Covid19 Drug Efficacy Statistical Analysis

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Abstract: Recently, a new SARS-CoV-2 coronavirus named COVID 19 sparked panic worldwide. More than 1000 ongoing therapeutics were dealing with it. However, the efficacy of these treatments was still fuzzy. In this paper, we analyzed 4 main types of treatments individually and mutually based on clinical trials data. T-test, models like COX and GEE logistic regression are adopted to evaluate the efficacy.

1. Introduction
COVID19, recently breakout worldwide, is a type of infectious disease caused by SARS CoV-2.\textsuperscript{1} By now, there are 49.8 million confirmed cases founded in 235 countries and causes 1.25 million deaths.\textsuperscript{2} Currently, many countries are investigating effective vaccinations or therapeutics to slow down the spread. On February 4th, scientist Zhenming Jin et al. firstly released the crystal structure 6LU7 of Covid-19 main protease with inhibitor N3.\textsuperscript{3} On April 16\textsuperscript{th}, Germany scientist published a research suggesting their successful clinical test on the improved serine protease TMPRSS2 inhibitor.\textsuperscript{4} The United States has already started their Vaccination Phase 3 trial and authorized Remdesivir in COVID19 treatment.\textsuperscript{5,6} Russia, being the first country to register COVID19 vaccination, claimed their success in August.\textsuperscript{7} China, responding to the seriousness of disease, has proposed various treatment plans to the WHO.\textsuperscript{8} By far, more than 1000 therapeutics were under clinical examinations in the world. Unfortunately, there is still no authorized therapeutics for COVID19. Although many drugs are proposed to be used in the treatment and they all faced different difficulties including neutralizing the virus and maintaining the activeness of antibodies. The effectiveness of these drugs is still questionable. In this paper, we will analyze the efficacy of those drugs being used in the Covid-19 clinical trials and predict the prospect of COVID19 treatments.
2. Material and Methods

Our team collected data from different credible medical papers and governmental websites. We divided all the therapeutics into five main categories: Antivirus, Antibiotic, Anti-malarial, Anti-parasitic and Immunity Modifiers. Antivirus is the most popular category. (Fig. 1) Nearly half of the therapeutics aim to prevent the entry of the virus or stop virus replication. (Fig. 2) Immunity Modifiers is the second popular one and surprisingly also the most studied one by American scientist. (Fig. 2) However, it is too hard to analyze it alone because it is usually used in combination with other drugs and not many data were released to the public. Immunity modifiers alone do not have sufficient data to draw a valid conclusion. We chose 1 or 2 most frequently used therapeutics in hospitals from each 4 categories and then compare different parameters including mortality, length to cure and EC 50 to sequence the efficacy of the drugs. After concluding the most efficient therapeutic for each category, we made comparisons between different categories to choose which one is the most promising drug for now.

For antiviral category we choose the drug Remdesivir and Lopinavir-Ritonavir. Remdesivir blocks RNA dependent RNA polymerase. Lopinavir-Ritonavir is a HIV protease inhibitor which is proposed as treatment because of its high in vitro activity. For anti-malaria category we choose hydroxychloroquine since it received EUA in March. The mechanism is not clearly known, but some scientists believed that change of PH will prevent viral entry. We choose antibiotics drug Azithromycin, anti-parasitic drug Nitazoxanide and Ivermectin which all functioned well against viral infections in the past records.
3. Results

3.1 Antiviral

According to the clinical trials conducted in American Hospital, there is no significant difference between patterns of number of volunteers at risk versus time for Remdesivir. (Fig. 3) To scientifically prove it, we conducted a T-test to test the difference between the number of recoveries. The P value of the test is 0.91, which is greater than 0.05. As a result, there is no difference between the number of recoveries. (Table 1) However, the length of recovery is shortened according to the paper. The placebo group needs 15 days for recovery (CI interval; 13 to 19). It is longer compared to the 95% confidence interval for Remdesivir group, which is 9 to 12 days (The median is 11 days). Additionally, the hazard ratio for death is 0.70. These data all prove that Remdesivir is effective in speeding up the treatment and decreases the risk of death.

Table 1. T test on Remdesivir and Placebo

|          | Mean | Var   | Positive | df  | t Stat | P(T<=t) one-tail | t Critical one-tail | t (T<=t) two-tail | t Critical two-tail |
|----------|------|-------|----------|-----|--------|------------------|---------------------|------------------|-------------------|
| Remdesivir | 173.8| 41911 |
| Placebo  | 187.4| 39937 | 6        | 10  | -0.116 | 0.455            | 1.812               | 0.91             | 2.228             |

Similar to Remdesivir, there is no statistically significant improvement after taking Lopinavir-Ritonavir. (Fig. 3,Table 2) However, with the immunity modifier IFN-B, the combination group had a significantly shorter median recovery time (7 days [IQR 5–11]) than the control group (12 days [8–15]; hazard ratio 4.37 [95% CI 1.86–10.24], p=0.0010).18

Figure 3. Comparison clinical trial on Remdesivir, Lopinavir-Ritonavir

Table 2. T test on Lopinavir-Ritonavir and Placebo

|          | Mean | Var   | Positive | df  | t Stat | P(T<=t) one-tail | t Critical one-tail | t (T<=t) two-tail | t Critical two-tail |
|----------|------|-------|----------|-----|--------|------------------|---------------------|------------------|-------------------|
| Lopinavir-Ritonavir | 56.33| 1152.33| 3        | 4   | -0.256 | 0.405            | 2.132               | 0.811            | 2.776             |
| Placebo  | 63.33| 1097.33| 3        |      |        |                  |                     |                  |                   |
3.2 Antibiotics

In 2020 JAN 23, Eli S.R. et al. reported a medical research (Fig. 4). This research took a random sample of all admitted patients with laboratory-confirmed COVID-19 in 25 hospitals in New York which represents 88.2% of patients in the New York region. The primary outcome measurement is in-hospital mortality.

Table 3. T test on Azithromycin and Placebo

|     | Mean | Var  | Positive | df  | t Stat | P(T<=t) one-tail | t Critical one-tail | P(T<=t) two-tail | t Critical two-tail |
|-----|------|------|----------|-----|--------|-----------------|-------------------|-----------------|-------------------|
| Azi | 195.5| 107  | 4        | 6   | -1.177 | 0.142           | 1.94              | 0.284           | 2.447             |
| Placebo | 204.75 | 140.25 | 4       |     |        |                 |                   |                 |                   |

We applied a T-test to prove the antibiotics Azithromycin are effective for the COVID-19 treatment. In this T-test, the p-value is 0.2839, which is not very high. (Table 3) If the drug has no effect on the treatment, the p-value will be 1. In this case, we can say that this drug has an effect.

Figure 5. Mortality comparison between anti-biotics and anti-malaria

From this research, using an adjusted model (Table 4), the estimated direct-adjusted mortality at 21 days was 18.9% (95% CI, 14.3%-23.2%) with hydroxychloroquine alone, 10.9% (95% CI, 5.8%-15.6%) with azithromycin alone, and 17.8% (95% CI, 11.1%-23.9%) with neither drug. (Fig. 5) No significant mortality difference was found between hydroxychloroquine alone and azithromycin alone (adjusted HR, 1.92 [95% CI, 0.99-3.74]).

Table 4. Efficacy comparison between anti-biotics and anti-malaria

| Outcome                                      | Model Type          | Estimate (95%CI) Hydroxychloroquine alone vs neither drug | Estimate (95%CI) Azithromycin alone vs neither drug | Estimate (95%CI) Hydroxychloroquine alone vs Azithromycin alone |
|----------------------------------------------|---------------------|----------------------------------------------------------|----------------------------------------------------|---------------------------------------------------------------|
| In-hospital death (hazard ratio)             | Cox proportional hazards | 1.08 (0.63-1.85)                                          | 0.56 (0.26-1.21)                                      | 1.92 (0.99-3.74)                                               |
| Cardiac arrest (odds ratio)                  | GEE logistic regression | 1.91 (0.96-3.81)                                          | 0.64 (0.27-1.56)                                      | 2.97 (1.56-5.64)                                               |
| Abnormal ECG findings (odds ratio)           | GEE logistic regression | 1.50 (0.88-2.58)                                          | 0.95 (0.47-1.94)                                      | 1.58 (0.77-3.24)                                               |
3.3 Anti-malaria
Same as above, anti-malaria drug Hydroxychloroquine has no statistical improvement since the P value of the T-test is greater than 0.05. Therefore, there is no difference between the number of recoveries. (Fig. 6)

Figure 6. Comparison clinical trial on Hydroxychloroquine

In the crude, patients who had received hydroxychloroquine were more likely to have had a primary end-point event than patients who did not (hazard ratio, 2.37; 95% CI, 1.84 to 3.02). However, by employing a multivariable regression, we can find that there was no significant association between hydroxychloroquine usage and the composite primary end point (hazard ratio, 1.04; 95% CI, 0.82 to 1.32).19

3.4 Anti-parasitic
Antiparasitic, referring to drugs acting against parasite, are usually used to repel parasites. Throughout several experiments and researches, some scientists noticed that some antiparasitic possibly have effects on 2019-nCoV. There are two kinds of antiparasitic, nitazoxanide and ivermectin, being tested effective for SARS Cov-2 Virus.

3.4.1 Nitazoxanide
In the measurement carried out by research team from Wuhan Institute of Virology, three primary factors including cytotoxicity, virus yield, and infection rate were tested. According to the research, nitazoxanide can inhibit the 2019-nCoV effectively at a low-micromolar concentration (EC50 = 2.12 μM; CC50 > 35.53 μM; SI > 16.76).20

3.4.2 Ivermectin
In recent years, ivermectin was proved efficient on inhibiting the activity of various viruses. The research team led by Leon Caly conducted the experiment about the effect of ivermectin on 2019-nCoV. Based on experiments conducted by this research team, ivermectin can control virus duplication in 24 to 48 hours. At 24 h, there was a 93% reduction in viral RNA load in the samples.21

In conclusion, both nitazoxanide and ivermectin have a prominent effect in inhibiting 2019-nCoV in vitro experiment. Their actual effectiveness on human body and safety are still needed to be studied.
4. Conclusions

We surprisingly figured that the combination of lopinavir-ritonavir and IFN-B is the most effective treatment. The mortality is largely reduced. (Fig. 7) The combination treatment only takes 7 days for recovery, which is half of the time that Lopinavir-Ritonavir alone needed (16 days). Patients also heal faster compared to 11 days when using Remdesivir only. However, the comparison has its limitations. The sample size difference is huge. (Fig. 8) Also, not all the data is transparent to the public. We suggest involving more volunteers in the clinical test in the future and making data accessible to more researchers. Up till now, antiviral is the most promising category for researchers to investigate.

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