Cantaurus, Vol. 29, 10-15, May 2021 © McPherson College Department of Natural Science

Prevalent comorbidities in hospitalized coronavirus (COVID 19) cases: evidence from a meta-analysis

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ABSTRACT

The novel coronavirus (SARS-CoV-2) has been the cause of worldwide shutdowns and mask mandates. This modern pandemic has led to an increase in study on who this virus attacks, how it attacks/spreads, and how to prevent it. With vaccines starting to be released, it is important to continue study to make sure people are staying safe from this virus. To understand better who is most affected by the virus, this meta-analysis investigates prevalent comorbidities in hospitalized coronavirus cases. Previous studies have shown that certain comorbidities such as obesity and diabetes can lead to more severe cases in coronavirus patients. The study used four studies on patients in the United States. Patients who also showed any of these comorbidities were analyzed; obesity (BMI>30), morbid obesity (BMI>35), diabetes, hypertension, chronic kidney disease, coronary heart disease, congenital heart failure, and COPD. First prevalence in overall cases were analyzed. The results from these studies in a meta-analysis showed that the most prevalent hospitalized cases were respectively hypertension, obesity, diabetes, and morbid obesity. Next these comorbidities were analyzed to understand which comorbidities were more prevalent in severe vs non-severe cases. After running the meta-analysis, the trend for severe vs non- severe was the same, which hypertension being most prevalent in the severe cases. These results are important in understanding why certain individuals are more at risk, determining factors by which the disease attacks, and helping to find beneficial treatments for sick patients.

Keywords: *Coronavirus, comorbidities, severe, non-severe*

INTRODUCTION

In December of 2019, an illness with pneumonia like symptoms was reported in growing numbers in Wuhan, China. In the following weeks, multiple cases in China and other countries were being reported. By February 12th of 2020, the World Health Organization had called a public health emergency and had linked the disease to a novel coronavirus, or coronavirus disease 2019 (COVID-19) (ZY, Zu. MD, Jiang, PP, Xu, QQ, Ni. GM, Lu. LJ, Zhang. 2020). As the virus began to spread, hospitals became overwhelmed, causing panic. Patients hospitalized with severe cases reported symptoms of a dry cough, difficulty breathing, fever, and more. Most lethal cases resulted in respiratory failure from acute respiratory distress syndrome (ARDS) (P, Mehta. Et al. 2020). By early March, the pandemic started to seriously threaten spread in the United states, causing universities to send students home, business to have employees work from home, and states to go into lock down. Even with many protocols put in place to prevent the spread, as of September 7, 2020, the United States had reported 6,261,216 cases and 188,513 deaths, making the mortality rate around 3% (CDC). Researchers are constantly reporting different forecasts for future coronavirus infections and deaths, however without a vaccine, the numbers will continue to rise until there is a natural herd immunity. This would mean that around 70% of the population, or 200 million people would have to be infected and then recover from the infection (Mayo Clinic). While most young, healthy individuals can be infected and experience less severe symptoms, research has shown that increasing age, male sex, and comorbidities increase the chance for severe and lethal cases.

According to recent research done in the New York City area, three comorbidities resulted in more severe cases, hypertension, obesity, and diabetes. Other comorbidities include cancer, chronic respiratory disease, immunosuppression, kidney disease, and liver disease (S. Richardson et. Al. 2020). Upon original understanding, SARS-CoV and SARS-CoV-2 bind to cells through an angiotensin-converting enzyme 2 (ACE2). ACE2 receptors are important to the body as it maintains the pleurisy of the lungs, which is especially important to protecting the lungs during infections like the coronavirus. People with comorbidities can be at risk, as they do not express correct levels of the ACE2 receptor, which can leave them more susceptible (L, Fang. G, Karakiulakis. M, Roth. 2020). People with comorbidities may struggle with immune responses and therefore may be more contagious, than healthier individuals (Albashir, A.A.D.). This makes studying comorbidities associated with severe coronavirus infection is important. Previous studies and meta-analysis have investigated similar data on comorbidities and COVID-19; however, it is important to maintain research with this ever-growing and novel coronavirus-2. The objective of this meta-analysis is to look at more recent

research in the United states, to view comorbidities are most prevalent in severe coronavirus cases.

MATERIALS AND METHODS

A search was conducted on JAMA network and PubMed. The dates for the article search was from March 1, 2020 through present. The search terms included "COVID-19, comorbidity, hospitalized, and deaths. There were 484 results. Studies were selected if data was available for the following comorbidities: obesity (BMI>30), morbid obesity (BMI>35), diabetes, hypertension, chronic kidney disease, coronary heart disease, congenital heart failure, and COPD in patients with COVID-19, severe cases, and lethal cases. The search was also limited to studies done on patients in the United States. Studies had to have a sample size of at least 30. A PRISMA diagram shown in figure 1, shows that identification, screening, eligibility, and included articles. Articles were included if they were a prospective and retrospective case series, retrospective cohort study, or epidemiological governmental reports. No systematic reviews or articles were included. The following information was taken from each source: date of publication, author, country, age, sex, number of patients with COVID-19, percentage of comorbidities, hospital/ICU admissions, and fatalities.

After researching different statistical programs, STATA was chosen for its properties, and ease of analyzing the data. Pooled estimates were calculated for the prevalence of the defined comorbidities in total COVID patients and severe vs non-severe. Based on the different categories on severity in the studies, severe cases included ICU admission or death, and non-severe included hospitalized or alive. I^2 statistic of heterogeneity will be performed on the data. Data will be analyzed with a 95% confidence interval and displayed on forest plots applied with the random effects model.

RESULTS

4 studies were analyzed in the meta-analysis. The total sample size was 11,363. All 11,363 participants in the meta-analysis tested positive for COVID-19. 58.68% were male and 41.32% were female, with an average age of 61.28 years. All four papers gave data to report the prevalence of 8 comorbidities (obesity (BMI>30), morbid obesity (BMI>35), diabetes, hypertension, chronic kidney disease, coronary heart disease, congenital heart failure, and COPD) found in COVID-19 patients. Of the 8 comorbidities presented, the top four most prevalent among total cases included hypertension (64.49%, 95% CI [53.31-75.67]), obesity (45.09%, 95% CI [25.87-64.32]), diabetes (36.85%, 95% CI [31.06-42.65]), and morbid obesity (26.75% 95% CI [15.73-37.77]). X^2 tests of

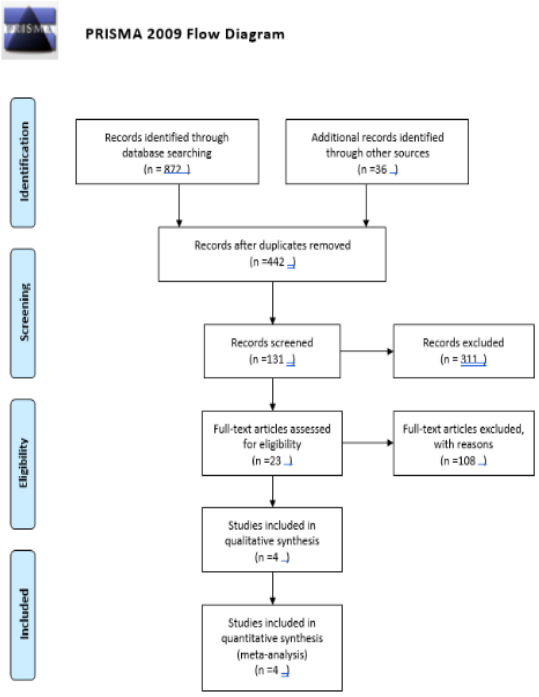

Figure 1. PRISMA flow diagram that was used to organize articles brought up from search conducted March 1, 2020 to present.

heterogeneity ranged from 90.98% to 99.22% (p=0.00), showing significant heterogeneity. Other less prevalent comorbidities included chronic kidney disease (21.65%), Coronary heart disease (14.29%), COPD (11.99%) and congestive heart failure (11.16%). Significant heterogeneity was seen in these groups as well except for congestive heart failure. All 95% confidence intervals are presented in figures 2 and 3.

3 of the 4 studies were used to analyze the prevalence of severe and non-severe cases in among the top 4 most common comorbidities. The results show that among the non-severe cases, the most to least relevant comorbidities were hypertension (53.32%, 95% CI [28.62-78.02]), Obesity (47.56%, 95% CI [24.25-70.88]), Diabetes (28.12%, 95% CI [16.12-39.83]), and morbid obesity (27.80%, 95% CI [9.71-45.88]). The X^2 test of heterogeneity ranged from 90.07%-97.34% suggesting significant heterogeneity.

In the severe cases, the same trend was followed ranked first (74.40%, 95% CI [53.42-95.37]), obesity (51.60%, 95% CI [38.83-64.38]), diabetes (43.99, 95% CI [30.76-57.23]), and morbid obesity (28.94%, 95% CI [16.54-41.35]). The tests of heterogeneity ran a little lower than that in the non-severe cases. However, were high enough to show significant heterogeneity. The results are shown in forest plots with the random effects model in figures 4 and 5.

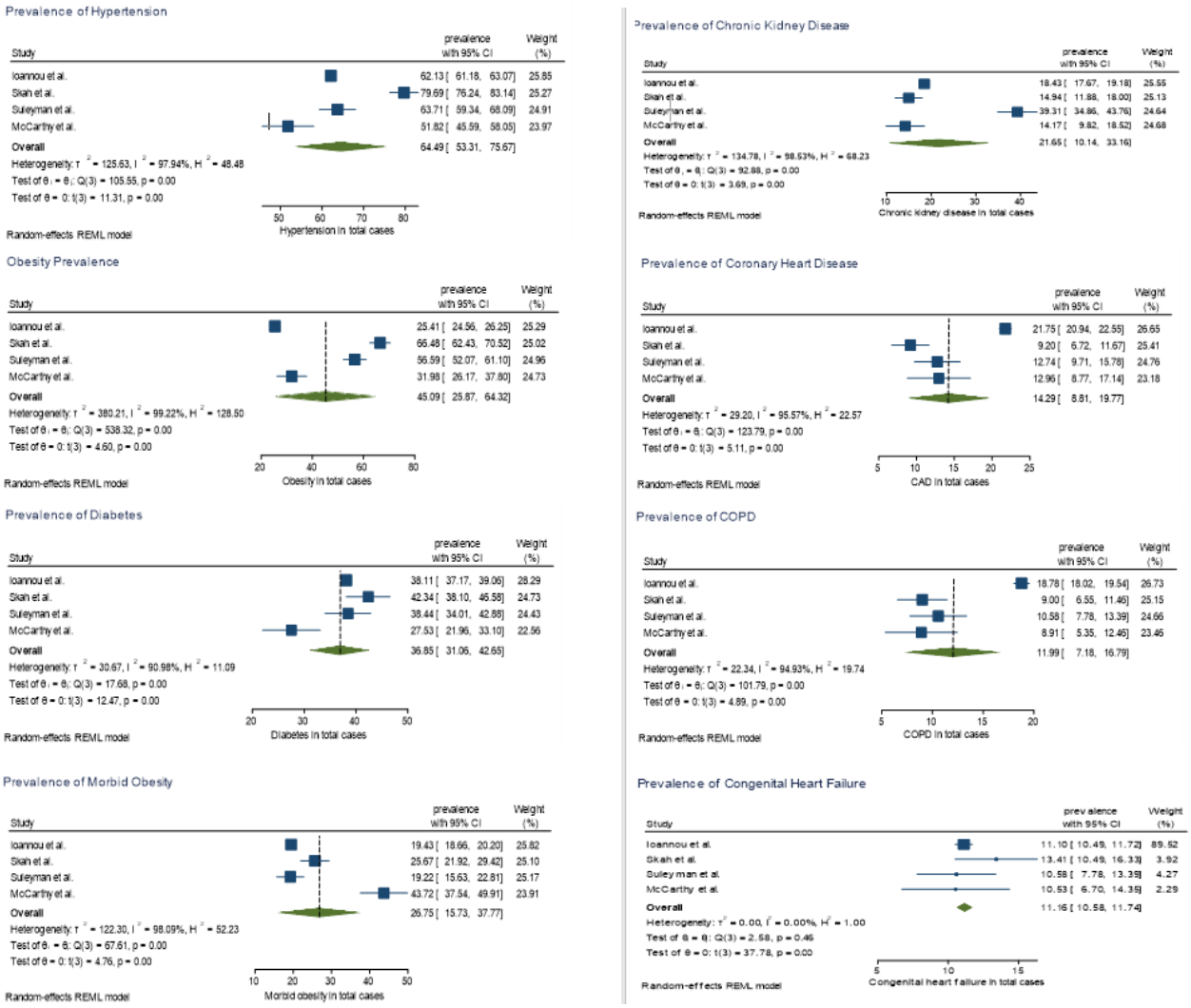

Figure 2. Prevalence of comorbidities; hypertension, obesity, diabetes, and morbid obesity. Tested for heterogeneity and a p-value of 0.00 and confidence interval of 95% on a random effects model.

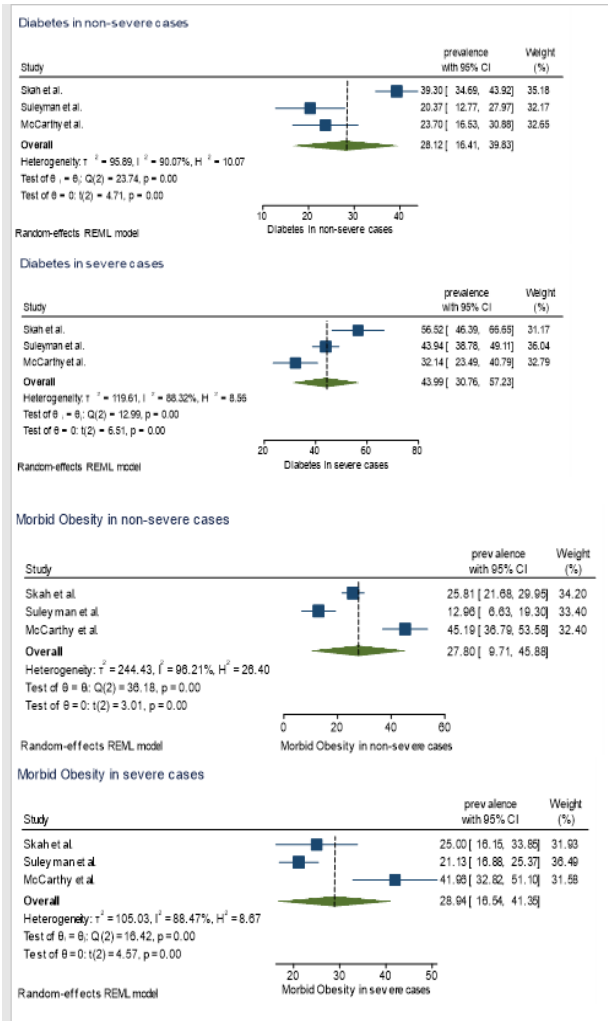

Figure 4. prevalence of severe and non-severe cases for diabetes and morbid obesity. All results performed on random effects model at a 95% confidence level and 0.00 p-value. Tested with X^2 heterogeneity.

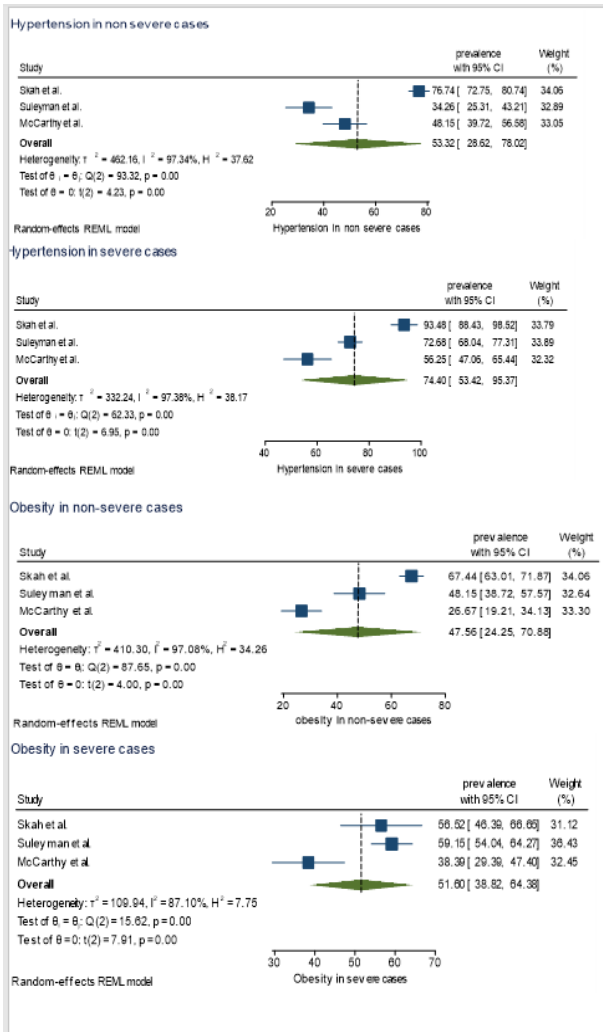

Figure 5. prevalence of severe and non-severe cases for hypertension and obesity. All results performed on random effects model at a 95% confidence level and 0.00 p-value. Tested with X^2 heterogeneity.

DISCUSSION

Increasing numbers of COVID-19 cases in the United States has lead to continual concern and overflow in the healthcare system. With efforts such as social distancing, mask mandates, and shut downs, it is importnatn to make sure that people stay safe, however more importantly higher risk patients safe. Early studies on COVID-19 patients suggested that comborbidites played a large role in the development of severe cases. The meta-analysis looked at the following comorbidities; obesity (BMI>30), morbid obesity (BMI>35), diabetes, hypertension, chronic kidney disease, coronary heart disease, congenital heart failure, and COPD, in severe and non-severe cases in patients in the United States. Results from this study can be helpful in identifying individuals more at risk, determining factors by which the disease attacks, and helping to find beneficial treatments for sick patients.

The results from the meta-analysis suggest that the top four comorbidities were hypertension, obesity, diabetes, and morbid obesity. When examining further, it was found the top four combordities that were most commonly found in severe cases ranked in the same way of hypertenstion, obesity, diabetes, and morbid obesity. Hypertension showed to be a significant combordity in all patients and very common in severe cases, however also showed to be most prevalent in the non-severe cases. This suggest that while people with hypertension have higher chances to feel more severe chances when they aquire the virus, there is also a decently high chance that they will recover. This also supports that covid is most prevelent in all cases. A previous study perfomred

among 5700 patients in New York revealed similar data with hypertension (56.6%), obesity (41.7%), and diabetes (33.8) (Richardson, S. Hirsh, JS. Narasimhan, M. Crawford, JM. McGinn, T. Davidson, KW. 2020). However other studies have reported diabetes being the most prevalent comorbidity (Mithal, A. Jevalikar, G. Sharma, R. Singh, Farooqui, KJ. Et. Al. 2020). The results also show that having any of the comorbidities gives a higher chance of having a severe case. In each of the meta-analyses done on severe vs non-severe cases, higher preveleances were seen in the severe cases for the top for comorbidities found. As this is still a new coronavirus, variances in studies are likely due to differences in the samples of the studies along with when these studies were examined.

It is important to examine what comorbidites are commonly presesnt in these cases to then understand why patients with these comorbidities tend to occupy the majority of severe cases. SARS-CoV-2 bind and have a strong affinity to target cells angiotension-converting enzyme 2 (ACE2). These enzymes are expressed in epithelial cells of the intestine, kidney, lungs, and blood vessels, and can reduce inflammation in these organs. This enzyme is not correctly regulated in both patients that have hypertension and diabetes, and are typically treated with ACE inhibitors and angiotensin II type-1 receptor blockers (ARBs), resulting in the upregulation of ACE2. It can be hypothesized that the increase of ACE2 activity can lead to the greater chance of SARS-CoV-2 entrance to the host cells (L. Fang, G. Karakiulakis, M. Roth 2020). This is a possible explanation for the prevalence of patients with severe cases having hypertension or diabetes. ACE2 can also be very over expressed in patients with obesity, as ACE2 is expressed significantly in adipose tissue. With increase of BMI, there is an increase in adipose tissue, and increase of ACE2 receptor expression. The adipose tissue may also account as a reserve that can contain a large viral load (Ianelli, A. Farve, G. Frey, S. Esnault, V. Gugenheim, J. Bouam, S. Schiavo, L. Tran, A. Alifano, M. 2020). This could be a reason for seeing the prevalence of obese and morbidbly obese patients in severe case categories.

Cytokine storm is another factor that ties many comorbidities together. The cytokine storm implies a hyperactive immune system that sends excess pro-inflamatory cytokines which can be harmful to the host by creating excess inflamation and organ failure (Sinha, P, Matthay, MA. Calfee, CS. 2020). This is a common phenomina seen in patients with COVID-19. Many studies suggest that ICU patients show higher levels of cytokine factors such as GCSF, IP10, MCP1, MIP1A, and TNFα than non-ICU patients. This would suggest that cytokine storm is more prevalent in severe cases, which by this meta-analysis is commonly people with comorbidities such as hypertension, diabetes, and obesity (Lucena, TMC. Silva Santos, AF. Lima, BR. Albuquerque Broborema, ME. Azevedo Silva, J. 2020). Cytokine storm can be very threatening, and these comorbidities only hinder the immune system more, allowing for cytokine storm to occur more often. People with diabetes already have an excessive pro-inflammitory response, mostly interleukin ((IL)-1, IL-6), and tumor necorsis factor ((TNF)- α). So when exposed to infections such as SARS-CoV-2, the response maybe exagerated even more (Pal, R. Bhansali, A. 2020). Simillarly, obese and morbidly obese patients who carry excess adipose tissue may be experiencing worse symptoms as their adipose tissue has preactivated cytokine factors (as listed previously). If Covid causes a cytokine storm, as shown in some studies, then in obese patients, the cytokine repsonse would be expressed at an even higher level (MacDaragh, P. Caplice, NM. 2020). This imbalance would cause the lungs to be unprotected and lead to worse symptoms and even death.

Vitamin D deficiency is a common trend amongs the comorbiditeis prevalent in this meta-analysis. Vitamin D deficiency can be considered a separate comorbidity by itself as it shows up to be prevalent in severe cases. In a recent study it was found that not only were more of their patient subjects with vitamin D deficiency hospitalized, but they needed more intnsive oxygen therapy and invasive mechanical ventilation. Respectively 22% and 64% of patients had vitamin D levels below 12 and 20 ng/mL (Radujkovic, A. Hippchen T. Tiwari-Heckler, S. Dreher, S. Boxberger, M. Merle, U. 2020.) Many studies have shown that vitamin deficiency is common in these comorbidites, creating an even weaker immune system. Vitamin D helps regulate the inflammatory responses in the body by decreasing the amount of iflammatory cytokines, and could therefore be helpful in preventing the cytokine storm (Aranow, C. 2012).

The meta-analysis has several potential limitations. All of the studies had significant heterogeneity as the definitions of severity for each article was different. The definition for severity for this meta-analysis included ICU adimitted patients and deaths. However this may have caused some bias in the statistical analysis. From study to study, age, gender, socioeconomic status, and ethnicities were not considered a factor. Many other studies show these facors to play an important role in the severity of cases. By not showing these factors, there may be missing influence. Another missing influence was current medications patients may have been on. It is understood that the comorbidities used in this meta-analysis often have ongoing treatments, however those were not taken into effect when running statistical analysis. It is also unknown if patients in the had one or more of the comorbidites, having more than one may have affected if they were categorized in the severe or non severe category. One of the

research articles included had significant data when showing which comorbidites were prevalent in all cases, however when it came to showing severe vs non-severe, it was not able to be included, due to the way data was presented.

While this meta-analysis shows that hypertension, obesity, diabetes, and morbid obesity were the most common comorbidites found in all cases and in severe cases, it is important to continually study this as the disease continues to spread. As recovered COVID-19 patients, will not have COVID-19 as a pre-existing condition, it will also be important to see how this intereacts with comorbidites moving forward. By using studies like this, connections can be made with the comorbidities and the mechanims that are being targeted by the virus. This further understanding will help in the gradaul reopening and may ease social distancing.

ACKNOWLEDGEMENTS

Thank you to the McPherson College Science department for all the continual support through this process. A special thanks to my advisors Dr. Karrie Rathbone and Dr. Jonathan Frye.

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