



Dynamical characteristics of the COVID-19 epidemic: Estimation from cases in Colombia



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ABSTRACT

Objective: To characterize the dynamics of the coronavirus disease 2019 (COVID-19) epidemic, for modeling purposes.

Methods: Data from Colombian official case information were collated for a period of 5 months. Dynamical parameters of the disease spread were then estimated from the data. Probability distribution models were identified, representing the time from symptom onset to hospitalization, to intensive care unit (ICU) admission, and to death. Kaplan–Meier estimates were also computed for the probability of eventually requiring hospitalization, needing ICU attention, and dying from the disease (the case fatality ratio).

Results: Probability distributions of the times and probabilities were computed for the population and for groups based on age and sex. The results showed that for the times that characterize the course of the disease for a given patient (time to hospitalization, ICU admission, or death), the variation from one age group to another was very small (around 10% of the fixed effect intercept) and the effect of sex was even smaller (around 1%). The course of the disease appeared to be very similar for all patients. On the other hand, the probability that a patient would advance from one stage of the disease to another (to hospitalization, ICU admission, or death) was heavily influenced by sex and age. The relative risk of death for male individuals was 1.7 times that of female individuals (based on 22 924 deaths).

Conclusions: The times from one stage of the disease to another were almost independent of the major patient variables (sex, age). This was in stark contrast to the probabilities of progressing from one stage to another, which showed a strong dependence on age and sex. Data also showed that the length of hospital and ICU stays were almost independent of sex and age. The only factor that affected this length was the eventual outcome of the disease (survival or death); the time was significantly longer for surviving patients.

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Introduction

Following the start of the first outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan in December 2019, the coronavirus disease 2019 (COVID-19) epidemic reached Europe early in 2020. The first cases in Colombia were imported from Europe, according to the genetic information obtained from these cases. At the time of writing, the virus genetic sequences available in Colombia show that most cases in the

country have come from Europe and the United States. The first officially reported case in Colombia appeared on March 6, 2020, imported from Italy, and the first COVID-19 death occurred on March 16, 2020.

Currently (September 13, 2020), the official total number of cases is 716 319, with 22 924 deaths. At this time, according to official Ministry of Health data, 599 385 patients have recovered, while 92 498 cases are officially active. At this point, there have been 44.95 deaths and 1405 cases per 100 000 people (INS: Instituto Nacional de Salud Colombia, 2020).

Starting on March 24, 2020, a strict country-wide lockdown was ordered in Colombia, which was gradually relaxed, due to the economic and social burden on citizens, notably in the low income

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sectors. As a result, the number of cases grew steadily, with more than 300 deaths each day by August 3, 2020 (INS: Instituto Nacional de Salud Colombia, 2020). By mid-September the daily number of new cases and deaths had started to decrease. In some cities, notably in the Amazon and Putumayo regions, with very scarce intensive care unit (ICU) capacity, some patients had to be transferred to other cities, mostly to Bogotá, as the number of severe cases surpassed the number of available ICU beds. Most of the exceeding cases still got critical clinical care at neighboring cities.

The pandemic continues, and new peaks have occurred and are expected beyond the study horizon. At this time (September 13, 2020), the peak of the epidemic has just passed, and both deaths and new cases have been falling for about a week, after a sustained plateau that lasted almost a month.

Several models have been proposed around the world to explain the local and global dynamics of the COVID-19 pandemic (Flaxman et al., 2020; Ray et al., 2020; Salje et al., 2020). These models rely on publicly available data to continuously update their projections (Ray et al., 2020). Parameters that describe the natural history of the disease have been estimated elsewhere, from many sources (Davies et al., 2020; Fateh-Moghadam et al., 2020; Heald-Sargent et al., 2020; Hu et al., 2020; Wu et al., 2020). These parameters are necessary to project the impact of the pandemic on local health systems (IHME COVID-19 Health Service Utilization Forecasting Team and Murray, 2020). The proportion of people infected who will develop symptoms within each age group has been estimated in Wuhan and other places (Wu et al., 2020). The duration of hospitalization was estimated to be around 7–14 days in China (Hu et al., 2020). In the present study, using official, publicly available data, random variable models were employed to represent the distribution of time from symptom onset to death, to hospital admission, and to ICU admission, as well as the probability of a registered patient ultimately requiring hospitalization, ICU care, or dying (the case fatality ratio, CFR).

One key parameter for the control of an epidemic, the CFR, constitutes an upper bound for the infection fatality rate (IFR) that quantifies the lethality of the disease. Estimation of the CFR is required to model the dynamics: this parameter is, approximately, the probability of one registered patient dying. The estimates need to consider the existence of active cases whose outcome is not yet decided (censoring). In this study, a commonly applied technique was used: the Kaplan–Meier method. This method, or variants thereof, has already been utilized to estimate the CFR in several locations. For modelling purposes and also for public health policy planning, the probability of a given person eventually needing hospitalization and the probability of a hospitalized patient requiring ICU admission are important parameters. Their estimation is subject to the same uncertainty and nuances as the CFR. All three are modelled here as a survival process.

The objective of this analysis was to provide detailed models for the main variables that characterize the course of the disease in a COVID-19 patient. These include the durations of the main stages of the disease and the probability of progressing from one stage to another: symptomatic to hospitalized; hospitalized to in the ICU; infected to dying. These are required for all detailed simulation models of the pandemic.

It appears that the dynamics of the process leading from infection to hospital admission, ICU admission, and death have not been described in detail elsewhere.

Materials and methods

The only materials used in this study were publicly available official data from the Colombian government.

Materials: data source

All data were obtained from the official COVID-19 epidemic data published daily by the Colombian Ministry of Health. These include a record for each person identified as infected with SARS-CoV-2 (INS: Instituto Nacional de Salud Colombia, 2020). Each case has a number to identify it, which serves to follow up that person throughout the disease course. The published records include the date of symptom onset (time of symptom onset, TSO) for most patients, as well as the date of report, date of death when applicable, and date of recovery. According to the metadata, the date of recovery is sometimes determined by tests, but it is more often inferred from the time since the date of symptom onset. Other information updated daily includes the state of the patient on that date and whether they are symptomatic or not.

Information on the current health state of the patients, the dates of admission to a hospital, and the dates of admission to an ICU are recorded. From this information, all of the time intervals and fractions can be determined. Since all information is recorded once a day, the minimum time resolution is 1 day. Thus, all measured intervals are integer-valued.

Daily case information was collected manually from the official site of the Colombian National Institute of Health for the period from April 3, 2020 to August 25, 2020, with a few data points missing, corresponding to dates where connection was not possible or the file was downloaded with errors. Currently, daily case information can be obtained from the Colombian government's open-data site (Covid-colombia, 2020). From these data, accumulated over time, approximate patient histories were recorded. Daily case information was then collated to reconstruct each patient's history.

The information collected for each case includes the patient's age, sex, and, for members of indigenous peoples, the ethnic group to which they belong. The dates of symptom onset (TSO), diagnosis, and death are also available, where appropriate. Age was converted to a discrete scale using the following age brackets: 0–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80+ years. The first age bracket includes all patients younger than 20 years old. An interval that is wider than those of the other groups was chosen because the number of cases in this first age group is smaller than in the other age groups and, for some analyses, the number was too small to permit proper estimation.

Methods

The first step of data treatment was to compute descriptive statistics of the characteristic times and fractions of the population. Next, stochastic models were obtained to model the probability distribution of those characteristics.

Computation of intervals and fractions

From daily information on patient conditions, the dates when the patient's health status changed were recorded. Then, using the sequence of state changes, the duration of each state was computed. Patients without a valid date of symptom onset were excluded from all analyses where this information was required (all except the probability of death, where the date of report, for asymptomatic patients, was used as the beginning of exposure). Similarly, for the computation of the time spent in the hospital and in the ICU, only those patients who had left the hospital or ICU, respectively, were considered. The intervals from TSO to hospital, to ICU admission, and to death were registered as the difference between the first date when the patient's state was registered as 'in hospital' or 'in ICU' and the symptom onset date, when applicable.

Statistical analysis

All analyses were performed using R programming and statistical software (R Core Team, 2020). Stochastic models were developed using Bayesian statistics with the brms package (Bürkner, 2018); brms is based on Stan, an open-source statistical modelling system.

In identifying adequate probability distributions to approximate characteristics of the epidemic in Colombia, several prospective random process candidates were tried. For the length of time from TSO to hospital or from TSO to death, lognormal, Weibull, and gamma continuous distributions and a zero inflated negative binomial discrete distribution were tried. The estimates were then compared using two different validation methods: the WAIC (widely used information criterion) and the LOO (leave one out cross validation) (see McElreath, 2020; Vehtari et al., 2017). In all cases discussed herein, both criteria favored the model that was eventually selected. For estimating probabilities or fractions, a survival model was applied using the Kaplan–Meier technique, based on the distribution of the times until the event occurred (Bogaerts et al., 2017; Verity et al., 2020). This is based on the hazard function $h(t)$, which may be computed from the distribution of time from symptom onset to the event. Since good approximations to the various times involved were found, they could then be used to compute the probabilities. For estimating survival probabilities, the R Survival package was used (Therneau and Grambsch, 2000).

Results

Time to death

The time from symptom onset to death was computed for all patients who died and who had information on symptom onset. This parameter is required for simulating the epidemic dynamics, especially for CFR and IFR estimation. Estimating this time during the early phases of the epidemic may require careful consideration of biases introduced by censoring due to errors in onset registration or lack of onset information (Verity et al., 2020). In our case, of the 22 924 patients who died, the TSO was known for 22 095, which was high enough so that a model could be fitted to the data without further consideration. As a reference for estimating the CFRs, it was noted that in this dataset, 90% of all deaths occurred between 3 and 35 days from TSO, and 829 (3.6%) deaths occurred in patients sheltering at home (did not receive hospital care). The distribution of times to death did not show any difference by sex (see Supplementary Material). Figure 1 shows the distribution of the times from symptom onset to death for the different age groups. A population-level model with a gamma likelihood, with $\mu = 15.4264$ (95% credible interval (CrI) 15.29–15.56) and shape parameter = 2.0325 (95% CrI 1.997–2.068), was found to adequately fit the data.

The average time from onset to death was determined for all of the age groups. This time could be accurately modeled by a gamma distribution, with varying intercepts for different age groups, as presented in the Supplementary Material.

Time to hospital and ICU admission

The length of time from symptom onset to hospital admission was recorded for $n_H = 50\,667$ patients nationwide, out of 619 750 cases. The corresponding data for 7521 patients admitted to ICUs were also recorded. From this information, probability distributions were found to accurately represent the distribution of the time between the onset of symptoms and hospitalization (T_{Hosp}) and from the onset of symptoms to admission to the ICU (T_{ICU}) (Figure 2).

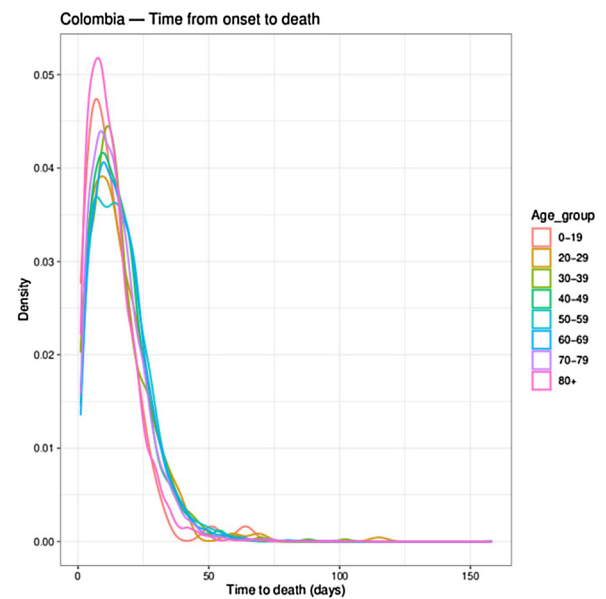


Figure 1. Probability density of time from symptom onset to death, by age group – Colombia.

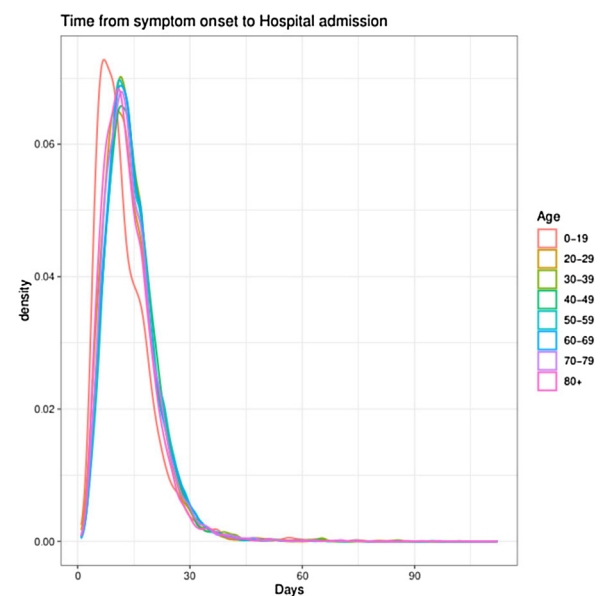


Figure 2. Probability density of time from symptom onset to hospitalization, by age group – Colombia.

The mean time to hospitalization estimated from the data was 14.27 days, with a median of 13 days. There were no significant differences between the sexes or age groups concerning the time to hospitalization.

As described in the Methods section, a gamma distribution was obtained as a good approximation; $\log(T_i) \sim \text{lognormal}(\mu, \text{shape})$ with $\mu = 15.427$ (95% CrI 15.287–15.569) and shape parameter = 2.033 (95% CrI 1.998–2.069).

A similar process was done to obtain the time from symptom onset to ICU admission. A total of 7521 complete observations were available. The mean time to ICU admission was 21.532 days. This time the best fit was achieved with a lognormal distribution with $\mu = 18.106$ (95% CrI 17.834467–18.374008) and $\sigma = 0.599$ (95% CrI 0.5889–0.6093). A model that conditions for the different age

groups was also obtained. Details are available in the Supplementary Material.

Length of hospital and ICU stay

The lengths of hospital stay ($n_H=11\,191$) and ICU stay ($n_{ICU}=6327$) were recorded for the patients for whom admission and discharge (or death) dates were available. The distribution of the time spent in the ICU showed a multimodal response, with two local maxima. This suggests the existence of at least two subpopulations with different responses or disease courses. No significant differences were observed by sex.

The probability density of hospital stay by disease outcome (Figure 3) showed that the patients who eventually died had a different distribution of this time than those who survived. The mean hospital stay for all patients was 15.43 days. For patients who died, the mean length of stay was 7.69 days; for those who survived, it was 36.23 days. In fact, some differences observed in length of stay for the older age groups were better explained when different death rates were taken into account. Thus the variation of probability of death for older ages is a confounder for the length of stay, more important than age and sex. In fact, the sex of the patient had a negligible effect on the length of hospital stay.

The mean length of ICU stay was estimated as 15.421 days. The mean stay for patients who died was 6.64 days and for those who survived was 24.4 days.

The multimodal distribution of the time in hospital suggests the use of a mixture models. However, it was found that separate models for the two subpopulations provided a good fit. The resulting model for patients who died was a lognormal(μ, σ) with $\log \mu = 3.5896$ (95% CrI 3.5806–3.5987) and $\sigma = 1.1261$ (95% CrI 1.1132–1.1400). The model for time in hospital (survivors) was a gamma distribution with $\mu = 36.219756$ (95% CrI 35.8959–36.5507) and shape = 2.0016 (95% CrI 1.9681–2.032).

Probability of death among registered cases

The computation of the CFR, i.e. the fraction of cases leading to death, requires consideration of the censored data due to currently infected patients who may die in the future.

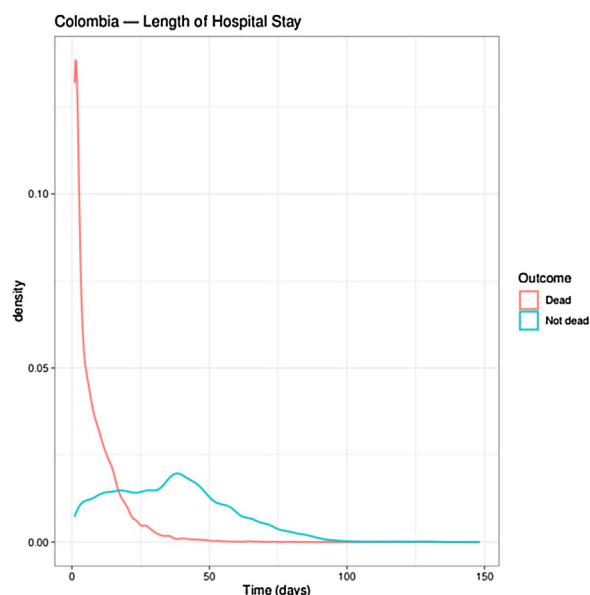


Figure 3. Probability density of length of hospital stay by outcome – Colombia.

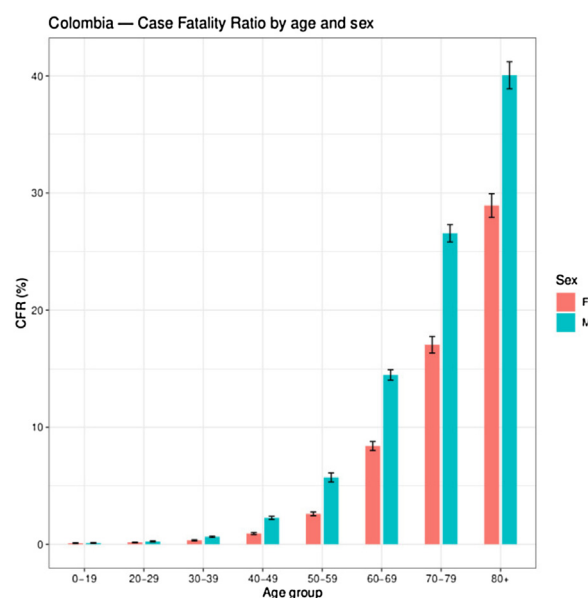


Figure 4. Case fatality ratio by age group and sex – Colombia.

The CFR by sex was estimated by Kaplan–Meier method as 3.8276% (95% CrI 3.775–3.8802%) for the population, 2.8165% (95% CrI 2.7498–2.8831%) for females, and 4.7882% (95% CrI 4.7076–4.8687%) for males. The male CFR was 70% greater than the female CFR, suggesting that males have a relative risk of death of 1.70 (odds ratio 1.73) with respect to females.

Wide differences were noted across the age groups. Estimated values of the CFR by age group and sex are shown in Figure 4. The corresponding estimated values are presented in the Supplementary Material. The probability of dying was found to be higher for males than for females, in all age groups. The CFR for males was 1.7 times that for females, at the population level. In fact, the CFR values were found to be higher for males in all age groups. The group with the largest relative difference was the 40–49 years group, in which the relative risk for males was found to be 2.45. Figure 4 shows the estimates for all age groups.

The overall CFR (3.83%) may be compared to the results from various countries, as published by Sudharsanan et al. (Sudharsanan et al., 2020). They have reported estimates ranging from high values for Italy (9.3%), the Netherlands (7.4%), and Spain (6.0%) to low values for South Korea (1.6%) and Germany (0.7%). Our estimate of the overall CFR in Colombia appears to be moderate. The large variation in CFR between age groups in Colombia appears to be wider than in most published results. For instance, Verity et al. (2020) reported estimates for Wuhan, with an overall rate of 3.67%, which is very close to our value, but the variation across age groups was not as great as in our estimates. Nevertheless, for the 80+ years age group, the ratio of censoring adjusted values to the crude estimate shows an even bigger ratio in their study ($1.57 = 23.3/14.8$) when compared to the present study ($1.1 = 35.25/32.094$).

Probability of hospitalization among registered patients

For modeling purposes it is necessary to have an estimate of the probability of hospitalization for registered patients. This probability was estimated as a survival process in which surviving individuals were those who never required hospitalization. This avoids underestimating the hospitalizations due to cases that are still active and might require hospital admission in the future (censoring). As with all the other surviving fractions, the proportion of cases needing hospital care was estimated using

the Kaplan–Meier method (Bogaerts et al., 2017; Ghani et al., 2005; Verity et al., 2020).

The raw percentage of hospitalized patients ($n_H=50\ 688$) admitted to an ICU ($n_{ICU}=5689$) was 11.22%. The Kaplan–Meier estimate of the fraction of hospitalized patients transferred to an ICU was 16.5289 (95% CrI 15.9973–17.0571).

The raw fraction of cases needing hospital care for the sample was 8.14% ($n_H=50\ 688$, $n=622\ 373$), and the corresponding estimate using the Kaplan–Meier method was 8.4496% (95% CrI 8.377–8.5221%). An estimate of the probability for the different age groups is given in the Supplementary Material; noticeable in the table is the high fraction of patients aged 80+ years, very close to the probability of death.

Probability of ICU admission among hospitalized patients

As mentioned before, the probability of ICU admission among hospitalized patients needs to be estimated while the outbreak is still active and censoring occurs due to the existence of patients currently hospitalized who might require ICU admission in the future. The estimation was done considering the process as a survival one, in which surviving individuals were those in the hospital who had not required ICU attention. A Kaplan–Meier model was also employed for this task.

The raw percentage of hospitalized patients (using $n_H=50\ 688$) admitted to an ICU ($n_{ICU}=7028$) was 13.87%. The resulting estimate of the percentage of hospitalized patients transferred to the ICU using the Kaplan–Meier method was 14.31% (95% CrI 13.98–14.64%). Estimates were also obtained for the different age groups, as shown in the Supplementary Material.

It should be noted that the highest fraction occurred in the 60–69 years age group and the fraction was comparatively lower in the 80+ years age group.

Discussion

In this study, models were used to estimate parameters related to the progression of disease for COVID-19 patients. The results were compared to those of previous reports elsewhere. Notably, our results differ from the data reported by different surveillance systems worldwide (World Health Organization, 2020). On May 21, 2020, the RNVE (National Epidemiological Surveillance) in Spain reported a mean of 6 days from symptom onset to the need for hospital care, and 9 days to ICU admission (ISCIII, 2020). This is in contrast to the data observed in the present study from Colombia, in which the estimated times were 14.26 days for hospital admission and 21.53 days for ICU admission. This might be attributed to the difference in demographic structure. However, as also shown by our results, the times were only very slightly affected by age or sex.

The overall mean Probability of death, hospitalization and ICU on both, hospitalization and ICU length, in our estimations differ from the data reported by the European Centre for Disease Prevention and Control (ECDC) in its report of April 8, 2020 (ECDC, 2020), which showed an average stay of 4 days on ICU for survivors, and 5 days for non-survivors in the UK; in Colombia, we found a length of hospitalization of 16.13 days and length of ICU stay of 8.63 days. The same report presents a mean length of hospital stay of 7 days for survivors and 8 days for non-survivors in the United States and China. In Colombia, those lengths were found to be 24.5 days for survivors and 7.04 days for non-survivors.

The ECDC reported a mean rate of hospitalization of 32% for the European community and 10.6% for the United States and China. The present study results show a similar rate of 9.46%. The raw data are slightly different, with a reported rate of 7.87%; Spain reported a marked variation with a hospitalization rate of 38.4%. Also, the

ECDC reported a rate of transfer from hospital to the ICU of 2.4%, similar to the RNVE data at 3.9%. The data observed in Colombia (14.25%) and the estimated rate (16.52%) are higher.

Our model estimated a death rate of 4.3%, more than twice the rate reported by the ECDC (1.5%) and about half the rate reported by the RNVE in Spain.

In summary, the data show a higher rate of hospitalization in European countries (32% ECDC and 38.4% RNVE versus 8.44% in Colombia) and also a longer hospital stay and ICU stay (7 days and 8 days for hospital stay in the United States and China, and 4 days and 5 days in the ICU in the UK versus 24.5 days and 7.04 days in hospital and 16.13 days and 8.63 days in the ICU in Colombia).

The CFR in Colombia was higher in the older age groups. The estimated CFR for the 80+ years age group was 39.6%. However, it should be noted that the crude CFR without adjusting for censoring was already quite high, at 31.8% (Verity et al., 2020).

The male CFR was 1.7 times the female CFR, i.e., the relative risk for males was 1.70 (odds ratio 1.73). Using a preliminary estimation of the overall fraction of registered cases as 0.12 of total infections due to under-reporting, as obtained by De la Hoz-Restrepo et al., 2020, and assuming uniform under-reporting rates by age, the IFR would be around 0.46%, a number that is not far from the estimated 0.6% in several countries. However, given the large differences in symptomatic infections in children and adults, this rate is most likely underestimated. Using age-specific under-reporting levels would improve this estimate. More precise seroprevalence studies that would allow the IFR to be estimated have not been presented at this time. A more accurate computation of this parameter will have to wait until more data are available.

The number of cases showed a slight bias towards male patients, who made up 51.5% of the registered cases. This is in contrast to the population composition, which is 48.4% male and 51.6% female. The estimate of the CFR for males was 70% higher than that for females. These values show that in Colombia, as has been found around the world, the effect of COVID-19 is more deadly for males than females.

The most striking result in this study is how little the factors of age and particularly sex affected the dynamics, represented by the various times from onset to the different states. The disease course in any given patient was found almost not to be affected by their characteristics. On the other hand, the probabilities of needing hospitalization, ICU care, or dying were very much dependent on age and especially sex. We have not found any references to this dichotomy for this disease or for any related diseases.

Although the estimates were based only on publicly available data, which are constantly adjusted, this is the data type that is usually available in the course of an epidemic. In fact, one of the secondary objectives of the study was to assess the possibility of estimating the main parameters of the epidemic dynamics using only publicly available data.

Several sources of uncertainty may have affected the results. The estimates of time to hospital admission and time to ICU admission were not based on actual hospital recorded admission dates but on inferred data obtained from the patient's state, as updated daily by the Colombian health authorities. The dates of death and symptom onset are more reliable, because those were officially reported by attending physicians to the epidemiological surveillance system. Data for asymptomatic patients are mainly associated with patients identified through contact tracing, because a random population-level testing campaign has not been in place. Recovery dates may also have wide uncertainty bands due to the lack of testing. Therefore, it was not considered worthwhile to include the time to recovery in this analysis. The high CFR values may be due to reduced testing. Testing was scarce at the beginning of the pandemic in Colombia, due to the lack of

laboratory facilities. The number of tests increased in July, and the CFR estimates for the last part of the period were in fact lower.

Limitations

This study only used official data published daily by the Colombian government. Although private conversations with some of the people in charge of gathering the information were held to assess the accuracy of the data, no further verification was possible. According to some responsible personnel, some changes may have been registered the day following the occurrence of the event. A potential limitation of this analysis is due to the lack of information on the proportion of deaths that were diagnosed as COVID-19 cases after death. Nevertheless, those patients diagnosed with COVID-19 after their death were already reported in the database; whether or not the test results were delayed, the information was eventually recorded. Furthermore, according to our data, only 3.6% of all those who died did not receive any kind of hospital care. Therefore, the error associated with this source of uncertainty is bounded. This reporting delay, however, does not mean that the date of death, the only information used to estimate the probabilities and durations, was inaccurately recorded, once it was recorded, only that it was recorded after the date of death. Once the test results are in, the database is updated. The only likely effect is a possible bias introduced by the test results pending, for patients who died, at the moment when the information was last accessed. To reduce the effect of delayed test results, the analysis of death times and proportions was based only on the latest information available at the end of the time period. Since the dates of death are always recorded, we believe that this source of uncertainty would have had a limited effect on the estimation of time to death and the probability of death. Including fewer deaths than the real number in the numerator may underestimate the CFR; so the worst scenario in the case of the present study is that the CFR may be lower than the true value. Other indicators obtained from this analysis are less likely to be biased by this limitation.

There was also a concern about the accuracy of the patient's daily location. Only 3.6% of COVID-19 patients who died did not receive medical care in hospital. This proportion is unlikely to bias the main estimates of CFR or time to death, since the date of death is not related to the likelihood of being tested for the virus. It was not possible to estimate the proportion of people who may have been misclassified regarding the site where they received medical care, i.e. hospital or ICU. Therefore, we cannot rule out some degree of uncertainty in the estimates of the times between onset of disease and ICU or hospital care. However, the estimates appear to be robust, with narrow credible intervals. A large proportion of misclassified people with time values widely departing from those with correct data would be necessary to produce a large bias in the estimates.

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Ethical approval

This study did not use any personal information. Only publicly available information was utilized. Animals were not involved, therefore, no ethical approval was necessary.

Conflict of interest

The authors declare no conflicts of interest.

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All data used in this work were prepared and made publicly available online by the Colombian National Institute of Health and the Ministry of Public Health.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.ijid.2021.01.053>.

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