


# Alterations in the coagulation markers did not show differences with the severity of COVID-19 in Peruvian patients: A cross-sectional single-center study

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## Abstract

**Background and Aims:** COVID-19 is a pandemic disease that can lead to altered lung function, systemic inflammatory events, and altered coagulation. During severe stages of the disease, changes in coagulation homeostasis increase, leading to thrombosis, and increased risk of death. In this cross-sectional study, we aimed to assess coagulation markers by COVID-19 severity in Peruvian adults.

**Methods:** During the second wave of infections, we included 186 adults diagnosed with COVID-19 (mean age  $53.3 \pm 16.3$  years). Patients were divided into mild, moderate, and severe stages of COVID-19, and coagulation markers included prothrombin time (PT), activated partial prothrombin time (aPTT), fibrinogen, D-dimer, and platelet count.

**Results:** Of the total, 120 (64.5%) were males and 39 (21%) were in the intensive care unit. We determine 104 (55.9%), 43 (24.7%), and 36 (19.4%) patients in mild, moderate, and severe stages of COVID-19, respectively. In the severe stage of COVID-19, patients had an average concentration of PT, aPTT, fibrinogen, D-dimer, and platelets of  $13.2 \pm 0.9$  s,  $28.9 \pm 4.3$  s,  $679.4 \pm 185.1$  mg/dL,  $1.9 \pm 3.1$   $\mu$ g/mL, and  $272.8 \pm 88.9$  cel/10 mm,<sup>3</sup> respectively. We found no differences in the concentration of each marker according to severity ( $p < 0.05$ ). Patients with severe COVID-19 had altered the aPTT, fibrinogen, D-dimer, and PT in 31 (57.4%), 48 (88.9%), 37 (68.5%), and 15 (27.8%) cases, respectively.

**Conclusions:** Our results showed that although there is an alteration in coagulation markers, mainly fibrinogen and D-fiber, there are no differences in concentration according to the severity of COVID-19.

## KEYWORDS

coagulation, COVID-19, D dimer, fibrinogen, prothrombin time, SARS-CoV-2

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## 1 | INTRODUCTION

COVID-19, an infectious disease caused by SARS-CoV-2, causes immunological changes and microcirculation problems that lead to long-term disease progression.<sup>1</sup> SARS-CoV-2 is jeopardizing public health worldwide, as the 20 epidemics that has beaten the humanity, the virus spreads rapidly, producing higher infection and mortality rates.<sup>2</sup> This malady of 2 years of existence has affected at the final of 2021 more than 270 million of infections and more than 5.5 million of deaths that is part of the prototype virus as its variations.<sup>3</sup>

The SARS-CoV-2 causes the COVID-19, an atypical pneumonia that can be manifested by severe respiratory symptoms, lung damage or be asymptomatic, that could be like a mild infection or progress to a severe stage with respiratory failure, compromising the cardiovascular system and dysfunction to coagulate, leaving consequences after the initial infection.<sup>3,4</sup> The inflammatory process caused during the infection evokes to a cytokinesis that causes a vascular disorder for coagulation that occurs generally in the severe disease.<sup>5</sup>

Two previous meta-analyses have demonstrated that the disorder for coagulation is part of the COVID-19, an important lower count of platelets, a shorter period of activated partial thromboplastin time (aPTT) and higher rates of D dimer, fibrinogen, and a longer prothrombin time (PT).<sup>6,7</sup> These disorders have as a consequence the hypercoagulability, a phenomenon currently in the severe stages of the COVID-19 which is an important factor of high oxygen requirements.<sup>8</sup> Coagulation disorders can be used to stratify the severity of COVID-19 and are associated with other poor prognostic outcomes (i.e., respiratory distress) and the aggressiveness of the disease (measured by lung involvement).

However, in many populations affected by COVID-19, coagulation disorders are associated with respiratory parameters that have not been fully assessed, resulting in current limitations in quantifying disease and determining its severity. In this regard, understanding the frequency of changes in coagulation profiles in patients with COVID-19 is important and necessary as it facilitates rapid clinical response and improved prediction of SARS-CoV-2 infection.

In our study, we evaluated the coagulation profile of patients with COVID-19 in a tertiary-care hospital in Lima, Peru. In addition, we have determined the association of the coagulation profile with a set of clinical features and oxygen function.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and location

This cross-sectional observational study was conducted during 2021 in the Hospital de Emergencias José Casimiro Ulloa, a 112-beds tertiary-care specialized hospital for medical and surgical emergencies in Lima. During the COVID-19 pandemic the emergencies linked with infections by SARS-CoV-2 have been prioritized and assisted by 857 healthcare professionals for continuous workflow.

### 2.2 | Populations, inclusion criteria, and definitions

Of a total of population assisted monthly ( $N = 722$ ) we have been added 186 patients that passed the inclusion criteria. The inclusion criteria were adult ( $>18$  years) of both sexes, with a currently diagnosis of COVID-19 (diagnosed by reaction of polymerase chain [PCR] and antigen test<sup>9</sup>) that had a clinical classification (mild, moderate, and severe ill) and the complete result of basal coagulation profile. The patients with COVID-19 were referred for clinical suspicion, initially were evaluated with antigen tests and then were confirmed by PCR.

Mild COVID-19 is defined as an acute respiratory infection (ARI) that has two of the following signs or symptoms: cough, malaise, sore throat, fever, and nasal congestion. Additionally, it may present with other symptoms such as taste changes, odor changes, and rashes. Moderate COVID-19 is defined as an ARI that meets some of the following criteria: dyspnea, respiratory rate greater than 22 breaths per min (BPM), oxygen saturation  $<95\%$ , altered level of consciousness, arterial hypotension or shock, clinical and/or radiologic signs of pneumonia, lymphocyte count  $<1000$  cel/ $10$  mm.<sup>3</sup> Severe COVID-19 is defined as any person with ARI with two or more of the following criteria: respiratory rate  $>22$  BPM or PaCO<sub>2</sub>  $<32$  mmHg, altered level of consciousness, systolic blood pressure  $<100$  mmHg, PaO<sub>2</sub>  $<60$  mmHg or PaFi  $<300$ , clinical signs of muscle fatigue (i.e., nasal flaring, thoracoabdominal imbalance), and serum lactate  $>2$  mosm/L.<sup>10</sup>

### 2.3 | Coagulation profile, data collection, and analysis

The coagulation monitoring has done using the autoanalyzer Cobas t511 (Roche). The coagulation profile includes the determination of PT, aPTT, fibrinogen, D-dimer, and the count of platelets. The laboratory results were obtained from the Sistema de Gestión del Laboratorio of the hospital where all clinical analysis reports are stored.

Data collection was conducted during the second wave of COVID-19 in Peru from January to April 2021. Data analysis was initially descriptive to estimate the frequencies of the continuous variables and the mean and the standard deviation of the categorical variables. We used paired *T*-test and ANOVA one-way with Bonferroni post hoc test to determine the differences of the values of the coagulation profile and the severity of the COVID-19. The analysis of association between the alterations of coagulation markers with the parameters of oxygen function and lung damage have been taken with the Spearman's test and Kendal-Tau b considering the  $p < 0.05$  and the confidence interval of 95% as the significant. The data analysis has done in SPSS v24.0.

### 2.4 | Ethical aspects

We followed the guidelines of the Declaration of Helsinki<sup>11</sup> and the project was approved by the hospital management and the Ethics and Research Committee (Document N°673-DG-118-2021-OADI-HEJCU).

### 3 | RESULTS

#### 3.1 | Characteristics of populations

Of the total, 120 (64.5%) were males and the average age was of  $53.3 \pm 16.3$  years-old (range 20–94 years). The most frequent age group was 51–60 years-old with 43 (23.1%) patients followed by 41–50 years-old with 38 (20.4%) patients. Seventy (37.6%) patients required hospitalization, 66 (35.5%) were outpatients, 39 (21.0%) were in the Intensive care unit, and 11 (5.9%) patients were admitted to the Shock COVID-19 Trauma Unit. According to the COVID-19 severity, 104

(55.9%) patients were in mild stage, 43 (24.7%) patients in moderate, and 36 (19.4%) patients in severe stage (Table 1).

On mild COVID-19 patients they had an average oxygen saturation and pulmonary compromise of  $95.7 \pm 3\%$  and  $9 \pm 10\%$ , respectively. The patients in moderate stage had an average oxygen saturation of  $92.1 \pm 5\%$  and pulmonary compromise of  $42.2 \pm 1\%$ . In the severe stage of COVID-19 the average oxygen saturation and pulmonary compromise was  $83.9 \pm 1\%$  and  $67.6 \pm 12\%$ , respectively.

**TABLE 1** Baseline characteristics of COVID-19 patients.

Characteristics	f	%
Sex		
Male	120	64.5
Female	66	35.5
Age group (years)		
20–30	17	9.1
31–40	25	13.4
41–50	38	20.4
51–60	43	23.1
61–70	36	19.4
>70	27	14.5
Place of care		
Outpatient	66	35.5
Hospitalization	70	37.5
ICU–COVID-19	39	21
Shock trauma center	11	5.9
COVID-19		
Mild	104	55.9
Moderate	43	24.7
Severe	36	19.4

Abbreviation: ICU, intensive care unit.

#### 3.2 | Coagulation and severity of COVID-19

The patients who have been COVID-19 on the mild stage had an average concentration of PT, aPTT, INR, fibrinogen, D-dimer, and platelets of  $13.4 \pm 2.3$  s (IC 95% 12.9–13.9),  $30 \pm 5.1$  s (IC 95% 29–30.9),  $1.1 \pm 0.2$  (IC 95% 1.0–1.1),  $500.9 \pm 161.2$  mg/dL (IC 95% 469.9–531.9),  $1.3 \pm 3.36$  µg/mL (IC 95% 0.6–1.9), and  $225.9 \pm 100.6$  cel/10 mm<sup>3</sup> (IC 95% 206.6–245.3), respectively. The patients with moderate stage of COVID-19 had an average concentration of PT, aPTT, INR, fibrinogen, D-dimer, and platelets of  $12.9 \pm 1.4$  s (IC 95% 12.9–13),  $29.1 \pm 0.2$  s (IC 95% 27.6–30.5),  $1.1 \pm 0.2$  (IC 95% 1.0–1.1),  $553.5 \pm 145.6$  mg/dL (IC 95% 511.4–595.6),  $1.1 \pm 1.6$  µg/mL (IC 95% 0.64–1.6), and  $285.4 \pm 124.4$  cel/10 mm<sup>3</sup> (IC 95% 249.4–321.3), respectively (Table 2).

The patients who have been on severe stage had an average concentration of PT, aPTT, INR, fibrinogen, D-dimer, and platelets of  $13.2 \pm 0.9$  s (IC 95% 12.9–13.4),  $28.9 \pm 4.3$  s (IC 95% 27.5–30.4),  $1.1 \pm 0.1$  (IC 95% 0.9–1.1),  $679.4 \pm 185.1$  mg/dL (IC 95% 618.9–739.8),  $1.9 \pm 3.1$  µg/mL (IC 95% 0.92–2.9), and  $272.8 \pm 88.9$  cel/10 mm<sup>3</sup> (IC 95% 243.8–301.9), respectively. We have not founded any difference in the concentration of coagulation profile markers according to the severity of COVID-19 ( $p > 0.05$ ) and genders ( $p = 0.887$ ).

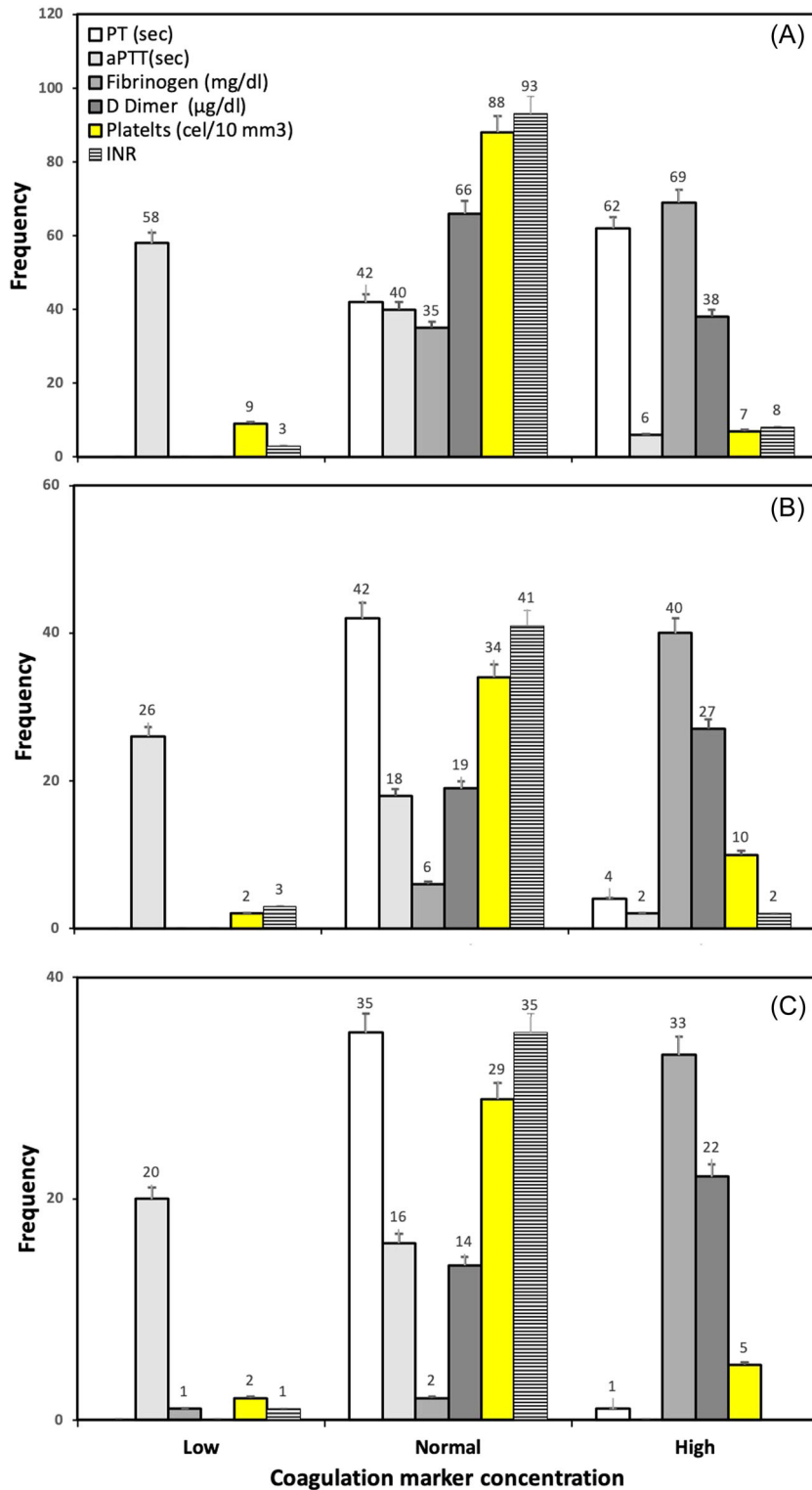
#### 3.3 | Coagulation values and oxygen function

In patients with mild COVID-19, PT, aPTT, D-dimer, and platelet counts were normal in 88.8%, 94.4%, 70.8%, and 91% of participants, respectively. Thus, 8 (9%) patients had thrombocytopenia, on 57 (64%) the fibrinogen was elevated and 26 (29%) patients had elevated rates of D-dimer in the blood. Findings of patients with moderate COVID-19

**TABLE 2** Average concentration of coagulation markers according to the severity of COVID-19 in Peruvian patients.

Coagulation marker	Normal range	COVID-19			p Value
		Mild	Moderate	Severe	
PT (s)	11–13.5	$13.4 \pm 2.3$	$13 \pm 1.4$	$13.2 \pm 0.9$	0.564
aPTT (s)	25–35	$30 \pm 5.1$	$29.1 \pm 5.1$	$29 \pm 4.3$	0.402
Fibrinogen (mg/dL)	200–400	$501 \pm 161.2$	$553 \pm 145.7$	$679.4 \pm 185.1$	1
D dimer (µg/mL)	<0.5	$1.3 \pm 3.4$	$1.1 \pm 1.6$	$1.9 \pm 3.1$	0.981
Platelets (cell/10 mm <sup>3</sup> )	150–350	$226.4 \pm 101$	$285.4 \pm 124.4$	$272.9 \pm 88.9$	0.211
INR	1	$1.1 \pm 0.2$	$1.1 \pm 0.2$	$1 \pm 0.1$	0.514

Abbreviations: aPTT, activated partial prothrombin time; PT, prothrombin time.



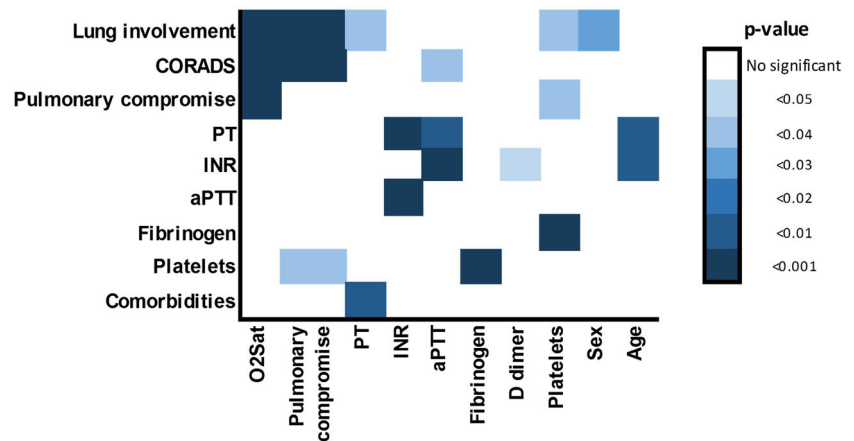
**FIGURE 1** Concentration levels of coagulation markers according to the severity of COVID-19 patients. (A) Mild, (B) moderate, and (C) severe COVID-19. Normal values: PT (11–14 s), aPTT (30–40 s), fibrinogen (200–400 mg/dL), D dimer (<0.5 µg/dL), platelets (150–350 cel/10 mm<sup>3</sup>), and INR (0.9–1.2). Data in N. aPTT, activated partial prothrombin time; PT, prothrombin time.

showed that 26 (60.55%) and 38 (88.4%) of patients had elevated D-dimer and fibrinogen rates, respectively, and 9 (20.9%) patients presented PT alterations. In addition, we found abnormal platelet counts with thrombocytosis and thrombocytopenia in 3 (7.0%) and 1 (2.3%) patients, respectively. In the severe stage of COVID-19, the aPTT, fibrinogen, D-dimer, and PT were found altered in 31 (57.4%), 48 (88.9%), 37 (68.5%), and 15 (27.8%) patients, respectively. Only 1 patient developed

thrombocytopenia, and the most significant subset of participants presented normal values for coagulation markers (Figure 1).

In addition, we have proved that the patient's age as a clinical variable has a direct relation with values of PT ( $p = 0.013$ ), D-dimer ( $p = 0.017$ ), and INR ( $p = 0.004$ ), and it has an inverse relation with oxygen level (O<sub>2</sub> sat). In addition, O<sub>2</sub> sat was negatively correlated with age ( $p = 0.031$ ), lung parenchymal involvement ( $p = 0.000$ ), and degree of lung

**FIGURE 2** Correlation results between coagulation profiles and characteristics of COVID-19 patients. aPTT, activated partial prothrombin time; PT, prothrombin time.



involvement ( $p = 0.001$ ). Likewise, we demonstrate that fibrinogen disturbance, platelet count, and prolonged aPTT are not associated with patient age, sex, or comorbidities ( $p > 0.05$ ) (Figure 2).

## 4 | DISCUSSION

This study has not demonstrated a difference in the concentration of the coagulation markers according to the severity of COVID-19 in Peruvian patients. In addition, patients presented higher levels of fibrinogen and D-dimer at all stages of the disease, although these values were not significant, they were associated with oxygen function parameters and lung dysfunction.

One of our strengths is that we have conducted the first coagulation disorder study in patients with COVID-19 in Peru. Interestingly, although fibrinogen and D-dimer were elevated in severe COVID-19 patients, this elevation did not appear to differ from moderate and mild stages of the disease. Another strength of the study was the analysis of the association between respiratory function outcomes and disease severity. In this study, we highlight the link between oxygen saturation and lung impairment in moderate and severe stages of COVID-19, however, these were not associated with coagulation marker concentrations at any stage.

During the 2.5 years of the COVID-19 pandemic, the coagulation markers have been recognized as key factors in the evaluation of the procoagulatory state in critical patients, even if its clinical scope continues in the study, its evaluation is not available in all countries or patients.<sup>12</sup> Recently, it exists a large number of publications focused on the hemostatic changes associated with COVID-19, since the first reports in China, showed elevated levels of D-dimer and PT, and low levels of fibrinogen and platelets that showed coagulation compromise, the severity of the disease, and mortality prognosis.<sup>13</sup>

Our findings demonstrated a high frequency of normal platelet count levels in all stages of COVID-19, consistent with previous studies reporting that platelet counts in COVID-19 are often normal or mildly reduced, and the thrombocytopenia is present in 12%–36% of patients.<sup>14,15</sup> This slight change in platelet concentration may be due to

the patient's anticoagulant therapy, which is part of the treatment regimen for moderate and severe stages of COVID-19 in Peru.<sup>16</sup>

Other studies have reported that longer PTs and elevated fibrinogen and D-dimer levels are associated with more aggressive disease.<sup>6,7,17</sup> In this study, patients with severe COVID-19 showed altered fibrinogen (88.9%) and D-dimer (68.5%), as well as prolonged aPTT (57.4%), with 2/3 of the altered markers coinciding with the increase. Although we did not find differences in D-dimer concentration across stages of COVID-19 or its association with other features of respiratory function, we found it increased in more than half of the cases. It has recently been shown in more than 38,000 patients that higher levels of D-dimer provide useful early clinical and prognostic information about the risk of disease progression and mortality.<sup>18</sup> For this reason, we highlight its use as the main marker of coagulation status in patients with COVID-19.

Overall, the coagulation results did not show significant differences between COVID-19 stages, which is inconsistent with several previous studies.<sup>6–8,18</sup> This homogeneity of concentrations may be attributed to the characteristics of the population analyzed. Research shows that, unlike Chinese or European populations, African-Americans tend to have more coagulation disorders than Caucasians, and they are more likely than Asians to develop pulmonary thromboembolism.<sup>19</sup> In the Peruvian population, it has been demonstrated that despite introgression of Spanish genes during the conquest in the 16th century, the 90% of the genes of the population are from native American ancestry and part is autochthonous of the Peruvian population.<sup>20</sup> This composition could infer the immune response, the physiological changes, the coagulation state, and the severity of COVID-19. Further research is needed to delve deeper into the role of genetic variation in populations affected by COVID-19.

Previous studies have reported that age, male gender, comorbidities, thrombocytopenia, lymphopenia, and elevated inflammatory markers (i.e., lactate dehydrogenase, C-reactive protein, and D-dimer) are strongly associated with disease severity.<sup>21</sup> Our findings suggest that gender and comorbidities are not associated with disturbances in coagulation parameters, however, participant age does correlate with oxygen saturation, which affects the extent of lung injury.

This study had limitations. First, this study is single-center and changes in coagulation marker concentrations may vary from patient to patient depending on the sample sizes tested. Second, some comorbidities (i.e., psychiatric disorders) have not been evaluated and they may have an impact on the results because the drugs used can affect the results of the coagulation test, mainly those that depend on vitamin K. Third, the study was cross-sectional and did not track markers based on mortality rate or disease progression. Fourth, we did not assess serum levels of Von Willebrand factor, antithrombin, factor VIII, and fibrinogen degradation products, which are emerging as potential clinical biomarkers.<sup>22</sup> Finally, the sample size may be linked to a random distribution of coagulation markers within the study population.

In conclusion, this study has demonstrated alteration in the coagulation profile, mainly of fibrinogen and D-dimer, in Peruvian COVID-19 patients. However, it has not been shown differences in the concentration of coagulation markers, fibrinogen, and D-dimer were increased in more than half of the patients. In addition, changes in oxygen saturation and lung damage were associated with the most severe stages of COVID-19, but not with coagulation markers during the disease. In addition, changes in oxygen saturation and lung damage were associated with the most severe stages of COVID-19, but not with coagulation markers during the disease.

#### AUTHOR CONTRIBUTIONS

**Jeel Moya-Salazar:** conceptualization; data curation; formal analysis; investigation; methodology; resources; supervision; validation; writing – original draft; writing – review & editing. **Liliana Y. Córdor:** conceptualization; data curation; investigation; resources. **Nahomi Zuñiga:** formal analysis; writing – original draft. **Alexis Jaime-Quispe:** data curation; formal analysis; methodology. **Belén Moya-Salazar:** data curation; formal analysis; methodology. **Karina Chicoma-Flores:** validation; writing – original draft; writing – review & editing. **Betsy Cañari:** methodology; validation; writing – original draft. **Hans Contreras-Pulache:** project administration; writing – review & editing. All authors have read and approved the final version of the manuscript.

#### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

#### TRANSPARENCY STATEMENT

The lead author Jeel Moya-Salazar affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

#### DATA AVAILABILITY STATEMENT

Jeel Moya-Salazar confirms that she had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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