

Article

Drug-Disease Severity and Target-Disease Severity Interaction Networks in COVID-19 Patients

Verena Schöning  and Felix Hammann *

Clinical Pharmacology and Toxicology, Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, 3010 Bern, Switzerland

* Correspondence: felix.hammann@insel.ch

Abstract: Drug interactions with other drugs are a well-known phenomenon. Similarly, however, pre-existing drug therapy can alter the course of diseases for which it has not been prescribed. We performed network analysis on drugs and their respective targets to investigate whether there are drugs or targets with protective effects in COVID-19, making them candidates for repurposing. These networks of drug-disease interactions (DDIs) and target-disease interactions (TDIs) revealed a greater share of patients with diabetes and cardiac co-morbidities in the non-severe cohort treated with dipeptidyl peptidase-4 (DPP4) inhibitors. A possible protective effect of DPP4 inhibitors is also plausible on pathophysiological grounds, and our results support repositioning efforts of DPP4 inhibitors against SARS-CoV-2. At target level, we observed that the target location might have an influence on disease progression. This could potentially be attributed to disruption of functional membrane micro-domains (lipid rafts), which in turn could decrease viral entry and thus disease severity.



Citation: Schöning, V.; Hammann, F. Drug-Disease Severity and Target-Disease Severity Interaction Networks in COVID-19 Patients.

Pharmaceutics **2022**, *14*, 1828.[https://doi.org/10.3390/](https://doi.org/10.3390/pharmaceutics14091828)[pharmaceutics14091828](https://doi.org/10.3390/pharmaceutics14091828)

Academic Editors: Paul Bogdan, Lucreția Udrescu, Mihai Udrescu and Ludovic Kurunczi

Received: 16 May 2022

Accepted: 27 August 2022

Published: 30 August 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Keywords: COVID-19; network analysis; drug-disease interaction; target-disease interaction; DPP4 inhibitors; lipid rafts; drug repurposing

1. Introduction

In Switzerland, patients seen by general practitioners have a median of two chronic conditions, and receive a median of two prescribed drugs [1]. The most common conditions are cardiovascular diseases, including arterial hypertension and lipid disorders, and diabetes [2]. Not only do drug-drug interactions increase with pill burden, but also the risk for drug-disease interactions (DDIs), where drugs that are beneficial in one disease may be harmful in another [3]. A drug's action is brought about by its interaction with molecular targets. The relationship is asymmetric, meaning that a given drug can interact with multiple targets, and one target with multiple drugs [4]. By consequence, the interaction of drugs with specific molecular targets can also influence the progression or severity of a disease, which could lead to a target-disease interaction (TDI).

The current pandemic of coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By now, several risk factors for severe COVID-19 progression are known, such as age [5,6], male sex [7,8], or obesity [9–12]. Additionally, common co-morbidities such as diabetes [13–15], cardiac [16,17] and pulmonary diseases [18,19], or dementia [20] can influence prognosis of COVID-19. Furthermore, both the number and the combination of certain co-morbidities have been found to be predictors of severity [21]. Several studies have already been conducted to analyze the influence of specific co-medications on COVID-19 incidence and progression. For example, hypertension is a common chronic condition and a risk factor for severe COVID-19 progression [22]. Some researchers analyzed the influence of anti-hypertensive drugs acting on the renin-angiotensin-aldosterone-system (RAAS)-system [23,24]. The majority of these studies provided evidence that angiotensin converting enzyme (ACE) inhibitors and

angiotensin-receptor blockers (ARBs) do not adversely affect the COVID-19 progression or may even be beneficial [22–28]. In general, studies showed that polypharmacy increases the risk for severe COVID-19 [29,30].

Network analysis is used to investigate a group of objects (e.g., friends, internet servers, patients, enzymes, or proteins) and their connection with each other. The objects are the nodes of the network, whereas the relationships are the edges connecting the nodes. One famous example is Zachary’s “karate club” network, which displays the pattern of friendships amongst the members of a university karate club [31]. In recent years, network analysis has increasingly been applied in the context of pharmacology, e.g., to investigate the relationships between drugs and their respective targets [4] or the relationship between proteins and metabolites [32]. In addition, several network studies on the repurposing of drugs against SARS-CoV-2 have been conducted, mainly as drug-target, target-human, viral-human, or protein-protein-interactions, or combinations thereof [32–34]. In addition, transcriptomes of COVID-19 patients, patients with related conditions and healthy controls were compared to identify possible drugs candidates for repurposing [35].

However, none of these studies used clinical data to investigate the influence of pre-existing drug treatment on patient outcomes as measure of disease severity.

The aim of this study was to analyze the impact of DDSIs and TDSIs on COVID-19 severity using network analysis as a tool to inform drug repurposing efforts and increase drug safety. We compared drugs on admission (i.e., drugs patients were taking before or on the day of admission) and their molecular targets in patients who tested positive for SARS-CoV-2, and used severe (required critical care or died) or non-severe outcome (outpatient or never requiring critical care) as endpoint.

2. Materials and Methods

2.1. Study Population

We carried out this retrospective study at the Insel Hospital Group (IHG), a tertiary hospital network with six locations and about 860,000 patients treated per year, making it the biggest health care provider in Switzerland. The Cantonal Ethics Committee of Bern approved the protocol (2020-00973). We considered all patients who tested positive for SARS-CoV-2 by reverse-transcriptase polymerase chain reaction (RT-PCR) assay on nasopharyngeal swabs at the IHG between 1st February through 16th November 2020—covering the ‘first wave’ and most of the ‘second wave’ of COVID-19 in the region (Figure 1).

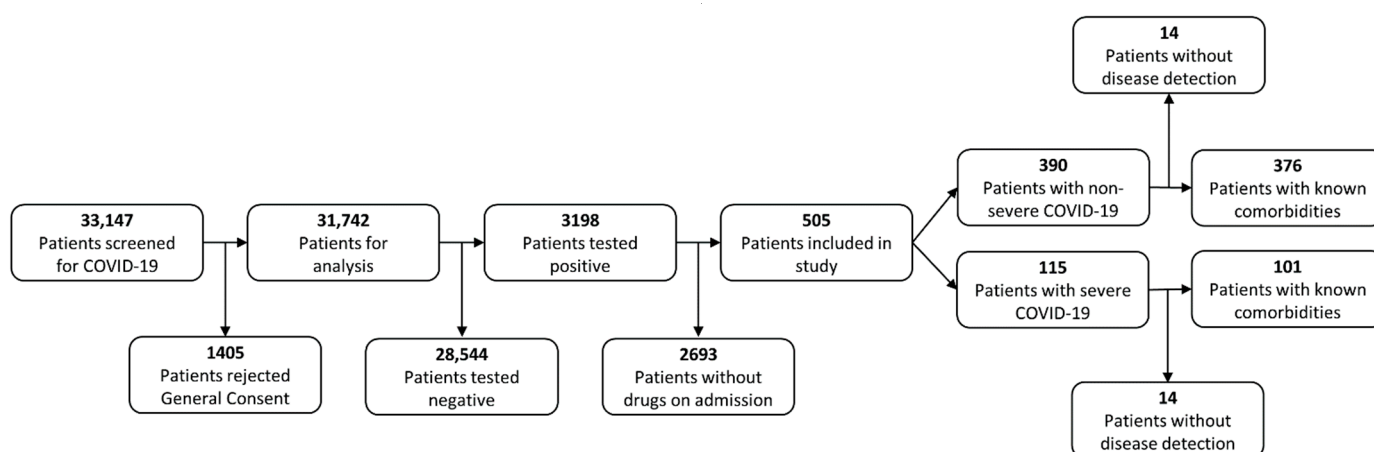


Figure 1. Flowchart of patient selection process.

For patients with no registered general research consent status, a waiver of consent was granted by the ethics committee. Objection to the general research consent of the IHG was an exclusion criterion for this study, whereas participation in other trials (including COVID-19 related treatment studies) was not. Disease progression was classified as *severe*

if, for any reason, an intensive care unit (ICU) admission was required at any stage, or the patient died during the stay. All other patients were classified as *non-severe*. We selected only patients for whom drugs on admission had been recorded. Therefore, this study included 115 severe and 390 non-severe COVID-19 patients. We identified pre-existing conditions using Natural Language Processing from a previous study [36]. For a total of 28 patients (14 non-severe and 14 severe cases), we could not perform disease detection. Characteristics of the study population are provided in Table 1.

Table 1. Characteristics of study population.

General Characteristics	Non-Severe (n = 390)	Severe (n = 115)	p Value
Age (years) Median (Q1, Q3)	67.00 (52.00, 77.00)	70.00 (60.50, 81.00)	<0.001
Sex Female (%)	155 (39.74%)	31 (26.96%)	0.017
BMI Median (Q1, Q3)	26.05 (23.51, 29.43)	27.73 (24.74, 31.70)	<0.006
Drugs on admission Median (Q1, Q3)	7.00 (4.00, 12.00)	8.00 (4.00, 13.00)	0.403
Diseases			
Arterial hypertension (%)	182 (48.40%)	64 (63.37%)	0.011
Chronic heart failure (%)	92 (24.47%)	37 (36.63%)	0.021
Atrial fibrillation (%)	57 (15.16%)	23 (22.77%)	0.095
Coronary heart disease (%)	52 (13.83%)	32 (31.68%)	<0.002
Coronary sclerosis (%)	9 (2.39%)	6 (5.94%)	0.136
Diabetes (%)	105 (27.93%)	34 (33.66%)	0.316
Dementia (%)	39 (10.37%)	15 (14.85%)	0.278

To study the effects of co-morbidities, we created four sub-groups:

1. Cardiac conditions (chronic heart failure, atrial fibrillation, coronary heart disease, and/or coronary sclerosis) (*n* = 184)
2. Arterial hypertension (*n* = 246)
3. Diabetes (including pre-diabetes, type 1 and 2 diabetes) (*n* = 139)
4. Dementia (*n* = 54)

Note: patients can be members of more than one group, e.g., 70 patients suffered from diabetes as well as from cardiac conditions.

2.2. Network Analysis

Drugs on admission (drugs taken before admission to the IHG) were obtained from the electronic health records (EHR). As this part of the EHR was not always complete, we also considered drugs administered in-house on the day of admission. This also mitigates the effect of patients transferred from other hospitals compared to patients who were initially admitted to the IHG.

We evaluated different levels of detail in drug classification. First, we compared the fourteen main groups of the Anatomical Therapeutic Chemical (ATC) classification system [37]. Then we selected 90 pharmacological, chemical subgroups or substances, which we categorized in 30 therapeutic groups. We identified drugs in the EHR by ATC codes. By and large, the drug groups and subgroups are based on the categorization of the ATC classification, but some minor deviations are present, e.g., acetylsalicylic acid was included as antithrombotic agents, whereas in the ATC code, it is grouped with the analgesics, an uncommon indication in Switzerland. Considering the hyper-thrombotic state of COVID-19 patients [38], we considered its rheological effect to be more important than its analgesic effect. Further information on our grouping is available in the supplements, Table S1.

Lastly, we analyzed the molecular targets of the drugs on admission. We used Drug-Bank [39] to map drugs to targets and their target locations.

As the two severity cohorts are imbalanced, we normalized the number of patients for network analysis in each drug (sub-)group by dividing them through the total number of patients in the respective cohort. The obtained value was used as weight in the network analysis.

A network consists of nodes connected by edges. A node's weight is determined by the number of patients receiving the drug, and an edge's weight by the number of patients receiving two drugs simultaneously. In our analysis, drugs, drug classes, and targets were represented as nodes and concurrent use or interaction was represented by connecting undirected edges. Therefore, the weights of nodes or edges are both positively correlated with drug use or target engagement.

2.3. Software and Statistical Tests

Data wrangling, analysis, and visualization were performed in GNU R (version 4.0.2, R Foundation for Statistical Computing, <http://www.R-project>). Statistical significance levels were defined at a p value of <0.05 , and determined with the Student's t -test for continuous parameters and Chi-square test for categorical parameters using the *stats* package (version 4.0.2). Network analysis was performed using the *igraph* package (Version 1.2.6) [40]. For network visualization, we used Gephi (Version 0.9.2) [41].

3. Results

3.1. Network Metrics

The main network metrics are presented in the supplements, Table S2. Main nodes (hubs) and main edges are defined as those with the highest weight, i.e., largest share of patients taking this drug or drug combination. All main nodes and edges are identical between the severity cohorts, except for one edge in the drug subgroups (non-severe: *other analgesics and antipyretics—heparin*; severe: *other analgesics and antipyretics—antibiotics*). The diameter of the network (maximum distance between any two nodes; or the longest shortest path), was in general larger in the severe cohort. Node betweenness centrality (betweenness, indicating how often a node lies on the shortest path between two other nodes) in the non-severe cohort was higher than in the severe cohort (43 and 24 drug subgroups, respectively). More molecular targets had a higher betweenness in the non-severe than in the severe cohort (418 and 124 molecular targets, respectively). In addition, betweenness values in the non-severe cohort were higher (median: 150 vs. 48 and mean: 225 vs. 104, respectively). In Table S2, we show nodes with the greatest differences in the betweenness between the cohorts.

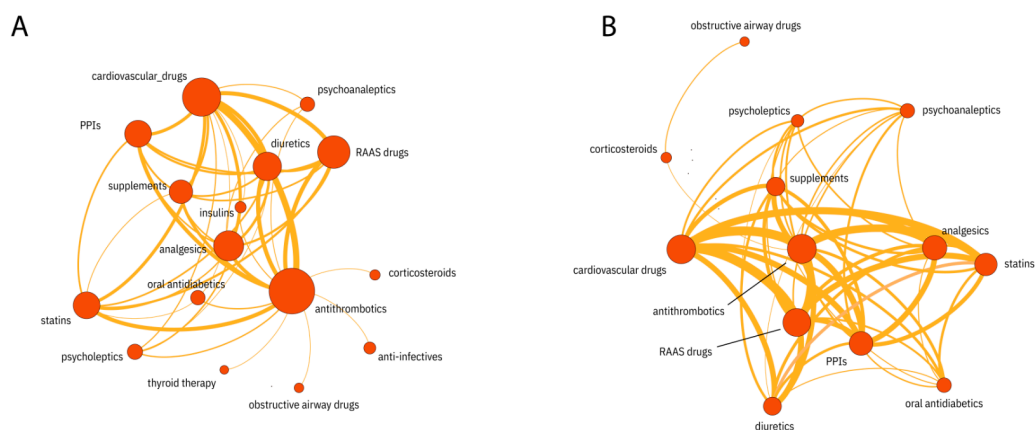
3.2. DDSI Network

There are significant differences ($p < 0.05$) in all three networks (anatomical/pharmacological group, drug group, and drug subgroup) with regards to the drugs (nodes, Table 2) and drug combinations (edges, Table 3) taken on admission. In all nodes and edges with significant differences, the percentage of occurrence was higher in the cohort with severe disease progression unless stated otherwise. As an example, visualization of the anatomical/pharmacological group network is shown in Figure 2.

Table 2. Significant nodes of the DDSI network.

Anatomical/Pharmacological Group	Non-Severe COVID-19 [%]	Severe COVID-19 [%]	p Value
Blood and blood forming organs	85.64	94.78	0.014
Various	4.1	10.43	0.018
Musculo-skeletal system	21.79	13.91	0.085
Drug Groups			
Anti-hemorrhagics	0.51	3.48	0.037
Diuretics	23.08	32.17	0.064
Cardiovascular drugs	36.67	46.09	0.087
Antiplatelet agents	23.08	31.3	0.095
Drug Subgroups			
NSAID	12.56	4.35	0.020
Loop diuretics ¹	14.87	24.35	0.025
Beta blockers ¹	26.41	37.39	0.030
Vitamin K and other hemostatics	0.51	3.48	0.037
Opioids ¹	10.51	17.39	0.068
Acetylsalicylic acid	21.28	29.57	0.085

¹ drug subgroups that were associated with death or severe COVID-19 by Iloanusi et al. and McKeigue et al. [29,30].

**Figure 2.** Drug group networks for severe (A) and non-severe (B) COVID-19 (only nodes with three or more edges are shown).

No differences can be observed in the anatomical/pharmacological group *Alimentary tract and metabolism* or any of the corresponding (sub-)groups between the severity cohorts considering all diseases. However, *anti-hyperglycemics*, specifically *dipeptidyl peptidase-4 (DPP4) inhibitors* and *sodium glucose co-transporter 2 (SGLT2) inhibitors* (only borderline significant, $p = 0.06$), were taken more often by non-severe COVID-19 patients with cardiovascular conditions or cardiovascular conditions and diabetes (see supplements, Table S3).

In the anatomical/pharmacological group *Blood and blood forming organs*, *anti-hemorrhagics* and *anti-platelet agents* (even though only borderline significant with $p = 0.095$), and within these groups, especially *Vitamin K and other hemostatics* and *acetylsalicylic acid* (only borderline significant, $p = 0.085$), respectively, were significantly different between the severity cohorts.

In the anatomical/pharmacological group *Cardiovascular system*, which showed no cohort difference, the drug group *diuretics* and *cardiovascular drugs* had a higher percentage in severe COVID-19. In the former group, *loop diuretics* and in the latter, *beta blockers* are significant differences over all patients regardless of co-morbidity.

Additionally, non-steroidal anti-inflammatory drugs (NSAIDs) were more often taken by patients with non-severe COVID-19, whereas the opposite was true for opioids (but only borderline significant).

Considering all patients, there are differences in combinations of drugs from anatomical/pharmacological group, drug group combinations, and drug subgroup combinations, but the weight of these edges (percentage of patients) is relatively low in most cases (<15%) (Table 3).

Table 3. Significant edges of the DDSI network.

Anatomical/Pharmacological Group Combinations		Non-Severe COVID-19 [%]	Severe COVID-19 [%]	p Value
Various	Alimentary tract and metabolism	3.85	10.43	0.012
	Nervous system	3.33	9.57	0.012
	Blood and blood forming organs	3.85	9.57	0.028
Drug Group Combinations		Non-Severe COVID-19 [%]	Severe COVID-19 [%]	p Value
Psycholeptics	Anti-hemorrhagics	0.26	3.48	0.011
Antiplatelet agents	Anti-infectives	7.44	15.65	0.013
Cardiovascular drugs	Diuretics	16.92	26.09	0.004
	Obstructive airway drugs	5.9	12.17	0.039
Drug Subgroup Combinations		Non-Severe COVID-19 [%]	Severe COVID-19 [%]	p Value
Antipsychotics ¹	Loop diuretics ¹	1.28	7.83	<0.001
	Opioids ¹	1.03	6.09	0.004
	Adrenergic inhalants	0.51	4.35	0.008
	Beta blockers ¹	2.82	8.7	0.012
	Proton pump inhibitors ¹	3.59	8.7	0.044
	Other analgesics	5.38	11.30	0.044
Heparin ¹	Direct Xa inhibitors ¹	0.51	4.35	0.008
	Loop diuretics ¹	4.62	10.43	0.036
Platelet inhibitors ¹	Antibiotics	7.44	14.78	0.026
	Loop diuretics ¹	5.13	11.3	0.032
	Beta blockers ¹	11.03	19.13	0.034
	Proton pump inhibitors ¹	10.00	17.39	0.045
	Potassium spare diuretics ¹	1.03	4.35	0.049
Potassium spare diuretics ¹	Acetylsalicylic acid	0.77	4.35	0.023
	Adrenergic inhalatives	0.51	3.48	0.037
Loop diuretics ¹	Opioids ¹	2.82	7.83	0.032
Vitamin K antagonists ¹	Thyroid	0.51	3.48	0.037
NSAID	Other analgesics	10.26	3.48	0.038
Beta blockers ¹	Acetylsalicylic acid	10.77	18.26	0.048

¹ drug subgroups that were associated with death or severe COVID-19 by Iloanusi et al. and McKeigue et al. [29,30].

However, the disease-specific analysis revealed that the combination of *anti-hyperglycemics* and *anti-coagulants* was more common in non-severe COVID-19 in patients with cardiac conditions or cardiac conditions and diabetes. In the latter cohort, the combination of *anti-hyperglycemics* and *statins* had a higher percentage in non-severe COVID-19 (see supplements, Table S4).

3.3. TDSI Network

The main molecular targets and their relative frequency per cohort are shown in the supplements, Figure S1. Molecular targets with highly significant ($p < 0.001$) differences are given in the supplements, Figure S2.

Differences in molecular targets can be divided into two groups. The first group comprises targets which interact with only one specific group of drugs, e.g., antithrombotic agents mostly interact with *coagulation factor X*, *P-selection*, and *antithrombin-III*, whereas diuretics may target members of the *solute carrier family 12*. The second group includes targets that cannot be assigned to just one indication or drug group. *Beta adrenergic receptors* are targets for anti-depressants, anti-hypertensives, and anti-arrhythmics. There are over 2690 significantly different edges in the molecular target network. In the supplements, we included the 30 most common edges in the network (Figure S3) and the highly significant edges ($p < 0.001$) (Figure S2).

In Figure 3, we present a filtered version of molecular target networks of both severity cohorts, where only nodes with three or more edges are shown.

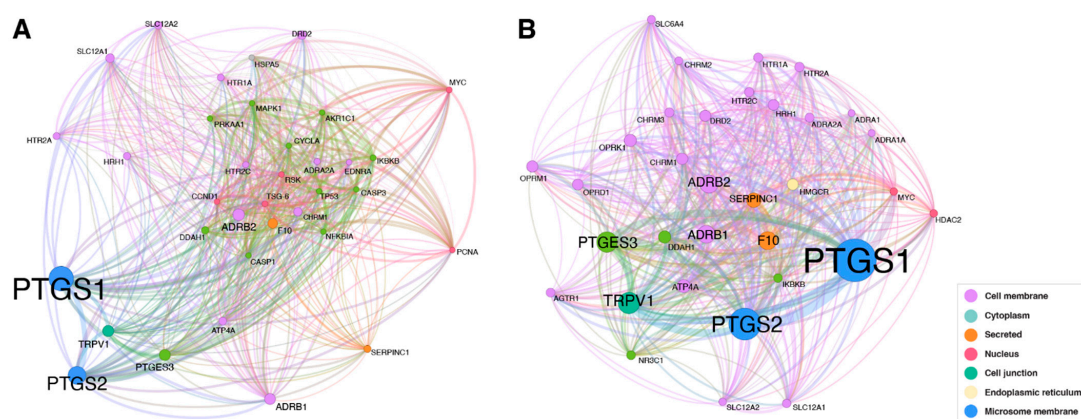


Figure 3. Molecular target networks for severe (A) and non-severe (B) COVID-19 (only nodes with three or more edges are shown); *ADRA1A/2A*: Alpha-1A/2A adrenergic receptor; *ADRB1/2*: Beta-1/2 adrenergic receptor; *AGTR1*: Type-1 angiotensin II receptor; *AKR1C1*: Aldo-keto reductase family 1 member C1; *ATP4A*: Potassium-transporting ATPase alpha chain 1; *CASP1/3*: Caspase-1/3; *CCND1*: G1/S-specific cyclin-D1; *CHRM1/M2/M3*: Muscarinic acetylcholine receptor M1/M2/M3; *CYCLA*: Cyclin A; *DDAH1*: N(G),N(G)-dimethylarginine dimethylaminohydrolase 1; *DRD2*: Dopamine D2 receptor; *EDNRA*: Endothelin-1 receptor; *F10*: Coagulation factor X; *HDAC2*: Histone deacetylase 2; *HMGR*: 3-hydroxy-3-methylglutaryl-coenzyme A reductase; *HRH1*: Histamine H1 receptor; *HSPA5*: 78 kDa glucose-regulated protein; *HTR1A/2A/2C*: 5-hydroxytryptamine receptor 1A/2A/2C; *IKKB*: Inhibitor of nuclear factor kappa-B kinase subunit beta; *MAPK1*: Mitogen-activated protein kinase 1; *MYC*: Myc proto-oncogene protein; *NFKB1A*: NF-kappa-B inhibitor alpha; *NR3C1*: Glucocorticoid receptor; *OPRD1*: Delta-type opioid receptor; *OPRK1*: Kappa-type opioid receptor; *OPRM1*: Mu-type opioid receptor; *PCNA*: Proliferating cell nuclear antigen; *PRKAA1*: 5'-AMP-activated protein kinase; *PTGES3*: Prostaglandin E synthase 3; *PTGS1/2*: Prostaglandin G/H synthase 1/2; *RSK*: Ribosomal protein S6 kinase alpha-3; *SERPINC1*: Antithrombin-III; *SLC12A1/2*: Solute carrier family 12 member 1/2; *SLC6A4*: Sodium-dependent serotonin transporter; *TP53*: Cellular tumor antigen p53; *TRPV1*: Transient receptor potential cation channel subfamily V member 1; *TSG-6*: Tumor necrosis factor-inducible gene 6 protein.

The color of the nodes indicates the location of the molecular target within the cell. In the non-severe cohort, more molecular targets are located within the cell membrane, whereas in the severe cohort more targets are located within the cytoplasm.

4. Discussion

The network analysis of drugs and their molecular targets revealed differences between the severity cohorts of COVID-19. Except for one edge, the main nodes (hubs) and edges are identical, however the weights were often slightly higher in the severe cohort. This suggests that the most important drugs and drug combinations are the same between the cohorts, but still, slightly more drugs and drug combinations are taken by the severe cohort. This may be indicative of a subpopulation with more co-morbidities. The larger diameter of the severe network indicates that the drugs and drug combinations are more heterogeneous in this cohort. This is supported by the generally lower betweenness of most nodes in this cohort in absolute values, but also in comparison to the non-severe cohort.

However, co-morbidities and co-mediations did not always result in a more severe course. Noteworthy here is the higher percentage of patients with cardiac conditions, or cardiac conditions and diabetes, using anti-hyperglycemics, especially DPP4 inhibitors, and to a lower degree SGLT2 inhibitors in the non-severe COVID-19 cohort. These patients had at least two co-morbidities, which are considered risk factors for a severe course [15,42,43], but had a more favorable outcome under these treatment regimens. DPP4 inhibitors have been shown to be reno- and cardio-protective through the suppression of oxidative stress, inflammation, and improvement of endothelial function [44]. Furthermore, there is evidence that SARS-CoV-2, like MERS-CoV (Middle East respiratory syndrome-related coronavirus), also uses the membrane-bound DPP4 enzyme for viral entry. An inhibition of this enzyme is speculated to reduce viral entry and replication [45,46]. In SARS-CoV-2, a functional network analysis revealed that DPP4 is required in viral processes for viral entry and infection. Furthermore, protein-chemical interaction networks revealed important interactions between DPP4 and the DPP4 inhibitor sitagliptin [47]. Additionally, in animal experiments, DPP4 inhibition resulted in a rise of soluble DPP4 [48,49] which could bind to plasma SARS-CoV-2, reducing the amount of virus able to infect cells [50]. Mutations in DPP4 genes, leading to reduced levels for soluble DPP4, were identified as risk factors for increased susceptibility for MERS-CoV [51]. Within an infected cell, sitagliptin inhibited the SARS-CoV-2 papain-like proteases (PLpro) in an in-cell protease assay [52]. Clinical literature on DPP4 inhibitors in COVID-19 is ambiguous; several studies and meta-analyses have showed favorable effects [53–56], while some have not [57–59]. A review of clinical trials with the DPP4 inhibitor sitagliptin found that most studies showed a favorable effect on COVID-19 progression [50]. Several potential modes of action are discussed apart from the above-mentioned decrease in viral entry, increase in soluble DPP4, or inhibition of viral proteases. It is hypothesized that DPP4 inhibitors might attenuate COVID-19-related cardiovascular injury including arrhythmia, acute coronary syndrome and heart failure [60]. In addition, DPP4 inhibition has anti-inflammatory and immunomodulatory properties by decreasing activation of nuclear factor kappa beta (NF- κ B) activation and expression of inflammatory cytokines [61,62]. These factors could also influence the progression.

A benefit of SGLT2 inhibitors is supported on pathophysiological grounds. SGLT2 inhibitors have been shown to downregulate systemic and adipose tissue inflammation by decreasing the expression of pro-inflammatory cytokines, lessen oxidative stress, and reduce sympathetic activity [63]. Furthermore, treatment with a SGLT2 inhibitors alleviated myocardial and renal fibrosis in mice [64]. In a large randomized trial with COVID-19 patients, treatment with dapagliflozin, a SGLT2 inhibitors, did not result in a statistically significant risk reduction in organ dysfunction and death, or speedier recovery [65].

Considering all patients, regardless of the diagnosed co-morbidities, there are some noteworthy differences in the drugs (nodes of the network, Table 2) used within the cohorts. Despite doubts early in the pandemic regarding the use of NSAIDs during COVID-19 [66], a systematic review and meta-analysis was not able to confirm this theoretical

risk [67]. In human cell cultures and mice, NSAIDs reduced pro-inflammatory cytokines, and dampened the humoral immune response to SARS-CoV-2 [68]. This protective effect might be explained by reversing the progressive inflammation in different organs [69]. Even though this study included only few patients on NSAIDs, they were still more common in non-severe patients and thus corroborated earlier studies. Comparisons to other antipyretics with no anti-inflammatory action (e.g., acetaminophen) are necessary.

Some drugs with significant differences between cohorts might be more indicative of the severity of the underlying condition and not interact with COVID-19 prognosis directly. Loop diuretics, for instance are used in more advanced stages of renal failure [70]. As poor renal function is indicative of severe COVID-19 [71,72], this correlation might be due to the severity of the pre-existing condition, not the drug itself. Beta blockers were more often used in the severe cohort, but this might be explained by the higher prevalence of cardiovascular co-morbidities in this cohort. However, loop diuretics, beta blockers, and opioids are also associated with death or severe COVID-19 in a polypharmacy setting [29,30].

Overall, a relatively small percentage of patients received antipsychotic drugs, and the difference between cohorts was not significant (8% and 13% in the non-severe and severe cohorts, respectively). However, combinations with other drugs such as loop diuretics, opioids, beta-blockers, or proton pump inhibitors were more often seen in patients in the severe cohort. The influence of antipsychotic drugs on COVID-19 infection risk and prognosis is currently under discussion. A retrospective study in 698 patients using antipsychotic drugs revealed a lower infection risk and a better prognosis compared to non-users [73]. Comparable results were also reported from a study in patients with a pre-existing diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder [74]. On the other hand, a systematic review and meta-analysis showed a correlation between antipsychotics and COVID-19 mortality [75]. However, the reviewed studies included patients on antipsychotics independently of diagnoses, considered antipsychotics as a single homogenous pharmacological group, and did not test for adherence [76]. Our results suggest that not the use of a specific drugs per se, but the combination with other drugs influences the risk for severe COVID-19. Therefore, a detailed analysis of the most significantly different drug combinations (edges of the network, Table 3) was performed. Most drug combinations were taken by less than 15% of the patients, which makes a detailed analysis of cause and effect difficult, but trends are visible. In all cases but one (NSAIDs/other analgesics) a greater proportion was seen in the severe cohort. However, this difference is not due to general polypharmacy, which is known to influence disease severity in COVID-19 [29,30], as the number of drugs on admission was not significantly different in both cohorts. Not only polypharmacy, but also specific drug classes influence severity in COVID-19 [29,30]. Drug classes with an increased risk for severe COVID-19 are highlighted in red in Table 3. In seven and in eleven drug combinations, one or both drugs, respectively, were considered high risk. All these combinations were more prevalent in the severe cohort. Only in one combination (NSAIDs/other analgesics), neither drug was considered high risk. Interestingly, a higher proportion of non-severe patients took that combination.

In proton pump inhibitors (PPIs), the effect of combination with other drugs can be seen. PPIs are taken to the same extent by the non-severe and severe cohort (32.6% and 33.9%, respectively, $p = 0.88$, data not shown). However, combinations of PPIs with antipsychotics or platelet inhibitors were more prevalent in severe patients. Several review articles evaluating the effects of PPIs on COVID-19 progression and mortality revealed high heterogeneity in the outcomes [77–80]. However, those studies did not control for co-medication, except for one which looked at NSAIDs [80]. In summary, studies on drug effects should also consider including and ideally control for co-medication.

In the molecular target network of the non-severe cohort, there are more targets located in the cell membrane. Several hypotheses could help explain this finding. One hypothesis is that interaction of drugs with cell membrane receptors might interfere with viral entry

into the cell. The host protein angiotensin-converting enzyme 2 (ACE2) is considered the main entry receptor for SARS-CoV-2 and the transmembrane serine protease 2 (TMPRSS2) an important priming enzyme required during this process [81,82]. In addition, other cell membrane receptors may be involved in cellular entry of SARS-CoV-2 [81,83,84], like neuropilin-1 [85,86], or DPP4 [45,46]. Interference may be direct if a drug targets a protein, which is also important for viral entry. Studies on SARS-CoV-2–human protein–protein interaction revealed hundreds of further possible targets [87–90], however there is only minimal overlap with the target we identified. However, interference may also be indirect due to changes in membrane organization that negatively impact any part of the viral replication cycle. Functionally organized micro-domains (lipid rafts), characterized by highly ordered and tightly packed lipid molecules, within the cell membrane may play a pivotal role in different processes during the viral life-cycle, including coronaviruses [91]. Lipid raft involvement in viral entry was already shown for the murine hepatitis virus, a betacoronavirus such as SARS-CoV-2 [92]. A further study used SARS-CoV-2 pseudo viruses to demonstrate the importance of cholesterol-rich membrane lipid raft for infection [93]. Micro-domains may increase the efficiency of infection by clustering enzymes and receptors in certain membrane area, thus allowing multivalent binding of virus particles, but are not an absolute requirement for the entry process [94]. Several drugs acting on specific the cell membrane targets were shown to disrupt lipid rafts [95]. These included targets we identified in the non-severe cohort, such as alpha- and beta-adrenergic receptors, and opioid receptors. As the network visualizations only include nodes with three or more edges, one might conclude that the combination of several drugs, which interfere with the integrity of the lipid rafts, have an influence on COVID-19 progression.

Our study has some limitations. The severity cohorts had some significant differences in demographics and co-morbidities. The severe cohort was significantly older, had a higher BMI, and a higher share of male patients, all factors which are known risk factors for severe COVID-19 [5–12]. Even though the differences are significant, they are still rather small (median age difference three years, median BMI difference 1.68 points), so that a detailed analysis of these factors would require a larger sample size to obtain enough power with an unknown effect size. Additionally, more patients in the severe cohort suffered from arterial hypertension, chronic heart failure and/or coronary heart disease, again established risk factors in COVID-19 [16,17,22]. However, the presence and even the severity of co-morbidities were indirectly accounted for by the analysis of prescribed drugs. The number of drugs on admission was not significantly different between the cohorts. Even though we were able to include a total of 505 patients in our analysis, the number of patients receiving one specific drug was still relatively low, especially in the disease cohorts. Therefore, significant differences were in some cases only seen in the high-level pooled groups. For this reason, we also reported borderline significant results ($0.05 < p < 0.1$), which could be interpreted as a weak signal and should be investigated in further research. Furthermore, we were mainly able to consider hospitalized patients because of data availability issues. As the IHG is an important regional medical center, some patients were transferred from smaller hospitals. Drugs given in these smaller hospitals are recorded on the drugs on admission list.

The analysis only focused on dual combinations. While we did perform cluster analyses to find more complex combinations, the data available did not support this. Furthermore, even though there were significant differences between the severity cohort with regards to age and sex, we did not control for that.

5. Conclusions

In summary, the use of a network approach allowed for studying the impact of drugs from a novel vantage point. Most importantly, autonomic targets appear to be influential on the course of disease in COVID-19, mostly in the form of off-target effects, possibly by disrupting lipid rafts and impeding viral entry. This also holds for DPP4 inhibitors, which are known to interact with adrenergic receptors [96]. The impact of interference with

autonomic receptors merits further study into potential future treatments for infection with SARS-CoV-2 and other viruses. Overall, our network analysis indicates that DPP4 inhibitors are related to a better prognosis for COVID-19 and thus represent potential repositioning drugs against SARS-CoV-2. Additionally, our study revealed (i) that drug-induced changes in cell membrane architecture might influence disease progression and (ii) that the influence of specific drugs on disease progression might be dependent on concurrent co-medication.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/pharmaceutics14091828/s1>, Table S1: Assignment of ATC codes to the drug groups and subgroups; Table S2: Important network metrics of DDSI and TDSI network; Table S3: Significant nodes of the DDSI network, disease specific; Table S4: Significant edges of the DDSI network, disease specific; Figure S1: Main target nodes; Figure S2: Target nodes with significant differences; Figure S3: Main target edges; Figure S4: Target edges with highly significant differences ($p < 0.001$).

Author Contributions: V.S.: formal analysis, investigation, methodology, software, visualization, writing; F.H.: conceptualization, formal analysis, methodology, software, supervision, visualization, writing. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was approved by the Cantonal Ethics Committee of Bern (Project-ID 2020-00973).

Informed Consent Statement: Participants either agreed to a general research consent or, for participants with no registered general research consent status (neither agreement nor rejection), a waiver of consent was granted by the ethics committee.

Data Availability Statement: The source code is available on GitHub: <https://github.com/cptbern/Covid19-network-analysis>.

Acknowledgments: We thank Noel Frey, Myoori Wijayasingham, and the Insel Data Science Center for database and infrastructure support.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Gnädinger, M.; Herzig, L.; Ceschi, A.; Conen, D.; Staehelin, A.; Zoller, M.; Puhon, M.A. Chronic conditions and multimorbidity in a primary care population: A study in the Swiss Sentinel Surveillance Network (Sentinella). *Int. J. Public Health* **2018**, *63*, 1017–1026. [CrossRef] [PubMed]
2. Déruaz-Luyet, A.; Goran, A.A.; Senn, N.; Bodenmann, P.; Pasquier, J.; Widmer, D.; Tandjung, R.; Rosemann, T.; Frey, P.; Streit, S.; et al. Multimorbidity and patterns of chronic conditions in a primary care population in Switzerland: A cross-sectional study. *BMJ Open* **2017**, *7*, e013664. [CrossRef] [PubMed]
3. Lynch, S.S. Drug Interactions. Available online: <https://www.msmanuals.com/home/drugs/factors-affecting-response-to-drugs/drug-interactions> (accessed on 14 September 2021).
4. Galan-Vasquez, E.; Perez-Rueda, E. A landscape for drug-target interactions based on network analysis. *PLoS ONE* **2021**, *16*, e0247018. [CrossRef] [PubMed]
5. Bencivenga, L.; Rengo, G.; Varricchi, G. Elderly at time of CORonaVirus disease 2019 (COVID-19): Possible role of immunosenescence and malnutrition. *GeroScience* **2020**, *42*, 1089–1092. [CrossRef]
6. Cunha, L.L.; Perazzio, S.F.; Azzi, J.; Cravedi, P.; Riella, L.V. Remodeling of the Immune Response with Aging: Immunosenescence and Its Potential Impact on COVID-19 Immune Response. *Front. Immunol.* **2020**, *11*, 1748. [CrossRef]
7. Peckham, H.; de Grujter, N.M.; Raine, C.; Radziszewska, A.; Ciurtin, C.; Wedderburn, L.R.; Rosser, E.C.; Webb, K.; Deakin, C.T. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ICU admission. *Nat. Commun.* **2020**, *11*, 6317. [CrossRef]
8. Klein, S.L.; Dhakal, S.; Ursin, R.L.; Deshpande, S.; Sandberg, K.; Mauvais-Jarvis, F. Biological sex impacts COVID-19 outcomes. *PLoS Pathog.* **2020**, *16*, e1008570. [CrossRef]
9. Kang, Z.; Luo, S.; Gui, Y.; Zhou, H.; Zhang, Z.; Tian, C.; Zhou, Q.; Wang, Q.; Hu, Y.; Fan, H.; et al. Obesity is a potential risk factor contributing to clinical manifestations of COVID-19. *Int. J. Obes.* **2020**, *44*, 2479–2485. [CrossRef]
10. Kwok, S.; Adam, S.; Ho, J.H.; Iqbal, Z.; Turkington, P.; Razvi, S.; Le Roux, C.W.; Soran, H.; Syed, A.A. Obesity: A critical risk factor in the COVID-19 pandemic. *Clin. Obes.* **2020**, *10*, e12403. [CrossRef] [PubMed]

11. Foldi, M.; Farkas, N.; Kiss, S.; Zadori, N.; Vancsa, S.; Szako, L.; Dembrovszky, F.; Solymar, M.; Bartalis, E.; Szakacs, Z.; et al. Obesity is a risk factor for developing critical condition in COVID-19 patients: A systematic review and meta-analysis. *Obes. Rev.* **2020**, *21*, e13095. [\[CrossRef\]](#)
12. Sattar, N.; McInnes, I.B.; McMurray, J.J.V. Obesity Is a Risk Factor for Severe COVID-19 Infection: Multiple Potential Mechanisms. *Circulation* **2020**, *142*, 4–6. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Zhu, L.; She, Z.-G.; Cheng, X.; Qin, J.-J.; Zhang, X.-J.; Cai, J.; Lei, F.; Wang, H.; Xie, J.; Wang, W.; et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab.* **2020**, *31*, 1068–1077.e3. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Tadic, M.; Cuspidi, C. The influence of diabetes and hypertension on outcome in COVID-19 patients: Do we mix apples and oranges? *J. Clin. Hypertens.* **2020**, *23*, 235–237. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Lim, S.; Bae, J.H.; Kwon, H.-S.; Nauck, M.A. COVID-19 and diabetes mellitus: From pathophysiology to clinical management. *Nat. Rev. Endocrinol.* **2021**, *17*, 11–30. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Ssentongo, P.; Ssentongo, A.E.; Heilbrunn, E.S.; Ba, D.M.; Chinchilli, V.M. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis. *PLoS ONE* **2020**, *15*, e0238215. [\[CrossRef\]](#)
17. Inciardi, R.M.; Adamo, M.; Lupi, L.; Cani, D.S.; Di Pasquale, M.; Tomasoni, D.; Italia, L.; Zacccone, G.; Tedino, C.; Fabbriatore, D.; et al. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. *Eur. Heart J.* **2020**, *41*, 1821–1829. [\[CrossRef\]](#)
18. Yang, J.; Zheng, Y.; Gou, X.; Pu, K.; Chen, Z.; Guo, Q.; Ji, R.; Wang, H.; Wang, Y.; Zhou, Y. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: A systematic review and meta-analysis. *Int. J. Infect. Dis.* **2020**, *94*, 91–95. [\[CrossRef\]](#)
19. Olloquequi, J. COVID-19 Susceptibility in chronic obstructive pulmonary disease. *Eur. J. Clin. Investig.* **2020**, *50*, e13382. [\[CrossRef\]](#)
20. Wang, Q.; Davis, P.B.; Gurney, M.E.; Xu, R. COVID-19 and dementia: Analyses of risk, disparity, and outcomes from electronic health records in the US. *Alzheimer's Dement.* **2021**, *17*, 1297–1306. [\[CrossRef\]](#)
21. Chudasama, Y.V.; Zaccardi, F.; Gillies, C.L.; Razieh, C.; Yates, T.; Kloecker, D.E.; Rowlands, A.V.; Davies, M.J.; Islam, N.; Seidu, S.; et al. Patterns of multimorbidity and risk of severe SARS-CoV-2 infection: An observational study in the U.K. *BMC Infect. Dis.* **2021**, *21*, 908. [\[CrossRef\]](#)
22. Hu, J.; Zhang, X.; Zhang, X.; Zhao, H.; Lian, J.; Hao, S.; Jia, H.; Yang, M.; Lu, Y.; Xiang, D.; et al. COVID-19 is more severe in patients with hypertension; ACEI/ARB treatment does not influence clinical severity and outcome. *J. Infect.* **2020**, *81*, 979–997. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Sato, K.; White, N.; Fanning, J.P.; Obonyo, N.; Yamashita, M.H.; Appadurai, V.; Ciullo, A.; May, M.; Worku, E.T.; Helms, L.; et al. Impact of renin–angiotensin–aldosterone system inhibition on mortality in critically ill COVID-19 patients with pre-existing hypertension: A prospective cohort study. *BMC Cardiovasc. Disord.* **2022**, *22*, 123. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Park, J.; Lee, S.-H.; You, S.C.; Kim, J.; Yang, K. Effect of renin-angiotensin-aldosterone system inhibitors on COVID-19 patients in Korea. *PLoS ONE* **2021**, *16*, e0248058. [\[CrossRef\]](#)
25. Braude, P.; Carter, B.; Short, R.; Vilches-Moraga, A.; Verduri, A.; Pearce, L.; Price, A.; Quinn, T.J.; Stechman, M.; Collins, J.; et al. The influence of ACE inhibitors and ARBs on hospital length of stay and survival in people with COVID-19. *IJC Heart Vasc.* **2020**, *31*, 100660. [\[CrossRef\]](#)
26. Vila-Córcoles, A.; Ochoa-Gondar, O.; Satué-Gracia, E.M.; Torrente-Fraga, C.; Gomez-Bertomeu, F.; Vila-Rovira, A.; Hospital-Guardiola, I.; de Diego-Cabanes, C.; Bejarano-Romero, F.; Basora-Gallisà, J. Influence of prior comorbidities and chronic medications use on the risk of COVID-19 in adults: A population-based cohort study in Tarragona, Spain. *BMJ Open* **2020**, *10*, e041577. [\[CrossRef\]](#)
27. Holt, A.; Mizrak, I.; Lamberts, M.; Lav Madsen, P. Influence of inhibitors of the renin-angiotensin system on risk of acute respiratory distress syndrome in Danish hospitalized COVID-19 patients. *J. Hypertens.* **2020**, *38*, 1612–1613. [\[CrossRef\]](#)
28. Jia, N.; Zhang, G.; Sun, X.; Wang, Y.; Zhao, S.; Chi, W.; Dong, S.; Xia, J.; Zeng, P.; Liu, D. Influence of angiotensin converting enzyme inhibitors/angiotensin receptor blockers on the risk of all-cause mortality and other clinical outcomes in patients with confirmed COVID-19: A systemic review and meta-analysis. *J. Clin. Hypertens.* **2021**, *23*, 1651–1663. [\[CrossRef\]](#)
29. Iloanusi, S.; Mgbere, O.; Essien, E.J. Polypharmacy among COVID-19 patients: A systematic review. *J. Am. Pharm. Assoc.* **2021**, *61*, e14–e25. [\[CrossRef\]](#)
30. McKeigue, P.M.; Kennedy, S.; Weir, A.; Bishop, J.; McGurnaghan, S.J.; McAllister, D.; Robertson, C.; Wood, R.; Lone, N.; Murray, J.; et al. Relation of severe COVID-19 to polypharmacy and prescribing of psychotropic drugs: The REACT-SCOT case-control study. *BMC Med.* **2021**, *19*, 51. [\[CrossRef\]](#)
31. Newman, M.E.J. *Networks: An Introduction*; Oxford University Press: Oxford, UK; New York, NY, USA, 2010.
32. Casas, A.I.; Hassan, A.A.; Larsen, S.J.; Gomez-Rangel, V.; Elbatriek, M.; Kleikers, P.W.M.; Guney, E.; Egea, J.; López, M.G.; Baumbach, J.; et al. From single drug targets to synergistic network pharmacology in ischemic stroke. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 7129–7136. [\[CrossRef\]](#)
33. Azad, A.K.M.; Fatima, S.; Capraro, A.; Waters, S.A.; Vafaei, F. Integrative resource for network-based investigation of COVID-19 combinatorial drug repositioning and mechanism of action. *Patterns* **2021**, *2*, 100325. [\[CrossRef\]](#) [\[PubMed\]](#)

34. Morselli Gysi, D.; do Valle, Í.; Zitnik, M.; Ameli, A.; Gan, X.; Varol, O.; Ghiassian, S.D.; Patten, J.J.; Davey, R.A.; Loscalzo, J.; et al. Network medicine framework for identifying drug-repurposing opportunities for COVID-19. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2025581118. [[CrossRef](#)] [[PubMed](#)]
35. Sibilio, P.; Bini, S.; Fiscon, G.; Sponziello, M.; Conte, F.; Pecce, V.; Durante, C.; Paci, P.; Falcone, R.; Norata, G.D.; et al. In silico drug repurposing in COVID-19: A network-based analysis. *Biomed. Pharmacother.* **2021**, *142*, 111954. [[CrossRef](#)]
36. Schöning, V.; Liakoni, E.; Drewe, J.; Hammann, F. Automatic identification of risk factors for SARS-CoV-2 positivity and severe clinical outcomes of COVID-19 using Data Mining and Natural Language Processing. *medRxiv* **2021**. [[CrossRef](#)]
37. WHO Collaborating Centre for Drug Statistics Methodology. *ATC Classification Index with DDDs*; WHO Collaborating Centre for Drug Statistics Methodology: Oslo, Norway, 2021.
38. Gu, S.X.; Tyagi, T.; Jain, K.; Gu, V.W.; Lee, S.H.; Hwa, J.M.; Kwan, J.M.; Krause, D.S.; Lee, A.I.; Halene, S.; et al. Thrombocytopenia and endotheliopathy: Crucial contributors to COVID-19 thromboinflammation. *Nat. Rev. Cardiol.* **2021**, *18*, 194–209. [[CrossRef](#)]
39. Wishart, D.S.; Knox, C.; Guo, A.C.; Shrivastava, S.; Hassanali, M.; Stothard, P.; Chang, Z.; Woolsey, J. DrugBank: A comprehensive resource for in silico drug discovery and exploration. *Nucleic Acids Res.* **2006**, *34*, D668–D672. [[CrossRef](#)] [[PubMed](#)]
40. Csárdi, G.; Nepusz, T. The Igraph Software Package for Complex Network Research. *InterJournal Complex Syst.* **2006**, *1695*, 1–9.
41. Bastian, M.; Heymann, S.; Jacomy, M. Gephi: An Open Source Software for Exploring and Manipulating Networks. In Proceedings of the International AAAI Conference on Web and Social Media, San Jose, CA, USA, 17–20 May 2009; Volume 3, pp. 361–362.
42. Wolff, D.; Nee, S.; Hickey, N.S.; Marschollek, M. Risk factors for COVID-19 severity and fatality: A structured literature review. *Infection* **2020**, *49*, 15–28. [[CrossRef](#)]
43. Singh, A.K.; Gupta, R.; Misra, A. Comorbidities in COVID-19: Outcomes in hypertensive cohort and controversies with renin angiotensin system blockers. *Diabetes Metab. Syndr.* **2020**, *14*, 283–287. [[CrossRef](#)]
44. Tomovic, K.; Lazarevic, J.; Kocic, G.; Deljanin-Ilic, M.; Anderluh, M.; Smelcerovic, A. Mechanisms and pathways of anti-inflammatory activity of DPP-4 inhibitors in cardiovascular and renal protection. *Med. Res. Rev.* **2019**, *39*, 404–422. [[CrossRef](#)]
45. Solerte, S.B.; Di Sabatino, A.; Galli, M.; Fiorina, P. Dipeptidyl peptidase-4 (DPP4) inhibition in COVID-19. *Acta Diabetol.* **2020**, *57*, 779–783. [[CrossRef](#)] [[PubMed](#)]
46. Bassendine, M.F.; Bridge, S.H.; McCaughan, G.W.; Gorrell, M.D. COVID-19 and comorbidities: A role for dipeptidyl peptidase 4 (DPP4) in disease severity? *J. Diabetes* **2020**, *12*, 649–658. [[CrossRef](#)] [[PubMed](#)]
47. Bardaweel, S.K.; Hajjo, R.; Sabbah, D.A. Sitagliptin: A potential drug for the treatment of COVID-19? *Acta Pharm.* **2021**, *71*, 175–184. [[CrossRef](#)]
48. Varin, E.M.; Mulvihill, E.E.; Beaudry, J.L.; Pujadas, G.; Fuchs, S.; Tanti, J.-F.; Fazio, S.; Kaur, K.; Cao, X.; Baggio, L.L.; et al. Circulating Levels of Soluble Dipeptidyl Peptidase-4 Are Dissociated from Inflammation and Induced by Enzymatic DPP4 Inhibition. *Cell Metab.* **2019**, *29*, 320–334.e5. [[CrossRef](#)]
49. Baggio, L.L.; Varin, E.M.; Koehler, J.A.; Cao, X.; Lokhnygina, Y.; Stevens, S.R.; Holman, R.R.; Drucker, D.J. Plasma levels of DPP4 activity and sDPP4 are dissociated from inflammation in mice and humans. *Nat. Commun.* **2020**, *11*, 3766. [[CrossRef](#)] [[PubMed](#)]
50. Mikhael, E.M.; Ong, S.C.; Sheikh Ghadzi, S.M. Efficacy and Safety of Sitagliptin in the Treatment of COVID-19. *J. Pharm. Pract.* **2022**, 8971900221102119. [[CrossRef](#)] [[PubMed](#)]
51. Alkharsah, K.R.; Aljaroodi, S.A.; Rahman, J.U.; Alnafie, A.N.; Al Dossary, R.; Aljindan, R.Y.; Alnimr, A.M.; Hussien, J. Low levels of soluble DPP4 among Saudis may have constituted a risk factor for MERS endemicity. *PLoS ONE* **2022**, *17*, e0266603. [[CrossRef](#)]
52. Narayanan, A.; Narwal, M.; Majowicz, S.A.; Varricchio, C.; Toner, S.A.; Ballatore, C.; Brancale, A.; Murakami, K.S.; Jose, J. Identification of SARS-CoV-2 inhibitors targeting Mpro and PLpro using in-cell-protease assay. *Commun. Biol.* **2022**, *5*, 169. [[CrossRef](#)]
53. Rhee, S.Y.; Lee, J.; Nam, H.; Kyoung, D.-S.; Shin, D.W.; Kim, D.J. Effects of a DPP-4 Inhibitor and RAS Blockade on Clinical Outcomes of Patients with Diabetes and COVID-19. *Diabetes Metab. J.* **2021**, *45*, 251–259. [[CrossRef](#)]
54. Rakhmat, I.I.; Kusmala, Y.Y.; Handayani, D.R.; Juliastuti, H.; Nawangsih, E.N.; Wibowo, A.; Lim, M.A.; Pranata, R. Dipeptidyl peptidase-4 (DPP-4) inhibitor and mortality in coronavirus disease 2019 (COVID-19)—A systematic review, meta-analysis, and meta-regression. *Diabetes Metab. Syndr.* **2021**, *15*, 777–782. [[CrossRef](#)]
55. Mirani, M.; Favacchio, G.; Carrone, F.; Betella, N.; Biamonte, E.; Morengi, E.; Mazziotti, G.; Lania, A.G. Impact of Comorbidities and Glycemia at Admission and Dipeptidyl Peptidase 4 Inhibitors in Patients with Type 2 Diabetes With COVID-19: A Case Series From an Academic Hospital in Lombardy, Italy. *Diabetes Care* **2020**, *43*, 3042. [[CrossRef](#)]
56. Pal, R.; Banerjee, M.; Mukherjee, S.; Bhogal, R.S.; Kaur, A.; Bhadada, S.K. Dipeptidyl peptidase-4 inhibitor use and mortality in COVID-19 patients with diabetes mellitus: An updated systematic review and meta-analysis. *Ther. Adv. Endocrinol. Metab.* **2021**, *12*, 2042018821996482. [[CrossRef](#)] [[PubMed](#)]
57. Fadini, G.P.; Morieri, M.L.; Longato, E.; Bonora, B.M.; Pinelli, S.; Selmin, E.; Voltan, G.; Falaguasta, D.; Tresso, S.; Costantini, G.; et al. Exposure to dipeptidyl-peptidase-4 inhibitors and COVID-19 among people with type 2 diabetes: A case-control study. *Diabetes Obes. Metab.* **2020**, *22*, 1946–1950. [[CrossRef](#)] [[PubMed](#)]
58. Zhou, J.-H.; Wu, B.; Wang, W.-X.; Lei, F.; Cheng, X.; Qin, J.-J.; Cai, J.-J.; Zhang, X.-J.; Zhou, F.; Liu, Y.-M.; et al. No significant association between dipeptidyl peptidase-4 inhibitors and adverse outcomes of COVID-19. *World J. Clin. Cases* **2020**, *8*, 5576–5588. [[CrossRef](#)]

59. Morieri, M.L.; Bonora, B.M.; Longato, E.; Di Camilo, B.; Sparacino, G.; Tramontan, L.; Avogaro, A.; Fadini, G.P. Exposure to dipeptidyl-peptidase 4 inhibitors and the risk of pneumonia among people with type 2 diabetes: Retrospective cohort study and meta-analysis. *Diabetes Obes. Metab.* **2020**, *22*, 1925–1934. [\[CrossRef\]](#) [\[PubMed\]](#)
60. Du, H.; Wang, D.W.; Chen, C. The potential effects of DPP-4 inhibitors on cardiovascular system in COVID-19 patients. *J. Cell. Mol. Med.* **2020**, *24*, 10274–10278. [\[CrossRef\]](#)
61. Dastan, F.; Abedini, A.; Shahabi, S.; Kiani, A.; Saffaei, A.; Zare, A. Sitagliptin Repositioning in SARS-CoV-2: Effects on ACE-2, CD-26, and Inflammatory Cytokine Storms in the Lung. *Iran. J. Allergy Asthma Immunol.* **2020**, *19*, 10–12. [\[CrossRef\]](#)
62. Mozafari, N.; Azadi, S.; Mehdi-Alamdarlou, S.; Ashrafi, H.; Azadi, A. Inflammation: A bridge between diabetes and COVID-19, and possible management with sitagliptin. *Med. Hypotheses* **2020**, *143*, 110111. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Koufakis, T.; Pavlidis, A.N.; Metallidis, S.; Kotsa, K. Sodium-glucose co-transporter 2 inhibitors in COVID-19: Meeting at the crossroads between heart, diabetes and infectious diseases. *Int. J. Clin. Pharm.* **2021**, *43*, 764–767. [\[CrossRef\]](#)
64. Li, X.-T.; Zhang, M.-W.; Zhang, Z.-Z.; Cao, Y.-D.; Liu, X.-Y.; Miao, R.; Xu, Y.; Song, X.-F.; Song, J.-W.; Liu, Y.; et al. Abnormal apelin-ACE2 and SGLT2 signaling contribute to adverse cardiorenal injury in patients with COVID-19. *Int. J. Cardiol.* **2021**, *336*, 123–129. [\[CrossRef\]](#)
65. Kosiborod, M.N.; Esterline, R.; Furtado, R.H.M.; Oscarsson, J.; Gasparian, S.B.; Koch, G.G.; Martinez, F.; Mukhtar, O.; Verma, S.; Chopra, V.; et al. Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol.* **2021**, *9*, 586–594. [\[CrossRef\]](#)
66. European Medicines Agency. EMA/136850/2020: EMA Gives Advice on the Use of Non-Steroidal Anti Inflammatories for COVID-19. Available online: https://www.ema.europa.eu/en/documents/press-release/ema-gives-advice-use-non-steroidal-anti-inflammatories-COVID-19_en.pdf (accessed on 6 December 2021).
67. Moore, N.; Bosco-Levy, P.; Thurin, N.; Blin, P.; Droz-Perroteau, C. NSAIDs and COVID-19: A Systematic Review and Meta-analysis. *Drug Saf.* **2021**, *44*, 929–938. [\[CrossRef\]](#)
68. Chen Jennifer, S.; Alfajaro Mia, M.; Chow Ryan, D.; Wei, J.; Filler Renata, B.; Eisenbarth Stephanie, C.; Wilen Craig, B.; Gallagher, T. Nonsteroidal Anti-inflammatory Drugs Dampen the Cytokine and Antibody Response to SARS-CoV-2 Infection. *J. Virol.* **2021**, *95*, e00014–21. [\[CrossRef\]](#)
69. Kelleni, M.T. Early use of non-steroidal anti-inflammatory drugs in COVID-19 might reverse pathogenesis, prevent complications and improve clinical outcomes. *Biomed. Pharmacother.* **2021**, *133*, 110982. [\[CrossRef\]](#)
70. Oh, S.W.; Han, S.Y. Loop Diuretics in Clinical Practice. *Electrolyte Blood Press.* **2015**, *13*, 17–21. [\[CrossRef\]](#) [\[PubMed\]](#)
71. Podestà, M.A.; Valli, F.; Galassi, A.; Cassia, M.A.; Ciceri, P.; Barbieri, L.; Carugo, S.; Cozzolino, M. COVID-19 in Chronic Kidney Disease: The Impact of Old and Novel Cardiovascular Risk Factors. *Blood Purif.* **2021**, *50*, 740–749. [\[CrossRef\]](#)
72. Schöning, V.; Liakoni, E.; Baumgartner, C.; Exadaktylos, A.K.; Hautz, W.E.; Atkinson, A.; Hammann, F. Development and validation of a prognostic COVID-19 severity assessment (COSA) score and machine learning models for patient triage at a tertiary hospital. *J. Trans. Med.* **2021**, *19*, 56. [\[CrossRef\]](#)
73. Canal-Rivero, M.; Catalán-Barragán, R.; Rubio-García, A.; Garrido-Torres, N.; Crespo-Facorro, B.; Ruiz-Veguilla, M.; Group, I.T.P. Lower risk of SARS-CoV2 infection in individuals with severe mental disorders on antipsychotic treatment: A retrospective epidemiological study in a representative Spanish population. *Schizophr. Res.* **2021**, *229*, 53–54. [\[CrossRef\]](#) [\[PubMed\]](#)
74. Nemani, K.; Conderino, S.; Marx, J.; Thorpe, L.E.; Goff, D.C. Association Between Antipsychotic Use and COVID-19 Mortality Among People with Serious Mental Illness. *JAMA Psychiatry* **2021**, *78*, 1391–1393. [\[CrossRef\]](#) [\[PubMed\]](#)
75. Vai, B.; Mazza, M.G.; Delli Colli, C.; Foiselle, M.; Allen, B.; Benedetti, F.; Borsini, A.; Casanova Dias, M.; Tamouza, R.; Leboyer, M.; et al. Mental disorders and risk of COVID-19-related mortality, hospitalisation, and intensive care unit admission: A systematic review and meta-analysis. *Lancet Psychiatry* **2021**, *8*, 797–812. [\[CrossRef\]](#) [\[PubMed\]](#)
76. Boland, X.; Dratcu, L. Antipsychotics and COVID-19: The debate goes on. *Lancet Psychiatry* **2021**, *8*, 1030. [\[CrossRef\]](#)
77. Zippi, M.; Fiorino, S.; Budriesi, R.; Micucci, M.; Corazza, I.; Pica, R.; de Biase, D.; Gallo, C.G.; Hong, W. Paradoxical relationship between proton pump inhibitors and COVID-19: A systematic review and meta-analysis. *World J. Clin. Cases* **2021**, *9*, 2763–2777. [\[CrossRef\]](#)
78. Fatima, K.; Almas, T.; Lakhani, S.; Jahangir, A.; Ahmed, A.; Siddiqui, A.; Rahim, A.; Qureshi, S.A.; Arshad, Z.; Golani, S.; et al. The Use of Proton Pump Inhibitors and COVID-19: A Systematic Review and Meta-Analysis. *Trop. Med. Infect. Dis.* **2022**, *7*, 37. [\[CrossRef\]](#)
79. Toubasi, A.A.; AbuAnzeh, R.B.; Khraisat, B.R.; Al-Sayegh, T.N.; AlRyalat, S.A. Proton Pump Inhibitors: Current Use and the Risk of Coronavirus Infectious Disease 2019 Development and its Related Mortality. Meta-analysis. *Arch. Med. Res.* **2021**, *52*, 656–659. [\[CrossRef\]](#)
80. Pranata, R.; Huang, I.; Lawrensia, S.; Henrina, J.; Lim, M.A.; Lukito, A.A.; Kuswardhani, R.A.T.; Wibawa, I.D.N. Proton pump inhibitor on susceptibility to COVID-19 and its severity: A systematic review and meta-analysis. *Pharmacol. Rep.* **2021**, *73*, 1642–1649. [\[CrossRef\]](#)
81. Jackson, C.B.; Farzan, M.; Chen, B.; Choe, H. Mechanisms of SARS-CoV-2 entry into cells. *Nat. Rev. Mol. Cell Biol.* **2021**, *23*, 3–20. [\[CrossRef\]](#)
82. Peng, R.; Wu, L.-A.; Wang, Q.; Qi, J.; Gao, G.F. Cell entry by SARS-CoV-2. *Trends Biochem. Sci.* **2021**, *46*, 848–860. [\[CrossRef\]](#) [\[PubMed\]](#)

83. Trbojević-Akmačić, I.; Petrović, T.; Lauc, G. SARS-CoV-2 S glycoprotein binding to multiple host receptors enables cell entry and infection. *Glycoconj. J.* **2021**, *38*, 611–623. [[CrossRef](#)] [[PubMed](#)]
84. Pruijboom, L. SARS-CoV 2; Possible alternative virus receptors and pathophysiological determinants. *Med. Hypotheses* **2021**, *146*, 110368. [[CrossRef](#)] [[PubMed](#)]
85. Daly James, L.; Simonetti, B.; Klein, K.; Chen, K.-E.; Williamson Maia, K.; Antón-Plágaro, C.; Shoemark Deborah, K.; Simón-Gracia, L.; Bauer, M.; Hollandi, R.; et al. Neuropilin-1 is a host factor for SARS-CoV-2 infection. *Science* **2020**, *370*, 861–865. [[CrossRef](#)] [[PubMed](#)]
86. Cantuti-Castelvetri, L.; Ojha, R.; Pedro Liliana, D.; Djannatian, M.; Franz, J.; Kuivanen, S.; van der Meer, F.; Kallio, K.; Kaya, T.; Anastasina, M.; et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. *Science* **2020**, *370*, 856–860. [[CrossRef](#)]
87. Gordon, D.E.; Jang, G.M.; Bouhaddou, M.; Xu, J.; Obernier, K.; White, K.M.; O'Meara, M.J.; Rezelj, V.V.; Guo, J.Z.; Swaney, D.L.; et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* **2020**, *583*, 459–468. [[CrossRef](#)]
88. Terracciano, R.; Preianò, M.; Fregola, A.; Pelaia, C.; Montalcini, T.; Savino, R. Mapping the SARS-CoV-2–Host Protein–Protein Interactome by Affinity Purification Mass Spectrometry and Proximity-Dependent Biotin Labeling: A Rational and Straightforward Route to Discover Host-Directed Anti-SARS-CoV-2 Therapeutics. *Int. J. Mol. Sci.* **2021**, *22*, 532. [[CrossRef](#)]
89. Kruse, T.; Benz, C.; Garvanska, D.H.; Lindqvist, R.; Mihalic, F.; Coscia, F.; Inturi, R.; Sayadi, A.; Simonetti, L.; Nilsson, E.; et al. Large scale discovery of coronavirus-host factor protein interaction motifs reveals SARS-CoV-2 specific mechanisms and vulnerabilities. *Nat. Commun.* **2021**, *12*, 6761. [[CrossRef](#)] [[PubMed](#)]
90. Khorsand, B.; Savadi, A.; Naghibzadeh, M. SARS-CoV-2-human protein-protein interaction network. *Inform. Med. Unlocked* **2020**, *20*, 100413. [[CrossRef](#)] [[PubMed](#)]
91. Helenius, A. Virus Entry: Looking Back and Moving Forward. *J. Mol. Biol.* **2018**, *430*, 1853–1862. [[CrossRef](#)] [[PubMed](#)]
92. Choi Keum, S.; Aizaki, H.; Lai Michael, M.C. Murine Coronavirus Requires Lipid Rafts for Virus Entry and Cell-Cell Fusion but Not for Virus Release. *J. Virol.* **2005**, *79*, 9862–9871. [[CrossRef](#)]
93. Li, X.; Zhu, W.; Fan, M.; Zhang, J.; Peng, Y.; Huang, F.; Wang, N.; He, L.; Zhang, L.; Holmdahl, R.; et al. Dependence of SARS-CoV-2 infection on cholesterol-rich lipid raft and endosomal acidification. *Comput. Struct. Biotechnol. J.* **2021**, *19*, 1933–1943. [[CrossRef](#)]
94. Sorice, M.; Misasi, R.; Riitano, G.; Manganelli, V.; Martellucci, S.; Longo, A.; Garofalo, T.; Mattei, V. Targeting Lipid Rafts as a Strategy Against Coronavirus. *Front. Cell Dev. Biol.* **2021**, *8*, 618296. [[CrossRef](#)]
95. Tsuchiya, H.; Mizogami, M. Interaction of drugs with lipid raft membrane domains as a possible target. *Drug Target Insights* **2020**, *14*, 34–47. [[CrossRef](#)]
96. Packer, M. Do DPP-4 Inhibitors Cause Heart Failure Events by Promoting Adrenergically Mediated Cardiotoxicity? *Circ. Res.* **2018**, *122*, 928–932. [[CrossRef](#)] [[PubMed](#)]