

# A Comprehensive Meta-Analysis of COVID-19 in Latin America

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## Abstract

**Background:** Latin America has become the epicenter of the coronavirus disease 2019 (COVID-19) pandemic. We aim to perform a systematic comparative review of the clinical characteristics that are associated with this disease in Latin American countries.

**Methods:** We conducted a systematic review of published articles, journal and/or epidemiological reports of confirmed COVID-19 cases in Latin America. Data were obtained either through publicly available information from Ministries of Health, published journal reports and/or unpublished datasets. We analyzed data from SARS-CoV-2 positive patients evaluated at healthcare centers and hospitals of 8 countries including Brazil, Peru, Mexico, Argentina, Colombia, Venezuela, Ecuador, and Bolivia, between March 1<sup>st</sup> and July 30<sup>th</sup>, 2020. These countries consist of a total population that exceeds 519 million. Demographics, comorbidities, and clinical symptoms were collected. Statistical descriptive analysis and correlation analyses of symptoms, comorbidities and mortality were performed.

**Results:** A total of 728,282 COVID-19 patients were included in this study. Of these, 52.6% were female. The average age was 48.4 years. Peru had the oldest cohort with 56.8 years and highest rate of females (56.8%) while Chile had the youngest cohort (39 years old). Venezuela had the highest male prevalence (56.7%). Most common symptoms were cough with 60.1% (Bolivia had the highest rate 78%), fatigue/tiredness with 52.0%, sore throat with 50.3%, and fever with 44.2%. Bolivian patients had fever as the top symptom (83.3%). GI symptoms included diarrhea which was highest in Mexico with 22.9%. Hypertension was among the top (12.1%) comorbidities, followed by diabetes with 8.3% and obesity at 4.5%. In multivariate analyses, the leading and significant comorbidities were hypertension ( $r = 0.83$ ,  $p = 0.02$ ), diabetes ( $r = 0.91$ ,  $p = 0.01$ ), and obesity ( $r = 0.86$ ,  $p = 0.03$ ). Mortality was highest in Mexico (16.6%) and lowest in Venezuela (0.9%) among the analyzed cohorts.

**Conclusion:** Overall, COVID-19 patients in Latin America display cough, fatigue, and fever as main symptoms. Up to 53% of patients with COVID-19 have GI manifestations. Different clinical symptoms were associated with COVID-19 in Latin American countries. Metabolic syndrome components were the main comorbidities associated with poor outcome. Country-specific management and prevention plans are needed and can be established from this meta-analysis.

**Keywords:** Coronavirus Disease-19; Pandemic; Gastrointestinal Manifestation; Diarrhea

**Abbreviations:** ACE2: Angiotensin Receptor 2; CI: Confidence Interval; COVID-19: Coronavirus Disease-19; GI: Gastrointestinal; RT-PCR: Real-time Polymerase Chain Reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; TMPRSS: Transmembrane Serine Protease

## Background

Latin America has recently experienced unique and unprecedented challenges with emerging viral diseases including Chikungunya and Zika, that were endemic to some regions [1,2]. However, the Coronavirus Disease 2019 (COVID-19) may be the most consequential to date [3,4]. On December 31<sup>st</sup>, 2019, in the city of Wuhan in Hubei province of China [4,5], the first reports of a pneumonia-like cluster of illnesses, whose common symptoms included fever, dry cough, and in some cases severely compromised breathing (i.e., dyspnea), was made public. The initial report indicated that most of the patients either worked at or visited a wet wholesale seafood market called Huanan Seafood Wholesale Market where live wild animals and meat were regularly traded and sold [6]. On January 7<sup>th</sup>, according to the World Health Organization (WHO), Chinese officials announced they had identified a new virus named 2019-nCoV and was identified as belonging to the coronavirus family, which includes SARS and the common cold. On January 10<sup>th</sup>, 2020, Chinese scientists published the entire genome of this new pathogen [6]. Although there are other currently circulating respiratory coronaviruses of the family Coronaviridae, genus Betacoronavirus, in the human population, this novel strain was more contagious, virulent, and stealthier. WHO officially named the disease COVID-19 (Coronavirus Disease 2019) [https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200211-sitrep-22-ncov.pdf?sfvrsn=6f80d1b9\\_4](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200211-sitrep-22-ncov.pdf?sfvrsn=6f80d1b9_4) [6]. On January 30<sup>th</sup>, WHO declared the outbreak a Public Health Emergency of International Concern (pandemic) and named the virus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) as the successor to SARS-CoV-1 on March 11<sup>th</sup>, 2020 [7]. As of September 5<sup>th</sup>, 2020, the disease globally killed more than 867,000 people and infected over 26 million, according to the evolving data compiled by Johns Hopkins University [8]. While most infected patients did not succumb to the disease, short- and long-term effects are yet to be assessed, especially as it pertains to non-lethal symptoms complications.

There is a heavy burden of COVID-19 in Latin America. Given the ongoing and continuous transmission, the high rates of subclinical infections, inconsistent and insufficient diagnostic testing from country to country, there are differences in attribution of infected cases and cause of death. Compared to the US, the high number of COVID-19 in Latin American nations is especially troubling because of the already fragile economies compounded by months of strict lockdowns and weaker healthcare systems. Latin American countries also harbor densely populated cities like Mexico City with 8,918,653 inhabitants, Sao Paulo with 11,253,503, Buenos Aires with 2,891,08 and urban slums that are hit with extreme poverty and overcrowded conditions, fertile grounds for community transmission of the virus and widespread propagation of the infection <https://worldpopulationreview.com/continents/latin-america-population> [9].

Brazil, the country hardest hit by the pandemic, may be under testing its public with the real figures probably being far higher [10]. The contribution to a higher infection and death rate might have come from the participation of millions of tourists in

carnivals in the streets of Rio de Janeiro, Sao Paulo, Salvador, and other cities which started the celebration on February 21<sup>st</sup>, 2020 [11]. However, the rapid spread of the pandemic and the small number of tests performed in many Latin American countries including Peru, Mexico, Argentina, Columbia, and Bolivia make it difficult to estimate the actual number of cases to initiate control measures, resource planning, or benchmarking with neighboring countries.

The confirmed reported cases of COVID-19 remain the most crucial data to understand the evolution of the disease and the symptoms that associate with it. The earliest cases of COVID-19 in China were identified through “pneumonia-like” cases of unknown origin [12]. However, the spread of the infection throughout the world including Latin America has revealed that there are numerous ailments including neurological, cardiovascular, immunological, and gastrointestinal that can associate with Covid-19 [13,14].

In this study, we performed a comparative analysis of the clinical characteristics, mortality, and symptoms of the confirmed COVID-19 cases reported in various Latin American countries that have made pertinent information publicly available, through

## Methods

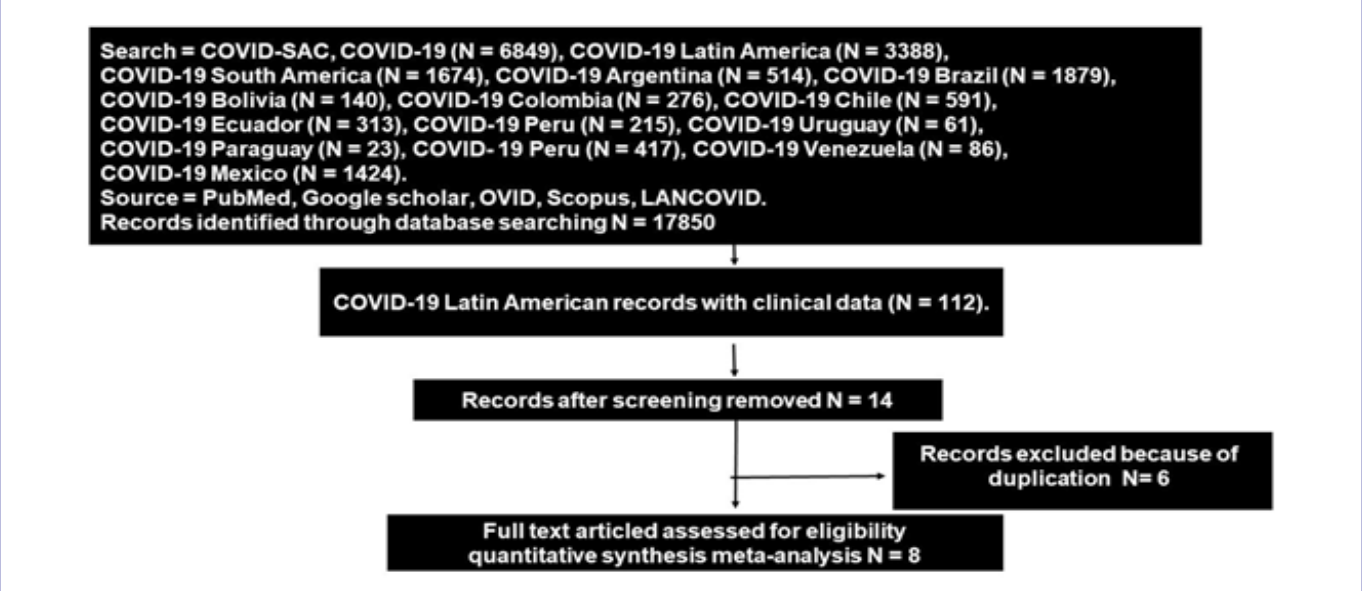
### Search Strategy and Selection Criteria

We conducted a systematic review of published articles using electronic databases such as PubMed, OVID, Scopus, Google Scholar, LANCOVID (Latin America research network on COVID), and other resources from official health organizations of countries in Latin America such as Ministries of Health, National Institutes of Hygiene, or Hospitals from January 1 through July 30, 2020. We included the following terms in the search bar: COVID-19 & Argentina; COVID-19 & Brazil; COVID-19 & Chile; COVID-19 & Colombia; COVID-19 & Ecuador; COVID-19 & Mexico; COVID-19 & Peru; COVID-19 & Venezuela; COVID-19 & Uruguay; COVID-19 & Paraguay; COVID-19 & Hispanic and Latin America or South America. Additionally, we searched for official and non-official press releases of patient and hospital data from government health institutions of the leading COVID-19 Latin American countries. We searched leading reference databases, primary published sources, and press releases from the various Ministries of Health of the respective Latin American countries. Case characteristics were described, including demographics, exposures, comorbidities, and symptoms. The protocol of this systematic review and analysis is in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines [15].

### Selection and Identification of Relevant Data

Using the listed inclusion and exclusion criteria, we first sorted the Latin American COVID-19 studies by title and abstract; then we compiled the papers by relevance and conducted a new selection process by a thorough review of the data. Based on detailed insights derived from the most relevant papers, we

revised our reference search criteria to obtain more refined papers for our systematic review. We incorporated studies that reported patients' characteristics and symptoms of interest. From the selected papers, tables were generated for each dataset on Microsoft Excel containing description and publication of each study, epidemiological report and/or clinical database). These tables included the following information for extracted data of each study (when available): Study author (year, location, hospital or city, state and country), date of the report, location, confirmed cases, deaths, mortality rate, average age, sex, headache (cephalea), cough, myalgias, fever, odynophagia, anosmia, dyspnea, ageusia, diarrhea, thoracic pain, abdominal pain, tachypnea, cyanosis, sore throat, nasal congestion, nausea and vomiting, fatigue or tiredness, joint pain, hypertension, diabetes mellitus, asthma, obesity, cardiovascular disease, chronic cardiopathy, chronic obstructive pulmonary disease, chronic kidney disease, chronic neurological disease, cancer, inflammatory bowel



**Figure 1:** Flow chart of search, screening, and selection of the relevant studies for Latin America COVID-19 meta-analysis.

disease, and tuberculosis (Figure 1).

**Inclusion criteria:** The following inclusion criteria were adopted to validate articles and reports' selection: Confirmed diagnosis of COVID-19 as reported by each country and referenced by WHO or cross-checked via World-Meter or Johns Hopkins University COVID-19 dashboard; No distinction about the number of diagnosed cases; No distinction about sex, age, severity of disease, inpatient or outpatient management, data collection date, treatment and outcome.

**Exclusion criteria:** The following exclusion criteria were adopted to filter out incomplete or ambiguous data: Studies where the cohort was not Latino or Hispanic, studies where the cases were not confirmed by RT-PCR, and studies with incomplete symptoms or comorbidities' report.

Statistical Analysis

The data provided by the Ministries of Health and hospitals of the eight Latin American countries were compared with the data available on public websites such as World Meter (<https://www.worldometers.info/coronavirus/>) and Johns Hopkins COVID-19 dashboard (<https://coronavirus.jhu.edu/map.html>). The following results were obtained: Peru (2 reports, 357,681 patients), Chile (306,440 patients), Argentina (36,749 patients), Mexico [unpublished] (1 unpublished database, 3,054), Ecuador (9,468 patients), Bolivia (107 patients), Venezuela (4,014

patients), and Brazil (10,713 patients). A total of 728,282 patients with a collective death toll of 25,008 (3.4%). Study design was based on a retrospective observational study. We combined the endpoints of the collected data from 8 different countries to detect the possible associations or trends between mortality and risk factors [16-18].

The adopted statistical methods were weighted descriptive statistics, t-test, independent sampletest and linear regression analysis as appropriate, where weights were associated with total number of cases in each country. The common symptoms and comorbidities were combined and analyzed by weighted analysis methods where applicable. Correlation coefficients were calculated together with regression analysis to establish associations between comorbidities and mortality. The effect of symptoms was reported using weighted analysis where weights were related to the size of the reported study. Except for age, all other variables are given as percentage of the number of total cases. SPSS (SPSS Inc., Chicago, IL, USA) was used for these

Results

Demographic and Clinical Characteristics

There were 728,282 confirmed cases in our study from 8 countries (Table 1). These countries are Peru, Ecuador, Bolivia, Mexico, Chile, Argentina, Venezuela, and Brazil. As for the characteristics of each cohort, there was no discrimination between patients who were hospitalized versus those treated at

Table 1: Demographics, symptoms and comorbidities of COVID-19 patients from Latin America.

|                                 | Argentina     | Bolivia   | Brazil       | Chile          | Ecuador      | Mexico       | Peru           | Venezuela    |
|---------------------------------|---------------|-----------|--------------|----------------|--------------|--------------|----------------|--------------|
| <b>Cumulative Cases</b>         | 36,749        | 107       | 10,713       | 306,440        | 9,468        | 3,054        | 357,681        | 4,014        |
| <b>Deaths</b>                   | 1,186         | 6 (7)     | 821          | 8,580          | 474          | 515          | 13,384         | 38           |
| <b>Mortality Rate</b>           | 3.2           | 5.6       | 7.7          | 2.3            | 5            | 17           | 3.7            | 0.9          |
| <b>Male (N)</b>                 | 46.9 (17,235) | 51.4 (54) | 44.8 (4,800) | 51.6 (158,123) | 55.4 (5,235) | 53.5 (1,634) | 43.2 (154,518) | 56.5 (2,272) |
| <b>Female (N)</b>               | 53.1 (19,514) | 48.5 (52) | 55.2 (5,913) | 48.4 (148,317) | 44.6 (4,223) | 46.4 (1,417) | 56.8 (203,163) | 43.4 (1,742) |
| <b>Average Age</b>              | M             | 43.9      | 44.8         | 39             | 40.7         | 47.3         | 56.8           | M            |
| <b>Cough (N)</b>                | 35.5 (13,046) | 78.8 (84) | 67.7 (7,252) | 57.6 (176,509) | 41.7 (3,948) | 67 (2,046)   | 65.3 (233,565) | M            |
| <b>Fatigue or Tiredness (N)</b> | M             | 51.5 (55) | M            | M              | 53.2 (5,037) | M            | 52 (185,994)   | M            |
| <b>Sore Throat (N)</b>          | M             | 37.9 (40) | 29.7 (3,181) | M              | M            | M            | 50.7 (181,344) | M            |
| <b>Fever (N)</b>                | 36.5 (13,413) | 83.3 (89) | 62.6 (6,706) | 38.8 (118,899) | M            | 77 (2,351)   | 49.4 (176,694) | M            |
| <b>Headache (N)</b>             | 26.1 (9,591)  | 53 (56)   | 51.2 (5,485) | 55 (168,542)   | 43 (4,071)   | 74 (2,260)   | 33.4 (119,465) | M            |
| <b>Myalgias (N)</b>             | 9 (3,307)     | 42.4 (45) | M            | 53.8 (164,865) | 35 (3,314)   | 63 (1,924)   | 18.3 (65,455)  | M            |
| <b>Odynophagia (N)</b>          | 27 (9,922)    | M         | M            | 30.1 (92,238)  | M            | 46 (1,484)   | M              | M            |
| <b>Nasal Congestion (N)</b>     | M             | M         | 38.8 (4,156) | M              | M            | 0 (0)        | 24.1 (86,201)  | M            |
| <b>Dyspnea (N)</b>              | 4.3 (1,580)   | M         | 28.7 (3,074) | 18.5 (56,691)  | M            | 48 (1,466)   | 28.3 (101,223) | M            |
| <b>Thoracic Pain (N)</b>        | 2.2           | M         | M            | 9.8 (30,031)   | M            | 32 (977)     | 9.3 (33,264)   | M            |
| <b>Anosmia (N)</b>              | M             | M         | M            | 16.1 (49,337)  | 36.1 (3,418) | 6 (183)      | 1.4 (5,007)    | M            |
| <b>Ageusia (N)</b>              | 12.9 (4,740)  | M         | M            | 12.8 (39,224)  | 37.1 (3,512) | 6 (183)      | 0.4 (1,430)    | M            |
| <b>Joint Pain (N)</b>           | 3.4 (1,249)   | M         | M            | M              | M            | 59 (1,802)   | 3.2 (11,446)   | M            |
| <b>Tachypnea (N)</b>            | 3.4 (1,249)   | M         | M            | 3 (9,193)      | M            | 4 (122)      | M              | M            |
| <b>Cyanosis (N)</b>             | M             | M         | M            | 0.6 (1,838)    | M            | 4 (122)      | M              | M            |
| <b>Diarrhea (N)</b>             | 3.1 (1,139)   | M         | 14.7 (1,575) | 10 (30,644)    | M            | 23 (702)     | 13.6 (48,644)  | M            |
| <b>Nausea and Vomits (N)</b>    | 1.2 (441)     | M         | M            | M              | M            | M            | 7.9 (28,256)   | M            |
| <b>Abdominal Pain (N)</b>       | 1.5 (551)     | M         | M            | 6.2 (18,999)   | M            | 17 (529)     | 2.9 (10,372)   | M            |
| <b>Hypertension (N)</b>         | 13.5 (4,961)  | 9.3 (10)  | M            | 16 (49,030)    | M            | 29 (885)     | 8.7 (31,118)   | 1.8 (72)     |
| <b>Diabetes (N)</b>             | 6.9 (2,535)   | 4.6 (5)   | 10.2 (1,093) | 8.8 (26,966)   | M            | 21 (641)     | 8 (28,614)     | 0.6 (24)     |
| <b>Obesity (N)</b>              | 5.5 (2,021)   | 5.6 (6)   | 5.6 (600)    | 3.9 (11,951)   | M            | 26 (794)     | 4.3 (15,380)   | M            |
| <b>Asthma (N)</b>               | 5.2 (1,911)   | M         | M            | 2.9 (8,886)    | M            | 4 (122)      | M              | 1.1 (44)     |
| <b>COPD (N)</b>                 | 1.8 (661)     | M         | 4.8 (514)    | 1.4 (4,290)    | M            | 4 (122)      | 2.8 (10,015)   | M            |



|                                     |             |         |                 |             |      |                      |             |          |
|-------------------------------------|-------------|---------|-----------------|-------------|------|----------------------|-------------|----------|
| CV Disease (N)                      | M           | M       | 23.7<br>(2,539) | 1.5 (4,596) | M    | 3 (91)               | M           | M        |
| Chronic Cardiopathy<br>(N)          | 2 (735)     | 1.8 (2) | M               | 1.3 (3,983) | M    | M                    | 1.5 (5,365) | 0.8 (32) |
| CKD (N)                             | 1.2 (441)   | M       | 1.1 (118)       | 1.2 (3,677) | M    | 5 (152)              | 1.5 (5,365) | 0.2 (8)  |
| Tuberculosis (N)                    | 1.3 (477)   | M       | M               | M           | M    | 0.1 (3)              | M           | M        |
| Immunocompromised<br>(N)            | 1.8 (661)   | M       | M               | 1 (3,064)   | M    | 3 (91)               | M           | M        |
| Cancer (N)                          | 2 (735)     | M       | M               | M           | M    | 0.3 (9)              | 1 (3,576)   | M        |
| Chronic Neurological<br>Disease (N) | 3.4 (1,249) | M       | M               | 0.6 (1,838) | M    | 0.3 (9)              | 1.1 (3,934) | M        |
| Chronic Hepatic<br>Disease (N)      | 0.4 (147)   | M       | M               | 0.3 (919)   | M    | 0.8 (24)             | M           | M        |
| References                          | [19]        | [20]    | [21]            | [22]        | [23] | Un-published<br>data | [24]        | [25]     |

CV = Cardiovascular; COPD = Chronic Obstructive Pulmonary Disease; CKD = chronic kidney disease; M = Missing Data. Collection date of the data is from March to July 2020.

ambulatory services and not admitted (outpatients). Argentina, Bolivia, Brazil, Chile, Ecuador, Mexico, and Peru datasets included both inpatients and outpatients. The Venezuela cohort included exclusively inpatient cases as per the law that made it mandatory to seek hospitalization for all infected cases, regardless of symptoms and presentations. As such this cohort is comparable to those from other countries. The largest cohort was from Chile with 306,440 (Table 1) confirmed cases and 8,580 deaths; second was Argentina with 36,749 patients and 1,186 deaths. Overall, the number of deaths for the included countries was 25,008 patients. Chile and Argentina were the ones that reported highest numbers of deaths. No treatment data was reported by any of the included studies and reports.

#### Adults <50 were the Most Common Age Group in Latin American COVID-19 Patients.

The average age for this Latin American cohort was 48.4 years (Table1). There were age differences in this cohort of COVID-19 patients. Ages ranged from 39 to 56.8 years. The cohort from Peru was the oldest with 56.8 years old average, in second Mexico with 47.4 years old and in third place Brazil with 44.8. The youngest cohort was from Chile with an average age of 39 years. However, the age differences between the 8 countries were not significant (KS test with  $p = 0.41$ ).

#### Sex Differences in Patients Diagnosed with COVID-19 in Latin America

The distribution of males and females was 47.3% versus 52.6%, respectively. The percentage of female COVID-19 patients was highest (56.8%) in Peru and Argentina (54%) while other Latin American countries showed lower percentages with Venezuela reporting the lowest (43.3%). The cohort from Venezuela reported the most males with 56.7%, while other countries had comparable rates with Ecuador (55.4%), Brazil (55.2%), Mexico (53.1%), Chile (51.6%), and Bolivia (51.4%). Peru reported the lowest percentage of COVID-19 male patients

with 43.2%. However, the 8 cohorts had comparable overall sex distributions (KS test  $p = 0.26$ ).

#### Cough and Fatigue were the Top Symptoms in Latin American COVID-19 Patients

According to the combined overall weighted average, the most common symptoms reported in the 8 Latin American countries for positive cases of SARS-CoV-2 infection were cough with 60.1%, fatigue/tiredness with 52.0%, sore throat with 50.3%, and fever with 44.2% (Table 1). Bolivia was the country that reported the highest positivity for cough (Figure 2A) 78.8%; at least 12% more than Mexico in second place. Ecuador reported the highest prevalence for fatigue followed by Peru and Bolivia with 52% and 51.5%, respectively (Figure 2C).

#### Fever was Not One of the Main Symptoms in Latin American COVID-19 Patients

While fever is one of the most common symptoms for COVID-19 in most of the world, that was not the case for the population we studied in Latin America. Fever was the 4<sup>th</sup> most common symptom with a mean of 44% after sore throat (50.3%) (Table 1). In our report, Bolivia was the region that reported 83.3% of fever, followed by Mexico with 76.6% and then at a much lower rate Peru with 49.4% (Figure 2B).

#### Gastrointestinal Manifestations were Highly Prevalent in Mexico COVID-19 Patients

Different gastrointestinal symptoms including diarrhea, abdominal pain, nausea, and vomiting were reported. Diarrhea was the most prevalent symptom being present in 11.5% of patients (Table 2). There was no characterization of the type of diarrhea, with respect to its blood, mucus, or pus content. It is important to mention that only Argentina, Chile, Mexico, and Peru (Figure 3) reported diarrhea on their symptoms and Mexico was the country with the highest prevalence (22.9%), followed by Peru with 13.6%. Diarrhea was followed by nausea and vomiting

**Table 2: Comparison of combined overall weighted averages for symptoms and comorbidities in COVID-19 patients from the selected 8 Latin American countries.**

|                              | N       | Min% | Maxi% | Mean |
|------------------------------|---------|------|-------|------|
| Cough                        | 713,555 | 35.5 | 78.8  | 60.1 |
| Fatigue or tiredness         | 367,256 | 51.5 | 53.2  | 52   |
| Sore throat                  | 368,501 | 37.9 | 50.7  | 50.3 |
| Fever                        | 704,087 | 36.5 | 83.3  | 44.2 |
| Headache                     | 724,268 | 26.1 | 73.3  | 42.9 |
| Myalgias                     | 724,268 | 9    | 63    | 33.9 |
| Odynophagia                  | 346,299 | 27   | 45.9  | 29.9 |
| Nasal congestion             | 360,791 | 0    | 24.1  | 23.8 |
| Dyspnea                      | 703,980 | 4.3  | 47.6  | 22.8 |
| Hypertension                 | 718,814 | 1.8  | 28.8  | 12.1 |
| Diarrhea                     | 703,980 | 3.1  | 22.9  | 11.5 |
| Thoracic pain                | 703,980 | 2.2  | 31.9  | 9.2  |
| Anosmia                      | 687,412 | 1.4  | 36.1  | 8.8  |
| Diabetes                     | 708,101 | 0.6  | 20.6  | 8.3  |
| Nausea and Vomiting          | 397,540 | 1.2  | 7.9   | 7.2  |
| Ageusia                      | 724,161 | 0.4  | 37.1  | 7    |
| Obesity                      | 714,800 | 3.9  | 25.6  | 4.5  |
| Abdominal pain               | 703,980 | 1.5  | 16.6  | 4.3  |
| Joint pain                   | 397,540 | 3.2  | 59    | 3.6  |
| Asthma                       | 361,026 | 1.1  | 5.6   | 3.2  |
| Tachypnea                    | 346,299 | 3    | 4     | 3    |
| COPD                         | 714,693 | 1.2  | 4     | 2.1  |
| Cyanosis                     | 320,263 | 0.6  | 29.7  | 1.6  |
| CV Disease                   | 309,550 | 1.5  | 3.1   | 1.5  |
| Chronic Cardiopathy          | 715,704 | 0.8  | 4.8   | 1.5  |
| CKD                          | 707,994 | 0.2  | 4.9   | 1.3  |
| Tuberculosis                 | 39,859  | 0.1  | 1.3   | 1.2  |
| Immunocompromised            | 346,299 | 1    | 2.9   | 1.1  |
| Cancer                       | 397,540 | 0.3  | 2     | 1    |
| Chronic neurological disease | 703,980 | 0.3  | 3.4   | 1    |
| Chronic hepatic disease      | 346,299 | 0.3  | 0.8   | 0.3  |

N = Number of patients that was used to analyze. Minimum and Maximum % = means the minimum/maximum average value that has been reported in this multi-center study by included reports. For example, minimum age means the smallest average age that has been reported and maximum age means the largest average age that has been reported.

in 7.2% of patients and lastly abdominal pain in 4.3% in the whole group analysis (Table 2). As for gastrointestinal diseases, the prevalence of chronic hepatic disease was 0.31% in positive cases and as such the least common comorbidity (Table 2).

#### Hypertension was the top Comorbidity in Latin American COVID-19 Patients

Among comorbidities, the reports showed that hypertension was the most common with an average of 12.1% followed by

diabetes with 8.3% and obesity with 4.5% (Table 2). Overall, 12.1% of the cohort had at least one comorbidity. It's also important to note that many patients presented multiple comorbidities. Differences for comorbidities were present among different countries. Mexico was the country with the highest prevalence of hypertension with (28.8%) followed by Chile with 16% (Figure 4A). For diabetes as well (Figure 4C). Mexico reported the highest prevalence with 20.6% followed by Chile with 8%. As for obesity (Figure 4B), Mexico had the highest

prevalence with 25.6% followed by Brazil with a 23.7%. As such, the cohort from Mexico was the most hypertensive, diabetic, and obese of all 8 countries.

Mortality was Highest in Mexico among Latin American Countries

Although we realize that, due to data heterogeneity, a valid comparison in mortality rates among the different countries may be biased, it might, nonetheless, provide a benchmark against which death rates between Latin America and other continents may be assessed. We analyzed the mortality rate for the 8 countries, and there are some important differences. The overall weighted average for the total population of our study showed that the mortality rate was 3.4%. In relation to the stratification of the mortality rate per country (Figure 5), there were mixed results, with Mexico reporting a mortality of 16.6%, followed by Brazil with 7.6% and then Bolivia with 5.6%. Venezuela reported the lowest mortality rate with 0.9%. Overall, there were several differences in the reported mortality rates.

Association of Mortality and Comorbidities in COVID-19 Patients

We explored the association of mortality rate as a dependent variable in univariate and multivariate analyses with several independent variables such as obesity, hypertension, diabetes, and asthma. Each of these analyses was statistically significant except for asthma. This set of data shows that hypertension, diabetes, and obesity are associated with mortality in COVID-19 patients in Latin America. A multiple regression analysis shows that the most influential factor is obesity followed by hypertension and diabetes.

Mortality and GI Manifestations in COVID-19 Patients in Latin America

We explored the association of mortality rate as a dependent variable in univariate and multivariate analyses with several independent variables such as GI symptoms. None of the symptoms including diarrhea, abdominal pain, nausea, and vomiting individually or collectively associated with mortality in Latin America (Figure 5).

Discussion

COVID-19 is a consequence of infection with the SARS-CoV-2 virus. It is well known from previous Coronaviruses infections that the respiratory system is the primary target [26]. Probably, because of the confined geographical nature and short-lived SARS-CoV-1 and MERS epidemics, the medical and scientific community did not explore other potential and secondary targets of coronaviruses. In this regard, the expansion of the current pandemic clearly showed that SARS-CoV-2 can target other systems that express ACE2 receptor and TMPRSS2 protein. Both are expressed in the Gastrointestinal (GI) system which makes it a potential target for the virus and can lead to GI symptoms [27]. Indeed, viral RNA particles have been detected in stool samples which raised another issue that pertains to fecal-oral transmission, be it in confined clinical and domestic

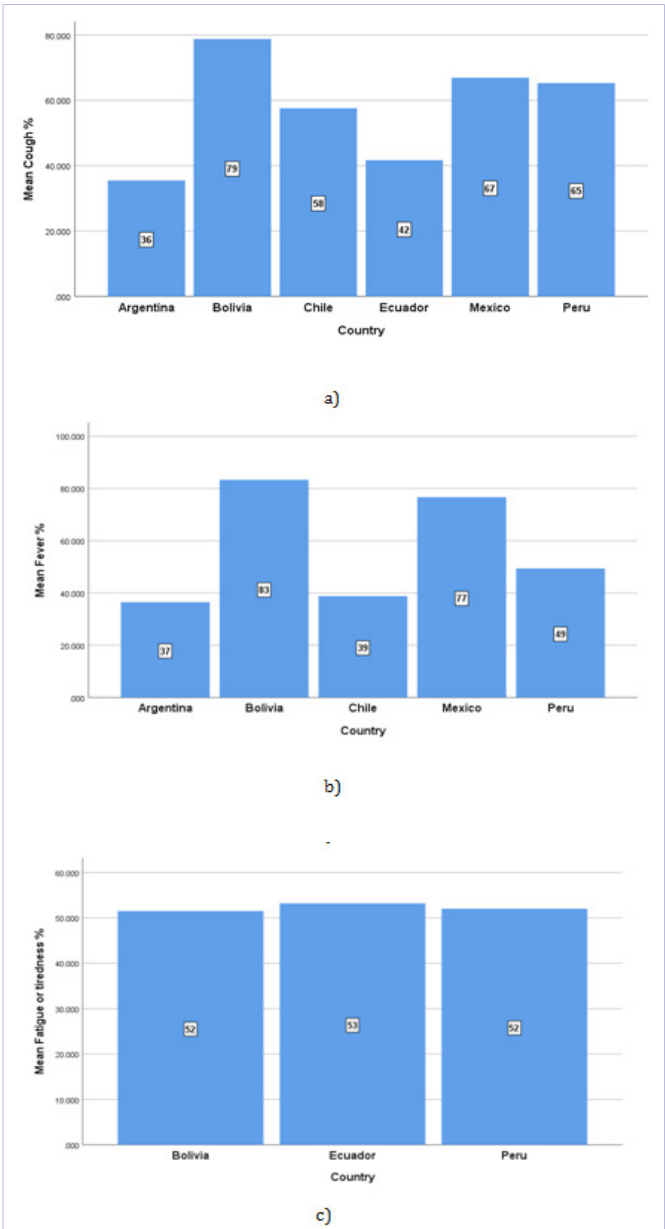
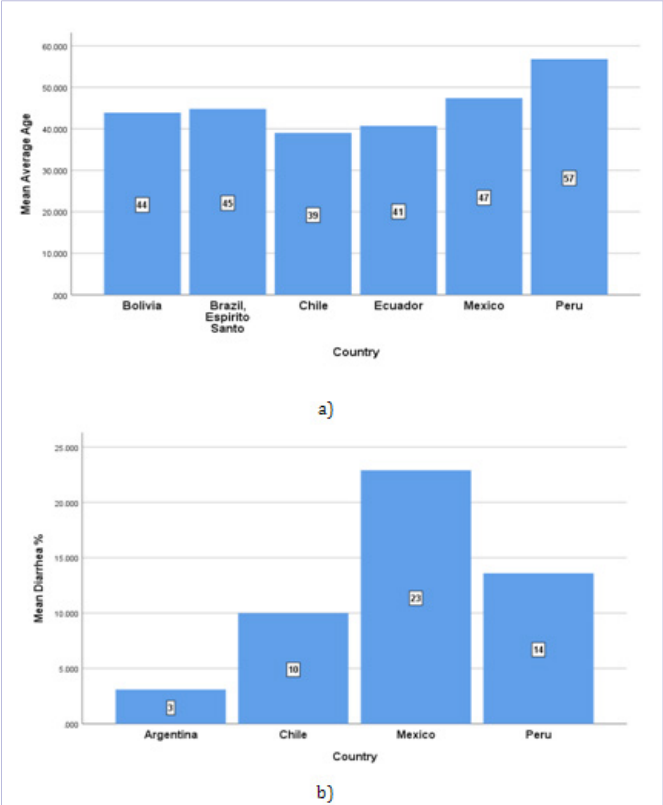


Figure 2: Comparison of cough (A), Fever (B), and fatigue/tiredness (C), in selected studies from different Latin American countries.

settings or through sewage systems [27]. However, we do not know the prevalence and frequency of SARS-CoV-2-associated gastrointestinal manifestations in Latin America and the virus-associated symptoms and outcomes, especially in the presence of comorbidities.

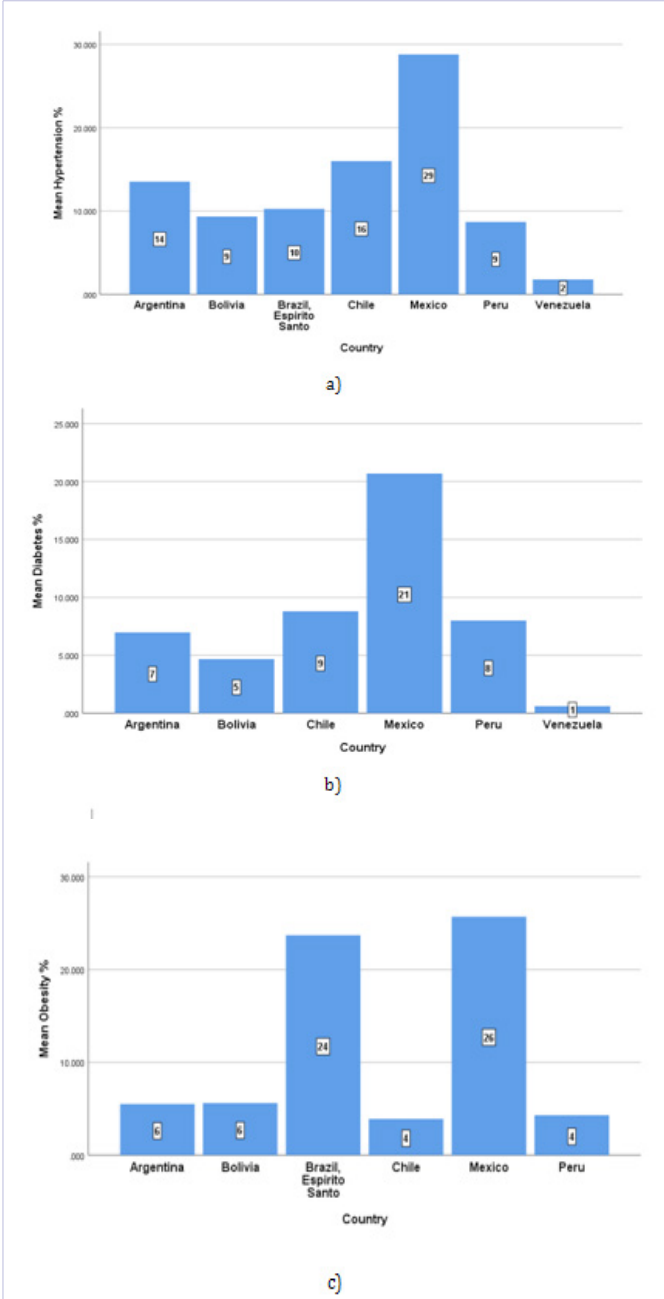
There is a scarcity of reports and publications by health institutions or investigators from Latin America. Nevertheless, one of the epicenters of the disease is in this region of the world. Taking into consideration factors such as difficult access to healthcare in several regions of Latin America, the high index of poverty, the low availability of clean water, and waste management that further exacerbate the pandemic's outcome, all these factors linked to social determinants of health [28,29].



**Figure 3:** Comparison of percent infected male (A), and diarrhea (B) in selected studies from different Latin American countries.

It would be prudent to study the most common symptoms and comorbidities to distinguish the high risk categories in order to utilize the scarce resources intelligently and wisely in a country/population-specific manner. Here we report the results of our systematic analysis using the published and available data to date, and report the presence of differences in gender distribution, age age range, symptoms, and comorbidities among the 8 Latin American cohorts. Hypertension and obesity were the predominant comorbidities and diarrhea the top GI symptom. Hypertension’s association with mortality was enhanced with older age.

Our study revealed that COVID-19 manifests differently in Latin America among the various regions. These differences are important to consider since their impact can influence management, treatment, and prevention approaches for better outcomes. The most common symptoms in Latin America are dry cough, fatigue, sore throat, and fever. Also, the most common comorbidities are obesity, hypertension, and diabetes [28,30]. This contrasts with what was reported by Maechler et al, from a Berlin testing center that indicates that the most common symptoms were fatigue, myalgia, and cough while top comorbidities were chronic lung disease and chronic heart disease [31]. These discrepancies reflect differences in risk factors from different populations that translate into different COVID-19 manifestations and outcomes. It is worth noting that these symptoms and comorbidities did not distribute similarly

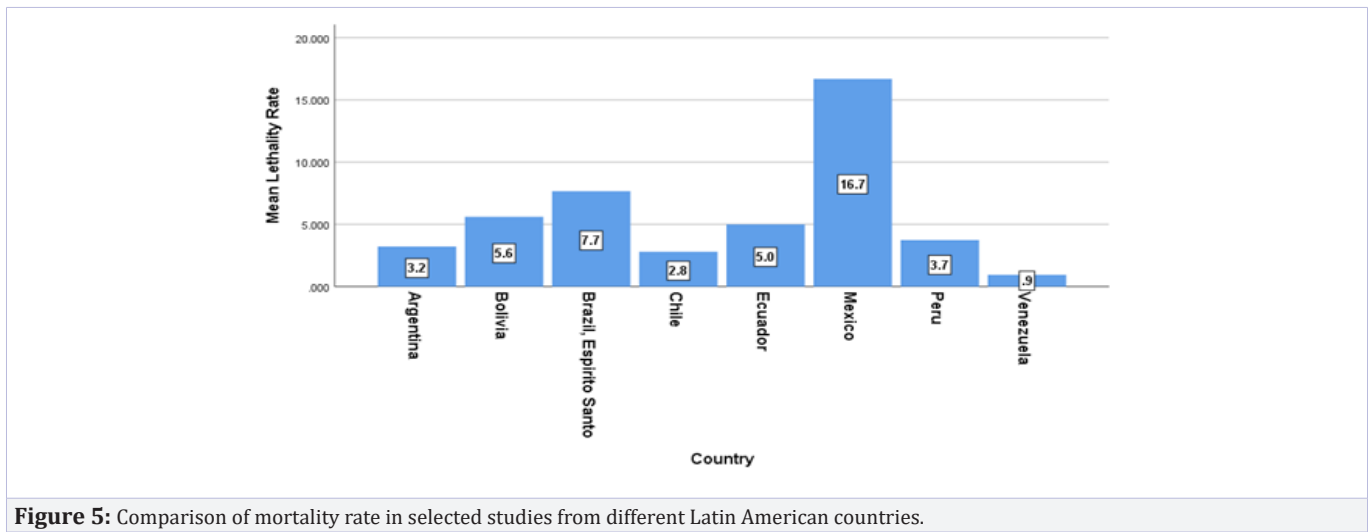


**Figure 4:** Comparison of hypertension (A), diabetes (B), and obesity (C) in selected studies from different Latin American countries.

among the eight studied nations. Mexico and Chile followed a similar profile as far as comorbidities are concerned.

There is a special mention about GI symptoms in our study. The prevalence of diarrhea was much higher than reported in other investigations [32-34]. This is probably because a higher prevalence of diarrhea in Latin American populations predated SARS-CoV-2 outbreak [31]. In our study, we examined the clinical aspects of the disease and compared the different demographics from every population and analyzed their association with mortality. According to our analysis, the cumulative mortality in





**Figure 5:** Comparison of mortality rate in selected studies from different Latin American countries.

Latin America is 3.4%, very close to the one reported worldwide based on the current data published by John Hopkins University [8]. Further comprehensive and prospective studies are needed to accurately assess COVID-19-associated mortality rates as it is very likely that many COVID-19-induced deaths were not reported leading to probable underestimation of mortality rates in this region of the world.

GI and liver manifestations such as anorexia, dysgeusia, nausea, vomiting, diarrhea, abdominal pain, and discomfort are common among patients with COVID-19. Hepatic involvement in this condition is reflected by abnormal liver enzymes and bilirubin levels. Few studies [35,36] showed that patients with the severe disease more often have GI symptoms and hepatic involvement. While the mechanisms of GI manifestations elicited by SARS-CoV-2 are still unknown, ACE2 expression in the esophagus, small and large intestines, likely play a role. Indeed, ACE2 was reported to be co-expressed with TMPRSS2 that is needed for the cleavage of the spike protein and the facilitation of the virus entry into the host GI system and thus aggravating systemic effects of the virus. While millions of patients have been discharged after testing negative in their nasopharyngeal specimens, a sizable portion of them still tested positive in their stools [37]. This group of patients should be the focus of next stringent monitoring methods as they are likely to play a role in the dissemination and recurrence of the disease. It will also be worth monitoring whether SARS CoV-2 persistence in the GI system will impact overall GI system functions.

Since mortality is the main outcome to avoid in this stage of the pandemic and especially in Latin America where vaccines are unlikely to be available soon, we performed different analyses to compare the impact of the top comorbidities on mortality. We found that obesity, hypertension, and diabetes were highly correlated with mortality, and that the presence of these conditions exacerbates the severity and outcome of COVID-19 infection. This result agrees with the reported cases in other studies.

Another pertinent element to highlight, is that the prevalence

of tuberculosis in our study was above 1.2%. There is a well-known high prevalence of tuberculosis in the region and the usage of BCG vaccination in Latin America. Many studies reported a potential effect of the BCG vaccine in providing heterologous protection [38] against other infections like the one from SARS-CoV-2. While the BCG vaccine role is still debated, future large and well-designed comparative studies might reveal whether it played any role in the outcome of the pandemic in Latin America.

Pandemic management differences and quality and access to healthcare facilities impacted outcome and data availability. Indeed, Venezuela for example showed the least mortality, which might be explained by free access to healthcare system and the fact that the treatment protocol includes hospitalizing every reported positive case [25]. In contrast, Mexico where only severe disease patients were hospitalized and less access to advanced care is available for the general population displayed the highest mortality rate [22,30]. In addition, the lockdown strategies differed between countries which affected the dynamics of transmission and infection rates. The availability of medical records is very critical for the precise interpretation of the data. Some publications like the one from Chile presented complete clinical data, while the same detailed data was not available for the other regions since most of them still use manual medical records.

A limitation of our study is its retrospective nature. We only listed studies that were available as published reports or on the web. Furthermore, some of them reported merely symptoms, others only comorbidities. There are many variables such as immune reaction and blood test, imaging, treatment, liver enzymes and other underlying diseases that are very important for the analysis but are missing in the analyzed data.

In conclusion, while the pandemic is still raging, vaccines still not available for all and therapeutics still in development, the only direct interventions readily available now are modifications of human behavior measures such as hygiene, social distancing, and mask-wearing to limit exposure and future infections along with effective clinical diagnostics to isolate patients efficiently

and cut the transmission chain. Since this disease is here to stay in the foreseeable future, strict measures need to be taken in Latin American countries to act on comorbidities such as obesity, hypertension and diabetes, all part of the metabolic syndrome. These comorbidities can be modified or controlled in public health strategies to mitigate the effect of the virus in this epicenter of the pandemic, as well as be aware of the most common presentations of the disease in the region.

## Author contributions

Study concept and design (HA), Data acquisition (AP, FA, MD, NG, LA, ZAS), Data analysis and interpretation (HA, HB, GO, AL, FA, EEL), Drafting of manuscript (HA, HB, AP, ZAS), Statistical analysis (GO), Obtained funding (HA), Material support (HA, HB). All Authors read and approved the manuscript.

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