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Research Article

On Containment Plan Amid COVID-19 in Red Zone Districts of India: Using Clinical Life Table and Cure Fraction Model

Gurprit Grover[1], Arpan Kumar Thakur[2]

[1,2]Department of Statistics, University of Delhi, Delhi, India.
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Corresponding Author:
Arpan Kumar Thakur, Department of Statistics, University of Delhi, Delhi-110007, India.
E-mail Id:
arpankmr3@gmail.com
Orcid Id:
https://orcid.org/0000-0001-7052-8351
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A B S T R A C T

Background and Objective: Ministry of Health and Family Welfare, Government of India took many measures to arrest the spread of COVID-19 disease. This research is intended to shed light on number of confirmed cases with respect to population density of the affected districts, to study the proportion of positives among total sample tested, to construct clinical life table of general population w.r.t. number of daily positive cases and to estimate the long-term survivors among general population.

Materials and Methods: Simple scatter plot has been used to see relation between population density and number of cases in different districts of India, cluster analysis technique is used for making cluster of Districts having similar features. Clinical life table is prepared for general population of affected Districts, and mixture & non-mixture cure fraction models used to estimate the proportion of long-term survivors (disease free survival) of general population.

Result: Median daily proportion of positives are found to be below 0.05. In 79 identified hot spot Districts average population is very high (36.29 lakhs) with population density of 3404 per square kilometre. Even among those Districts there are huge inter cluster differences w.r.t. number of cases and population density. Clinical life table is constructed for general population of 429 affected Districts, increasing pattern in hazard is found even though study period is small. Long term survivors of disease is simulated and found to be 99.812%.

Conclusion: Government ought to make cluster of Districts among red zone Districts, clustering should be based on number of cases and population density. Different containment strategy may be prepared for each cluster of Districts.

Keywords: COVID-19, Clinical Life Table, Cluster Analysis, Cure Fraction Model

Introduction

Whole world is facing the biggest public health crisis of century, the current coronavirus disease came into global discourse on December 31, 2019, the day China notified the World Health Organization about pneumonia of an unknown genesis. Disease first appeared in Wuhan city of Hubei Province of China. The disease spread to more Provinces of China in ensuing days and further to the whole world. The outbreak was declared a Public Health Emergency of International Concern on January 30, 2020.[1,2]

From the daily situation report published by WHO on April 20, 20203, total confirmed cases are 2314621 and total deaths due to COVID-19 are 157847. For the South East Asia region (India, Indonesia, Thailand, Bangladesh, Sri Lanka, Myanmar, Maldives, Nepal, Timor-Leste, Bhutan) total cases till 19 April 2020 are 29576 and total deaths are 1225.

In this region, India alone accounts for 58.37% of the total cases and 44.32% of the total deaths. In Indonesia the pandemic has taken community transmission route and all other countries are either on sporadic cases detection phase or on cluster of cases detection phase.

To limit the spread of transmission and death toll Government of India is taking all necessary measures but India being a democratic republic it ought to strike a fine optimal strategy in protecting health, minimizing economic and social unsettling, and respecting human rights.

In India pandemic first set foot in the State of Kerala on January 30, 2020. In very short span of time it is wreaking havoc all over India except for North- Eastern States. Indian Council of Medical Research (ICMR) is spearheading the pandemic management through its various arms spread across the country. It formulates guidelines, coordinates with related government agency/ ministry, promotes research and development of associated treatments and preventions.

The current testing strategy (April 9, 2020) released by ICMR is as follows: All symptomatic individuals who have undertaken international travel in the last 14 days. All symptomatic contacts of laboratory confirmed cases, all symptomatic health care workers. All patients with Severe Acute Respiratory Illness (fever AND cough and/or shortness of breath), Asymptomatic direct and high-risk contacts of a confirmed case should be tested once between day 5 and day 14 of coming in his/ her contact.

For hotspots area, all symptomatic influenza like illness (fever, cough, sore throat, runny nose) (a). Within 7 days of illness – rRT-PCR, (b). After 7 days of illness – Antibody test (If negative, confirmed by rRT-PCR).

The paper is designed as follows: in the next section 2, various data sources and brief explanation of methods to be used are given. In section 3 results and implications are provided followed by section 4, where final conclusion and insights drawn from research are presented.

Materials and Methods

Material

The data of total number of cases, daily number of tested has been scrapped from crowd sourced website https://www.covid19india.org/, population data from census of India 2011 (http://censusindia.gov.in/) and population density from District of India website (http://districts.nic.in/). To update the population of the Districts to the current time, the annual population growth rate data was used from the published reports of World Bank (https://data.worldbank.org/indicator/SP.POP.GROW?locations=IN). Other sources of COVID-19 data are John Hopkins (https://coronavirus.jhu.edu/), World Health Organization's daily situation report (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports). But for this study COVID-19 data only taken from first source.

Method

Cluster Analysis is a data mining technique where clusters are formed from the objects/observations that belongs to same class. Here similar objects are grouped in one cluster and dissimilar objects are grouped in another cluster, clustering will be performed using R software package version 3.5.2. Most of times cluster analysis is used as a pre-processing step for other statistical techniques and algorithms. It is applied in marketing, land use study, insurance, city planning, medical imaging etc.[5,6]

Clinical Life Table

As name suggest this life table technique is used to study the nature of the survival functions, hazard and death density functions of various kinds of survival time data arising in medical research and diagnosis.[7-9]

Mixture Cure Fraction Model

Let C be the probability of an individual being a long-term survivor and (1 - C) be the probability of a patient being infected with COVID-19. Then, Berkson et al.[10] defined the survival function at any time t as:

$$S(t) = C + (1 - C) * S_u(t) \quad (1)$$

Where, $Su(t)$ is the survival function of the susceptible population which may be assumed to follow some life time distribution. Probability density function $f(t)$ of the overall population is written as:

$$f(t) = (1 - C) * fu(t) \quad (2)$$

Where $fu(t)$ is the probability density function of susceptible population.

Now let (t_i, δ_i) be the observed data of size n, where t_i is the survival time of the i^{th} patient and δ_i is censoring indicator variable which is defined as follows: $\delta_i = 0$ for right-censored observation and $\delta_i = 1$ for complete observation (i = 1, 2, ..,n).

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Consequently, the individual's contribution to the likelihood function can be written as:

$$L_i = [f(t_i)]^{\delta i}\,[S(t_i)]^{(1-\delta i)} \quad (3)$$

$$= [(1-C)f_u(t_i)]^{\delta i}\,[C + (1-C)S_u(t_i)]^{(1-\delta i)}$$

Hence, complete likelihood is given by:

$$L = \prod_{i=1}^{n} L_i = \prod_{i=1}^{n} [(1-C)f_u(t_i)]^{\delta}[C + (1-C)S_u(t_i)]^{(1-\delta)} \quad (4)$$

Parameters can be estimated by maximizing the complete data likelihood in equation (4) using Open BUGS software package using Gibbs sampling approach.[11-18]

Non-Mixture Cure Rate Model

In order to accommodate the changes (like second and third wave of disease that reduces event free survival that may occur during the study, a non-mixture cure rate models can be used. It is defined as:

$$S(t) = \exp[(\ln C) * F_u(t)] \quad (5)$$

Where 'C' is the probability of an Individual being long-term survivor and $Fu(t) = 1 - Su(t)$ is the distribution function for susceptible individual.

In the model (5), ith (i= 1, 2, . . , n) individual's contribution in the likelihood function can be written as:

$$Li = [h(t_i)]^{\delta i}\,[S(t_i)] = [-(lnC)\,fu(t_i)]^{\delta i}\,exp[(lnC) * Fu(t_i)] \quad (6)$$

Hence, complete data likelihood is given by:

$$L = \Pi Li = \Pi[-(lnC)\,fu(t_i)]^{\delta i}\,exp[(lnC) * Fu(t_i)]$$

here product if from i=1 to n parameters of the above two models will be estimated by Gibbs sampling in the Bayesian framework.[19]

Result

Table 1, presents the country data obtained from crowd sourced data repository that take feed from various updates published by ICMR on almost real time basis. Daily proportion of positives is calculated as daily positives/daily tested, Figure 1 shows the simple bar plot of daily number of tested and daily number of positives. Due to some discrepancy in observation and unavailability of data only up to 19 April 2020 cases are taken.

Figure 1, gives the line plot of daily proportion of positives, it is observed that on 10th April and on 18th proportion of positive are 0.07107 and 0.06127 respectively. For remaining 17 days of observation proportion of positives are in the band of 0.03 to 0.06. Two period moving averages smooths the spikes on those two days and shrinks it to band of 0.03 to 0.06. On performing Wilcoxon signed rank test on proportion of positives with null Hypothesis (H_0): The median proportion of positive is equal to 0.05 per day versus alternate Hypothesis (H_1): The median proportion of positive is less than 0.05 per day. At 95% level of confidence null hypothesis get rejected so the median daily proportion of positive is less than 0.05. So, on an around 50% of the days, proportion of positives are less than 0.05.

Table 1.Testing status from April 1 to April 19, 2020

Date	Cumulative tested	Cumulative positives	Daily tested	Daily positives	Daily proportion of positives
1.	47951	1637	5000	234	0.04680
2.	55851	2056	7900	419	0.05304
3.	69245	2653	13394	597	0.04457
4.	79950	3113	10705	460	0.04297
5.	89534	3554	9584	441	0.04601
6.	101068	4135	11534	581	0.05037
7.	114015	4616	12947	481	0.03715
8.	127919	5114	13904	498	0.03582
9.	144910	5705	16991	591	0.03478
10.	161330	6872	16420	1167	0.07107
11.	179374	7703	18044	831	0.04605
12.	195748	8312	16374	609	0.03719
13.	217554	9341	21806	1029	0.04719
14.	244893	10307	27339	966	0.03533
15.	274599	11297	29706	990	0.03333
16.	302956	12581	28357	1284	0.04528
17.	335123	14098	32167	1517	0.04716
18.	372123	16365	37000	2267	0.06127
19.	401586	17615	29463	1250	0.04243

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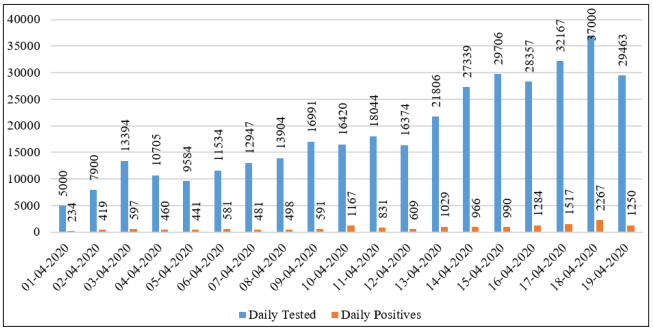

Figure 1.Day wise number of tests performed and positive cases

The total number of districts affected by this pandemic is 429 (as per the Ministry of Health 22 April 2020). These districts houses the whooping 106.5 Crores population (with base population taken from census 2011, Govt. of India and yearly average population growth taken from World Bank data to estimate the each district's current population). If we take current population of India as 135 Crores (approx.) then around 78.88% of the population are exposed to the risk of COVID-19. Average population of these 429 Districts are 2351506 (23.5 Lakhs) with population density of 1358 per square kilometre.

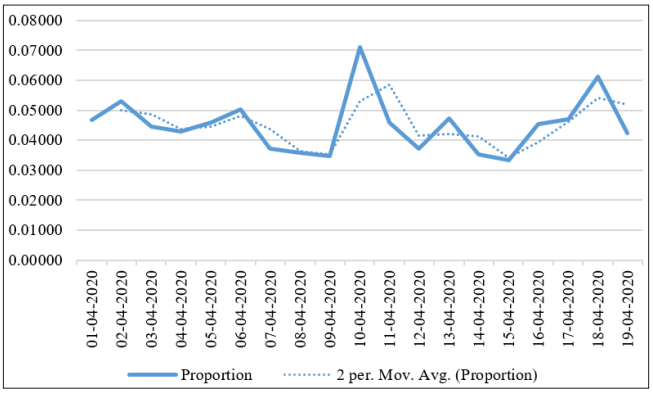

Figure 2.Daily proportion of positives

Fortunately, not all 429 Districts are equally infected. As per the guidelines of the Ministry of Health and Family Welfare about segregating Districts in Red (Hot Spot), Yellow and Green Zones, red zones Districts are those with highest caseload contributing to over 80% of the total cases in India. By applying the said criteria the following 79 out of 429 affected Districts contributes to over 80% of the total cases (Table 2).

In these 79 Districts, total number of cases are 13844 which is over 80% of the total positive cases 17246. For the above Districts average population is 3629037 (36.29 Lakhs) which was only 23.5 Lakhs for 429 Districts combined. Similarly population density is 3404/ $(km)^2$ for red zone districts which was only 1358/ $(km)^2$ for 429 Districts combined. So, there is high risk of spreading of disease in these hot spot Districts as compared to Districts that currently falls in yellow and green zones. One obvious reason for this is, the fact that till date COVID-19 only affected the urban agglomeration where population densities are highest.

Table 2.Name of district (number of positive cases)

Mumbai (3029)	Guntur (128)	South Delhi (70)	Bhubaneswar (46)
Ahme-dabad (1298)	West Delhi (122)	Erode (70)	Madurai (46)
Indore (915)	Tiruppur (109)	Nellore (67)	Thanjavur (46)
Pune (660)	Bharatpur (102)	Mumbai Sub Ur (67)	North 24 Parganas (46)
Jaipur (537)	Kota (99)	Tirunelveli (62)	Prakasam (44)
Hyderabad (472)	G.B. Nagar (98)	Sasnagar (61)	Nagapattinam (44)
Thane (465)	Nashik (96)	North Delhi (60)	Baramulla (43)
Surat (338)	Tonk (95)	Banswara (60)	Theni (43)
Chennai (303)	Kannur (92)	Kanpur (59)	South West Delhi (42)
Bhopal (277)	Bengaluru (89)	Nagpur (58)	Faridabad (42)
Agra (241)	Mysuru (84)	Firozabad (58)	Belagavi (42)
Jodhpur (228)	Bandipora (81)	Moradabad (58)	Karur (42)
Vadodara (188)	Srinagar (79)	Nuh (57)	Dhaar (41)
Central Delhi (184)	Howrah (79)	Nizamabad (56)	Khargon (41)
Kolkata (170)	Krishna (76)	Cheng-alpattu (53)	Ghaziabad (41)
Kasaragode (170)	Nagpur (76)	Namakkal (50)	Rajkot (40)
Lucknow (167)	Dindigul (76)	Tiruch-irapalli (50)	Ranipet (39)
Kurnool (158)	Suryapet (75)	Shahadara (48)	East Delhi (38)
Coimbatore (133)	Meerut (75)	Jalandhar (48)	Gurgaon (38)
South East Delhi (130)	Sahar-anpur (72)	Thiruvallur (48)	

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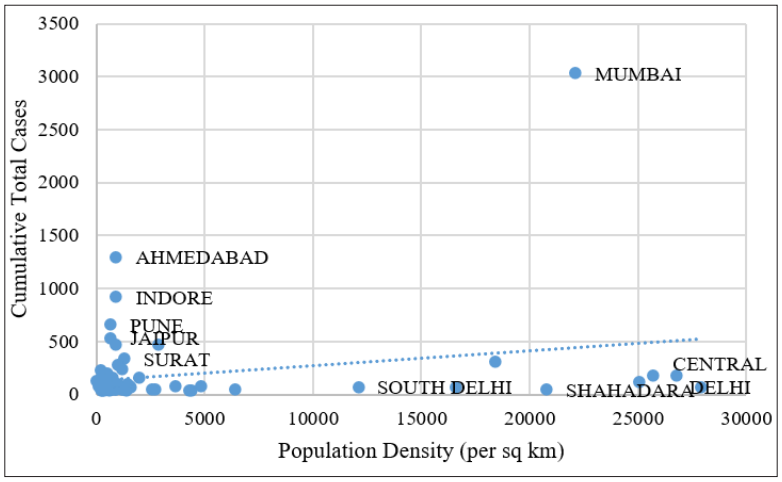

Figure 3.Scatter plot of population density and number of cases in hot spot districts

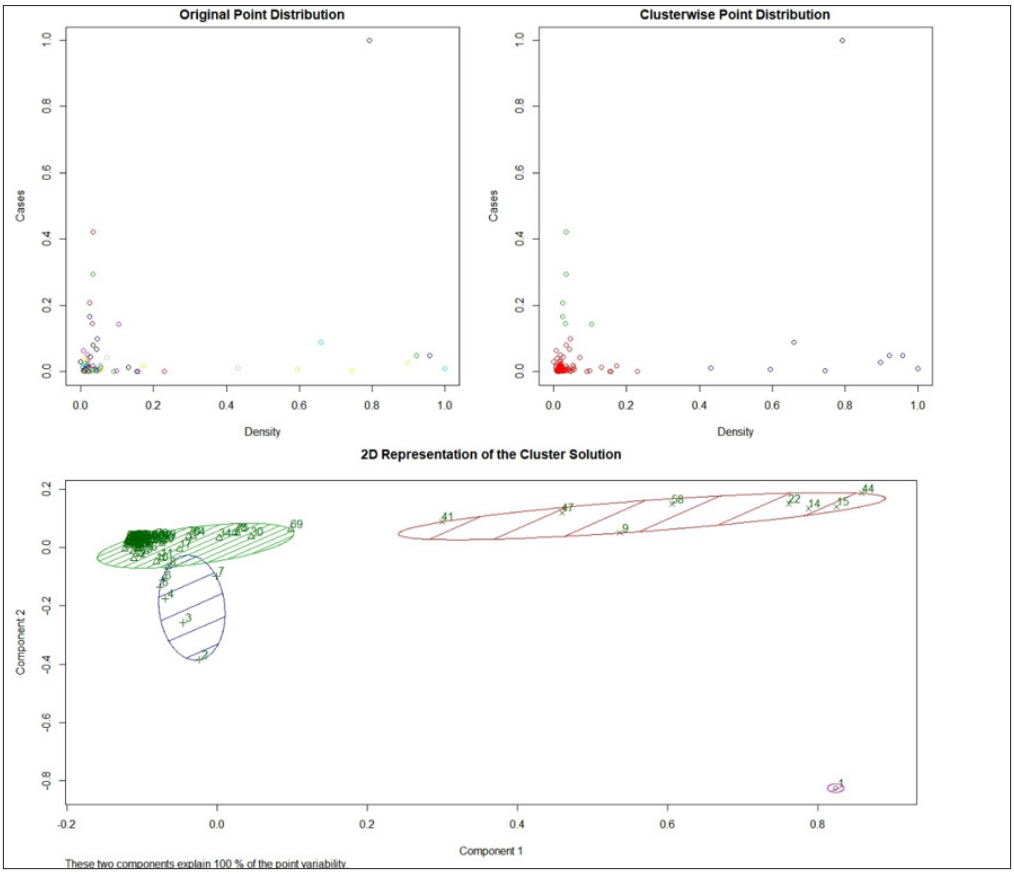

Figure 4.Cluster of districts based on total cases and population density

For 79 hot spot Districts correlation between population density and number of cases 0.2166 (and is significant at 10% confidence level). Figure 3 gives the simple scatter plot between population density and cumulative cases in 79 identified hot spot Districts. By visually inspecting the graph, one may get the rough idea about similarities between Districts with respect to density and cases.

In order to make cluster of Districts, a normalization of variable is performed (to change the values of numeric variable into a common scale). K means clustering algorithm has been employed to accomplish the cluster-making task. Graph (Figure 4) at top left shows the original point distribution on normalized values, top right graph shows the cluster wise point distribution. Graph at bottom depicts the four cluster solution in 2-dimension. Table 3, presents the name of Districts that falls in different clusters along with average number of cases and population density of each cluster.

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Table 3.Name of districts in each cluster

Cluster	Districts	Average number of cases	Average density (square km)
Cluster 1	Mumbai	3029	22113
Cluster 3	Ahmedabad	724.5	1156.33
	Indore		
	Pune		
	Jaipur		
	Hyderabad		
	Thane		
Cluster 4	Chennai	129.75	21659.125
	Central Delhi		
	Kolkata		
	West Delhi		
	South Delhi		
	Mumbai Sub Ur		
	North Delhi		
	Shahadara		
Cluster 2	All remaining 64 Districts	84.84	1041.06

On close examination of clusters it is observed that cluster 4 which now has average number of positive cases of 129.75 (which seems quite low as compared to cluster 1 and cluster 3) but that cluster has very high average population density of 21659.12 per square kilometre, which is alarming, as higher the population density there is higher risk of disease proliferation.

Table 4, gives clinical life table with starting population of 1006444833. Starting population is obtained from total combined population of 429 affected districts and is treated as number of people exposed to risk of contacting COVID-19 during study period. Various columns of life table are as follows: d_i = daily positive cases, n_i = number exposed to the risk of contacting COVID-19 (in this case it is total population of disease affected Districts), conditional proportion of infection (q_i) is defined as d_i/n_i, conditional proportion of surviving (p_i) is as ($1-q_i$), cumulative proportion surviving $[S(t_i)] = p_{i-1}\, S(t_{i-1})$ with $S(t_1) = 1$. Estimated probability density function $f(t_i) = q_i\, S(t_i)$ which is probability of getting infected in i^{th} day, hazard function $[h(t_i)] = q_i/(1+p_i))$ which is the number of infections per unit time in the interval divided by average number of survivors at mid-point of interval. Cumulative hazard [H(t)] is simply the cumulative sum of hazard [h(t)].

Figure 5, shows the survival function plotting, clearly the slope is in downward direction. Although, decrement is quite small but when one think in terms of general population it will give significant number of infected persons in short lap of time. Figure 6 and 7 gives the hazard and cumulative hazard plotting of general population.

Table 4.Clinical life table

Date	Mid-point	D (Positives)	n_i	q_i	p_i	S(t)	f(t)	h(t)	H(t)
01-Apr	0.5	234	1006444833	2.32502 E-07	0.999999767	1	2.32502 E-07	2.32502 E-07	2.32502 E-07
02-Apr	1.5	419	1006444599	4.16317 E-07	0.999999584	0.999999767	4.16317 E-07	4.16317 E-07	6.48819 E-07
03-Apr	2.5	597	1006444180	5.93177 E-07	0.999999407	0.999999351	5.93177 E-07	5.93178 E-07	1.242 E-06
04-Apr	3.5	460	1006443583	4.57055 E-07	0.999999543	0.999998758	4.57054 E-07	4.57055 E-07	1.69905 E-06
05-Apr	4.5	441	1006443123	4.38177 E-07	0.999999562	0.999998301	4.38176 E-07	4.38177 E-07	2.13723 E-06
06-Apr	5.5	581	1006442682	5.77281 E-07	0.999999423	0.999997863	5.7728 E-07	5.77281 E-07	2.71451 E-06
07-Apr	6.5	481	1006442101	4.77921 E-07	0.999999522	0.999997285	4.7792 E-07	4.77921 E-07	3.19243 E-06
08-Apr	7.5	498	1006441620	4.94813 E-07	0.999999505	0.999996808	4.94811 E-07	4.94813 E-07	3.68724 E-06
09-Apr	8.5	591	1006441122	5.87218 E-07	0.999999413	0.999996313	5.87215 E-07	5.87218 E-07	4.27446 E-06

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10-Apr	9.5	1167	1006440531	1.15953 E-06	0.99999884	0.999995726	1.15953 E-06	1.15953 E-06	5.43399 E-06
11-Apr	10.5	831	1006439364	8.25683 E-07	0.999999174	0.999994566	8.25679 E-07	8.25683 E-07	6.25968 E-06
12-Apr	11.5	609	1006438533	6.05104 E-07	0.999999395	0.99999374	6.051 E-07	6.05104 E-07	6.86478 E-06
13-Apr	12.5	1029	1006437924	1.02242 E-06	0.999998978	0.999993135	1.02241 E-06	1.02242 E-06	7.8872 E-06
14-Apr	13.5	966	1006436895	9.59822 E-07	0.99999904	0.999992113	9.59814 E-07	9.59822 E-07	8.84702 E-06
15-Apr	14.5	990	1006435929	9.83669 E-07	0.999999016	0.999991153	9.8366 E-07	9.8367 E-07	9.83069 E-06
16-Apr	15.5	1284	1006434939	1.27579 E-06	0.999998724	0.999990169	1.27578 E-06	1.27579 E-06	1.11065 E-05
17-Apr	16.5	1517	1006433655	1.5073 E-06	0.999998493	0.999988894	1.50729 E-06	1.5073 E-06	1.26138 E-05
18-Apr	17.5	2267	1006432138	2.25251 E-06	0.999997747	0.999987386	2.25248 E-06	2.25251 E-06	1.48663 E-05
19-Apr	18.5	1250	1006429871	1.24201 E-06	0.999998758	0.999985134	1.242 E-06	1.24201 E-06	1.61083 E-05

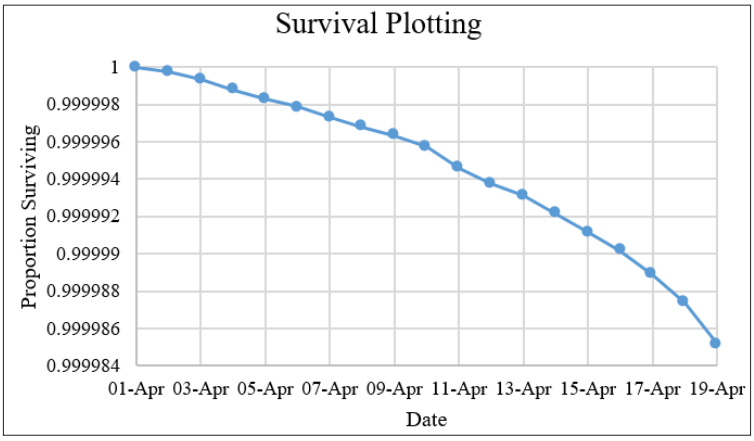

Figure 5.Survival plot from clinical life table

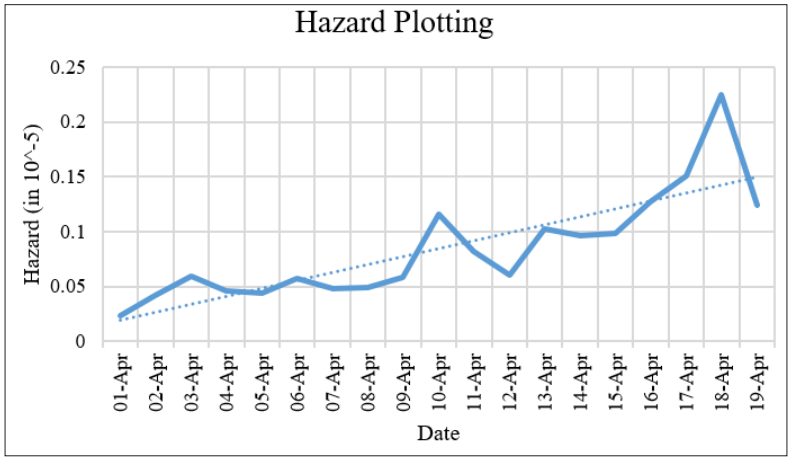

Figure 6.Hazard plot from clinical life table

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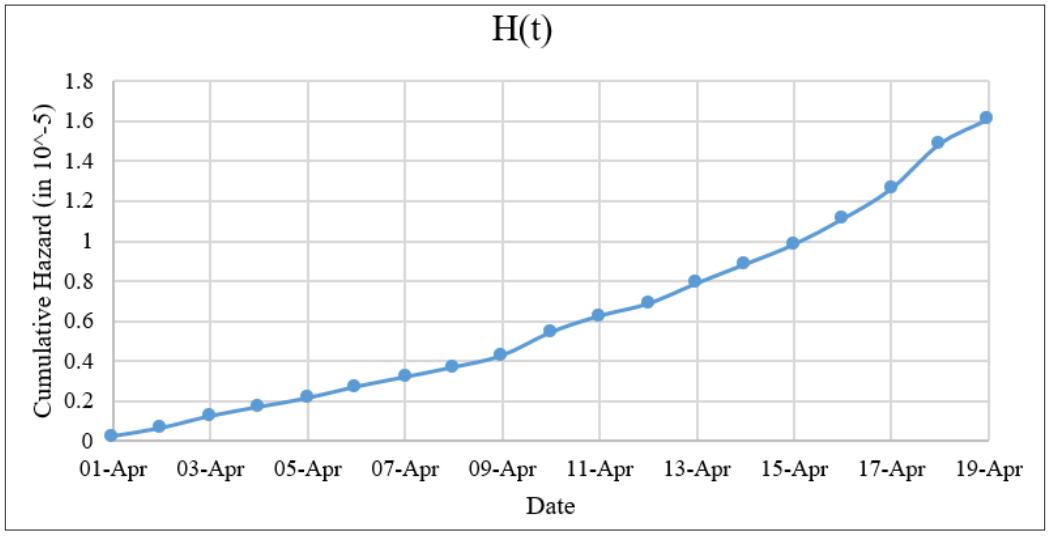

Figure 7.Cumulative hazard plot from clinical life table

Table 5.Cure fraction models

Exponential Mixture Cure Model					
	Mean	**SD**	**MC_error**	**Median**	**DIC**
λ	0.003671	0.01174	0.002024	6.14E-04	370.2
C	0.99812	0.02628	0.004209	0.9803	
Exponential Non- Mixture Cure Model					
	Mean	**SD**	**MC_error**	**Median**	**DIC**
λ	0.003329	0.01181	0.002037	5.20E-04	372.0
C	0.9579	0.02944	0.004926	0.9753	
Gamma Mixture Cure Model					
	Mean	**SD**	**MC_error**	**Median**	**DIC**
γ	2.04	0.1183	0.01262	2.048	401.3
C	0.9937	0.05523	0.005395	0.9992	
Gamma Non- Mixture Cure Model					
	Mean	**SD**	**MC_error**	**Median**	**DIC**
Γ	0.001989	0.01649	0.001544	2.37E-04	414.8
C	0.9831	0.009568	0.001048	0.9972	
Weibull Mixture Cure Model					
	Mean	**SD**	**MC_error**	**Median**	**DIC**
α	0.02301	0.1501	0.01328	0.003975	393.0
γ	0.08431	0.06585	0.007913	0.1008	
C	0.1953	0.09628	0.01665	0.2325	
Weibull Non- Mixture Cure Model					
	mean	**SD**	**MC_error**	**Median**	**DIC**
α	0.002857	0.02225	0.002316	5.51E-04	396.9
γ	0.1274	0.07803	0.01057	0.1582	
C	0.97815	0.01977	0.00810	0.98375	

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Define event of interest as "onset of COVID-19" with baseline as 1 April 2020 for general population then the survival time for each individual will be "COVID-19 free survival". As mentioned earlier, the observation period of this study is first 19 days of April month. So, keeping in mind the highly contagious nature of disease if we assume that those who are COVID free during this period are long-term survivors. We simulated one million data points to get survival times, on applying mixture and non-mixture cure fraction model using Open BUGS software package we get the following results (Table 5). From table the model that gives least DIC value is exponential mixture cure model with DIC value of 370.2 and cure fraction 0.99812, i.e. after 19 days of pandemic (base shifted to 1 April) around 99.812% of general population will be COVID-19 free.

Conclusion

Without thorough study, temporary measures like contentious blanket lockdown the resulting slowing down of economy is inevitable. Due to this COVID-19 menace, global giant economies are at cusp of following the rocky path ahead.

To mitigate the repercussions of COVID-19 containment, strategist should prepare the plan at micro level amidst pandemic.

Currently Government of India is segregating Districts in red, yellow and green zones. Here we suggest to augment the plan for red zone Districts. There should be different cluster containment plans for various Districts that falls into red zone. Each District ought to have plan based on clinical life table for general population. Life table must be fed with data pertaining to migration of people to/ from the District, birth, death due to natural causes, death due to other diseases, death due to accidents.

If provided data on proper COVID-19 free survival for each District then probabilistic models like cure fraction can be used to find proportion of long-term survivors in foreseeable future that would be helpful in planning.

Conflict of Interest: None

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