The Role of Vitamin D in Suppressing Cytokine Storm in COVID-19 Patients and Associated Mortality

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Abstract

Background

Statistical analysis of data obtained from hospitals and clinics across the world has been analyzed to illuminate new insights into characteristics of COVID-19 and to discern whether a link exists between severe cases of COVID-19 that feature cytokine storm and vitamin D (Vit D) deficiency.

Method

Daily admission, recovery and deceased rate data for patients with COVID-19 from countries with over 5,000 confirmed cases through March 21, 2020, were selected. A potential association between severe Vit D deficiency and age-specific case fatality (CFR) was investigated. Reported medical characteristics of 793 COVID-19 patients were used to evaluate the intensity of cytokine storm in severe COVID-19 using C-reactive protein (CRP) levels. Medical data reported from a national study of 3,848 participants in 2007-2008 was used to investigate the association between Vit D status and CRP. Odds ratio and risk factors from these conditions were used to predict the potential impact of Vit D on the reduction of cytokine storm and severe COVID-19.

Findings

Age-specific CFR in Italy, Spain, and France (70 yo ≤ age < 80 yo) was substantially higher (>1.9 times) than other countries (Germany, South Korea, China); for the elderly (age ≥70 yo), Italy and Spain present the highest CFR (>1.7 times that of other countries). The age-specific ratio of confirmed cases in Italy, Spain, and France has also been substantially higher than in other countries. A more severe deficiency of Vit D (mean 25-hydroxyvitamin D (25OHD) concentration <0.25 ng/L) is reported in Italy and Spain compared to other countries. Our analysis of the reported clinical data (25OHD, CRP) from multiple studies suggests that elimination of severe Vit D deficiency reduces the risk of high CRP levels (odds ratio of 2) which may be used as a surrogate marker of cytokine storm which was estimated to a potential reduction in severe COVID-19 cases of up to 15%.

Interpretation

The substantially higher age-specific CFR and the age-specific ratio of confirmed cases in Italy and Spain (countries with low mean 25OHD level) suggest a potential link between severe Vit D deficiency and severe COVID-19, which can lead to a higher CFR. No direct link between the performance of health care systems, the age distribution of the nation, or Vitamin A deficiency and the CFR of COVID-19 were observed. Our analysis of the published data on the status of Vit D and CRP levels (in the US) and laboratory data (CRP levels) reported from 792 patients in China suggests that a proper supplementation of Vit D across populations may reduce the number of severe COVID-19 cases by up to 15 percentage points by lowering the risk factors related to cytokine storm. Our analysis did not eliminate the possibility of the circulation of different sub-genera of COVID-19 across the globe or other factors.

1. Introduction

The recent global outbreak of COVID-19 imposed catastrophic impacts on every society, specifically among elderly populations. Currently no treatment or vaccine has been produced which has led many researchers to look for approaches that can reduce the number of severe COVID-19 cases and consequently reduce the mortality rate of the disease. Time series analysis of the number of confirmed, deceased and recovered cases illuminates patterns of how COVID-19 has impacted different populations, which may help us to better understand the defense mechanisms of the immune system against COVID-19 and develop effective treatments for the viral infection. Italy and Spain have reported a substantially higher crude death rate than other countries [1,2] despite presenting a higher ranking in overall health care system performance [3]. Some experts have suggested analysis of age-specific case fatality ratio (CFR) and time-delayed adjusted mortality ratio for a more informative study of COVID-19 infection [4,5]. Initial reports and data obtained from various studies suggest that the elderly (age ≥70 yo) have disproportionately been impacted by COVID-19. The substantially higher CFR of the elderly population compels an age-specific analysis of COVID-19 data. Protection against viral infections is provided by the innate immune system and adaptive immune system. Many individuals have died due to complications from some of the main risk factors for COVID-19 such as ARDS, pneumonia, acute kidney failure, acute heart failure, and rhabdomyolysis.

Clinical data obtained from COVID-19 patients in China reported high concentrations of cytokines such as GCSF, IP10, MCP1, MIP1A, and TNFα in patients admitted to the ICU, which indicates the presence of cytokine storm in severe COVID-19 cases [6]. The innate (in very young populations) and adaptive (elderly populations) immune system plays an important role in regulating cytokine levels in viral infections. The impact of Vit D in enhancing immune response (including flu and previous coronaviruses) has widely been studied and firmly established [7–9]. Vit D can also suppress cytokine storm, which may substantially increase the chances of avoiding a severe case of COVID-19 [10,11]. Some researchers have suggested a potential association between Vit D and CFR during the 1918-1919 viral influenza pandemic, also through suppression of cytokine storm [12]. To the best of our knowledge, no randomized blinded experiment has yet reported Vit D

status and cytokine levels in patients with COVID-19. C-reactive proteins (CRP) are substances produced by the kidneys when the body is trying to fix damage to arteries, cells, and tissue from autoimmunity, infection, and other causes [13]. CRP could be used as a nonspecific marker to indirectly measure the severity of a cytokine storm during a severe COVID-19 case. In this article, we have used the reported patient-level data on the association between Vit D and CRP [14] to model and predict the potential impact of Vit D supplementation in the management and alleviation of cytokine storm (estimated by patient-level CRP data) which may lead to the reduction of severe COVID-19 cases. Country-level statistics on Vit D deficiency, COVID-19 mortality, age-adjusted CFR and other demographic variables have been investigated and discussed.

2. Methods

Data Collection

Data regarding the number of affected cases, deaths and recoveries from COVID-19 was obtained from Kaggle [15] as of April 1. The age distribution of the countries was calculated from a data set provided by the United Nations [16]. Age-specific CFR and age distribution of confirmed patients were calculated/estimated based on confirmed data available from national agencies including the Spanish Ministry of Health as of April 1 [17], Korean Centers for Disease Control and Prevention (KCDC) as of April 1[18], France public health (santé publique Francesante) [19] and Higher Institute of Health in Italy (Istituto Superiore di Sanità) [20] and Robert Koch Institute [21] The Hubei data is estimated based on the results reported in a recent article [22].

Data Analysis

Time-adjusted case mortality ratio (CMR) was estimated as the number of deceased patients on day N divided by the number of confirmed patients on day N-8. The age-specific case fatality rate was calculated as the number of deceased patients divided by the total number of confirmed patients (within the age group) on each day. When the age brackets between the released data were different adjustments are considered based on the equal distribution assumption within the age bracket. Age distribution of Germany was used in our calculation to more accurately estimate the age adjusted CFR and ration of confirmed cases based on the raw data available by the national agency.

3. Results

3.1. COVID-19 Fatality

Time-Adjusted Mortality (Crude)

The calculation of the actual mortality rate of COVID-19 is a challenging task, as the number of deceased patients and the number of confirmed patients at time of infection is unknown [4]. Stricter and more and bureaucratic screening policies implemented by many countries not only makes the calculation of the actual mortality rate more challenging, but also makes it difficult to determine a metric for the fair comparison of statistics between different countries. Analysis of the time events reported from 41 deceased patients in Wuhan (Hubei, China) shows a median time of 8 days between admission and time of death, and 14 days between onset of symptoms and time of death (shown in inset in the Figure 1) [23].

In order to determine a fair metric for comparison of the data between countries, a time delay of 8 days was used in calculation of mortality rate. The time-adjusted mortality rate (8 days) in each country reached a steady state and remained stable over (at least) the next 20 days as demonstrated in Figure 1. It appears that COVID-19 is progressing across these countries with four different mortality rates. Italy and Spain have presented a substantially higher mortality rate compared to the other countries (28.3%, 34.6%, respectively). The mortality rate in the United Kingdom, France, Iran and the US (20.2%,17.4%,14.1%, and 13.5%, respectively) is substantially lower than Italy and Spain, however, it is higher than in China and Switzerland (4.6%,5.0%, respectively). Germany and South Korea report the lowest mortality rates (2%, 1.8%, respectively).

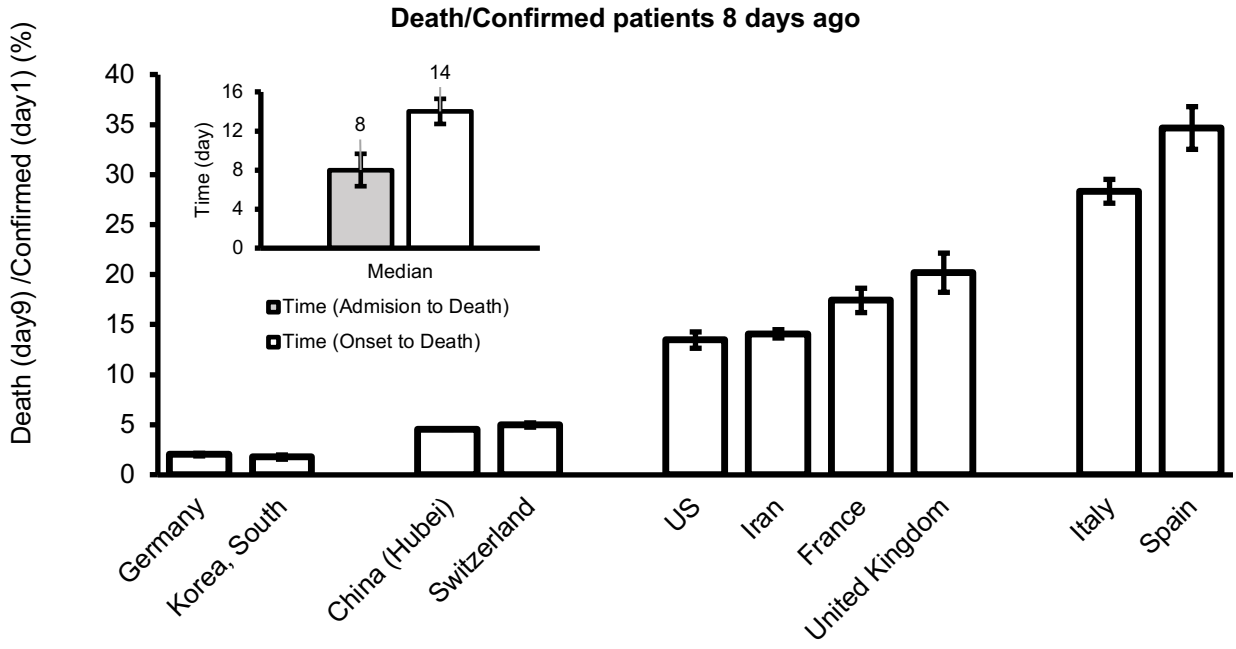

Figure 1- Mortality rate of COVID-19 in different countries (calculated as of April 1, 2020). The image in the inset shows the median time between admission and death or symptom onset and death obtained from 41 death cases of COVID-19 in Wuhan, Hubei, China. Error bars are calculated as the standard error of the reported data.

Age-Specific CFR

Age-specific CFR for the elderly with COVID-19 for the age brackets of 70 yo ≤ age < 80 yo and age ≥70 yo was estimated from the available data and results are shown in Figure 2. Italy, Spain, and France are presenting a substantially higher CFR (>1.9) than Germany, China, and South Korea in the age bracket of 70 yo ≤ age < 80 yo. Italy and Spain present a considerably higher CFR (1.6) for patients age ≥ 70 Germany, South Korea, and China (Hubei).

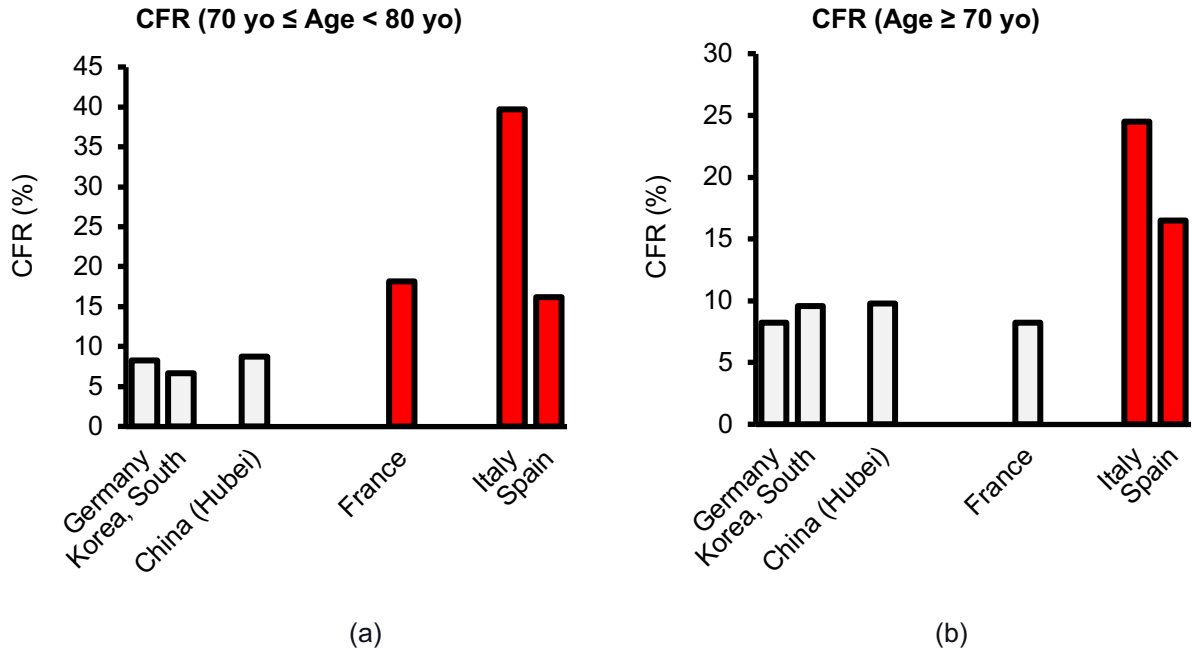

Figure 2- Adjusted age CFR for (a) 70 yo ≤ Age < 80 yo, and (b) CFR Age ≥70 yo. Results from Hubei is estimated based data collected from 44 671 patients [22], for Italy based on 94 312 , for Spain based on 63002 [17], for South Korea based on 9241 cases [18], Germany based on 36508 cases [21] , France based on 6378 [19].

The considerable difference in CFR for COVID-19 among the elderly in Italy and Spain suggests the possibility of unknown factors that substantially increase the fatality rate of COVID-19 in the elderly. These variables include the age distribution of confirmed patients, the total number of tested cases (country screening policy), immune system among the population, and other factors.

Confirmed Cases (Age-Adjusted Ratio)

The ratio of confirmed patients in the age bracket of 70 yo ≤ age < 80 yo and age ≥ 70 yo (showing in Figure 3) shows that elderly people have been disproportionately likely to display symptoms of COVID-19. The age distribution of countries (shown in Supplementary Material) cannot explain the demonstrated gap in the ratio of confirmed elderly cases. A recent study has shown that 60% of patients confirmed with COVID-19 do not show symptoms and can remain undetected [15]. It is not clear if this disproportionately high number of confirmed patients in Italy, Spain, and France is due to a targeted exposure of the elderly to the virus or the inability of their immune system in managing severe COVID-19.

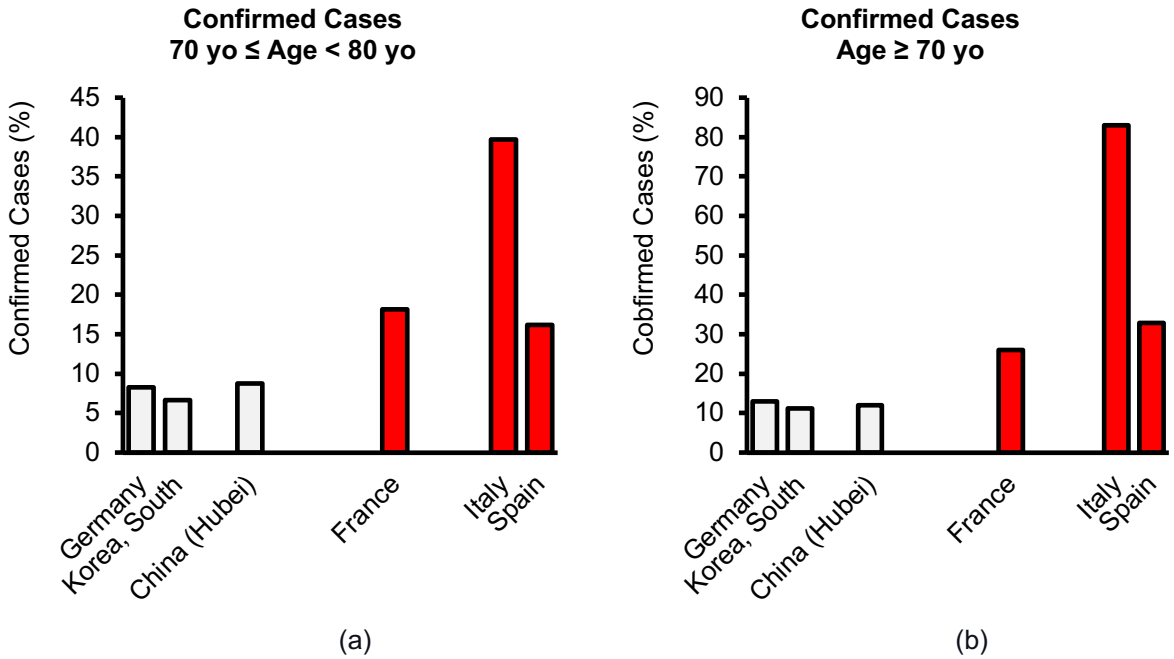

Figure 3- Age distribution of confirmed patients for age brackets of (a) 70 yo ≤ Age < 80 yo) and (b) CFR Age ≥ 70 yo. Results from Hubei is estimated based data collected from 44 671 patients [22], for Italy based on 94 312, for Spain based on 63002 [17], for South Korea based on 9241 cases [18], Germany based on 36508 cases [21], France based on 6378 [19].

Ratio of Confirmed Cases/ Tested Cases

In response to COVID-19, countries have implemented different strategies for screening patients for the disease. Germany and S. Korea have committed to mass population screening while the UK, France, Spain, Italy, and the United States have limited their efforts to only tests patients with severe symptoms, such as shortness of breath. The ratio of confirmed cases to tested cases for each country (shown in Figure 4 (a)) indicates that Italy and Spain have a substantially higher ratio of confirmed cases from testing (> 4.5 times higher than Germany). This suggests that the actual number of patients with COVID-19 in those countries is greatly higher than the reported figures. The majority of undetected COVID-19 patients in those countries should thus be younger people who display mild symptoms. This could be a reason for the notably higher ratio of confirmed elderly patients with COVID-19 in Italy and Spain compared to other countries, since the age distribution of the countries (shown in Figure 4(b)) cannot fully explain the reported numbers. In addition, the large number of patients with COVID-19 and the highly contagious nature of the virus make it less likely for the virus to target a specific age group in those countries.

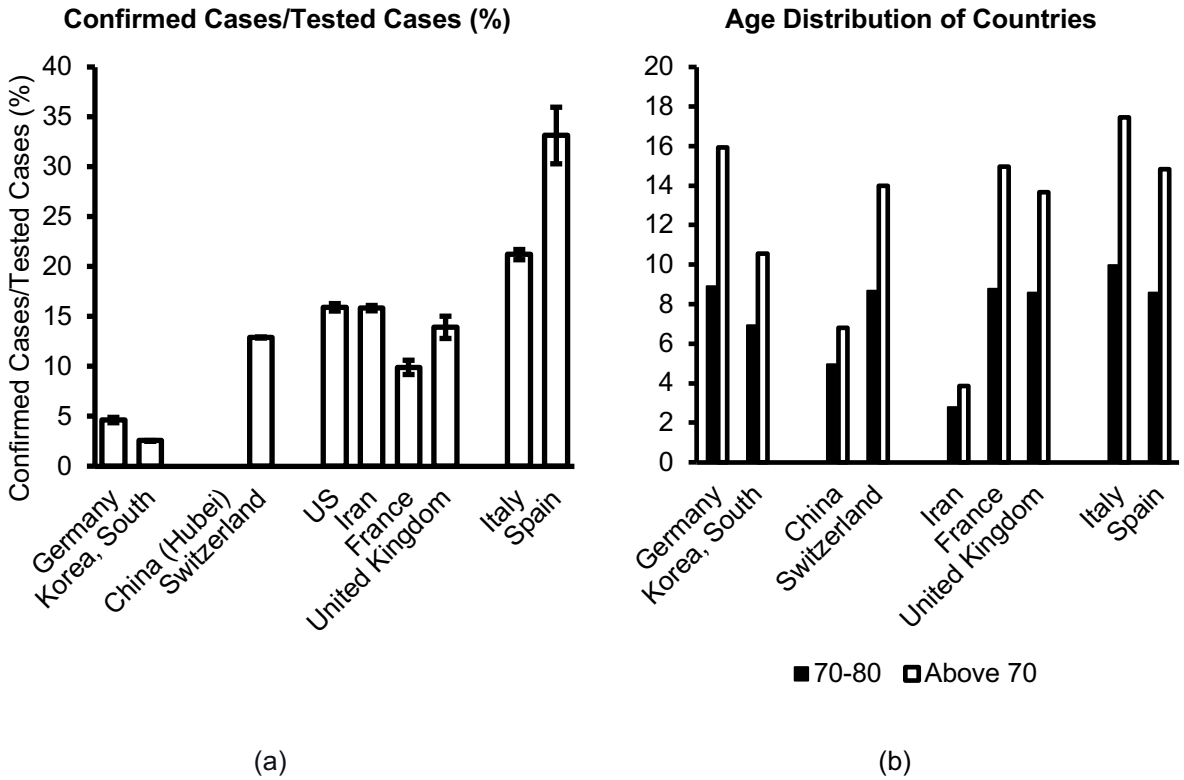

Figure 4- (a)The ratio of confirmed to tested cases in each country. (b) Age distribution of countries studied in this article [16].

Age Distribution of Confirmed, Hospitalized and Admitted to ICU Cases

The age distribution of the patients who were hospitalized admitted to the ICU and the deceased is illustrated in Figure 5. The results presented here demonstrate a pattern containing two peaks (one in very young patients and one in the elderly population). We hypothesis that cytokine storm and immunosuppression is a major reason for the admission of patients to ICU [24]. A cytokine storm might have been activated by the innate immune system in the very young population (< 4 yo) while the adaptive immune system could have produced the cytokine storm in the elderly (highlighted in red in the picture). A substantially higher number of elderly patients (age > 60 yo) admitted to the hospital (Figure 5 (a)), and the notably higher ratio of deceased patients in the population (Figure 5 (d)) suggests the potential importance of management of the adaptive immune system in patients with COVID-19. These results suggest the aberrant responses of the innate immune system in the elderly population may lead to cytokine storms which causes them to be admitted to the ICU at a higher ratio. The higher ratio of deceased to admitted to ICU patients in the elderly population (age ≥ 70) suggests the threshold for severe consequences of cytokine storm is substantially lower for them after aging. The high ratio of children (age < 4 yo) admitted to the ICU might also be linked to the interaction of their innate immune system with COVID-19. The very low ratio of deceased to admitted to ICU patients suggest a high threshold against the consequence of this battle among them.

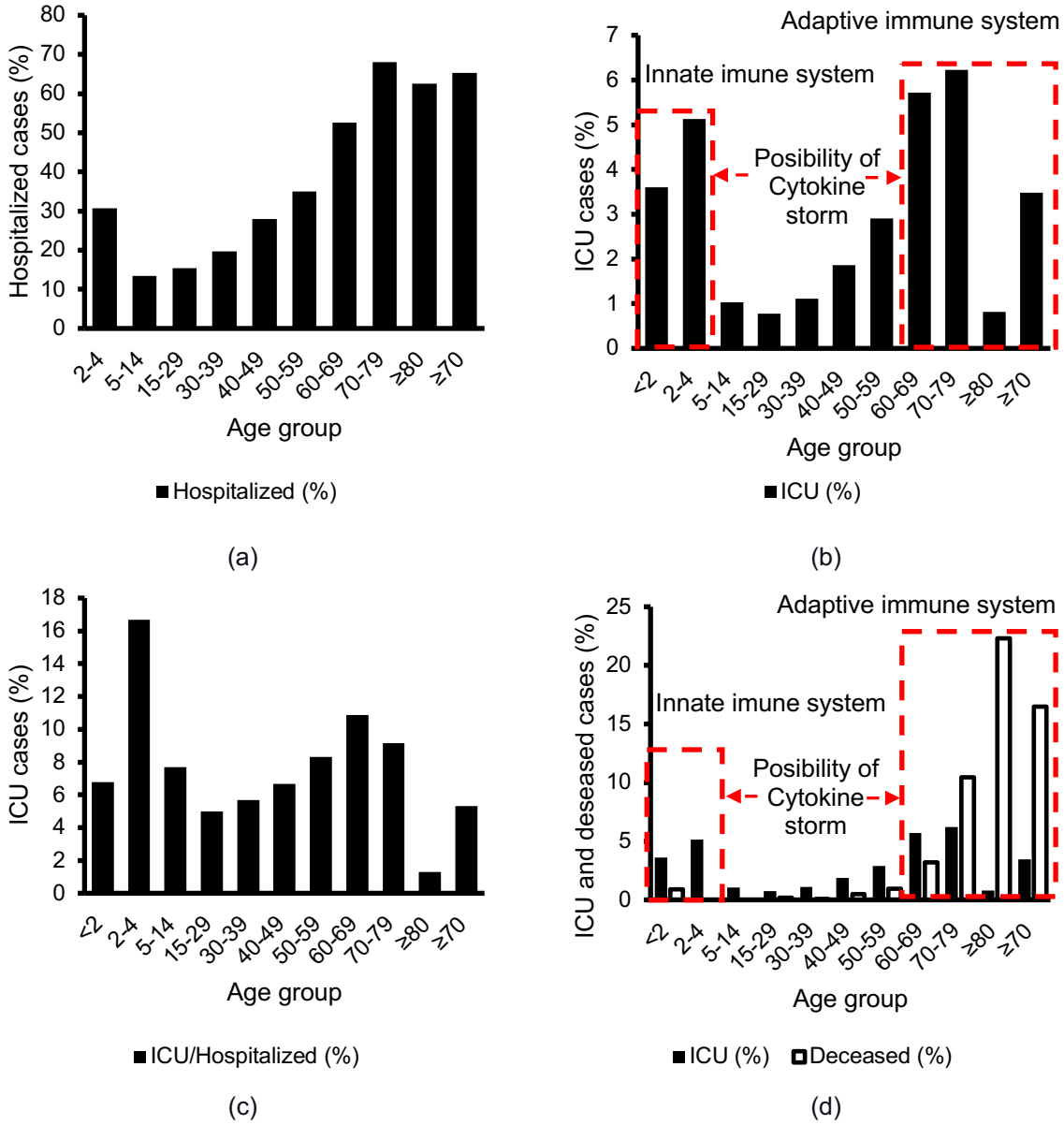

Figure 5- Age distribution of the a) hospitalized, b) admitted to ICU, c) ratio of admitted to the ICU to the hospitalized, d) admitted to ICU, deceased in Spain based on data from 63002 cases [17].

3.2. Vit D Deficiency in Different Countries

Status of Vit D deficiency in countries such as Germany, S. Korea, China, Switzerland, Iran, France, United Kingdom, Italy, and Spain has been evaluated in different studies by measuring mean 25-hydroxyvitamin D (25OHD) concentration, and the results are shown in Figure 6. The figure shows that Italy, Spain, and France are the three countries with a mean 25OHD concentration smaller than the threshold defined for severe Vit D deficiency. Italy, with a reported mean 25OHD concentration of 19.9 and Spain, with reported 25OHD concentration of 22.5, have presented the highest mortality rates despite having a better health system performance ranking. These nations' age distribution (shown in the supplementary material) does not justify such a trend. Evaluation of the age

distribution of the confirmed patients would suggest that Italy and Spain present a higher mortality rate than South Korea, Iran, and China, however, it does not fully explain the current gap. For example, the death rate (number of dead/number of the confirmed patients on the same day) among patients aged > 80 in Italy (26%) is substantially higher than in South Korea (17%). In addition, the age distribution variation within confirmed patients in European countries cannot explain the gap between Italy/Spain and Germany, Switzerland, France, and the UK. More importantly, the case fatality is substantially higher in Italy and Spain even if considering specifically at the elderly (age-adjusted CFR shown in Figure 2). This led us to further investigate the impact of severe Vit D deficiency on the increase in mortality rate.

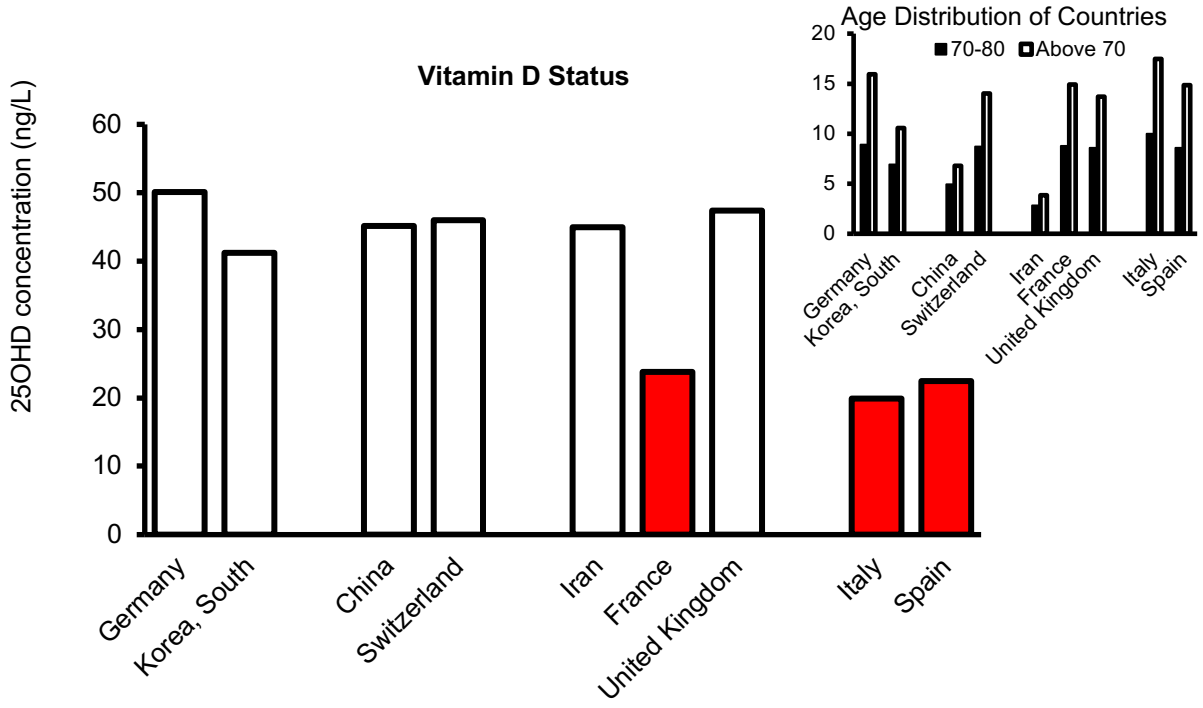

Figure 6- Vit D status is compared via the mean concentration of 25OHD in each country. The data is obtained from independent studies in each country [25–31]. Age distribution of the countries are illustrated in the inset at the top right [16].

Sensitivity Analysis

The results presented in Figures 2, 3 & 6 show that countries such as Spain and Italy with a severe Vit D deficiency report a substantially higher mortality rate (crude) and adjusted CFR for ages 70 yo ≤ age < 80 yo and age ≥ 70 yo than Germany, South Korea, China, Switzerland, Iran, the US, and UK (countries with less severe Vit D deficiency). A key issue is that these countries have not all used the same screening policy. As a result, countries that do relatively little testing tend not to detect mild disease but do show a similar rate of severe disease detection, since severe cases are eventually tested as symptoms worsen. Thus, low-testing countries would exhibit a higher fatality rate. The large ratio of confirmed cases at age > 70 in countries with more restrict screening policies

such as France, Spain and Italy compared to the countries with less restrict screening policy suggests that mild undetected diseases are more likely to be a part of the younger population. This suggests the impact of screening policy for comparison of the CFR for the elderly (age ≥ 70) is less sensitive than the impact of screening policy on the crude mortality rate.

A sensitivity analysis was conducted where the mortality rate was adjusted based on the ratio of confirmed/tested cases and the result is provided in the Figure 7 (inset). To reduce the error of our model we limited our analysis to the countries with a similar confirmed/tested case ratio (Italy, France, Iran, USA, China, Switzerland) and excluded Germany, South Korea, and Spain. In this analysis, we adjusted the mortality rate in each country based on the condition that a fixed confirmed/tested case ratio of 9.9% (confirmed/tested case ratio of France) exists in all data sets. This adjustment is done by including more undetected mild COVID-19 cases in the raw data of other countries. In this modeling, we hypothesized that the undetected mild COVID-19 in all countries is a population of subjects with confirmed/tested ratio of 4.95% (half of the current ratio of confirmed cases in France). The adjusted data (shown in Figure 7) shows France and Italy (countries with the lowest mean 25OHD levels) present a notable higher mortality rate than Iran, US, Switzerland.

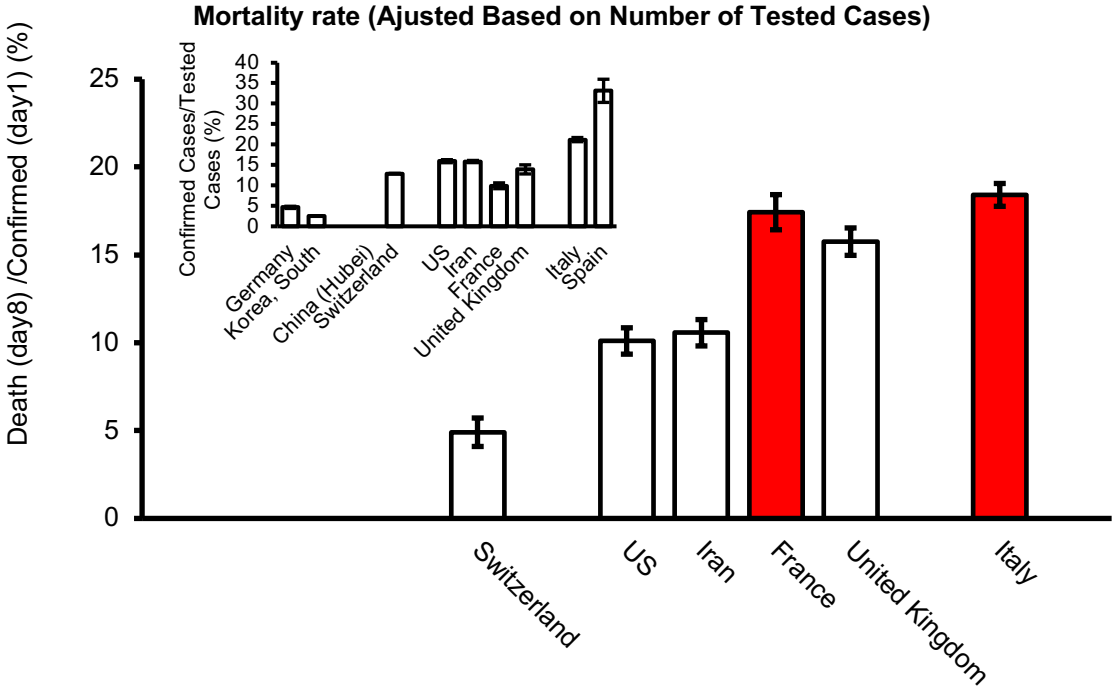

Figure 7- Mortality rate (Death (day8) /Confirmed (day1)) after adjustment for equal number of tested cases. The ration of confirmed/tested cases used for this adjustment is shown on top left in the inset.

4. Theory and Analysis based on Patient Level Clinical Data

4.1. Vit D and Immune System

Immunosenescence reduces the chance of survival in patients presenting with COVID-19, perhaps because the body's line of defense may weaken through deficiencies in nutrients and vitamins. For example, it is well established that the expression of Vit D receptors in interactions with immune cells such as T-cells, B-cells, and antigen-presenting cells leads to immune regulation by enhancing the innate immune system and suppressing the adaptive immune system [8,9]. Overactivation of the adaptive immune system can lead to cytokine storm and its suppression via Vit D can reduce the cytokines level.

4.2. Vit D and ACE2 Pathway, Hypertension, and Diabetes

Clinical data from COVID-19 patients suggests a higher risk for the development of severe COVID-19 in patients with prior hypertension or diabetes [6,6,32–34]. Patients with these conditions are treated with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs) which increase the expression of angiotensin-converting enzyme 2 (ACE2) which can lead to severe infection with COVID-19 [35]. Variation in ACE2 expression may play an important role in growth rate and severity of COVID-19 [36].
The genetic mechanisms underlying hypertension and its association via ACE2 expression to Vit D has been widely investigated [37–39]. Hypertension in severe COVID-19 patients is characterized by an activated renin-angiotensin system (RAS) in the lungs. Vit D neuroprotective mechanisms during hypertension through the ACE2/Ang(1–7)/MasR pathway helps to reduce the risk of RAS [7]. Intensive study of over 11,321 participants has demonstrated the impact of Vit D on lowering the risk of RAS [40]. Trigger of RAS through Vit D deficiency [41] reduces lung efficiency by the development of fibrosis over time [42]. This suggests that patients in Italy and Spain with severe Vit D deficiency may be at higher risk of severe COVID-19.

In addition, Vit D plays an important role in regulating inflammatory cytokines (suppressing inflammatory and boosting anti-inflammatory cytokines [43,43,44]) and CRP [45] which substantially reduces the risk of infection and cardiovascular disease (CVD). A substantially high odds ratio of inflammatory cytokines [6] and CRP [14] in patients with severe COVID-19 further underlines the potential importance of Vit D in boosting the immune system and reducing the risk factors for severe COVID-19.

4.3. Analysis of Available Clinical Data

The clinical data from confirmed COVID-19 patients in China (up to 52 hospitals in 30 provinces) shows a substantially higher frequency of cases with CRP ≥ 10 mg among patients with severe COVID-19 (81.5%, 110 cases out of 135) than patients with a mild form of the disease (56.5%, 371 cases out of 658) [14]. The relationship between high CRP and Vit D has been widely investigated in different clinical studies. A recent history of CVD among COVID-19 patients has shown another important risk factor for which an association with Vit D needs to be investigated.

4.4. Potential Impact of Severe Vit D Deficiency on Positive (High) CRP

CRP production in the liver and its subsequent concentration in plasma is increased in response to inflammation. Laboratory data collected nationwide from 3,840 participants (by NHANES in 2007-2008) and analyzed by Li et al shows a strong relationship between severe deficiency of Vit D and a high (positive) level of CRP [46]. Analysis of the reported data (without any adjustment of the demographic variables) is shown in Figure 8 and suggests an odds ratio of 2 and risk factor of 1.4 for a high CRP plasma in subjects with severely deficient Vit D (25OHD < 25 ng/l).

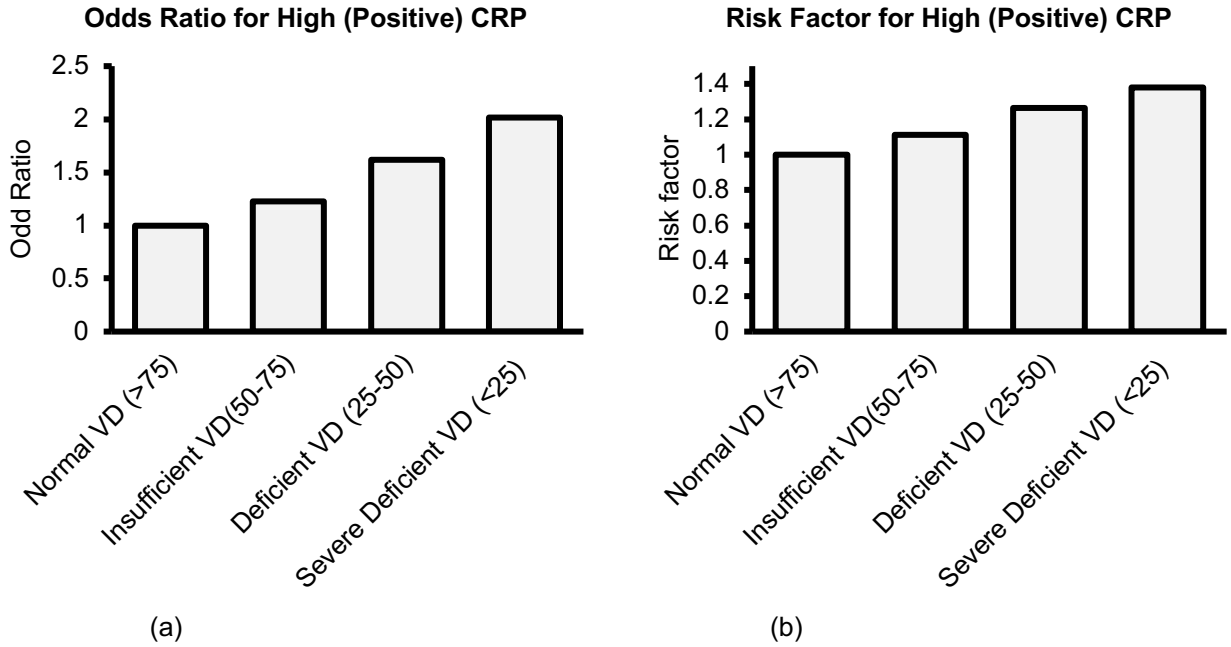

Figure 8- (a) Odd ratios (b) Risk factor of high (positive) CRP for different status of Vit D. The plots are provided based on data reported by Li et al [46].

This means that subjects with a severe deficiency of Vit D have 1.4 times higher risk for production of high CRP. It is hypothesized that Vit D deficiency increases the risk for Cytokine storm in COVID-19 patients and increases the concentration of CRP in a similar fashion as it is reported in healthy controls (Figure 9). It is also hypothesized that risk if a high CRP increases the chance of severe COVID-19.

Sufficient supplementation of Vit D might have inhibited damage to the body, leading to less frequent production of a high concentration of CRP. The risk of high CRP in patients with normal Vit D levels is 0. 45 and reaches 0.63 in patients with severe deficiency of Vit D. Using the data provided in the Table 1&2, the risk of a severe COVID19 given Vit D status is calculated based on the equation 1.

Table 1. The risk associated with CRP status given severe COVID19, and COVID-19 given CRP status is provided/calculated based on the data reported in a recent study [14].

	Number of patients/Total (Risk)
Risk of High CRP	481/793 (0.61)
Risk of Low CRP	312/793 (0.39)
Risk of High CRP given Severe COVID-19	110/135(0.81)
Risk of Low CRP given Sever COVID-19	25/135(0.19)
Risk of Severe COVID19 given High CRP	110/481 (0.23)
Risk of Severe COVID19 given Low CRP	25/316 (0.08)
Risk of Mild COVID-19 given High CRP	371/666(0.56)
Risk of mild COVID19 given Low CRP	285/656(0.44)

Table 2. The risk associated with high CRP given Vit D status is provided/calculated based on the data reported in a study [46].

25(OH)D (nmol/mL)	High CRP/Low CRP (Risk of High CRP)
at Normal Vit D (>75)	495/597 (0.45)
at Insufficient Vit D (50-75)	729/717 (0.50)
at Deficient Vit D (25-50)	639/476 (0.57)
at Severe Deficient Vit D (<25)	122/73 (0.63)

$$\text{Risk (severe COVID-19|Severe Deficient Vit D)} = p\,(\text{High CRP}|\text{Severe Deficient Vit D}) \times p(\text{Severe COVID-19}|\text{High CRP}) + p\,(\text{Low CRP}|\text{Severe Deficient Vit D}) \times p\,(\text{Severe COVID-19}|\text{Low CRP}) \quad (1)$$

In an ideal scenario, Severe Vit D Deficiency increases the risk of high CRP levels by 17% (63%-45% =17%). As the results the Risk (Severe COVID-19|Severe Deficient Vit D) = $0.63\times(110/481) + 0.37\times(25/316) = 0.173$ while the Risk (Severe COVID-19|Normal Vit D) = $0.45\times(110/481) + 0.55\times(25/316) = 0.146$. This calculation suggests the potential for 15.6% reduction in the risk of severe COVID-19 cases by Vit D.

4.5. Potential Impact of Severe Vit D Deficiency on CVD

A recent study suggests a respective case fatality rate (CFR) of 2.3% and 10.5% for COVID-19 patients with and without CVD history in Wuhan (China). [22]. This makes it important to determine a mechanism for reducing the risk factor for CVD.

Li et al analyzed data obtained from a nationwide study (from 2007-2008 in the US) on 3,840 participants to illuminate the association between Vit D and high CRP with CVD (an important risk factor of COVID-19). They developed a model which adjusts demographic variables (such as age, race, gender, and others) and demonstrated that as Vit D deficiency becomes more serious the odds ratio for CVD increases, where an odds ratio of 1.9 (95% confidence interval (CI) [1.06, 3.40], P-value = .0317) is obtained at severe Vit D deficiency (25OHD<25 nm/L) [46]. The relative risk factor for an odds ratio

of 1.9 [46] and an estimated baseline ratio of 0.1 is calculated as 1.7 based on equation 1 [47].

$$\text{Relative risk} = \text{odds ratio} / (1 - p_0 + (p_0 \times \text{odds ratio})) \quad (2)$$

where p_0 is the baseline risk. Normal status of Vit among a population reduces the risk for CVD by 42% (calculated from a risk factor of 1.7). Reduction the CVD% among a population will reduces the risk of a severe COVID-19.

Discussion

Based on the highly contagious nature of COVID-19 and the notably lower percentage of confirmed younger cases (and their very low CFR) we suggest that young patients, especially very young children, do get infected but are nearly asymptomatic. Age-adjusted CFR shows that case fatality steadily increases with age in all countries. A notably different age-adjusted CFR is partially due to different screening and admission policies in different countries. For example, in South Korea and Germany a higher number of patients with mild symptoms are admitted. Italy and Spain have a substantially higher ratio of confirmed patients with age ≥ 70 yo. This suggests these countries are missing a large number of young patients with mild symptoms and could be the reason for their notably higher mortality rate among their confirmed patients compare to Germany, South Korea, and China. However, these idiosyncrasies (in screening strategies) do not fully explain the phenomenon. A substantially higher age-adjusted CFR (age ≥ 70 yo) is observed in Italy, Spain, and France (countries with more severe Vit D deficiency) than Germany, South Korea, and China (Countries with less severe Vit D deficiency). Adjustment of screening method (same ratio of confirmed/tested cases) for countries with similar screening methods (US, France, Iran, Switzerland, UK, and Italy) shows France (Country with the most severe Vit D deficiency) has reported the highest mortality rate. The statistics available at country level suggests patients' adaptive immune system may have been responding differently among the patients at different age group and also among the population (countries) with severe Vit D deficiency.

The inability of the innate immune system in managing COVID-19 and a shortage in memory B cells leads to misfire and overactivation of the adaptive immune system by producing a high level of cytokines (cytokine storm). The aberrant responses of the innate immune system in the elderly (compare to the younger patients) may increase the risk of the viral load [48] which intensifies the activation of the adaptive immune system and production of cytokine storm among this population. This cytokine storm (reported in COVID-19 patients [49]) brings complications such as ARDS, exacerbation of the effects of pneumonia, acute kidney failure, acute heart failure, and rhabdomyolysis [14] that in some cases becomes fatal. In addition, a weaker cytokine storm among the elderly population can be more fatal (than in the younger population) as the threshold for severe consequences of lung damage is substantially lower for them after aging. Even moderate lung damage due to cytokine storm may lead to hypoxemia that in turn results in mortality due to underlying complications such as CVD.

The time interval for the development of a notable adaptive immune response is estimated as a week, which is consistent with the current median time to death in COVID-19 patients (14 days) [23,50]. The possible role of ibuprofen in worsening COVID-19 treatment [51] can be explained by its action on suppression of innate immunity [52,53]

which leads to overactivation of the adaptive immune system that may intensify the cytokine storm and become fatal in elderly patients [54,55]. Vit D, on the other hand, may help by boosting the innate immunity (to reduce the viral load) and by suppressing the adaptive immune system (which may further reduce cytokine storm) [8,9]. The role of Vit D in regulating immunity [8,9] and reduction of cytokine storm may avoid the complications caused by a cytokine storm in the elderly population.

5. Conclusion

Italy, Spain (countries with severe VitD deficiency) have a notably higher ratio of confirmed elderly patients (age ≥ 70 yo) and also a higher CFR among the elderly population (age ≥ 70 yo) than other countries such as Germany, China, and South Korea. A sensitivity analysis among the countries with similar screening methods (US, France, Iran, Switzerland, UK, and Italy) shows France (a country with the more severe Vit D deficiency) has reported a notably higher adjusted (a fixed confirmed/tested ratio) mortality rate which fits into the hypothesis.

We suggested (based on the observed patient-level clinical data [6]) that the aberrant responses of the innate immune system in the elderly (compare to the younger subject) may increase the risk of the COVID19 viral load. The increased viral load causes overactivation of adaptive immune system that produces a cytokine storm. Patient-level CRP data were used as a surrogate marker of cytokine storm and its link and association with Vit D status was used to suggest a potential link between Vit D severe deficiency and the number severe COVID-19 cases. Our analysis suggested a 15% reduction in the number of severe COVID-19 cases given a normal Vit D status within a population. With the availability of data showing a direct link between Vit D status and specific markers of cytokines, a more accurate estimation could be estimated.

Acknowledgment

The authors would like to thank Benjamin D Keane for his assistance in preparing the paper. The authors would also like to acknowledge generous support from the Carinato Charitable Foundation, Mark and Ingeborg Holliday, Kristin Hudson & Rob Goldman, and Ms. Susan Brice & Mr. Jordi Esteve.

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