How Diabetes affects the outcome of COVID-19

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ABSTRACT

Current literature considers that individuals who have Type 1 and 2 diabetes are a vulnerable group and are at great risk of contracting COVID-19, risking increased complications, and higher mortality rate. Insufficient scientific research data can result in uncertain conclusions. Due to great necessity for quantitative descriptions of trends and predictions, researchers were forced to make assumptions to fill data gaps. The goal of this paper was to minimize uncertainty in the reviewed data outcomes. Varying results could have occurred from lack of research details, confounding factors, and assumptions made throughout data analysis. To resolve these issues, our study is composed of three parts: biological analysis of COVID-19 infection, summary of multiple sources to demonstrate data correlation, consistency with biological conclusions, and quantitative characterization. This study compares calculations of mortality odds ratio (OR) and hazard ratio (HR) fully adjusted for other comorbidities and those not fully adjusted for other comorbidities. Overall diabetes OR not fully adjusted is 3.85, and the fully adjusted one is 1.28. The Type 1 diabetes OR not fully adjusted is 3.51, and the fully adjusted one is 2.39 – 2.86. The Type 2 diabetes OR not fully adjusted is 2.03, and the fully adjusted one is 1.37-1.8. With age, mortality rates for diabetics increase significantly, especially with the presence of other underlying conditions. As an example, the HR calculated for individuals with impaired renal function - eGFR <15 in Type 1 diabetics is 8.35, and in Type 2 diabetics is 4.91.

Introduction

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has spread among millions of people and resulted in about 4 million deaths worldwide [1]. The World Health Organization labelled the virus as COVID-19 [2]. The virus infects the body by the binding its spike protein to the angiotensin-converting enzyme 2 (ACE2) which is located in many different tissues in the body [3]. This can cause great damage to the upper respiratory tract, as well as to lungs, heart, and kidneys. Pre-existing conditions, such as type 1 and type 2 diabetes [4,5], increase the risk of developing a case of COVID-19 with greater chances of severe disease progression or death [6]. This paper presents the most reflective literature results that show the impact of Type 1 and Type 2 diabetes on the outcome of COVID-19 infection. To accomplish this goal biological mechanisms of COVID-19 that determine the connection between diabetics and COVID-19 infection were analyzed. Multiple sources of data were reviewed and filtered to select consistent and correlated medical data aligned with biological concepts. The selected data sets were used for quantitative characterization of mortality rates among diabetics.

1. Biological concepts of COVID-19: influence of diabetes

COVID-19 biological nature and transmission of the virus were described in a number of papers [7,8,9, 10, 11]. Covid-19 is a single-stranded RNA-enveloped virus [4]. The spike (S) protein of SARS – CoV-2 which plays a key role in the receptor recognition and cell membrane fusion process, is composed of two subunits, S1 and S2. The S1 subunit contains a receptor-binding domain that recognizes and binds to the host receptor ACE2, while the S2 subunit mediates viral cell membrane fusion by forming a six-helical bundle via the two-heptad repeat domain.

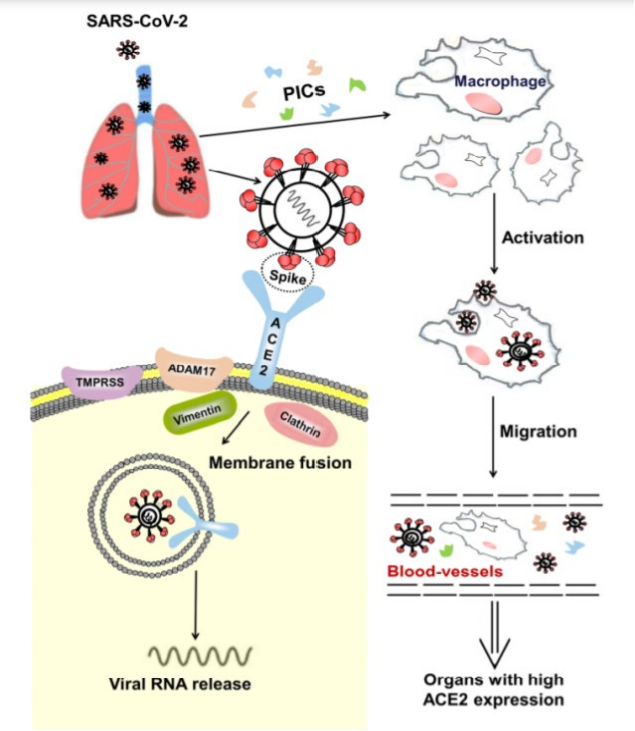

Fig 1. COVID-19 binding to ACE2 receptors, and infection process [7].

This model demonstrates how the spike protein binds to the ACE2 on cells which initiates a cascade of harmful effects. Membrane proteins including transmembrane protease serine 2 (TMPRSS2) and disintegrin metallopeptidase domain 17 (ADAM17) also play a role in infection. After the spike protein binds to ACE2, the virus ACE2 complex undergoes receptor mediated endocytosis which allows the virus to enter cells. Receptor mediated endocytosis is a process where specific molecules, in this case COVID-19, enter cells after binding to the receptors. TMPRSS2 has a major role in the cleaving of spike proteins that is necessary for membrane fusion of the viral membrane with the vesicle membrane, allowing the COVID-19 virus to infect target cells [7]. ADAM17 is able to cleave the ACE2 enzyme and can result in ectodomain shedding. Vimentin is thought to be a co-receptor for COVID-19 and increases the inflammatory response to infection. Goblet secretory cells which are abundant in the upper and lower respiratory tract have high levels of vimentin and COVID-19 infection can result in respiratory distress [23]. Clathrin coats endocytic vesicles and aids internalization in increasing efficiency of transporting the virus into cells [10]. In response to virus, the proinflammatory cytokines (PICS) activate macrophages which further contribute to COVID-19 spread when entering the blood stream [8]. Phagocytosis of the virus can result in infected macrophages that harbor the virus. At least some of the viruses escape destruction and continue to infect rather than combat the virus. This greatly contributes to virus replication across the body because infected lung macrophages are thought to be carried into the blood stream and disseminated to other organs with high levels of ACE2 expression [9,11]. Viral infection causes similar effects in individuals with type 1 and type 2 diabetes. When the virus enters the lungs, kidney, heart, or pancreatic islet cells, organ injury and insulin deficiency are likely outcomes in diabetics. COVID-19 infection leads to destruction of the ACE2 enzyme (which also functions as the virus receptor) is not able to control inflammation. This leads to further damage to the organs in the body such as the kidneys and heart. The main role of the ACE2 enzyme is to offset the product of ACE, which is angiotensin II, by preventing inflammation and fluid retention. The ACE2 enzyme is responsible in producing a peptide which is angiotensin 1 (1-7) and acts as an antagonist to the ACE (angiotensin converting enzyme) product which is angiotensin II (1-8). This can result in vasoconstriction where the tissues receive less oxygenated blood. As

a result, this can raise blood pressure. The ACE2 enzyme is vital to the body and is present in many organs such as the kidneys, intestines, heart, and lungs and is responsible for wound-healing and maintaining steady blood pressure. When the body is facing COVID-19 infection, ACE2 enzymes are unable to properly limit the side effects of angiotensin II peptides produced by ACE. Therefore, due to the disrupted balance in the ACE2 and Ang-II/angiotensin-(1–7) equilibrium, the body can undergo organ damage [13]. When COVID-19 binds to the ACE2, it inhibits its function and makes them unable to control the signaling of the Angiotensin II peptides which leads to further inflammation [14]. The harmful effects Angiotensin II peptides are not diminished and are able to perform their function to injure tissues in the body since the ACE2 enzymes are not able to modulate its effects. When the virus enters the lungs, diabetic individuals face increased difficulties with breathing. As the virus continues to replicate, more immune cells are activated leading to an oversupply, also known as a "cytokine storm." This results in further lung inflammation, which makes breathing very difficult or even impossible. This" storm" is induced by increased levels of pro-inflammatory cytokines, chemokines, and the production of autoantibodies, all of which are major causes of disease progression. The proinflammatory cytokines then activate macrophages which specialize in phagocytosis which result in macrophage-phagocytosed viruses. Although macrophages are generally known to combat viruses' thorough phagocytosis, in this case the virus is disseminated across the body because the macrophages carry the virus within them [18]. The extensive presence of pro-inflammatory cytokines greatly contributes to disease pathogenesis and increase the severity of side effects such as lung damage and hypertension [15].

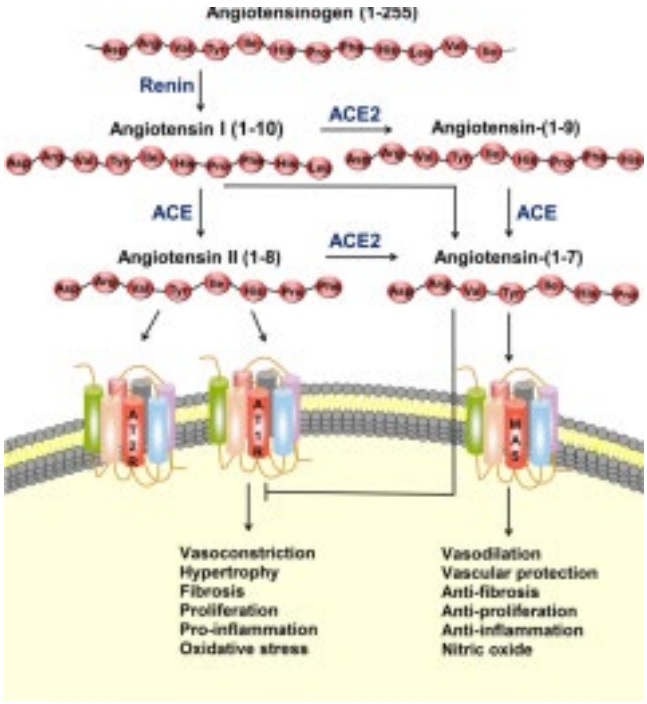

Fig 2. The RAS (renin-angiotensin system), Angiotensin conversions [16].

This figure showing the Angiotensin conversions that take place which are crucial to balanced bodily function. The protease renin converts Angiotensinogen to Angiotensin-I. Then, the ACE converts Angiotensin I to Angiotensin II (1-8). This diagram highlights the balancing role that the ACE2 enzyme plays in homeostasis. ACE2 converts Angiotensin I (1-10) to Angiotensin I (1-9) and converts Angiotensin II (1-8) to Angiotensin II (1-7). If this conversion does not take place, many harmful effects occur including oxidative stress, fibrosis, vasoconstriction, and more [16]. This conversion is blocked by COVID-19 because the spike protein binds to the ACE2 enzyme and inhibits the conversion function [15]. This results in an imbalance of the RAS and dramatically decreases the concentration of Angiotensin (1-7). Angiotensin (1-7) binds to the MAS1 oncogene receptor (MAS) and helps to control inflammation, cell

growth, and prevents tissue scar ring. It is remarkable how the deletion of one amino acid, Phenylalanine, has a reversing effect on the biology of the RAS system.

Several studies have found that diabetics have an abnormally high number of ACE2 receptors which contributes to a more rapid increase in viral load. The virus is able to spread more rapidly because the virus enters the body through these receptors. These enzymes are present in many vital tissues in the body as well such as the lungs, heart, and kidneys. Spread the infection in the body stimulate B-cell damage and the occurrence of a cytokine storm that can result in newly onset diabetes or at admission hyperglycemia (high blood sugar) because it can interfere with balancing hormonal responses in the body and cause further inflammation [14]. Abnormal high number of ACE2 receptors in people with Type 1 and Type 2 diabetes is the major factor that causes more severe progression of the disease and higher mortality rate. In addition, patients with Type 1 diabetes at increased danger of developing ketoacidosis, a serios complication that occurs when a body produces high level of blood acids. Diabetic ketoacidosis in severe dehydration exacerbating other severe complications, such as sepsis observed in COVID-19 patients.

2. Medical Data

The data sources used in this paper include a number of publications [17,18,19,20,21]: associations of type 1 and type 2 diabetes with COVID-19-related mortality in England; risk factors for COVID-19 disease in people with diabetes in Scotland; and clinical characteristics and risk factors for mortality in a large data set from Mexico. All papers conducted whole population or cohort studies accounting for various factors, using emergency care numbers, number of people alive registered with a general practice, and number of diagnosed diabetics. Also, in the study we used USA CDC materials [21] - separate percentages of diabetics and people with no diabetes hospitalized with COVID-19. Strength and weaknesses of the reviewed studies are discussed.

Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England [17,18]

This study focused on the comparison of independent effects of diabetes in hospital COVID-19 deaths in England during the period of March 1 to May 11, 2020. Due to lack of data of COVID-19 infection rate, a whole population study was conducted which contained 61,414,470 individuals who were alive: 263,830 had type 1 diabetes, 2,864,670 had type 2 diabetes, and 58244220 had no diabetes. Infection rates were estimated using National Diabetes Audit (NDA), UK National Health Service (NHS), and Hospital Episode Statistics (HES)(a record of all hospital admission records in England), and civil death registrations from the Office for National Statistics (ONS). This paper gathered data on different groups of diabetics such as race, sex, region, coronary heart disease, ethnicity, index of multiple deprivation, and age, in England to document in-hospital deaths. This paper contained the largest population data ever analyzed to date of 61.4 million people using unadjusted mortality rates. The unadjusted rate per 100,000 people of in-hospital mortality from COVID-19 with type 1 diabetes the unadjusted mortality rate was 138(124-153). For those with type 2 diabetes the mortality rate was 260 (254-265). It was also found that as age increases, the risk of dying increases very rapidly. A weakness of this study is that its death rates are for the population as a whole, not just those who were infected due to their lack of PCR infection data. Their most important contribution was calculating odds ratios to compare the association between COVID-19 infection and type 1 vs type 2 diabetes. After adjusting for comorbidity factors, such as age, sex, deprivation, ethnicity, and geographical region the odds ratios for death in people with type 1 diabetes was 3.51 (3.16-3.90) and 2.03 (1.97-2.09) for type 2 diabetes. After further adjusting for heart failure and strokes, the calculated mortality odds ratio number decreased - the odds ratios for death in people with type 1 diabetes became 2.86 (2.58-3.18) and 1.8 (1.75-1.86) for type 2 diabetes.

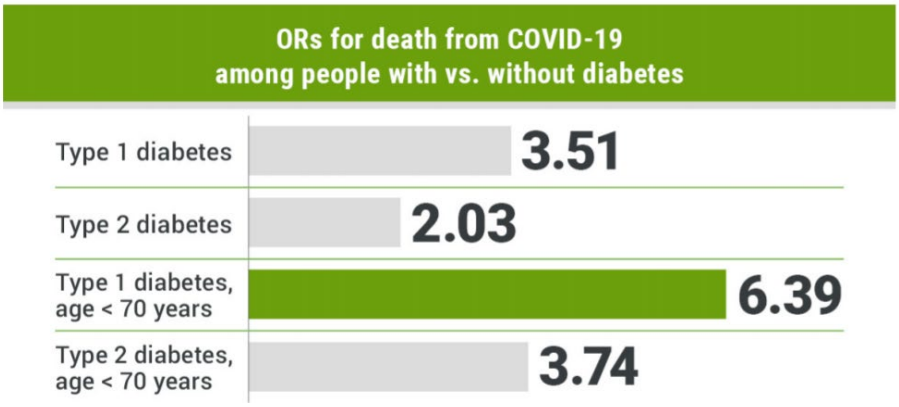

Fig 3. Mortality ORs from COVID-19 among people with vs. without diabetes [17].

The picture highlights that individuals having Type 1 diabetes prior to COVID 19 infection results in a higher risk of mortality in comparison to those that previously had Type 2 diabetes prior to infection. Both, however, pose a great threat in comparison to those who do not have diabetes prior to COVID-19 infection.

Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England [19]

Different from the previous, this paper conducted a population-based cohort study with a smaller population which used national datasets tracking diabetes and death numbers across the country to evaluate the association between modifiable risk factors and COVID-19 deaths. The number of deaths from type 1 and 2 diabetes were calculated and compared with 2017- 2019 numbers for the same months to calculate differences in death rates pre COVID-19. By comparing mortality rates from the past 3 years, this study shows that the COVID-19 pandemic is associated with a large increase in total deaths of people with both type 1 and type 2 diabetes. A very important finding worthy of highlighting from this data is that there were approximately 3500 more deaths per week in known diabetics primarily due to COVID-19. This demonstrated the increased risk that diabetics experience due to COVID-19 infection. This connection was established after the data was adjusted for common factors to ensure the most accurate results.

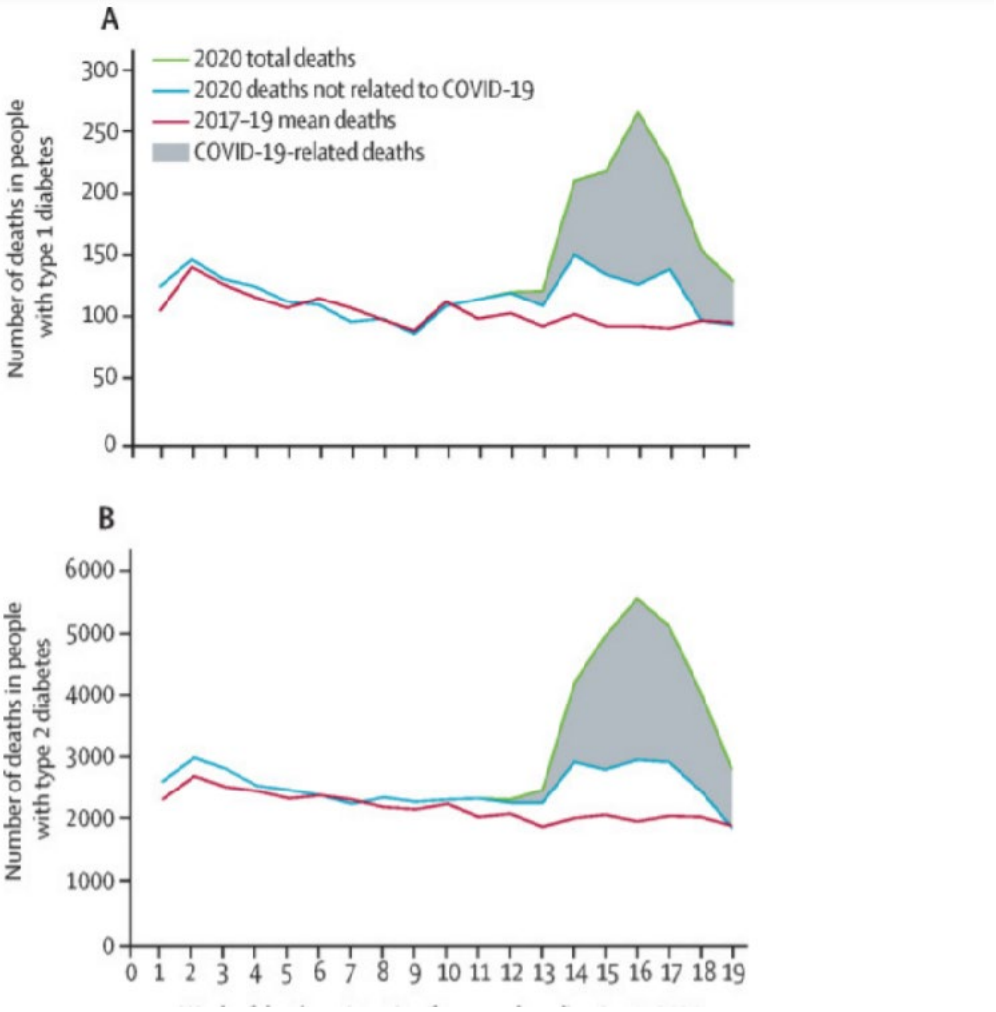

Fig. 4: The grey area signifies the extra deaths among diabetics over the time period of COVID-19 than any time in the past 3years [19].

A strength of this study is that mortality rates of diabetics without a confirmed diagnosis of COVID 19 (prior to the COVID-19 outbreak) enable calculation of the hazard ratio. As a result of this study, it was observed that COVID-19 deaths in diabetics and those with obesity and poorly managed blood glucose has an increased risk when compared to other types of deaths in the given time period. This paper collected data on a wide variety of ethnic groups, age groups, and gender which included individuals in 98 percent of general practices in England. There were 264,390 type 1 diabetics and 2,874,020 type 2 diabetics included in the analysis. Hazard ratios were calculated for the probability of mortality in different groups that have diabetes and COVID-19. The hazard ratios differed for a variety of factors such as a certain prevalence of a type of diabetes among certain ethnicities. This paper used a cohort study to ensure the most accurate results using a better matched group of people to evaluate. The hazard ratio calculated for individuals with impaired renal function - eGFR (Estimated Glomerular Filtration Rate) <15 in type 1 diabetics is 8.35, and in type 2 diabetics is 4.91. This shows that after adjusting for other comorbidities, type 1 diabetes is associated with increased risk. Data in this this study include nearly all people diagnosed with type 1 and type 2 diabetes in England and data for risk factors from before the COVID-19 pandemic. The results are therefore likely to be applicable to other countries with similar populations and health-care systems.

Risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland [18]

This paper collected data over a longer time period: from March 1st to July 31st 2020, and combined data on both in-hospital and out-of-hospital COVID-19related deaths. PCR confirmed positive COVID-19 tests were used to identify positive patients. There were 5,463,300 total participants and 319,349 who had diabetes in Scotland and were tested for 35 outside variables. They also identified more types of risks such as previous hospital admissions and increased exposure to drug classes which provides for the most possible accurate study. A major finding was that in type 1 diabetes OR was 2.396 (1.815–3.163; p<0.0001), and for type 2 diabetes OR was 1·369 (1.276–1.468; p<0.0001).

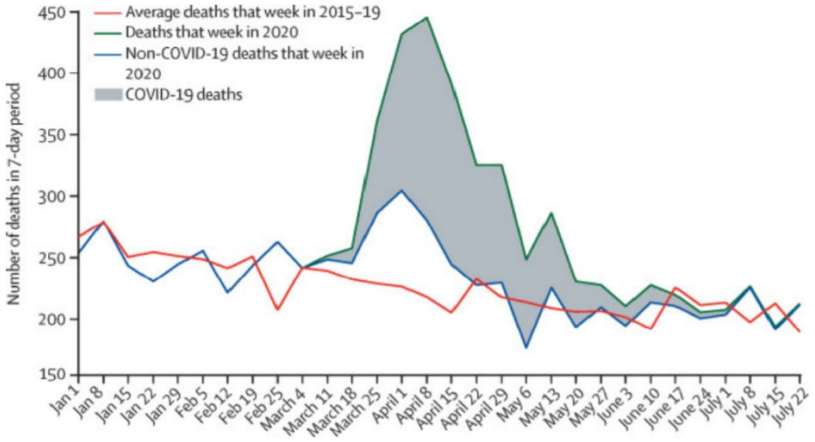

Fig. 5: COVID-19 excess deaths when comparing to the average amount of deaths in 2015–19[18].

Between March 1 and July 31, 2020, the first wave of the pandemic, it was found that there were 1228 excess deaths when comparing to the average amount of deaths in 2015–19: 963 of these deaths were due to COVID-19. The grey area signifies the excess deaths throughout this time period due to COVID 19 which is similar to the graph distribution in the 2nd English paper [19].

Clinical characteristics and risk factors for mortality in diabetics with COVID-19 in a large data set from Mexico [20]

The paper analyzes data from 331,298 individuals with PCR- confirmed COVID 19 to assess the risks of various comorbidities. Additional data was collected to explore confounding variables such as smoking, sex, age, and other comorbidities. The paper listed clinical characteristics, as well statistics on survivor, non-survivor, and total infected population. From this data, odds ratios were calculated to determine whether the association between different clinical groups with diabetes and COVID-19 yields a positive or negative correlation. All odds ratios calculated (with the exception of two) demonstrated that clinical groups with diabetes are at much greater risk of death if infected with COVID-19. Univariant analysis yield OR equaled to 3.85 (3.77–3.85), and multivariant analysis yield was 1.29 (1.24-1.34). A weakness of this study is that there is no differentiation between type 1 and type 2 diabetes. This shows that having diabetes prior to COVID-19 infection causes much greater risk for mortality. Evidenced by calculations in the paper, groups such as over 80 years of age can be at 60.65 times more risk of death. Some groups had very high odds ratios.

Mortality rate in USA [21]

In order to reduce variation of confounding variables from state to state that could negatively affect the data, only 14 states with similar quarantine policies and diabetes prevalence over 10 percent (COVID-19 stats, CDC report) were selected for analysis. These policies included mandatory quarantine and urged distancing for returning travelers to minimize the spread of infection. The Pearson correlation coefficient [22] was calculated to establish the correlation between the percentage of diabetes and mortality rate of COVID-19 in US from state to state. The results are presented in Fig. 6.

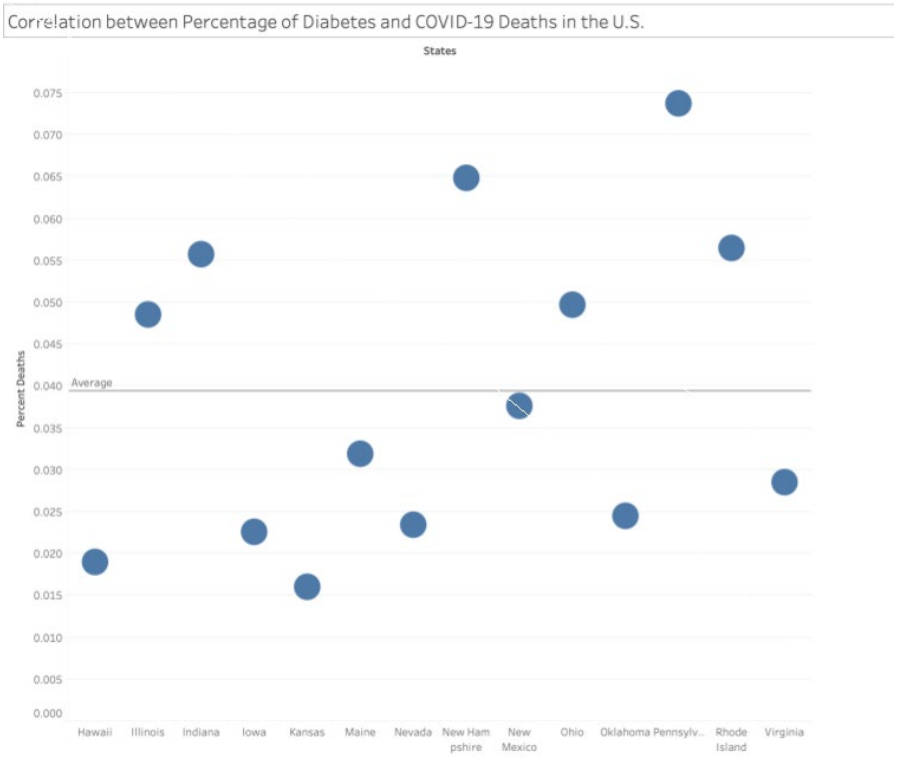

Fig. 6: The percentage of COVID-19 mortality in people with diabetes vs. states in the US

It was hoped to find a similar connection between diabetes and COVID-19 infection per state. However, the final computed Pearson correlation coefficient was 0.22. The manner by which these points are plotted demonstrates that there is no clear trend or pattern. Poor correlation between states was caused by a number of factors: different quality of healthcare, different population density and distribution, lack of the reliable data from hospitals and due to imperfect protocol of data collection.

Many of all people affected by coronavirus who develop severe complications, often resulting in death, have medical pre-existing conditions. According to CDC report nearly 90% of adult patients hospitalized with COVID-19 in US had one or more underlying diseases (see Fig. 7).

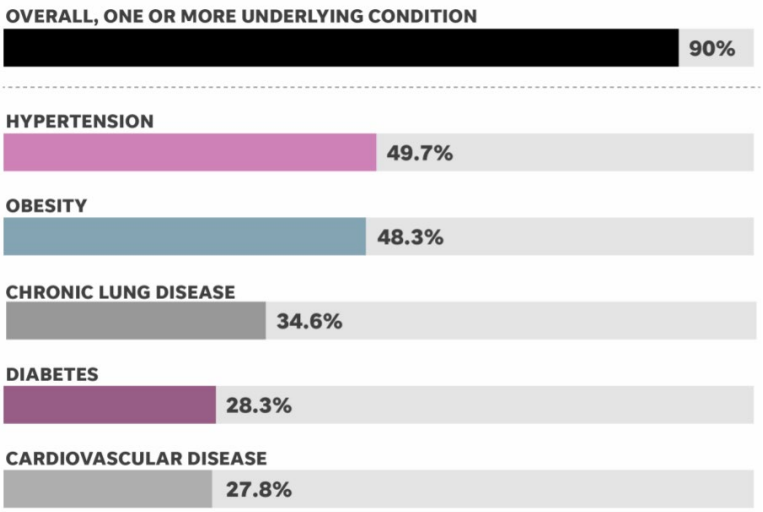

Fig. 7: Conditions present in adult patients hospitalized with coronavirus in US [14].

This figure displays the percentages of infected individuals with underlying comorbidities. Underlying conditions negatively affects the deadly outcome of COVID-19 [21]. There is direct link between hospitalized number of patients with severe complications and deaths from COVID-19. Ratio of percentage of hospitalized diabetics to percentage of patients hospitalized with no underlying conditions can serve as approximate measure of severity of the disease mortality from the virus. This approach to estimate diabetics severity of the disease and mortality gives **a number ~ 2.83** which is similar to the numbers of OR presented in the above studies.

3. Discussion and Quantitative characterization

All of the discussed studies show a tight association with increased death rates for diabetics with COVID-19. It was clearly demonstrated that having diabetes prior to COVID-19 infection increases the risk of poor outcomes such as intensive care or death. In these papers the risk was estimated by odds ratios or hazard ratios for COVID-19 patients with pre-existing type 1 or type 2 diabetes. Odds ratios determine the relative odds of death between two groups with diabetes and with no preexisting conditions. A ratio of 1 indicates no association, greater than 1 indicates a positive association, lower than 1 indicates a negative association between the two groups. Hazard ratios represent the instantaneous risk over a given time period of the study. Both numbers indicate how a condition changes the risk of a certain outcome over time intervals in the period of study. In this case, the condition would be diabetes, and the risk would be the risk of death from COVID-19. These numbers help us to understand whether diabetes and risk of death from COVID-19 are correlated and if so, how closely.

Table 1: Summary the ORs, and demonstration of similarity between odd's ratios calculated in the selected papers.

Source of data	T1 Diabetes	T2 Diabetes	Overall OR Diabetes (univariate analysis)	Overall OR Diabetes (multivariate analysis
England [18,22,23,27], not fully adjusted	3.51 (3.16-3.90)	2.03 (1.97-2.09)		
England [18,22,23,27], fully adjusted	2.86 (2.58-3.18)	1.8 (1.75-1.86)		
Scotland [26], fully adjusted	2.396 (1.82-3.16)	1.369 (1.28-1.47)		
Mexico [19], fully adjusted			3.855 (3.77-3.95)	1.288 (1.24-1.34)
USA, CDC report*			2.83	

* Estimate by author based on CDC data - ratio of percentage of hospitalized diabetics to percentage of patients hospitalized with no underlying conditions was used as approximate measure of diabetic's mortality from the virus.

In the England papers [18,22,23,27], the initial numbers were calculated after only adjusting for age, sex, deprivation, ethnicity, and geographical region. After further adjusting for heart failure and strokes, the calculated mortality odds ratio number decreased however type 1 diabetics remained to have a higher risk of death. In the Scottish paper [26] authors also identified more types of risks such as previous hospital admissions and increased exposure to drug classes. The Mexican paper [19] used combined numbers of type 1 and type 2 diabetics to calculate their odds ratios. After observing two of more variables in the multivariate analysis, the number still continues to show an increased risk of death in comparison to non-diabetics. Because US mortality data calculated on state-by-state basis was inconclusive we used ratio of percentage of hospitalized diabetics to percentage of patients hospitalized with no underlying conditions as approximate measure of diabetic's mortality from the virus. The estimated diabetics mortality was ~ **2.83** close to **ORs** presented in the other papers. Diabetics with more than one underlying condition face even more challenges. As an example, the hazard ratio calculated for individuals with impaired renal function - eGFR (Estimated Glomerular Filtration Rate) <15 in type 1 diabetics is 8.35,-and in type 2 diabetics is 4.91 [19]. The mortality rates of individuals with diabetics and COVID-19 increases with age. This fact is demonstrated in [18], see Fig. 8.

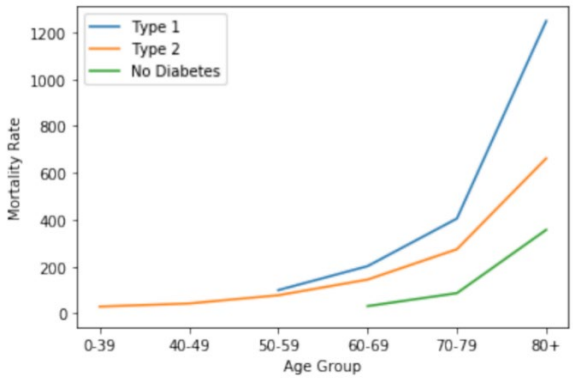

Fig. 8: COVID-19 mortality rate per 100,000 persons in hospitals from March 2020 to 11th May 2020 categorized by the type of diabetes [18].

Different age groups separated into three different categories: Type 1 Diabetes, Type 2 Diabetes, and No Diabetes. This figure demonstrates how the fatality rates of individuals with diabetics and COVID-19 increases with age. It is observed that the green line which represents the group of people with no diabetes increases with age similar to the other lines. However, the number of deaths is still significantly lower in comparison to those with diabetes. Evidenced by calculations in the paper [20], groups such as over 80 years of age can be at 60.65 times more risk of death.

Conclusion

This paper describes the biological etiology of COVID-19 illness, systematizes and quantifies the COVID-19 medical data available in public domain. Correlation within the revised information and consistency with biological hypotheses were used as a criterion for database determination. The evidence for the increased risk of severe progression of the disease and often death in patients with diabetes was demonstrated. Higher mortality rate was observed among individuals with Type 1 than among the ones with Type 2 diabetes. Other more susceptible groups such as older people, and people with more than one underlying condition face even more challenges throughout this dangerous pandemic.

Possible directions of the future work:

1. COVID-19 gene study: Little is known about the specific parts of the gene; the makeup of the gene cannot be thoroughly constructed or displayed at this point because no thorough genetic studies are released. The gene mutation study of great importance to predict and find treatment for new variants of COVID-19
2. Pre-existing conditions and confounding factors affecting COVID-19: Although many connections have been made between various pre-existing conditions and the likelihood of contracting the virus, there are no guaranteed results due to the virus's unique process of infection and makeup.
3. Improvement of medical data collection: As more patient-by-patient case studies in the future will be conducted, it will be more efficient in computing contraction rate, progression of the disease severity, mortality odds ratios for different pre-existing conditions and varying confounding factors.

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