Systematic analysis of electronic health records identifies drugs reducing risk of COVID-19 hospitalization and severity

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Abstract

Background

SARS-Cov-2 is a new virus causing a pandemic of primarily respiratory illness designated as Coronavirus Disease 2019 (COVID-19). This disease is associated with excess mortality, particularly among the elderly, raising concerns for public health. It is crucial to identify whether existing medications could protect against adverse outcomes of COVID-19 infection.

Methods

We performed a population-based study among members of Clalit Health Services (CHS), the largest healthcare provider in Israel. CHS centrally manages electronic health records (EHR) including medication purchases for over 4.5 million members. Since the disease outbreak through October 10, 2020, 8,681 adult patients aged between 18 and 95 have been hospitalized for COVID-19, among them 3,777 in severe condition. Two case-control matched cohorts were assembled to assess which drugs taken by patients in the month preceding a SARS-CoV-2 positive test, affected risks of COVID-19 hospitalization. Significance of the associations was assessed using Fisher's exact test and Benjamini-Hochberg correction for multiple testing.

Results

Several drugs and pharmacy sold products were significantly associated with reduced odds ratios of SARS-CoV-2 hospitalization: ubiquinone (OR=0.25, $p<0.001$), ezetimibe (OR=0.51, $P<0.001$), rosuvastatin (OR=0.75, $p<0.001$) and flecainide (OR=0.30, $p<0.01$). Additionally, acquisition of surgical masks, latex gloves and several ophthalmological products were associated with decreased risk for hospitalization.

Conclusion

Ubiquinone, ezetimibe and rosuvastatin, all related to the cholesterol synthesis pathway, are associated with reduced hospitalization rate and decreased severity in hospitalized patients. These findings set the basis for specific prospective randomized control trials that should be carried out to carefully assess their protective effects.

Background

SARS-Cov-2 is a new single-stranded RNA virus, which was first identified in December 2019, and has rapidly spread into a global pandemic of primarily respiratory illness designated as Coronavirus Disease 2019 (COVID-19). This disease is associated with significant mortality, particularly among elderly or overweight individuals, raising considerable concerns for public health. Until a vaccine or specifically designed therapies are available, it is urgent to identify whether existing medications have protective effects against COVID-19 complications from available real-world data. This is the aim of this case-control study which was performed on electronic health records (EHR) from Clalit Health Services (CHS), the largest healthcare provider in Israel.

Methods

We collected from the Clalit Health Services (CHS) data warehouse selected variables from the EHR of adult patients aged 18 to 95 years, who had been tested positive for SARS-CoV-2 between the beginning of the pandemics and until September 25, and were admitted for hospitalization until October 10, 2020. Each patient was assigned an index date, which is the first date at which a positive PCR test SARS-CoV-2 test was collected for the patient. Patients' demographic characteristics were queried, along with existing comorbidities, clinical characteristics including BMI, and glomerular filtration rate (GFR) as of February 2020. For each patient, the list of drugs or products acquired in CHS pharmacies was collected for the preceding month, defined as 35 to 2 days before the index date.

We assigned the hospitalized COVID-19 patients to two distinct case-control cohorts, which differ in the pool from which control individuals were selected. *In cohort 1*, control patients were chosen among the general population of CHS members. Since we can select controls from among millions of individuals, we took 5 controls for each case (5:1), and comprehensively controlled by matching baseline attributes, including age, gender, BMI category, socio-economic and smoking status, chronic kidney disease (CKD) stage for patients with renal impairment, and main comorbidities diagnoses (hypertension, diabetes, chronic kidney disease (CKD), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), malignancy, ischemic heart disease). We assigned to each control the same index date as the matched case, verified that the patient was still alive and a member of CHS at this date, and collected EHR data for controls in a similar manner to that described for cases. This cohort is designed to identify drugs that affect the overall risk for hospitalization for COVID-19, where the effect could combine a decreased risk of detectable infection, and a decreased risk for hospitalization once infected.

In cohort 2, control patients were chosen among patients who had a positive test for SARS-CoV-2 but had not been hospitalized as of October 10, 2020. Given the smaller size of the pool from which controls can be drawn, we matched only two controls for each case patient. Attributes which were matched were the age, gender, smoking status, Adjusted Clinical Groups® (ACG) measure of comorbidity[1] and presence of obesity diagnosis. The index date taken was the date of first positive SARS-CoV-2 test both for cases and controls. This cohort is more specifically suited to identify drugs that are associated with a decreased risk for COVID-19 hospitalization in patients who had proven infection with the virus. In both cohorts, there were a minority of individuals for which a full match could not be found; these cases were dropped from their respective cohorts and excluded from the analyses.

Reliable identification of medications procured for the last 35 days is enabled by the fact that in CHS, distinct prescriptions are issued for each calendar month. When medications are provided in advance for multiple months, the date at which the prescription for each month of treatment begins is recorded.

In each cohort, and for each medication anatomical therapeutic chemical (ATC) class, we computed the odds ratio for hospitalization according to the number of patients who acquired a medication of the class between 35 days and 2 days preceding the index date, in the case and the control groups. Medications found to be significantly associated with hospitalization were also tested for association with disease severity, using a nested analysis in sub-cohorts of patients from the main cohort grouped by disease severity, according to the scale defined by the World Health Organization (WHO): mild (3), serious (4), severe (5-7), deceased (8).

Based on the results from the two cohorts, which highlighted a significant protective effect for ubiquinone, ezetimibe, and a statin, which are often prescribed in combination, we subsequently investigated the association between various combinations of these drugs and the outcomes using the same approach.

This study has been approved by the CHS Institutional Review Board (IRB) with a waiver of informed consent, approval number: COM-0046-20. Patients' data were extracted and processed from CHS data-warehouse using programs developed inhouse in Python and SQL. Identifying patient data were removed prior to the statistical analyses in accordance to the protocol approved by the CHS IRB.

Statistical analysis

Odds ratios for acquisition for drugs in the case versus control groups and statistical significance were assessed by Fisher's exact test. P-values below 0.05 were considered significant. Correction for multiple testing was performed using the Benjamini-Hochberg procedure[2], which gives an estimation

of the false discovery rate (FDR) in the list. Statistical analyses were performed in R statistical software version 3.6 (R Foundation for statistical computing).

Results

Through October 10, 2020, 8,681 adult patients between aged 18 and 95 had a recorded COVID-19 related hospitalization in the CHS database. The matching procedure was able to identify control individuals from the general population in ratio 5:1 for 6,202 patients in the first cohort, and control patients in ratio 2:1 from 6,919 SARS-CoV-2 positive individuals in the second cohort. The characteristics of the matched populations are shown in **Table 1.**

In each of the two cohorts, we counted the number of patients from each group who acquired drugs and other medical products from each Anatomical Therapeutic Chemical (ATC) and computed the odds ratios and p-values using Fisher's test. The distribution of odds ratio for drugs for which the p-value was significant ($p<0.05$) is shown in **Figure 1.** The odds ratios for most drugs are neutral or associated with an increased risk of COVID-19 hospitalization. Only a small fraction of the products are associated with decreased risk: 1.15% for cohort 1, and 1.75% in cohort 2.

Table 2 presents the list of drugs/products that were found to be negatively associated with COVID-19 hospitalization in a statistically significant manner in cohort 1 **(A)** and in cohort 2 **(B)**. We display items for which the p-value is below 0.05, and for which the false discovery rate (FDR) is less than 0.30, meaning that at least 70% of the items in the displayed list are expected to have a true protective effect. Items are sorted by decreasing order of significance, so that the associations that are the least likely to have happened by chance are displayed first.

The most significant medications in both cohorts are ubiquinone, ezetimibe, and rosuvastatin. It is remarkable that these three drugs act on the cholesterol and ubiquinone synthesis pathways, which both stem from the mevalonate pathway[3]; the intermediate product at the branch point is farnesyl polyphosphate (FPP). Ubiquinone is a food supplement available over the counter (OTC) in Israel, which is often recommended to patients prone to muscular pain and receiving a statin treatment[4]. Since Ezetimibe, statins and ubiquinone are often used in combination, we performed a nested analysis to more specifically evaluate the impact of possible combinations on the risk of hospitalization. **Table 3** presents the odds ratio and p-values associated with acquisition of statins, ubiquinone, and ezetimibe alone and in combination in the whole cohort, and in sub-cohorts of hospitalized patients defined by disease severity. Ubiquinone's protective effect appears to be more pronounced when given in combination with a statin (OR=0.122, P=0.008, first cohort, for hospitalization in moderate condition). Remarkably, the protective effect of ezetimibe is the strongest

when this molecule is taken without a statin (OR=0.275, P=0.037, second cohort for severe hospitalization), while the effect observed when ezetimibe is taken with a statin is similar to the effect of the statin alone. Also identified by both cohorts is flecainide, an antiarrhythmic medication, for which the difference in usage rate among hospitalized patients is significant both in cohorts 1 and cohort 2. Several additional protective drugs observed in cohort 2 include risedronic acid (OR=0.593, p=0.002), a drug usually prescribed for osteoporosis; several drugs acting at synapses of different types (bupropion, donepezil, mirabegron); vitamins (vitamin B12 combination, retinol for the eye), and minerals (calcium-zinc, magnesium).

A significant protective effect is interestingly observed for several non-drug items that could act as a barrier in both cohorts: surgical masks, latex gloves, eye care wipes (sterile wipes for eye hygiene), artificial tears, eye drops and ointments.

Discussion

We identified several drugs and products that are significantly associated with reduced odds for COVID-19 hospitalization, both in the general population, and in patients with laboratory proven SARS-CoV-2 infection. Major strengths of our study include: (i) the large sample of hospitalized COVID-19 patients, (ii) the ability to collect comprehensive data about individual demographic and comorbidity characteristics and to build matched case and control populations, (iii) the ability to track hospitalizations and disease severity, owing to a central database established by the Israeli Ministry of Health and, (iv) the capacity to track which drugs and products have been acquired by patients in the period that have preceded SARS-CoV-2 infection, owing to comprehensive digital systems integration in CHS.

The dual cohort design, with control individuals taken from the general population in the first cohort and from individuals positive for SARS-CoV-2 in the second cohort, with each using different matching criteria, mitigates potential bias that could affect each cohort. The two cohorts allow to evaluate the protective effect of drugs that act either by reducing the initial risk of infection, or by reducing the risk of hospitalization in those infected. Analyses are based on items procured between 35 and 2 days before the initial positive test. This window was chosen in accordance to the monthly renewal of prescription policy in place in CHS, with a blackout of 2 days which was intended to exclude acquisitions related to initial symptoms of the disease.

Limitations are related to this study being observational in nature. Best efforts were made to use matching so that patients in case and controls are similar regarding most of the known factors for disease severity, and notably, age, obesity, smoking, and baseline comorbidity. We aimed to get a good tradeoff between controlling for confounding factors by rigorous matching and keeping enough

patients so that cohorts are representative of the general population. Our analysis is based on medication acquisition in pharmacies and does not ascertain that medications purchased were used. Notably, some of the drugs associated with a protective effect may have been stopped during patient's hospitalization so that our analysis may have underestimated the full achievable benefit for some of the drugs. Conversely, since drugs tested here were acquired before patients were positive for SARS-CoV-2, the protective effect of some of the drugs may be fully attained only when treatment is started before or early in the infection.

Bearing these potential limitations in mind, our analyses point to several different viral vulnerability points, which can potentially be exploited to effectively fight the virus with drugs that are already available. The drugs identified as protective are ubiquinone, which is a food supplement with a very good safety profile that does not even require a prescription in Israel; rosuvastatin and ezetimibe, two drugs prescribed routinely to reduce cholesterol, and who are considered safe. These findings are in line with previous reports that RNA viruses need cholesterol to enter cells, for virion assembly, and to maintain structural stability[5–8], and that prescribing statins may protect against infection with RNA viruses such as members of family *Flaviviridae*, including Dengue virus, Zika virus, and West Nile virus[9–11]. The involvement of the cholesterol/ubiquinone pathway is further confirmed by the fact that risedronic acid, a drug acting on the enzyme farnesyl pyroposhpate synthase[12] which catalyzes the production of FPP from which the cholesterol and the Ubiquinone synthesis pathways split[3], is identified as protective as well, even though it is prescribed for osteoporosis regardless of the presence of hypercholesterolemia.

Taken together, our findings lend (albeit indirect) support to the possibility that SARS-CoV2 hijacks the cholesterol synthesis pathway, possibly to boost production of the cellular cholesterol it needs as an RNA virus. The fact that ubiquinone protects against severe disease, suggests that SARS-CoV2 may tilt the mevalonate pathway towards cholesterol synthesis and away from ubiquinone synthesis. Such a pathway imbalance would ultimately result in deficiency of ubiquinone that could lead to cell death unless counteracted by ubiquinone supplementation.

Another medication that appears protective is flecainide, an antiarrhythmic drug that blocks sodium channels in the heart, and inhibits ryanodine receptor 2 (RyR2), a major regulator of sarcoplasmic release of stored calcium ions. It may prevent apoptosis by release of calcium from the ER, once the cell mitochondria cease to function. An expert review recommended that patients with arrhythmia who get COVID-19 should continue flecainide treatment if already prescribed[13]. In our study, the protective effect observed in both cohorts is even more marked for severe patients. If this effect is confirmed in clinical trials, this drug, which can be given intravenously[14], could be administered in patients in respiratory distress, even if unconscious.

Reassuringly, we find items that act as a barrier among the most protective items, including surgical masks, latex gloves, eye wipes, eye drops, and ointments. The protective effect against hospitalization is observed foremost among patients from cohort 2 in which controls are already SARS-CoV-2 positive. This suggests that barrier products could protect not only against the initial risk of infection, but also by reducing the severity in patients already infected. In our cohorts, we observe a beneficial effect for many ophthalmologic preparations, which raises the possibility that autoinoculation of the virus to the eyes could play a part in disease virulence, a prospect supported by the fact eyeglass wearers were at decreased risk for COVID-19 hospitalization[15]. Until the meaning of these findings is fully understood, it may be wise to advise COVID-19 patients to avoid touching their eyes to reduce the risk of complications.

In conclusion, considering the observed protective effects of ubiquinone, ezetimibe, rosuvastatine, risedronate and flecainide in this large population analysis, we recommend to further investigate these and other products identified by this study, in prospective trials aimed to reduce disease severity in COVID-19 patients.

Contributors

All authors provided final approval to publish. AI, IF and AT had access to the raw data. AI designed the study. AI, AS, AC, IF, AT, KC, SS, ES, ER and GL contributed to data analysis and interpretation. AI, AS, ER and GL contributed to the drafting of the article.

Declaration of interests

The authors declare no conflict of interest

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References

1. Shadmi E, Kinder K, Abrams C, Weiner JP. Assessing socioeconomic health care utilization inequity in Israel: impact of alternative approaches to morbidity adjustment [Internet]. 2011 [cited 2020 Sep 4]. Available from: http://www.biomedcentral.com/1471-2458/11/609

2. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J R Stat Soc Ser B [Internet] 1995 [cited 2020 Oct 9];57(1):289–300. Available from: https://rss.onlinelibrary.wiley.com/doi/full/10.1111/j.2517-6161.1995.tb02031.x

3. Buhaescu I, Izzedine H. Mevalonate pathway: a review of clinical and therapeutical implications. Clin Biochem [Internet] 2007;40(9–10):575–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17467679

4. Qu H, Guo M, Chai H, Wang W-T, Gao Z-Y, Shi D-Z. Effects of Coenzyme Q10 on Statin-Induced Myopathy: An Updated Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc [Internet] 2018;7(19):e009835. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30371340

5. Sun X, Whittaker GR. Role for influenza virus envelope cholesterol in virus entry and infection. J Virol [Internet] 2003;77(23):12543–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14610177

6. Aizaki H, Morikawa K, Fukasawa M, et al. Critical role of virion-associated cholesterol and sphingolipid in hepatitis C virus infection. J Virol [Internet] 2008;82(12):5715–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18367533

7. Rossman JS, Jing X, Leser GP, Balannik V, Pinto LH, Lamb RA. Influenza virus m2 ion channel protein is necessary for filamentous virion formation. J Virol [Internet] 2010;84(10):5078–88. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20219914

8. Bajimaya S, Hayashi T, Frankl T, Bryk P, Ward B, Takimoto T. Cholesterol reducing agents inhibit assembly of type I parainfluenza viruses. Virology [Internet] 2017;501:127–35. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27915128

9. Gower TL, Graham BS. Antiviral activity of lovastatin against respiratory syncytial virus in vivo and in vitro. Antimicrob Agents Chemother [Internet] 2001;45(4):1231–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11257039

10. Whitehorn J, Nguyen CVV, Khanh LP, et al. Lovastatin for the Treatment of Adult Patients With Dengue: A Randomized, Double-Blind, Placebo-Controlled Trial. Clin Infect Dis [Internet] 2016;62(4):468–76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26565005

11. Osuna-Ramos JF, Reyes-Ruiz JM, Del Ángel RM. The Role of Host Cholesterol During Flavivirus Infection. Front Cell Infect Microbiol [Internet] 2018;8:388. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30450339

12. Tsoumpra MK, Muniz JR, Barnett BL, et al. The inhibition of human farnesyl pyrophosphate synthase by nitrogen-containing bisphosphonates. Elucidating the role of active site threonine 201 and tyrosine 204 residues using enzyme mutants. Bone [Internet] 2015;81:478–86. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26318908

13. Wu C-I, Postema PG, Arbelo E, et al. SARS-CoV-2, COVID-19, and inherited arrhythmia syndromes. Hear Rhythm [Internet] 2020;17(9):1456–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32244059

14. Antonelli D, Feldman A, Freedberg NA, Darawsha A, Rosenfeld T. [Intravenous flecainide administration for conversion of paroxysmal atrial fibrillation in the emergency room]. Harefuah [Internet] 2006;145(5):342–4, 398. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16805213

15. Zeng W, Wang X, Li J, et al. Association of Daily Wear of Eyeglasses With Susceptibility to Coronavirus Disease 2019 Infection. JAMA Ophthalmol [Internet] 2020;Available from: http://www.ncbi.nlm.nih.gov/pubmed/32936214

Table 1: Demographics and Clinical characteristics of the two matched cohorts of patients (hospitalized vs. non-hospitalized)

	Cohort 1		Cohort 2	
	COVID-19 hospitalized (cases)	**not hospitalized (controls)**	**COVID-19 hospitalized (cases)**	**not hospitalized (controls)**
n	6202	31010	6919	13838
Age (mean (SD))	56.8 (18.9)	57.2 (18.7)	59.0 (19.1)	59.2 (18.9)
Gender female (%)	3156 (50.9)	15780 (50.9)	3491 (50.5)	6982 (50.5)
Hospitalization severity (n (%))				
mild condition	**2747 (44.3)**		**2839 (41.0)**	
moderate condition	**1093 (17.6)**		**1215 (17.6)**	
severe condition	**1775 (28.6)**		**1987 (28.7)**	
deceased	**587 (9.5)**		**878 (12.7)**	
Smoking status (%)				
never smoker	4856 (78.3)	23748 (76.6)	5298 (76.6)	10596 (76.6)
past smoker	853 (13.8)	4492 (14.5)	1083 (15.7)	2166 (15.7)
current smoker	408 (6.6)	2365 (7.6)	472 (6.8)	944 (6.8)
Nb visits at primary doctor last year (mean (SD))	6.7 (7.2)	6.6 (6.7)	7.0 (7.6)	6.5 (6.7)
Comorbidity (%)				
Arrhythmia	532 (8.6)	2597 (8.4)	867 (12.5)	1505 (10.9)
Asthma	348 (5.6)	1897 (6.1)	465 (6.7)	914 (6.6)
Congestive Heart Failure (CHF)	131 (2.1)	655 (2.1)	504 (7.3)	635 (4.6)
Chronic Obstructive Pulmonary Disease (COPD)	92 (1.5)	460 (1.5)	397 (5.7)	516 (3.7)
Diabetes	1817 (29.3)	9085 (29.3)	1846 (30.1)	9230 (30.1)
Hypertension	2289 (36.9)	11501 (37.1)	3043 (44.0)	5468 (39.5)
Ischemic Heart Disease (IHD)	864 (13.9)	4320 (13.9)	1252 (18.1)	2110 (15.2)
Malignancy	803 (11.6)	1702 (12.3)	803 (11.6)	1702 (12.3)
Chronic Kidney Disease (CKD)	66 (1.1)	330 (1.1)	6200 (89.6)	13032 (94.2)
Obesity (documented diagnosis)	2365 (38.1)	11022 (35.5)	2818 (40.7)	5636 (40.7)
Body Mass Index (BMI) (mean (SD))	28.7 (5.7)	28.6 (6.5)	29.1 (6.3)	28.5 (5.7)
BMI group (%)				
<18.5	70 (1.1)	350 (1.1)	92 (1.3)	189 (1.4)
18.5-25	1567 (25.3)	7835 (25.3)	1728 (25.0)	3635 (26.3)
25-30	2326 (37.5)	11630 (37.5)	2452 (35.4)	5048 (36.5)
30-35	1468 (23.7)	7340 (23.7)	1603 (23.2)	3374 (24.4)
35-40	543 (8.8)	2715 (8.8)	676 (9.8)	1137 (8.2)
>40	228 (3.7)	1140 (3.7)	368 (5.3)	455 (3.3)

Glomerular Filtration Rate (GFR) (mean (SD))	92.8 (22.7)	91.9 (21.7)	86.6 (28.5)	89.1 (23.4)
Chronic Kidney Disease (CKD) staging (n (%))				
G1	3786 (61.0)	18471 (59.6)	3770 (54.5)	7700 (55.6)
G2	1923 (31.0)	10196 (32.9)	2076 (30.0)	4664 (33.7)
G3a	352 (5.7)	1755 (5.7)	482 (7.0)	887 (6.4)
G3b	121 (2.0)	520 (1.7)	276 (4.0)	368 (2.7)
G4	17 (0.3)	48 (0.2)	109 (1.6)	127 (0.9)
G5			42 (0.6)	22 (0.2)
Dialysis	3 (0.0)	20 (0.1)	164 (2.4)	70 (0.5)

Table 2: Most significant associations for medications acquired in the 30 days preceding the index date in two matched cohorts

A. **First matched cohort** *(N = 6,202 hospitalization cases, N=31,010 controls taken from the general population)*

ATC code and class	use in case	use in control	case %	control %	odds ratio [95% Conf. Int.]	p-value	FDR BH
C10AX09 Ezetimibe	50	484	0.81	1.56	0.513 [0.375,0.688]	0.00000	0.00
C10AA07 Rosuvastatin	235	1556	3.79	5.02	0.746 [0.645,0.858]	0.00003	0.00
A16AX30 Ubiquinone 10	5	100	0.08	0.32	0.249 [0.079,0.602]	0.00033	0.01
N06AX12 Bupropion	3	60	0.05	0.19	0.250 [0.050,0.766]	0.00656	0.07
Eye Care Wipes	0	28	0.00	0.09	0.000 [0.000,0.704]	0.00970	0.10
C01BC04 Flecainide	4	66	0.06	0.21	0.303 [0.080,0.813]	0.00976	0.10
N06AB10 Escitalopram	154	946	2.48	3.05	0.809 [0.676,0.963]	0.01537	0.14
A12AX05 Calcium-Zinc	0	24	0.00	0.08	0.000 [0.000,0.830]	0.02430	0.18
Surgical Mask	2	44	0.03	0.14	0.227 [0.027,0.871]	0.02668	0.20
N06DA02 Donepezil	18	154	0.29	0.50	0.583 [0.336,0.954]	0.03061	0.21
Latex gloves with talc	1	31	0.02	0.10	0.161 [0.004,0.967]	0.03314	0.23
C03AA03 Hydrochlorothiazide	96	602	1.55	1.94	0.794 [0.632,0.988]	0.04011	0.26

B. **Second matched cohort** *(N = 6,919 hospitalization cases, N=13,838 controls taken from patients SARS-CoV-2 positive)*

ATC code and class	use in case	use in control	case %	control %	odds ratio [95% Conf. Int.]	p-value	FDR BH
A16AX30 Ubiquinone 10	5	54	0.07	0.39	0.185 [0.058,0.458]	0.00001	0.00
C10AX09 Ezetimibe	61	204	0.88	1.47	0.594 [0.438,0.796]	0.00029	0.01
C10AA07 Rosuvastatin	268	679	3.87	4.91	0.781 [0.673,0.904]	0.00070	0.01
M05BA07	45	151	0.65	1.09	0.593	0.00174	0.02

Risedronic Acid					[0.415,0.834]		
D11AX10 Finasteride	0	16	0.00	0.12	0.000 [0.000,0.518]	0.00231	0.03
D04AA13 Dimetindene (topical)	14	62	0.20	0.45	0.451 [0.233,0.815]	0.00487	0.05
G04BD12 Mirabegron	17	68	0.25	0.49	0.499 [0.275,0.859]	0.00790	0.08
B03BA51 VIT.B12 combinations	17	67	0.25	0.48	0.506 [0.278,0.873]	0.01042	0.10
S01XA02 Retinol (eye ointment with vitamin A)	1	17	0.01	0.12	0.118 [0.003,0.750]	0.01065	0.10
Eye Care Wipes	0	11	0.00	0.08	0.000 [0.000,0.797]	0.02035	0.16
C09AA08 Cilazapril	11	46	0.16	0.33	0.477 [0.223,0.936]	0.02418	0.18
S01KA01 Hyaluronic Acid (artificial tears)	5	29	0.07	0.21	0.344 [0.104,0.900]	0.02706	0.19
Latex gloves with talc	1	15	0.01	0.11	0.133 [0.003,0.866]	0.02959	0.20
Surgical Mask	1	15	0.01	0.11	0.133 [0.003,0.866]	0.02959	0.20
G03AC09 Desogestrel (contraceptive pills)	2	18	0.03	0.13	0.222 [0.025,0.928]	0.03049	0.21
A12CC04 Magnesium Citrate	24	79	0.35	0.57	0.606 [0.367,0.969]	0.03553	0.23
C01BC04 Flecainide	7	32	0.10	0.23	0.437 [0.163,1.009]	0.04185	0.25
S01ED53 Timolol-Latanoprost	11	44	0.16	0.32	0.499 [0.232,0.983]	0.04381	0.26
G04BE03 Sildenafil	55	151	0.80	1.09	0.726 [0.523,0.997]	0.04479	0.26

Numbers are of patients from the group who have acquired a medication from the class in the last month before the index date

P-values are calculated according to Fisher's exact test. Medications are sorted by increasing order of p-values.

False Discovery Rate (FDR) calculated according to Benjamini-Hochberg (BH) procedure. Are shown in this table ATC classes for which the p-value is less than 0.05, and for which the FDR q-value is less than 0.3 (at least 70% are expected to be true positive).

Table 3: Examination of the association between combinations of medications associated with the ubiquinone and cholesterol synthesis pathways and the risk of hospitalization, and severity of hospitalization

A. **First matched cohort (controls are SARS-CoV-2 negative)**

Drugs acquired by patients in the 30 days preceding the index date	**hospitalized all**		**hospitalized serious**		**hospitalized severe**		**death**	
	OR	**pval**	**OR**	**pval**	**OR**	**pval**	**OR**	**pval**
Ubiquinone	0.249	0.000	0.254	0.007	0.355	0.079	0.708	1.000
Ubiquinone with Statin	0.224	0.003	0.122	0.008	0.179	0.054		
Ezetimibe	0.742	0.000	0.768	0.010	0.743	0.014	0.556	0.054
Ezetimibe without Statin	0.478	0.005	0.434	0.017	0.360	0.015		
Rosuvastatin	0.739	0.000	0.696	0.000	0.716	0.001	0.691	0.072

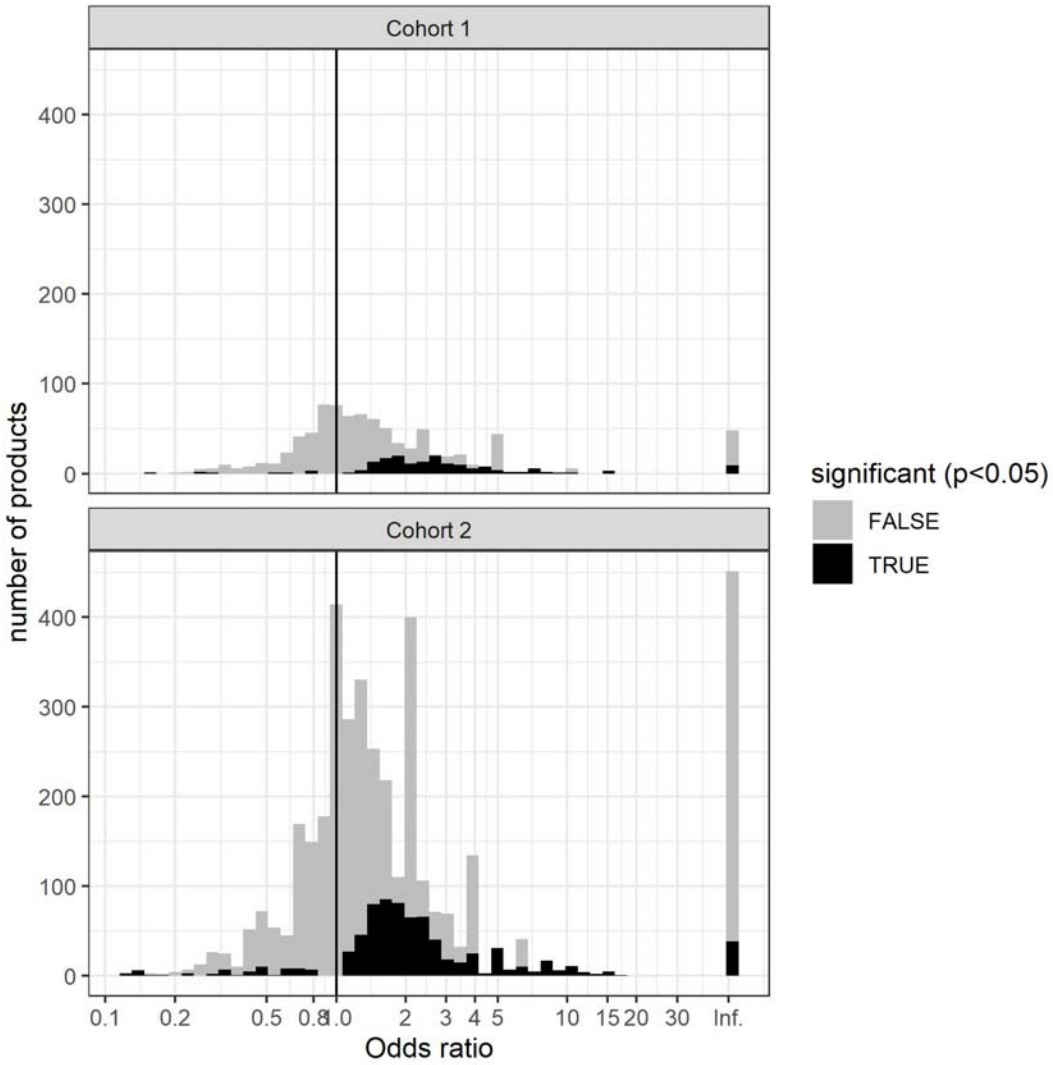
B. **Second matched cohort (controls are SARS-CoV-2 positive)**

Drugs acquired by patients in the 30 days preceding the index date	**hospitalized all**		**hospitalized serious**		**hospitalized severe**		**death**	
	OR	**pval**	**OR**	**pval**	**OR**	**pval**	**OR**	**pval**
Ubiquinone	0.185	0.000	0.171	0.000	0.239	0.000	0.800	0.000
Ubiquinone with Statin	0.205	0.000	0.174	0.000	0.222	0.000	0.500	0.000
Ezetimibe	0.831	0.031	0.836	0.031	0.831	0.031	0.487	0.031
Ezetimibe without Statin	0.538	0.037	0.377	0.037	0.275	0.037	0.153	0.037
Rosuvastatin	0.780	0.001	0.698	0.001	0.687	0.001	0.530	0.001

OR: Odds ratio

Displayed are only associations for which p-values are less than 0.10

Figure 1: Histogram showing the distribution of the odd ratios of medications that were found to have a significant association (P<0.05, black) with the outcome in cohorts 1 and 2



The overwhelming majority of medications are associated with neutral effect (gray) or increased risk for hospitalization (black, OR>1), only a few are associated with decreased risk (black, OR<1)