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COVID-19 outbreak reproduction number estimations and forecasting in Marche, Italy

Nalini Chintalapudi^{a,*}, Gopi Battineni^a, Getu Gamo Sagaro^a, Francesco Amenta^{a,b}

^a E-health and Telemedicine Center, University of Camerino, Camerino, 62032, Italy

^b Research Department, International Radio Medical Centre (C.I.R.M.), Rome, 00144, Italy



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ABSTRACT

Background: COVID-19 disease is becoming a global pandemic and more than 200 countries were affected because of this disease. Italy is one of the countries is largely suffered with this virus outbreak, and about 180,000 cases (as of 20 April 2020) were registered which explains the large transmissibility and reproduction case numbers.

Objective: In this study, we considered the Marche region of Italy to compute different daily transmission rates (R_t) including five provinces in it. We also present forecasting of daily and cumulative incidences associated after the next thirty days. The Marche region is the 8th in terms of number of people infected in Italy and the first in terms of diffusion of the infection among the 4 regions of the center of Italy.

Methods: Epidemic statistics were extracted from the national Italian Health Ministry website. We considered outbreak information where the first case registered in Marche with onset symptoms (26 February 2020) to the present date (20 April 2020). Adoption of incidence and projections with R statistics was done.

Results: The median values of R_t for the five provinces of Pesaro and Urbano, Ancona, Fermo, Ascoli Piceno, and Macerata, was 2.492 (1.1–4.5), 2.162 (1.0–4.0), 1.512 (0.75–2.75), 1.141 (1.0–1.6), and 1.792 (1.0–3.5) with 95% of CI achieved. The projections at end of 30th day of the cumulative incidences 323 (95% CI), and daily incidences 45 (95% CI) could be possible.

Conclusions: This study highlights the knowledge of essential insights into the Marche region in particular to virus transmission dynamics, geographical characteristics of positive incidences, and the necessity of implementing mitigation procedures to fight against the COVID-19 outbreak.

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Introduction

The novel coronavirus-19 (nCoV-19) or COVID-19 epidemic has started in Wuhan, China and rapidly spreading across the world and more than two million people got infected. It is a kind of infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Sun et al., 2020). This virus is easily spread among humans either by having close contact with an infected person or tiny droplets when people sneeze, cough, or talk. The severe diseases associated with COVID-19 are relatively high for the population with the definition of elevated risk factors and relatively moderate for the general population (Brooke and Jackson, 2020). Preventive measures can be effective in reduction of virus transmission in the general public and in defined risk

groups (elder groups), but this rate is not fully assessed. However, it can spread at a rapid pace without having any effective mitigation measures.

The basic reproduction number (R_0) is an indicator of average number of possible infected people though the person who already had an infection. It explains how contagious is the disease and its precise estimation will highly important for epidemiologists especially when exposing to new pandemics like COVID-19. The total attack rate or individual percentage who got illness during COVID-19 outbreak in a defined population must be one of disease attribute which appears most plausibly predicted by R_0 estimation.

The key factors of impact and magnitude of COVID-19 epidemic is not fully known, but in analysis of WHO committee in China had drawn some conclusions on transmission of COVID-19 (Aylward and Liang, 2020). This committee mentioned 25% of infection possibly done through pre-symptomatic individuals, transmission might occur in households, and there is no evidence available for re-infection after patient recovered. In Woelfel et al. (2020),

* Corresponding author.

E-mail address: nalini.chintalapudi@unicam.it (N. Chintalapudi).

German scholars highlighted viral shedding can possibly occur after several days or few weeks of recovery. All these factors could affect the alterations in R_0 value.

However, R_0 is the one of the important characteristics of epidemic that may interest to public health bodies and governance to formulate possible preventive measures. For instance, after imposition of the mitigation measures like social distancing, home quarantine in China has largely controls the COVID-19 disease spread and growth rates become negative in most locations (Kraemer et al., 2020). With R_0 (=2.5) in China, many experts believed that from 20 to 60% of global population could be infected (Hellewell et al., 2020). To reduce R_0 , WHO had urged countries to practice infection prevention and control (IPC) to slow down the viral spread in community. To support this, a modeling developed by (Lee et al., 2012) mentioned contact monitoring or self quarantine could do possible decay of R_0 , eventually reduce the COVID-19 epidemic. In addition, government measures including immediate quarantine of potentially infected patients, household isolation, and eventual lockdown among high hitting cities (as did in Italy) could mitigate this epidemic. In this study, we estimate virus reproduction numbers by fitting exponential infection growth rates across both daily and weekly basis, also forecasting done by using day to day assessment through single observations.

There is a constant increase in numbers of severe and fatal cases among many European countries, and countries like UK, Italy, Spain, France, and etc. are already reported community spread across countywide (Kinross et al., 2020). The virus influences vulnerable groups such as the elder population, and individuals already with chronic diseases. The impact of increased community spread could be high, with an excess of healthcare capacity or medical centers are affected and the high number of healthcare staff needs an isolation or had infected (Kinross et al., 2020; Spiteri et al., 2020). After enforcement of mitigation measures such as imposition of lockdown, restrictions on international travelers, and demanded self-isolation was helped to reduce the community transmission and in absence of these measures high range of epidemic was observed. Depending on the highest daily virus transmission, there is a continuous growth of infectious patients all over the European countries, in particular, Italy and Spain (Chintalapudi et al., 2020). In Italy, the death toll and patient count is constantly jumping for the last two months. At the date of 20 April 2020, 181,228 cases were infected includes to 24,114 deaths.

The daily virus reproduction number (R_t) is in a purpose to understand the transmission rates of a new virus epidemics and often encountered in public health literature. Serial interval (SI) is the duration between the onset symptom of initial case and onset symptom of the second case in the transmission chain. In the early virus epidemic at Wuhan center, the mean SI of 7.5 days (95% CI, 5.3–19), and R_t was estimated to 2.2 (95% CI, 1.4–3.9) in Li et al. (2020). In Italy, R_t is estimated ranging from 2.76 to 3.25 and SI estimated 6.6 (95% CI, 0.7–19) which results from the third-highest number of infected cases and death toll after the USA, and Spain (Liu et al., 2020; Remuzzi and Remuzzi, 2020). Studies have indicated that R_t was reduced to 1.05 (95% CI, 0.41–2.39) from 2.35 (95% CI, 1.15–4.77) after imposing the travel restrictions in Wuhan (Li et al., 2020).

In this study, we focused on calculating the daily reproduction number R_t in Marche (Italy) region and established a predictive model for the next thirty days. The Marche region is the 8th in terms of number of people infected in Italy and the first in terms of diffusion of the infection among the 4 regions of the center of Italy. Understanding the dynamics of early transmission and assessment ineffectiveness of mitigation measures is important to evaluate the potential of sustained transmission occurred among other cities of the Marche region. Individual R_t values of all five provinces in Marche were computed and compared. This study highlights the

knowledge discovery of the COVID-19 outbreak, especially in disease transmission, and the necessity of mitigation measures to control.

Methods

Reproduction number estimation

Marche region is a part of the central Italy, and is enclosed with five individual provinces of Ancona, Ascoli Piceno, Fermo, Macerata, and Pesaro, and Urbino. We computed R_t values of each province based confirmed cases, and the data retrieved with daily basis that published from Italian health ministry (Ministero della Salute, 17 April 2020). To estimate the early virus transmission and forecasting among the Marche, we employed the 'incidence' and 'projections' package of R statistics. This particular package implements a simple, probability-based prediction of R_t with the help of branching process couples with Poisson likelihood. The adopted model requires knowledge of serial interval distribution over symptom onset dates. Transmissibility is defined by weighting R_0 with the likelihood of SI mass function of a corresponding day (Cori et al., 2013). Usually when $R_0 > 1$, the infection might spread over the population to a large extent, and more efforts are needed to control the pandemic. R_t is the average of secondary cases infected from the single infected individual if conditions remain the same as at time t (Fraser, 2007). For R_t estimation, assumption of mean and serial interval (i.e., the delay between primary and secondary symptom onset dates) parameters was done. Since in the absence of sufficient information on cluster outbreak for SI estimation, we assumed SI of Marche region was equal to that of the COVID-19 Lombardy region with a mean of 6.6 days and a standard deviation of 3.1 days (Ricci, 2020). We evaluated individual R_t values for over five individual provinces with maximum-likelihood (ML) estimation. The function `get_R` was used to estimate the most likelihood of R_t values. To derive the other statistics, we used `sample_R` with a bootstrap strategy of 1000 times re-sampling to get a large sample of likely R_t values.

To evaluate R_t we included the same methodology presented in Aylward et al. (2014). R_t also defines as the ratio of the quantity of daily basis new infections (I_t), to ultimate infectiousness of infected people at time t can be approximated by Poisson distribution, is given as

$$I_t \sim \text{Pois} \left(R_t \sum_{s=0}^t \varphi(s) c(t-s) \right) \quad (1)$$

where $C(t)$ is the daily number of new cases from the date of onset symptom (i.e., $t = 1$ to T),

$\varphi(s)$ is the generation time distribution associated with SI distribution which calculated at time s , and R_t is the net reproduction number.

The likelihood function \mathcal{L} with observation time t (from 1 to T) of basic reproduction number given as

$$\mathcal{L} = \prod_{t=1}^T P(I_t; R_t \sum_{s=1}^t \varphi(s) c(t-s)) \quad (2)$$

where $P(k; \lambda)$ is the probability mass function of the Poisson distribution. To estimate R_0 , assumptions were made during the period where epidemic observed exponential growth $R_t = R_0$ and used the above procedure.

Forecast of future incidences

To evaluate the case projections, we applied both incidence and projection R packages to find out daily incidence outbreaks, and case forecasting. We simulated future incidences using a branching

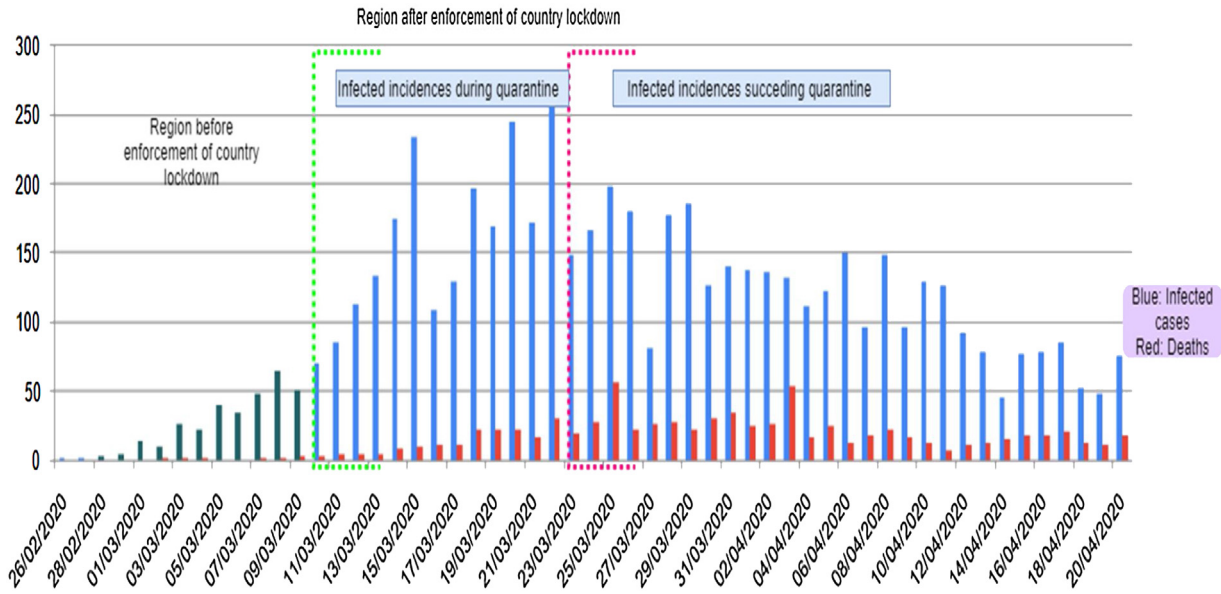


Figure 1. The daily number of new confirmed symptomatic COVID-19 cases in Marche by date of onset (N = 5826). The blue colored bars present the epidemic before the country lockdown enforcement.

process model that respects the renewal equation of (Fraser, 2007), assumes that Poisson offspring distribution was used for inference. For its simplicity, we implemented a simple linear regression method that can be used to fit the exponential growth of infected incidences over time and applied linear regression over the incidence data. Between the developing and diminishing periods of a pandemic, the date represents the epidemic peak can be assessed. We implemented function estimate peak () with multinomial bootstrapping to calculate the total number of known cases, and bootstrap never samples zero-frequency days. This function restores the estimated peak of confidence interval (CI) along with the bootstrap forecasts. We built the incidence objects by loading the incidence function, on the date of onset variable with the argument of the default interval because we considered the daily incidence. We applied the R projection package for epidemic trajectories simulation and to predict daily and cumulative incidence. The prediction model was done by considering existing of daily incidence data, estimated reproductive number, and serial interval distribution using a discrete package. We performed the prediction of daily as well as

cumulative incidence for the next 30 days (from April 20 to May 20, 2020) by using bootstrap resampling (1000 times). Besides, we presented both daily, and cumulative incidences range by graph for the next 30 days. Finally, we employed the R statistics software version 3.6.2 for model development as well as statistical analysis.

Results

Preliminary virus epidemics

The first case was identified on 26 February 2020 in Marche from the Pesaro and Urbino province. As of 20 April 2020, a total of 5,826 people were identified as COVID-19 positive among conduction of 42,782 tests all over the Marche region including five provinces (COVID-19 Cases (Coronavirus Disease) in Marche (Region, Italy) – Map, Statistics and Charts, 22 April 2020). One day before the announcement of country lockdown 8 March 2020, 198 people were infected include happening of seven deaths. The day to day progression of an epidemic was presented in Figure 1. The trends of average infected cases during eight weeks pandemic can

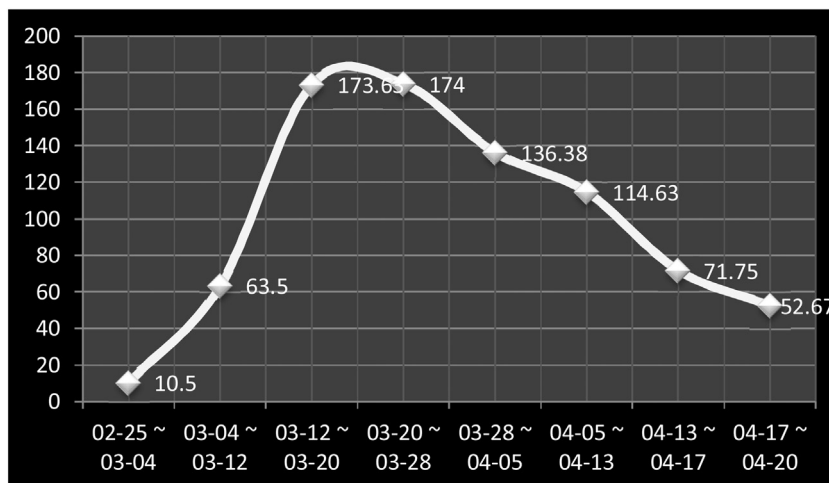


Figure 2. Average infected cases per day during eight weeks of the pandemic.

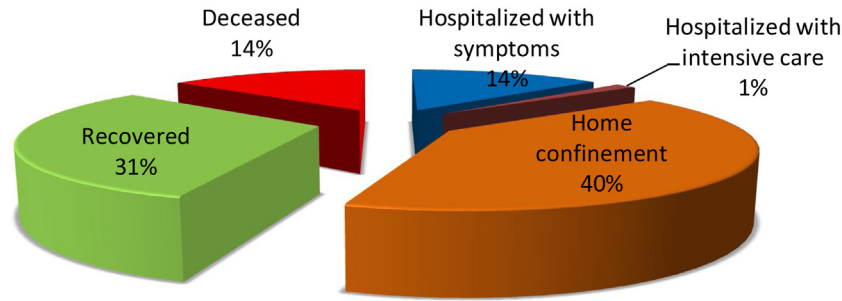


Figure 3. Category wise case distribution (until 20/04/2020).

be observed in Figure 2. Current patient status distribution (Figure 3) and province wise incidence distribution growth (Figure 4) also analyzed in this study.

Reproduction values and forecasting

The overall SI distribution of COVID-19 in the Marche region was computed in Figure 5A. Using the SI value mentioned above, we estimated the maximum likelihood (ML) of reproduction value was 1.852 (0.6–2.3) with 95% of CI on virus outbreak in early phases (Figure 5B). The distribution of R values histogram plot with the bootstrap technique can be observed in Figure 5C. Besides, we also computed the reproduction values of individual provinces based on case incidences by maintaining similar SI. The ML of R median value for Pesaro and Urbano, Ancona, Fermo, Ascoli Piceno, and Macerata was achieved 2.492 (1.1–4.5), 2.162 (1.0–4.0), 1.512 (0.75–

2.75), 1.141 (1.0–1.6), and 1.792 (1.0–3.5) with 95% of CI respectively (Figure 6A–E).

Based on the existing data and estimated R-value of the entire Marche region, we also forecasted the possible number of newly infected cases on a weekly basis for the next month. From Figure 7a the average forecast of new cases with 95% CI for the first four weeks was 8 (5–10), 13 (9–18), 15 (13–22), and 23 (20–36) respectively. The prediction of cumulative incidences was depicted in Figure 7b, which mentions the consecutive weekly median cumulative incidences with 95% CI was 12 (7–28), 31 (18–77), 63 (21–158), and 121 (26–282) respectively.

Discussion

In this study, we provided an assessment of the COVID-19 outbreak and transmission dynamics among the five provinces of the Marche region. After the first case had identified in Pesaro and Urbino, a rapid increase in infected cases in the first few days had been observed. On March 1, in Ancona first case was identified. As of this constant epidemic progress, the infection has sustained to other provinces in the region causes health burdens and increment necessity of ventilators especially among high-risk patients like elders.

Moreover, among about 1.5 million in Marche population, 5826 people are infected explains that atleast four per a thousand inhabitants were tested positive. Other than Marche, the at least infected inhabitants in Lombardy was 7–8 (95% CI), in Emilia-Romagna was 5–6 (95% CI), in Piedmont was 4–5 (95% CI), and Veneto was 3–4 (95% CI) were recorded per thousand residents. However, compared to mentioned Italian regions, Marche is

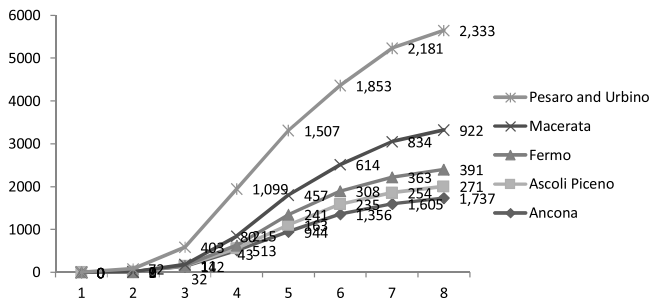


Figure 4. Province wise case distribution growths.

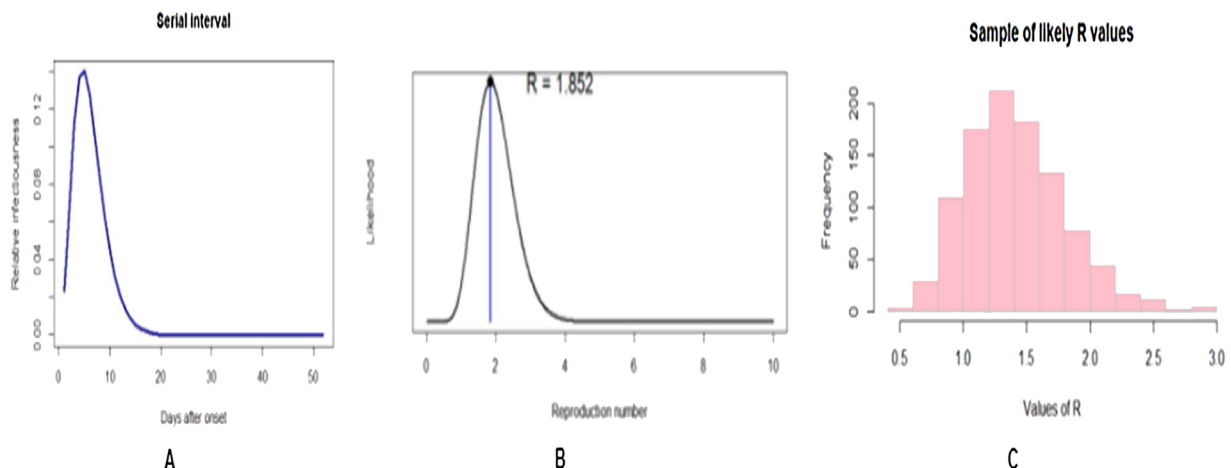


Figure 5. The serial interval distribution of virus outbreak of Marche region (A), median reproduction number value (B), and histogram plot of ML of R-value (C).

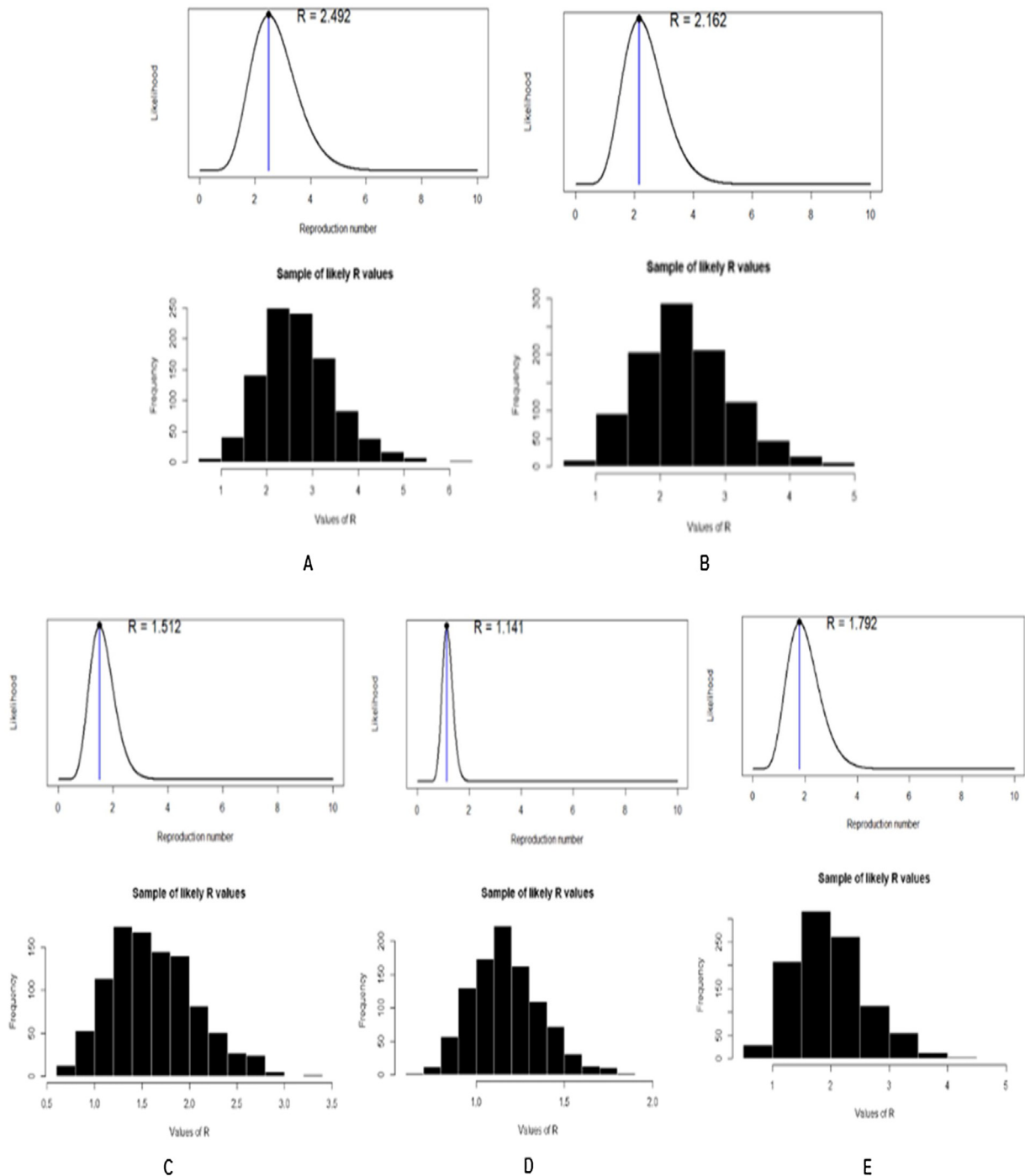


Figure 6. Maximum likelihood average reproduction number of five provinces; median R of Pesaro and Urbano equals 2.492 (A), Ancona equals to 2.162 (B), Fermo equals to 1.512 (C), Ascoli Piceno equals to 1.141 (D), and Macerata equals to 1.792 (E) with 95% of CI.

attaining a good recovery rate under implementing local governor health policies.

We calculated virus transmission rates (R_t) of different provinces in Marche. R_t does not only measure the inherent infectiousness of disease and also depends on different factors including contact rates among the city population and longevity of contagious period, and it can be varied with the city to city. Though R_t can valuable concept in the hands of experts, but the procedure of defining, interpreting, and applying is away from straightforward. Because of its simple nature towards infectious disease dynamics covers the difficulty of this metric. Since due to the availability of insufficient information about cluster cases to

identify serial distribution, estimating R in this study had become complex. As of this, we made assumptions with a mean serial interval of 6.6 days and a standard deviation of 3.1 days what had been observed in Lombardy, Italy which was the worst COVID-19 outbreak region.

The overall transmission rate in Marche was calculated as 1.852 during exponential growth of the epidemic and indicates that each infected individual can cause virus distribution to two members. The COVID-19 outbreak in Wuhan, China estimated median R_t value is between 2.2 and 2.7 (Kucharski et al., 2020), while small scale outbreaks such as one that appeared onboard the diamond princess ship estimated to 2.2 (Mizumoto and Chowell, 2020).

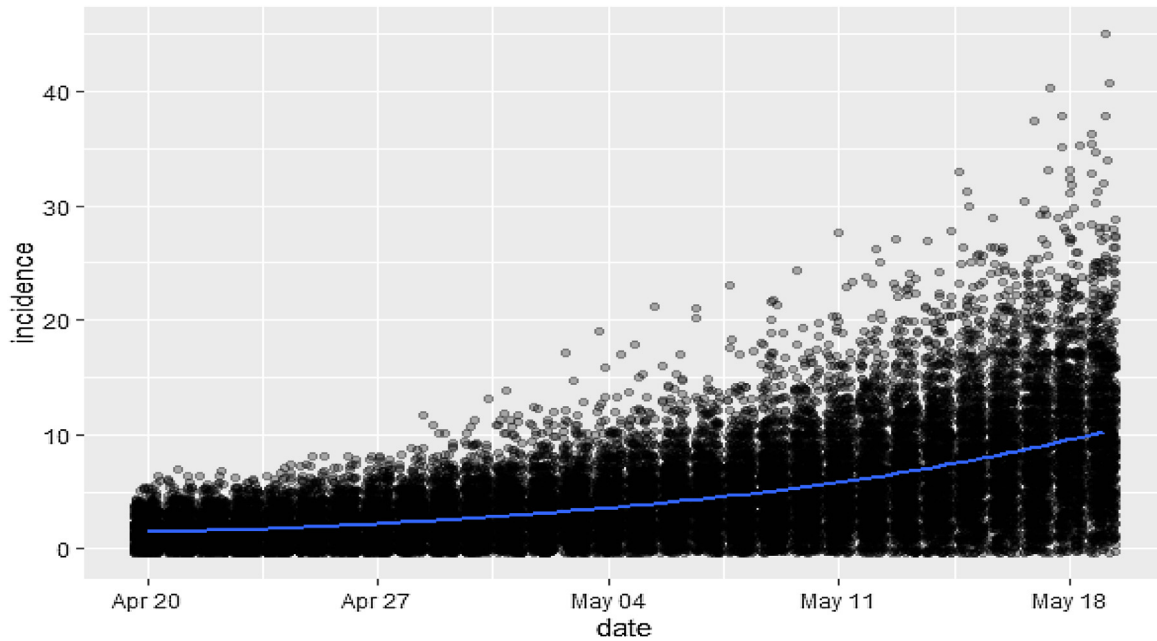


Figure 7. (a) Probable number of new infections for the next one month with achieved R of Marche. (b) Probable number of cumulative incidences for next one month with achieved R of Marche.

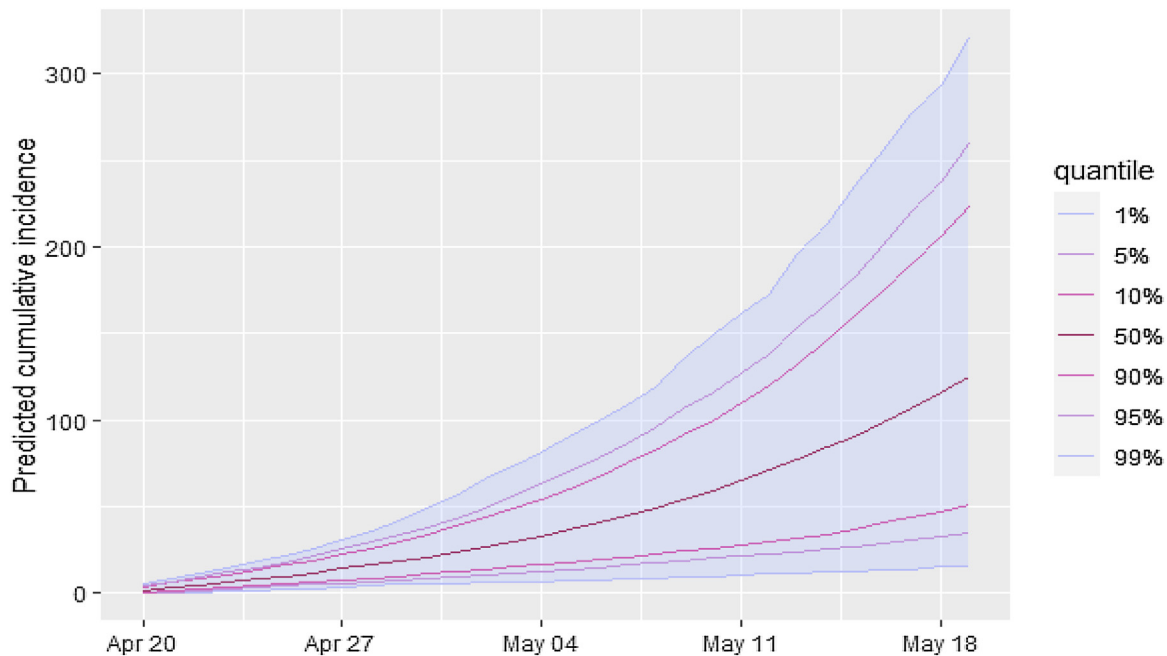


Figure 7. (Continued)

Whereas in South Korea R_t estimated as 1.5 which is the lowest possible value that appeared in north Asian countries (Shim et al., 2020). However, the daily reproduction number can highly fluctuate over time, but rather homogenous across distinct geographical locations. Similar to this, the R_t was slightly started to decayed since the last weeks of Marche. To estimate the maximum likelihood of R_t of Marche, we adopted a bootstrapping method over 1000 resamples that evaluated from 0.6 to 2.3 (95% CI).

Besides, we computed the R_t values of individual provinces of Marche with the exponential growth (EG) method. In EG, R_t can be calculated as the transformation of exponential growth, which

estimated by the Poisson regression model over the exponential growth of an outbreak, below the assumption of gamma distribution of time generation (Liu et al., 2020). The R_t was 2.492 (1.1–4.5) for Pesaro and Urbano, 2.162 (1.0–4.0) for Ancona, 1.792 (1.0–3.5) for Macerata, 1.512 (0.75–2.75) for Fermo, and 1.141 (1.0–1.6) for Ascoli Piceno. This kind of analysis was also observed by calculating transmissibility monitoring among European countries and achieved R_t of 3.27 [3.17–3.38] for Italy, 5.08 [4.51–5.74] for Spain, 6.07 [5.51–6.69] for Germany, and 6.32 [5.72–6.99] for France with EG methods (Yuan et al., 2020).

We also conducted forecasting daily incidences and cumulative incidences of Marche outbreak for the next thirty days. It is evident from the study, the outbreak size and daily incidence largely depend on the daily reproductive number. However, we perform projections with R_t remains unchanged, the daily incidences can be varied with the distinct percentile of inhabitants. The projections concluded that at the end of the 30th day the cumulative incidences 323 (95% CI), and daily incidences 45 (95% CI) might be reached. These values might be gradually reduced if local governance stops transmissibility of the virus by putting continuous efforts on contact tracing, and identifying symptomatic and asymptomatic cases. This analysis highlights the importance of controlling transmissibility among Marche inhabitants. Our study has some limitations. Primarily, because of the non-availability of information on the cluster outbreak, we adopted the values of SI, and the standard deviation in R_t estimation from the study on Lombardy, which might hamper the importance of this analysis. Second, general patients are forcing in confined to home, could affect the natural process of disease transmission. Finally, the present analysis was conducted based on the extracted data of Italian national Health Ministry, a hindrance in case reporting or case confirmation the computed R_t could be underestimated.

To sum up, rather than having the presence of mentioned limitations, this study could provide insights into virus transmission dynamics, geographical characteristics of positive incidences, and the necessity of implementing mitigation procedures to fight against the COVID-19 outbreak. This kind of study can enhance the chances of disease reduction not only in Marche, but also in other Italian regions.

Contributors

NC: data analysis, methods, and results; GB: study design, manuscript preparation, and statistical analysis; GGS: development of forecasting models, and FA: final revision and study approval.

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Ethical approval

Not required any ethical approval for this study

Conflicts of interest

No author does not have any conflicts of interest.

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