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PII: S2667-0968(21)00009-4
DOI: https://doi.org/10.1016/j.jjimei.2021.100016
Reference: JJIMEI 100016

To appear in: International Journal of Information Management Data Insights

Received date: 28 February 2021
Revised date: 10 May 2021
Accepted date: 11 May 2021

Please cite this article as: Amir Karami, Brandon Bookstaver, Melissa Nolan, Parisa Bozorgi, Investigating Diseases and Chemicals in COVID-19 Literature with Text Mining, International Journal of Information Management Data Insights (2021), doi: https://doi.org/10.1016/j.jjimei.2021.100016

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Investigating Diseases and Chemicals in COVID-19 Literature with Text Mining

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Abstract
Given the rapidly unfolding nature of the COVID-19 pandemic, there is an urgent need to streamline the literature synthesis of the growing scientific research to elucidate targeted solutions. Traditional systematic literature review studies have restrictions, including analyzing a limited number of papers, having various biases, being time-consuming and labor-intensive, focusing on a few topics, and lack of data-driven tools. This research has collected 9,298 papers representing COVID-19 research published through May 5, 2020. We used frequency analysis to find highly frequent manifestations and therapeutic chemicals, representing the importance of the two biomedical concepts. This study also applied topic modeling that provided 25 categories showing associations between the two overarching categories. This study is beneficial to researchers for obtaining a macro-level picture of literature, to educators for knowing the scope of literature, and to policymakers and funding agencies for creating scientific strategic plans regarding COVID-19.

Keywords: Chemical, Drug, Disease, Symptom, Text mining, SARS-CoV-2, COVID-19, Literature

1. Introduction
An unprecedented outbreak of pneumonia of unknown etiology in Wuhan City, Hubei province in China, emerged in December 2019. In January 2020, the World Health Organization (WHO) declared the Chinese outbreak of COVID-19 to be a Public Health Emergency of International Concern, posing a high risk to countries with vulnerable health systems [1]. In March 2020, the World Health Organization announced the COVID-19 pandemic. As of June 16, 2020, the number of positive cases was more than 8 million globally, with over 438,000 deaths [2]. These numbers continue to rise daily, and this pandemic has impacted nearly all aspects of life with schools closed, many businesses shuttered, travel curtailed, and major sports events canceled.

The WHO emergency committee has stated that the spread of COVID-19 may be interrupted by early detection, isolation, prompt treatment, and the implementation of a robust system to trace contacts.

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Other strategic objectives include a means of ascertaining clinical severity, the extent of transmission, and optimizing treatment options [3]. The outbreak has posed significant threats to international health and the economy. In the absence of treatment for this virus, there is an urgent need to find alternative methods to find possible solutions from the current literature.

In March 2020, the White House Office of Science and Technology Policy issued a call to action to the Nation’s artificial intelligence experts to utilize text and data mining techniques that can help the science community answer high-priority scientific questions related to COVID-19. This call to action addresses the fact that the vast majority of research scientists cannot afford to spend copious amounts of their time analyzing this growing literature dataset. Also, the traditional systematic literature review is a time-consuming and labor-intensive process. Therefore, computational methods can help experts rigorously find unbiased, statically meaningful patterns in COVID-19 literature. This study identifies and investigates clinical manifestations of disease and therapeutic chemical compounds in COVID-19 research papers and discloses the relationship between diseases and chemicals.

2. Literature Review

To summarize research papers on a specific topic, researchers develop traditional surveys that involve finding, evaluating, and analyzing relevant publications [4]. Several traditional literature review surveys were developed on the COVID-19 pandemic [5]. The surveys have focused on some main issues, including symptoms (e.g., fever [6]), the coincidence of COVID-19 and other diseases (e.g., cardiovascular disease [7]), and treatments (e.g., using Remdesivir [8,9]). While the traditional literature review studies and current tools offer valuable information. However, these studies suffer from some limitations:

- First, researchers select a sample of relevant papers, not all related papers. For example, one recent study reviewed less than 150 research papers related to COVID-19 [10].
- Second, selecting a sample of relevant research by traditional approaches could be prone to various biases, such as focusing on specific journal articles or highly cited studies.
- Third, the traditional literature review process is a time-consuming and labor-intensive one.
- Fourth, current literature reviews are often topic-specific, limited to a few diseases or chemicals.
- Fifth, replicating results generated by previous review studies is a difficult task.
- Sixth, while research search engines (e.g., PubMed) provide access to research papers, they do not offer a data-driven tool or propose a limited analysis (e.g., LitCovid).

We developed a query from the PubMed website (https://pubmed.ncbi.nlm.nih.gov/advanced/) and found that more than 31 million documents were published between 1781 and 2020 on PubMed, that more than 127,000 of those documents contain “COVID-19.” This huge amount of text data shows that there is a need to explore large collections of research databases. Big data studies are associated with a wide range of domains, from academic libraries [11–13] to health recommender systems [14,15]. Big data is also a key component in biomedical research applications [16]. Big data mining methods have been very effective and efficient in automatically identifying patterns from big biomedical data. For example, text mining methods have been utilized for new biomedical discoveries [17]. Text mining includes “the methods of machine learning and statistics with the goal of recognizing patterns and disclosing the hidden information in text data” [18]. Text mining methods aim to obtain information from documents, discover novel patterns, and identify relationships between concepts [19].

To address the limitations of traditional surveys, big data and text mining methods can assist in investigating large sets of written word data in an efficient and effective way [20]. Text mining methods have been utilized for literature review surveys relevant to depressive disorder [21], wearable technology [22], biomedical [16,23], big data [24], medical case reports [25], services management and marketing [26]. However, text mining has not been used for analyzing infectious
diseases literature. This research provides a fast data-driven framework to analyze COVID-19 related papers to overcome the limitations of traditional literature review studies.

3. Methods

In this section, the construction of our dataset is described, followed by frequency analysis and relationship analysis (Fig. 1). We also provide more details on the application of topic modeling for this research.

3.1. Data

We used the COVID-19 article collection of LitCovid through May 5, 2020 [27]. This collection was annotated with six entity types, including gene, disease, chemical, mutation, species, and cell line. While we focused on chemical and disease concepts in this paper, future research could utilize the rest of the entities to provide a better understanding of the literature. The rest of our analysis is based on the identified chemical and disease concepts, not the whole text of the COVID-19 articles.

3.2. Frequency Analysis

Frequency analysis plays an important role in text mining. This analysis is based on measuring the frequency of chemical and disease concepts. This analysis shows the number of papers containing a disease or a chemical. This is a binary process to find whether a disease or a chemical was used in a paper. If a disease or a chemical occurred once or multiple times in a paper, it would be 1. Otherwise, it would be 0. Frequency analysis has been used for different applications such as opinion mining [28] and content analysis [29,30]. Frequency analysis starts with splitting a document into a sequence of tokens by space between words (terms). To apply frequency analysis to our data, we utilized the unnest_tokens function in the R tidytext package [31] and the count function in the plyr R package [32] to extract tokens and find the total frequency.

3.3. Relationship Analysis

Next, we turned our attention to find relationships between our two overarching categories. Co-occurrence analysis, clustering, and topic modeling can assist in identifying relationships between entities; however, we decided to use topic modeling because current literature illustrates better performance for topic modeling than co-occurrence analysis [33]. In addition, topic modeling can disclose the relationship between documents and clusters (categories) [34]. Topic models are a class of hidden variable models, structured distributions in which observed data interact with hidden random variables. With a hidden-variable model, the practitioner can posit a hidden structure in the observed data, and then learn that structure using posterior probabilistic inference.

Among different topic models, latent Dirichlet allocation (LDA) is a valid and popular model. LDA has been used for different applications [35] such as analyzing online reviews [36], social media data...
[37–42], biomedical literature [22], and neurology case reports [25]; this application to COVID-19 literature is novel. In our data, LDA assumes that there is an exchange between articles (documents) and biomedical concepts (words). LDA can find categories representing a cluster of related words (terms).

The outputs of LDA for n documents (papers), m words, and t categories, are two matrices. The first one is the probability of each of the words in each category or \( P(W_i|C_k) \), and the second one is the probability of each of the categories in each document or \( P(C_k|D_j) \) [30]:

\[
\begin{align*}
\text{Words} & \quad \begin{bmatrix} P(W_1|C_1) & \cdots & P(W_i|C_k) & \cdots & P(W_m|C_t) \\ \vdots & \ddots & \vdots & \ddots & \vdots \\ P(W_1|C_1) & \cdots & P(W_1|C_k) & \cdots & P(W_1|C_t) \end{bmatrix} & \quad \text{Categories} & \quad \begin{bmatrix} P(C_1|D_1) & \cdots & P(C_1|D_j) & \cdots & P(C_1|D_n) \\ \vdots & \ddots & \vdots & \ddots & \vdots \\ P(C_t|D_1) & \cdots & P(C_t|D_j) & \cdots & P(C_t|D_n) \end{bmatrix}
\end{align*}
\]

The top words in each category based on the order of \( P(W_i|C_k) \) represent the categories. To find the related documents (papers) for each topic, we sorted \( P(C_k|D_j) \) from the highest value to the lowest one. The top documents have the highest probability of being related to a category. To disclose the relationship between diseases and chemicals, we used LDA. Before applying LDA, we needed to estimate the optimum number of clusters. We utilized five methods, of which four were developed in the R ldatuning package [43] and the fifth method was \( c_v \) developed in the Python gensim package [44]. While the maximum value of the three methods of the five estimation methods shows the optimum point, the minimum value of the two methods illustrates the optimum point. To combine the result of the five methods, we used the Technique of Order Preference Similarity to the Ideal Solution (TOPSIS), which is a multi-criteria decision analysis method [45] developed in the R topsis package [46]. The output of TOPSIS offered the optimum number of clusters at 25.

We measured the log-likelihood for five sets and found that the log-likelihood reached its approximate maximum before 4000 iterations. To assess the robustness of LDA, we compared the log-likelihood for five sets of 4000 iterations. The comparison indicated no significant difference (p-value > 0.05) between the iterations regarding their mean and standard deviation (Fig. 2). Then, we used the Mallet implementation of LDA [47] to cluster diseases and chemicals. We set the number of topics and iterations at 25 and 4000, respectively. Appendix A shows 25 clusters of disease and chemical terms. Each term was labeled as a chemical (e.g., remdesivir, chemical) or a disease (e.g., infection, disease). We provided one research example offered by LDA for each cluster containing some of the terms in the cluster. These examples can assist researchers in having a better understanding of the relationships.
4. Results

The annotated collection with 9,298 records was obtained on May 5, 2020. We found 3645 disease-related and 2434 chemical-related terminology in the investigation (Table 1).

|            | #Tokens | #Unique Terms | Minimum Frequency | Max Frequency | Median |
|------------|---------|---------------|-------------------|--------------|--------|
| Chemicals  | 7612    | 2434          | 1                 | 318          | 1      |
| Diseases   | 33838   | 3645          | 1                 | 7100         | 1      |

Table 1: Statistics of Diseases and Chemicals

Frequency analysis of disease-related terminology assisted in finding highly frequent symptoms and clinical aspects of diseases. We did not apply any pre-processing methods (e.g., stemming) to allow opportunities for all relationships to develop in an unbiased manner. Fig.3 displays the top-50 list of disease-related terminology unearthed by our frequency analysis. Several overlapping clinical terms and iteratives were involved, including “SARS-CoV-2; COVID; coronavirus; COVID-19; coronavirus 19; novel coronavirus.” We removed the top four terms, including Covid-19, Infection, Coronavirus-2019, and Infected from Fig.3. A few trends were noted by frequency analysis of disease-related variables. First, multiple search terms are related to COVID-19 disease (n=16), highlighting the confusion around naming this clinical disease and the inconsistency of search terms and/or literature references used. A few of these terms include the virus’s common name ‘SARS-CoV-2,’ generalized ‘coronavirus,’ a shortened disease name of ‘covid,’ the provisional name ‘2019 n-CoV,’ and others. Second, a similar trend of multiple annotations of pulmonary disease terminology was noted. In general, vague terms were used more frequently (infection, pneumonia, fever, death) compared to less commonly used detailed clinical terms (cardiovascular, inflammation, dyspnea). Infectious disease transmission route terminology was infrequently used (zoonotic, respiratory). Comorbidities and risk factors for severe diseases were moderately referenced (diabetes, hypertension). Interestingly, geographical terms (e.g., United States, China, and Italy) or population specific terms (e.g., elderly, nursing home, and cruise ship) were not identified in our frequency analysis. Using the same methodology, we executed a frequency analysis of therapeutic chemicals related to SARS-CoV-2 infection. As noted in Fig.4, chemical compounds were notably less frequently utilized in the scientific literature than clinical manifestations of diseases.
Fig. 3. Top-50 High Frequent Disease-Related Terminology Identified via Frequency Analysis.
Fig. 4. Top-50 High Frequent Chemical-Related Terminology Identified via Frequency Analysis.
Compounds already licensed for use in other clinical conditions were the most commonly correlated terms: Lopinavir/Ritonavir (HIV), Hydroxychloroquine (Malaria), Remdesivir (Hepatitis C and Ebola), and Tocilizumab (Rheumatoid Arthritis). The involvement of a few terms was hard to distinguish (e.g., oxygen, carbon dioxide, nitrogen) between their relevance to pharmaceutical clinical trial measurement outcomes versus being a spill-over artifact of respiratory-related clinical manifestations of diseases. Additionally, a limitation of the frequency analysis was the inability to distinguish the interactions between multiple drug compounds, such as Lopinavir-Ritonavir. The full list of chemicals and diseases is available at https://github.com/amir-karami/COVID-19-Chemicals-Diseases.

Table 2: Summary of pertinent LDA Relationship Analysis.

| Category | Disease or Symptom | Chemical Element or Drug |
|----------|--------------------|--------------------------|
| C1 | Infection; SARS; COVID 19; Pneumonia; Inflammation | Serine; Oxygen |
| C2 | Coronavirus; Inflammation; Acute Respiratory Distress Syndrome; Coagulation; Disseminated Intravascular Coagulation; Sepsis | Tocilizumab; Vitamin D; Heparin |
| C3 | Coronavirus; Pneumonia; Inflammation; Immunodeficiency | Lopinavir/Ritonavir; Steroid; LPV/R; EEA |
| C4 | Infection; Coronavirus; Coughing; Cross Infection | Water; Alcohol |
| C5 | COVID Coronavirus; Corona Myocarditis | FFPs; Carbon Dioxide; Copper; LPV; TCM; Stainless Steel |
| C6 | Mortality | Remdesivir; Lopinavir; Ribavirin; Ritonavir; Chloroquine; Favipiravir; Oseltamivir |
| C7 | Middle East Respiratory Syndrome; MERS; SARS; Severe Acute Respiratory Syndrome; Pneumonia; Infections; Death | N/A |
| C8 | Malaria; Rheumatoid Arthritis; Rheumatides; SLE; Systemic Lupus Erythematosus; Autoimmunes | Hydroxychloroquine; Chloroquine; Chlorouquin; Phosphate; Barielitinib |
| C9 | Coronavirus; Infection; Anxious; SAR; CO; Infections | TCB |
| C10 | Coronavirus; Deaths; Infection; Infection; Emphasis; Multi Organ Failure; Toxicity | Oxygen; Colchicine; Situazione |
| C11 | Diabetes; Hypertension; Diabetes Mellitus; Mortality; Novel Coronavirus; Obesity; Diabetes; Respiratory Infections | Glucose; Ibuprofen |
| C12 | Cancer; Tumor; Bleeding; Lung Cancer; Malignancies; Hemorrhage | Formalin; Dexamethasone |
| C13 | Coronavirus; Acute Kidney Injury; Liver; Death | Nitrogen; Urea; Creatinine; Bilirubin |
| C14 | Cough; Fever; Infection; Pneumonia; Deaths | Oxygen |
| C15 | Fever; Cough; Fatigue; Diarrhea; Pneumonia; Dry Cough; Myalgia; Shortness of Breath; Vomiting; Dyspnea | N/A |
| C16 | Acute Respiratory Distress Syndrome; ARDS; Pneumonia; Respiratory Failure; Septic Shock; Death | Oxygen |
| C17 | Infection; Pneumonia; Ncov Infection; Fever; Deaths | N/A |
| C18 | Infection; Pneumonia | Water; Penicillin; Streptomycin; Dmenn; Carbon; PBS; Sds; Sulfic Acid |
| C19 | Coronavirus; Respiratory Syndrome; Pneumonia; Pleural Effusion; Pyoxia; Chest Tightness | Steroids |
| C20 | Inflammation; Viral Infection; Coronavirus Infection; Acute Respiratory Syndrome; Virus Infection; Toxicity; Fibrosis | N/A |
| C21 | Anxiety; Pain; Depression; Stress; Fatigue; Infectious; Psychiatric; Delirium | Melatonin |
| C22 | SARS Coronavirus Infection; Cytotoxicity; Acute Respiratory Infections | Hydrogen; Serine; Oligonucleotides; Glycine; Asparagus |
| C23 | Hypertension; Diabetes; Cardiovascular; Death; Respiratory Failure; Myocarditis; Infection | Aldosterone |
| C24 | Coronavirus; QT Prolongation; QT Cyst Prolongation | Hydroxychloroquine; Chloroquine; Azithromycin; Hqc; Tocilizumab; Cq; Qct |
| C25 | Viral Infection; Infection; Virus Infection; Toxicity; HIV | Lipid; ATP |

Table 2 provides a summary of our relationship analysis findings comparing disease-related and therapeutic chemical compound-related terminologies in Appendix A. The summarization of Appendix A is based on removing duplicate concepts and splitting each category into two parts: diseases or symptoms and chemical or drug. For example, category 1 in Appendix A contains the following terms: infection_disease, sars_cov infected_disease, infections_disease, pneumonia_disease,
serine_chemical, inflammation_disease, oxygen_chemical, sars_cov_infection_disease, critically_ill_disease, and covid_disease. This category contains five terms related to disease or symptoms, including infection, SARS, COVID19, pneumonia, and inflammation, and two terms related to chemical or drug, including serine and oxygen.

Each row of Table 2 shows a category, including the relationships between diseases and chemicals. For example, the first row shows C1 illustrating the relationships between five diseases (symptoms), including infection disease, SARS, COVID-19, pneumonia, and inflammation, between two chemicals, including serine and oxygen, and between the five diseases and two chemicals. While most categories contain statistically relevant combinations of terminology from both categories, four (C7, C15, C17, and C20) combinations did not result in chemical-associated terminology. This is likely due to the higher usage of disease-related terminology in current scientific literature, suggesting that current publications predominate on clinical manifestations of disease with a lower focus on therapeutic options.

5. Discussion

In just a few months, the COVID-19 literature has exponentially grown to over thousands of scientific publications [48]. The vast majority of research scientists cannot afford to spend their time analyzing this dataset. Also, the traditional literature review survey is a time-consuming and labor-intensive process. Therefore, computational methods can help experts find patterns in this dataset. This paper utilized text mining methods to identify associations between diseases and chemicals in thousands of COVID-19 papers. Our approach provided a bird's eye view to understand the importance of diseases and chemicals for researchers using frequency analysis and disclose their possible relationship using topic modeling. The frequency of the two bioconcepts showed the most discussed chemicals and diseases. The list of diseases contained diseases, conditions, sequela, and symptoms. The list of chemicals showed chemical elements and known drugs that have been utilized for non-COVID-19 diseases.

By April 2021, (MED1) remdesivir, (MED2) dexamethasone, (MED3) baricitinib, (MED4) anticoagulation drugs (e.g., heparin), (MED5) fever, aches, and pain reducers (e.g., ibuprofen), (MED6) Vitamin D, (MED7) tocilizumab, (MED8) monoclonal antibodies, (MED9) convalescent plasma, (MED10) bamlanivimab plus etesevimab (Alla), and (MED11) casirivimab plus imdevimab (Alla), were found to be helpful medications for hospitalized people [49,50]. While our data collection was developed in May 2020, our research identified seven (MEDs 1-7) out of the 11 medications.

On February 2021, the Center for Disease Control and Prevention (CDC) announced the following 11 COVID-19 symptoms: (S1) fever, (S2) cough, (S3) shortness of breath or difficulty breathing, (S4) fatigue, (S5) pains in muscle or body, (S6) headache, (S7) nausea or vomiting, (S8) diarrhea, (S9) new loss of taste or smell, (S10) sore throat, and (S11) congestion or runny nose [51]. Out of the 11 symptoms, this research identified eight symptoms (S1-S8).

On March 2021, CDC also announced medical risk factors that can lead to severe illness from COVID-19, including (RF1) cancer, (RF2) kidney disease, (RF3) lung diseases, (RF4) diabetes, (RF5) heart conditions, (RF6) HIV, (RF7) liver disease, (RF8) overweight and obesity, (RF9) down syndrome, (RF10) Immunocompromised state, (RF11) pregnancy, (RF12) sickle cell disease, (RF13) dementia, (RF14) smoking, (RF15) blood stem cell transplant, (RF16) stroke, and (RF17) substance use disorders [52]. Out of these 17 risk factors, eight factors (RF1-RF8) appeared in our findings.

5.1 Contributions to Literature

The detected diseases and chemicals can assist researchers in finding relevant studies. The relationship between diseases and chemicals in a category (1) can be used as hypotheses for further
investigation, (2) has the ability to help with long term effects from COVID-19, (3) assist with vaccine discovery and monitoring of vaccine-related effects, and (4) can show real word management patterns.

This study has some advantages over classic literature review research. First, while current research has analyzed a limited number of research papers, this study provided an analysis of thousands of papers. Second, traditional literature review studies utilized qualitative methods to develop a codebook based on a limited data sample of related papers. This approach might not capture all main patterns. However, this paper got the benefit of using machine learning methods without a codebook. Third, this study provided an efficient process to avoid the time-consuming and labor-intensive processes of traditional qualitative methods.

5.2 Implications for practice

With the rapid growth of biomedical research publications, there is a continuous need to systematically and efficiently analyze the publications. This study is beneficial to researchers for obtaining a macro-level picture of literature, to educators for knowing the scope of literature, to journals for exploring most discussed diseases and chemicals, and to policymakers and funding agencies for creating strategic science plans regarding COVID-19. This paper can also offer a new approach for academic libraries to facilitate identifying research trends and patterns of a large number of papers in not only COVID-19 but also other domains.

5.3 Limitations

While this study provides a new perspective on COVID-19 literature, it has some limitations. First, the data was collected from a single source. Second, this research focused on papers published in English. Third, we collected papers published by May 2020. Fourth, this study is limited to two biomedical concepts. Fifth, the categories of chemical and disease concepts do not show relationships or prescribed treatments. So, they should be seen as suggestions for medical practitioners. Sixth, we focused on the frequency and categories of diseases and chemicals. However, we did not consider the results of relevant studies. For example, we do not know whether the identified medicines were useful for COVID-19 treatment. Future work could address the limitations by collecting both English and non-English papers published during several years from multiple sources and analyzing other biomedical concepts such as genes.

6. Conclusion

The COVID-19 pandemic has impacted nearly every aspect of life and has posed significant threats to international health and the economy. In the absence of treatment for this virus, there is an urgent need to find possible solutions from the current literature. While traditional literature review studies provide valuable insights, these studies have limitations, including analyzing a limited number of papers, having various biases, being time-consuming and labor-intensive, focusing on a few topics, and lack of data-driven tools. This study fills the mentioned limitations and gaps in the literature and practice by analyzing diseases and chemicals with text mining methods in a corpus containing COVID-19 research papers and by finding associations between the two biomedical concepts. Appreciating this context is vital due to the lack of a systematic large-scale literature review survey and the importance of fast literature review during the current COVID-19 pandemic for developing treatments.

This study describes a cohesive research plan that will significantly help COVID-19 researchers streamline publication search for timely informed decision making. Better knowledge of COVID-19 literature should impact our understanding of biomedical concepts and provide better preparation for future waves of COVID-19 and other infectious diseases.
Conflicts of interest
The authors state that they have no conflict of interest

Acknowledgments
This work is partially supported by a xxx from xxx. All opinions, findings, conclusions, and recommendations in this paper are those of the authors and do not necessarily reflect the views of the funding agencies.

Appendix A.

25 categories, including ten diseases or chemicals and one research example containing some of the words in a category.

| C1 | Example | C14 | Example |
|----|---------|-----|---------|
| infection_disease |  | infected_disease |  |
| sars_cov_infected_disease | [53] | cough_disease |  |
| infections_disease |  | fever_disease |  |
| pneumonia_disease |  | infection_disease |  |
| serine_chemical |  | oxygen_chemical |  |
| inflammation_disease |  | infectio_disease |  |
| oxygen_chemical |  | pneumonia_disease |  |
| sars_cov_infection_disease |  | death_disease |  |
| critically_ill_disease |  | died_disease |  |
| covid_disease |  | mortality_disease |  |

| C2 | Example | C15 | Example |
|----|---------|-----|---------|
| mortality_disease |  | fever_disease |  |
| tocilizumab_chemical | [55] | cough_disease |  |
| coronavirus_disease |  | fatigue_disease |  |
| acute_respiratory_distress_syrdome_disease |  | diarrhea_disease |  |
| vitamin_d_chemical |  | pneumonia_disease |  |
| coagulopathy_disease |  | dry_cough_disease |  |
| disseminated_intravascular_coagulation_disease |  | myalgia_disease |  |
| heparin_chemical |  | shortness_of_breath_disease |  |
| sepsis_disease |  | vomiting_disease |  |
|  |  | dyspnea_disease |  |

| C3 | Example | C16 | Example |
|----|---------|-----|---------|
| coronavirus_disease |  | acute_respiratory_distress_syrdome_disease |  |
| novel_coronavirus_disease | [57] | ards_disease |  |
| pneumonia_disease |  | critically_ill_disease |  |
| infection_disease |  | pneumonia_disease |  |
| lopinavir/ritonavir_chemical |  | oxygen_chemical |  |
| steroid_chemical |  | mortality_disease |  |
| lrp/r_chemical |  | respiratory_fiure_disease |  |
| eea_chemical |  | died_disease |  |
| immunodeficiency_disease |  | death_disease |  |
| inability_disease |  | septic_shock_disease |  |

| C4 | Example | C17 | Example |
|----|---------|-----|---------|
| infection_disease |  | infection_disease |  |
| water_chemical | [59] | novel_coronavirus_infected_pneumonia_disease |  |
| alcohol_chemical |  | pneumonia_disease |  |
| coronavirus_disease |  | novel_coronavirus_pneumonia_disease |  |
| coronavirus_disease |  | infected_disease |  |
| coughing_disease |  | infections_disease |  |
| infected_disease |  | novc_infection_disease |  |
| covid_disease |  | fever_disease |  |
| cross_infection_disease |  | novel_coronavirus_infection_disease |  |
| hydrogen_peroxide_chemical |  | doaths_disease |  |

| C5 | Example | C18 | Example |
|----|---------|-----|---------|
| coronavirus_disease |  | water_chemical |  |
| corona_virus_disease | [61] | infected_disease |  |
| f_klg_chemical |  | pneumonia_disease |  |
| carbon_dioxide_chemical |  | penicillin_chemical |  |

[53] [54] [55] [56] [57] [58] [59] [60] [61] [62]
| C6 | Example | C19 | Example |
|----|---------|-----|---------|
| copper_chemical | lpv_chemical | tcm_chemical | coronary_syndrome_disease |
| infarction_disease | stainless_steel_chemical | streptomycin_chemical | dmem_chemical |
| carbon_chemical | pbs_chemical | sds_chemical | sialic_acid_chemical |
| C7 | Example | C20 | Example |
| middle_east_respiratory_syndrome_disease | infected_disease | sars_disease | severe_acute_respiratory_syndrome_disease |
| pneumonia_disease | infection_disease | infections_disease | death_disease |
| inflammation_disease | viral_infections_disease | viral_infection_disease | coronavirus_infection_disease |
| C8 | Example | C21 | Example |
| hydroxychloroquine_chemical | chloroquine_chemical | malaria_disease | rheumatoid_arthritis_disease |
| rheumatic_diseases_disease | chloroquine_phosphate_chemical | sle_disease | systemic_lupus_erythematosus_disease |
| autoimmune_diseases_disease | baricitinib_chemical | C10 | Example |
| C9 | Example | C22 | Example |
| coronavirus_disease | infection_disease | infected_disease | covid_disease |
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