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# Clinical features and mortality predictors of older hospitalized patients with severe COVID-19 in Lima, Peru

Teodoro J. Oscanoa[1,2], José Amado-Tineo[1,3], Ricardo Ayala-García[3], Roxana Mamani-Quiroz[3], Javier Matta-Pérez[3], Ángel Ardiles-Melgarejo[3], Carlos Marcos-Hernández[3], Waldo Taype-Huamaní[3], Jefferson Rojas-Guimaray[3], Sthephany Matos-Santiváñez[3], Loyda Miranda-Chávez[3], Ana Deza-Sime[3], Moisés Apolaya-Segura[4,5], Roman Romero-Ortuno[6,7]

[1] Universidad Nacional Mayor de San Marcos, Facultad de Medicina, Lima, Perú; [2] Universidad de San Martin de Porres, Facultad de Medicina Humana, Hospital Almenara, ESSALUD, Lima, Perú; [3] Hospital Nacional Edgardo Rebagliati Martins, ESSALUD, Lima, Perú; [4] Universidad de San Martin de Porres, Centro de Investigación de Epidemiología Clínica y Medicina Basada en Evidencias, Lima, Perú; [5] Instituto de Evaluación de Tecnologías Sanitarias e Investigación (IETSI), ESSALUD, Lima, Perú; [6] Discipline of Medical Gerontology, School of Medicine, Trinity College Dublin, Dublin, Ireland; [7] Global Brain Health Institute, Trinity College Dublin, Dublin, Ireland

**Background and aims**. The objective of our study was to describe the clinical features of severe COVID-19 in older (compared to younger) hospitalized patients in a tertiary care centre in Lima, Peru.
**Methods**. A retrospective observational study was conducted that included patients hospitalized for severe COVID-19 between March and May 2020. The clinical features of the older group (age ≥ 60 years) were compared with those of younger patients (age < 60 years). A classification and regression tree (CRT) was computed to evaluate and visualize the main predictors of mortality in the total sample.
**Results**. The study included 339 patients, 213 in the older and 126 in the younger group. Mortality was higher in the older group, 76.5% vs. 42.1% ($p < 0.001$). Within the older group, factors associated with higher mortality were older age ($p = 0.006$), hypertension ($p = 0.039$) and obesity ($p = 0.034$). The older group had higher D-Dimer ($p = 0.044$), C-reactive protein (CRP) ($p = 0.031$) and total bilirubin ($p = 0.007$); and lower lymphocyte count ($p = 0.003$), albumin ($p < 0.001$) and Alanine aminotransferase (ALT) ($p = 0.003$). In the older group, CRT showed that the best predictor of mortality was the chest Computed Tomography Total Severity Score, with those with a score over 12 having 85.2% mortality.
**Conclusions**. Mortality in patients hospitalized with severe COVID-19 was high, especially in older patients. In the latter, mortality was best predicted by an objective radiological marker of chest disease.

**Key words**: SARS-CoV-2, COVID-19, mortality, older age, risk factors

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**Correspondence**
Teodoro J. Oscanoa
Facultad de Medicina, Universidad Nacional Mayor de San Marcos. Drug Safety Research Center, Facultad de Medicina Humana, Universidad de San Martín de Porres. Hospital Almenara, ESSALUD, Lima, Perú. Av. Alameda del Corregidor 1502, La Molina 15024. Lima, Perú. Email: tjoscanoae2017@gmail.com; toscanoae@usmp.pe

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## INTRODUCTION

Before the COVID-19 pandemic, older age was a recognised risk factor for greater severity and mortality in infections, and SARS-CoV-2 infection has not been an exception. Factors that may confer older people greater

susceptibility to severe COVID-19 include a previous pro-inflammatory state, higher expression and activity of NLRP3 (cryopyrin) in immune cells, higher viral load in the nasopharynx, and higher levels of ACE2 in the lungs [1]. In the meta-analysis by Sighal et al., which included 46 studies with 13,624 patients aged ≥ 60 years, 51% had severe disease and 22% progressed to critical disease; the most frequent comorbidities were hypertension (48%), diabetes mellitus (22%) and cardiovascular diseases (19%); common symptoms were fever (83%), cough (60%) and dyspnea (42%); and oxygen support and mechanical ventilation were required in 84 and 21%, respectively [2]. In their meta-analytic study on COVID-19 mortality, Qiu et al. found that 67% of the deceased had a mean age of 70 years [3]. It should be noted that both meta-analyses included studies from the USA, Asia and Europe, but none from Latin America.

Until July 22, 2021, three Latin American countries – Peru, Mexico and Ecuador – were among the 10 with the highest COVID-19 fatality in the world, with mortality proportions of 9.3, 8.8 and 6.4%, respectively [4]. During 2020 in Peru, COVID-19 deaths accounted for 74.1% (95% CI 73.9-74.7%) of total excess deaths in those aged ≥ 60 years, with even higher mortality in the region of Lima [5]. The causes of high COVID-19 mortality in Peru are complex and against a backdrop of low public expenditure on health (3% of the Gross Domestic Product) and a low number of acute hospital beds (29 per million inhabitants) compared to other countries [6]. However, whether the clinical characteristics of severe COVID-19 in people over 60 years of age were different compared to younger people remained to be elucidated.

To further understand factors associated with COVID-19 mortality in Peru, the present study aimed to describe the clinical features and associated mortality of severe COVID-19 in hospitalized older patients in a tertiary care hospital in Lima, Peru.

## MATERIALS AND METHODS

This was a retrospective, observational study in the Hospital Nacional Edgardo Rebagliati Martins of EsSalud, a tertiary care hospital in Lima, Peru. We reviewed the medical records of hospitalized patients between March and May 2020 who were diagnosed with severe SARS-CoV-2 infection, as confirmed by reverse transcription polymerase chain reaction. Severe COVID-19 was defined as having a peripheral oxygen saturation on admission of less than 93% (on room air) and/or pulmonary involvement greater than 30% on the total severity score (TSS) in the pulmonary tomography [7].

### Inclusion criteria

Adults (aged ≥ 18 years) were included. The sample was divided into two age groups: older (≥ 60 years old) and younger (< 60 years old).

### Study variables

In the review of medical records, patient data was collected including age, sex, history of type 2 diabetes mellitus, arterial hypertension, obesity and other comorbidities, admission symptomatology and discharge outcome. The Combined Age Charlson Comorbidity Index CA-CCI [8] was calculated (see Table I). Additional data collected included information on thoracic computerized tomography (CT) scans, blood lymphocyte count, serum biomarker levels (see Table II) and treatment measures (antiviral, anticoagulation, antibiotic, corticosteroid therapy, and respiratory support) (see Table III).

### Statistical analysis

The mean and standard deviation (SD), as well as the frequency and percentage, were used to describe data. For continuous variables, comparisons between two independent groups were made using the Student's t test for normally distributed variables and the Mann-Whitney U test for those without a normal distribution, while for nominal data we used the Chi-square test.

Statistical comparisons were supplemented with a Classification and Regression Tree (CRT) to evaluate and visualize the main predictors of mortality in the total sample. The technique employed was an exhaustive Chi-square automatic interaction detection method (CHAID) to evaluate the main predictors of mortality among all collected characteristics.

All statistical analyses were computed with SPSS version 27. The level of statistical significance was set as $p < 0.05$.

### Ethical approval

This study was approved by the Research Ethics Committee for COVID-19 by expedited review on 05-18-2020 in accordance with resolution No. 42-IETSI-ESSALUD-2020. The necessary strategies were implemented to maintain the privacy of patient information.

## RESULTS

The study included 339 patients with a mean age of 63.6 (SD 15.3) years (range 23 to 99 years), and 72.3% were male. Overall, 76.5% of the older sample died (163 deceased and 50 survivors), compared to 42.1% of the younger sample (53 deceased and 73 survivors) ($p < 0.001$). Table I shows a comparison of the clinical characteristics between the older and younger groups, and a comparison of the clinical characteristics between older patients who died

**Table I.** Clinical features of severe COVID-19 in hospitalized patients in a Hospital in Lima, Peru.

| | Total | | Older group (> 60 years) | | Younger group (< 60 years) | | P | Deceased (> 60 years) | | Survivors (> 60 years) | | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Demographics** | n = 339 | % or SD | n = 213 | % or SD | n = 126 | % or SD | | n = 163 | % or SD | n = 50 | % or SD | |
| Mean age (years) | 63.6 | 15.3 | 72.8 | 9.5 | 47.9 | 9.0 | < 0.001 | 73.8 | 9.5 | 69.6 | 9.1 | 0.006 |
| Male | 245 | 72.3 | 153 | 71.8 | 92 | 73.0 | 0.813 | 119 | 73.0 | 34 | 68 | 0.492 |
| Female | 94 | 27.7 | 60 | 28.2 | 34 | 27.0 | 0.813 | 44 | 27.0 | 16 | 32 | 0.492 |
| **Comorbidities** | | | | | | | | | | | | |
| Hypertension | 132 | 39.0 | 104 | 48.8 | 28 | 22.2 | < 0.001 | 86 | 52.8 | 18 | 36 | 0.039 |
| Type 2 diabetes | 80 | 23.6 | 61 | 28.6 | 19 | 15.1 | 0.005 | 51 | 31.3 | 10 | 20 | 0.123 |
| Obesity | 77 | 22.7 | 33 | 15.5 | 44 | 34.9 | < 0.001 | 30 | 18.4 | 3 | 6 | 0.034 |
| Heart failure | 4 | 1.2 | 4 | 1.9 | 0 | 0 | | 3 | 1.8 | 1 | 2 | 0.942 |
| Chronic kidney disease | 22 | 6.5 | 19 | 8.9 | 3 | 2.4 | 0.018 | 18 | 11.0 | 1 | 2 | 0.050 |
| Cancer | 10 | 3.0 | 7 | 3.3 | 3 | 2.4 | 0.943 | 3 | 1.8 | 4 | 8 | 0.033 |
| Dementia | 11 | 3.2 | 11 | 5.2 | 0 | 0 | 0.010 | 9 | 5.5 | 2 | 4 | 0.934 |
| Coronary heart disease | 11 | 3.2 | 10 | 4.6 | 1 | 0.8 | 0.050 | 8 | 4.9 | 2 | 4 | 0.959 |
| Chronic lung disease | 11 | 3.2 | 11 | 5.2 | 0 | 0 | 0.010 | 8 | 4.9 | 3 | 6 | 0.945 |
| Dyslipidemia | 4 | 1.2 | 2 | 0.9 | 2 | 1.6 | 0.960 | 1 | 0.6 | 1 | 2 | 0.951 |
| Cerebrovascular disease | 6 | 1.8 | 6 | 2.8 | 0 | 0 | | 4 | 2.5 | 2 | 4 | 0.923 |
| Persistent atrial fibrillation | 5 | 1.5 | 4 | 1.9 | 1 | 0.8 | 0.946 | 4 | 2.45 | 0 | 0 | |
| Hypothyroid | 5 | 1.5 | 1 | 0.5 | 4 | 3.2 | 0.893 | 1 | 0.6 | 0 | 0 | |
| Liver disease | 1 | 0.3 | 1 | 0.5 | 0 | 0 | | 1 | 0.6 | 0 | 0 | |
| History of tuberculosis/ bronchiectasis | 9 | 2.7 | 6 | 2.8 | 3 | 2.4 | 0.998 | 5 | 3.1 | 1 | 2 | 0.690 |
| Parkinson's disease | 4 | 1.2 | 4 | 1.9 | 0 | 0 | | 3 | 1.8 | 1 | 2 | 0.993 |
| Mean combined Age Charlson Comorbidity Index (CA-CCI) | 2.6 | 1.9 | 3.6 | 1.5 | 0.9 | 1.1 | < 0.001 | 3.69 | 1.47 | 3.22 | 1.6 | 0.055 |
| **Clinical symptoms** | | | | | | | | | | | | |
| Fever | 201 | 59.3 | 115 | 54.0 | 86 | 68.3 | 0.001 | 86 | 52.8 | 29 | 58 | 0.517 |
| Cough | 187 | 55.2 | 110 | 51.6 | 77 | 61.1 | 0.091 | 81 | 49.7 | 29 | 58 | 0.305 |
| Dyspnoea | 253 | 74.6 | 156 | 73.2 | 97 | 77.0 | 0.445 | 119 | 73.0 | 37 | 74 | 0.906 |
| Diarrhoea | 28 | 8.3 | 15 | 7.0 | 13 | 10.3 | 0.290 | 9 | 5.5 | 6 | 12 | 0.118 |
| Odynophagia | 39 | 11.5 | 23 | 10.8 | 16 | 12.7 | 0.597 | 15 | 9.2 | 8 | 16 | 0.635 |
| Headache | 17 | 5.0 | 6 | 2.8 | 11 | 8.7 | 0.016 | 4 | 2.5 | 2 | 4 | 0.923 |
| Anosmia | 4 | 1.2 | 4 | 1.9 | 0 | 0 | 0.122 | 3 | 1.8 | 1 | 2 | 0.993 |
| Chest pain | 11 | 3.2 | 6 | 2.8 | 5 | 4.0 | 0.564 | 5 | 3.1 | 1 | 2 | 0.958 |
| **Mortality** | 216 | 63.7 | 163 | 76.5 | 53 | 42.1 | < 0.001 | | | | | |

versus survived. Table II shows the same comparisons for laboratory and radiological findings, and Table III for treatments received. As Table I shows, older and younger had a similar proportion of male sex (72-73%). Sex was not associated with mortality in the older group (p = 0.492).

### Comorbidities

As clinically expected, the mean CA-CCI was significantly higher in the older group (p < 0.001). For example, there were higher proportions of hypertension (p < 0.001), type 2 diabetes (p = 0.005), chronic kidney

disease (p = 0.018), chronic lung disease (p = 0.010), and dementia (p = 0.010) in the older group. However, the prevalence of obesity was higher in the younger group (p < 0.001) (Tab. I).

Within the older group, factors that were associated with mortality were advancing age (p = 0.006), hypertension (p = 0.039), and obesity (p = 0.034) (more frequent in the deceased). The number of older people with a diagnosis of cancer was small, but cancer seemed less frequent in the deceased group (p = 0.033).

### Clinical symptoms

Symptoms that were significantly less frequent in the older group were fever (p = 0.001) and headache (p = 0.016). Within the older group, none of the recorded symptoms were associated with mortality on correlation analyses (Tab. I).

### Laboratory and radiological findings (Tab. II)

The older group had lower lymphocyte count (p = 0.003), and higher D-Dimer (p = 0.044), CRP (p = 0.031), and total bilirubin (p = 0.007) levels; but they had lower albumin (p < 0.001) and ALT levels (p = 0.003) compared to the younger group. Within the older group, mortality was associated with higher TSS score (p = 0.002), higher D-Dimer (p = 0.031), higher LDH (p = 0.004), and lower albumin (p = 0.007).

### Treatments (Tab. III)

Older people seemed less likely to receive mechanical ventilation (p = 0.014), but within the older group those who received it had higher mortality (p = 0.008). Older people who died had almost universally received antibiotic (p = 0.005), in a greater proportion than older survivors. Deceased older people were more likely to have received a steroid (p = 0.019). Otherwise, there seemed to be no significant treatment differences between younger and older groups, and between deceased and alive older patients.

### Classification and regression tree

The classification and regression tree included as predictors all the features reported in Tables I, II and III, with mortality as a target outcome. The age group (younger *versus* older) was not forced as the first variable in the model. Results are presented in Figure 1. In the older group, the best predictor of mortality was the CT Total Severity Score, with those with a score over 12 having 85.2% mortality. Among the latter, those who received mechanical ventilation had 93.0% mortality. In

**Table II.** Laboratory and radiological findings of patients with COVID-19 in a Hospital in Lima, Peru.

| | Total | | | Older group (≥ 60 years) | | | Younger group (< 60 years) | | | P | Deceased (≥ 60 years) | | | Survivors (≥ 60 years) | | | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | N | Mean | SD | | N | Mean | SD | N | Mean | SD | |
| Total severity score (TSS, 0-20) | 332 | 13.2 | 4.1 | 208 | 13.3 | 4.1 | 124 | 12.9 | 4.0 | 0.335 | 159 | 13.8 | 4.2 | 49 | 11.8 | 3.5 | 0.002 |
| Lymphocyte count ($\times 10^9$/L) | 316 | 1111.8 | 1026.2 | 201 | 981.2 | 929.9 | 115 | 1340.1 | 1144.6 | 0.003 | 157 | 984.7 | 1027.7 | 44 | 968.6 | 436.0 | 0.915 |
| D-dimer ug/ml | 251 | 6.3 | 10.0 | 153 | 7.3 | 10.9 | 98 | 4.7 | 8.5 | 0.044 | 116 | 8.4 | 11.5 | 37 | 4.0 | 8.0 | 0.031 |
| Fibrinogen mg/dl | 288 | 790.4 | 247.8 | 185 | 785.4 | 262.91 | 103 | 799.4 | 219.0 | 0.647 | 144 | 777.6 | 263.2 | 41 | 813.1 | 263.3 | 0.447 |
| Ferritin ng/mL | 139 | 1321.0 | 1239.4 | 77 | 1328.7 | 1273.9 | 62 | 1311.3 | 1205.4 | 0.935 | 57 | 1384.1 | 1287.8 | 20 | 1170.9 | 1252.3 | 0.523 |
| Aspartate aminotransferase (AST, U/L) | 299 | 77.6 | 111.6 | 187 | 69.7 | 55.6 | 112 | 90.8 | 167.3 | 0.115 | 145 | 71.4 | 59.3 | 42 | 63.8 | 40.3 | 0.433 |
| C-reactive protein (mg/L) | 244 | 18.8 | 11.0 | 150 | 20.0 | 10.9 | 94 | 16.9 | 11.1 | 0.031 | 109 | 20.8 | 10.4 | 41 | 18.0 | 11.9 | 0.158 |
| Lactate dehydrogenase (LDH) U/L | 267 | 457.4 | 244.0 | 166 | 442.1 | 169.7 | 101 | 482.5 | 331.3 | 0.190 | 127 | 467.5 | 179.81 | 39 | 359.5 | 93.5 | 0.004 |
| Total bilirubin (g/dl) | 288 | 0.7 | 0.6 | 178 | 0.8 | 0.7 | 110 | 0.6 | 0.3 | 0.007 | 136 | 0.9 | 0.7 | 42 | 0.6 | 0.28 | 0.056 |
| ProBNP (pg/ml) | 48 | 2747.1 | 7234.8 | 33 | 3810.4 | 8532.3 | 15 | 408.0 | 890.7 | 0.133 | 22 | 5457.7 | 10111.8 | 11 | 515.6 | 572.9 | 0.118 |
| Troponin ng/L | 204 | 0.04 | 0.15 | 131 | 0.05 | 0.18 | 73 | 0.02 | 0.04 | 0.135 | 103 | 0.06 | 0.19 | 28 | 0.05 | 0.16 | 0.905 |
| Albumin (g/dl) | 287 | 3.5 | 0.5 | 178 | 3.4 | 0.5 | 109 | 3.7 | 0.4 | < 0.001 | 139 | 3.4 | 0.5 | 39 | 3.6 | 0.5 | 0.007 |
| $SatO_2$ (%) | 281 | 89.7 | 9.4 | 175 | 89.6 | 8.7 | 106 | 90.0 | 10.5 | 0.694 | 139 | 89.0 | 9.3 | 36 | 91.6 | 5.7 | 0.112 |
| Alanine aminotransferase (ALT, U/L) | 299 | 74.5 | 80.9 | 187 | 61.4 | 49.0 | 112 | 96.4 | 112.9 | 0.003 | 145 | 60.8 | 49.3 | 42 | 63.4 | 48.4 | 0.762 |

**Table III.** Treatments in patients with severe COVID-19 in a Hospital in Lima, Peru.

| | Total | | Older group (≥ 60 years) | | Younger group (< 60 years) | | P | Deceased (≥ 60 years) | | Survivors (≥ 60 years) | | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n = 339 | % | n = 213 | % | n = 126 | % | | n = 163 | % | n = 50 | % | |
| Anti-COVID-19 therapy | | | | | | | | | | | | |
| Hydroxychloroquine + azithromycin | 250 | 73.8 | 155 | 72.8 | 95 | 75.4 | 0.787 | 116 | 71.2 | 39 | 78 | 0.567 |
| None | 20 | 5.9 | 12 | 5.6 | 8 | 6.4 | 0.787 | 10 | 6.1 | 2 | 4 | 0.567 |
| Other (hydroxychloroquine, azithromycin, oseltamivir, ivermectin) | 69 | 20.3 | 46 | 21.6 | 23 | 18.3 | 0.460 | 37 | 22.7 | 9 | 18 | 0.480 |
| Antibiotic | | | | | | | | | | | | |
| No | 17 | 5 | 10 | 4.7 | 7 | 5.6 | | 4 | 2.5 | 6 | 12 | |
| Yes | 322 | 95 | 203 | 95.3 | 119 | 94.4 | 0.726 | 159 | 97.5 | 44 | 88 | 0.005 |
| Corticosteroid | | | | | | | | | | | | |
| No | 153 | 45.1 | 97 | 45.5 | 56 | 44.4 | | 67 | 41.1 | 30 | 60 | |
| Yes | 186 | 54.9 | 116 | 54.5 | 70 | 55.6 | 0.845 | 96 | 58.9 | 20 | 40 | 0.019 |
| Anticoagulation therapy | | | | | | | | | | | | |
| No | 155 | 45.7 | 94 | 44.1 | 61 | 48.4 | | 67 | 41.1 | 27 | 54 | |
| Yes | 184 | 54.3 | 119 | 55.9 | 65 | 51.6 | 0.444 | 96 | 58.9 | 23 | 46 | 0.108 |
| Mechanical ventilation | | | | | | | | | | | | |
| No | 201 | 59.3 | 137 | 64.3 | 64 | 50.8 | | 97 | 59.5 | 40 | 80 | |
| Yes | 138 | 40.7 | 76 | 35.7 | 62 | 49.2 | 0.014 | 66 | 40.5 | 10 | 20 | 0.008 |

the younger group, the main predictor of mortality was receiving mechanical ventilation (64.5% mortality).

The CRT was repeated without entering treatment-related factors and the result obtained is reported in Figure 2. According to this model, in the older group the main predictor of mortality was still TSS, and in those above the TSS cutoff of 12, the lack of fever on presentation was associated with 91.9% mortality. In the younger group, a CRP higher than 20 was associated with higher mortality (56.9%).

## DISCUSSION

The present study, conducted in a tertiary care centre in Lima, Peru, found that mortality in severe COVID-19 was higher in older people and was associated with advancing age, hypertension and obesity. The older group had higher D-Dimer, C-reactive protein (CRP) and total bilirubin levels; and lower lymphocyte count, albumin and ALT levels compared to the younger group. In the older group, the best predictor of mortality was the CT Total Severity Score, with those with a score over 12 having 85.2% mortality. Among the latter, the lack of fever on presentation was associated with even higher mortality.

The first case of COVID-19 in Peru was reported in Lima on March 6, 2020; and the first death occurred on March 19 [9]. In the present study, as clinically expected, we found that mortality was higher in older patients. Overall mortality was high, but this should be seen in the light of the fact that our study only included hospitalized patients with severe COVID-19. Comparatively, Yang et al. reported the mortality of patients with severe COVID-19 hospitalized between Dec 24, 2019 to Jan 26, 2020 in Wuhan Jin Yin-tan hospital (Wuhan, China), which was 74% in patients over 60 years old [10]. In a study carried out between 13 January to 12 February 2020 in the Tongji Hospital in Wuhan, China, Cheng et al. reported 83% mortality in people over 60 years of age [11]. In France, Guillon et al. found that mortality in COVID-19 patients admitted to ICU was 36.3% and 62.5% in those older than 65-69 and ≥ 80 years, respectively; while the mortality at 6 months was 43.3% and 72.1%, respectively [12]. In the UK, Chinnadurai et al. reported a mortality of 40% in a study with patients admitted between March 23, 2020 and April 30, 2020, where the median age was 74 years and frailty was identified as a significant predictor of mortality [13]. In a meta-analysis of 46 studies published between December 2019 to May 3rd, 2020, Sighal et al. found that mortality in those aged > 60 years was 15% (5-26%) in China and 11% (3-20%) outside China; however, in this meta-analysis only 51% had severe infection [2]. In another meta-analysis that included 33 studies published between December 2020 and 24 April 2020, Macedo et al. found that the mortality in general patients admitted to hospital was 11% (8-17%), but in patients with

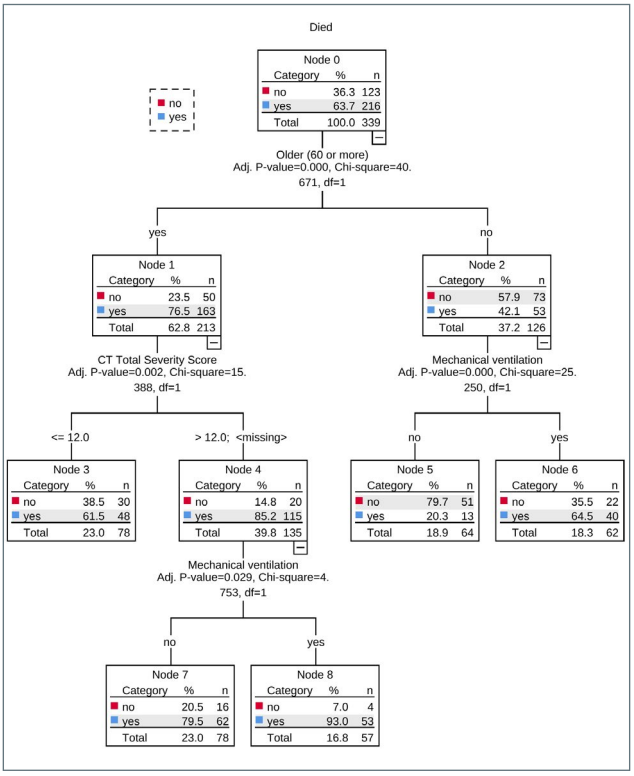


**Figure 1.** Results of the Classification and Regression Tree predicting mortality in the total sample. Predictors entered: Older (60 or more), Male sex, Hypertension, Type 2 Diabetes, Obesity, Chronic respiratory disease, Chronic heart failure, Chronic kidney disease, Cancer, Dementia, Chronic ischaemic heart disease, Dyslipidemia, Stroke, Atrial Fibrillation, Parkinson's disease, Hypothyroidism, Liver cirrhosis, Tuberculosis, Charlson Comorbidity Index (age adjusted), O2 saturation (on air), Fever, Cough, Diarrhoea, Headache, Sore throat, Chest pain, Loss of smell, Shortness of breath, CRP, Lymphocyte count, Bilirubin, Albumin, AST, LDH, Troponin, NT-pro-BNP, D-dimer, ALT, Fibrinogen, Ferritin, CT Total Severity Score, hydroxychloroquine + azithromycin, No anti-covid treatment, Other anti-covid treatment, Antibiotic, Steroid, Anticoagulant, Mechanical ventilation. Growing method: CHAID. Dependent variable: Died.

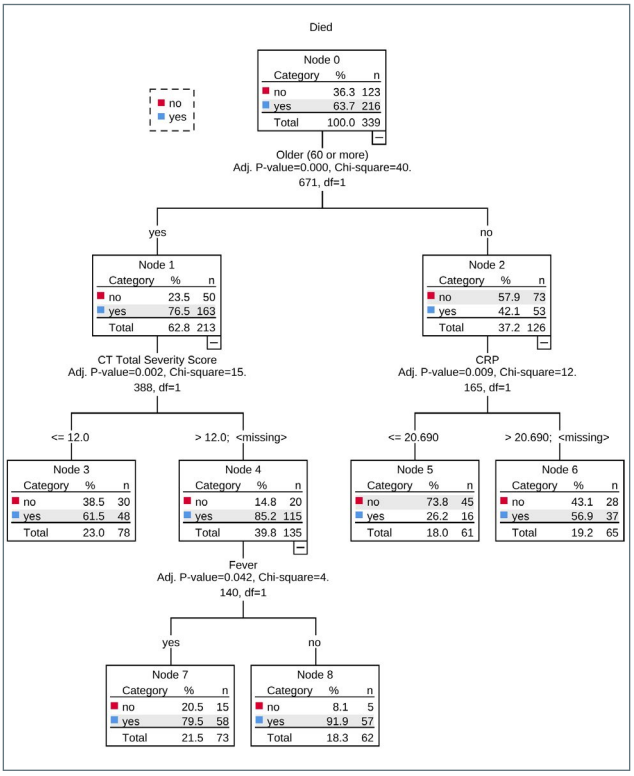


**Figure 2.** Results of the Classification and Regression Tree predicting mortality in the total sample. Predictors entered: Older (60 or more), Male sex, Hypertension, Type 2 Diabetes, Obesity, Chronic respiratory disease, Chronic heart failure, Chronic kidney disease, Cancer, Dementia, Chronic ischaemic heart disease, Dyslipidemia, Stroke, Atrial Fibrillation, Parkinson's disease, Hypothyroidism, Liver cirrhosis, Tuberculosis, Charlson Comorbidity Index (age adjusted), O2 saturation (on air), Fever, Cough, Diarrhoea, Headache, Sore throat, Chest pain, Loss of smell, Shortness of breath, CRP, Lymphocyte count, bilirubin, Albumin, AST, LDH, Troponin, NT-pro-BNP, D-dimer, ALT, Fibrinogen, Ferritin, CT Total Severity Score. Growing method: CHAID. Dependent variable: Died.

critical illness it was 41% (31-51%); however, only in 13/33 studies the mean age was over 60 years [14]. In Brazil, Mascarello et al. reported a mortality of 32% in hospitalized and ICU older patients (> 60 years) admitted between February 28th, 2020 and September 1st, 2020 [15]. For the contextual interpretation of mortality from COVID-19, it is necessary to take into account that mortality in general and especially in older people decreased after June 17, 2020 when dexamethasone was added to the standard therapy [16]. Li Guandi et al. analyzed a cohort of older (> 70 years) patients from China, European regions, and North America who did not receive dexamethasone and found that mortality was 75% [17].

The finding that sex was not associated with mortality in the older group is consistent with previous reports that COVID-19 mortality is characterized by an increased in mortality in men up to 60-69 years, after which this difference decreases, becoming minimal after the age of 80 [18-20]. This trend could be consistent with a survival effect, which leaves the healthiest men in the sample [21]. We found that the lack of fever on presentation together with a CT TSS over 12 was associated very high mortality (92%) in the older group. In a meta-analysis that included 15 studies with patients with a mean age of 64 years, Shi et al. found no relationship between the presence of fever and mortality [22]. In another meta-analysis that included 13 studies with patients with a mean age of 49 years, Zheng et al. found that the presence of fever (temperature ≥ 37.3°C) was significantly less

frequent in the critical / deceased groups [23]. Tan et al. studied patients who died from COVID-19 and found that compared to younger patients, older patients (> 70 years) had a lower frequency of fever [24]. Recently, other studies have confirmed that the frequency of fever in COVID-19 is lower in older people [25-27]. This could be explained by the hypothesis that in older people with severe COVID-19 the cellular hyper-functions and systemic hyper-inflammation may lead to cellular exhaustion, such as exhaustion of lymphocytes (lymphopenia) and loss of functions at late stages [28].

In the present study, we found that CT-TSS > 12 was the best predictor of mortality in hospitalized older patients with severe COVID-19. The CT-TSS has recently been validated with good interobserver agreement [29], and has also been used in Peru with similar results [30]. Other chest CT severity scales have been shown to be good predictors of mortality in COVID-19. In China, Hu et al. found an association between a score > 14 (range: 0-20) with mortality from COVID-19 in a group of patients with a mean age of 67 years [31]. Using another semi-quantitative CT severity score (range: 0-24), Abbasi et al. found that in patients with a median age of 58 years, a score > 10 had a sensitivity of 84% and specificity of 66% for in-hospital mortality from COVID-19 [32]. In a group of patients with a mean age of 63, Francone et al. found that a CT score of ≥ 18 (range 0-25) was associated with increased mortality on both univariate and multivariate analyses [33]. Although CT thorax is a good predictor of mortality in COVID-19, it has the potential disadvantages that it is not available in all hospital emergency departments, may increase staff exposures, and requires transport of potentially unstable patients out of critical care areas [32].

In our study, in older patients the mean lymphocyte and leukocyte counts were lower compared to younger people. In a meta-analytic study, lymphopenia and leukopenia were found in 52 and 20% of older people, respectively [2]. Lymphopenia has been associated with mortality, especially in older people [34-36]. Possible mechanisms of lymphopenia in severe COVID-19 may include the fact that the lymphocyte expresses ACE2 and this is directly affected by the virus, interleukin (IL) -6 and other pro-inflammatory cytokines to produce lymphocyte apoptosis [37,38], pulmonary infiltration [39], and inhibition of lymphocytes by metabolic molecules produced by metabolic disorders, such as hyperlactic acidemia [40]. Another mechanism could be the reduction of lymphatic organs such as the thymus or spleen, and impaired thymic function in older patients [41]. CD3 +, CD4 +, and CD8 + T cell counts are significantly lower in patients with severe COVID-19 compared to those with mild disease [37,42]. In older people, a process known as immunosenescence that increases susceptibility of older adults to infection must be added to the mechanisms described; in addition, a sub-clinical chronic low-grade state of systemic inflammation called inflammaging, characterized by elevated serum levels of acute phase proteins (e.g. C-reactive protein) and pro-inflammatory cytokines (e.g. TNF-α, IL-6, and IL-8) could also be implicated [43,44].

In the present study, we found that D-dimer levels were higher in older people. D-dimer is produced during fibrin breakdown and is a marker of fibrinolytic activity, and has been used to screen patients with venous thromboembolism, but it also increases in inflammation and can predict a poor outcome in sepsis. It has been reported that 38% of older patients with COVID-19 had increased D-dimer, but no patients were diagnosed with venous thromboembolism during the hospitalization [45]. In the context of severe COVID-19, high D-dimer levels seem to represent a severe inflammatory state together with proinflammatory cytokines, in which it has been observed that the alveolar hemostatic balance is shifted towards a predominance of prothrombotic activity [46]. D-dimer as a prognostic marker of mortality, especially in older people, could be related to the inflammation progression and the presence of hypoxia, which results in an overall hypercoagulable state or even disseminated intravascular coagulation with eventual death in patients with severe SARS-CoV-2 infection [3].

We found that older patients presented with lower concentrations of albumin and lower ALT levels compared to those under 60 years of age. A meta-analytic study found that lower serum albumin concentrations were significantly associated with disease severity and adverse outcomes in COVID-19 patients, although the mean age of the patients studied was 53 years [47]. The finding that older people had lower levels of albumin and ALT would be in favor of the hypothesis that in severe COVID-19 there is risk of liver dysfunction.

With a trend towards statistical significance (p = 0.055), we found that the Combined Age-CCI (CA-CCI) score seemed higher in older people who died from severe COVID-19; significant findings in this direction have been described in two studies in South Korea [48,49]. The Charlson Comorbidity Index (CCI) was developed in 1987 and validated as a measure of 1-year mortality risk and burden of disease [50]. In 1994, the Combined Age-CCI (CA-CCI) score was validated, which was added to age as an independent predictor of mortality [8]. In a meta-analytic study, Tuty-Kuswardhani et al. found that a CCI score of ≥ 3 was prognostically associated with mortality and associated with a composite of poor outcomes in COVID-19 patients [51]. On the other hand, in the present study the frequency of obesity was higher in patients under 60 years of age; in a recent meta-analysis it was found that obesity is associated with higher incidence of

intensive care unit admission, invasive mechanical ventilation and in-hospital mortality [35,52].

### Limitations

The present study has limitations, including its single centre, retrospective, observational design. When interpreting our findings, it should be noted that the group of patients described corresponds to the first COVID-19 wave in Lima, Peru, in 2020. Due to the acute pressures on the health system, some patients did not have a laboratory test or pulmonary CT. The results of the study cannot be extrapolated to the population of Peru because the study was carried out in a reference hospital, where only serious patients arrived, most of whom were referred from lower-level hospitals. The present study was focused on highlighting the clinical characteristics of older adults; however, it was not possible to study the characteristics of virus itself, and it has later been shown that different SARS-CoV-2 variants could be related with different severity and mortality (53). In addition, we did not collect electrocardiographic information from the medical charts, which could be relevant in arrhythmia-related deaths potentially caused by medications that increase the risk of QTc interval prolongation [54].

In conclusion, mortality in patients hospitalized with severe COVID-19 was high. Patients older than 60 years had higher mortality than those younger than 60 years. In older patients, mortality was best predicted by an objective radiological marker of chest disease.

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### Conflict of interest statement

The Authors declare no conflict of interest.

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### Author contributions

The Authors contributed equally to the work.

### Ethical consideration

This study was approved by the Institutional Ethics Committee (if applicable, please specify name of the Institution ESSALUD-Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru.) (approval number/protocol number resolution No. 42-IETSI-ESSALUD-2020.).

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

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