IDENTIFYING SIDE EFFECTS OF SOME DRUGS USED IN COVID-19 TREATMENT

Abstract— **In order to increase the success in Covid 19 treatment, many drug suggestions are presented in the literature and clinical studies are shared. However, using more than one drug together can cause serious side effects in patients. Therefore, detecting drug-drug interactions of the drugs used will be of great importance in the treatment of Covid 19. In this study, interaction of 8 drugs used for Covid 19 treatment with 645 different drugs and possible side effect estimates were produced by using Graph Convolutional Networks. Organ systems and diseases in which these 8 drugs cause the most negative effects have been identified. In addition, it is known that some of these 8 drugs are used together in Covid-19 treatment. Side effects caused by using these drugs together are shared. With the experimental results obtained, it is aimed to facilitate the selection of drugs and increase the success of treatment in Covid 19 treatment according to the patient.**

Keywords— Covid 19, Graph Convolutional Networks, Drug Drug Interaction, Adverse Drug Reaction

I. INTRODUCTION

As of December 2019, a coronavirus species that can be transmitted from person to person has been identified in Wuhan, China (F. Wu et al., 2020). The disease called Covid-19 posed a risk to be declared as a pandemic by the World Health Organization (WHO) in a short time (WHO, 2020). As of the date of the study, more than 6.4 million people were infected with this disease and 373,334 people died. It is seen that scientists and researchers have published thousands of clinical trial results and articles in this process to provide treatment methods for the disease (Sanders et al., 2020). An important part of these studies examines the use of existing drugs for Covid-19 treatment and suggests possible treatment methods (Colson et al., 2020; Stebbing et al., 2020; Zhou et al., 2020).

One of the issues that should be examined before recommending a drug to the patient and after treatment is the side effects of the drug. Research shows that multiple drug use (polypharmacy) significantly increases drug side effects (Colley & Lucas, 1993; Guthrie et al., 2015). For older patients, the probability of polypharmacy is generally increased. However, studies clearly show that as the number of drugs used increases, the negative effects seen in patients also increase (Hajjar et al., 2007; Lavan & Gallagher, 2016; Tatum et al., 2019). Therefore, it is vital to predict drug-drug interaction (DDI) and adverse drug reactions (ADR) for the drug to be used in the treatment of a disease (Colley & Lucas, 1993; Pirmohamed et al., 2004). Knowing the side effects and DDI of the drugs recommended in Covid-19 treatment will play an important role in the success of the treatment.

According to statistical studies, the vast majority of Covid-19 patients are seen at age 50 and over (Sobotka et al., 2020). According to the results of polypharmacy studies, regular and multiple drug use is over 60% in this age group (Guthrie et al., 2015). When these two examinations are evaluated together, it is understood that the rates of multiple drug use of Covid-19 patients are quite high. For this reason, the importance of DDI studies increases in Covid-19 treatment. Recognizing the drugs used regularly by the patient is a factor that will directly affect the selection of the drugs to be used in the treatment process. Many studies show that treatment success has increased significantly thanks to patient-focused drug combinations (Makiani et al., 2017; W. Sun et al., 2016). The role of DDI studies to improve success in Covid-19 therapy is better understood with previous studies.

With advancing technology, alternative methods have been developed for clinical studies in DDI detection. Today, DDI researches are carried out with many computer-based methods (Zhao et al., 2010). In this paper, possible interactions of drugs used in Covid-19 treatment will be examined by using graph convolutional networks. The aim of the study is to create a projection on the interactions of drugs used in Covid-19 treatment with other drugs. In this way, it is aimed to contribute to increasing the success of the

treatment by reducing the negative effects of the drugs. Answers to the following questions were sought for each of the 8 drugs examined within the scope of the study.

- Which drugs used with this drug will have the most dangerous side effects?
- What are the most common side effects as a result of using another drug with this drug?
- Side effects caused by the drug are mostly for which disease or organ system?

II. RELATED WORK

Past studies are examined in two different sections. Firstly, DDI studies for Covid-19 treatment were investigated. Then, DDI studies and methods with different approaches were examined.

A. DDI Studies for the Treatment of COVID 19

Drug interactions for different drugs and disease groups were examined during the treatment of the disease. For example, it is recommended that the risks should be evaluated well before using Ritonavir / Lopinavir drugs in patients with kidney transplantation (Bartiromo et al., 2020). In addition, the need for guides to be prepared on this subject was emphasized. In a different study, possible effects of drugs were investigated according to the patients heart rhythm graphics (Roden et al., 2020). This research shares the side effects of the combination of Hydroxychloroquine and Azithromycin used together in Covid-19 treatment. In a more comprehensive research, interactions of 4 different drug groups were examined (Elens et al., 2020). In addition to these studies, there are websites that are opened to online access by universities and pharmaceutical research laboratories (*COVID-19 Drug Information*, 2020; *Medscape Drug Reference Database*, 2020; *Liverpool COVID-19 Interactions*, 2020).

B. Computer Based DDI Studies

Extracting complex relationships from big data has become possible with today's technology and data mining methods. Since the concept of DDI focuses on the relationships between drugs, many studies have been done on this subject with data mining methods (Vilar et al., 2018). In such studies, a corpus with pharmacological data on drugs is usually used. The next step is to apply data mining methods to extract relationships from this corpus (Hammann & Drewe, 2014; Iyer et al., 2014; Lorberbaum et al., 2016).

Another method of relationship extraction in information technologies is the use of neural networks (Niepert et al., 2016). These structures, consisting of nodes and edges, allow studies that can reveal the relationships between drugs when shown by graphs. Many studies have been presented to the literature with this approach (Lim et al., 2018; Liu et al., 2016; X. Sun et al., 2019). In these studies, nodes were interpreted as drugs, and edges were interpreted as interactions between drugs.

There are also DDI studies specific to a group of drugs or to drugs used to treat a disease, rather than focusing on the entire drug network. For example; various studies have been conducted for cancer prevention drugs (Jiang et al., 2020; Preuer et al., 2018) or for high blood pressure patients or medications used in treatment (Bacic-Vrca et al., 2010; Martha et al., 2015). In these studies, only the risks and interactions for the examined group are calculated. Therefore, in addition to a general medical corpus, additional data needs may occur with case or disease focus. However, it becomes possible to obtain faster results because it focuses on a certain region instead of the relationships formed on the whole network.

In 2018, a DDI research called Decagon was made which predict the interactions of 645 drugs. (Zitnik et al., 2018). The work done by Zitnik et al.'s is open to development and its models are shared so that it can be used in different projects. Then, a study (ESP) (Cohen & Widdows, 2017) representing semantic predictions in pharmacological data was combined with Decagon (Burkhardt et al., 2019). The work done by Burkhardt et al.'s is a resource for existing DDI researches, thanks to its rapid training and ease of reuse. In this study, in addition to the biomedical data and graph structure presented by Decagon, the infrastructure of the study conducted by Burkhardt is used.

III. MATERIAL AND METHODS

A. Datasets

In this study, data from the study shared by Burkhardt et al.'s and pre-trained vectors suitable for reuse are used (Burkhardt et al., 2019). The dataset cluster contains the following data from Decagon.

- 964 different polypharmacy side effects derived from a wider side effect dataset (Tatonetti et al., 2012), each seen at least 500 times.
- Graph network consisting of 645 drugs and 19085 protein nodes (4,651,131 drug-drug, 18596 drug-protein node)
- Graph network hosting protein-protein and drug-protein relationships (total 8,083,300 pieces)

Lite-Covid data set was used to determine the drugs used in Covid-19 treatment. Covid-19 focused articles published in Pubmed are updated daily and added to this dataset. As of the day of the study, there are bibliographic format and summaries of 17288 studies within the dataset.

B. DDI with Graph Convolutional Networks (GCN)

Convolutional Neural Networks (CNN) and GCN are quite similar in architectural structure. But the difference of GCN is that it uses graphs as input (Bastings et al., 2017). A standard GCN architecture is shown in Figure 1.

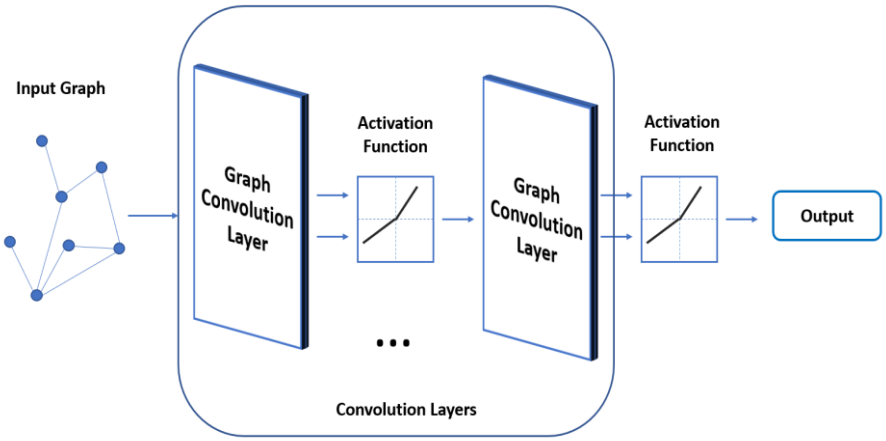

Fig 1. GCN Work Architecture

It is aimed to explore graph properties and signals for GCN (Kipf & Welling, 2019). It is assumed that each node has the properties it has from neighboring nodes and the relationships it establishes with these nodes (Z. Wu et al., 2019). Thanks to the Convolution layers and activation function (such as ReLU), the properties of all nodes are scanned. Depending on the study, the GCN output can be produced in different formats as a graph, feature or representation of bilateral relations.

Detection of relationships over biomedical data is one of the main study areas of GCN (Zhang et al., 2019). In DDI studies or graf-based studies for the detection of side effects and ADRs are available in the literature. Through these studies, DDI predictions are carried out with different approaches. In the Decagon study, a graph containing drug and protein nodes was created. This graph structure is shown in Figure 2.

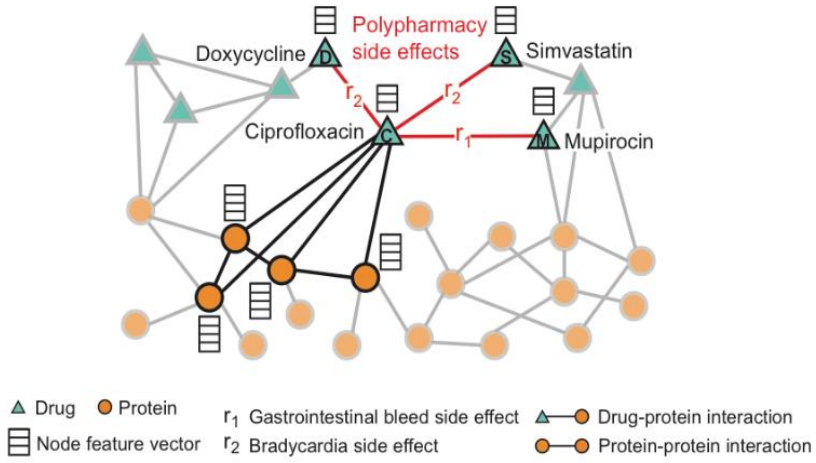

Fig 2. General view of the graph from the Decagon Study, where the nodes and their relationships are defined (Zitnik et al., 2018)

As seen in Figure 2, estimates of possible side effects are produced by examining drug-drug, drug-protein and protein-protein interactions. In the study, the graph seen in Figure 2 is used as the GCN input and the results of drug interaction (in the form of drug1, drug2, side_effects) are obtained as output. Using this infrastructure, Burkhardt et al.'s has also classified side effects according to diseases or organ systems (Burkhardt et al., 2019).

C. Choosing of The Target Drugs

In this study, a combination of three different sources was used to select the drugs whose interaction with other drugs would be calculated. The first is the Decagon study, in which we use the network infrastructure. Another source is the LitCovid dataset, which compiles Covid-19 oriented studies on PubMed. At the last stage, it is the online system called "covid19-druginteractions.org" that predicts drug interactions and is shared by Liverpool University.

Firstly, 645 drugs from the Decagon project were choosen in the 'drug_names' dataset, along with their drug names. In the next step, the frequency of being in the LitCovid dataset was measured for each of these drugs. Thus, it is aimed to identify the most mentioned drugs in Covid 19 studies published in PubMed. In order to measure how many times the drugs passed in the dataset, a series of operations were performed in the LitCovid data set. In order not to cause misleading results in the frequency calculation of the terms that are mentioned in the same article, only the abstract sections of the studies were searched. In this way, it is easier to measure how many papers includes a drug through and to get more consistent results. Data preprocessing steps have been applied to reduce the dataset only to the 'abstract' sections and make it searchable. On normalized data, 645 drugs were subjected to frequency measurement, respectively.

After frequency measurement on LitCovid dataset, 543 drugs were observed to never pass in the dataset. The average frequency of passing the remaining 102 drugs in the dataset was calculated as 9.06 on average. However, when we remove the 8 most frequently used drugs in this list, the frequency of passing the remaining 94 drugs in the dataset falls below 3. For this reason, experiments continued with a focus only on the first 8 drugs. The mentioned drugs are shown in Table 1 with the frequency of passing in the dataset. In addition, Table 1 shows whether the drugs obtained by the LitCovid scan are available in the system of www.covid19-druginteractions.org.

Table 1. Frequency of drugs according to LitCovid dataset and covid19-druginteractions.org

Drug Name	***Drug Frequency in LitCovid***	***Existence in the covid19-druginteractions.org system (Liverpool Uni.)***
Hydroxychloroquine	265	✓
Chloroquine	191	✓
Azithromycin	88	✓
Heparin	47	-
Clozapine	24	-
Ritonavir	15	✓
Ribavirin	13	✓
Atazanavir	6	✓

It has been observed that 6 of the selected drugs are also available on the 'www.covid19-druginteractions.org' website designed to show drug interactions for Covid-19.

Although Heparin and Clozapine drugs are not found in this system, they appear to be the subject of many studies for Covid-19 treatment (Leung et al., 2020; Perna et al., 2020; Tang et al., 2020; Thachil, 2020). Some of the studies on these drugs have been carried out in the form of clinical trials directly in patients with Covid-19. These studies show the use of drugs on the case. Considering their frequent history in the literature, Heparin and Clozapine drugs were included in this study.

D. Experiments

Experiments were carried out by modifying the project shared by Burkhardt and using the pre-trained vectors of this project (*GitHub - Hannahburkhardt/Predicting_ddis_with_esp: Predicting Adverse Drug-Drug Interactions with Neural Embedding of Semantic Predications*, n.d.). Thus, there was no need for the re-vectorization and training of the Decagon network of medicines and proteins. Only the drugs selected in the previous section were sent to the side effect estimation module used in the project as input. This module was then updated in the format for each input, where interactions with all drugs in the network are monitored and the 5 highest scoring results are produced. Whether the side effects defined in the project are included in any disease or organ system can be measured. In another update, all the side effect results resulting from the interaction of target drugs with other drugs were classified, and the organ systems and the disease groups that these drugs may cause the most were measured. The way the project works and its differences from previous works is shown in Figure 3.

Cue	Explanation	Result
P(KIDNEY_FAILURE)	What side effects occur in similar drug combinations as kidney failure?	1.000:KIDNEY_FAILURE 0.904:ACUTE_KIDNEY_FAILURE 0.871:ANAEMIA 0.870:CARDIAC_FAILURE
S(aspirin)⊗C(warfarin)	What side effects might be caused by taking aspirin and warfarin together?	0.363:FIBROSING_ALVEOLITIS 0.347:PAROTITIS 0.341:HAEMARTHROSIS 0.339:NECK_MASS

I

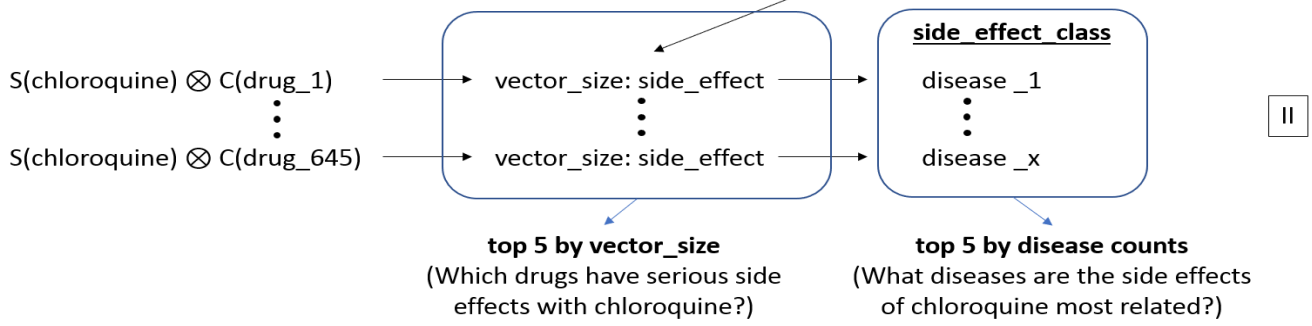

Fig 3. Updates on past studies and showing the logic of the current study with the example of Chloroquine. For Part I (Burkhardt et al., 2019)

The first part, shown as Section I in Figure 3, shows the arthitecture of the past study, while the second part represent the arthitecture of the current study. The vector representation shown in Figure 3 was created by adding the ESP study onto the Decagon study. These vectors are between 0 and 1, indicating that the effect will increase as you get closer to 1 and will decrease as you get closer to 0. Throughout the study, all other drugs shown in Table 1 were subjected to the same steps, with the Chloroquine shown in the example.

IV. Results And Discussion

In this section, the results for each of the drugs are examined under sub-headings. In order to compare the effects of the drugs in general, the chart with all drugs is presented in Figure 4. While creating the graphic shared in Figure 4, 645 drugs in the dataset were used. After the interactions of each drug examined, the resulting side effects were classified. If a drug causes the same side effect as 25 or more drugs, these side effects are added to the chart. Thus, the most common side effects of the 8 drugs used in the experiments in the same drug set were visualized.

While counting side effects, the seen of side effects rates were not taken into consideration. Regardless of these rates, the focus is on which disease group is mostly produced as a result of side effects. However, more detailed data are presented in tables in next headins, considering the rates of side effects.

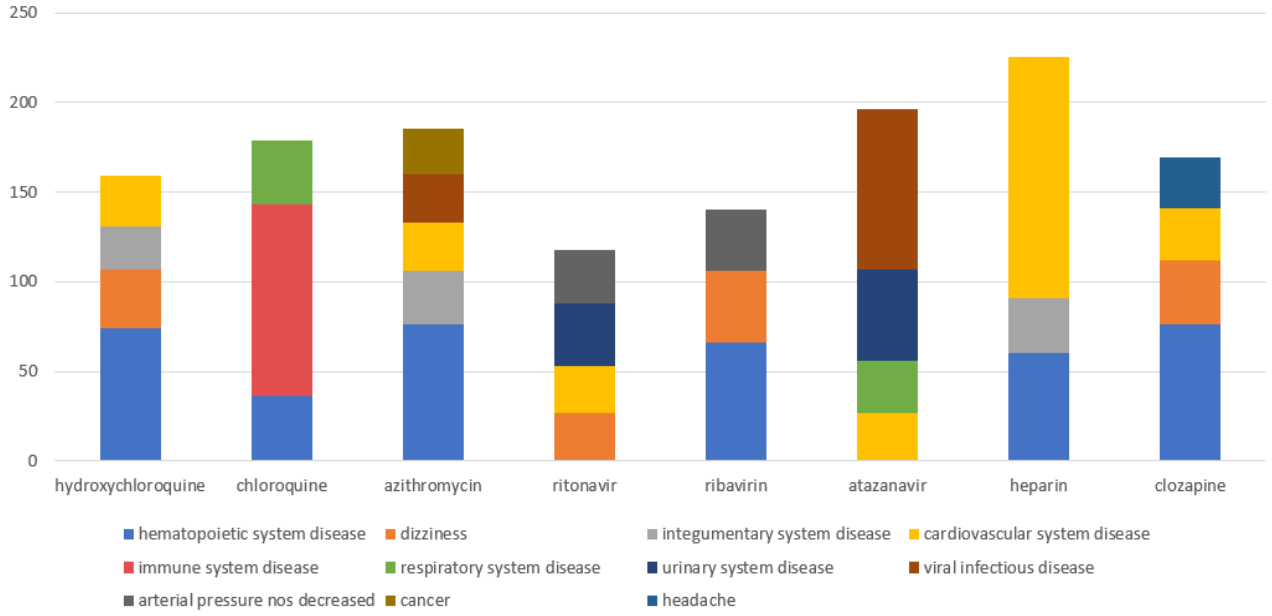

Fig 4. The most common side effects of drugs according to the results of the experiment

In Figure 4, it is shared which drugs or system side effects are most frequently seen. When the graphic is examined, it is possible to make inferences that Heparin has more cardiovascular system side effects than other drugs and Chloroquine causes more side effects on the immune system. These datas are important to create a general drug interaction projection. But the reactions of the drugs will be examined in more detail in the sub-headings.

According to Figure 4, it can be observed that the most common side effects of drugs are hematopoietic system diseases and cardiovascular system diseases. For this reason, patients with a diagnosis of Covid 19 positive, having any of these disease groups will be of great importance in treatment. Following this summary share, there are sub-headings for each drug that answer the questions below.

- Which are the most dangerous drugs to use with the drug?
- What are the most common side effects related to the use of other drugs with this drug?
- Common side effects are for which disease or organ system?

Ribavirin

According to the results obtained after the experiments, the drugs with the highest rate of side effects with Ribavirin are shown in Table 2. The table shows between 2 and 5 side effects for each drug. The reason for this variability is that different edges on the graph can show the same side effects.

Table 2. The riskiest drugs and possible side effects with Ribavirin concomitant.

Drug Name	***Side Effects That Can Be Seen With Ribavirin Concomitant***	***Side Effect Rates (0-1)***
pregabalin	ABNORMAL_GAIT	0.689
	BALANCE_DISORDER	0.680
	APTYALISM	0.678
	DIPLOPIA	0.675
fluticasone	ACUTE_BRONCHITIS	0.667
	POLYARTHRITIS	0.655

	BRONCHITIS	0.655
duloxetine	ANOSMIA	0.666
	EXCESSIVE_SLEEPINESS	0.658
	ABNORMAL_GAIT	0.654
valdecoxib	ARTHRITIS	0.663
	ACID_REFLUX	0.658
	OSTEOARTHRITIS	0.654
varenicline	APTYALISM	0.654
	AMNESIA	0.649
	INSOMNIA	0.647

As a result of the experiments, the riskiest drugs to be used with Ribavirin are listed in Table 2. Among the 644 other drugs used in the study with Ribavirin, the most common side effects are shown in Table 3. There is an important issue to be considered when examining the datas in this table. In the study, for the interaction of two drugs, a side effect prediction is always produced. These estimates vary between 0 and 1. Approaching the values to 1 increase the likelihood of side effects. Approaching the vector produced in the experiment to 0 may mean that it should be ignored, but all the side effects produced in the study were included in the calculation. For this reason, an alternative display is presented in second column, considering the rates of effects. In the second part of Table 3, while preparing the side effects column with the highest impact rate, the vectors created for that side effect are averaged. Tables will be created in the same format for other drugs to be examined later in the study.

Table 3. Side effects according to the average frequency and effect rate depending on drug use with Ribavirin.

Most Common Side Effects	***Number***	***Side Effects with the Highest Effect Rate***	***Side Effect Average (0-1)***
THROMBOCYTOPENIA	42	BALANCE_DISORDER	0.680
DIZZINESS	40	DIPLOPIA	0.675
ARTERIAL_PRESSURE_NOS_DECREASED	34	ACUTE_BRONCHITIS	0.667
ASPERGILLOSIS	27	ANOSMIA	0.666
NEUTROPENIA	26	ARTHRITIS	0.663

According to Table 3, due to the use of different drugs together with Ribavirin, it is likely that thrombocytopenia and dizziness complaints may be seen. However, even though it is not very common, in some drug combinations (such as ribavirin-pregabalin), the loss of balance and the possibility of double vision have been calculated to be quite high.

Chloroquine

The drugs with the highest rate of side effects in use with Chloroquine are listed in Table 4.

Table 4. Drugs with the highest rate of side effects when used with Chloroquine.

Drug Name	**Side Effects That Can Be Seen When Using With Chloroquine**	**Side Effect Rates (0-1)**
methotrexate	CANDIDA_INFECTION	0.639
	LUNG_NEOPLASMS	0.634
	ADENOPATHY	0.632
prednisolone	PELIOSIS	0.571
	INTERSTITIAL_NEPHRITIS	0.561
	BILIRUBINAEMIA	0.559
	AGRANULOCYTOSES	0.559

folate	HERPES_ZOSTER	0.555
	ADENOCARCINOMA	0.550
	ANGIITIS	0.548
	SKIN_LESION	0.548
omeprazole	ANGIITIS	0.548
	LUNG_NEOPLASMS	0.545
	NIGHT_SWEAT	0.544
lisinopril	BUNDLE_BRANCH_BLOCK_LEFT	0.546
	CARDIOMYOPATHY	0.536

When Table 4 is examined, Methotrexate, Prednisolone, Folate, Omeprazole and Lisinopril drugs together using with Chloroquine show the highest rate of ADR. The side effects seen with Methotrexate drug, which is generally used in cancer patients, are also mostly observed for cancer disease (Holmboe et al., 2012). These results can be interpreted as reducing the effect of Methotrexate if Chloroquine and Methotrexate drugs are used together. Because 'adenopathy' that affects the lymph nodes or 'lung neoplasms' in the lungs are often observed in cancer cases (Asamura et al., 2008; Gunn et al., 2013). It is possible to establish such connections in other drugs in the table. Table 5 examines the most common side effects with Chloroquine.

Table 5. Side effects according to average frequency and effect rate due to drug use with Chloroquine.

Most Common Side Effects	**Number**	***Side Effects with the Highest Effect Rate***	**Side Effect Rate (0-1)**
PRIMARY_BILIARY_CIRRHOSIS	107	CANDIDA_INFECTION	0.633
TRACHEITIS	45	ADENOPATHY	0.632
ANAEMIA_HYPOCHROMIC	36	LUNG_NEOPLASMS	0.589
KIDNEY_TRANSPLANT	35	PELIOSIS	0.569
CERVICAL_VERTEBRAL_FRACTURE	27	INTERSTITIAL_NEPHRITIS	0.561

According to Table 5, Chloroquine has the possibility of showing the side effect defined as 'primary biliary cirrhosis' with one of every 6 drugs in the experiment set. A study shows that this side effect is more effective on women (Nguyen et al., 2010). With the interpretation of such datas by experts, it is aimed to increase the success shown in Covid 19 treatment.

Ritonavir

Drugs with the highest rate of side effects when used with Ritonavir are listed in Table 6.

Table 6. Drugs with the highest rate of side effects when used with Ritonavir.

Drug Name	**Side Effects That Can Be Seen When Using With Ritonavir**	**Side Effect Rates (0-1)**
tenofovir_disoproxil_fumarate	BLOOD_IN_URINE	0.717
	ACUTE_KIDNEY_FAILURE	0.712
	HYPERGLYCAEMIA	0.711
atazanavir	INTERSTITIAL_NEPHRITIS	0.689
	ALLERGIC_DERMATITIS	0.683
	DISORDER_RENAL	0.682
	ASPARTATE_AMINOTRANSFERASE _INCREASE	0.681

tmc114	KIDNEY_FAILURE	0.657
	ANAEMIA	0.652
fosamprenavir	HEAD_ACHE	0.654
	NAUSEA	0.647
	FATIGUE	0.641
valganciclovir	SEPSIS	0.652
	PLEURAL_EFFUSION	0.643
	THROMBOCYTOPENIA-2-INV	0.639

It is seen that Ritonavir has a very high rate of side effects with the drugs described in Table 6. Among these drugs, special attention should be paid to Atazanavir. Because this drug is a drug that is examined in our study and used in Covid 19 treatment (Luykx et al., 2020). The side effects that may occur if the two drugs are used together are mentioned in detail in the subheading of Atazanavir. In Table 7, the most common side effects with other drugs are examined.

Table 7. Side effects according to average frequency and effect rate due to drug use with Ritonavir

Most Common Side Effects	Number	Side Effects with the Highest Effect Rate	Side Effect Rate (0-1)
RENAL_TUBULAR_ACIDOSIS	35	BLOOD_IN_URINE	0.712
ARTERIAL_PRESSURE_NOS_DECREASED	30	ALLERGIC_DERMATITIS	0.620
DIZZINESS	27	DERMATITIS_MEDICAME	0.589
HIV_DISEASE	27	NTOSA DISORDER_RENAL	0.610
CARDIOVASCULAR_COLLAPSE	26	BRONCHITIS	0.604

According to Table 7, the most common side effect of Ritonavir is seen as 'renal tubular acidosis'. The reason for 'hiv disease' among other popular side effects is the use of Ritonavir in HIV treatment (Orrell et al., 2017). This result shows that some drugs reduce the effect of Ritonavir (on HIV) and cause it to lose its treatment properties.

Azithromycin

The drugs with the highest rate of side effects in use with Azithromycin are listed in Table 8.

Table 8. Drugs with the highest rate of side effects when used with Azithromycin.

Drug Name	Side Effects That Can Be Seen When Using With Azithromycin	Side Effect Rate (0-1)
thyroxine	ARTHRITIS_INFECTIVE	0.643
	VITAMIN_D_DEFICIENCY	0.628
	MACROCYTOSIS	0.626
	SOFT_TISSUE_INJURIES	0.625
bupropion	APPENDECTOMY	0.638
	HYPERMETROPIA	0.637
naproxen	ARTHRITIS_INFECTIVE	0.629
	HYPERMETROPIA	0.624
	APPENDECTOMY	0.623
	BLOOD_PRESSURE_ABNORMAL	0.620

nicotinic_acid	CEREBRAL_VASCULAR_DISORDER	0.622
	DRY_EYE	0.618
	CARCINOMA_OF_THE_COLON	0.615
acetaminophen	FIBROSING_ALVEOLITIS	0.617
	ANISOCORIA	0.615
	BRONCHIOLITIS	0.615
	ENCEPHALITIS_VIRAL	0.613

According to Table 8, the drugs with the highest rate of side effects in use with Azithromycin are seen as Thyroxin, Bupropion, Naproxen, Nicotinic Acid and Acetaminophen. In addition to these datas, Azithromycin and Hydroxychloroquine drugs are used together in Covid 19 treatment (Gautret et al., 2020). Interactions between these two drugs were calculated under the heading of Hydroxychloroquine. The most common side effects when using other 644 drugs with Azithromycin are shown in Table 9.

Table 9. Side effects according to average frequency and effect rate due to drug use with Azithromycin

Most Common Side Effects	Number	Side Effects with the Highest Effect Rate	Side Effect Rate (0-1)
THROMBOCYTOPENIA	39	APPENDECTOMY	0.630
NEUTROPENIA	37	MACROCYTOSIS	0.626
LYELL	30	HYPERMETROPIA	0.625
CARDIOVASCULAR_COLLAPSE	27	SOFT_TISSUE_INJURIES	0.625
BONE_MARROW_FAILURE	25	CEREBRAL_VASCULAR_DISORDER	0.622

According to Table 9, the most common side effects with Azithromycin are 'thrombocytopenia' and 'neutropenia'. These two side effects are included in the hematopoietic system with the classification in the experiments. Based on this data, special attention should be paid when using Azithromycin in patients with hematopoietic system disease in Covid 19 treatment.

Heparin

The drugs with the highest side effect rate when used with heparin are listed in Table 10.

Table 10. Drugs with the highest rate of side effects when used with Heparin

Drug Name	Side Effects That Can Be Seen When Using with Heparin	Side Effect Rate (0-1)
leucovorin	LEUCOPENIA	0.563
	HYPOGAMMAGLOBULINAEMIA	0.548
	DISORDER_LUNG	0.543
	MULTIFOCAL_LEUKOENCEPHALOPATHY	0.541
cytosine_arabinoside	HYPOGAMMAGLOBULINAEMIA	0.563
	BILIRUBINAEMIA	0.546
	MULTIFOCAL_LEUKOENCEPHALOPATHY	0.545
pamidronate	SOFT_TISSUE_INFECTION	0.562
	FISTULA	0.555
	PERIODONTAL_DISEASE	0.539
propofol	LYELL	0.559

	CEREBRAL_ARTERY_EMBOLISM	0.549
	CARCINOMA_OF_THE_COLON	0.615
bupropion	ANIMAL_BITE	0.548
	CLUSTER_HEADACHE	0.539
	DEFAECATION_URGENCY	0.536
	MUMPS	0.532

According to Table 10, the rates of side effects of Heparin do not reach 0.6 in any drug. Among the drugs examined within the scope of the experiments, this ratio stands out as the lowest level. Other drugs with the highest rate of ADR were Leucovorin, Cytosine Arabinoside, Pamidronate, Propofol and Bupropion. Although the rate of side effects with these drugs is low compared to other test drugs, especially the excess number of side effects shown on the cardiovascular system is clearly seen in Figure 4 and Table 11.

Table 11. Side effects according to average frequency and effect rate due to drug use with heparin

Most Common Side Effects	Number	Side Effects with the Highest Effect Rate	Side Effect Rate (0-1)
CARDIOVASCULAR_COLLAPSE	70	CLUSTER_HEADACHE	0.539
HEART_ATTACK	64	PERIODONTAL_DISEASE	0.539
LYELL	31	HYPOGAMMAGLOBULINAEMIA	0.537
NEUTROPENIA	30	DERMATITIS_EXFOLIATIVE	0.537
THROMBOCYTOPENIA	30	STATUS_EPILEPTICUS-INV	0.533

According to Table 11, Heparin can cause discomfort in the cardiovascular system for one out of every 5 drugs in the test set. The effects of this drug on the cardiovascular system and side effects such as thrombocytopenia are supported by past studies (Su et al., 2005; Walenga & Bick, 1998). For this reason, other diseases of the patient should be taken into account in the process of using Heparin for individual or drug combinations in Covid 19 treatment.

Hydroxychloroquine

In Table 12, five drugs with the highest rate of side effects are shared when used together with Hydroxychloroquine.

Table 12. Drugs with the highest rate of side effects when used with Hydroxychoroquine

Drug Name	Side Effects That Can Be Seen When Using With Hydroxychloroquine	Side Effect Rate (0-1)
rofecoxib	CERUMEN_IMPACTION	0.645
	EASY_BRUISABILITY	0.633
	SPONDYLITIS	0.633
	SOFT_TISSUE_INJURIES	0.625
salbutamol	CHOLECYSTITIS_ACUTE	0.631
	ATRIAL_SEPTAL_DEFECT	0.618
	ENDOCRINE_DISORDER-2	0.616
quetiapine	NEPHROGENIC_DIABETES_INSIPIDUS	0.627
	SCHIZOAFFECTIVE_DISORDER	0.623
	PSYCHOSEXUAL_DISORDER	0.620
acetaminophen	SERUM_SICKNESS	0.623
	DUODENAL_ULCER_PERFORATION	0.622
	HYPOGAMMAGLOBULINAEMIA	0.620

	NODULE_SKIN	0.619
azithromycin	HYPERLIPAEMIA	0.620
	NEPHROSCLEROSIS	0.616
	HERNIA	0.606

The five riskiest drugs used with Hydroxychloroquine are shared in Table 12. Particular attention should be paid to the use of Hydroxychloroquine with Azithromycin. As mentioned previous, both drugs are used in Covid 19 treatment. In case of using these drugs together, side effects such as 'hyperlipidaemia' and 'nephrosclerosis' occur. In previous studies, it is seen that both of these side effects cause hypertension (Freedman et al., 1995; Krone & Müller-Wieland, 1990). Concomitant use of these drugs can be considered dangerous in patients at risk of hypertension. These datas contribute to increase the success in Covid 19 treatment in line with the main goal of the study. In Table 13, the most common side effects related to the use of Hydroxychloroquine are shared.

Table 13. Side effects according to average frequency and effect rate due to drug use with Hydroxychloroquine

Most Common Side Effects	Number	Side Effects with the Highest Effect Rate	Side Effect Rate (0-1)
THROMBOCYTOPENIA	42	EASY_BRUISABILITY	0.633
DIZZINESS	33	HYPERLIPAEMIA	0.620
NEUTROPENIA	32	NODULE_SKIN	0.619
CARDIOVASCULAR_COLLAPSE	28	ERYSIPELAS	0.615
LYELL	24	SCLERODERMA	0.611

According to the experimental results shown in Table 13, one of the most common side effects related to the use of Hydroxychloroquine is seen as 'Thrombocytopenia'. This data is also supported by past studies (Demir et al., 2014). In addition, it can be seen that it may cause dizziness due to its use with 33 different drugs. The general view of the side effects of the drug according to the systems is detailed in Figure 4.

Atazanavir

In Table 14, five drugs with the highest rate of side effects are shared when used with the drug Atazanavir.

Table 14. Drugs with the highest rate of side effects when used with Atazanavir.

Drug Name	Side Effects That Can Be Seen When Using With Atazanavir	Side Effect Rate (0-1)
lamivudine	DERMATITIS_MEDICAMENTOSA	0.642
	HEPATITIS_TOXIC	0.641
	LYMPHOMA	0.640
	PELIOSIS	0.636
ritonavir	LYMPHOMA	0.589
	NEPHROTIC_SYNDROME	0.589
	DERMATITIS_MEDICAMENTOSA	0.588
	PELIOSIS	0.584
efavirenz	DERMATITIS_MEDICAMENTOSA	0.571
	NEPHROTIC_SYNDROME	0.571
	LYMPHOMA	0.570
	DISEASE_OF_LIVER	0.567

indinavir	NODULE	0.570
	HERPES_SIMPLEX	0.567
	HIVE	0.567
didanosine	DISEASE_OF_LIVER	0.556
	DERMATITIS_MEDICAMENTOSA	0.556
	NEPHROTIC_SYNDROME	0.555

As a result of the experiments, the riskiest drugs to be used with Atazanavir are listed in Table 14. Among these drugs, Ritonavir, which is in the second place, draw attention. Because this drug is similarly used in Covid 19 treatment. For this reason, the side effects of the two drugs together should be carefully examined. In addition to the side effects seen in these drugs, Table 15 presents the most common side effects related to Atazanavir use.

Table 15. Side effects according to the average frequency and effect rate of drug use associated with Atazanavir.

Most Common Side Effects	Number	Side Effects with the Highest Effect Rate	Side Effect Rate (0-1)
HIV_DISEASE	89	HEPATITIS_TOXIC	0.575
RENAL_TUBULAR_ACIDOSIS	51	CYST	0.573
CRYPTOCOCCOSIS	47	NODULE	0.569
PNEUMOCYSTIS_CARINII_PNEUMONIA	29	DISEASE_OF_LIVER	0.567
CARDIOVASCULAR_COLLAPSE	27	HIVE	0.567

According to the experiments, the most common side effect of Atazanavir due to multiple drug use is seen as 'hiv_disease'. Frequent occurrence of this side effect can be interpreted as the effect of Atazanavir is restricted by 89 different drugs. Because Atazanavir drug is known as a drug used in HIV treatment (Wood, 2008). When these datas are evaluated, it can be concluded that many drugs can suppress the effect of Atazanavir in Corona 19 treatment. In addition, 'toxic hepatitis' is seen in the first place among the ADRs seen with the highest effect rate in Table 15. In previous studies, the increase of bilirubin value due to the use of Atazanavir singularly or with Ritonavir has been found to be due to toxic hepatitis (Burger et al., 2008). Although the other values remained constant in the serum analysis, the change of this value was observed. With the anticipation of such side effects, success is expected to increase in Covid 19 treatment.

Clozapine

As a result of the experiments, the drug estimates that will produce the highest rate of side effects with Clozapine are shared in Table 16.

Table 16. Drugs with the highest rate of side effects when used with Clozapine.

Drug Name	Side Effects That Can Be Seen When Using With Clozapine	Side Effect Rate (0-1)
risperidone	PSYCHOSES	0.613
	EXCESSIVE_THIRST	0.611
	NARCOLEPSY	0.599
bupropion	BIRTH_DEFECT	0.606
	BLEEDING_GUMS	0.596
thyroxine	BLEEDING_GUMS	0.605
	NODULE_SKIN	0.601
	HYDRONEPHROSIS	0.600

	LUNG_NEOPLASMS	0.597
quetiapine	EXCESSIVE_THIRST	0.601
	PSYCHOSES	0.595
	ALCOHOL_CONSUMPTION	0.594
acetaminophen	HYDRONEPHROSIS	0.601
	MULTIFOCAL_LEUKOENCEPHALOPATHY	0.598
	NODULE_SKIN	0.598

Table 16 lists the drugs that cause the highest rate of side effects with Clozapine. The excessive psychological effects seen with the use of these drugs draw attention. This is because Clozapine is used in the treatment of schizophrenia or similar psychological disorders (Warnez & Alessi-Severini, 2014). Therefore, it is possible to conclude that some drugs suppress Clozapine's treatment effect. The most common side effects and rates with other drugs are presented in Table 17.

Table 17. Side effects according to average frequency and effect rate due to drug use with Clozapine

Most Common Side Effects	Number	Side Effects with the Highest Effect Rate	Side Effect Rate (0-1)
THROMBOCYTOPENIA	44	EXCESSIVE_THIRST	0.606
DIZZINESS	36	NODULE_SKIN	0.599
NEUTROPENIA	32	NARCOLEPSY	0.599
CARDIOVASCULAR_COLLAPSE	29	HYDRONEPHROSIS	0.598
HEAD_ACHE	28	LUNG_NEOPLASMS	0.597

According to Table 17, the most common side effect associated with polypharmacy together with Clozapine is seen as 'thrombocytopenia'. These results have been confirmed by past studies and have been reported that other side effects such as 'neutropenia' are also common with the drug (Kate et al., 2013). Within the scope of these datas, the effects of Clozapine use for therapeutic purposes for Covid 19 on the psychological system and hematopoietic system should be taken into consideration. It is also observed that the drug often causes side effects such as dizziness and headache.

****(CONCLUSİON)****

With the experiments, DDI estimates were produced for 8 different drugs known to be used in Covid 19 treatment. In this process, the infrastructures and results of past studies have been used (Burkhardt et al., 2019; Zitnik et al., 2018). Within the scope of the study, in order to be able to perform drug treatment according to the patient, the systems and diseases in which each drug has the most side effects have been identified. A projection is presented to create alternative drugs or methods in the treatment of patients with these diseases or at risk. In addition, other drugs with the highest probability of side effects were calculated. As a result of this calculation, it is aimed to contribute to Covid 19 treatment of patients who are in regular medication use. It is very important to determine if there is a possibility that the new drug will react negatively with the drugs used regularly by the patient. For this reason, five different drugs that produce the highest negative interaction score with each drug and their possible side effects were shared in the study. In this process, based on the literature, negative drug interactions of the drugs known to be used together in Covid 19 treatment were also noted. With the outputs obtained as a result of the experiments, suggestions that will contribute to the choices of drug treatment of experts against Covid 19 and facilitate their choices are presented.

In the study, five possible side effects were calculated for each drug to be used with the other drug. As a result of these procedures, 25.800 possible side effects occurred for 8 drugs. Since it is not possible to share this much data within the scope of the article, only the first 5 drugs with the highest side effect rate are reported. For this reason, it is planned to transfer the study to the web environment that can show all results. Another possible study in the future will be a web-based project that will list the negative effects of the two

drugs selected and indicate their rates. Similarly, a web infrastructure that controls the suitability of the drugs used for Covid 19 can be developed according to the current diseases and the drugs used by the patient. Increasing the dataset to more than 645 drugs will increase the contribution to the literature. Therefore, adding new drugs and proteins to the graph used in the current study is important in order to create an infrastructure that can be used in many DDI studies.

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