**Factors associated to the duration of localized lockdowns during the COVID-19 pandemic in Chile**

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**Abstract**

**Background**: Since SARS-CoV-2 began striking residents of Wuhan, China, several countries have implemented containment measures, mainly lockdowns and social distancing. These approaches varied widely, and their efficacy is currently being studied.

**Methods**: This study explored demographic, socioeconomic and epidemiological factors associated to the duration of lockdowns in Chile between March 25th and December 25th, 2020, using joint models for longitudinal and time-to-event data, where the number of days of lockdown for each Chilean commune and longitudinal information were modelled jointly.

**Results**: Overcrowding, active cases, and positivity were significantly associated to the duration of lockdown, being identified as risk factors for longer lockdown. Specifically, the increment of one point in the overcrowding implies an increase of 39.5% in the lockdown period.

**Conclusion**: Joint models for longitudinal and time-to-event data permitted the identification of factors associated to the duration of lockdowns in Chile.

**Keywords:** Epidemiology, joint model, longitudinal outcome, survival outcome.

**Key Messages**

* Demographic and socioeconomic factors are important when studying COVID-19 lockdown duration since lockdown directly impacts the economy.
* Please add an epidemiological point.
* Joint models are a valuable tool when there is interest in investigating both longitudinal and time-to-event outcome jointly.
* The availability of examples and R codes encourage the application of joint models in different contexts.

1. **Introduction**

At the beginning of 2020, when the World Health Organization (WHO) declared COVID-19 a pandemic, countries started to implement containment measures to reduce viral transmission, mainly lockdowns and social distancing. Rapidly, more than half of the global population was under strict forms of movement restrictions and social distancing. The approaches taken by national governments varied widely and their efficacy has been investigated. Alfano and Ercolano [1], for instance, studied the efficacy of lockdown measures in 202 countries. They proved that, on average, lockdown reduces COVID-19 contagious, and its efficiency starts after approximately 3 weeks. A study in Wuhan, China, evaluated the efficacy of flight restrictions implemented to the Hubei province. [2] On the other hand, a French study focused on lockdown exit strategies. [3] They pointed out, for instance, that lifting lockdown without exit strategy would lead to large rebound effects.

In Chile, the first measures were kindergarten and school closing, followed by country borders closure. Few days later, on March 25th, the government started to implement localized lockdowns at the commune level, which is the smallest administrative division in Chile. Lockdowns were established by the Chilean government based on several criteria defined by the Chilean Ministry of Health. Basically, four indicators were considered: the total number of active cases, the increment in the incidence of active cases, the total number of active cases per km², and the availability of beds in the intensive care unit (ICU). These indicators were analysed individually for each commune (see Section 2 for more details about Chilean administrative division).

The Ministry of Health also established criteria for ending lockdowns. At regional level, the occupancy of the ICU system should be less than or equal to 85% and the percentage of positivity of the polymerase chain reaction (PCR) exams less than 10% in the previous seven days. At the commune level, a steady decline in new cases during the previous 21 days was required, which means the effective reproductive number was less than or equal to 1. In addition, there should be a capacity to track and isolate 90% of new confirmed cases in less than 48 hours, and to identify and track 75% of contacts of those cases for 14 days.

Although the criteria to begin and end a lockdown were clearly established by the Chilean government, there is still no strong scientific evidence to support them; thus, they could be arguable. Motivated by this concern, the main goal of this study was to explore demographic, socioeconomic and epidemiological factors associated to the duration of localized lockdown in Chile. To pursue our objectives, we used joint models for longitudinal and time-to-event data, which considered both the number of days of lockdown for each Chilean commune and the longitudinal information, jointly.

1. **Material and methods**
   1. **Study location**

Localized in South America, Chile occupies a long and narrow coastal strip between the Andes and the Pacific Ocean. It borders Peru to the north, Bolivia to the northeast, and Argentina to the east. Besides, the country is geographically divided into 16 regions, which are the first-level administrative division of the country. Each region is divided into provinces, which are the second-level administrative division, resulting in a total of 56 provinces. The third level of the administrative division are the communes (or municipalities), totaling 346 communes, in which 166 were considered in this study.

According to the Chilean National Institute of Statistics (INE), the estimated country population was 19,458,173 inhabitants in 2020, much of it concentrated in the Metropolitan Region, whose capital city is Santiago. Regarding the communes, only 55 of 346 have more than 100,000 inhabitants, the median population being 18,546 inhabitants (minimum 138, maximum 646,000). Chile is among the largest economy in Latin America; however, despite its economic progress and poverty reduction over the last few decades, there is great social inequality. According to the World Bank, the Chilean per capita gross domestic product was 14,896.45 USD in 2019 and decreased 5.8% in 2020. [4] Such economic complications could be related to the lockdown duration.

* 1. **Outcomes**

In follow-up studies two type of data can be collected: information collected over time (longitudinal data) and time until an event of interest occurs (survival data). In this study, both were included as outcomes. For the time-to-event analysis, we considered the number of days a commune was under lockdown; to do so, we recorded the number and duration of lockdown set up in Chile between March 25th and December 25th, 2020. In case a commune was still under lockdown on December 25th, it was considered as a right-censored observation. In general, lockdowns were set up at the commune-level; however, at the beginning of the pandemic some lockdowns were established at greater administrative division levels (i.e., province). In this study, lockdowns were considered as commune-level. For the longitudinal analysis, we studied several epidemiological factors. As this information varies over time, we used the weekly average value during the period the commune was on lockdown. The epidemiological information was collected based at first or third levels of the administrative division and corresponded to the number of active cases per commune, the number of asymptomatic and symptomatic cases per region, the number of patients in ICU per region, the number of deaths per commune according to their residence, and number of PCR exams performed per region. All this information was considered as the number per 100,000 inhabitants.

An active case was defined as a living person who met the definition criteria of suspected case with a positive sample of SARS-CoV-2, whose date of onset of symptoms in the notification was less than or equal to 11 days, i.e., people capable of transmitting the infection. From the number of asymptomatic and symptomatic cases, and the number of PCR exams performed per region, we calculated a new longitudinal outcome, the positivity, which was expressed as the percentage of cases relative to the number of PCR exams:

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* 1. **Predictors**

Demographic and socioeconomic factors were considered as predictors for the time-to-event model; these consisted of population size (in 100,000 inhabitants), number of immigrants (per 100,000 inhabitants), overcrowding (number of people over the number of households), a socioeconomic development index (SDI, between 0 and 1), and a rural index of the communes (from 0 to 100). For obtaining SDI, different indicators were aggregated, including economy (monthly per capita income and poverty), education (average years of schooling), and housing and sanitation (good and acceptable housing material and sewerage or septic tank). [5] For the calculation of the rural index, it was considered the percentage of rural population, the proportion of local employment occupied in primary sectors and the population density. Then, an average of these three values was calculated, resulting in the rural index (see [6] for more details). Besides, in this study, we considered whether the commune held the regional or province city and whether a commercial airport or harbour is present in it. Apart from demographic and socioeconomic factors, we also included a binary covariate indicating if it was the first or second time that the commune was under lockdown.

* 1. **Statistical modelling**

The two sources of information presented in this study are often analyzed separately. However, in some situations, one may also be interested in the association between longitudinal measurements and the event of interest, in these cases a joint analysis is indicated (see [7] for a comparison between two approaches). The approach used in these situations depends on the type of the time-dependent covariates. [8] When this information is exogenous, i.e., variables whose cause is external to the model, an extended Cox model [9] could be used. On the other hand, when the longitudinal covariates are endogenous, i.e., variables that are changed or determined by their relationship with others, it is necessary to use a new class of models known as joint models. [10]

The idea behind joint modelling of longitudinal and time-to-event data is to couple a model for repeated measurements with a survival model so that it can help to explain the event of interest. Probably, the most common joint model specification is to connect a mixed effects sub-model fitted to describe the evolution of the longitudinal information with a proportional hazard sub-model fitted to the survival information. For a long time, this approach had been limited to a single longitudinal and a single time-to-event outcome. However, a model with multiple longitudinal and/or multiple time-to-event outcomes can also be considered. [11, 12] Thus, a joint model for longitudinal outcomes can be formulated as follows:

where represents the k-variate vector of continuous longitudinal measurement for the th commune at time . This vector is modelled by a mixed effects sub-model, where denotes the regression coefficients associated with the design vector for the fixed effects . Besides, denotes the design vector for the random for the commune . Finally, represents the model error term. The longitudinal sub-model included fixed intercepts and random slopes. The joint model is completed with the time-to-event sub-model. In this case, the outcome is modelled by a proportional hazard. This kind of strategy focuses directly on the hazard function , considering the baseline hazard function, , and a second term that includes baseline covariates, , and the true and unobserved value of longitudinal outcome for the commune at time , which is denoted by and modelled by the longitudinal sub-model. Finally, α represents the association between the longitudinal and time-to-event outcome.

In this study, we were interested in investigating the time until a Chilean commune comes out of lockdown, which motivated the use of time-to-event sub-model. In addition, we wanted to add epidemiological information to the study (Section 2.2); such information was obtained at the commune-level and over time during the follow-up period. Consequently, the most indicated strategy was to build a mixed longitudinal sub-model. Finally, the joint approach did the connection between both parts, including the information obtained by the longitudinal model in the time-to-event model. Active cases, ICU patients, and deaths were logarithmically transformed for joint analysis, while positivity was handled as percentage.

* 1. **Model building process and model validation**

The model was built in two stages. First, we fitted univariate joint models for each of the longitudinal covariates (active cases, ICU patients, deaths, and positivity). At this point, we identified that the association between number of deaths and the duration of lockdown was not statistically significant, i.e., p-value was higher than 0.05. Then, a bivariate joint model was fitted considering pairs of the significant variables. Finally, a trivariate joint model was fitted, however, the association between ICU patients and the duration of lockdown was not statistically significant. Consequently, the bivariate model including number of active cases and positivity was considered as the final version.

The second stage was aimed to select the social and demographic covariates included in the bivariate joint model. To do so, we used the stepwise backward elimination approach, starting from a full model, which included all the predictors described in Section 2.3. Covariates with the highest p-values were removed from the model one at a time until all predictors were below the significance threshold (p-value ≤ 0.05). Finally, the joint model included two longitudinal information, number of active cases and positivity, and two demographic and socioeconomic factors, overcrowding and rural index.

1. **Results**
   1. **Descriptive analysis**

During the study period (between March 25th and December 25th, 2020), 166 communes were under lockdown once and 19 (11.4%) twice. Of all communes, 16 (9.6%) are regional capital and 26 (15.7%) are province capital cities. In addition, there are commercial airport in 9 (5.4%) of them and commercial harbour in 10 (6%). Commune’s population size ranged between 2,000 and 646,000 inhabitants with a median population density of 122,390 and a median overcrowding of 2.73 people per household (Table 1).

According to the United Nations, in 2019, 4.92% of the Chilean population was composed of immigrants, which totals almost one million people. Particularly in this study, four of the 166 communes had no immigrants. On the other hand, the Chilean capital was the one with greater concentration of immigrants, 22,008 each 100,000 inhabitants. The rurality index of the considered communes also varied greatly, while some communes were entirely urban, others were made up of almost 80% of rural area. Something similar happens with SDI, which varied between 26% and 99%.

Table 1: Descriptive statistics for variables included in the model building process.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Covariate** | **Mean** | **Median** | **SD** | **Range** |
| Population density | 2,287.91 | 122.39 | 4,539.39 | 0.13 – 21,706.08 |
| Immigrants | 2,634.38 | 1,098.46 | 3,809.27 | 0.00 – 22,007.88 |
| Population | 1.13 | 0.82 | 1.15 | 0.02 - 6.46 |
| Overcrowding | 2.75 | 2.73 | 0.40 | 1.41 - 3.69 |
| SDI | 0.60 | 0.60 | 0.14 | 0.26 - 0.99 |
| Rural index | 41.62 | 41.20 | 16.17 | 0.38 - 78.63 |
| Active cases | 84 | 65 | 80 | 0 - 807 |
| ICU | 5 | 5 | 2 | 2 - 13 |
| Deaths | 61 | 41 | 50 | 0 - 207 |
| Positivity | 0.07 | 0.06 | 0.04 | 0.01 - 0.33 |

Regarding the epidemiology information, there was a great variation across the communes. The average weekly number of active cases ranged from zero up to 807 cases per 100,000 people, where five people entered the ICU and 60 people died. The positivity varied between 1% and 33% depending on the commune. More details about the continuous features considered in this study can be seen in the Table 1.

* 1. **Joint model**

Results from the longitudinal sub-model showed that the number of active cases and the percentage of positivity decreased during the lockdown (Table 2). However, besides of identifying this behaviour, our main goal is to know whether number of active cases and percentage of positivity were associated to the duration of lockdowns. Thus, in the joint model, α indicates the change in the hazard for a unit change in the underlying subject-specific value of the longitudinal outcome and thus determines the strength of the association. Specifically, both longitudinal outcomes, number of active cases and percentage of positivity, and time-to-event outcome were significantly associated ( and , respectively). An increase in these factors implies longer lockdown.

Regarding demographic and socioeconomic factors, the joint model showed that overcrowding is significantly associated to the duration of lockdown (p-value < 0.005), Table 2. This association suggests that an alteration in this covariate leads to changes in the hazard of a commune leave a lockdown. Specifically, the increment of one point in the overcrowding implies an increase of 39.5% in the time of lockdown, i.e., greater overcrowding implies longer lockdown.

##### Table 2: Bivariate joint model. Coefficient estimates, standard errors, and p-values for explanatory variables in both longitudinal and time-to-event sub-model, and hazard ratio (HR) estimates with their corresponding 95% confidence intervals (CI). correspond to the active cases and to the positivity.

|  |  |  |  |
| --- | --- | --- | --- |
| **Longitudinal sub-model:** | | | |
| **Variable** | **Estimate** | **Std. Error** | **p-value** |
| Intercept | 5.440 | 0.149 | <0.0001 |
| Active cases | -2.740 | 0.294 | <0.0001 |
| Intercept | 0.218 | 0.013 | <0.0001 |
| Positivity | -0.408 | 0.037 | <0.0001 |
| **Time-to-event sub-model:** | | | | |
| **Variable** | **Estimate** | **Std. Error** | **p-value** | **HR (CI 95%)** |
| Overcrowding | -0.928 | 0.397 | 0.019 | 0.395 (0.182, 0.861 |
|  | -0.769 | 0.229 | <0.0001 | 0.463 (0.296, 0.726) |
|  | -24.120 | 3.204 | <0.0001 | 0.000 (0.000, 0.000) |

* 1. **Reproducibility material**

To facilitate the reproducibility of this study, both the data and R code are provided in the supplementary materials available at <https://github.com/COVID0248/JM>. Besides, details about the data source are also available.

1. **Discussion and conclusion**

The aim of this paper was to investigate how demographic, socioeconomic, and epidemiological factors are associated to the duration of lockdowns in Chile. We found that apart from epidemiological information such as active cases and positivity, demographic and socioeconomic information such as overcrowding and rural index were also significantly associated to the duration of local lockdowns. We used multivariate joint model to explain these associations, providing useful and practical information to support governmental decisions regarding local lockdowns.

In the clinical field, it is common to have longitudinal and time-to-event outcomes in the same study. Then, we have realized that similar situations also occur in more generic scenarios as COVID-19 lockdowns. In this study, we proposed a joint modelling framework to investigate more about Chilean lockdowns and factors related to them. [13] used a similar strategy when develop a dynamic risk prediction model for COVID-19 prognosis considering longitudinal measures. [14] used joint approach to study the association of oxygen saturation to fraction of inspired oxygen ratio and time to death of patients diagnosed with COVID-19. However, at the best of our knowledge, there are no similar studies focused on duration of lockdown.

Joint models are an important tool in studies interested in the association between longitudinal measurements and the event of interest, making this approach gain great visibility. Although we have not presented several details about joint model, we encourage our reader to look for more details about this modelling. [7, 12] presented good tutorials focusing on how to use joint models in different contexts in epidemiology. Besides, we have also provided the real dataset as well as the R code used to develop this paper, available at <https://github.com/COVID0248/JM>. Then, all our work can be reproducible by the reader.

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