

١ T3 Thyroid hormone deficiency is an important factor in the prognosis of death  
٢ in SARS-Cov-2 patients  
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## Abstract

There are some reports about Triiodothyronine (T3) reduction in some SARS-Cov-2 patients. Based on a rigorous machine learning classification, we have found that the T3-Level is the key-control-variable for fatal outcomes in reported metabolomics data of these patients. The Lower levels of T3 is associated with unbalanced states of the immune system: down-regulation of T3 is associated with up-regulation of "CD4/CD8 ratio". This phenomenon could yield severe autoimmune reactions and could be responsible for fatal outcomes of SARS-Cov-2. So the people who have lower levels of T3 in their blood are at a higher level of mortality risk. Furthermore, there is an evidence about downregulation effect of T3 against proinflammatory mechanisms of SARS-Cov-2: "the proinflammatory cytokines IL-1 $\beta$  and IL-6 that are downregulated by induction of the TREM2 pathway were downregulated by T3 and sobetirome in microglia and macrophages that have been stimulated with the pro-inflammatory SARS-CoV-2 spike protein". The molecular docking study shows T3 and T4 have comparable docking scores, in comparisons with Remdesivir, Trigonelline and Emodin (The COVID-19 Docking Server was served) for binding to some COVID-19 proteins. A linear regression model (with Correlation Coefficient =0.98) is found that correlates Urinary Iodine Concentration (UIC) and SARS-Cov-2 mortality rates of 91 countries, till 24 Feb 2021. It is important because the iodine metabolism is related to thyroid state and functions. Age, diabetes, obesity, ethnicity, gender, genetics, epigenetics, and environmental factors (like pollutions and ionizing-radiation) affect people's T3 blood-level. It could exactly explain the reported effects of those risk factors.

## Keywords

T3 Thyroid hormone, SARS-Cov-2, prognosis of death, machine learning, Epidemiology

Dear Chief Editor,

We hope you are staying safe and healthy through this pandemic state.

There are some reports about Triiodothyronine (T3) reduction in some SARS-Cov-2 patients[1][2][3][4] [19]. Based on a rigorous machine learning classification [5], we have found that the T3-Level is the key-control-variable for fatal outcomes in reported metabolomics data[6] of these patients (Figure-1 and Figure-2).

Based on prior research literature, The Lower levels of T3 is associated with unbalanced states of the immune system: down-regulation of T3 is associated with up-regulation of "CD4/CD8 ratio"[9]. This phenomenon could yield severe autoimmune reactions and could be responsible for fatal outcomes of SARS-Cov-2 [10]. So the people who have lower levels of T3 in their blood are at a higher level of mortality risk.

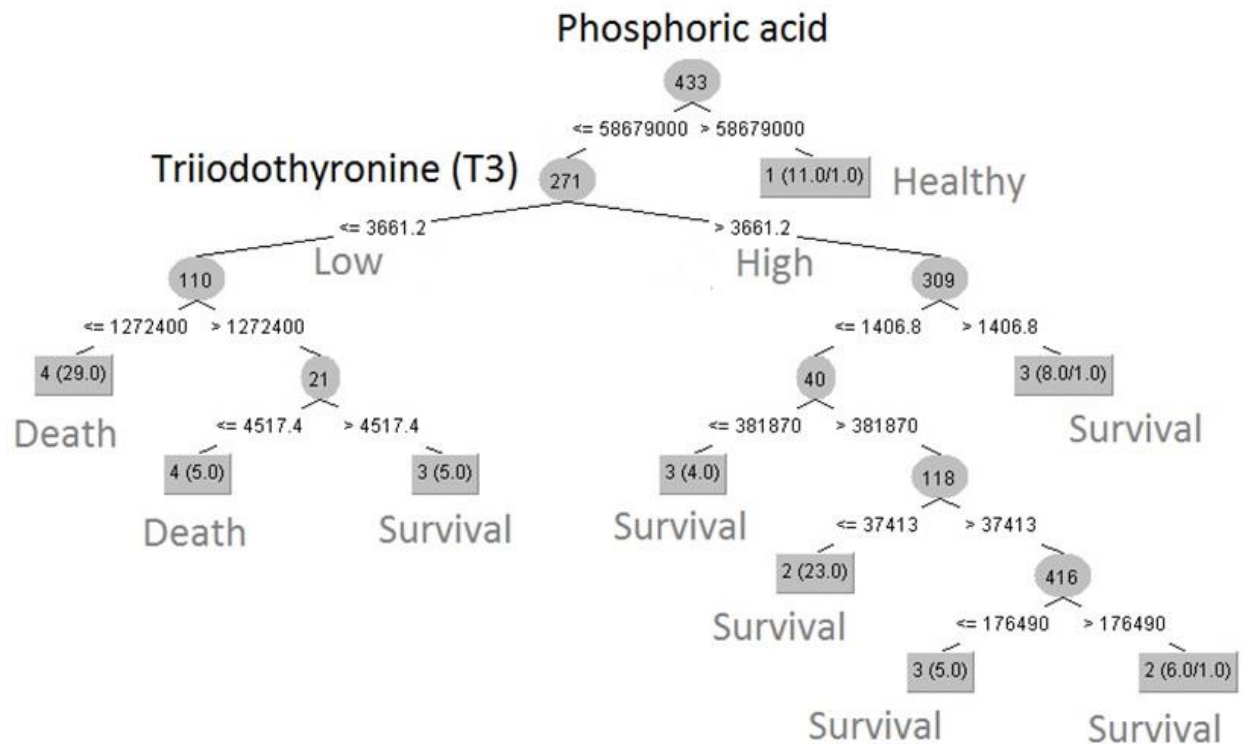
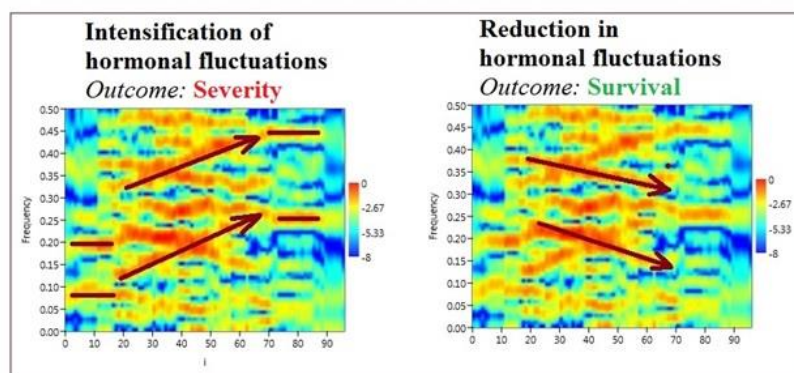
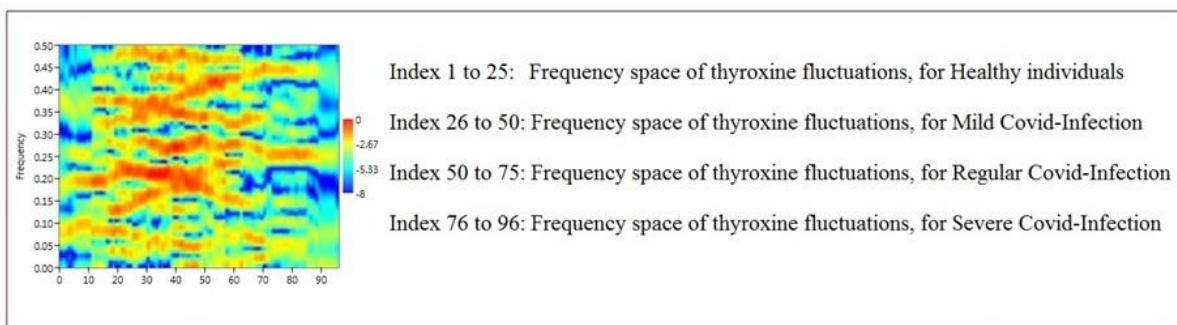
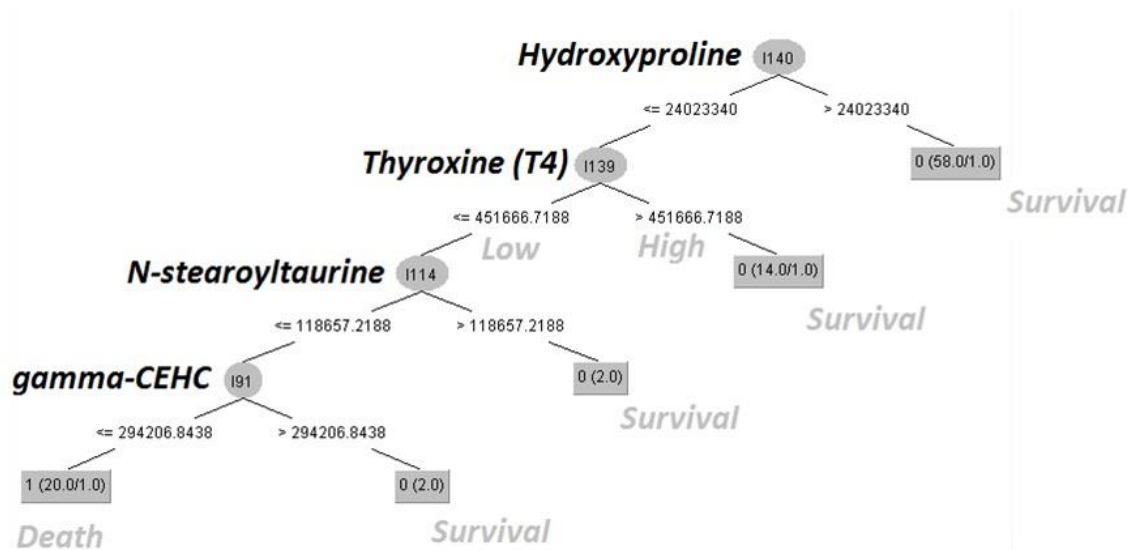


Figure 1- The resulting decision tree of J48 classification algorithm suggests that the key control variable of "death" and "survive" in sever Covid-19 cases is the level of T3 thyroid hormone in the blood [5].



Source of Raw Data:

Shen, Bo, Xiao Yi, Yaoting Sun, Xiaojie Bi, Juping Du, Chao Zhang, Sheng Quan et al. "Proteomic and metabolomic characterization of COVID-19 patient sera." Cell 182, no. 1 (2020): 59-72.

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Figure 2- T4 importance and fluctuations, computed for another COVID-19 metabolomic data [7]. An important part of T3 in the body is supplied by the conversion of t4 to it [8]. Therefore, T4 fluctuations lead to t3 fluctuations.

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Furthermore, there is an evidence about downregulation effect of T3 against proinflammatory mechanisms of SARS-Cov-2: ” the proinflammatory cytokines IL-1 $\beta$  and IL-6 that are downregulated by induction of the TREM2 pathway were downregulated by T3 and sobetirome in microglia and macrophages that have been stimulated with the pro-inflammatory SARS-CoV-2 spike protein”[11].

The molecular docking study shows T3 and T4 have comparable docking scores, in comparisons with Remdesivir, Trigonelline and Emodin (The COVID-19 Docking Server was served [13]) for binding to some COVID-19 proteins (Table-1 and Figure-3). Also, the compound Nicotinate mononucleotide with the formula C<sub>11</sub>H<sub>15</sub>NO<sub>9</sub>P<sup>+</sup> could inhibit RNA-dependent RNA polymerase (RdRp (RTP site)) protein in COVID-19 coronavirus, with a Score Value of -9.3 (kcal / mol). This is better than the amount for the Remdesivir molecule (-9.2 (kcal / mol)) to inhibit the same protein. Since inhibition of this protein plays a key role in the inhibitory function of Remdesivir against COVID-19 virus [14], we can see the Nicotinate mononucleotide compound as an alternative to Remdesivir in inhibiting this coronavirus. Since the molecular weight of Nicotinate mononucleotide (336 g / mol) is approximately half that of Remdesivir (603 g / mol), it is better in terms of both protein adhesion and absorption capacity. Since the main precursor of Nicotinate mononucleotide, Trigonelline alkaloid, is a naturally occurring plant secondary metabolite, and Nicotinate mononucleotide itself is present in mammalian biomolecular pathways, it is likely to be more available, more cost-effective, and more non-toxic and be better than Remdesivir.

Table 1- The Docking Study Results

	Molecular Weight	Main Protease		RdRp(RTP site)		Nsp14(N7-MTase)	
	(g/mol)	Score Value (kcal/mol)	RF Score Value (pKd)	Score Value (kcal/mol)	RF Score Value (pKd)	Score Value (kcal/mol)	RF Score Value (pKd)
<b>Trigonelline (N-methylNicotinate)</b>	137.14	-4.4	4.24	-6.10	4.47	-5.7	4.37
<b>Emodin</b>	270.24	-7.20	5.76	-8.5	5.7	-8.8	6.18
<b>T3 Hormone -Sulfate-</b>	731	-6.70	5.32	-8.0	6.16	-8.5	6.62
<b>T4 Hormone -Sulfate-</b>	856.9	-7.00	5.57	-7.90	5.88	-7.9	6.26
<b>Remdesivir</b>	602.6	-7.70	6.59	-9.20	6.78	-9.9	7.28
<b>Nicotinic acid D-ribonucleotide (Nicotinate Mononucleotide)</b>	336.21	-7.00	5.01	<b>-9.30</b>	5.29	-7.70	4.96
<b>Ethyl 2-[2-(aminocarbonyl)-4-chlorophenoxy]nicotinate</b>	320.73	-6.40	6.17	-7.30	7.29	-7.60	6.29
<b>Curcumin Nicotinate</b>	578.6			-8.30	<b>7.41</b>		

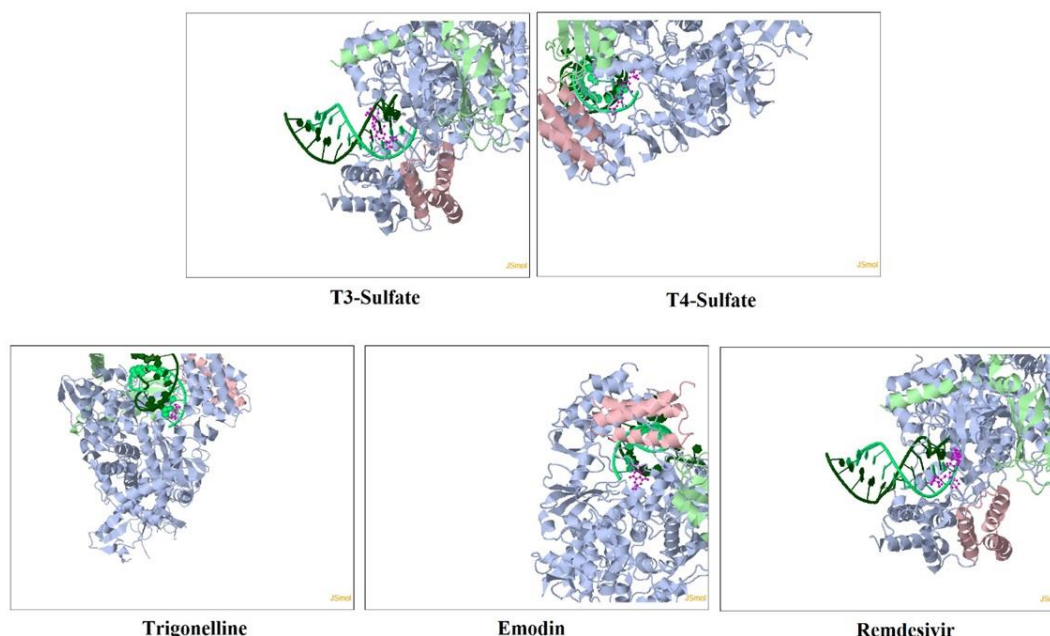


Figure 3- Docking Models for RdRp(RTP site).

A linear regression model (with Correlation Coefficient =0.98) is found that correlates Urinary Iodine Concentration (UIC) and SARS-Cov-2 mortality rates of 91 countries, till 24 Feb 2021 (Figure-4, Figure-5 and Figure-6). It is important because the iodine metabolism is related to thyroid state and functions. Age, diabetes, obesity, ethnicity, gender, genetics, epigenetics, and environmental factors (like pollutions and ionizing-radiation) affect people's T3 blood-level. It could exactly explain the reported effects of those risk factors in COVID-19.

## OCEANIC IODINE, WIND DIRECTION AND COUNTRIES SEVERELY AFFECTED BY COVID-19 MORTALITY

The United States, Mexico, India, Brazil, the United Kingdom, and continental Europe are unfortunately experiencing the highest rates of SARS-Cov-2 mortality. These countries are right next to the hotspots of iodine release in the oceans (Figure-7) [15]. In terms of the prevailing wind directions on Earth, we find that there is strong evidence for the "geographical coincidence" of "Oceanic Iodine Hotspots", and the "SARS-Cov-2 mortality Hotspots."

In the last six months, for Aug 2021, fluctuations in the daily SARS-CoV-2 mortality rate on five continents have been synchronous (Figure-8). This indicates the global nature of the cause of these fluctuations, so the effect of which is observed simultaneously on

different continents. The only global factor that can account for such precise and coordinated fluctuations on the five continents is climate and atmospheric factors. A close look at the details of the chart above for the last 6 months shows that the fluctuations start on the South American continent and then transfer to the rest of the continents with a delay of few days. The release of iodine from the surface of the ocean and then its movement in the atmosphere as atmospheric iodine, which can play a hormonal and regulatory role in the body after inhalation, can be a candidate for the latent factor. This means that in addition to its important infectious dimension, COVID-19 disease also has an allergic or hormonal dimension in exacerbating the condition.

We have already seen wind time-dependent time trends for SARS-Cov-2 intensification in Europe, Asia, and also within Iran (both temporal and directional) [16] [17]. These three types of evidence (geographical, temporal, and directional) suggest that the main cause of the corona's rise and fall in different regions is the "released oceanic iodine" reaching different areas by wind ( Interestingly, iodine is also carried by aerosol particles, which our face-masks can absorb and prevent their inhalation). The finding itself (relation between oceanic iodine and SARS-Cov-2 hotspots) suggests that part of the SARS-COV-2 multisystem syndrome is due to hormonal or allergic reactions to inhaled iodine, which pave the way for the COVID-19 virus to flourish further in the body.

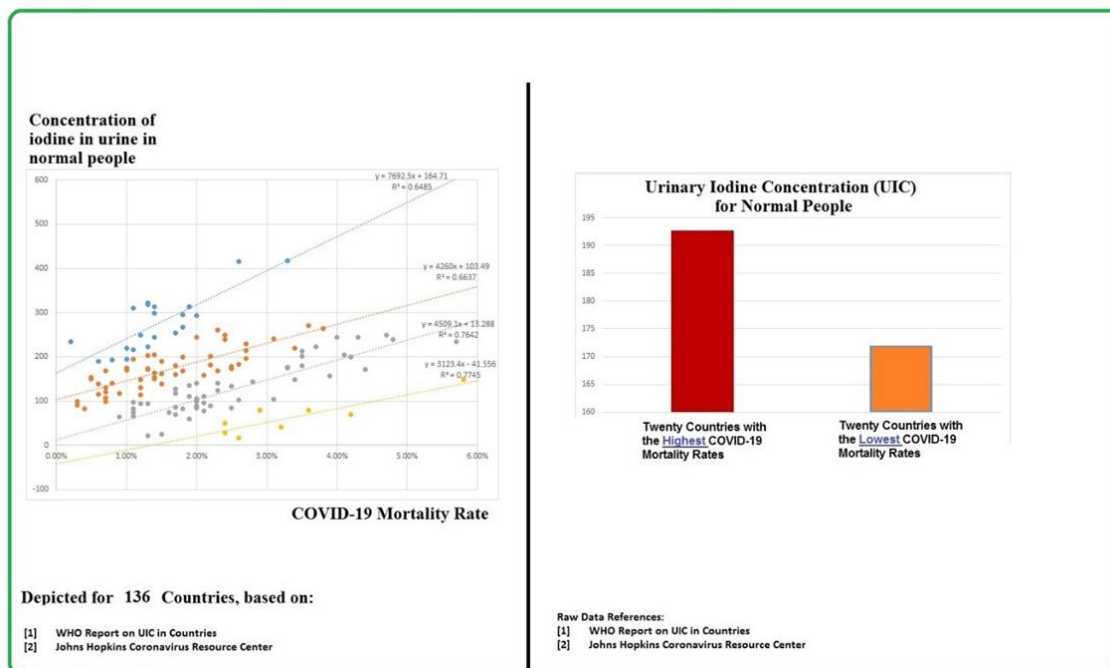
The solution can be anti-iodine modulators whose effect on the body on thyroid hormones is the opposite of the effect of excess iodine (such as Trigonelline, coffee, Bell pepper, turmeric, ginger, etc.). Therefore, these body of evidences suggests that Trigonelline can be a drug for the prevention and treatment of this syndrome, in this way.

More than five clinical and metabolomics studies in the United States, China, France, Italy and the United Kingdom [18] have shown the effect of Trigonelline levels in the blood as a prognosis of non-deterioration and deterioration in SARS-Cov-2 patients: those with higher Trigonelline levels in the blood, Their condition has not worsened. Trigonelline is found in fenugreek seeds, coffee especially Arabic, bell peppers, etc.

From 52 days before 17 August 2021 (i.e. from 26 and 27 June), the incidence of SARS-CoV-2 Cases in the following areas has been rising simultaneously and before that it was either constant or declining: Iran, USA, Germany, Netherlands, France, Spain, Italy, Australia and the whole world (Figure-9). The secretion of some thyroid hormones appears to decrease in summer [21], and the 26 June was almost the beginning of summer in the middle latitudes of the northern hemisphere. According to previous findings, a decrease in thyroid hormone apparently causes vulnerability to the severe form of SARS-CoV-2. Therefore, this coordination in the COVID-19 peak in these areas can be considered as a possible evidence of the effect of thyroid hormone levels on the severity of SARS-CoV-2.

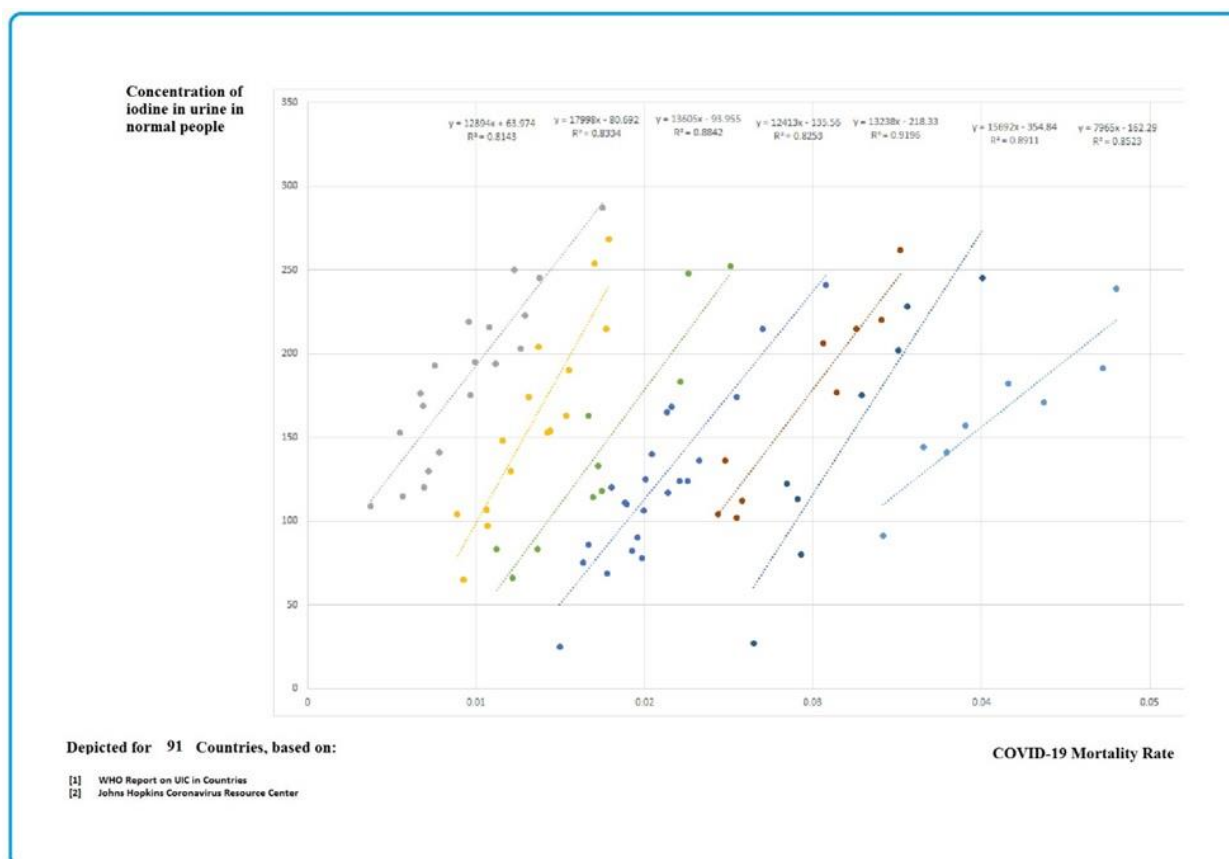
Best Regards,

The Authors



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١٤١ Figure 4- UIC and Covid-19 for 136 countries.



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١٤٣ Figure 5- UIC and Covid-19 for 91 countries.



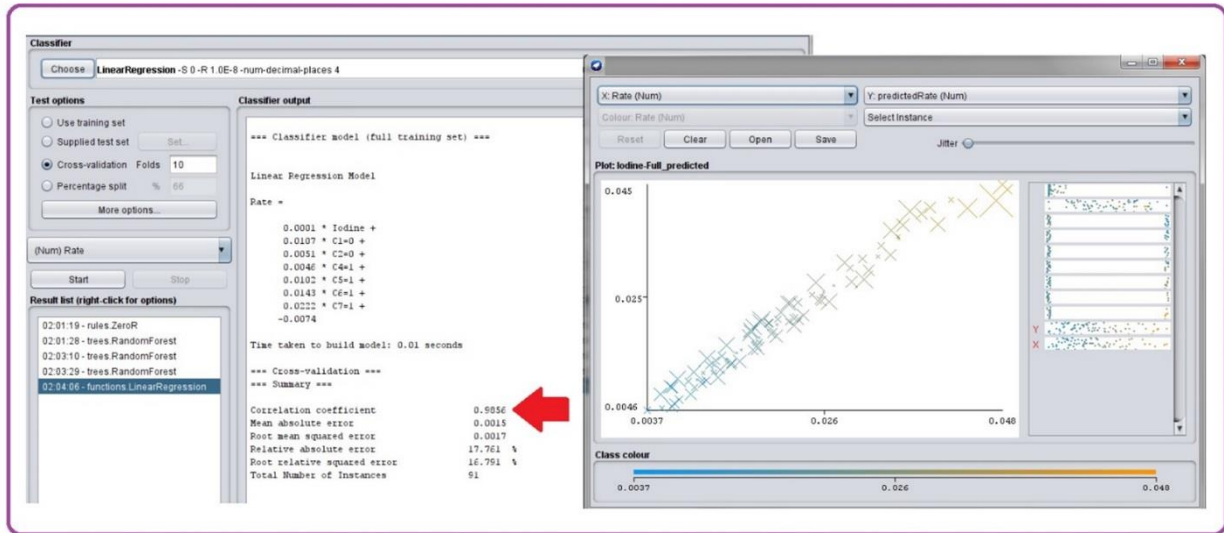


Figure 6- A linear Regression Model for (# of Cases, UIC, Mortality Rate) for 91 countries. The model correlation coefficient is 0.98. The calculations are done by WEKA[12].

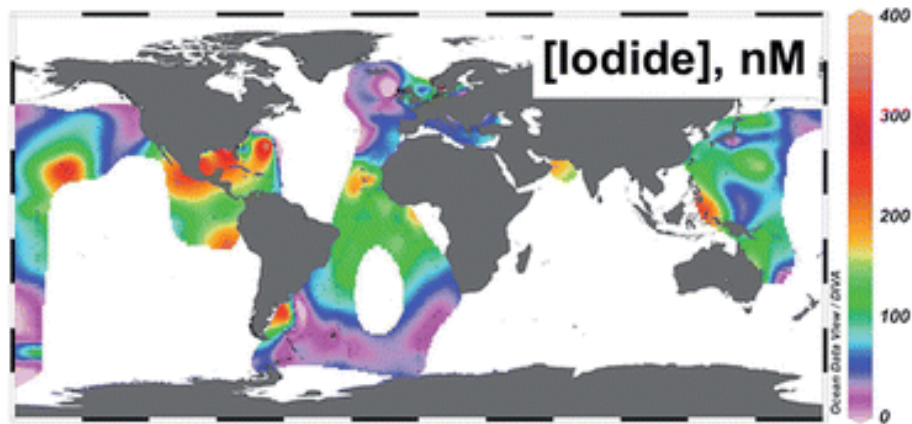


Figure 7- Hotspots of iodide at the sea surface [14].

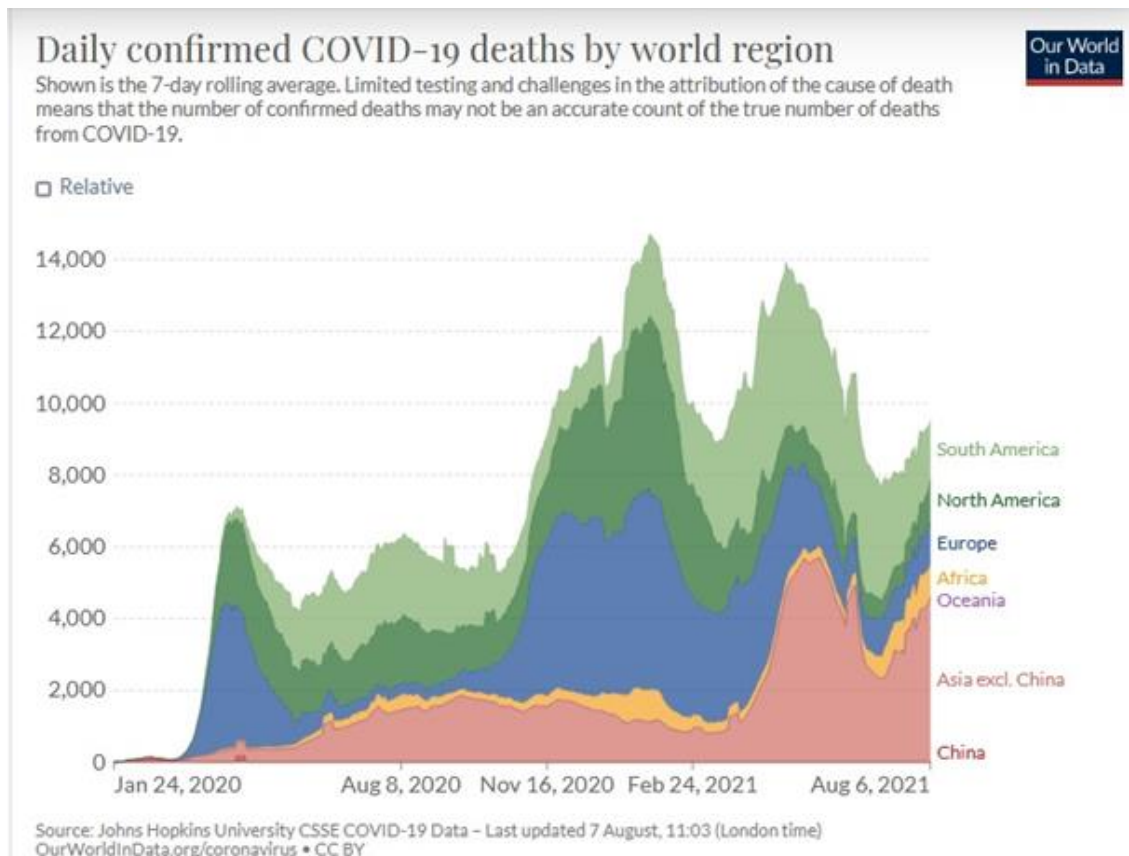


Figure 8- In the last six months, in the above diagram [20], fluctuations in the daily SARS-CoV-2 mortality rate on five continents have been synchronous.

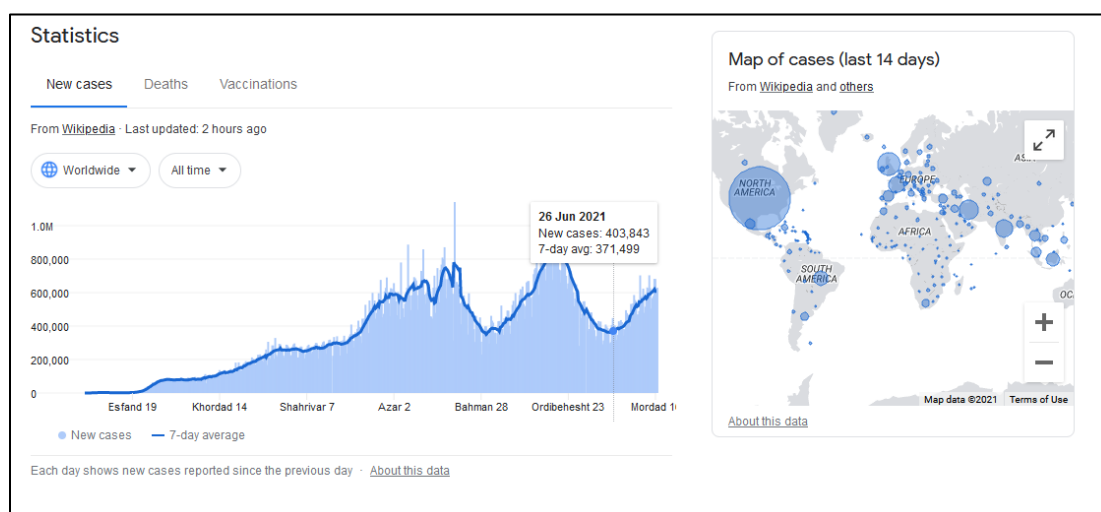


Figure 9- From Google.com, On 17 Aug 2021, based on JHU world COVID-19 data.

## **Conflicts of Interest**

We have no conflict of interest to declare.

## **Consent statement/Ethical approval:**

Not applicable.

## **Funding Statement**

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