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## Relationship between COVID-19 severity and fluoride levels of drinking water among children in Karnataka state, India: An epidemiological study

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### Abstract

**Background:** The severity and susceptibility to COVID-19 infection are the two main epidemiological factors influenced by the host and environmental factors. Environmental factors like drinking water fluoride levels have a direct role in depleting Vitamin D and serum calcium level in the body which were found to have a positive effect on the recovery from COVID-19.

**Aim and objective:** To find out if there is any association between the severity of COVID-19 and ground water fluoride level among children and young adults in Karnataka.

**Settings and Design:** Ecological/Correlational study design

**Methods:** Ground water fluoride levels of districts of Karnataka was obtained from the Government of India Central Ground Water Board's Ministry of Water Resources River Development and Ganga Rejuvenation Year Book 2016-17 and 2018-19 and data on COVID-19 mortality under the age group of 20 years was obtained from the media bulletin of The Ministry of Health and Family Welfare, Government of Karnataka.

**Statistical analysis:** Descriptive analysis was performed and Pearson's correlation was used to find out the linear association between the variables.

**Results:** The higher percentage of death due to COVID-19 was observed among males (65.8%) of age 16-20 (52.6%) years and around 71.8% of COVID-19 associated death among children and young adults were not associated with any co-morbidity. The ground water fluoride levels exhibit statistically significant linear strong positive ( $r=+0.734$ ;  $P=0.024$ ) correlation with the Case Fatality Rate (CFR).

**Conclusion:** The severity of COVID-19 was observed to be severe in the high concentration of ground water fluoride areas in Karnataka.

**Keywords:** COVID-19, drinking water, fluoride, vitamin D

### Introduction

Coronavirus disease is a highly infectious pandemic caused by severe acute respiratory syndrome virus 2 (SARS-CoV-2). The disease was first identified in December 2019 in Wuhan, China and since then it has spread over various continents affecting most countries in the world [1]. Among those infected, it has been observed that elderly individuals account for a large portion of fatal cases inducing a large heterogeneity in the age distribution of mortality [2]. Elderly age group are more susceptible to have some co-morbidities, which have been reported as risk factors for severe COVID-19 infections [2, 3]. On the contrary, the recent publications reported that the age distribution of mortality from COVID-19 suggests no large difference of susceptibility by age [2]. This indicates that the presence of co-morbid conditions plays a major role in determining the severity of COVID-19, rather than the age factor. Younger age-groups, in the absence of co-morbidities, show a higher severity of COVID-19.

The severity and susceptibility to COVID-19 infection are the two major epidemiological factors, which have direct influence on the heterogeneity of mortality by age. Both these factors are dependent on the host and environmental factors. Environmental factors like socio-cultural, life style habits and consumption of food and water have direct or indirect effect on the severity and susceptibility to COVID-19 [2].

Fluoride is the ionic form of fluorine, which is highly electronegative in nature and has a high affinity towards calcium ions and calcified tissues in the body [4]. The major source of fluoride is ground water. Fluoride is considered as double-edged sword, known for its anticaries effect and prolonged intake of high amount of fluoride causes dental and skeletal fluorosis. High concentrations of fluoride and other minerals/elements have been detected in groundwater in different parts of India. More than 60% of water for irrigation and 85% of rural drinking water supplies in India were obtained from ground water [5, 6]. In urban areas, there is extensive use of ground water because there are innumerable borewells. Karnataka is one of the states with a high prevalence of fluorosis and around 14% of total population in Karnataka live in these highly fluoridated areas (>1.5 mg/L) [5, 7].

High ingestion of fluoride reduces the serum concentration of calcium and Vitamin D3 [8]. There is a paucity in literature on the association of water fluoride levels and severity of COVID-19. An increased level of serum Vitamin D3 has been found to have a positive effect on the recovery from COVID-19. It can be hypothesised that there is an association between levels of fluoride in drinking water and severity of COVID-19. The aim of the present observational study was to find out if there is an association of the water fluoride level and the severity of COVID-19 among children and young adults in Karnataka.

## Subjects and Methods

### Data collection

Ground water fluoride levels of the districts affected by COVID-19 in state of Karnataka was obtained from the Government of India Central Ground Water Board's Ministry of Water Resources River Development and Ganga Rejuvenation Year Book 2016-17 and 2018-19 [9]. Data related to COVID-19 mortality under the age group of 20 years in each district of Karnataka was obtained from the media bulletin of The Ministry of Health and Family Welfare, Government of Karnataka [10]. Deaths associated with co-morbidities in population under 20 years of age were excluded. Data collected was subjected to statistical analysis using Statistical Package for Social Sciences (SPSS) version 20, IMB Chicago.

### Statistical analysis

Descriptive analysis was performed and Pearson's correlation to find out the correlation between ground water fluoride levels and severity of COVID-19 among children and young adults in Karnataka.

## Results

All COVID-19 related deaths under the age of 20 years from

April 2020 to the month of September 2020 in different districts of Karnataka state were selected for the epidemiological study.

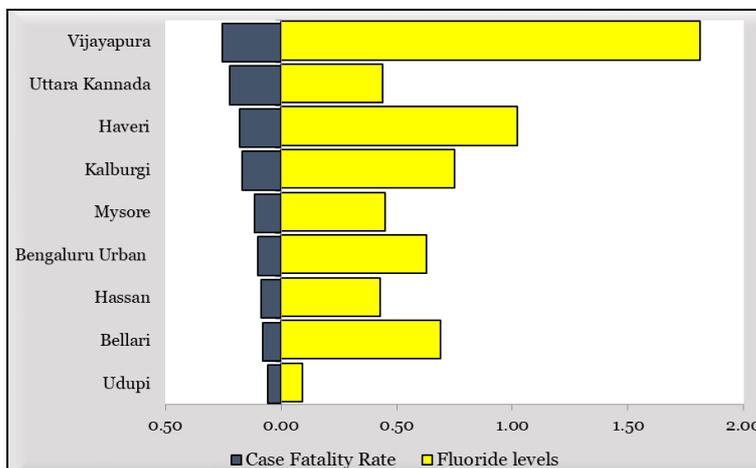
Table 1 shows the demographic characteristics of the subjects included in the study. The higher percentage of death due to COVID-19 is observed among male (65.8%) subjects belonging to the age group of 16-20 (52.6%) years. It was observed that around 71.8% of death due to COVID-19 among children and young adults were not associated with any co-morbidities. Approximately 13% of COVID-19 related deaths were associated with hypertension (12.8%) followed by diabetes mellitus (2.6%), carcinoma (2.6%), leukemia (2.6%), chronic kidney disease (2.6%), seizures (2.6%) and cerebro-vascular accident (CVA) (2.6%).

**Table 1:** Demographic characteristics of the study group

		Frequency	Percentage
Districts	Bellari	2	5.3
	Bengaluru Urban	16	42.1
	Dakshina Kannada	3	7.9
	Gadag	1	2.6
	Hassan	3	7.9
	Haveri	1	2.6
	Kalburgi	3	7.9
	Mandya	1	2.6
	Mysuru	3	7.9
	Udupi	1	2.6
	Uttara Kannada	2	5.3
	Vijayapura	2	5.3
Age Group	1-5	7	18.4
	6-10	5	13.2
	11-15	6	15.8
	16-20	20	52.6
Sex	Male	25	65.8
	Female	13	34.2
Co morbidities	Nil	28	71.8
	CA	1	2.6
	Leukemia	1	2.6
	DM	1	2.6
	HT	5	12.8
	CKD	1	2.6
	Seizures	1	2.6
CVA	1	2.6	

### COVID-19 Case Fatality Rate

Using the data on total deaths due to the infection of COVID-19 and the total number of active cases, Case Fatality Rate (CFR) was calculated. CFR is the proportion of death due to COVID-19 compared to the total number of individuals diagnosed with COVID-19 for the period of time (First week of April 2020 to first week of September). CFR represents the measure of COVID-19 severity. (Graph 1).

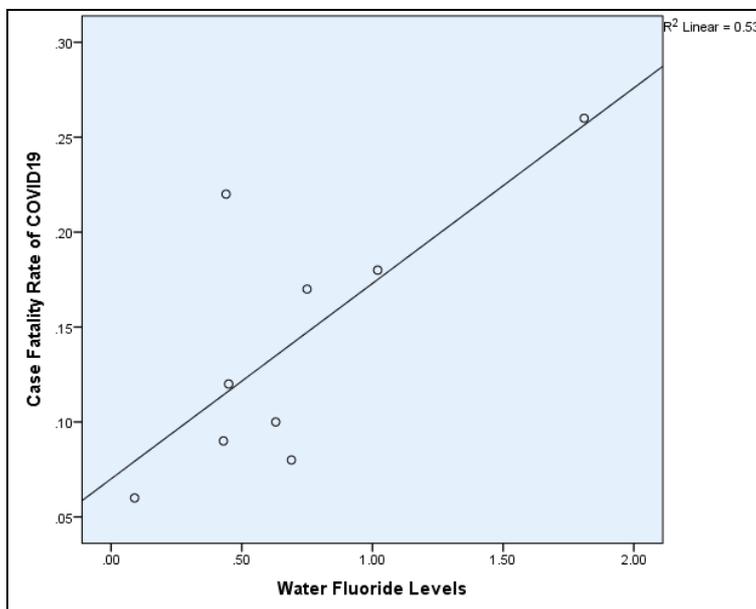


**Graph 1:** Distribution of case fatality rate (CFR) of COVID-19 under the age of 20 years and drinking water fluoride levels in different districts of Karnataka

**Correlation of ground water fluoride level with CFR**

The ground water fluoride levels exhibit statistically significant linear highly positive ( $r=+0.734$ ;  $P=0.024$ )

correlation with the CFR (Table 2; Graph 2). This indicates that the ground water fluoride level and severity of COVID-19 (Case Fatality Rate) grow in same direction.



**Graph 2:** Scattered plot between fatality rate (CFR) of COVID-19 under the age of 20 years and drinking water fluoride levels in different districts of Karnataka

**Table 2:** Correlation between fatality rate (CFR) of COVID-19 under the age of 20 years and drinking water fluoride levels in different districts of Karnataka.

Case Fatality Rate	Water Fluoride Levels	
	N	9
	r	0.734
	p value	0.024*

\* $p < 0.05$  is significant; N: Number of districts used for the study; r: Pearson’s Correlation Coefficient

**Discussion**

The present study shows the epidemiological evidence indicating the differences in mortality and morbidity due to COVID-19 across different districts of Karnataka which can be partly explained by the ground water fluoride levels. The appearing scientific data evidently recommends that associated co-morbidities are often related with increase in severity and or mortality of COVID-19 patients [11]. It was also reported that co-morbidities increases as the age advances and is more common in individuals above 65 years

of age [12]. Hence, using data on children and young adults without any co-morbidities provide a clear picture on the linear association of fluoride level in drinking water and deaths due to COVID-19. In the present study CFR was used to measure the severity of COVID-19 as it is one of the sensitive tools to measure the virulence of epidemics [13]. In the present research it was observed that males dominated severe outcomes from COVID-19 when compared to females which are parallel with the worldwide outcome statistics of COVID-19. The reason is due to the mechanistic differences in the expression and activity of angiotensin-converting enzyme 2 (ACE2) as well as in antiviral immunity among males and females [14]. Around 72% of the death from COVID-19 were detected in individuals below the age of 20 years with no co-morbidities. This is contradicting the result of systematic review, which exhibited children show milder severity, better prognosis and very rare death when compared to the adults [15].

A positive strong linear correlation was found between

ground water fluoride levels with case fatality rate of COVID-19. It was observed from the result of the present research that COVID-19 severity is much higher in the area with higher ground water fluoride levels in different districts of Karnataka state. This indicates that as the level of fluoride in drinking ground water increases, the severity of COVID-19 also increases. The reason for the strong positive correlation of fluoride and severity of COVID-19 is connected with the molecular action of fluoride on calcium and Vitamin D function within the cell.

**Relation of drinking water fluoride with Vitamin D and Calcium**

The observational researches and animal trials exhibit that vitamin D deficiency was more commonly observed in the subjects who drink fluoridated water [8, 16]. The inverse association of vitamin D level and drinking water fluoride levels remained intact even after the exposure to more sunlight and less pollution. Earlier studies have stated that high concentrations of fluoride consumption can react with the ionic calcium and form insoluble complexes with calcium, which can markedly decline gastrointestinal absorption of fluoride and calcium, causing hypocalcaemia [17]. The researchers have evidenced that a raise in fluoride plasma levels causes a drop in calcium transport across the renal tubule plasma membrane and endoplasmic reticulum (ER) and decreases the levels of calcium pump proteins in isolated kidney membranes [18].

**Relation of Calcium and Vitamin D with COVID-19**

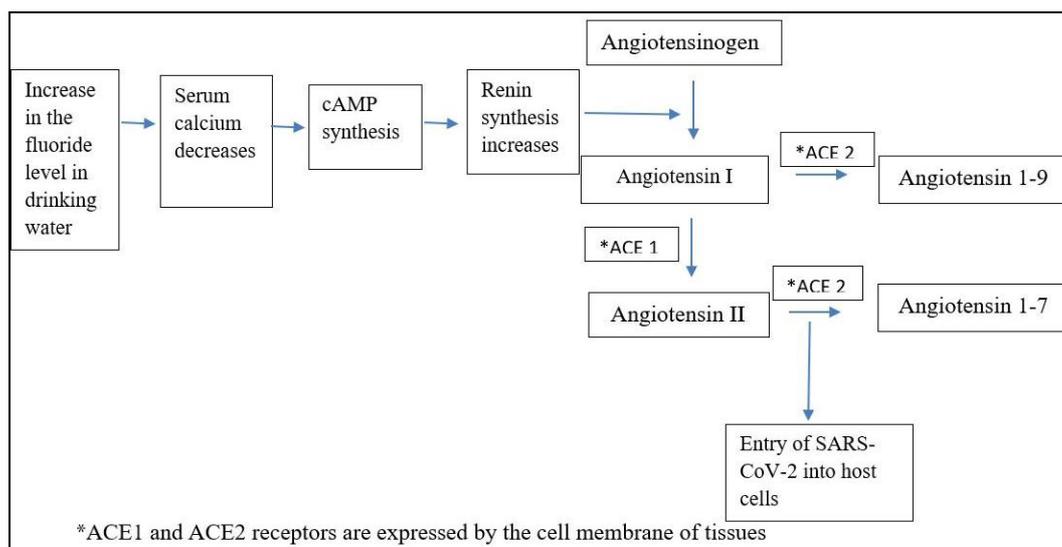
Renin-angiotensin system (RAS), which plays important roles in balancing the physiological and pathophysiological balance of the body and Angiotensin-Converting Enzyme 2 (ACE2), which is the most representative bioactive peptide in the RAS. Most of the researches provide evidence that SARS-CoV-2 enter host cells via the ACE2 receptor by binding the viral spike glycoprotein to the tip of subdomain I of ACE2. Coronaviruses are single-stranded RNA viruses with spike glycoproteins that have two subunits; one subunit, S1 that, binds to the receptors on the cell surface; the other subunit, S2

that fuses with the cell membrane. A host transmembrane serine protease, TMPRSS2, promotes entry of SARS-CoV-2 by activating the spike and cleaving ACE-2. TMPRSS2 also acts on the S2 subunit of the spike glycoprotein, causing an irreversible conformational change, activating it, and facilitating fusion of the virus to the cell membrane. The virus then enters the cell [19].

The calcium level has a direct or indirect effect on balancing RAS system. It has been observed that lowering of the extracellular calcium concentration causes a prominent enhancement of renin secretion from the kidneys. cAMP is the dominant second messenger for renin secretion. cAMP synthesis by adenylyl cyclase V activity is the target for the classic renin-stimulating pathways. The role of calcium is to modulate the enzymatic activities which integrate to balance cAMP synthesis and degradation. Thus, calcium itself does not directly control renin secretion but modifies the amplitude of the response to classic signalling pathways [20]. (Figure 1)

Regarding, acute lung injury in COVID-19, the data available so far has designated that an unhindered immune reaction in the host is the main course which leads to “cytokine storm”. The effect of it is prevalent tissue damage with dysfunctional coagulation [21]. This amplifies the severity of the disease and becomes the cause of death.

Several studies have explained about the strong inverse relationship between circulating Vitamin D levels in blood and respiratory infections, including SARS-CoV-2 infections [22]. Vitamin D plays a crucial role in the immune system along with its other chief roles in maintaining bone health, calcium–phosphorus metabolism and stimulation of insulin production. Vitamin D3, which is the active metabolite of Vitamin D, has inhibiting effect on T cell proliferation and activation. Alongside, vitamin D shunts the formation of pro-inflammatory cytokines and augment the production of anti-inflammatory cytokines [23, 24]. The recent researches exhibit that the COVID-19 patients display a higher inflammatory response with vitamin D deficiency. This all interprets into amplified mortality in vitamin D deficient COVID-19 patients [21].



**Fig 1:** Role of fluoride level in drinking water in COVID-19 susceptibility

In conclusion, the present epidemiological research findings provide a strong baseline hypothesis to make future decision making and also opens the vista for further researches in this direction. If controlled trials find this relationship to be

causative, the inferences are immense and would present a greater help in policy making and helping prevent infection, especially in the endemic region of fluorosis.

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