant distribution between the patient in the interventional study and

other patients in other clinical centers in Israel during the same period (OR: 1.36, 0.59 to 3.1; $p = 0.44$). SGTF, S-gene target failure, serves as a proxy for identifying B.1.1.7 cases^{97,98}. Hazard ratios (HR) and the related p-values were calculated by a Cox regression model. Odds ratios (ORs) and the related p-values were calculated using Fisher's exact test (methods). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. In boxplots, x is the mean; center line is median; box limits are 25th and 75th percentiles; whiskers extend to 1.5× the interquartile range (IQR) from the 25th and 75th percentiles; dots are outliers. # indicates that the hazard ratios were calculated using Firth's correction for monotone likelihood with profile likelihood confidence limits.

Table S1. Characteristics of COVID-19 patients in the cohort. SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, chronic obstructive pulmonary disease; SpO₂, oxygen saturation; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range. Continuous variables were compared with a two-sample t-test and categorical variables with Fisher's exact test.

		Full population
Any Metabolic Regulating Drugs		1,156
	Fibrates	21
	Statins	927
	Thiazolidinediones	37
	SGLT2 Inhibitors	55
	IRE1α inhibitors	282
	Metformin	322
No Metabolic Regulating Drugs		2,077

Drug Type: Any Metabolic Regulating Drugs

		Full population		
		Any Metabolic Regulating Drugs	No Metabolic Regulating Drugs	p value
Clinical Characteristics on Admission	Age, median (IQR)	69.20 (60.5-78.2)	47.40 (32.6-64.0)	<.0001
	Female gender, n (%)	466 (40.3%)	1,014 (48.8%)	<.0001
	Heart rate, median (IQR), bpm	83.00 (73.0-94.0)	85.00 (75.0-96.0)	0.0003
	SBP, median (IQR), mmHg	131.0 (117.0-147.0)	122.0 (111.0-135.0)	<.0001
	DBP, median (IQR), mmHg	73.0 (64.0-82.0)	74.0 (66.0-82.0)	0.2831
	SpO2, median (IQR)	95.0 (93.0-97.0)	96.0 (94.0-98.0)	<.0001
	Temperature (P.O), median (IQR)	36.9 (36.6-37.3)	36.9 (36.7-37.3)	0.7806
	Smoking, n (%)	49 (4.2%)	44 (2.1%)	0.0009
Comorbidities on Admission	Asthma, n (%)	36 (3.1%)	69 (3.3%)	0.8361
	COPD, n (%)	60 (5.2%)	35 (1.7%)	<.0001
	Hypertension, n (%)	702 (60.7%)	325 (15.6%)	<.0001
	Diabetes, n (%)	636 (55.0%)	187 (9.0%)	<.0001
	Coronary heart disease, n (%)	349 (30.2%)	88 (4.2%)	<.0001
	Obesity, n (%)	125 (10.8%)	87 (4.2%)	<.0001
	Dyslipidemia, n (%)	485 (42.0%)	121 (5.8%)	<.0001
	Cerebrovascular disease, n (%)	100 (8.7%)	33 (1.6%)	<.0001
	Chronic liver disease, n (%)	24 (2.1%)	18 (0.9%)	0.0053
	Chronic kidney disease, n (%)	25 (2.2%)	14 (0.7%)	0.0003
Laboratory Examination on Admission	Platelet count, median (IQR)	201.0 (153.0-260.0)	208.0 (162.0-265.0)	0.4677
	Neutrophil count, median (IQR)	4.4 (3.0-6.4)	4.2 (2.8-6.6)	0.1724
	Lymphocyte count, median (IQR)	0.9 (0.6-1.3)	1.1 (0.7-1.6)	0.0018
	C-reactive protein, median (IQR)	8.4 (2.7-16.9)	4.2 (1.0-12.7)	0.0003
	Cardiac Troponin, median (IQR)	8.4 (2.7-16.9)	4.2 (1.0-12.7)	0.0589
	Ferritin, median (IQR)	335.0 (158.1-818.0)	240.3 (73.0-581.0)	0.0021
	Creatinine, median (IQR)	88.0 (72.0-142.0)	72.0 (59.0-87.0)	0.1607
	LDH, median (IQR)	273.0 (212.0-364.0)	236.0 (184.0-316.0)	0.0002
	D-dimer, median (IQR)	0.8 (0.5-1.5)	0.6 (0.3-1.3)	0.8673
	T.Bilirubin, median (IQR)	7.9 (5.9-11.1)	8.5 (6.3-11.9)	0.0373
	Lactic Acid, median (IQR)	2.1 (1.6-3.0)	2.2 (1.6-3.1)	0.7865
	Glucose, median (IQR)	6.5 (5.4-9.5)	5.4 (4.7-6.5)	<.0001
Statistical Outcomes	Follow-up days, median (IQR)	5.5 (2.4-11.8)	2.5 (1.1-6.4)	<.0001
	ICU admission, n (%)	231 (20.0%)	269 (13.0%)	<.0001
	Mechanically Ventilated/ECMO, n (%)	116 (10.0%)	97 (4.7%)	<.0001
	Non-invasive positive pressure ventilation, n (%)	38 (3.3%)	32 (1.5%)	0.0015
	Oxygen Supplementation, n (%)	611 (52.9%)	595 (28.6%)	<.0001
	28-Day In Hospital Death, n (%)	134 (11.6%)	106 (5.1%)	<.0001
	Alive, n (%)	997 (86.2%)	1,946 (93.7%)	<.0001

Drug Type: Fibrates

		Full population		
		Fibrates	No Metabolic Regulating Drugs	p value
Clinical Characteristics on Admission	Age, median (IQR)	70.10 (57.8-77.0)	47.40 (32.6-64.0)	<.0001
	Female gender, n (%)	8 (38.1%)	1,014 (48.8%)	0.3843
	Heart rate, median (IQR), bpm	82.00 (76.0-90.0)	85.00 (75.0-96.0)	0.3416
	SBP, median (IQR), mmHg	128.0 (114.0-142.0)	122.0 (111.0-135.0)	0.1126
	DBP, median (IQR), mmHg	71.0 (59.0-80.0)	74.0 (66.0-82.0)	0.9377
	SpO2, median (IQR)	94.0 (93.0-96.0)	96.0 (94.0-98.0)	0.0073
	Temperature (P.O), median (IQR)	36.9 (36.6-37.1)	36.9 (36.7-37.3)	0.3887
	Smoking, n (%)	0 (0.0%)	44 (2.1%)	1.0000
Comorbidities on Admission	Asthma, n (%)	0 (0.0%)	69 (3.3%)	1.0000
	COPD, n (%)	0 (0.0%)	35 (1.7%)	1.0000
	Hypertension, n (%)	13 (61.9%)	325 (15.6%)	<.0001
	Diabetes, n (%)	11 (52.4%)	187 (9.0%)	<.0001
	Coronary heart disease, n (%)	3 (14.3%)	88 (4.2%)	0.0596
	Obesity, n (%)	4 (19.0%)	87 (4.2%)	0.0112
	Dyslipidemia, n (%)	13 (61.9%)	121 (5.8%)	<.0001
	Cerebrovascular disease, n (%)	0 (0.0%)	33 (1.6%)	1.0000
	Chronic liver disease, n (%)	1 (4.8%)	18 (0.9%)	0.1747
	Chronic kidney disease, n (%)	0 (0.0%)	14 (0.7%)	1.0000
Laboratory Examination on Admission	Platelet count, median (IQR)	248.0 (202.0-276.0)	208.0 (162.0-265.0)	0.0413
	Neutrophil count, median (IQR)	4.9 (3.4-7.5)	4.2 (2.8-6.6)	0.5079
	Lymphocyte count, median (IQR)	1.3 (0.9-1.6)	1.1 (0.7-1.6)	0.6963
	C-reactive protein, median (IQR)	10.2 (5.5-12.8)	4.2 (1.0-12.7)	0.1535
	Cardiac Troponin, median (IQR)	10.2 (5.5-12.8)	4.2 (1.0-12.7)	0.0058
	Ferritin, median (IQR)	367.4 (271.0-884.0)	240.3 (73.0-581.0)	0.8574
	Creatinine, median (IQR)	95.0 (72.0-121.0)	72.0 (59.0-87.0)	0.0754
	LDH, median (IQR)	268.5 (200.0-314.0)	236.0 (184.0-316.0)	0.8507
	D-dimer, median (IQR)	0.7 (0.5-1.2)	0.6 (0.3-1.3)	0.9689
	T.Bilirubin, median (IQR)	8.1 (6.1-15.8)	8.5 (6.3-11.9)	0.9102
	Lactic Acid, median (IQR)	1.7 (1.6-2.7)	2.2 (1.6-3.1)	0.6437
	Glucose, median (IQR)	6.7 (5.4-9.1)	5.4 (4.7-6.5)	0.0849
Statistical Outcomes	Follow-up days, median (IQR)	5.0 (3.2-8.7)	2.5 (1.1-6.4)	0.8395
	ICU admission, n (%)	2 (9.5%)	269 (13.0%)	1.0000
	Mechanically Ventilated/ECMO, n (%)	3 (14.3%)	97 (4.7%)	0.0749
	Non-invasive positive pressure ventilation, n (%)	0 (0.0%)	32 (1.5%)	1.0000
	High Flow Oxygen, n (%)	2 (9.5%)	164 (7.9%)	0.6799
	28-Day In Hospital Death, n (%)	0 (0.0%)	106 (5.1%)	0.6220
	Alive, n (%)	21 (100.0%)	1,946 (93.7%)	0.6376

Drug Type: Statins

		Full population		
		Statins	No Metabolic Regulating Drugs	p value
Clinical Characteristics on Admission	Age, median (IQR)	69.30 (61.0-78.0)	47.40 (32.6-64.0)	<.0001
	Female gender, n (%)	359 (38.7%)	1,014 (48.8%)	<.0001
	Heart rate, median (IQR), bpm	82.00 (72.0-93.0)	85.00 (75.0-96.0)	<.0001
	SBP, median (IQR), mmHg	131.0 (117.0-147.0)	122.0 (111.0-135.0)	<.0001
	DBP, median (IQR), mmHg	73.0 (64.0-82.0)	74.0 (66.0-82.0)	0.1149
	SpO2, median (IQR)	95.0 (93.0-97.0)	96.0 (94.0-98.0)	<.0001
	Temperature (P.O), median (IQR)	36.9 (36.6-37.3)	36.9 (36.7-37.3)	0.4415
	Smoking, n (%)	46 (5.0%)	44 (2.1%)	<.0001
Comorbidities on Admission	Asthma, n (%)	26 (2.8%)	69 (3.3%)	0.4995
	COPD, n (%)	53 (5.7%)	35 (1.7%)	<.0001
	Hypertension, n (%)	553 (59.7%)	325 (15.6%)	<.0001
	Diabetes, n (%)	493 (53.2%)	187 (9.0%)	<.0001
	Coronary heart disease, n (%)	307 (33.1%)	88 (4.2%)	<.0001
	Obesity, n (%)	100 (10.8%)	87 (4.2%)	<.0001
	Dyslipidemia, n (%)	432 (46.6%)	121 (5.8%)	<.0001
	Cerebrovascular disease, n (%)	86 (9.3%)	33 (1.6%)	<.0001
	Chronic liver disease, n (%)	21 (2.3%)	18 (0.9%)	0.0027
	Chronic kidney disease, n (%)	23 (2.5%)	14 (0.7%)	<.0001
Laboratory Examination on Admission	Platelet count, median (IQR)	196.0 (150.0-255.0)	208.0 (162.0-265.0)	0.1069
	Neutrophil count, median (IQR)	4.5 (3.0-6.4)	4.2 (2.8-6.6)	0.1587
	Lymphocyte count, median (IQR)	0.9 (0.7-1.3)	1.1 (0.7-1.6)	0.0033
	C-reactive protein, median (IQR)	7.9 (2.6-16.9)	4.2 (1.0-12.7)	0.0078
	Cardiac Troponin, median (IQR)	7.9 (2.6-16.9)	4.2 (1.0-12.7)	0.0429
	Ferritin, median (IQR)	341.0 (155.0-827.9)	240.3 (73.0-581.0)	0.0014
	Creatinine, median (IQR)	90.0 (72.5-152.0)	72.0 (59.0-87.0)	0.1460
	LDH, median (IQR)	273.0 (212.0-363.0)	236.0 (184.0-316.0)	0.0002
	D-dimer, median (IQR)	0.8 (0.5-1.5)	0.6 (0.3-1.3)	0.3800
	T.Bilirubin, median (IQR)	8.0 (5.9-11.2)	8.5 (6.3-11.9)	0.0362
	Lactic Acid, median (IQR)	2.2 (1.5-3.0)	2.2 (1.6-3.1)	0.8763
	Glucose, median (IQR)	6.5 (5.3-9.5)	5.4 (4.7-6.5)	0.0002
Statistical Outcomes	Follow-up days, median (IQR)	5.7 (2.4-12.5)	2.5 (1.1-6.4)	<.0001
	ICU admission, n (%)	186 (20.1%)	269 (13.0%)	<.0001
	Mechanically Ventilated/ECMO, n (%)	94 (10.1%)	97 (4.7%)	<.0001
	Non-invasive positive pressure ventilation, n (%)	29 (3.1%)	32 (1.5%)	0.0072
	High Flow Oxygen, n (%)	151 (16.3%)	164 (7.9%)	<.0001
	28-Day In Hospital Death, n (%)	112 (12.1%)	106 (5.1%)	<.0001
	Alive, n (%)	793 (85.5%)	1,946 (93.7%)	<.0001

Drug Type: IRE1α inhibitors

		Full population		
		IRE1α inhibitors	No Metabolic Regulating Drugs	p value
Clinical Characteristics on Admission	Age, median (IQR)	70.00 (60.4-80.0)	47.40 (32.6-64.0)	<.0001
	Female gender, n (%)	135 (47.9%)	1,014 (48.8%)	0.7996
	Heart rate, median (IQR), bpm	83.00 (72.0-93.0)	85.00 (75.0-96.0)	0.0045
	SBP, median (IQR), mmHg	138.0 (122.0-150.0)	122.0 (111.0-135.0)	<.0001
	DBP, median (IQR), mmHg	74.0 (65.0-84.0)	74.0 (66.0-82.0)	0.3948
	SpO2, median (IQR)	95.0 (93.0-97.0)	96.0 (94.0-98.0)	0.0002
	Temperature (P.O), median (IQR)	37.0 (36.7-37.5)	36.9 (36.7-37.3)	0.0540
	Smoking, n (%)	6 (2.1%)	44 (2.1%)	1.0000
Comorbidities on Admission	Asthma, n (%)	9 (3.2%)	69 (3.3%)	1.0000
	COPD, n (%)	12 (4.3%)	35 (1.7%)	0.0097
	Hypertension, n (%)	223 (79.1%)	325 (15.6%)	<.0001
	Diabetes, n (%)	138 (48.9%)	187 (9.0%)	<.0001
	Coronary heart disease, n (%)	80 (28.4%)	88 (4.2%)	<.0001
	Obesity, n (%)	33 (11.7%)	87 (4.2%)	<.0001
	Dyslipidemia, n (%)	112 (39.7%)	121 (5.8%)	<.0001
	Cerebrovascular disease, n (%)	15 (5.3%)	33 (1.6%)	0.0003
	Chronic liver disease, n (%)	4 (1.4%)	18 (0.9%)	0.3243
	Chronic kidney disease, n (%)	7 (2.5%)	14 (0.7%)	0.0085
Laboratory Examination on Admission	Platelet count, median (IQR)	195.5 (155.0-253.0)	208.0 (162.0-265.0)	0.4585
	Neutrophil count, median (IQR)	4.4 (2.9-6.6)	4.2 (2.8-6.6)	0.6049
	Lymphocyte count, median (IQR)	0.9 (0.6-1.2)	1.1 (0.7-1.6)	<.0001
	C-reactive protein, median (IQR)	9.0 (2.7-17.5)	4.2 (1.0-12.7)	0.0196
	Cardiac Troponin, median (IQR)	9.0 (2.7-17.5)	4.2 (1.0-12.7)	0.2798
	Ferritin, median (IQR)	364.0 (186.4-901.5)	240.3 (73.0-581.0)	0.0723
	Creatinine, median (IQR)	97.0 (78.0-147.0)	72.0 (59.0-87.0)	0.9016
	LDH, median (IQR)	273.0 (211.0-381.0)	236.0 (184.0-316.0)	0.0461
	D-dimer, median (IQR)	0.9 (0.5-1.7)	0.6 (0.3-1.3)	0.9668
	T.Bilirubin, median (IQR)	8.6 (6.2-11.3)	8.5 (6.3-11.9)	0.3932
	Lactic Acid, median (IQR)	2.0 (1.4-2.5)	2.2 (1.6-3.1)	0.0746
	Glucose, median (IQR)	6.4 (5.4-9.0)	5.4 (4.7-6.5)	0.0954
Statistical Outcomes	Follow-up days, median (IQR)	6.1 (3.2-12.6)	2.5 (1.1-6.4)	0.0042
	ICU admission, n (%)	63 (22.3%)	269 (13.0%)	<.0001
	Mechanically Ventilated/ECMO, n (%)	33 (11.7%)	97 (4.7%)	<.0001
	Non-invasive positive pressure ventilation, n (%)	13 (4.6%)	32 (1.5%)	0.0016
	High Flow Oxygen, n (%)	51 (18.1%)	164 (7.9%)	<.0001
	28-Day In Hospital Death, n (%)	29 (10.3%)	106 (5.1%)	0.0014
	Alive, n (%)	246 (87.2%)	1,946 (93.7%)	0.0003

Drug Type: Metformin

		Full population		
		Metformin	No Metabolic Regulating Drugs	p value
Clinical Characteristics on Admission	Age, median (IQR)	69.00 (61.4-76.4)	47.40 (32.6-64.0)	<.0001
	Female gender, n (%)	146 (45.3%)	1,014 (48.8%)	0.2552
	Heart rate, median (IQR), bpm	85.00 (74.0-96.0)	85.00 (75.0-96.0)	0.6602
	SBP, median (IQR), mmHg	126.0 (115.0-144.0)	122.0 (111.0-135.0)	<.0001
	DBP, median (IQR), mmHg	72.5 (65.0-81.0)	74.0 (66.0-82.0)	0.3411
	SpO2, median (IQR)	95.0 (93.0-97.0)	96.0 (94.0-98.0)	<.0001
	Temperature (P.O), median (IQR)	36.9 (36.6-37.4)	36.9 (36.7-37.3)	0.4533
	Smoking, n (%)	11 (3.4%)	44 (2.1%)	0.1592
Comorbidities on Admission	Asthma, n (%)	14 (4.3%)	69 (3.3%)	0.3275
	COPD, n (%)	12 (3.7%)	35 (1.7%)	0.0270
	Hypertension, n (%)	208 (64.6%)	325 (15.6%)	<.0001
	Diabetes, n (%)	322 (100.0%)	187 (9.0%)	<.0001
	Coronary heart disease, n (%)	95 (29.5%)	88 (4.2%)	<.0001
	Obesity, n (%)	43 (13.4%)	87 (4.2%)	<.0001
	Dyslipidemia, n (%)	135 (41.9%)	121 (5.8%)	<.0001
	Cerebrovascular disease, n (%)	23 (7.1%)	33 (1.6%)	<.0001
	Chronic liver disease, n (%)	6 (1.9%)	18 (0.9%)	0.1225
	Chronic kidney disease, n (%)	3 (0.9%)	14 (0.7%)	0.4900
Laboratory Examination on Admission	Platelet count, median (IQR)	210.0 (161.0-270.0)	208.0 (162.0-265.0)	0.2644
	Neutrophil count, median (IQR)	4.2 (3.1-5.7)	4.2 (2.8-6.6)	0.8720
	Lymphocyte count, median (IQR)	1.0 (0.7-1.4)	1.1 (0.7-1.6)	0.0088
	C-reactive protein, median (IQR)	9.1 (2.9-17.8)	4.2 (1.0-12.7)	0.0040
	Cardiac Troponin, median (IQR)	9.1 (2.9-17.8)	4.2 (1.0-12.7)	0.2420
	Ferritin, median (IQR)	257.9 (111.8-546.3)	240.3 (73.0-581.0)	0.5919
	Creatinine, median (IQR)	85.0 (69.0-113.0)	72.0 (59.0-87.0)	0.5150
	LDH, median (IQR)	265.0 (209.0-344.0)	236.0 (184.0-316.0)	0.1118
	D-dimer, median (IQR)	0.7 (0.5-1.4)	0.6 (0.3-1.3)	0.6486
	T.Bilirubin, median (IQR)	7.6 (6.0-10.4)	8.5 (6.3-11.9)	0.0006
	Lactic Acid, median (IQR)	2.4 (1.7-2.9)	2.2 (1.6-3.1)	0.7737
	Glucose, median (IQR)	7.9 (6.0-11.4)	5.4 (4.7-6.5)	<.0001
Statistical Outcomes	Follow-up days, median (IQR)	4.8 (2.4-9.6)	2.5 (1.1-6.4)	0.0143
	ICU admission, n (%)	65 (20.2%)	269 (13.0%)	0.0009
	Mechanically Ventilated/ECMO, n (%)	33 (10.2%)	97 (4.7%)	0.0002
	Non-invasive positive pressure ventilation, n (%)	12 (3.7%)	32 (1.5%)	0.0122
	High Flow Oxygen, n (%)	54 (16.8%)	164 (7.9%)	<.0001
	28-Day In Hospital Death, n (%)	27 (8.4%)	106 (5.1%)	0.0250
	Alive, n (%)	289 (89.8%)	1,946 (93.7%)	0.0124

Drug Type: SGLT2 Inhibitors

		Full population		
		SGLT2 Inhibitors	No Metabolic Regulating Drugs	p value
Clinical Characteristics on Admission	Age, median (IQR)	65.70 (58.2-75.5)	47.40 (32.6-64.0)	<.0001
	Female gender, n (%)	15 (27.3%)	1,014 (48.8%)	0.0015
	Heart rate, median (IQR), bpm	88.00 (77.0-99.0)	85.00 (75.0-96.0)	0.4966
	SBP, median (IQR), mmHg	122.0 (110.0-137.0)	122.0 (111.0-135.0)	0.5296
	DBP, median (IQR), mmHg	71.5 (62.0-79.0)	74.0 (66.0-82.0)	0.3748
	SpO2, median (IQR)	94.0 (92.0-96.0)	96.0 (94.0-98.0)	<.0001
	Temperature (P.O), median (IQR)	36.8 (36.6-37.4)	36.9 (36.7-37.3)	0.7199
	Smoking, n (%)	0 (0.0%)	44 (2.1%)	0.6277
Comorbidities on Admission	Asthma, n (%)	1 (1.8%)	69 (3.3%)	1.0000
	COPD, n (%)	1 (1.8%)	35 (1.7%)	0.6128
	Hypertension, n (%)	39 (70.9%)	325 (15.6%)	<.0001
	Diabetes, n (%)	55 (100.0%)	187 (9.0%)	<.0001
	Coronary heart disease, n (%)	22 (40.0%)	88 (4.2%)	<.0001
	Obesity, n (%)	5 (9.1%)	87 (4.2%)	0.0855
	Dyslipidemia, n (%)	24 (43.6%)	121 (5.8%)	<.0001
	Cerebrovascular disease, n (%)	2 (3.6%)	33 (1.6%)	0.2277
	Chronic liver disease, n (%)	2 (3.6%)	18 (0.9%)	0.0923
	Chronic kidney disease, n (%)	1 (1.8%)	14 (0.7%)	0.3252
Laboratory Examination on Admission	Platelet count, median (IQR)	173.0 (138.0-224.0)	208.0 (162.0-265.0)	0.0002
	Neutrophil count, median (IQR)	4.6 (3.1-6.4)	4.2 (2.8-6.6)	0.7960
	Lymphocyte count, median (IQR)	0.8 (0.6-1.1)	1.1 (0.7-1.6)	0.0002
	C-reactive protein, median (IQR)	10.9 (4.1-21.2)	4.2 (1.0-12.7)	0.1351
	Cardiac Troponin, median (IQR)	10.9 (4.1-21.2)	4.2 (1.0-12.7)	0.0184
	Ferritin, median (IQR)	263.0 (158.0-669.5)	240.3 (73.0-581.0)	0.5007
	Creatinine, median (IQR)	99.0 (75.0-120.0)	72.0 (59.0-87.0)	0.0346
	LDH, median (IQR)	288.0 (195.0-401.0)	236.0 (184.0-316.0)	0.4213
	D-dimer, median (IQR)	0.7 (0.4-1.6)	0.6 (0.3-1.3)	0.0747
	T.Bilirubin, median (IQR)	7.8 (6.4-11.6)	8.5 (6.3-11.9)	0.8140
	Lactic Acid, median (IQR)	2.4 (1.8-3.1)	2.2 (1.6-3.1)	0.8862
	Glucose, median (IQR)	8.9 (6.1-9.9)	5.4 (4.7-6.5)	<.0001
Statistical Outcomes	Follow-up days, median (IQR)	7.7 (3.8-13.1)	2.5 (1.1-6.4)	0.2203
	ICU admission, n (%)	16 (29.1%)	269 (13.0%)	0.0018
	Mechanically Ventilated/ECMO, n (%)	8 (14.5%)	97 (4.7%)	0.0047
	Non-invasive positive pressure ventilation, n (%)	3 (5.5%)	32 (1.5%)	0.0594
	High Flow Oxygen, n (%)	12 (21.8%)	164 (7.9%)	0.0013
	28-Day In Hospital Death, n (%)	10 (18.2%)	106 (5.1%)	0.0006
	Alive, n (%)	45 (81.8%)	1,946 (93.7%)	0.0026

Drug Type: Thiazolidinediones

		Full population		
		Thiazolidinediones	No Metabolic Regulating Drugs	p value
Clinical Characteristics on Admission	Age, median (IQR)	61.70 (58.0-70.0)	47.40 (32.6-64.0)	<.0001
	Female gender, n (%)	18 (48.6%)	1,014 (48.8%)	1.0000
	Heart rate, median (IQR), bpm	92.00 (80.0-99.0)	85.00 (75.0-96.0)	0.2216
	SBP, median (IQR), mmHg	131.0 (121.0-144.0)	122.0 (111.0-135.0)	0.0022
	DBP, median (IQR), mmHg	76.0 (65.0-82.0)	74.0 (66.0-82.0)	0.9832
	SpO2, median (IQR)	95.0 (93.0-96.0)	96.0 (94.0-98.0)	0.0395
	Temperature (P.O), median (IQR)	37.1 (36.8-37.5)	36.9 (36.7-37.3)	0.3582
	Smoking, n (%)	0 (0.0%)	44 (2.1%)	1.0000
Comorbidities on Admission	Asthma, n (%)	0 (0.0%)	69 (3.3%)	0.6317
	COPD, n (%)	2 (5.4%)	35 (1.7%)	0.1356
	Hypertension, n (%)	23 (62.2%)	325 (15.6%)	<.0001
	Diabetes, n (%)	37 (100.0%)	187 (9.0%)	<.0001
	Coronary heart disease, n (%)	12 (32.4%)	88 (4.2%)	<.0001
	Obesity, n (%)	8 (21.6%)	87 (4.2%)	0.0002
	Dyslipidemia, n (%)	15 (40.5%)	121 (5.8%)	<.0001
	Cerebrovascular disease, n (%)	4 (10.8%)	33 (1.6%)	0.0035
	Chronic liver disease, n (%)	1 (2.7%)	18 (0.9%)	0.2860
	Chronic kidney disease, n (%)	1 (2.7%)	14 (0.7%)	0.2334
Laboratory Examination on Admission	Platelet count, median (IQR)	218.0 (161.0-311.0)	208.0 (162.0-265.0)	0.1659
	Neutrophil count, median (IQR)	4.6 (2.6-5.8)	4.2 (2.8-6.6)	0.7137
	Lymphocyte count, median (IQR)	1.2 (0.9-1.4)	1.1 (0.7-1.6)	0.3101
	C-reactive protein, median (IQR)	6.7 (1.2-14.8)	4.2 (1.0-12.7)	0.0613
	Cardiac Troponin, median (IQR)	6.7 (1.2-14.8)	4.2 (1.0-12.7)	0.7016
	Ferritin, median (IQR)	192.1 (70.0-295.5)	240.3 (73.0-581.0)	0.0099
	Creatinine, median (IQR)	79.0 (62.0-103.0)	72.0 (59.0-87.0)	0.1521
	LDH, median (IQR)	282.0 (187.5-401.5)	236.0 (184.0-316.0)	0.0811
	D-dimer, median (IQR)	0.6 (0.4-0.7)	0.6 (0.3-1.3)	<.0001
	T.Bilirubin, median (IQR)	7.2 (6.4-9.8)	8.5 (6.3-11.9)	0.0353
	Lactic Acid, median (IQR)	1.9 (1.6-2.5)	2.2 (1.6-3.1)	0.1144
	Glucose, median (IQR)	10.2 (6.5-12.5)	5.4 (4.7-6.5)	<.0001
Statistical Outcomes	Follow-up days, median (IQR)	4.9 (2.6-11.0)	2.5 (1.1-6.4)	0.3565
	ICU admission, n (%)	8 (21.6%)	269 (13.0%)	0.1363
	Mechanically Ventilated/ECMO, n (%)	5 (13.5%)	97 (4.7%)	0.0302
	Non-invasive positive pressure ventilation, n (%)	2 (5.4%)	32 (1.5%)	0.1180
	High Flow Oxygen, n (%)	6 (16.2%)	164 (7.9%)	0.1150
	28-Day In Hospital Death, n (%)	4 (10.8%)	106 (5.1%)	0.1228
	Alive, n (%)	32 (86.5%)	1,946 (93.7%)	0.0849

Table S2. Observational comparison between unique patients visits in Hadassah medical center taking metabolic regulators and unique patients in various hospitalization conditions in patients with COVID-19 taking metabolic regulators in different periods.. Patients taking thiazolidinediones (n=37; p<0.001), metformin (n=321; p<0.01), SGLT2 inhibitors (n=54; p<0.001), statins (n=924; p<0.001), or telmisartan (IRE1 α inhibitor; n = 278; p<0.001) were over-represented across all severity indicators, while patients taking fibrates (n=21) were significantly underrepresented in hospital admissions (p=0.02) and were not over-represented in other severity indicators regardless of the period examined.

Period for non-COVID-19 hospital visits: 1 Year

		Fibrates	Statins	Thiazolidinediones	SGLT2 Inhibitors	IRE1 α inhibitors	Metformin	All subjects Over 30
Non COVID-19 Hospitalization	N	794	9,661	115	543	3,166	3,988	51,483
	%	1.54%	18.77%	0.22%	1.05%	6.15%	7.75%	100.0%
COVID-19 Hospitalization	N	21	924	37	54	278	321	2,806
	%	0.75%	32.93%	1.32%	1.92%	9.91%	11.44%	100.0%
	Relative Risk (compared to non COVID-19 hospital visits)	0.49	1.75	5.90	1.82	1.61	1.48	1.00
	95% Lower Confidence Limit	0.32	1.66	4.08	1.38	1.43	1.33	
	95% Upper Confidence Limit	0.75	1.86	8.53	2.41	1.81	1.64	
	p-value	0.0010	<.0001	<.0001	<.0001	<.0001	<.0001	
COVID-19 ICU	N	2	185	8	16	62	65	480
	%	0.42%	38.54%	1.67%	3.33%	12.92%	13.54%	100.0%
	Relative Risk (compared to non COVID-19 hospital visits)	0.27	2.05	7.46	3.16	2.10	1.75	1.00
	95% Lower Confidence Limit	0.07	1.83	3.66	1.94	1.66	1.39	
	95% Upper Confidence Limit	1.08	2.30	15.19	5.15	2.66	2.20	
	p-value	0.0640	<.0001	<.0001	<.0001	<.0001	<.0001	
COVID-19 Deceased within 28 days	N	0	112	4	10	29	27	237
	%	0.00%	47.26%	1.69%	4.22%	12.24%	11.39%	100.0%
	Relative Risk (compared to non COVID-19 hospital visits)	0.00	2.52	7.56	4.00	1.99	1.47	1.00
	95% Lower Confidence Limit	N.E.	2.20	2.81	2.17	1.41	1.03	
	95% Upper Confidence Limit	N.E.	2.88	20.31	7.38	2.80	2.10	
	p-value	N.E.	<.0001	<.0001	<.0001	<.0001	0.0339	

Table S2A. Observational comparison between unique patients visits Hadassah medical center during 11/2018-2019 taking metabolic regulators and unique patients in various hospitalization conditions in patients with COVID-19 taking metabolic regulators.

Period for non-COVID-19 hospital visits: 5 Years

		Fibrates	Statins	Thiazolidinediones	SGLT2 Inhibitors	IRE1α inhibitors	Metformin	All subjects Over 30
Non COVID-19 Hospitalization	N	3,249	46,030	490	2,057	12,675	17,536	249,939
	%	1.30%	18.42%	0.20%	0.82%	5.07%	7.02%	100.0%
COVID-19 Hospitalization	N	21	924	37	54	278	321	2,806
	%	0.75%	32.93%	1.32%	1.92%	9.91%	11.44%	100.0%
	Relative Risk (compared to non COVID-19 hospital visits)	0.58	1.79	6.73	2.34	1.95	1.63	1.00
	95% Lower Confidence Limit	0.38	1.69	4.83	1.79	1.75	1.47	
	95% Upper Confidence Limit	0.88	1.89	9.38	3.06	2.19	1.81	
	p-value	0.0114	<.0001	<.0001	<.0001	<.0001	<.0001	
COVID-19 ICU	N	2	185	8	16	62	65	480
	%	0.42%	38.54%	1.67%	3.33%	12.92%	13.54%	100.0%
	Relative Risk (compared to non COVID-19 hospital visits)	0.32	2.09	8.50	4.05	2.55	1.93	1.00
	95% Lower Confidence Limit	0.08	1.87	4.25	2.50	2.02	1.54	
	95% Upper Confidence Limit	1.28	2.34	17.00	6.57	3.22	2.42	
	p-value	0.1070	<.0001	<.0001	<.0001	<.0001	<.0001	
COVID-09 Deceased within 28 days	N	0	112	4	10	29	27	237
	%	0.00%	47.26%	1.69%	4.22%	12.24%	11.39%	100.0%
	Relative Risk (compared to non COVID-19 hospital visits)	0.00	2.57	8.61	5.13	2.41	1.62	1.00
	95% Lower Confidence Limit	N.E.	2.24	3.24	2.79	1.72	1.14	
	95% Upper Confidence Limit	N.E.	2.94	22.84	9.42	3.39	2.32	
	p-value	N.E.	<.0001	<.0001	<.0001	<.0001	0.0075	

Table S2B. Observational comparison between unique patients visits Hadassah medical center during 11/2015-2020 taking metabolic regulators and unique patients in various hospitalization conditions in patients with COVID-19 taking metabolic regulators.

Period for non COVID-19 hospital visits: 10 Years

		Fibrates	Statins	Thiazolidinediones	SGLT2 Inhibitors	IRE1α inhibitors	Metformin	All subjects Over 30
Non COVID-19 Hospitalization	N	6,491	84,039	1,015	4,220	26,282	36,164	532,493
	%	1.22%	15.78%	0.19%	0.79%	4.94%	6.79%	100.0%
COVID-19 Hospitalization	N	21	924	37	54	278	321	2,806
	%	0.75%	32.93%	1.32%	1.92%	9.91%	11.44%	100.0%
	Relative Risk (compared to non COVID-19 hospital visits)	0.61	2.09	6.92	2.43	2.01	1.68	1.00
	95% Lower Confidence Limit	0.40	1.98	4.99	1.86	1.79	1.52	
	95% Upper Confidence Limit	0.94	2.20	9.58	3.17	2.25	1.87	
	p-value	0.0251	<.0001	<.0001	<.0001	<.0001	<.0001	
COVID-19 ICU	N	2	185	8	16	62	65	480
	%	0.42%	38.54%	1.67%	3.33%	12.92%	13.54%	100.0%
	Relative Risk (compared to non COVID-19 hospital visits)	0.34	2.44	8.74	4.21	2.62	1.99	1.00
	95% Lower Confidence Limit	0.09	2.18	4.39	2.60	2.07	1.59	
	95% Upper Confidence Limit	1.36	2.73	17.43	6.82	3.30	2.50	
	p-value	0.1282	<.0001	<.0001	<.0001	<.0001	<.0001	
COVID-09 Deceased within 28 days	N	0	112	4	10	29	27	237
	%	0.00%	47.26%	1.69%	4.22%	12.24%	11.39%	100.0%
	Relative Risk (compared to non COVID-19 hospital visits)	0.00	2.99	8.85	5.32	2.48	1.68	1.00
	95% Lower Confidence Limit	N.E.	2.62	3.34	2.90	1.76	1.18	
	95% Upper Confidence Limit	N.E.	3.43	23.44	9.77	3.49	2.39	
	p-value	N.E.	<.0001	<.0001	<.0001	<.0001	0.0043	

Table S2C. Observational comparison between unique patients visits Hadassah medical center during 11/2010-2020 taking metabolic regulators and unique patients in various hospitalization conditions in patients with COVID-19 taking metabolic regulators.

Table S3. Characteristics of patients included in the study. Patients were included in the study were between the age of 45-100, that were hospitalized for more than 3 days (N=1,438). SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, chronic obstructive pulmonary disease; SpO2, oxygen saturation; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range Continuous variables were compared with a two-sample t-test and categorical variables with Fisher's exact test.

		Severe Population
Any Metabolic Regulating Drugs		790
	Fibrates	16
	Statins	640
	Thiazolidinediones	26
	SGLT2 Inhibitors	44
	IRE1 α inhibitors	209
	Metformin	216
No Metabolic Regulating Drugs		648

Drug Type: Any Metabolic Regulating Drugs		Severe Population		
		Any Metabolic Regulating Drugs	No Metabolic Regulating Drugs	p-value
Clinical Characteristics on Admission	Age, median (IQR)	71.00 (62.8-79.9)	65.60 (55.0-76.4)	<.0001
	Female gender, n (%)	322 (40.8%)	253 (39.0%)	0.5166
	Heart rate, median (IQR), bpm	83.00 (73.0-94.0)	85.00 (75.0-98.0)	0.0156
	SBP, median (IQR), mmHg	130.0 (116.0-147.0)	126.0 (112.0-139.0)	<.0001
	DBP, median (IQR), mmHg	71.0 (63.0-81.0)	73.0 (64.0-82.0)	0.2379
	SpO2, median (IQR)	95.0 (92.0-97.0)	95.0 (93.0-97.0)	0.8270
	Temperature (P.O), median (IQR)	36.9 (36.6-37.4)	37.0 (36.7-37.4)	0.0142
	Smoking, n (%)	41 (5.2%)	18 (2.8%)	0.0231
Comorbidities on Admission	Asthma, n (%)	25 (3.2%)	26 (4.0%)	0.3940
	COPD, n (%)	51 (6.5%)	27 (4.2%)	0.0614
	Hypertension, n (%)	516 (65.3%)	212 (32.7%)	<.0001
	Diabetes, n (%)	451 (57.1%)	111 (17.1%)	<.0001
	Coronary heart disease, n (%)	255 (32.3%)	67 (10.3%)	<.0001
	Obesity, n (%)	87 (11.0%)	51 (7.9%)	0.0478
	Dyslipidemia, n (%)	354 (44.8%)	76 (11.7%)	<.0001
	Cerebrovascular disease, n (%)	84 (10.6%)	21 (3.2%)	<.0001
	Chronic liver disease, n (%)	17 (2.2%)	12 (1.9%)	0.7112
	Chronic kidney disease, n (%)	20 (2.5%)	11 (1.7%)	0.3619
Laboratory Examination on Admission	Platelet count, median (IQR)	205.0 (156.0-264.0)	209.0 (151.0-269.0)	0.6720
	Neutrophil count, median (IQR)	4.7 (3.2-6.9)	4.8 (3.0-7.5)	0.2725
	Lymphocyte count, median (IQR)	0.9 (0.6-1.2)	0.8 (0.6-1.1)	0.6585
	C-reactive protein, median (IQR)	10.8 (4.1-18.2)	12.3 (4.9-21.8)	0.0583
	Cardiac Troponin, median (IQR)	10.8 (4.1-18.2)	12.3 (4.9-21.8)	0.3213
	Ferritin, median (IQR)	384.8 (184.6-1010.0)	549.0 (264.5-1022.3)	0.7977
	Creatinine, median (IQR)	95.0 (74.0-152.0)	80.0 (65.0-102.0)	0.5235
	LDH, median (IQR)	293.0 (227.0-399.0)	301.5 (234.5-399.5)	0.4295
	D-dimer, median (IQR)	0.9 (0.5-1.8)	1.0 (0.6-2.0)	0.0531
	T.Bilirubin, median (IQR)	7.9 (5.9-11.0)	8.7 (6.3-12.3)	0.0510
	Lactic Acid, median (IQR)	2.2 (1.5-3.0)	2.3 (1.7-3.4)	0.2598
	Glucose, median (IQR)	6.7 (5.5-9.8)	6.0 (5.1-7.6)	0.0124
Statistical Outcomes	Follow-up days, median (IQR)	8.5 (5.0-15.2)	8.0 (4.8-14.2)	0.6642
	ICU admission, n (%)	205 (25.9%)	179 (27.6%)	0.5100
	Mechanically Ventilated/ECMO, n (%)	106 (13.4%)	76 (11.7%)	0.3807
	Non-invasive ventilation, n (%)	31 (3.9%)	28 (4.3%)	0.7896
	High Flow Oxygen, n (%)	170 (21.5%)	125 (19.3%)	0.3250
	28-Day In Hospital Death, n (%)	109 (13.8%)	77 (11.9%)	0.3049
	Survival, n (%)	658 (83.3%)	547 (84.4%)	0.6147

Drug Type: Fibrates		Severe Population		
		Fibrates	No Metabolic Regulating Drugs	p-value
Clinical Characteristics on Admission	Age, median (IQR)	65.65 (57.8-76.5)	65.60 (55.0-76.4)	0.7625
	Female gender, n (%)	7 (43.8%)	253 (39.0%)	0.7970
	Heart rate, median (IQR), bpm	85.50 (78.5-93.5)	85.00 (75.0-98.0)	0.8733
	SBP, median (IQR), mmHg	120.0 (113.5-133.0)	126.0 (112.0-139.0)	0.8394
	DBP, median (IQR), mmHg	71.0 (58.0-77.0)	73.0 (64.0-82.0)	0.9954
	SpO2, median (IQR)	94.0 (93.0-95.0)	95.0 (93.0-97.0)	0.3247
	Temperature (P.O), median (IQR)	36.8 (36.6-37.3)	37.0 (36.7-37.4)	0.2855
	Smoking, n (%)	0 (0.0%)	18 (2.8%)	1.0000
Comorbidities on Admission	Asthma, n (%)	0 (0.0%)	26 (4.0%)	1.0000
	COPD, n (%)	0 (0.0%)	27 (4.2%)	1.0000
	Hypertension, n (%)	12 (75.0%)	212 (32.7%)	0.0008
	Diabetes, n (%)	10 (62.5%)	111 (17.1%)	<.0001
	Coronary heart disease, n (%)	2 (12.5%)	67 (10.3%)	0.6780
	Obesity, n (%)	4 (25.0%)	51 (7.9%)	0.0362
	Dyslipidemia, n (%)	13 (81.3%)	76 (11.7%)	<.0001
	Cerebrovascular disease, n (%)	0 (0.0%)	21 (3.2%)	1.0000
	Chronic liver disease, n (%)	1 (6.3%)	12 (1.9%)	0.2739
	Chronic kidney disease, n (%)	0 (0.0%)	11 (1.7%)	1.0000
Laboratory Examination on Admission	Platelet count, median (IQR)	248.0 (202.0-266.0)	209.0 (151.0-269.0)	0.1919
	Neutrophil count, median (IQR)	5.6 (3.1-7.7)	4.8 (3.0-7.5)	0.9169
	Lymphocyte count, median (IQR)	1.1 (0.8-1.4)	0.8 (0.6-1.1)	0.8953
	C-reactive protein, median (IQR)	10.2 (5.8-12.5)	12.3 (4.9-21.8)	<.0001
	Cardiac Troponin, median (IQR)	10.2 (5.8-12.5)	12.3 (4.9-21.8)	0.0470
	Ferritin, median (IQR)	319.7 (271.0-884.0)	549.0 (264.5-1022.3)	0.0642
	Creatinine, median (IQR)	106.0 (76.0-144.0)	80.0 (65.0-102.0)	0.0406
	LDH, median (IQR)	292.5 (227.5-326.0)	301.5 (234.5-399.5)	0.0240
	D-dimer, median (IQR)	0.7 (0.5-1.2)	1.0 (0.6-2.0)	0.7175
	T.Bilirubin, median (IQR)	8.1 (6.1-11.1)	8.7 (6.3-12.3)	0.5229
	Lactic Acid, median (IQR)	2.2 (1.6-3.2)	2.3 (1.7-3.4)	0.6759
	Glucose, median (IQR)	7.6 (5.5-9.3)	6.0 (5.1-7.6)	0.0967
Statistical Outcomes	Follow-up days, median (IQR)	7.1 (4.4-9.3)	8.0 (4.8-14.2)	0.0294
	ICU admission, n (%)	2 (12.5%)	179 (27.6%)	0.2579
	Mechanically Ventilated/ECMO, n (%)	3 (18.8%)	76 (11.7%)	0.4229
	Non-invasive ventilation, n (%)	0 (0.0%)	28 (4.3%)	1.0000
	High Flow Oxygen, n (%)	2 (12.5%)	125 (19.3%)	0.7489
	28-Day In Hospital Death, n (%)	0 (0.0%)	77 (11.9%)	0.2389
	Survival, n (%)	16 (100.0%)	547 (84.4%)	0.1496

Drug Type: Statins		Severe Population		
		Statins	No Metabolic Regulating Drugs	p-value
Clinical Characteristics on Admission	Age, median (IQR)	71.40 (63.0-79.4)	65.60 (55.0-76.4)	<.0001
	Female gender, n (%)	249 (38.9%)	253 (39.0%)	1.0000
	Heart rate, median (IQR), bpm	82.00 (73.0-93.0)	85.00 (75.0-98.0)	0.0026
	SBP, median (IQR), mmHg	130.0 (116.0-147.0)	126.0 (112.0-139.0)	0.0003
	DBP, median (IQR), mmHg	71.0 (63.0-81.0)	73.0 (64.0-82.0)	0.1256
	SpO2, median (IQR)	95.0 (92.0-97.0)	95.0 (93.0-97.0)	0.9039
	Temperature (P.O), median (IQR)	36.9 (36.6-37.3)	37.0 (36.7-37.4)	0.0017
	Smoking, n (%)	38 (5.9%)	18 (2.8%)	0.0060
Comorbidities on Admission	Asthma, n (%)	17 (2.7%)	26 (4.0%)	0.2146
	COPD, n (%)	46 (7.2%)	27 (4.2%)	0.0218
	Hypertension, n (%)	414 (64.7%)	212 (32.7%)	<.0001
	Diabetes, n (%)	358 (55.9%)	111 (17.1%)	<.0001
	Coronary heart disease, n (%)	227 (35.5%)	67 (10.3%)	<.0001
	Obesity, n (%)	67 (10.5%)	51 (7.9%)	0.1221
	Dyslipidemia, n (%)	314 (49.1%)	76 (11.7%)	<.0001
	Cerebrovascular disease, n (%)	73 (11.4%)	21 (3.2%)	<.0001
	Chronic liver disease, n (%)	15 (2.3%)	12 (1.9%)	0.5653
	Chronic kidney disease, n (%)	19 (3.0%)	11 (1.7%)	0.1427
Laboratory Examination on Admission	Platelet count, median (IQR)	201.0 (150.0-256.0)	209.0 (151.0-269.0)	0.2331
	Neutrophil count, median (IQR)	4.7 (3.2-6.9)	4.8 (3.0-7.5)	0.3250
	Lymphocyte count, median (IQR)	0.9 (0.6-1.2)	0.8 (0.6-1.1)	0.6862
	C-reactive protein, median (IQR)	10.4 (4.0-18.1)	12.3 (4.9-21.8)	0.0171
	Cardiac Troponin, median (IQR)	10.4 (4.0-18.1)	12.3 (4.9-21.8)	0.1820
	Ferritin, median (IQR)	401.0 (187.7-1065.5)	549.0 (264.5-1022.3)	0.6674
	Creatinine, median (IQR)	98.0 (75.0-168.0)	80.0 (65.0-102.0)	0.6077
	LDH, median (IQR)	295.0 (225.0-398.5)	301.5 (234.5-399.5)	0.1511
	D-dimer, median (IQR)	0.9 (0.5-1.7)	1.0 (0.6-2.0)	0.0268
	T.Bilirubin, median (IQR)	8.1 (5.9-11.2)	8.7 (6.3-12.3)	0.0868
	Lactic Acid, median (IQR)	2.2 (1.5-3.0)	2.3 (1.7-3.4)	0.2992
	Glucose, median (IQR)	6.6 (5.4-9.7)	6.0 (5.1-7.6)	0.0303
Statistical Outcomes	Follow-up days, median (IQR)	9.0 (5.0-16.2)	8.0 (4.8-14.2)	0.5010
	ICU admission, n (%)	165 (25.8%)	179 (27.6%)	0.4885
	Mechanically Ventilated/ECMO, n (%)	87 (13.6%)	76 (11.7%)	0.3162
	Non-invasive ventilation, n (%)	24 (3.8%)	28 (4.3%)	0.6718
	High Flow Oxygen, n (%)	134 (20.9%)	125 (19.3%)	0.4871
	28-Day In Hospital Death, n (%)	91 (14.2%)	77 (11.9%)	0.2159
	Survival, n (%)	528 (82.5%)	547 (84.4%)	0.3687

Drug Type: IRE1α inhibitors		Severe Population		
		IRE1α inhibitors	No Metabolic Regulating Drugs	p-value
Clinical Characteristics on Admission	Age, median (IQR)	72.40 (61.9-81.0)	65.60 (55.0-76.4)	<.0001
	Female gender, n (%)	108 (51.7%)	253 (39.0%)	0.0016
	Heart rate, median (IQR), bpm	83.00 (71.0-93.0)	85.00 (75.0-98.0)	0.0232
	SBP, median (IQR), mmHg	138.0 (121.0-150.0)	126.0 (112.0-139.0)	<.0001
	DBP, median (IQR), mmHg	73.0 (64.5-83.0)	73.0 (64.0-82.0)	0.4490
	SpO2, median (IQR)	95.0 (92.0-97.0)	95.0 (93.0-97.0)	0.9760
	Temperature (P.O), median (IQR)	37.0 (36.6-37.5)	37.0 (36.7-37.4)	0.8154
	Smoking, n (%)	4 (1.9%)	18 (2.8%)	0.6201
Comorbidities on Admission	Asthma, n (%)	9 (4.3%)	26 (4.0%)	0.8418
	COPD, n (%)	11 (5.3%)	27 (4.2%)	0.5617
	Hypertension, n (%)	168 (80.4%)	212 (32.7%)	<.0001
	Diabetes, n (%)	108 (51.7%)	111 (17.1%)	<.0001
	Coronary heart disease, n (%)	60 (28.7%)	67 (10.3%)	<.0001
	Obesity, n (%)	26 (12.4%)	51 (7.9%)	0.0514
	Dyslipidemia, n (%)	86 (41.1%)	76 (11.7%)	<.0001
	Cerebrovascular disease, n (%)	12 (5.7%)	21 (3.2%)	0.1450
	Chronic liver disease, n (%)	3 (1.4%)	12 (1.9%)	1.0000
	Chronic kidney disease, n (%)	5 (2.4%)	11 (1.7%)	0.5574
Laboratory Examination on Admission	Platelet count, median (IQR)	202.0 (150.0-259.0)	209.0 (151.0-269.0)	0.6610
	Neutrophil count, median (IQR)	4.6 (3.2-6.9)	4.8 (3.0-7.5)	0.2312
	Lymphocyte count, median (IQR)	0.8 (0.6-1.2)	0.8 (0.6-1.1)	0.3665
	C-reactive protein, median (IQR)	10.8 (3.8-19.0)	12.3 (4.9-21.8)	0.1812
	Cardiac Troponin, median (IQR)	10.8 (3.8-19.0)	12.3 (4.9-21.8)	0.8934
	Ferritin, median (IQR)	371.0 (196.0-1037.0)	549.0 (264.5-1022.3)	0.6256
	Creatinine, median (IQR)	98.0 (78.0-149.0)	80.0 (65.0-102.0)	0.0910
	LDH, median (IQR)	293.0 (223.0-391.0)	301.5 (234.5-399.5)	0.7861
	D-dimer, median (IQR)	0.9 (0.5-1.8)	1.0 (0.6-2.0)	0.0039
	T.Bilirubin, median (IQR)	8.6 (6.1-11.0)	8.7 (6.3-12.3)	0.2153
	Lactic Acid, median (IQR)	2.0 (1.4-2.5)	2.3 (1.7-3.4)	0.0294
	Glucose, median (IQR)	6.5 (5.4-9.2)	6.0 (5.1-7.6)	0.2140
Statistical Outcomes	Follow-up days, median (IQR)	8.0 (5.0-17.2)	8.0 (4.8-14.2)	0.4196
	ICU admission, n (%)	58 (27.8%)	179 (27.6%)	1.0000
	Mechanically Ventilated/ECMO, n (%)	31 (14.8%)	76 (11.7%)	0.2316
	Non-invasive ventilation, n (%)	11 (5.3%)	28 (4.3%)	0.5690
	High Flow Oxygen, n (%)	46 (22.0%)	125 (19.3%)	0.4259
	28-Day In Hospital Death, n (%)	25 (12.0%)	77 (11.9%)	1.0000
	Survival, n (%)	178 (85.2%)	547 (84.4%)	0.8266

Drug Type: Metformin		Severe Population		
		Metformin	No Metabolic Regulating Drugs	p-value
Clinical Characteristics on Admission	Age, median (IQR)	70.00 (63.0-77.0)	65.60 (55.0-76.4)	<.0001
	Female gender, n (%)	88 (40.7%)	253 (39.0%)	0.6880
	Heart rate, median (IQR), bpm	85.00 (75.0-96.0)	85.00 (75.0-98.0)	0.5429
	SBP, median (IQR), mmHg	125.0 (115.0-142.0)	126.0 (112.0-139.0)	0.2763
	DBP, median (IQR), mmHg	71.0 (64.0-79.5)	73.0 (64.0-82.0)	0.4166
	SpO2, median (IQR)	94.0 (92.0-96.0)	95.0 (93.0-97.0)	0.0836
	Temperature (P.O), median (IQR)	36.9 (36.6-37.4)	37.0 (36.7-37.4)	0.1806
	Smoking, n (%)	10 (4.6%)	18 (2.8%)	0.1871
Comorbidities on Admission	Asthma, n (%)	8 (3.7%)	26 (4.0%)	1.0000
	COPD, n (%)	10 (4.6%)	27 (4.2%)	0.8461
	Hypertension, n (%)	148 (68.5%)	212 (32.7%)	<.0001
	Diabetes, n (%)	216 (100.0%)	111 (17.1%)	<.0001
	Coronary heart disease, n (%)	75 (34.7%)	67 (10.3%)	<.0001
	Obesity, n (%)	29 (13.4%)	51 (7.9%)	0.0205
	Dyslipidemia, n (%)	98 (45.4%)	76 (11.7%)	<.0001
	Cerebrovascular disease, n (%)	21 (9.7%)	21 (3.2%)	0.0004
	Chronic liver disease, n (%)	3 (1.4%)	12 (1.9%)	0.7728
	Chronic kidney disease, n (%)	3 (1.4%)	11 (1.7%)	1.0000
Laboratory Examination on Admission	Platelet count, median (IQR)	208.5 (161.0-269.0)	209.0 (151.0-269.0)	0.6917
	Neutrophil count, median (IQR)	4.3 (3.1-6.2)	4.8 (3.0-7.5)	0.1057
	Lymphocyte count, median (IQR)	0.9 (0.6-1.3)	0.8 (0.6-1.1)	0.7193
	C-reactive protein, median (IQR)	11.6 (4.3-19.0)	12.3 (4.9-21.8)	0.6999
	Cardiac Troponin, median (IQR)	11.6 (4.3-19.0)	12.3 (4.9-21.8)	0.9552
	Ferritin, median (IQR)	266.1 (116.0-602.0)	549.0 (264.5-1022.3)	0.2271
	Creatinine, median (IQR)	89.0 (72.0-123.0)	80.0 (65.0-102.0)	0.1944
	LDH, median (IQR)	284.0 (218.0-371.0)	301.5 (234.5-399.5)	0.0210
	D-dimer, median (IQR)	0.9 (0.5-1.7)	1.0 (0.6-2.0)	0.1736
	T.Bilirubin, median (IQR)	7.3 (5.8-10.0)	8.7 (6.3-12.3)	0.0001
	Lactic Acid, median (IQR)	2.4 (1.8-3.0)	2.3 (1.7-3.4)	0.7171
	Glucose, median (IQR)	8.0 (5.9-11.5)	6.0 (5.1-7.6)	<.0001
Statistical Outcomes	Follow-up days, median (IQR)	7.0 (4.6-13.2)	8.0 (4.8-14.2)	0.5834
	ICU admission, n (%)	57 (26.4%)	179 (27.6%)	0.7915
	Mechanically Ventilated/ECMO, n (%)	30 (13.9%)	76 (11.7%)	0.4034
	Non-invasive ventilation, n (%)	11 (5.1%)	28 (4.3%)	0.7049
	High Flow Oxygen, n (%)	50 (23.1%)	125 (19.3%)	0.2408
	28-Day In Hospital Death, n (%)	22 (10.2%)	77 (11.9%)	0.5395
	Survival, n (%)	188 (87.0%)	547 (84.4%)	0.3794

Drug Type: SGLT2 Inhibitors		Severe Population		
		SGLT2 Inhibitors	No Metabolic Regulating Drugs	p-value
Clinical Characteristics on Admission	Age, median (IQR)	69.00 (61.6-75.7)	65.60 (55.0-76.4)	0.2478
	Female gender, n (%)	12 (27.3%)	253 (39.0%)	0.1490
	Heart rate, median (IQR), bpm	88.00 (77.0-99.5)	85.00 (75.0-98.0)	0.4980
	SBP, median (IQR), mmHg	121.0 (110.0-135.5)	126.0 (112.0-139.0)	0.3341
	DBP, median (IQR), mmHg	71.5 (61.5-79.0)	73.0 (64.0-82.0)	0.6649
	SpO2, median (IQR)	94.0 (91.0-96.0)	95.0 (93.0-97.0)	0.0850
	Temperature (P.O), median (IQR)	36.9 (36.6-37.4)	37.0 (36.7-37.4)	0.3652
	Smoking, n (%)	0 (0.0%)	18 (2.8%)	0.6211
Comorbidities on Admission	Asthma, n (%)	0 (0.0%)	26 (4.0%)	0.4006
	COPD, n (%)	1 (2.3%)	27 (4.2%)	1.0000
	Hypertension, n (%)	32 (72.7%)	212 (32.7%)	<.0001
	Diabetes, n (%)	44 (100.0%)	111 (17.1%)	<.0001
	Coronary heart disease, n (%)	19 (43.2%)	67 (10.3%)	<.0001
	Obesity, n (%)	3 (6.8%)	51 (7.9%)	1.0000
	Dyslipidemia, n (%)	17 (38.6%)	76 (11.7%)	<.0001
	Cerebrovascular disease, n (%)	2 (4.5%)	21 (3.2%)	0.6522
	Chronic liver disease, n (%)	2 (4.5%)	12 (1.9%)	0.2218
	Chronic kidney disease, n (%)	1 (2.3%)	11 (1.7%)	0.5484
Laboratory Examination on Admission	Platelet count, median (IQR)	175.5 (143.0-229.0)	209.0 (151.0-269.0)	0.0024
	Neutrophil count, median (IQR)	5.4 (3.4-6.6)	4.8 (3.0-7.5)	0.1378
	Lymphocyte count, median (IQR)	0.8 (0.6-1.1)	0.8 (0.6-1.1)	0.4074
	C-reactive protein, median (IQR)	12.5 (6.1-22.1)	12.3 (4.9-21.8)	0.4754
	Cardiac Troponin, median (IQR)	12.5 (6.1-22.1)	12.3 (4.9-21.8)	0.0637
	Ferritin, median (IQR)	263.0 (127.0-704.5)	549.0 (264.5-1022.3)	0.0019
	Creatinine, median (IQR)	97.0 (73.0-127.0)	80.0 (65.0-102.0)	0.0222
	LDH, median (IQR)	311.0 (204.0-403.0)	301.5 (234.5-399.5)	0.0864
	D-dimer, median (IQR)	0.7 (0.5-1.6)	1.0 (0.6-2.0)	0.0047
	T.Bilirubin, median (IQR)	7.5 (6.2-11.6)	8.7 (6.3-12.3)	0.7310
	Lactic Acid, median (IQR)	2.4 (1.8-3.1)	2.3 (1.7-3.4)	0.9011
	Glucose, median (IQR)	8.8 (6.1-9.5)	6.0 (5.1-7.6)	0.0272
Statistical Outcomes	Follow-up days, median (IQR)	8.7 (5.0-14.4)	8.0 (4.8-14.2)	0.1621
	ICU admission, n (%)	16 (36.4%)	179 (27.6%)	0.2268
	Mechanically Ventilated/ECMO, n (%)	8 (18.2%)	76 (11.7%)	0.2290
	Non-invasive ventilation, n (%)	3 (6.8%)	28 (4.3%)	0.4390
	High Flow Oxygen, n (%)	12 (27.3%)	125 (19.3%)	0.2386
	28-Day In Hospital Death, n (%)	10 (22.7%)	77 (11.9%)	0.0553
	Survival, n (%)	34 (77.3%)	547 (84.4%)	0.2063

Drug Type: Thiazolidinediones		Severe Population		
		Thiazolidinediones	No Metabolic Regulating Drugs	p-value
Clinical Characteristics on Admission	Age, median (IQR)	62.80 (58.2-72.0)	65.60 (55.0-76.4)	0.4919
	Female gender, n (%)	13 (50.0%)	253 (39.0%)	0.3075
	Heart rate, median (IQR), bpm	86.50 (78.0-99.0)	85.00 (75.0-98.0)	0.5692
	SBP, median (IQR), mmHg	133.5 (121.0-144.0)	126.0 (112.0-139.0)	0.0881
	DBP, median (IQR), mmHg	73.5 (56.0-82.0)	73.0 (64.0-82.0)	0.5032
	SpO2, median (IQR)	94.0 (90.0-96.0)	95.0 (93.0-97.0)	0.4716
	Temperature (P.O), median (IQR)	37.1 (36.8-37.5)	37.0 (36.7-37.4)	0.7326
	Smoking, n (%)	0 (0.0%)	18 (2.8%)	1.0000
Comorbidities on Admission	Asthma, n (%)	0 (0.0%)	26 (4.0%)	0.6175
	COPD, n (%)	1 (3.8%)	27 (4.2%)	1.0000
	Hypertension, n (%)	19 (73.1%)	212 (32.7%)	<.0001
	Diabetes, n (%)	26 (100.0%)	111 (17.1%)	<.0001
	Coronary heart disease, n (%)	10 (38.5%)	67 (10.3%)	0.0002
	Obesity, n (%)	5 (19.2%)	51 (7.9%)	0.0562
	Dyslipidemia, n (%)	13 (50.0%)	76 (11.7%)	<.0001
	Cerebrovascular disease, n (%)	4 (15.4%)	21 (3.2%)	0.0127
	Chronic liver disease, n (%)	1 (3.8%)	12 (1.9%)	0.4032
	Chronic kidney disease, n (%)	1 (3.8%)	11 (1.7%)	0.3788
Laboratory Examination on Admission	Platelet count, median (IQR)	219.5 (169.0-321.0)	209.0 (151.0-269.0)	0.1464
	Neutrophil count, median (IQR)	4.8 (3.8-5.9)	4.8 (3.0-7.5)	0.2333
	Lymphocyte count, median (IQR)	1.1 (0.9-1.4)	0.8 (0.6-1.1)	0.7478
	C-reactive protein, median (IQR)	8.4 (1.2-16.9)	12.3 (4.9-21.8)	<.0001
	Cardiac Troponin, median (IQR)	8.4 (1.2-16.9)	12.3 (4.9-21.8)	0.7994
	Ferritin, median (IQR)	192.1 (108.0-430.0)	549.0 (264.5-1022.3)	<.0001
	Creatinine, median (IQR)	79.5 (63.0-101.0)	80.0 (65.0-102.0)	0.0465
	LDH, median (IQR)	314.0 (234.0-437.0)	301.5 (234.5-399.5)	0.6508
	D-dimer, median (IQR)	0.5 (0.4-0.7)	1.0 (0.6-2.0)	<.0001
	T.Bilirubin, median (IQR)	7.5 (6.2-9.4)	8.7 (6.3-12.3)	0.0151
	Lactic Acid, median (IQR)	1.9 (1.5-2.8)	2.3 (1.7-3.4)	0.2110
	Glucose, median (IQR)	8.9 (6.3-12.5)	6.0 (5.1-7.6)	0.0004
Statistical Outcomes	Follow-up days, median (IQR)	6.2 (4.5-12.4)	8.0 (4.8-14.2)	0.1845
	ICU admission, n (%)	7 (26.9%)	179 (27.6%)	1.0000
	Mechanically Ventilated/ECMO, n (%)	4 (15.4%)	76 (11.7%)	0.5359
	Non-invasive ventilation, n (%)	2 (7.7%)	28 (4.3%)	0.3239
	High Flow Oxygen, n (%)	5 (19.2%)	125 (19.3%)	1.0000
	28-Day In Hospital Death, n (%)	4 (15.4%)	77 (11.9%)	0.5399
	Survival, n (%)	21 (80.8%)	547 (84.4%)	0.5846

Table S4. Cox regression model of 28-days mortality in the treatment groups versus control. Adjusted HR and p-values were calculated based using a Cox regression model adjusting for age, gender, and pre-existing comorbidities (smoking, asthma, COPD, DM, hypertension, diabetes, coronary heart disease, obesity, dyslipidemia, cerebrovascular disease, chronic liver disease, and chronic kidney disease). There were no deaths recorded in fibrate patients, resulting in monotone likelihood (nonconvergence of likelihood function, a Firth's penalized maximum likelihood bias reduction method was implemented to calculate hazard ratios and confidence intervals. Thiazolidinediones and SGLT2 inhibitors users show a significantly higher risk of death within 28 days of hospitalization (adjusted risk). # indicates that the hazard ratios were calculated using Firth's correction for monotone likelihood with profile likelihood confidence limits.

	Full population		Severe Population	
	Hazard Ratio [95%CI] Drug vs. No Metabolic Drug Used	p value	Hazard Ratio [95%CI] Drug vs. No Metabolic Drug Used	p value
Any Metabolic Regulating Drugs	0.971 [0.666;1.415]	0.8785	0.989 [0.645;1.518]	0.9608
Fibrates	0.492 [0.003;2.811] #	0.4920 #	0.562 [0.004;4.609] #	0.7008 #
Statins	1.120 [0.645;1.943]	0.6876	1.128 [0.608;2.092]	0.7024
Thiazolidinediones	2.576 [0.811;8.181]	0.1086	3.594 [1.041;12.412]	0.0431
SGLT2 Inhibitors	2.211 [0.976;5.012]	0.0573	2.574 [1.073;6.175]	0.0341
IRE1α inhibitors	0.876 [0.525;1.461]	0.6118	0.971 [0.547;1.721]	0.9188
Metformin	0.850 [0.481;1.503]	0.5762	0.872 [0.460;1.656]	0.6759

Table S5. Comparative Cohort of the Outpatient Lipid Clinics of the University of Bologna and of the Niguarda Hospital in Milan

	All (N=2123)	Statin (N=1791)	Fenofibrate (N=220)	Both (N=112)	
% Total		84,4%	10,4%	5,3%	
<i>Demographics</i>					p
Age, years	59.6 ± 15.3	59.2 ± 15.2	60.8 ± 15.4	62.9 ± 16.3	0.023
Female, n (%)	1102 (51.9)	955 (53.3)	93 (42.2)	54 (48.2)	0.006
<i>Comorbidities</i>					p
Obesity, n (%)	410 (19.3)	338 (18.9)	47 (21.4)	25 (22.3)	0.480
COPD, n (%)	203 (9.6)	174 (9.7)	21 (9.5)	8 (7.1)	0.668
ASCVD, n (%)	454 (21.4)	379 (21.2)	25 (11.4)	50 (44.6)	<0.001
<i>COVID</i>					p
Personal history of COVID	177 (8.3)	164 (9.2)	7 (3.2)	6 (5.4)	0.005
Contact with affected people	254 (12.0)	205 (11.4)	27 (12.3)	22 (19.6)	0.648

Table S5A. Characteristics of included patients stratified by lipid-lowering treatment. Cohort of 2,123 patients (M: 48.1%, F: 51.9%) on statins (1,791, mean age 59,2±15.2 years), fenofibrate (220, mean age 60,7±15.4 years) or both (112, mean age 62,9±16.3 years) were interviewed. Patients on statins were significantly younger than those on both drugs (p=0.023). 177 patients received a diagnosis of COVID by molecular swab: 9.2% of statin treated subjects, 3.2% of fenofibrate treated ones, and 5.4% of those treated with both statins and fenofibrate (p=0.005) without differences in the source of exposition (family members, co-workers; p=0.648).

		All (N=2123)	Statin (N=1791)	Fenofibrate (N=220)	Both (N=112)	
	% Total		84.4%	10.4%	5.3%	
COVID severity	No infection	Count	1946	1627	213	106
		% in COVID severity	100.0%	83.6%	10.9%	5.4%
		% in Lipid Lowering Drugs	91.7%	90.8%	96.8%	94.6%
	Mild	Count	146	134	6	6
		% in COVID severity	100.0%	91.8%	4.1%	4.1%
		% in Lipid Lowering Drugs	6.9%	7.5%	2.7%	5.4%
	Severe	Count	31	30	1	0
		% in COVID severity	100.0%	96.8%	3.2%	0.0%
		% in Lipid Lowering Drugs	1.5%	1.7%	0.5%	0.0%
	Total	Count	2123	1791	220	112
		% in COVID severity	100.0%	84.4%	10.4%	5.3%
		% in Lipid Lowering Drugs	100.0%	100.0%	100.0%	100.0%

Table S5B. Disease severity stratified by lipid-lowering treatment. 134 reported mild COVID-19 symptoms and 31 patients reported severe COVID-19 symptoms, requiring hospitalization: 1.7% of statin treated subjects, 0.5% of fenofibrate treated ones, and 0% of those treated with both statins and fenofibrate (p=0.022) without differences in the source of exposition (**Table S5A**).

	Personal history of COVID		
	Yes (N=177)	No (N=1946)	p
<i>Demographics</i>			
Age, years	44.7 ± 19.2	60.7 ± 14.3	<0.001
Female, n (%)	88 (49.7)	1014 (52.1)	0.542
<i>Comorbidities</i>			
Obesity, n (%)	47 (26.6)	363 (18.7)	0.011
COPD, n (%)	25 (14.1)	178 (9.1)	0.031
ASCVD, n (%)	56 (31.6)	398 (20.5)	0.001
<i>Lipid-lowering treatment</i>			
Statin, n (%)	164 (92.7)	1627 (83.6)	0.002
Fenofibrate, n (%)	7 (4.0)	213 (10.9)	0.003
Both, n (%)	6 (3.4)	106 (5.4)	0.241
<i>COVID exposure</i>			
Contacts with affected people	45 (25.4)	209 (10.7)	<0.001

Table S5C. Characteristics of included patients according to personal history of COVID. Patients affected by COVID were more frequently obese, with COPD and/or cardiovascular diseases, and had strict contact with COVID affected subjects, independent of the lipid-lowering treatment.

	Personal history of COVID		p
	Yes (N=45)	No (N=209)	
<i>Demographics</i>			
Age, years	51.7 ± 18.3	57.4 ± 15.0	0.109
Female, n (%)	24 (46.7)	116 (55.5)	0.791
<i>Comorbidities</i>			
Obesity, n (%)	4 (8.9)	37 (17.7)	0.145
COPD, n (%)	5 (11.1)	9 (4.3)	0.070
ASCVD, n (%)	10 (22.2)	35 (16.7)	0.383
<i>Lipid-lowering treatment</i>			
Statin, n (%)	42 (93.3)	163 (78.0)	0.018
Fenofibrate, n (%)	2 (4.4)	25 (12)	0.138
Both, n (%)	1 (2.2)	21 (10.0)	0.09

Table S5D. Characteristics of patients exposed to contact with affected people (n=254). Out of 254 patients reporting contact with affected people, 45 became positive to COVID. 93.3% were in treatment with statins 4.4% with fenofibrate and 4.5% with both (p=0.059). Affected to exposed to positive contacts ratio according to background lipid-lowering was 20.5% in patients treated with statins 7.4% with fenofibrate and 4.5% with both (p=0.059).

Table S6. Comparative cohort in the American veteran's health administration (VHA) registry

	<i>Fenofibrate users</i>	<i>Non-users</i>	<i>Fenofibrate users</i>	<i>Non-users</i>	<i>Standardized Difference After Matching</i>
	<i>Before Matching</i>		<i>After 1:5 Matching</i>		
Fenofibrate users (N=4,492) vs. non-users (N=915,403)					
Mean Age, years	53.7	57.9	57.2	57.9	6.3%
BMI, kg/m ²	32.6	32.7	31.1	32.3	0.8%
Male sex	97%	93%	93%	93%	1.4%
Black race	8%	19%	19%	20%	2.9%
Cardiovascular disease	9%	7%	6%	7%	5.1%
Heart failure	1%	1%	1%	1%	3.9%
Diabetes mellitus	39%	22%	20%	22%	3.9%
Chronic lung disease	19%	19%	17%	19%	4.8%
Chronic liver disease	6%	6%	5%	6%	3.7%
Dementia	3%	3%	1%	3%	8.3%
Current or former smoker	35%	31%	32%	31%	2.9%
Fenofibrate users (N=4,492) vs. statin users (N=401,811)					
Mean Age, years	53.7	59.2	59.4	59.1	2.3%
BMI, kg/m ²	32.6	32.5	31.4	32.4	1.6%
Male sex	97%	95%	96%	95%	3.2%
Black race	8%	18%	16%	18%	4.8%
Cardiovascular disease	9%	9%	8%	9%	4.0%
Heart failure	1%	2%	1%	2%	2.3%
Diabetes mellitus	39%	29%	28%	29%	2.2%
Chronic lung disease	19%	19%	18%	19%	3.6%
Chronic liver disease	6%	5%	5%	5%	1.8%
Dementia	3%	3%	2%	2%	1.1%
Current or former smoker	35%	31%	30%	31%	2.8%
Fenofibrate users (N=4,492) vs. TZD users (N=9,045)					
Mean Age, years	53.8	57.0	56.7	57.0	2.5%
BMI, kg/m ²	32.2	33.1	32.5	32.8	1.6%
Male sex	96%	95%	95%	95%	2.0%

Black race	8%	18%	18%	18%	0.1%
Cardiovascular disease	9%	6%	6%	6%	1.0%
Heart failure	2%	9%	1%	1%	1.9%
Diabetes mellitus	37%	100%	100%	100%	0.7%
Chronic lung disease	19%	16%	16%	16%	0.3%
Chronic liver disease	6%	5%	5%	5%	0.6%
Dementia	3%	2%	2%	2%	2.2%
Current or former smoker	35%	26%	25%	26%	1.0%

Table S6A. Characteristics of fenofibrate users compared with non-users before and after PSM

	<i>Fenofibrate users, median (IQR)</i>	<i>Non-users, median (IQR)</i>	<i>Median difference (95% CI)</i>	<i>Median difference (95% CI) after matching</i>
Fenofibrate users vs. non-users	5 (3, 10)	5 (2, 13)	0 (-5, 5)	-2 (-14, 11)
Fenofibrate users vs. statin users	5 (3, 10)	5 (2, 11)	0 (-3, 3)	-2 (-12, 8)
Fenofibrate users vs. TZD users	5 (3, 10)	5, (2, 14)	0 (-6, 6)	-2 (-7, 3)

Table S6B. Median duration of hospitalization among fenofibrate users vs. non-users

	<i>Fenofibrate users Events / Total N (%)</i>	<i>Non-users Events / Total N</i>	<i>OR (95% CI) after matching</i>
Fenofibrate users vs. non-users			
SARS-CoV-2 positive	32 / 4,492 (0.7%)	5,108 / 915,403 (0.6%)	0.78 (0.47-1.28)
COVID-19 hospitalization	15 / 4,492 (0.3%)	2,008 / 915,403 (0.2%)	0.60 (0.28-1.28)
Mechanical ventilation	3 / 4,492 (0.1%)	240 / 915,403 (0.1%)	0.45 (0.13-1.51)
COVID-19 death	1 / 4,492 (0.02%)	260 / 915,403 (0.03%)	0.98 (0.14-7.01)
Fenofibrate users vs. statin users			
SARS-CoV-2 positive	32 / 4,492 (0.7%)	3,052 / 401,811 (0.8%)	0.91 (0.54-1.53)
COVID-19 hospitalization	15 / 4,492 (0.3%)	1,221 / 401,811 (0.3%)	0.78 (0.37-1.65)
Mechanical ventilation	3 / 4,492 (0.1%)	144 / 401,811 (0.1%)	0.51 (0.15-1.75)
COVID-19 death	1 / 4,492 (0.02%)	108 / 401,811 (0.03%)	0.74 (0.10-5.33)
Fenofibrate users vs. TZD users			
SARS-CoV-2 positive	32 / 4,492 (0.7%)	110 / 9,045 (1.2%)	0.52 (0.32-0.86)
COVID-19 hospitalization	15 / 4,492 (0.3%)	43 / 9,045 (0.5%)	0.70 (0.39-1.26)
Mechanical ventilation	3 / 4,492 (0.1%)	6 / 9,045 (0.1%)	0.60 (0.13-2.71)
COVID-19 death	1 / 4,492 (0.02%)	5 / 9,045 (0.1%)	0.40 (0.05-3.45)

Table S6C. SARS-CoV-2 infection and COVID-19 severity among fenofibrate users vs. non-users

Parameters	Fenofibrate (N = 15)	Control (N = 144)	p value
Clinical Characteristics on Admission			
Age, median (IQR)	64 (47-73)	60 (48.9-68.5)	0.8412
Female gender, n (%)	9 (60%)	58 (40.3%)	0.3547
Heart rate, median (IQR), bpm	85 (79-93)	88 (77-98)	0.667
SBP, median (IQR), mmHg	129 (118.5-136)	126 (116.8-143)	0.9483
DBP, median (IQR), mmHg	77 (70-82.5)	74 (68.8-81.3)	0.608
%SpO2, median (IQR)	91 (90-92)	93 (91-95)	0.0107
%FiO2, median (IQR)	29 (29-29)	29 (25-33)	0.2532
Lesions on chest CT, n (%)	14 (93.3%)	131 (91.0%)	1
Temperature (P.O), median (IQR)	37.1 (36.9-37.3)	37.1 (36.8-37.6)	0.7611
Smoking, n (%)	0 (0%)	5 (3.5%)	1
Comorbidities on Admission			
Asthma, n (%)	1 (6.7%)	2 (1.4%)	0.268
COPD, n (%)	0 (0%)	6 (4.2%)	1
Hypertension, n (%)	8 (53.3%)	52 (36.1%)	0.4583
Diabetes, n (%)	6 (40%)	40 (27.8%)	0.5796
Chronic heart disease, n (%)	1 (6.7%)	28 (19.4%)	0.4737
Obesity, n (%)	7 (46.7%)	19 (13.2%)	0.0184
Dyslipidemia, n (%)	8 (53.3%)	37 (25.7%)	0.1776
Cerebrovascular disease, n (%)	0 (0%)	1 (0.7%)	1
Chronic liver disease, n (%)	2 (13.3%)	4 (2.8%)	0.116
Chronic kidney disease, n (%)	3 (20%)	0 (0%)	0.0012
Laboratory Examination on Admission			
Platelets count, median (IQR)	190 (169.5-204.5)	189 (156-255)	0.8048
Neutrophil count, median (IQR)	3.8 (2.8-4.5)	3.7 (2.8-5.3)	0.6879
Lymphocyte count, median (IQR)	1 (0.8-1.8)	0.8 (0.7-1.1)	0.1303
C-reactive protein, median (IQR)	8.7 (5.1-11)	11.9 (5.8-15.5)	0.1652
Cardiac Troponin, median (IQR)	17 (14.5-18.5)	6 (3.5-16)	0.0209
Ferritin, median (IQR)	495.9 (286.2-683.4)	504 (220.1-1160.8)	0.9264
Creatinine, median (IQR)	73 (62.5-86)	80 (67-91)	0.3939
LDH, median (IQR)	517 (458-653)	347 (270-441)	<0.001
D-dimer, median (IQR)	0.7 (0.4-1.1)	0.8 (0.5-1.3)	0.4763
T.Bilirubin, median (IQR)	6.2 (5.6-8)	8.6 (6.6-11.6)	0.0123
Lactic Acid, median (IQR)	2 (1.3-2.2)	2 (1.7-2.4)	0.6784
Glucose, median (IQR)	6.5 (5.8-8.8)	6.1 (5.3-7.5)	0.2286
Statistical Outcomes			
Follow-up days, median (IQR)	7 (5.5-7.5)	9.3 (6.8-14)	<0.001
ICU admission, n (%)	0 (0%)	24 (16.7%)	0.2249
Deaths, n (%)	0 (0%)	8 (5.6%)	1
Rehospitalization, n (%)	0 (0%)	25 (17.4%)	0.2285
Mechanically Ventilated/ECMO, n (%)	0 (0%)	11 (7.6%)	0.6014
High Flow Oxygen, n (%)	1 (6.7%)	36 (25%)	0.3147
Weaned-off Supplemental Oxygen by Day 7	14 (93.3%)	53 (39.3%)	0.0052

Table S7. Characteristics of patients compared to the patients in the interventional study. 15

Participants who met the inclusion criteria were assigned to intervention with nanocrystallized fenofibrate (TriCor®, AbbVie Inc., North Chicago, IL USA) at a dose of 145 mg (1 tablet) once per day. Standard care for severe-hospitalized COVID-19 patient was provided according to local practice: antiviral treatment, vitamin D3, low-dose glucocorticoids, convalescent plasma, and supportive care as well as antipyretic for symptoms of fever (products containing paracetamol, or non-steroidal anti-inflammatories such as aspirin and ibuprofen) and dextromethorphan for symptoms of cough. Standard chronic treatments were continued unless COVID-19, clinical status, or fenofibrate treatment was a contraindication for the treatment. Control patients were collected from the observational study's database and filtered to patients that meet the inclusion criteria, admitted with low immunoinflammatory stress (NLR<10 at admission), and treated according to the standard care used in the interventional study. SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, chronic obstructive pulmonary disease; SpO2, oxygen saturation; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range. Continuous variables were expressed as median [IQR] and were compared with a Mann-Whitney U test. Categorical variables were expressed as a count and percentage (%) and compared with a chi-squared test or Fisher's exact test. The sample size is detailed in each display item.

Table S8. Cox regression model of 28-days mortality in the treatment group versus control. Adjusted HR and p-values were calculated based using an unadjusted Cox regression model, a Cox regression model adjusting for age, gender, and pre-existing comorbidities (smoking, asthma, COPD, DM, hypertension, diabetes, coronary heart disease, obesity, dyslipidemia, cerebrovascular disease, chronic liver disease, and chronic kidney disease) or a Cox regression model adjusting for significantly different patient characteristics, obesity, chronic kidney disease and SpO2.

	Hazard Ratio [95%CI]	p value
Unadjusted	3.637 [2.067;6.398]	7.46E-06
Adjusted for age, gender, and pre-existing comorbidities	3.940 [2.223; 6.982]	2.63E-06
Adjusted for obesity, chronic kidney disease and SpO2	3.635 [1.938; 6.818]	5.78E-05

Table S8A. Cox regression model of 28-days hospital discharge

	Hazard Ratio [95%CI]	p value
Unadjusted	2.873 [1.661; 4.970]	1.61E-04
Adjusted for age, gender, and pre-existing comorbidities	3.296 [1.866; 5.822]	3.99E-05
Adjusted for obesity, chronic kidney disease and SpO2	4.517 [2.344; 8.706]	6.65E-06

Table S8B. Cox regression model of 28-days oxygen withdrawal

	Hazard Ratio [95%CI]	p value
Unadjusted	0.262 [0.002; 2.444]	0.2868
Adjusted for age, gender, and pre-existing comorbidities	0.307 [0.002; 2.865]	0.3575
Adjusted for obesity, chronic kidney disease and SpO2	0.313 [0.077; 3.300]	0.4025

Table S8C. Cox regression model of 28-days mortality. There were no deaths recorded in treatment patients, resulting in monotone likelihood (nonconvergence of likelihood function, a Firth's penalized maximum likelihood bias reduction method was implemented to calculate hazard ratios and confidence intervals.

Figure S1. Transcriptional metabolic signature of infection in COVID-19 patients' samples and SARS-CoV-2 infected primary cells. (A) Venn diagrams describing the relationship between differentially expressed genes (DEG), metabolic genes (GO:0008152), and lipid metabolism genes (GO:0006629) in COVID-19 patient sample groups including epithelial cells isolated by bronchoalveolar lavage (lavage) and post-mortem lung biopsies (autopsy), as well as primary small airway epithelial cells (alveoli) and primary bronchial epithelial cells (bronchial) infected with SARS-CoV-2. **(B)** Sunburst graphs showing the coverage of composite metabolic terms (Levy et al., 2016) on general metabolic response induced by SARS-CoV-2 infection. Lipid and mitochondrial metabolism dominate the transcriptional metabolic signature of infection across all four sample groups. **(C)** Heat map of metabolic and stress pathway-associated genes (**Figure 1D**) across four sample groups. Red and green boxes are up and downregulated by infection, respectively. # indicates a small sample size.

Figure S2. Single-cell characterization of lung epithelial cells isolated by bronchoalveolar lavage from severe COVID-19 patients. (A) T-distributed stochastic neighbour embedding (tSNE) plot shows clustering of 5,231 lung epithelial cells (*methods*) isolated by bronchoalveolar lavage. Point coordinates were calculated based on Non-negative matrix factorization (NMF) of top over-dispersed genes (*methods*). (B) Violin graphs and tSNE plots of composite expression levels identifying the cell type and state of each of the defined clusters (Plasschaert et al., 2018). (C) Schematic of ER stress pathways superimposed with pathway-associated genes. Red and green boxes are up and downregulated by infection, respectively. * marks differentially regulated genes ($n=3$, $FDR < 0.05$). Red arrows note putative activation pathways based on the transcriptional response. XBP1S/U is the ratio of IRE1-spliced over the un-spliced form of XBP1.

Figure S3

Figure S3. qRT-PCR of ER stress genes induced by expression of SARS-CoV-2 proteins. Gene expression analysis of ER stress-related genes in primary bronchial epithelial cells expressing different SARS-CoV-2 proteins for 72 hours. * p<0.05, ** p<0.01, *** p<0.001 in a 2-sided heteroscedastic student's t-test against control. Error bars indicate S.E.M.

Figure S4. PPAR α agonists in SARS-CoV-2 infection *in vitro* (A) Relative viability and viral load in SARS-CoV-2 infected bronchial epithelial cells treated with different metabolic regulators for 5 days. (B) Microscopic analysis of lipid accumulation in ORF3a expressing bronchial epithelial cells treated with different PPAR α agonists. * $p<0.05$, ** $p<0.01$, *** $p<0.001$. Bar = 50 μ m.

Figure S5. The host-immune response in hospitalized COVID-19 patients in different metabolic interventions. (A-D) Dynamic changes in (A) neutrophils, (B) lymphocytes, (C) monocytes, and (D) platelets levels during 21-day hospitalization in treatment and non-treatment groups (Control). The centerline shows the mean value while the 95% confidence interval is represented by the shaded region.

Figure S6. Analysis of variant emergence dynamics and distribution during the study period in participants and other hospitalized patients. (A) sample distribution (left) and relative abundance (left), with and without SGTF by day from 30 November 2020 to 28 February 2021. (B) Stratified relative abundance of samples with and without SGTF of patients in the interventional study (left) and of other hospitalized patients (right) from 16 December 2020 to 28 February 2021. (C) Distribution comparison of sample distribution with and without SGTF in stratified periods. Odds ratios (ORs) and the related p-values were calculated using Fisher's exact test (methods). SGTF, S-gene target failure, serves as a proxy for identifying B.1.1.7 cases (Brown et al., 2021; Davies et al., 2021).

Figure S7. Observational Study Flow Chart

Supplementary Files

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- [TableS9.xlsx](#)
- [TableS11.pdf](#)
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