

Common drugs, vitamins, nutritional supplements and COVID-19 mortality

STEVEN LEHRER¹ and PETER H. RHEINSTEIN²

¹Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY 10029;

²Severn Health Solutions, Severna Park, MD 21146, USA

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Abstract. The FDA has approved only one drug, remdesivir, for the treatment of COVID-19. The FDA has granted an emergency use authorization for the rheumatoid arthritis treatment drug, baricitinib (Olumiant), for the treatment of COVID-19 in some cases. For this reason, investigators have paid considerable attention to the association between commonly used drugs and the outcome of patients with COVID-19. Aspirin and ibuprofen have been reported to reduce the mortality rate. Omeprazole can increase mortality. In addition, some studies have demonstrated that famotidine diminishes mortality, while others have indicated that famotidine leads to a poorer prognosis. The present study used UK Biobank (UKB) data to assess the association of commonly used drugs with COVID-19 mortality. Data processing was performed on Minerva, a Linux mainframe with Centos 7.6. The UK Biobank Data Parser (ukbb_parser) was used, a python-based package that allows easy interfacing with the large UK Biobank dataset. The results revealed that aspirin and omeprazole were associated with an elevated mortality rate. Ibuprofen-related mortality was lower than laxative-related mortality. Aspirin users were also significantly older than other subjects. The association with mortality of cholesterol-lowering medications, blood pressure-lowering medications, hormone replacement and oral contraceptives in 134 female subjects revealed insignificant variability. The association of nutritional supplements in 238 subjects with mortality indicated that variability was insignificant. The lower mortality linked to the supplementation of vitamin D and vitamin B, presumably B complex, has been previously observed. On the whole, the present study demonstrates that although some of the associations described among drugs and COVID-19 are not novel, the utility of a new source, UKB, may prove to be useful in further examining these associations.

Introduction

Therapy for COVID-19, particularly during the early stages of infection, is urgently required. Although COVID-19 is mostly self-limited, up to 20% of symptomatic cases will develop severe or critical disease with clinical manifestations, including pneumonia, acute respiratory distress syndrome, multiorgan system dysfunction, hypercoagulation and hyperinflammatory manifestations. Over 47 million cases of COVID-19 globally have resulted in >1.2 million deaths (1).

The FDA has approved only one drug, remdesivir, for the treatment of COVID-19. In addition, the FDA has granted an emergency use authorization for the use of baricitinib (Olumiant; used for the treatment of rheumatoid arthritis) for the treatment of COVID-19 in some cases. For this reason, investigators have paid considerable attention to the association between the administration of commonly used drugs with the outcome of patients with COVID-19. Aspirin (2-5) has been reported to reduce mortality. However, as regards other drugs, some studies have recommended that ibuprofen should be avoided (6-8). In addition, the use of omeprazole has been shown to increase mortality (9). At least one report has indicted that famotidine decreases mortality (10), while another indicates that the use of famotidine leads to a poorer prognosis (11).

Data and methods

UK Biobank (UKB). UKB data were used to assess the association of common drugs with COVID-19 mortality. Electronic linkage between UKB records and National Health Service COVID-19 laboratory test results in the UK were available from March 16, to April 26, 2020, including the peak of daily COVID-19 laboratory-confirmed cases. During this time period, the testing of older age groups was largely restricted to hospital inpatients exhibiting clinical signs of infection. Thus, test positivity is considered a good marker of severe COVID-19 (12). COVID-19 mortality in the UK was recorded as 900 deaths per day at this time.

For the data used in the present study, the inclusion criteria were a positive test for COVID-19, and the exclusion criteria were negative COVID-19 test or no test results.

Correspondence to: Dr Steven Lehrer, Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, New York, NY 10029, USA
E-mail: steven.lehrer@mssm.edu

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Data processing and statistical analysis. Data processing was performed on Minerva, a Linux mainframe with Centos 7.6,

at the Icahn School of Medicine at Mount Sinai. The UKB Data Parser (ukbb_parser) was used, which is a python-based package that allows easy interfacing with the large UK Biobank dataset (13). Data were analyzed using one-way analysis of variance (ANOVA), Tukey's post hoc test, logistic regression, and Fisher's exact test. Statistical analysis was performed using SPSS version 22.

Results

The present study evaluated data from 376 subjects, 49% female, 51% male. The age of the subjects was 55.7 ± 9.1 (mean \pm SD) years. The COVID-19 mortality rate was 20.5%.

The association between the use of aspirin, ibuprofen, paracetamol (acetaminophen), ranitidine, omeprazole and laxatives with mortality in 376 subjects, 517 responses is shown in Table I. The variability was significant ($P=0.011$, two-tailed Fisher's exact test).

As regards the use of Fisher's exact test, it should be noted that this is a statistical test used to determine whether there are non-random associations between categorical variables. Only in Table I does such an association exist, suggesting that the variation in mortality rates of aspirin, ibuprofen, paracetamol (acetaminophen), ranitidine, omeprazole and laxatives is meaningful. In the other tables, variability was not significant, suggesting that the differing mortalities may not be meaningful. Given the large number of agents examined, the present study performed as few comparison tests as possible. When performing hypothesis tests with multiple comparisons, eventually a result could occur that appears to demonstrate statistical significance in the dependent variable, even when there is none.

Aspirin and omeprazole were associated with an increased mortality. Ibuprofen-related mortality was lower than laxative-related mortality. Aspirin users were significantly older ($P<0.001$, one-way ANOVA; Fig. 1).

The association with mortality of cholesterol-lowering medications, blood pressure-lowering medications, insulin, hormone replacement and oral contraceptives in 134 female subjects and 173 responses is shown in Table II. The variability was insignificant ($P=0.077$, two-tailed Fisher's exact test). The age (mean \pm SD) of the female subjects by medication are shown in Fig. 2. Oral contraceptive users were significantly younger than hormone replacement users ($P<0.05$, Tukey's range test). The hormone replacement users were significantly younger than the users of cholesterol-lowering medications and blood pressure-lowering medications ($P<0.05$, Tukey's range test). The effect of age on survival was significant; however, the effect of hormones on survival was not (Table III).

The association of nutritional supplements with mortality is shown in Table IV. The lower mortality linked to vitamin D and vitamin B supplementation, presumably B complex, has been previously observed (14,15). There was no significant difference in the mean age ($P=0.071$, one-way ANOVA; data not shown).

The association of mineral and other dietary supplements with mortality, in 294 subjects, 456 responses is shown in Table V. The variability was insignificant ($P=0.983$, two-tailed Fisher's exact test).

Table I. Association of aspirin, ibuprofen, paracetamol (acetaminophen), ranitidine, omeprazole and laxatives with mortality.

| Drug | Count and % | Alive | Deceased | Total |
|-----------------|-----------------|--------|----------|-------|
| Aspirin | Count | 84 | 35 | 119 |
| | % With drug use | 70.60% | 29.40% | |
| Ibuprofen | Count | 106 | 15 | 121 |
| | % With drug use | 87.60% | 12.40% | |
| Paracetamol | Count | 150 | 34 | 184 |
| | % With drug use | 81.50% | 18.50% | |
| Ranitidine | Count | 11 | 4 | 15 |
| | % With drug use | 73.30% | 26.70% | |
| Omeprazole | Count | 38 | 14 | 52 |
| | % With drug use | 73.10% | 26.90% | |
| Laxatives | Count | 18 | 8 | 26 |
| | % With drug use | 69.20% | 30.80% | |
| No. of subjects | Count | 299 | 77 | 376 |

There were 517 responses, 376 subjects. The variability is significant ($P=0.011$, two-tailed Fisher exact test). Aspirin and omeprazole have elevated mortality. Ibuprofen mortality (12.4%) is lower than laxative mortality (30.8%).

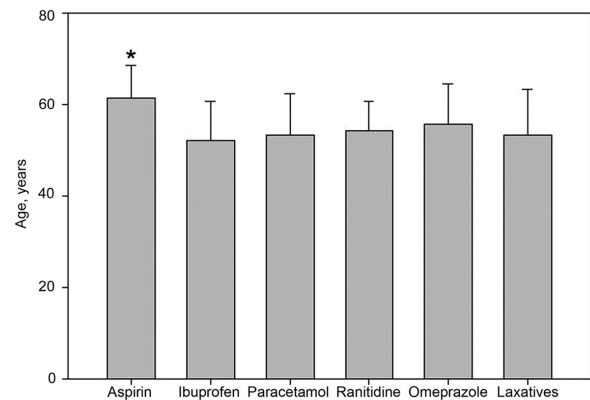


Figure 1. Age (mean \pm SD) of subjects, both sexes, by medication. Aspirin users were significantly older ($P<0.001$, one-way analysis of variance).

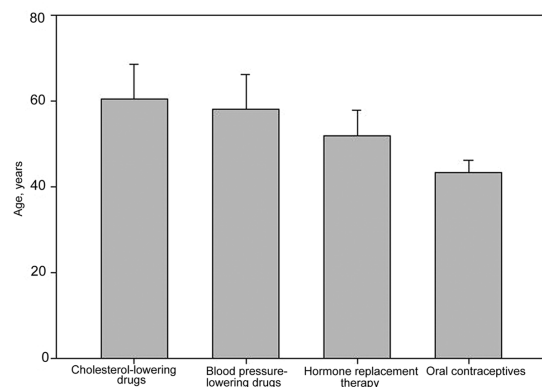


Figure 2. Age (mean \pm SD) of female subjects by medication. Oral contraceptive users were significantly younger than hormone replacement users ($P<0.05$, Tukey's range test). The hormone replacement users were significantly younger than users of cholesterol lowering medications and blood pressure lowering medications ($P<0.05$, Tukey's range test). There were no age-related data available for insulin users.

Table II. Association with mortality of cholesterol lowering medications, blood pressure lowering medications, insulin, hormone replacement and oral contraceptives.

| Sex | Type of drug | Count and % | Alive | Deceased | Total |
|----------------|-----------------------------|-----------------|--------|----------|-------|
| Female | Cholesterol-lowering | Count | 35 | 12 | 47 |
| | | % With drug use | 74.50% | 25.50% | |
| | Blood pressure-lowering | Count | 53 | 16 | 69 |
| | | % With drug use | 76.80% | 23.20% | |
| | Insulin therapy | Count | 5 | 2 | 7 |
| | | % With drug use | 71.40% | 28.60% | |
| | Hormone replacement therapy | Count | 29 | 2 | 31 |
| | | % With drug use | 93.50% | 6.50% | |
| | Oral contraceptives | Count | 17 | 1 | 19 |
| | | % With drug use | 94.40% | 5.60% | |
| No. of females | | Count | 103 | 21 | 134 |

The association was examined in 134 female subjects, 173 responses. The variability was insignificant ($P=0.077$, two-tailed Fisher's exact test).

Table III. Effect age and hormones on survival.

| | 95% LB | OR | 95% UB | P-value |
|----------|--------|-------|--------|---------|
| Age | 1.149 | 1.188 | 1.228 | <0.001 |
| Hormones | 0.102 | 0.477 | 2.240 | 0.348 |

Logistic regression was performed for hormone use (yes or no) and age, independent variables, and alive or deceased dependent variable. ORs, 95% confidence intervals (LB and UB) are shown. The effect of age on survival was significant ($P<0.001$) with survival decreased by a factor of 1.88 with each year of age. The effect of hormone use was not significant ($P=0.348$). OR, odds ratio; LB, lower bound; UB, upper bound.

Table IV. Association of nutritional supplements with mortality.

| Supplement | Count and % | Alive | Deceased | Total |
|-----------------------|-----------------|--------|----------|-------|
| Vitamin A | Count | 14 | 3 | 17 |
| | % With drug use | 82.40% | 17.60% | |
| Vitamin B | Count | 31 | 5 | 36 |
| | % With drug use | 86.10% | 13.90% | |
| Vitamin C | Count | 50 | 15 | 65 |
| | % With drug use | 76.90% | 23.10% | |
| Vitamin D | Count | 26 | 3 | 29 |
| | % With drug use | 89.70% | 10.30% | |
| Vitamin E | Count | 21 | 3 | 24 |
| | % With drug use | 87.50% | 12.50% | |
| Folate | Count | 17 | 5 | 22 |
| | % With drug use | 77.30% | 22.70% | |
| Multivitamins | Count | 128 | 35 | 163 |
| | % With drug use | 78.50% | 21.50% | |
| Total no. of subjects | Count | 189 | 49 | 238 |

Data are shown for 238 subjects, 356 responses. Variability was insignificant. The lower mortality associated with vitamin D and vitamin B (presumably B complex) has been previously observed (13,14). The variability was insignificant ($P=0.696$, two-tailed Fisher's exact test).

Table V. Association of mineral and other dietary supplements with mortality.

| Supplement | Count and % | Alive | Deceased | Total |
|------------------------------------|-----------------|--------|----------|-------|
| Fish oil (including cod liver oil) | Count | 166 | 40 | 206 |
| | % With drug use | 80.60% | 19.40% | |
| Glucosamine | Count | 97 | 27 | 124 |
| | % With drug use | 78.20% | 21.80% | |
| Calcium | Count | 39 | 11 | 50 |
| | % With drug use | 78.00% | 22.00% | |
| Zinc | Count | 28 | 6 | 34 |
| | % With drug use | 82.40% | 17.60% | |
| Iron | Count | 20 | 6 | 26 |
| | % With drug use | 76.90% | 23.10% | |
| Selenium | Count | 13 | 3 | 16 |
| | % With drug use | 81.30% | 18.80% | |
| Total no. of subjects | Count | 238 | 56 | 294 |

Data are shown for 294 subjects, 456 responses. The variability was insignificant ($P=0.983$, two-tailed Fisher's exact test).

Discussion

In hospitalized UKB COVID-19 patients, common comorbidities are hypertension, coronary heart disease, atrial fibrillation, type 2 diabetes and dementia. All these conditions are associated with an increased mortality (12).

Coagulopathy and blood clots are a significant adverse event in patients with COVID-19. Aspirin inhibits the coagulation due to its effect on platelets and has been reported to improve patient prognosis (3-5). The present study was not able to confirm this observation as the patients on aspirin in the current sample were significantly older and therefore less

likely to survive. Many patients were no doubt using aspirin for cardioprotection and/or arthritis. Clinical trials, as for example, the FREEDOM-COVID study (ClinicalTrials.gov identifier: NCT04512079), are attempting to determine the best anticoagulant strategy for patients admitted to general medical wards. The ranitidine bismuth citrate combination has been shown to suppress SARS-CoV-2 replication and to relieve virus-associated pneumonia in Syrian hamsters (16); however, this effect may not occur in patients with COVID-19 taking ranitidine. In the present study, ibuprofen-related mortality (12.4%) was lower than laxative-related mortality (30.8%), suggesting that ibuprofen does not worsen the clinical outcome (7,8).

Cholesterol-lowering medications, blood-pressure lowering medications, hormone replacement therapy and oral contraceptives seem to have minimal effects on patient outcome. The younger age of subjects on hormone replacement therapy and oral contraceptive users most probably explains their reduced mortality.

Nutritional supplements may increase survival. Mortality in an Italian nursing home during the COVID-19 pandemic was shown to be reduced with vitamin D supplementation (14). A vitamin D/magnesium/vitamin B12 combination in older-aged COVID-19 patients was associated with a significant reduction in the proportion of patients with clinical deterioration requiring oxygen support, intensive care support, or both (15). Vitamin D may be a critical host factor to prevent COVID-19 (17), although this hypothesis remains controversial (18,19). To prevent the cytokine storm, the use of *N*-acetylcysteine in both the prevention and adjuvant therapy of COVID-19 has been suggested; however, the UKB did not have information on this substance (20).

In conclusion, although some of the associations described herein among drugs and COVID-19 are not novel, the present study demonstrates the utility of a new source, the UKB, in further examining these associations. The association of lifestyle, comorbidities, medication and phenotypic information with patient outcomes will become an invaluable source as more UKB data become available on subjects tested for COVID-19 (21).

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Availability of data and materials

All data generated or analyzed during this study are included in this published article or are held by UK Biobank.

Authors' contributions

SL and PHR contributed equally to the conception, writing and data analysis of the present study.

Ethics approval and consent to participate

All patient data were from the UK Biobank. The UK Biobank application for the present study was approved as UKB project 57245, SL and PHR.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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