Polytechnic Journal. 2022. 12(1): 141-148
ISSN: 2313-5727
http://journals.epu.edu.iq/index.php/polytechnic

RESEARCH ARTICLE

Prevalence of mortality among covid-19 patients in Kurdistan Region and various parts of the world and the role of ecological and environmental factors in shaping SARS-CoV-2 virulence

Muayad A. Mahmud[1]

[1] Department of Medical Laboratory, Shaqlawa Technical College, Erbil Polytechnic University, Erbil, Kurdistan Region, Iraq

***Corresponding author:**
Muayad A. Mahmud, Department of Medical Laboratory, Shaqlawa Technical College, Erbil Polytechnic University, Erbil, Kurdistan Region - Iraq.

E-mail:
muayad.mahmud@epu.edu.iq

Received: 10 April 2021
Accepted: 07 June 2022
Published: 14 August 2022

DOI
10.25156/ptj.v12n1y2022.pp141-148

ABSTRACT

Evolutionary theories predict that virulence (host death due to a pathogen) positively associates with the pathogen transmission rates to new susceptible hosts. Severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2), the causative agent of coronavirus disease 2019 (covid-19) pandemic, like other RNA viruses, has quite variable genetic content due to its unique nucleus enzymes thus mutations can continuously occur during viral replications. Phenotype variations among new viral progeny can include individuals with different replication rates, infectivity, stability in the abiotic environment, and transmission rate. Here, the rate of transmission to new susceptible hosts may be affected by the pathogen's vitality in the physical environments, and host-related factors such as control measures and vaccination. In this study, we analyzed the mortality rates of covid-19 positive patients among various parts of the world and explain the role of several factors in determining SARS-CoV-2 virulence. We found a weak negative correlation (R^2 = 0.3) between the mortality rate of covid-19 patients and each of death rates due to cancer diseases (F = 9.135, P = 0.006) and the number of medical doctors per 10,000 populations (F = 8.104, P = 0.009). Other factors such as the prevalence of current daily tobacco smoking in males/females, life expectancy in males/females, general death rates, cardiovascular diseases, prevalence of COPD, prevalence of asthma and average yearly temperature did not associate with death rates among covid-19 patients. In conclusion, adequacy of healthcare services and proper infection prevention measures are the key factors to reduce the covid-19 mortality rate. More studies are required to better understand the management of SARS-CoV-2 virulence management.

Key Words: covid-19, SARS-CoV-2, virulence, ecology, mortality

INTRODUCTION

The most understandable characteristic of a pathogen includes its ability to harm its host. From evolutionary biologists' perspective, virulence is defined as pathogen-induced damage to the host which broadly entails a reduction of growth, reproduction, and life expectancy of hosts (Zhan et al., 2002). Pathogens extract energy resources from hosts to obtain requirements for their survival, and their virulence (pathogenicity level) is likely to be an inevitable side effect of their relationship with hosts. As the health condition and mobility of hosts can play important role in the transmission of pathogens with the direct life cycle, virulence can, in turn, affect fitness components of pathogens themselves (Hammerschmidt and Kurtz, 2005). The defense mechanism of hosts (innate and acquired immune responses) is accountable to combat pathogens (Schmid-Hempel, 2009). Pathogen-induced damage is likely to trigger host immune responses which can also create a selection on pathogen virulence (Schmid-Hempel, 2009; Woolhouse et al., 2002). Therefore, pathogens and their hosts can create strong selection pressure on each other which leads to host-pathogen coevolution in many ecological interactions in nature (Mahmud et al., 2017). One of the most interesting questions of evolutionary biologists regarding host-pathogen interactions includes how changes are induced in pathogen virulence? Can insights from the adaptation of virulence increase our understanding about the application of virulence management and controlling of infectious diseases (Bull, 1994; Woolhouse et al., 2002; Ebert and Bull, 2003)

The theory of virulence evolution has become well known since 1979 when two researchers (Anderson and May) integrated theoretical models with empirical data to study host-parasite interactions (Anderson and May, 1979; May and

Anderson, 1979). Their studies describe the association between host population and a pathogen transmission rate (also see Best, 2010). Their model has replaced the conventional understanding of virulence which was suggesting that pathogens continuously evolve to become lesser virulent until they become benign because harming hosts can in turn impact their fitness. The newly suggested model rejects the classical understanding of virulence evolution predicting that the outcomes of host-pathogen coevolution are bound to the virulence-transmission relationship (Anderson and May, 1982). Abiotic environmental factors including temperature can either directly affect the durability of detached pathogens and hence the transmission success (Walter and Ewald, 2004) or, indirectly influence pathogens through alteration of life-history traits of their hosts (Lopez Pascua et al., 2012).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which caused coronavirus disease 2019 (covid-19) pandemic is an RNA virus. Worldwide, as of June 4th, 2022, SARS- CoV-2 has caused more than 528 million infections and 6.3 million deaths (WHO, 2021a). Like most RNA viruses, SARS-CoV-2 is genetically inconsistent (Day et al., 2020). Since September 2020, the evolution of SARS- CoV-2 has been documented by genetic mutations described as “variants” which can alter virus characteristics such as infectivity and transmissibility perhaps in response to changes in immune responses of different human populations (Harvey et al., 2021). It is expected that SARS-Cov-2 evolution is driven by globalizing factors leading to both continuous local adaptations and emerging of region-specific variants (Rochman et al., 2021). Some of these changes particularly in the nucleocapsid (N) protein and the receptor-binding domain of the spike (S) protein can alter viral fitness such as transmission efficacy and virulence (WHO, 2021b). Consequently, several variants of SARS-CoV-2 have been reported in different parts of the world with different biological properties particularly in their ability to spread. For example, the Alpha variant was first identified in September 2020 which had approximately 50% higher transmission rate than initial strains of the virus and this caused a large second wave of covid-19 infections in the UK (Braybrook et al., 2021). The Beta variant was identified in May 2020 in South Africa and it was more transmissible than the Alpha variant (Koyama et al., 2020). Gamma variant, was identified in November 2020 in Brazil and this strain shared similarities in its protein character with Alpha and Beta strains, but it was lesser transmissible than the Alpha variant (Braybrook et al., 2021). Delta variant was discovered in April 2021 in India and it is also more transmissible than the Alpha variant (Farinholt et al., 2021). Lambda variant was identified in August 2020 in Peru. World Health Organisation has described the Delta strain as a “variant of concern” and has recently referred to Lambda strain as a "variant of interest" which is suspected to be more virulent and more contagious than earlier variants (Agwa et al., 2021; WHO, 2021b).

A large part of the damage which is done to the human host by SARS-CoV-2 involves over-reactivity of the human immune system broadly described as cytokine storm syndrome which in severe cases may lead to multi-organ failure (Henderson et al., 2020). It has been well established that the severity of covid-19 greatly varies within and between human populations (ranging from asymptomatic to very severe). Several factors are found to associate with the disease severity including viral strain, the human race, age, sex, lifestyle, and others. It has been proven that since Sep 2020, SARS-CoV-2 is continuously mutating (Harvey et al., 2021; Callaway, 2020). Thus, there is a possibility that the virus acquires the ability to adapt to the changes in immune responses of the human population, and consequently, virus evolution leads to changes in transmission and virulence (Day et al., 2020; King, 2021). Adding to that, some reports suggest that the new variants particularly the Delta strain can cause a higher mortality rate (Davies et al., 2021) particularly to under-five youngsters and the elderly (Wang et al., 2020).

As per the trade-off model, pathogen transmission and density of a susceptible host are positively correlated hence decreased density of susceptible hosts is likely to select for a decrease in the pathogen transmission rate (Boots and Mealor, 2007; Day et al., 2020). It is also expected that viral transmission and its virulence are genetically coupled, therefore, we can anticipate virulence to decrease corresponding to the decrease in host density. Here, a decrease in the host density (human population) does not refer to the mortality rate of infected and uninfected hosts, but it is achieved by social distances resulting in self-shading (see Boots and Mealor, 2007; Cressler et al., 2016).

It has been reported that various host related factors such as age, sex, comorbidity risks including life expectancy, pulmonary and cancer diseases may associate with covid-19 induced death (Fountoulakis et al., 2020). Environmental factors including temperature may particularly affect the SARS-COR-2 fitness in the physical environment (Morris et al., 2020; Aboubakr et al., 2021; Ren et al., 2020). In this study, we examine the difference of the mortality rates of covid-19 patients among the cities in Kurdistan Region-Iraq and on international scales among 25 countries. We also study the influence of several host related factors and comorbidity risks as well as an environmental factor on the covid-19 induced mortality rates. The factors included the prevalence of current daily tobacco smoking in males and females, life expectancy in males and females, death rates, cardiovascular diseases, cancer diseases, number of medical doctors per 10 000 populations, prevalence of chronic obstructive pulmonary diseases (COPD), prevalence of asthma and average yearly temperature as abiotic variable in 25 countries including Iraq. These factors were chosen to be examined whether they associate with the pathogen induced mortality so as to draw our predictions about the future evolution of SARS-COR-2 virulence.

1. Methodology

1.1 Data source

Local covid-19 related data of Kurdistan Region-Iraq (KRG) were downloaded using KRG's covid-19 dashboard (KRG-MOH, 2022). These data included total infection number, recovery number and covid-19 confirmed number during March 1st 2020 until March 5th 2022.

Regarding covid-19 for 25 countries (listed in table 1) using WHO's online resource (WHO, 2021b). These data included infection rates, recovery and confirmed death rates from the date that covid-19 was reported per country until Feb 22nd, 2022. These countries were chosen because the required data regarding covid-19 disease and ecological and environmental factor were available from online resources.

We used WHO's online resource (WHO, 2021b) to download the death percentage of three age classes (75+, 55-74 and 35-54) of cardiovascular and cancer patients in the 25 countries (table 1) with the minimum, medium and maximum covid-19 associated death cases. We downloaded data on the number of medical doctors per 10,000 population from WHO's webpage (WHO, 2020). Prevalence of asthma was age-standardized for the countries was obtained from "Our World in Data" webpage (Our-World-in-Data, 2019). We downloaded the average life expectancy for men and women from "WorldData.info" webpage (WorldData.info, 2022). Global prevalence of COPD was obtained from supplementary data to a published review by Adeloye et al. (2022). Global prevalence of male and female tobacco smokers was obtained from the online published book "Global Atlas on cardiovascular disease prevention and control" edited by Mendis et al. (2011). Average yearly temperature was obtained from the official website of Lebanese-Economic-Forum (1990).

1.2 Statistics

For the 25 countries involved in this study, we used a linear regression model to examine the relationship between the prevalence of covid-19 mortality rate and each of six ecological and one environmental factors. In total, the seven factors included "death percentage of three age classes (75+, 55-74 and 35-54) of cardiovascular and cancer patients; the number of medical doctors per 10,000 populations; average asthma rate; average COPD rate; average life expectancy for men and women; rate of male and female tobacco smokers and an abiotic environmental variable included the average yearly temperature per country".

The death rate was calculated using the equation "number of confirmed deaths/ total number of infected individuals *100". A Graph Pad Prism software (version 7) was used for all the statistical analysis and graph preparations.

2. Results

Using local data, as displayed below (fig. 2) death rates were found to be slightly higher in Halabja and Sulaymaniah cities compared to Duhok, Erbil and other Iraqi cities, but the difference was statistically not significant (Chi-square = 1.963, df = 4, P value = 0.743).

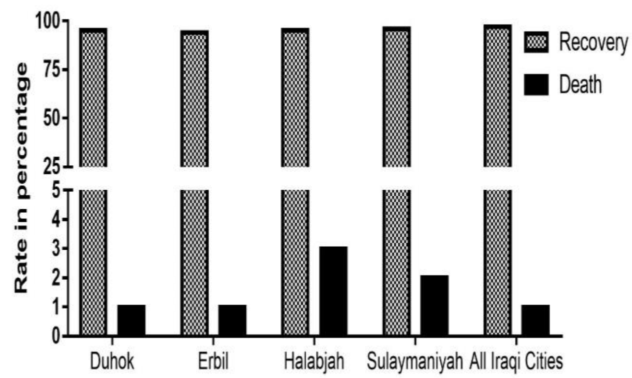

Figure 1. Comparing recovery and death rates of covid-19 positive cases among KRG cities including Duhok, Erbil, Halabja and Sulaymaniah, and the average of equivalents rates in the rest of Iraqi cities.

There was a considerable difference in the covid-19 induced death rate among the 25 countries (Chi-square = 1683, df = 24, P value < 0.001). some of these countries were classified as with the highest death rate (Bosnia and Herzegovina, Ecuador, Egypt, Syrian Arab Republic and Mexico), with intermediate level of death rate (Iraq, Greece, Venezuela, Canada, Oman, United, States of America, Azerbaijan, Italy, Albania, Slovakia and Kazakhstan) and others with the lowest death rate (Iceland, Norway, New Zealand, Singapore, Denmark, Australia, Qatar, Mongolia and Cyprus) as displayed in figure 2 and table 1.

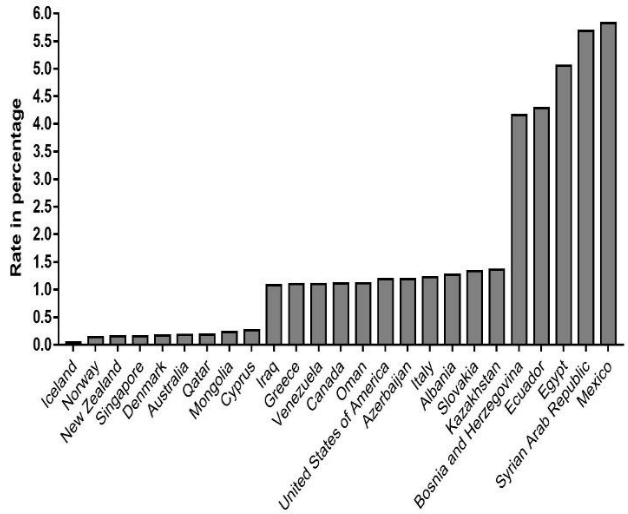

Figure 2. Bar chart displaying covid-19 associated death rates in 25 countries.

The mortality rate of covid-19 patients did not correlate with any of the prevalence of current daily tobacco smoking in males and females, life expectancy in males and females, death rates, cardiovascular diseases, Prevalence of COPD, prevalence of asthma and average yearly temperature in 25 countries including Iraq. There was a significant weak negative correlation (R^2 = 0.3) between mortality rate of covid-19 patients and each of death rates due to cancer diseases [F (1, 23) = 9.135, P = 0.006] and medical doctors (per 10,000 population) [F (1, 23) = 8.104, P = 0.009] (table 2).

Table 1. Displaying the percentage of covid-19 associated death rate, prevalence of current daily tobacco smoking in males and females, life expectancy in both genders and death rate, death percentage due to cardiovascular diseases and cancer diseases in three age classes (75+, 55-74 and 35-54), the number of Medical doctors per 10 000 population, global prevalence of COPD, prevalence of asthma and Average yearly temperature was obtained from online resource for 25 countries with the minimum, medium and maximum covid-19 associated death cases

No	Country	covid-19 mortality	Tobacco smoking in males	Tobacco smoking in females	Life expectancy males	Life expectancy females	Death rate	Cardiovascular diseases 75+	Cardiovascular diseases 74-55	Cardiovascular diseases 35-54	Cancer 75+	Cancer 55-74	Cancer 35-54	Medical doctors (per 10 000)	COPD	Asthma Prevalence 2019	average yearly temperature
1	Iceland	0.05	23.0	13.0	81.70	84.50	6.30	76.30	19.10	3.80	53.10	39.40	6.50	41.42	18.00	7.90	-0.70
2	Norway	0.14	23.0	40.5	81.60	84.90	7.60	79.90	17.20	2.50	51.20	41.90	6.10	50.47	16.70	7.36	1.50
3	New Zealand	0.16	23.0	13.0	80.30	83.90	6.90	75.10	20.20	4.20	48.20	41.30	9.40	36.18	2.10	7.00	10.55
4	Singapore	0.16	23.0	13.0	81.50	86.10	5.00	53.60	36.40	9.00	39.80	47.50	11.60	24.60	8.90		26.45
5	Denmark	0.17	23.0	40.5	79.60	83.60	9.30	73.60	22.80	3.30	47.70	45.60	6.20	42.25	17.40	5.29	7.50
6	Australia	0.18	23.0	13.0	81.20	85.30	6.70	78.20	17.20	4.10	51.20	39.70	8.10	41.29	3.50	9.66	21.25
7	Qatar	0.19	12.0	1.0	79.30	82.10	1.20	20.40	37.00	28.60	18.10	44.60	30.60	24.85	6.60	3.69	27.15
8	Mongolia	0.23	59.0	5.0	66.00	74.30	6.30	36.10	38.60	22.30	21.70	52.80	22.20	38.52	11.50	2.24	1.55
9	Cyprus	0.27	59.0	40.5				72.90	22.60	4.20	48.00	42.60	8.30	31.44	4.90	7.69	18.45
10	Iraq	1.08	23.0	5.0	68.70	72.80	4.70	42.60	41.40	10.80	18.20	44.60	24.10	9.66	6.20	3.62	21.24
11	Greece	1.10	56.5	40.5	78.60	83.70	11.70	78.80	17.00	3.90	54.70	37.50	7.10	63.07	18.40	5.79	15.40

12	Venezuela	1.10			68.30	76.00	7.10	51.40	35.40	11.30	29.70	45.50	19.10	17.30	12.10	4.06	25.35
13	Canada	1.11	12.0	13.0	79.70	83.90	7.60	72.00	23.20	4.30	48.20	43.30	7.70	24.23	17.30	5.32	-5.10
14	Oman	1.12	12.0	1.0				33.40	41.90	14.20	19.90	50.70	18.80	17.74	5.60	4.22	25.60
15	USA	1.19	23.0	13.0	74.50	80.20	8.70	64.40	27.80	7.00	43.00	46.40	9.50	26.10	6.40	11.25	8.55
16	Azerbaijan	1.19	0.0	13.0	70.60	75.60	5.60	44.50	42.10	10.90	16.90	47.70	29.20	31.68	6.70	2.14	11.95
17	Italy	1.23	33.0	13.0	80.10	84.70	10.50	82.00	15.40	2.40	52.00	40.10	7.10	39.48	11.70	4.33	13.45
18	Albania	1.27	56.5	5.0	77.20	80.30	8.10	61.40	31.40	5.00	26.90	52.00	17.50	18.25	12.10	3.02	11.40
19	Slovakia	1.34	56.5	13.0				66.00	29.20	4.50	36.30	53.00	9.60	35.65	13.80	3.29	6.80
20	Kazakhstan	1.36	33.0	13.0	67.10	75.50	7.20	39.20	41.40	16.80	17.40	57.00	21.40	40.71	7.80	1.70	6.40
21	Bosnia and Herzegovina	4.16	33.0	40.5	75.00	80.00	10.90	65.60	29.10	4.70	34.40	52.80	11.90	21.62	14.40	4.77	9.85
22	Ecuador	4.29	12.0	1.0	74.50	80.00	5.10	58.70	28.00	9.50	39.20	37.80	16.10	22.20	5.60	4.18	21.85
23	Egypt	5.05	33.0	1.0	69.90	74.50	5.80	35.20	43.10	12.90	14.30	52.10	23.00	7.46	8.20	3.65	22.10
24	Syrian Arab Republic	5.68	56.5					42.80	35.30	15.20	23.00	42.60	22.40	12.87	7.00	3.44	17.75
25	Mexico	5.83	23.0	5.0	72.30	77.90	6.10	56.70	30.70	9.50	31.60	41.80	19.10	24.25	20.60	2.95	21.00

.

Table 2. Tabular results of linear regression examining the relationship between the mortality rate of covid-19 patients and each of prevalence of current daily tobacco smoking in males and females, life expectancy in males and females, death rates, cardiovascular diseases, cancer diseases, medical doctors (per 10 000 population), prevalence of COPD, asthma prevalence 2019 and average yearly temperature in 25 countries including Iraq.

Linear Regression	prevalence of current daily tobacco smoking in males	prevalence of current daily tobacco smoking in females	Life expectancy males	Life expectancy females	Death rates	Cardiovascular Diseases	Cancer diseases	Medical doctors (per 10 000 population)	Prevalence of COPD	Asthma Prevalence 2019	Average yearly temperature
Goodness of Fit											
R square	0.00	0.05	0.14	0.16	0.00	0.07	0.28	0.26	0.01	0.13	0.07
Sy.x	17.13	14.23	5.10	4.00	2.42	1.19	1.17	11.63	5.41	2.32	9.06
Is slope significantly non-zero?											
F	0.10	1.08	3.18	3.68	0.03	1.75	9.14	8.10	0.19	3.17	1.65
DFn, DFd	1, 21	1, 21	1, 19	1, 19	1, 19	1, 23	1, 23	1, 23	1, 23	1, 22	1, 23
P value	0.75	0.31	0.09	0.07	0.87	0.20	0.01	0.01	0.67	0.09	0.21
Data											
Number of X values	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00
Maximum number of Y replicates	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Total number of values	23.00	23.00	21.00	21.00	21.00	25.00	25.00	25.00	25.00	24.00	25.00
Number of missing values	2.00	2.00	4.00	4.00	4.00	0.00	0.00	0.00	0.00	1.00	0.00

3. Discussion

The key risk factors that are expected to determine death rates caused by covid-19 disease include age, prevalence of tobacco smoking, life expectancy, death rates, cardiovascular diseases, cancer diseases, number of medical carers, prevalence of COPD, prevalence of asthma and the abiotic factor including environmental temperature (Fountoulakis et al., 2020). We used KRG's covid-19 dashboard and WHO's online resources to examine the covid-19 associated death rate within KRG cities and to compare it among 25 countries. Locally, death rates were found to be slightly higher in Halabja and Sulaymaniah cities compared to Duhok, Erbil and other Iraqi cities. Internationally, some countries such as Bosnia and Herzegovina, Ecuador, Egypt, Syrian Arab Republic and the United Mexican States had clearly higher covid-19 associated death rate than other countries.

Host cognition may affect a pathogen's evolutionary dynamics by inducing a decrease in its fitness components such as transmission rate. For example, practicing social distancing, wearing masks, using gloves or hand sanitizers can have the potential to decrease virus spread. Due to a lack of strict compliance with the disease-related public health measures the transmission rate of SARS-CoV-2 has been high enough to let the virus undergo remarkable mutations. Researchers suggest that the original strain of SARS-CoV-2 that arose from China has now been almost all replaced by mutant strains comprising structural changes in the spike protein of the virus (Hou et al., 2020). Continuously emerging new variants has allowed the virus to evolve for larger transmissibility in humans (Callaway, 2020). This suggests that mutation in the viral spike protein tends to make virus variants evolve new characteristics which may lead to unexpected outcomes from virulent strains in the future (Harvey et al., 2021). Therefore, scientists highly recommend a continuous implementation of control measures by the public (Henderson, 2021). Otherwise, the virus would consistently have a high progeny rate which will allow continuously emerging new variants with probably higher infectivity and virulence.

Although some findings suggest that low temperature and relatively low humidity allow SARS-CoV-2 to remain infectious for long periods outside the host body (SanJuan-Reyes et al., 2021; Aboubakr et al., 2021), in the current study, there was no association between the prevalence of covid-19 mortality and the average yearly temperature. Understanding the durability of a pathogen in the external environment can help to make better predictions about its transmission and risk analysis (Walter and Ewald, 2004). SARS-CoV-2 is described as a highly contagious virus having the ability to transmit via aerosols, respiratory droplets, and contacts (Ren et al., 2020). Physical touch with contaminated surfaces can be a potential route of viral transmission. It has been reported that the novel SARS-CoV-2 can remain infectious outside the host body for a longer period than its ancestral families such as SARS-CoV and MERS-CoV (Goh et al., 2020; SanJuan-Reyes et al., 2021). It has also been found that strains of SARS-CoV-2 show different stability/survival rates on surfaces (Ren et al., 2020). These findings might alert that continuously emerging new variants can lead to changes in the viral stability in the abiotic environment.

We found a weak, but significant negative correlation between mortality rate among covid-19 positive cases and the rate of death due to cancer diseases and number of available physicians. Inadequacy of healthcare services including number of physicians and number of hospitals may have caused lower numbers of cases being diagnosed with covid-19, lesser therapeutic intervention and eventually higher death rates (Wirawan and Januraga, 2021). It has been reported that cancer patients are at increased risk of contracting SARS-CoV-2 infection with a higher proportion requiring higher risk of death (Curigliano, 2020). On contrary, we found that there is a negative correlation between death rates due to cancer and the death rate caused by covid-19. Centers for Disease Control and Prevention has listed the cancer disease as the top risk factor for Severe covid-19 (CDC, 2022) and therefore this negative association might be explained by strict control measures have been applied by the 25 countries to contain cancer patients during the pandemic time (Mattiuzzi et al., 2021).

While the covid-19 pandemic is still a serious threat to public health, the courses of disease extent remain ambiguous and continuously discovered new SARS-CoV-2 variants make a large concern about the virulence evolution of the virus. Studies have found that newly emerged variants have a higher fitness at least by increasing virus transmission rate. The evidence of evolving variants with higher transmission efficacy could represent a significant evolutionary step toward higher virulence in the future.

4. conclusions

Depending on the available data and theoretical models in the literature we expect that management of the future risks of SARS-CoV-2 virulence evolution can only be achieved by providing proper healthcare services, implying strict infection prevention measures for vulnerable people and control of the disease spread. We conclude that more studies are required to determine the key factors driving virulence of SARS-CoV-2 virus.

5. Acknowledgement

We would like to thank the members of covid-19 dashboard team from the Ministry of Health/ KRG-Iraq for continuously providing updates about the covid-19 pandemic which greatly helped preparation of this study.

References

Aboubakr, H. A., Sharafeldin, T. A. & Goyal, S. M. 2021. Stability of SARS-CoV-2 and other coronaviruses in the environment and on common touch surfaces and the influence of climatic conditions: A review. Transbound Emerg Dis, 68(2), pp 296-312.

Adeloye, D., Song, P., Zhu, Y., Campbell, H., Sheikh, A. & Rudan, I. 2022. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. The Lancet Respiratory Medicine, 10(5), pp 447-458.

Agwa, S. H. A., Kamel, M. M., Elghazaly, H., Abd Elsamee, A. M., Hafez, H., Girgis, S. A., Ezz Elarab, H., Ebeid, F. S. E., Sayed, S. M., Sherif, L. & Matboli, M. 2021. Association between Interferon-Lambda-3 rs12979860, TLL1 rs17047200 and DDR1 rs4618569 Variant Polymorphisms with the Course and Outcome of SARS-CoV-2 Patients. Genes (Basel), 12(6), pp 830.

Anderson, R. M. & May, R. M. 1979. Population biology of infectious diseases: Part I. Nature, 280(361-367.

Anderson, R. M. & May, R. M. 1982. Coevolution of hosts and parasites. Parasitology, 85(411-426.

Best, A. 2010. The evolution and coevolution of host defence. PhD thesis, University of Sheffield, Sheffield.

Boots, M. & Mealor, M. 2007. Local Interactions Select for Lower Pathogen Infectivity. Science, 315(5816), pp 1284–1286.

Braybrook, E., Pandey, S., Vryonis, E., Anderson, N. R., Young, L. & Grammatopoulos, D. K. 2021. Screening for the alpha variant of SARS-CoV-2 (B.1.1.7) the impact of this variant on circulating biomarkers in hospitalised patients. medRxiv, 2021.06.18.21258699.

Bull, J. J. 1994. Perspective: virulence. Evolution, 48(5), pp 1423-1437.

Callaway, E. 2020. The coronavirus is mutating — does it matter? Nature, NEWS FEATURE.

CDC 2022. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals, https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html, [Accessed 22 May 2022].

Cressler, C. E., Mc, L. D., Rozins, C., J, V. D. H. & Day, T. 2016. The adaptive evolution of virulence: a review of theoretical predictions and empirical tests. Parasitology, 143(7), pp 915-930.

Curigliano, G. 2020. Cancer Patients and Risk of Mortality for COVID-19. Cancer Cell, 38(2), pp 161-163.

Davies, N. G., Jarvis, C. I., Group, C. C.-W., Edmunds, W. J., Jewell, N. P., Diaz-Ordaz, K. & Keogh, R. H. 2021. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. Nature, 593(7858), pp 270-274.

Day, T., Gandon, S., Lion, S. & Otto, S. P. 2020. On the evolutionary epidemiology of SARS-CoV-2. Curr Biol, 30(15), pp R849-R857.

Ebert, D. & Bull, J. J. 2003. Challenging the trade-off model for the evolution of virulence: is virulence management feasible? Trends in Microbiology, 11(1), pp 15-20.

Farinholt, T., Doddapaneni, H., Qin, X., Menon, V., Meng, Q., Metcalf, G., Chao, H., Gingras, M.-C., Farinholt, P., Agrawal, C., Muzny, D. M., Piedra, P. A., Gibbs, R. A. & Petrosino, J. 2021. Transmission event of SARS-CoV-2 Delta variant reveals multiple vaccine breakthrough infections. medRxiv, 2021.06.28.21258780.

Fountoulakis, K. N., Fountoulakis, N. K., Koupidis, S. A. & Prezerakos, P. E. 2020. Factors determining different death rates because of the COVID-19 outbreak among countries. J Public Health (Oxf), 42(4), pp 681-687.

Goh, G. K., Dunker, A. K., Foster, J. A. & Uversky, V. N. 2020. Rigidity of the Outer Shell Predicted by a Protein Intrinsic Disorder Model Sheds Light on the COVID-19 (Wuhan-2019-nCoV) Infectivity. Biomolecules, 10(2), pp.

Hammerschmidt, K. & Kurtz, J. 2005. Evolutionary implications of the adaptation to different immune systems in a parasite with a complex life cycle. Proceedings of the Royal Society B, 272(1580), pp 2511-2518.

Harvey, W. T., Carabelli, A. M., Jackson, B., Gupta, R. K., Thomson, E. C., Harrison, E. M., Ludden, C., Reeve, R., Rambaut, A., Consortium, C.-G. U., Peacock, S. J. & Robertson, D. L. 2021. SARS-CoV-2 variants, spike mutations and immune escape. Nat Rev Microbiol, 19(7), pp 409-424.

Henderson, E. 2021. Scientists call for strict control measures to reduce the spread of new COVID-19 variants News: Medical Science, https://www.news-medical.net/news/20210125/Scientists-call-for-strict-control-measures-to-reduce-the-spread-of-new-COVID-19-variants.aspx [Accessed 14 Oct 2021].

Henderson, L. A., Canna, S. W., Schulert, G. S., Volpi, S., Lee, P. Y., Kernan, K. F., Caricchio, R., Mahmud, S., Hazen, M. M., Halyabar, O., Hoyt, K. J., Han, J., Grom, A. A., Gattorno, M., Ravelli, A., De Benedetti, F., Behrens, E. M., Cron, R. Q. & Nigrovic, P. A. 2020. On the Alert for Cytokine Storm: Immunopathology in COVID-19. Arthritis & rheumatology (Hoboken, N.J.), 72(7), pp 1059-1063.

Hou, Y. J., Halfmann, P., Ehre, C., Kuroda, M. & Dinnon, K. H. 2020. SARS-CoV-2 D614G variant exhibits efficient replication ex vivo and transmission in vivo. Science, 370(6523), pp 1464-68.

King, A. 2021. The coronavirus could end up mild like a common cold. New scientist (1971), 249(3318), pp 12-13.

Koyama, T., Platt, D. & Parida, L. 2020. Variant analysis of SARS-CoV-2 genomes. Bull World Health Organ, 98(7), pp 495-504.

KRG-MOH 2022. Latest information about corona virus. https://gov.krd/coronavirus/dashboard/ [Accessed 1 March 2022).

Lebanese-Economic-Forum 1990. Average yearly temperature (1961-1990, Celsius) - by country. https://web.archive.org/web/20150905135247/http://lebanese-economy-forum.com/wdi-gdf-advanced-data-display/show/EN-CLC-AVRT-C/ [Accessed 21 May 2022].

Lopez Pascua, L., Gandon, S. & Buckling, A. 2012. Abiotic heterogeneity drives parasite local adaptation in coevolving bacteria and phages. Journal of Evolutionary Biology, 25(1), pp 187-195.

Mahmud, M. A., Bradley, J. E., MacColl, A. D. C. & Hopkins, W. 2017. Abiotic environmental variation drives virulence evolution in a fish host–parasite geographic mosaic. Functional Ecology, 31(11), pp 2138-2146.

Mattiuzzi, C., Lippi, G. & Henry, B. M. 2021. Healthcare indicators associated with COVID-19 death rates in the European Union. Public Health, 193(41-42.

May, R. M. & Anderson, R. M. 1979. Population biology of infectious diseases: Part II. Nature, 280(5722), pp 455-461.

Mendis, S., Puska, P. & Norrving, B. 2011. Global Atlas on cardiovascular disease prevention and control. Published by the World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization. .

Morris, D. H., Yinda, K. C., Gamble, A., Rossine, F. W., Huang, Q., Bushmaker, T., Fischer, R. J., Matson, M. J., van Doremalen, N., Vikesland, P. J., Marr, L. C., Munster, V. J. & Lloyd-Smith, J. O. 2020. The effect of temperature and humidity on the stability of SARS-CoV-2 and other enveloped viruses. bioRxiv.

Our-World-in-Data 2019. Asthma prevalence. https://ourworldindata.org/grapher/asthma-prevalence [Accessed 21 May 2022].

Ren, S. Y., Wang, W. B., Hao, Y. G., Zhang, H. R., Wang, Z. C., Chen, Y. L. & Gao, R. D. 2020. Stability and infectivity of coronaviruses in inanimate environments. World J Clin Cases, 8(8), pp 1391-1399.

Rochman, N. D., Wolf, Y. I., Faure, G., Mutz, P., Zhang, F. & Koonin, E. V. 2021. Ongoing global and regional adaptive evolution of SARS-CoV-2. Proceedings of the National Academy of Sciences, 118(29), pp e2104241118.

SanJuan-Reyes, S., Gomez-Olivan, L. M. & Islas-Flores, H. 2021. COVID-19 in the environment. Chemosphere, 263(127973.

Schmid-Hempel, P. 2009. Immune defence, parasite evasion strategies and their relevance for 'macroscopic phenomena' such as virulence. Philosophical Transactions of the Royal Society B, 364(1513), pp 85-98.

Walter, B. A. & Ewald, P. W. 2004. Pathogen survival in external environment and the evolution of virulence. Biological Reviews, 79(849-869.

Wang, R., Hozumi, Y., Zheng, Y. H., Yin, C. & Wei, G. W. 2020. Host Immune Response Driving SARS-CoV-2 Evolution. Viruses, 12(10), pp.

WHO 2020. Medical doctors (per 10 000 population). https://www.who.int/data/gho/data/indicators/indicator-details/GHO/medical-doctors-(per-10-000-population) [Accessed 26 May 2022].

WHO 2021a. WHO Coronavirus (COVID-19) Dashboard With Vaccination Data. https://covid19.who.int/ [Accessed 8 Sep 2021].

WHO 2021b. Tracking SARS-CoV-2 variants. https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/ [Accessed 14 July 2021].

Wirawan, G. B. S. & Januraga, P. P. 2021. Correlation of Demographics, Healthcare Availability, and COVID-19 Outcome: Indonesian Ecological Study. Front Public Health, 9(605290.

Woolhouse, M. E. J., Webster, J. P., Domingo, E., Charlesworth, B. & Levin, B. R. 2002. Biological and biomedical implications of the co- evolution of pathogens and their hosts. Nature Genetics, 32(569-576.

WorldData.info 2022. Life expectancy for men and women. https://www.worlddata.info/life-expectancy.php [Accessed 21 May 2022].

Zhan, J., Mundt, C. C., Hoffer, M. E. & B.A.Mcdonald 2002. Local adaptation and effect of host genotype on the rate of pathogen evolution: an experimental test in a plant pathosystem. Journal of Evolutionary Biology, 15(634–647).