RISK OF DEATH, HOSPITALIZATION AND ICU ADMISSION BY SARS-CoV-2 VARIANTS IN PERU, A RETROSPECTIVE STUDY

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Highlights

- COVID-19 clinical outcomes are significantly related to the SARS-CoV-2 variant.
- Lambda is the most lethal variant in Peru.
- High hospitalization rates are associated with Mu variant.
- High ICU admission rates are associated with Gamma variants.
ABSTRACT

Objectives: Peru has had the highest death toll from the pandemic worldwide, but it is not clear what the effects of the different variants on these outcomes are. The study aimed to evaluate the risk of death, hospitalization and ICU admission of COVID-19 according to the SARS-CoV-2 variants detected in Peru from March 2020-February 2022.

Methods: Retrospective study using open-access databases published by the Peruvian Ministry of Health. Databases of genomic sequencing, death, COVID-19 cases, hospitalization and ICU, and vaccination were used. Crude and adjusted Cox proportional hazards regressions with clustered variances were modeled to calculate the hazard ratio of outcomes by variant.

Results: Lambda had the highest risk of death (HR 1.92, 95%CI 1.37-2.68), and Delta the lowest (HR 0.50, 95%CI 0.31-0.82). Mu had the highest risk of hospitalization (HR: 2.39, 95%CI 1.56-3.67), and Omicron the lowest (HR 0.45, 95%CI 0.23-0.90), and Gamma had the highest ICU admission rate (HR 1.95, 95%CI 1.40-2.71).

Conclusion: SARS-CoV-2 variants showed distinctive risks of clinical outcomes, which could have implications for the management of infected persons during the pandemic.

Keywords: SARS-CoV-2 variants, Clinical outcomes, COVID-19, Peru
INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared a pandemic for COVID-19, a disease caused by SARS-CoV-2, which is characterized by the development of a series of signs and symptoms in the infected population, including respiratory, psychiatric, cardiovascular problems, among others [1].

Since the discovery of the Wuhan virus, D614G or original strain, different variants and lineages have been identified in such a relatively short time, indicating that SARS-CoV-2 has a higher mutation rate compared to other viruses [2]. While Omicron is the predominant variant, there have been approximately 600 variants of which those currently circulating can be classified as Variants of Interest (VOI) and Variants of Concern (VOC) [3]. These variations in the virus genome did not only bring structural differences, especially in the Spike protein, but also in virulence, with diversity in disease severity and transmissibility [4].

The virulence of SARS-CoV-2 may differ between geographic locations because some local strains have differential virulence compared to others. This is due to multiple mutations in its genetic sequence that can lead to increases in infectivity, pathogenicity, and antigenic capacity [5]. The variants identified to date have presented a heterogeneous geographic distribution, causing mortality and morbidity rates in different proportions depending on the affected country or continent [5]. It is mentioned that ancestry could play an important role in the response of the immune system against SARS-CoV-2, attributing higher infection rates to Latin and African Americans compared to those of European descent. In this sense, the impact that each variant of interest or concern can generate may vary according to the population in which it is distributed [6]. This information will be vital for implementing
public health measures to control the spread of variants with local predominance and based on local characteristics.

Worldwide, one of the countries most affected by the pandemic has been Peru, currently reporting 3.29 million cases, positivity of 11.64% and a case fatality rate of 7.22%. Mortality in Peru is associated with male sex, older people, and presence of with co-morbidities, in particular obesity and diabetes mellitus [7]. It was initially considered that residence at high altitudes, Peru is a country with a wide distribution of altitudes, was a protective factor against SARS-CoV-2 infections and death, but later studies found that this was not correct [8, 9].

As part of the pandemic mitigation plan, the Peruvian government developed a nationwide genomic surveillance project with the objective of sequencing positive patients with a cycle threshold (Ct) ≤30, based on the Pan American Health Organization recommendations [10], determining the variant or lineage from which their infection originated for epidemiological control. Nonetheless, it is not clear what the effects of the different variants were in the Peruvian population.

Understanding how the different variants are associated with severe outcomes such as death, hospitalization or ICU admission could lead to the development of specific mitigation strategies and variant-specific treatments. Therefore, the aim of the present study was to assess the risk of death, hospitalization and ICU admission by SARS-CoV-2 variants in Peru from March 2020 to February 2022.

MATERIALS AND METHODS
Study Design and Population

The study was designed as a retrospective cohort, and included people infected with SARS-CoV-2 who were notified through the national platform for disease control and epidemiological surveillance (Netlab 2.0), and whose samples were selected for genome sequencing. The results are reported in the same platform, and published in the open-access databases by the Peruvian Ministry of Health.

Data Record and Merging

The deaths, cases, hospitalization, genome sequencing data and vaccination information were obtained from the open access databases of the Peruvian Ministry of Health (Supplementary material 1).

The open-access databases identify each individual only by means of an encrypted code. Personal data such as name, telephone number or specific residential address are not included. The merging of the five databases was performed using the encrypted code, which allowed us to construct a timeline of the disease from sample collection to outcome (death, hospitalization or ICU admission) over a 30-day period. The initial database used for the fusion process was the SARS-CoV-2 sequencing database, which included all patients infected with the identified SARS-CoV-2 variant.

We included 10,733 registries from people ≥18 years-old, with high viral load (Ct≤30), with or without symptoms whose sample was genome sequenced and reported in the Netlab 2.0 and published in the open access COVID-19 databases of the Peruvian Ministry of Health.
Variables

The outcomes evaluated were death, hospitalization and ICU admission over a 30-day period, considering day 1 as the sampling date. This period was considered since it is related to the possible acute effects of COVID-19 and not to those of long-COVID.

A total of five categories of SARS-CoV-2 variants were considered: Lambda, Gamma, Delta, Mu, Omicron and Others. Classification was performed based on WHO variants, the lineage list and Pango nomenclature [11]. Since the Alpha and Zeta variants were of low prevalence in Peru, they were included in the Others category.

Other variables considered were the number of doses of SARS-CoV-2 vaccine taken before the time of infection, age (years), sex, number of hospital and ICU beds for COVID-19 available within the province of residence up to seven days before the onset of the outcome. Information on region and province and district of residence was also included.

Statistical Analysis

Descriptive statistics were performed showing mean and standard deviation for numerical variables, and absolute and relative frequencies for categorical variables. Pearson's chi-square was used to test for the association between SARS-CoV-2 variants and death, hospitalization or ICU admission. Survival analysis for death, hospitalization, and ICU admission according to variant was analyzed graphically with the Kaplan-Meier method.
A time-to-event analysis was performed using the Cox proportional hazards model to assess the association of the different variants with death, hospitalization, and ICU admission. Three separate models were developed, one for each covariate-adjusted outcome:

Equation 1. - Adjusted Cox regression model for death

\[ h(t|X) = h_0(t) \exp(\beta_{1\text{variant}} + \beta_{2\text{sex}} + \beta_{3\text{age}} + \beta_{4\text{doses}} + \beta_{5\text{hospitalization}} + \beta_{6\text{ICU}} + \beta_{7\text{beds}} + \beta_{8\text{ICUbeds}} + \epsilon) \]

Equation 2. - Adjusted Cox regression model for hospitalization

\[ h(t|X) = h_0(t) \exp(\beta_{1\text{variant}} + \beta_{2\text{sex}} + \beta_{3\text{age}} + \beta_{4\text{doses}} + \beta_{7\text{beds}} + \epsilon) \]

Equation 3. - Adjusted Cox regression model for ICU admission

\[ h(t|X) = h_0(t) \exp(\beta_{1\text{variant}} + \beta_{2\text{sex}} + \beta_{3\text{age}} + \beta_{4\text{doses}} + \beta_{7\text{beds}} + \epsilon) \]

where \( h(t|X) \) is the hazard at the time \( t \) of the outcome adjusted on covariates, \( h_0(t) \) is the baseline hazard for the outcome, \( \exp(\beta_{1\text{variant}}) \) is the hazard ratio for the outcome of infection with a given variant compared to the other variants (e.g. Delta infected vs all non-Delta infected), \( \exp(\beta_{2\text{sex}}) \) is the hazard ratio of the outcome being a male compared to being a male, \( \exp(\beta_{3\text{age}}) \) is the hazard ratio of the outcome for age as a continuous variable, \( \exp(\beta_{4\text{doses}}) \) are the hazard ratios of the outcome of being vaccinated with 1, 2 or 3 doses compared to 0 doses, \( \exp(\beta_{5\text{hospitalization}}) \) is the hazard ratio of death when
hospitalized compared to not being hospitalized, \( \exp(\beta_{6\text{ICU}}) \) is the hazard ratio of death of those who were ICU admitted compared to non-ICU, \( \exp(\beta_{7\text{beds}}) \) is the outcome for number of available hospital beds quintiles up to 7-days prior the death date, \( \exp(\beta_{8\text{ICUbeds}}) \) is the hazard ratio of death and ICU for number of available ICU beds quintiles up to 7-days prior to the date of death, and \( \varepsilon \) is the error term. Proportional hazards assumption was tested using Schoenfeld residuals, and linearity of numeric variables evaluated using Martingale-based residuals. Standard error was adjusted with clustered variances; region of residence was considered as the cluster.

An established reference group was not set because sequencing was restricted to sample with a Ct\( \leq \)30, limiting the variants detected for this study. So, when calculating the hazard ratio for a particular variant with its confidence interval at 95%, the reference group is considered as the hazard of the outcome for all the other variants (e.g. hazard of death for Delta vs hazard of death for all non-Delta). The Omicron variant is generally considered a low-risk variant [12, 13], so to assess whether the results were consistent, a sensitivity analysis was performed, leaving the Omicron variant out of the categorization. All statistical analysis were done using STATA 17.0 software, and statistical significance was considered as a p-value <0.05.

RESULTS

In Table 1 is observed that up to February 2022, Delta was the most prevalent variant of COVID-19, followed by Lambda and Gamma. The other variants represented only 6.8% of total.
There was a clear dominance of Lambda variant from February to mid-August 2021. Delta variant became the most prevalent variant by September until December 2021 in which Omicron began to spread, surpassing Delta by January 2022 (Figure 1).

Table 2 presents the results of bivariate analysis of the associations between the variants and outcomes. There were significant associations with death, hospitalization and ICU admission. Lambda had the highest percentage of deaths, Mu and Gamma the highest hospitalization and ICU admission, respectively.

In the survival analysis it can be seen that all variants except Delta and Omicron showed a higher cumulative mortality, although a flatter slope can be observed for Omicron (Figure 2A). In regard of hospitalization, a similar pattern can be observed (Figure 2B); and for ICU admission, Lambda and Omicron variants showed lower cumulative incidence of ICU admission, and Gamma variant the highest (Figure 2C).

The crude and adjusted hazard ratios are showed in Table 3. For death, infections with Gamma and Lambda variants were risk factors, while Delta and Omicron had a hazard ratio below 1 in the crude analysis, but after adjustment for covariates, only Delta variant showed a decreased HR for death compared to all other variants (HR: 0.50, 95%CI 0.31 - 0.82).

For hospitalization, in both the crude and adjusted analysis, Mu variant presented an increased HR compared to all other groups (HR 2.31, 95%CI 1.56 - 3.67), while Omicron showed a reduction for hospitalization risk of 55% after adjusting for covariates. For ICU admission, Lambda variant showed a reduction of 38% in the risk of the outcome but only in
the crude analysis, while Gamma variant exhibited a higher risk compared to all other groups (HR 1.95, 95%CI 1.40 - 2.71).

In the sensitivity analysis, the results obtained were similar to those of the full models, meaning that the effect of the variant was not diluted by Omicron (Supplementary Table 1).

**DISCUSSION**

This study aimed to determine the impact of SARS CoV-19 variants on mortality, hospitalization and ICU admission in Peru. We found that those infected with the Lambda variant had a higher risk of death, while those infected with Delta variant presented the lowest death risk. In the case of hospitalization, the Mu variant had the highest risk.

The Omicron variant was associated with the lowest risk of death and hospitalization in the crude analysis. This is in accordance with its higher transmissibility, but lower severity observed worldwide [14, 15]. Regarding ICU admission, we have observed that Gamma variant had the highest risk.

Different to other countries, especially those in Europe and North America [16], Peru did not have much representability of alpha variant. It is generally considered to have a higher risk of mortality, hospitalization and ICU admission compared to the wild-strain [5]. Also, even though the number of cases infected with the Alpha variant was small (n=14) in our study, it was not significantly associated with hospitalization and ICU admission, while the mortality associated with it was lower. An earlier study also reported a lower risk of hospitalization in association with the Alpha variant [17].
Although both the Delta and Lambda variants are capable of immune evasion, the Lambda variant is associated with mutations L452R and F490S that makes it easier for it to bond with the ACE2 receptor [18]. This could explain its association with adverse health outcomes even in vaccinated persons [19], and thus the higher associated mortality in this study.

Gamma variant was associated with a higher risk of ICU admission (HR: 1.95, 95%CI 1.4 - 2.71). Similar findings have been reported from studies in Canada [20] and France [21], and could be explained by the capability of this variant to provoke severe symptoms in young and middle-age patients, including those without comorbidities [22, 23]. Mu variant was associated with the highest risk for hospitalization in our patients in contrast to the results from a study in Colombia [24], although the Colombian study was done with data from a single state, while we used nationwide data, giving more robust estimates, thus explaining the difference. Also, it is possible that genetic differences between both populations could be involved [25].

It is noteworthy that Lambda variant was associated with the highest risk of death. Lambda variant was first detected in Peru in August 2020, it presents 19 mutations of which 7 are in the Spike protein, which is linked to higher chances of evasion of neutralizing antibodies [4, 19] and immune resistance [26]. It is possible that, since the variant originated in Peru, its mutations are focused on the host genome, in this case Andean population, this being similar to the hospitalization in India for Delta variant infections [27].

Although the study period comprised the first three waves of the COVID-19 pandemic in Peru, it was not possible to fit the regression models by pandemic wave since there were only
15 observations for the first wave. However, we did factor in the availability of beds, which act as a proxy variable.

The study has some limitations. First, information came from secondary databases, which might be attended by a possible information bias due to misclassification or inadequate data recording, especially in areas with lower technology access and trained personnel. Second, SARS-CoV-2 sequencing was not broadly performed before the second wave and considering that only samples with specific criteria were considered for sequencing, during subsequent waves it is possible that some variants were not identified. Third, a stablished reference group was not possible to be set because only samples with a Ct$\leq$30 were eligible for sequencing, and considering that not all the samples are sequenced, it is possible that representativeness of certain variants was lost. The pandemic waves have distinctive traits that could act as confounders in our model, nonetheless, one of the main characteristics was the availability of hospital and ICU beds, which can be considered as a proxy, but some information could not be controlled. Factors such as ambient air pollution [28] were not considered in this study due to lack of data. These limitations should be considered in further studies.

In conclusion, the different variants had distinctive effects on clinical outcomes which could have implications for the management of infected persons during the pandemic.

**CONFLICT OF INTERESTS**

The authors declare that they have no conflict of interest.
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ETHICAL APPROVAL STATEMENT

The study was approved by the Universidad Peruana Cayetano Heredia Institutional Review Board (SIDISI: 204170).

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REFERENCES


**FIGURE CAPTIONS**

**Figure 1:** Variation in number of cases of SARS-CoV-2 variants during the study period.

Data before December 1st, 2020 is not shown due to the low number of sequencing in those days, and for better data visualization.
Figure 2: Kaplan-Meir survival analysis plots for Death (2A), Hospitalization (2B) and ICU Admission (2C) by SARS-CoV-2 variant.
Table 1. Sample characteristics (N=10721)

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>39.75 ± 17.28</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Feminine</td>
<td>5618 (52.4)</td>
</tr>
<tr>
<td>Masculine</td>
<td>5107 (47.6)</td>
</tr>
<tr>
<td>Variant</td>
<td></td>
</tr>
<tr>
<td>Gamma</td>
<td>1350 (12.5)</td>
</tr>
<tr>
<td>Delta</td>
<td>4331 (40.4)</td>
</tr>
<tr>
<td>Lambda</td>
<td>3019 (28.1)</td>
</tr>
<tr>
<td>Mu</td>
<td>149 (1.3)</td>
</tr>
<tr>
<td>Omicron</td>
<td>1139 (10.6)</td>
</tr>
<tr>
<td>Others£</td>
<td>733 (6.8)</td>
</tr>
<tr>
<td>Deaths</td>
<td>283 (2.64)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>554 (5.2)</td>
</tr>
<tr>
<td>ICU admissions¥</td>
<td>139 (25.1)</td>
</tr>
</tbody>
</table>

*Displays mean ± standard deviation.
£Includes Alpha and Zeta variants.
¥Percentage calculated based on total of hospitalized people.
Table 2. Number of deaths, hospitalizations and ICU admissions by SARS-CoV-2 variants

<table>
<thead>
<tr>
<th>Variant</th>
<th>Deaths n(%)</th>
<th>p*</th>
<th>Hospitalizations n(%)</th>
<th>p*</th>
<th>ICU admissions n(%)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma</td>
<td>51 (3.9)</td>
<td></td>
<td>83 (6.2)</td>
<td></td>
<td>37 (44.1)</td>
<td></td>
</tr>
<tr>
<td>Delta</td>
<td>69 (1.6)</td>
<td></td>
<td>237 (5.4)</td>
<td></td>
<td>69 (29.2)</td>
<td></td>
</tr>
<tr>
<td>Lambda</td>
<td>123 (4.1)</td>
<td>&lt;0.001</td>
<td>169 (5.6)</td>
<td>&lt;0.001</td>
<td>36 (20.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mu</td>
<td>4 (2.7)</td>
<td></td>
<td>17 (11.4)</td>
<td></td>
<td>3 (17.7)</td>
<td></td>
</tr>
<tr>
<td>Omicron</td>
<td>12 (1.1)</td>
<td></td>
<td>23 (1.9)</td>
<td></td>
<td>3 (13.6)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>23 (3.1)</td>
<td></td>
<td>22 (2.9)</td>
<td></td>
<td>8 (38.1)</td>
<td></td>
</tr>
</tbody>
</table>

Deaths and Hospitalizations percentages are calculated based on the total number of infected by each variant. ICU admissions percentages were calculated based on the total number of hospitalized people by each variant. Others include Alpha and Zeta variants.

*pPearson Chi-squared.
Table 3: Crude and adjusted Cox regression analysis of death, hospitalization and ICU admission by variants*

<table>
<thead>
<tr>
<th>Variant</th>
<th>Death cHR</th>
<th>Death aHR</th>
<th>Hospitalization cHR</th>
<th>Hospitalization aHR</th>
<th>ICU admission cHR</th>
<th>ICU admission aHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gam</td>
<td>1.54 (1.13)</td>
<td>1.24 (0.85)</td>
<td>1.24 (0.98)</td>
<td>1.20 (0.75)</td>
<td>1.92 (1.33)</td>
<td>1.95 (1.40)</td>
</tr>
<tr>
<td>ma</td>
<td>- 2.08</td>
<td>- 1.83</td>
<td>- 1.56</td>
<td>- 1.93</td>
<td>- 2.78</td>
<td>- 2.71</td>
</tr>
<tr>
<td>Delta</td>
<td>0.47 (0.36)</td>
<td>0.50 (0.31)</td>
<td>1.12 (0.94)</td>
<td>1.00 (0.75)</td>
<td>1.09 (0.79)</td>
<td>0.90 (0.59)</td>
</tr>
<tr>
<td>Lam</td>
<td>1.99 (1.58)</td>
<td>1.92 (1.37)</td>
<td>1.13 (0.94)</td>
<td>1.17 (0.73)</td>
<td>0.62 (0.43)</td>
<td>0.69 (0.42)</td>
</tr>
<tr>
<td>bda</td>
<td>- 2.53</td>
<td>- 2.68</td>
<td>- 1.35</td>
<td>- 1.87</td>
<td>- 0.91</td>
<td>- 1.13</td>
</tr>
<tr>
<td>Mu</td>
<td>1.02 (0.38)</td>
<td>1.75 (0.53)</td>
<td>2.31 (1.42)</td>
<td>2.39 (1.56)</td>
<td>0.57 (0.18)</td>
<td>0.56 (0.19)</td>
</tr>
<tr>
<td>Omi</td>
<td>0.37 (0.21)</td>
<td>0.71 (0.35)</td>
<td>0.36 (0.34)</td>
<td>0.45 (0.23)</td>
<td>0.42 (0.13)</td>
<td>0.46 (0.10)</td>
</tr>
<tr>
<td>cron</td>
<td>- 0.66</td>
<td>- 1.41</td>
<td>- 0.55</td>
<td>- 0.90</td>
<td>- 1.33</td>
<td>- 2.02</td>
</tr>
<tr>
<td>Other</td>
<td>1.21 (0.79)</td>
<td>0.75 (0.30)</td>
<td>0.56 (0.37)</td>
<td>0.58 (0.40)</td>
<td>1.32 (0.65)</td>
<td>1.43 (0.73)</td>
</tr>
<tr>
<td>rs</td>
<td>- 1.86</td>
<td>- 1.85</td>
<td>- 0.86</td>
<td>- 0.85</td>
<td>- 2.70</td>
<td>- 2.81</td>
</tr>
</tbody>
</table>

*Each variant model considers the reference group as the combined hazard of all other variants.

Crude Hazard Ratio (cHR) and adjusted Hazard Ratio (aHR) with 95% confidence interval are presented.

HR and 95%CI in bold letters are p<0.05.

Death model controlled for sex, age, number of COVID-19 vaccine doses, hospitalization, ICU admission and availability of hospitalization and ICU beds during the week of admission.

Hospitalization model controlled for sex, age, number of COVID-19 vaccine doses and availability of hospitalization beds during the week of admission.

ICU Model controlled for sex, age, number of COVID-19 vaccine doses and ICU rooms availability during the week of UCI admission.
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: