# Clinical-epidemiologic variation in patients treated in the first and second wave of COVID-19 in Lambayeque, Peru: A cluster analysis

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A R T I C L E   I N F O

A B S T R A C T

*Objectives:* To identify differences in the clinical and epidemiologic characteristics of patients during the first and second waves of the COVID-19 pandemic at the EsSalud Lambayeque health care network, Peru.
*Methods:* An analytical cross-sectional study of 53,912 patients enrolled during the first and second waves of COVID-19 was conducted. Cluster analysis based on clustering large applications (CLARA) was applied to clinical-epidemiologic data presented at the time of care. The two pandemic waves were compared using clinical-epidemiologic data from epidemiologic surveillance.
*Results:* Cluster analysis identified four COVID-19 groups with a characteristic pattern. Cluster 1 included the largest number of participants in both waves, and the participants were predominantly female. Cluster 2 included patients with gastrointestinal, respiratory, and systemic symptoms. Cluster 3 was the "severe" cluster, characterized by older adults and patients with dyspnea or comorbidities (cardiovascular, diabetes, obesity). Cluster 4 included asymptomatic, pregnant, and less severe patients. We found differences in all clinical-epidemiologic characteristics according to the cluster to which they belonged.
*Conclusion:* Using cluster analysis, we identified characteristic patterns in each group. Respiratory, gastrointestinal, dyspnea, anosmia, and ageusia symptoms were higher in the second COVID-19 wave than the first COVID-19 wave.

## Introduction

COVID-19 caused by SARS-CoV-2 began in late 2019 in Wuhan City, China, and spread rapidly worldwide (Guo *et al.*, 2020). As of March 2022, the World Health Organization reported approximately 483 million confirmed cases and around 6 million deaths from this disease (WHO, 2021). Likewise, Peru, one of the countries most affected by COVID-19, reported nearly 3 million confirmed cases and 212,157 deaths (WHO, 2021), reporting the highest mortality rate (652.58 deaths per 100,000 population) worldwide (Mortality Analyses, 2021).

Differences in the clinical-epidemiologic profiles of individuals with COVID-19 were observed. This variation can be attributed to some important characteristics, such as a country's preparedness level, socioeconomic status, variant type, and vaccination coverage, among others (Zhang *et al.*, 2022). For example, in South

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Africa, during the Omicron wave, it was seen that infection rates were higher than previous epidemic waves, but were not as severe (Jassat *et al.,* 2022). In England, during the first and second pandemic waves, there was a decrease in the mortality rate between 2020 and 2021. However, this change was not noticeable for older people and people with comorbidities, such as for ethnic minorities (Gray *et al.,* 2021). In India, there was a significantly higher mortality and complication rate in the second wave, with more casesbeing observed among those who are young and those without comorbidities (Kumar *et al.,* 2021). There was also an outbreak of mucormycosis during the second wave associated with the virus variant and glycemic dysregulation (Arora *et al.,* 2021). A similar situation was observed in Bangladesh, as mortality was more common among elder patients and those with comorbidities (Hossain *et al.,* 2021). In a more regional context, Brazil reported data related to the Gamma variant of concern, which mostly affected younger people without comorbidities during the second pandemic wave compared to the first outbreak.

In Peru, the first wave of COVID-19 began in March 2020, peaking in August and ending in December 2020 (WHO, 2021), while the second wave began in January 2021 and culminated in June 2021, with the maximum number of infections and deaths being recorded in April (WHO, 2021). Lambayeque was one of the regions that was most affected by COVID-19 (Díaz-Vélez *et al.,*), and it ranked in the highest quartile of mortality and surpassing even the national death rate, with a regional mortality rate of 612.2 deaths (CDC Peru, 2021). The first wave of COVID-19 began in Lambayeque in March 2020, reached its peak in May, and ended in December 2020, while the second wave started in January and ended in June 2021 (CDC Peru, 2021).

The clinical presentation of COVID-19 includes cough, nasal congestion, fever, chest pain, and shortness of breath (Griffin *et al.,* 2021; Jiang *et al.,* 2020), varying according to the level of clinical classification (mild, moderate, severe, and critical) (Instituto de Evaluación de Tecnologías en Salud e Investigación, 2021). Previous studies have described clinical differences between the first and second waves, particularly in terms of age groups, symptomatology, and disease severity (Area *et al.,* 2021; Friston *et al.,* 2020; Iftimie *et al.,* 2021; Mocanu *et al.,* 2021; Mollinedo-Gajate *et al.,* 2021; Salyer *et al.,* 2021; Soriano *et al.,* 2021; Vinceti *et al.,* 2021).

In Peru, the second wave presented a more significant acceleration in infections, deaths, and bed occupancy in the intensive care units and intermediate care units, affecting mainly the elder and pregnant women (Huatuco-Hernández *et al.,* 2021). The emergence of the second wave of COVID-19 may have been associated with the circulation of new variants with a higher virulence, transmissibility, and lethality, such as the British variant B.1.1.7 and Brazilian variant P.1, as reported by the National Institute of Health after performing genomic sequencing (CDC-Perú, 2021).

There is no documented evidence on the clinical-epidemiologic profile for the patients treated in the two waves of SARS-CoV-2 infection in Peru, much less at the regional level. In addition, there is little genomic surveillance at the local level to identify the sequence of the viral genome to identify clinical patterns according to the main SARS-CoV-2 strains, and, thus, provide an approximation of the clinical-epidemiologic differences of both waves, which could represent an effective tool in public health decision-making for the prevention and control of COVID-19 in the Lambayeque region. This study aimed to describe the main clinical and epidemiologic differences between the first and second waves of COVID-19 in the Lambayeque region, Peru, by analyzing the clinical follow-up records of the patients treated in hospitals of the EsSalud Lambayeque health care network. (Díaz-Vélez *et al.,* 2021).

## Methods

### Study design

An analytical cross-sectional study was carried out to determine the clinical and epidemiologic differences among the patients treated for COVID-19 in institutions belonging to the EsSalud health network in Lambayeque, during the first and second waves of the COVID-19 pandemic.

### Population and sample

The population consisted of patients treated for COVID-19 in institutions belonging to EsSalud from March 2020 to September 2021. The sample was made up of 53,912 patients with a suspected COVID-19 infection recorded in the Notification System of the Ministry of Health (NotiWebMINSA). A non-probabilistic census-type sampling was applied. Confirmed or suspected COVID-19 patients, new or continuing EsSalud user patients, and individuals who had been treated and notified in the NotiWeb System in EsSalud Lambayeque service networks during the aforementioned period were included. Patients with incomplete clinical records and those with absent clinical records for the variables of interest were excluded.

### Instruments and variables

The study variables were collected, analyzed, and divided into three sections: general data of the notification and of the patient, the date of notification, and the classification of the case. General epidemiological variables included sex, age, and categorized age (children: 0-11 years, adolescents: 12-17 years, young: 18-20 years, adult: 30-59 years, and the older adults: 60 years and older). Clinical variables were subclassified into: (i) clinical manifestations with which the case type was recorded according to severity, date of symptom onset if the patient was isolated, and when they were isolated; (ii) symptoms- the presentation of cough, sore throat, nasal congestion, shortness of breath, fever, chills, malaise, diarrhea, nausea/vomiting, headache, anosmia, ageusia, ear pain, irritability/confusion, muscle pain, chest pain, abdominal pain, and joint pain, (iii) recording of clinical signs, body temperature, presence of pharyngeal exudate, conjunctival injection, seizure, coma, dyspnea/tachypnea; and lastly, d) comorbidities including pregnancy, postpartum period ($<6$ weeks), presence of cardiovascular disease, diabetes, liver disease, neurological/neuromuscular disease, obesity, immunodeficiency, kidney disease, liver damage, chronic lung disease, and cancer.

### Procedures and techniques

Two databases were used in this study: (i) the clinical follow-up database of the "Oficina de Inteligencia Sanitaria de Red Prestacional Lambayeque-EsSalud" and (ii) the epidemiological notification file database of the NotiWeb Epidemiological Surveillance System of the National Center for Epidemiology, Prevention and Control of Diseases, Peru.

The NotiWeb database was exported and matched with the clinical follow-up database using an identity document as the identifier code. A quality control process was then carried out to identify inconsistent data, and out-of-range and/or incomplete values. Subsequently, a variable called "type of pandemic wave" was created, in which the clinical-epidemiologic characteristics of the patients were grouped according to the period of each pandemic wave. The first wave was defined between the months of March 2020 to December 2020, and the second wave was between
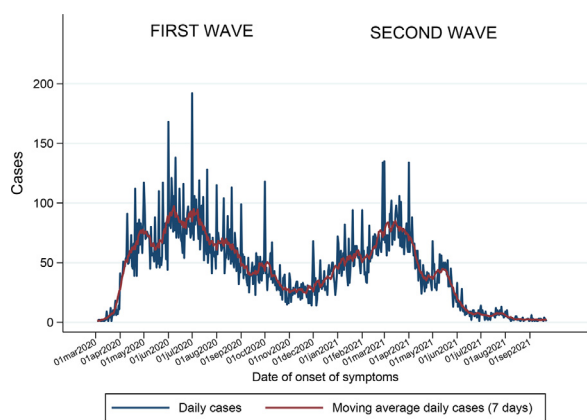
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**Figure 1.** Epidemiological curve of confirmed COVID-19 cases in the Lambayeque health care network during the first and second waves according to the date of symptom onset.

January 2021 to September 2021. This made it possible to identify the clinical pattern of each wave and identify the clinical-epidemiologic differences between each time period. Finally, the data were statistically analyzed.

*Statistical analysis*

The data were analyzed using the statistical program Stata v16.0 (StataCorp LP, College Station, Texas, USA).

For descriptive analysis of numerical variables, the best measure of central tendency and dispersion was calculated, and, for categorical variables, the absolute and relative frequencies were estimated. In the bivariate analysis, chi-square test was used after evaluating the assumption of expected frequencies. Fisher's exact test (categorical variables) was also used to compare the categorical clinical-epidemiologic variables between patients treated in the first and second waves. For numerical variables (age, length of hospitalization), the Student's *t*-test was used after evaluating the assumption of normal distribution and homoscedasticity. The Mann-Whitney U test was also used. *P*-values <0.05 were considered statistically significant.

In addition, an epidemiological curve was constructed based on the date of onset of symptoms of the first and second pandemic waves. The database was collapsed according to the date of onset of symptoms, and the variable weekly moving average of cases was created. Subsequently, case trends of each pandemic wave were estimated, and cumulative daily curves and weekly moving averages were plotted.

Clustering large applications (CLARA) was used as a clustering method to identify the groups of patients with similar clinical characteristics. This method is an option for large data because it works with a resampling scheme by taking smaller random subsamples and polling them to propose the results (Kassambara, 2017) and we used CLARA as implemented by the function clara of "cluster" package in R version 4.1.2. The silhouette method was used to determine the optimal number of clusters while accounting for epidemiological considerations.

*Ethical aspects*

The research protocol was approved by the ethics committee of the Almanzor Aguinaga Asenjo National Hospital with registration code No. CIE-RPL 047-SET-2021. In addition, the research protocol was registered in the repository of health research projects of the National Institute of Health-Peru (PRISA-INS). The study was carried out following the ethical principles of the Declaration of

**Table 1**
Clinical-epidemiological characteristics of patients with COVID-19 during the first and second waves.

| Variables | Pandemic wave | | | |
| --- | --- | --- | --- | --- |
| | First wave (n = 36938) | | Second wave (n = 16974) | |
| | N | % | n | % |
| **Age (years)[a]** | 44.87 ± 20.5 | | 47.92 ± 20.8 | |
| **Age (categorized)** | | | | |
| Child (0-11) | 1859 | 5 | 626 | 3.7 |
| Adolescent (12-17) | 1451 | 3.9 | 535 | 3.2 |
| Young (18-29) | 5570 | 15.1 | 2431 | 14.3 |
| Adult (30-59) | 18539 | 50.2 | 8092 | 47.7 |
| Older adult (60-) | 9519 | 25.8 | 5290 | 31.2 |
| **Gender** | | | | |
| Female | 20803 | 56.3 | 8444 | 49.8 |
| Male | 16135 | 43.7 | 8530 | 50.3. |
| **Clinical characteristics** | | | | |
| General malaise | 16721 | 45.3 | 12044 | 71.0 |
| Cough | 16578 | 44.9 | 9556 | 56.3 |
| Sore throat | 14003 | 37.9 | 7205 | 42.5 |
| Fever | 12162 | 32.9 | 6215 | 36.6 |
| Headache | 11640 | 31.5 | 6219 | 36.6 |
| Nasal congestion | 6817 | 18.5 | 4473 | 26.4 |
| Muscle pain | 6185 | 16.7 | 3826 | 22.5 |
| Respiratory distress | 6569 | 17.8 | 3586 | 21.1 |
| Diarrhea | 5089 | 13.8 | 3096 | 18.2 |
| Chills | 521 | 1.4 | 1787 | 10.5 |
| Chest pain | 3923 | 10.6 | 1738 | 10.2 |
| Nausea | 2274 | 6.2 | 1257 | 7.4 |
| Anosmia | 334 | 0.9 | 1158 | 6.8 |
| Ageusia | 290 | 0.8 | 977 | 5.8 |
| Dyspnea | 1314 | 3.6 | 972 | 5.7 |
| Abdominal pain | 1082 | 2.9 | 596 | 3.5 |
| Ear pain | 48 | 0.1 | 204 | 1.2 |
| Pharyngeal exudate | 343 | 0.9 | 104 | 0.6 |
| Irritability | 298 | 0.8 | 79 | 0.5 |
| Conjunctival injection | 108 | 0.3 | 44 | 0.3 |
| Seizure | 8 | 0.0 | 2 | 0.0 |
| **Comorbidities** | | | | |
| Cardiovascular disease | 4078 | 11.0 | 2445 | 14.4 |
| Diabetes | 2236 | 6.1 | 1251 | 7.4 |
| HIV | 42 | 0.1 | 12 | 0.1 |
| Kidney disease | 364 | 1.0 | 215 | 1.3 |
| Lung disease | 371 | 1.0 | 110 | 0.7 |
| Cancer | 399 | 1.1 | 281 | 1.7 |
| Obesity | 208 | 0.6 | 921 | 5.4 |
| Pregnancy | 1208 | 3.3 | 574 | 3.4 |

[a] Mean and SD

Helsinki. The confidentiality of the clinical records of the patients selected for the investigation was preserved. Anonymized codes were used to manage and analyze the information, and only the study investigators had access to the data.

**Results**

Between March 2020 and September 2021, two heterogeneous waves of COVID-19–positive cases were recorded. The first wave peaked in August 2020, followed by a decrease in the number of confirmed cases. In December 2020, economic reactivation in Peru began, meaning that there were no longer restrictions on access to public spaces and normal activities. This coincided with the onset of the second wave of the pandemic in January 2021, which peaked in April 2021. The peak of the second pandemic wave was slightly lower than that recorded for the first wave. The epidemiologic curve of confirmed cases in the Lambayeque health care network continued to decrease. The weekly moving average was much lower than that observed during the peak of the first and second pandemic waves (Figure 1).

Table 1 shows the epidemiologic and clinical characteristics of patients enrolled during the first and second waves of the COVID-

**Table 2**
Characteristics of the participants according to clusters.

| Characteristics | Overall N = 53,912[a] | 1 n = 16,832[a] | 2 n = 14,284[a] | 3 n = 11,680[a] | 4 n = 11,116[a] | P-value[b] |
|---|---|---|---|---|---|---|
| **COVID-19 pandemic wave** | | | | | | <0.001 |
| First wave | 36,938 (68.5%) | 10,700 (63.6%) | 8,805 (61.6%) | 6,816 (58.4%) | 10,617 (95.5%) | |
| Second wave | 16,974 (31.5%) | 6,132 (36.4%) | 5,479 (38.4%) | 4,864 (41.6%) | 499 (4.5%) | |
| **Year** | | | | | | <0.001 |
| 2020 | 36,938 (68.5%) | 10,700 (63.6%) | 8,805 (61.6%) | 6,816 (58.4%) | 10,617 (95.5%) | |
| 2021 | 16,974 (31.5%) | 6,132 (36.4%) | 5,479 (38.4%) | 4,864 (41.6%) | 499 (4.5%) | |
| **Gender** | | | | | | <0.001 |
| Female | 29,247 (54.2%) | 11,311 (67.2%) | 7,775 (54.4%) | 3,436 (29.4%) | 6,725 (60.5%) | |
| Male | 24,665 (45.8%) | 5,521 (32.8%) | 6,509 (45.6%) | 8,244 (70.6%) | 4,391 (39.5%) | |
| **Age (years)** | | | | | | <0.001 |
| Mean (SD) | 45.8 (20.6) | 38.9 (18.7) | 42.7 (18.1) | 63.6 (16.3) | 41.7 (20.0) | |
| Median (IQR) | 45.0 (31.0, 61.0) | 38.0 (26.0, 52.0) | 42.0 (29.0, 56.0) | 65.0 (53.0, 76.0) | 39.0 (28.0, 56.0) | |
| **Range** | 0.0, 103.0 | 0.0, 100.0 | 0.0, 103.0 | 0.3, 103.0 | 0.0, 101.0 | |
| **Age group** | | | | | | <0.001 |
| 0-4 | 1,098 (2.0%) | 521 (3.1%) | 129 (0.9%) | 11 (0.1%) | 437 (3.9%) | |
| 5-9 | 927 (1.7%) | 540 (3.2%) | 224 (1.6%) | 9 (0.1%) | 154 (1.4%) | |
| 10-14 | 1,278 (2.4%) | 671 (4.0%) | 391 (2.7%) | 10 (0.1%) | 206 (1.9%) | |
| 15-17 | 1,168 (2.2%) | 519 (3.1%) | 359 (2.5%) | 30 (0.3%) | 260 (2.3%) | |
| 18-29 | 8,001 (14.8%) | 3,132 (18.6%) | 2,549 (17.8%) | 238 (2.0%) | 2,082 (18.7%) | |
| 30-59 | 26,631 (49.4%) | 8,865 (52.7%) | 7,891 (55.2%) | 4,144 (35.5%) | 5,731 (51.6%) | |
| 60-79 | 11,747 (21.8%) | 2,347 (13.9%) | 2,405 (16.8%) | 5,154 (44.1%) | 1,841 (16.6%) | |
| 80-103 | 3,062 (5.7%) | 237 (1.4%) | 336 (2.4%) | 2,084 (17.8%) | 405 (3.6%) | |
| **Case type** | | | | | | <0.001 |
| Asymptomatic | 11,157 (20.7%) | 278 (1.7%) | 159 (1.1%) | 122 (1.0%) | 10,598 (95.3%) | |
| Symptomatic | 42,755 (79.3%) | 16,554 (98.3%) | 14,125 (98.9%) | 11,558 (99.0%) | 518 (4.7%) | |

[a] n (%)
[b] Pearson's Chi-square test; Kruskal-Wallis's rank sum test; Fisher's exact testIQR = Interquartile range

19 pandemic in the Lambayeque health care network. Compared to the first wave, the second wave was characterized by patients with a higher mean age (47.92 vs 44.87) and a higher proportion of older adults (31.2% vs 25.8%) and males (50.3% vs 43.7%). Regarding signs and symptoms, a higher frequency of cough (56.3 vs 44.9%), nasal congestion (26.4% vs. 18.5%), respiratory distress (29.5% vs 25.3%), diarrhea (20.9% vs 17.3%), headache (39.0% vs 36.7%), and dyspnea (5.7% vs 3.6%) was observed during the second wave compared to the first. In addition, compared to the first wave, the second wave had a higher proportion of patients with cardiovascular disease (14.4% vs 11.0%), diabetes (7.4% vs 6.1%), cancer (1.7% vs 1.1%) and obesity (5.4% vs 0.6%). In contrast, there was a higher frequency of lung disease in the first wave compared than the second (1.0% vs 0.7%).

*Cluster analysis*

From a purely statistical perspective, four clusters were determined to be the optimal number of clusters (Supplementary Figure 1). The population was categorized into these four clusters, and comparative tables and figures were made to characterize the patterns. The characteristics of the participants of the four clusters are shown in Table 2. All the clinical-epidemiologic characteristics varied among the groups (P-values < 0.005).

Figure 2a shows that cluster 1 was the most frequent cluster (N = 16,832; 31.2%), while the least frequent was cluster 4 (N = 11,116; 20.6%). Figure 2b shows the distribution of clusters according to pandemic waves. Cluster 1 predominated in the first (N = 10,700; 29%) and second waves (N = 6132; 36.1%). Cluster 4 was the second most frequent in the first wave (N = 10,617; 28.7%) and the least frequent in the second wave (N = 499; 2.9%). There was a statistically significant difference in the cluster distribution between the two pandemic waves (P < 0.001). Figure 2c shows the distribution of individuals by cluster according to epidemiological weeks (EW). In EW 12-2020, clusters 1 (0.4%) and 2 (0.6%) were the most frequent. However, a progressive increase in cluster 4 was

observed between EW 13 to 25, with cluster 4 being predominant between EW 26 to SE 44 and finally, less frequent between EW 45 to 53 in 2020. In addition, cluster 3 increased and became more frequent in the second wave of 2021, while clusters 1 and 2 fluctuated, but seemed to be the most stable over time.

Figure 3a shows the age distribution according to cluster, with cluster 3 having a greater age distribution. Figure 3b presents the distribution of the age groups. The age group between 30 and 59 years of age was the most predominant in clusters 1 (52.7%), 2 (55.2%), and 4 (51.6%), while in cluster 3, the age group comprising patients between 60 and 79 years of age predominated (44.1%). Figure 3c shows that the female sex was more frequent in clusters 1 (67.2%), 2 (54.4%), and 4 (60.5%), while male sex was predominant in cluster 3 (70.6%). In Figure 3, clusters 1 (98.4%), 2 (98.9%), and 3 (99%) comprised predominantly of symptomatic patients, while cluster 4 was characterized by asymptomatic patients (95.3%).

Patients in cluster 3 presented with the most severe clinical characteristics. Dyspnea was more predominant in cluster 3 (60.6%) compared to the other clusters, and chest pain was more frequent in cluster 2 (23.6%). The frequency of patients with cardiovascular disease, diabetes, and obesity was higher in cluster 3 compared to the remaining groups (Figure 4).

**Discussion**

*Clinical-epidemiological variation in the first and second waves of the pandemic*

In the second wave of the COVID-19 pandemic, there was a greater number of older adult patients and a lower frequency of children and adolescents. These results are similar to those reported by Soriano *et al.* (2021) in a medical center in Madrid, Spain, in which a slightly higher, albeit not statistically significant, mean age was observed in the second wave compared to the first wave. However, these findings differ from those reported in sim-
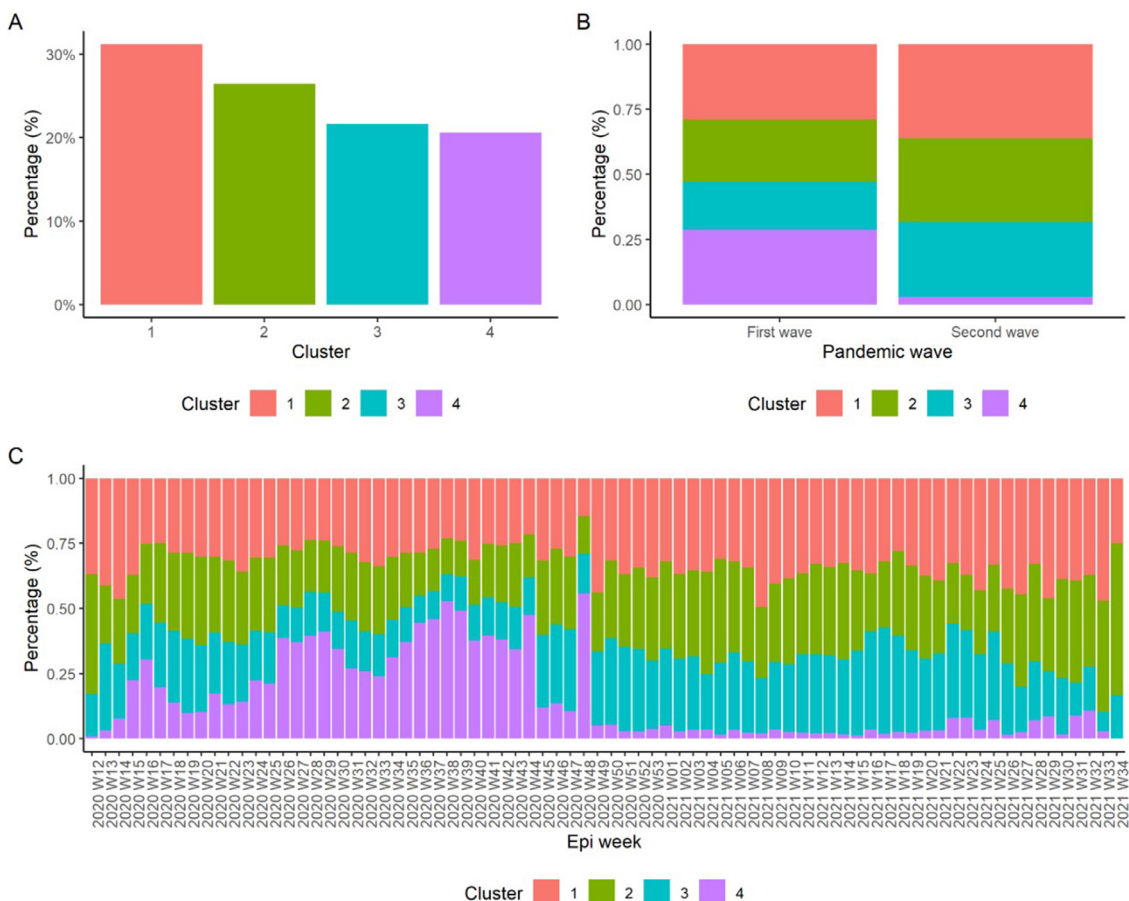
**Figure 2.** Cluster analysis according to pandemic wave and EW. EW, epidemiological week

ilar studies conducted in China (Fan *et al.*, 2021), Japan (Saito *et al.*, 2021), and Italy (Vinceti *et al.*, 2021). In a hospital in Spain, younger patients were predominant in the second wave (Iftimie *et al.*, 2021). In Sudan, fewer elder patients with COVID-19 were reported in the third wave compared to the second wave (23.9% vs 76.1%), although there were no significant differences (Abd El-Raheem *et al.*, 2021). In Peru, younger people, especially children, may not have been severely affected by the pandemic during the second wave, because during the first outbreak there were concerns about the increasing rates of infection. This situation was possibly because of the fear of the contagion after cases of multi-systemic inflammatory syndrome in children were reported (Yáñez *et al.*, 2020).

There was a higher frequency of male patients in the second wave compared to the first wave. This result is similar to that described in a systematic review, in which a higher incidence of COVID-19 was found in males (Li *et al.*, 2020). However, our finding is in contrast to that described in a similar study conducted in a university clinic in Madrid, Spain, in which differences were very small and not statistically significant (47.7% vs 46.2%) (Soriano *et al.*, 2021). Another study in Spain identified a higher frequency of males in the second wave compared to the first wave, particularly in hospitalized patients with severe SARS-CoV-2 infection (70.8% vs 64.5%) (Mollinedo-Gajate *et al.*, 2021). In Sudan, no significant differences were observed based on sex during the pandemic waves (Abd El-Raheem *et al.*, 2021).

There were more patients with chronic diseases in the second wave compared to the first wave. This finding is similar to that reported in Spain, in which a higher frequency of patients with cardiovascular diseases was observed, whereas the number of diabetic patients decreased, although no significant differences were

found in the analysis (Iftimie *et al.*, 2021). However, our results differ from those reported in Japan, in which a lower prevalence of patients with cardiovascular, cerebrovascular, respiratory, renal, diabetic, and obese comorbidities was observed in the second wave compared to the first wave (Saito *et al.*, 2021). Our findings are also contrary to those in Sudan, in which the frequency of patients with comorbidities markedly reduced in the third wave compared to the second wave of the COVID-19 pandemic (Abd El-Raheem *et al.*, 2021).

In addition, we found that there were more patients with cancer and neoplastic diseases in the second wave compared with the first wave, albeit without significant differences, similar to what was reported in Spain. (Iftimie *et al.*, 2021). In contrast, these results are contrary to the findings of Saito *et al.* (2021) in Japan, who reported a greater number of patients with neoplasms in the first wave of the COVID-19 pandemic.

In relation to the clinical manifestations of COVID-19, we found a significant increase in the frequency of cough, nasal congestion, respiratory distress, fever, malaise and diarrhea, headache, muscle pain, and abdominal pain in the second wave compared to the first wave. In contrast, dyspnea increased by 3% in the second wave, as opposed to the fewer number of patients with fever, dyspnea, cough, and diarrhea reported by Simona *et al.*. However, only cough showed significant differences between each wave of the pandemic (Iftimie *et al.*, 2021).

*Cluster analysis based on CLARA*

In this study, the four clusters evolved over time, according to EW. Cluster 3 was the most severe cluster, showing an increase in the number of patients during the second pandemic wave, which
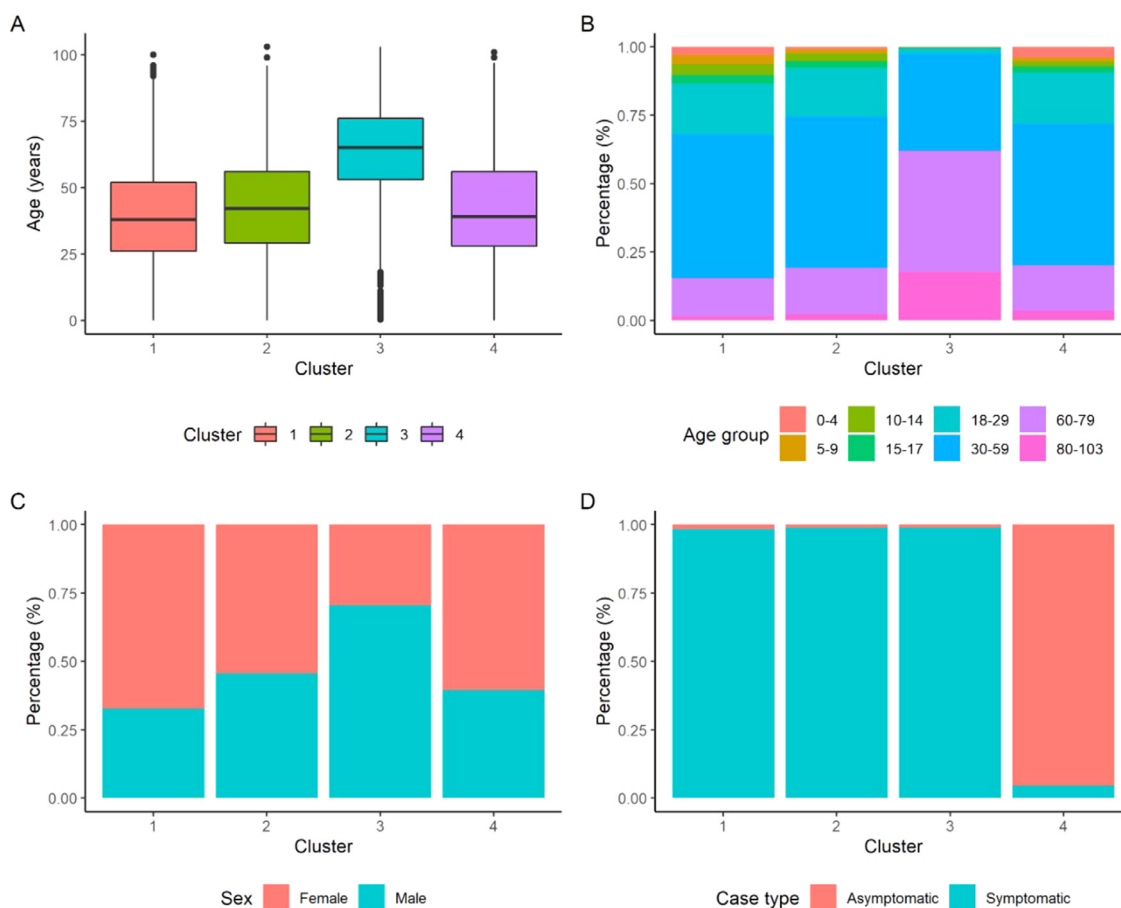
**Figure 3.** Clinical characteristics of the participants according to cluster of affiliation (i)

could be explained by the low availability of medical oxygen in the Peruvian territory during both the first and second waves of COVID-19 (Fraser, 2020; Herrera-Añazco *et al.,* 2021; Schwalb and Seas, 2021). In addition, cluster 2 remained constant over time, whereas cluster 4 predominated in the first pandemic wave and then significantly declined.

According to the CLARA analysis, we identified four distinct clusters. Cluster 1 comprised mostly of female patients and was characterized as the most frequent cluster during the two pandemic waves. Cluster 2 was characterized by gastrointestinal, respiratory, and systemic symptoms and had the second highest incidence of dyspnea. Cluster 3 was characterized by dyspnea, which was the most severe clinical feature in our analysis. Cluster 4 was mainly characterized by asymptomatic presentation, with a higher frequency of pregnant women and fewer cases of dyspnea.

We found significant differences in age among the four clusters. This is important because multiple studies have identified older age as a factor associated with greater severity of COVID-19 (Klaiber *et al.,* 2021; Palmieri *et al.,* 2020). We observed significant differences among the groups based on sex. This is consistent with what was reported in a study conducted in China, in which a cluster analysis based on factor analysis of mixed data was performed, and no differences in age and sex were found among the three clusters (Han *et al.,* 2021). This evaluation is relevant to determine the impact of age and sex on mortality in patients with COVID-19 (Wenham *et al.,* 2020).

Cluster 1 did not show a characteristic clinical pattern in comparison with the other groups evaluated. This cluster included the largest number of individuals with the highest proportion of females and was the most predominant in the two pandemic waves

evaluated in this study. With respect to age, this cluster was characterized by the highest proportion of children and adolescents between 5 and 17 years of age, as well as young people and adults. These results are similar to those described in a cluster study of COVID-19 patients by a French group. Their cluster 3 was made up of young patients with gastrointestinal symptoms and had the highest survival rate (96.5%) (Bondeelle *et al.,* 2021).

Cluster 2 presented a high frequency of patients with risk factors for COVID-19, including cardiovascular disease, diabetes, obesity, and pulmonary disease, and was only surpassed by the "severe" cluster 3. These results partially coincide with a cluster study conducted in France that showed a higher proportion of systemic, respiratory, and gastrointestinal symptoms in cluster 3, characterized by the highest survival rate in onco-hematology patients (Bondeelle *et al.,* 2021). Our findings also partially coincide with a study performed in China, in which cough was predominant in group B, classified as the "intermediate-severe" group. However, the presence of respiratory, gastrointestinal, and systemic symptoms was higher in the group A or "severe" group (Han *et al.,* 2021). Our results coincide with those described in a similar study conducted in Spain, in which cluster 4 was characterized by diarrhea, vomiting, and abdominal pain, while cluster 3 was characterized by headache, sore throat, and arthromyalgia (Rubio-Rivas *et al.,* 2020). Finally, cluster 2 of our study presented the highest frequency of anosmia and ageusia, similar to that described mainly in cluster 2 in a Spanish cluster analysis study (Rubio-Rivas *et al.,* 2020).

Cluster 3 was characterized by dyspnea, the most severe sign among the four groups, and thus, this cluster was described as the "severe" group. This cluster is similar to what was described in an

| Clinical characteristics | Cluster 1 (%) | Cluster 2 (%) | Cluster 3 (%) | Cluster 4 (%) |
|---|---|---|---|---|
| Diarrhea | 6.5 | 42.3 | 8.6 | 0.3 |
| Nausea | 1.8 | 19.7 | 2.7 | 0.9 |
| Abdominal pain | 0.8 | 8.0 | 1.2 | 2.4 |
| Cough | 43.9 | 80.8 | 61.3 | 0.4 |
| Sore throat | 44.8 | 75.8 | 24.0 | 0.3 |
| Nasal congestion | 23.5 | 46.1 | 5.9 | 0.6 |
| Pharyngeal exudate | 0.7 | 1.6 | 0.7 | 0.1 |
| Chest pain | 5.8 | 23.6 | 11.1 | 0.1 |
| Fever | 17.7 | 70.4 | 45.5 | 0.2 |
| Chills | 0.5 | 13.3 | 2.7 | 0.0 |
| Irritability | 0.1 | 1.2 | 1.5 | 0.2 |
| Joint pain | 1.6 | 10.4 | 1.8 | 0.3 |
| Muscle pain | 11.7 | 44.4 | 14.2 | 0.4 |
| Headache | 31.6 | 73.0 | 17.7 | 0.5 |
| General malaise | 45.1 | 83.5 | 75.7 | 3.8 |
| Anosmia | 1.7 | 7.1 | 1.4 | 0.3 |
| Ageusia | 1.3 | 6.2 | 1.2 | 0.2 |
| Conjunctival injection | 0.0 | 0.7 | 0.4 | 2.0 |
| Ear pain | 0.1 | 1.2 | 0.4 | 0.1 |
| Dyspnea | 1.7 | 23.3 | 60.6 | 0.2 |
| Seizure | 0.0 | 0.0 | 0.0 | 0.0 |
| Pregnancy | 3.7 | 0.8 | 0.1 | 9.3 |
| Obesity | 1.7 | 3.1 | 3.3 | 0.1 |
| Diabetes Mellitus | 4.3 | 6.2 | 12.4 | 3.9 |
| Cardiovascular disease | 8.1 | 11.7 | 24.3 | 5.9 |
| HIV | 0.1 | 0.2 | 0.1 | 0.0 |
| Kidney disease | 0.7 | 0.8 | 2.1 | 1.0 |
| Lung Disease | 0.6 | 0.9 | 1.8 | 0.4 |
| Cancer | 1.2 | 0.9 | 1.7 | 1.4 |

**Figure 4.** Clinical characteristics of the participants according to cluster of affiliation (ii).

onco-hematological hospital in France, in which a cluster analysis was performed in COVID-19 patients where the majority of patients presented with dyspnea (mainly in cluster 3 [88%]) and this manifestation differed among clusters, making it important to address as a serious prognostic factor (Bondeelle et al., 2021). In a study performed in China, the second highest proportion of dyspnea was found in patients in cluster A with greater severity (35.2%) (31). This finding is also consistent with that described in a cluster analysis of just over 12,000 patients hospitalized for COVID-19 in Spain, in which cluster 1 accounted for the highest in-hospital mortality, and was characterized by being the largest cluster and comprising the triad of fever, cough and dyspnea (34).

Cluster 3 was dominated by the largest number of individuals with comorbidities, similar to what was described by Bondeelle et al. (2021) who identified a higher proportion of comorbidities in patients grouped in cluster 2, characterized by the lowest survival rate (50.6%). Moreover, our findings align with those of a study carried out in the United States following a cluster analysis that found >50% of patients with the lowest proportion of SARS-CoV-2 positivity were without comorbidities, concluding that the presenting comorbidities represent a risk factor for severe COVID-19 (35).

In addition, cluster 3 consisted of older adult male patients, which is consistent with a study performed in France, in which cluster 2 was made up of older adult patients who required oxygen therapy and had alterations in the C-reactive protein levels (Bondeelle et al., 2021). This is also similar to a study by Liang Han

et al. who found that their more severe cluster A was characterized by a higher mean age and proportion of male patients (31). We also found a high frequency of dyspnea in cluster 2. However, we observed a lower frequency of dyspnea in clusters 1 (1.7%) and 4 (<1%), which could therefore represent the groups with less severity in the clinical evolution of these patients.

Cluster 4 included the highest number of pregnant women and children ranging in age from 0 to 4 years old, which could explain the fact that this group was also characterized by the predominance of being asymptomatic (Figure 3d). The number of clinical manifestations in these populations have been reported to be lower than other groups (Allotey et al., 2020; Mehta et al., 2020; Yanes-Lane et al., 2020). In addition, this cluster had the lowest number of individuals with severe systemic and gastrointestinal diseases. However, this cluster had the second highest number of patients with renal disease and cancer, surpassed only by cluster 4. This is similar to what was found in a French study, in which only 4% of the patients in cluster 1 had an acute renal failure (Bondeelle et al., 2021; Cholankeril et al., 2020; Pan et al., 2020; Tian et al., 2020; Zhang et al., 2020).

*Public health relevance*

This epidemiologic analysis of the COVID-19 pandemic in the Lambayeque region is relevant for public health decision-making at the regional level, especially at the level of the health care net-

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works of the social health insurance of our country since it provides a better understanding of the clinical-epidemiologic behavior of each wave of the pandemic. The decision to perform the cluster analysis was based on the importance of capturing clinical patterns at the population level and assessing how they evolve over time between the two pandemic waves. Another reason for deciding on this analysis based on the clinical manifestations was of the large gap in the care of moderate, severe, and critical COVID-19 patients in Peru. Indeed, an interesting proportion of patients were managed at home, and there was a high proportion of oligoasymptomatic patients who probably did not agree to undergo a confirmatory test for COVID-19 because of the fragmentation of the health system caused by the health emergency long before the pandemic.

### Limitations and strengths

This research has some limitations. First, there may be potential information bias because the clinical-epidemiological variables were not obtained from the clinical histories of the patients selected for the present study. In addition, it was not possible to obtain the measurement of biochemical parameters such as glucose, fibrinogen, and D-dimer (Mollinedo-Gajate *et al.,* 2021). Nor was it possible to analyze the variation in pharmacological therapy (use of anticoagulants, corticosteroids, etc.) administered to patients with COVID-19 infection, (12) and, particularly in the cluster analysis, it was not possible to obtain measurements of severe outcomes such as hospitalizations and death in critical units, biochemical markers, and hospital stay, among others. Second, there may be a selection bias, given that our findings cannot be inferred to the entire study population of patients at the national level or patients present in the Lambayeque region during the first and second waves of the pandemic since the data were collected only from the patients enrolled in the EsSalud Lambayeque health care network. Third, due to the cross-sectional design of the study, it is not possible to attribute causality among the clinical and epidemiological characteristics that were associated with the first and second pandemic waves. Fourth, information on medication usage was unavailable, and therefore we could not determine the effect of medications on the development of the clinical-epidemiological features in each epidemic wave. More research should be performed using this data, especially on self-medication and other therapeutic alternatives used in Peru (Quispe-Cañari *et al.,* 2021; Vasquez-Elera *et al.,* 2022; Villena-Tejada *et al.,* 2021). Nevertheless, this study analyzed a large and diverse sample of patients treated for COVID-19 in the health care networks of the Lambayeque region and the findings obtained to allow the development of future studies aimed at identifying the clinical-epidemiological variation of COVID-19 patients at local and regional levels, including diagnostic and therapeutic variables, to explain the most relevant factors between each pandemic wave.

### Conclusions

In this study, differences in the clinical and epidemiological features of COVID-19 were found between the first and second epidemic waves in Peru. Older age, male sex, comorbidities, and presence of neoplastic disease were more common in the second than in the first outbreak. These characteristics were also related to an increased number of clinical manifestations that occurred during the second wave (featured by dyspnea but also other respiratory and gastrointestinal symptoms). According to the CLARA analysis, four distinct clusters were identified. Cluster 1 was characterized by being the most frequent of the two pandemic waves and was made up of the largest number of women. Cluster 2 was characterized by gastrointestinal, respiratory, and systemic symptoms and

had the second highest incidence of dyspnea. Cluster 3 was characterized by a higher number of older adults with comorbidities, and dyspnea was the most severe clinical feature. Cluster 4 was mainly characterized by asymptomatic presentation, with a higher frequency of pregnant women and fewer cases of dyspnea. This clinical-epidemiological analysis provides a better understanding of the complex behavior of each epidemic wave and can inform future public health decision-making in local and regional health care networks.

### Declaration of competing interest

The authors have no conflicts of interests to declare.

### CRediT authorship contribution statement

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### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.07.045.

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