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# Clinical characteristics and in-hospital mortality of patients with COVID-19 in Chile: A prospective cohort study

Francisco J. González[1,2] | Fabián A. Miranda[1,2,3] | Sebastián M. Chávez[1,2,3] | Abraham I. Gajardo[1,3] | Ariane R. Hernández[1,2,3] | Dannette V. Guiñez[1,2,3] | Gonzalo A. Díaz[1,2,3] | Natalia V. Sarmiento[1,2] | Fernando E. Ihl[1,2] | María A. Cerda[1,2,3] | Camila S. Valencia[1,2] | Rodrigo A. Cornejo[1,3]

[1]Department of Internal Medicine, University of Chile Clinical Hospital, University of Chile, Santiago, Chile

[2]Internal Medicine Section, University of Chile Clinical Hospital, University of Chile, Santiago, Chile

[3]Critical Care Unit, University of Chile Clinical Hospital, University of Chile, Santiago, Chile

**Correspondence**
Francisco J. González, Internal Medicine Department, University of Chile Clinical Hospital, University of Chile, Santos Dumont 999, Independencia, Santiago 8380000, Chile.
Email: fgonzalez@hcuch.cl

## Abstract

**Aims of this study:** To describe the Latin American population affected by COVID-19, and to determine relevant risk factors for in-hospital mortality.

**Methods:** We prospectively registered relevant clinical, laboratory, and radiological data of adult patients with COVID-19, admitted within the first 100 days of the pandemic from a single teaching hospital in Santiago, Chile. The primary outcome was in-hospital mortality. Secondary outcomes included the need for respiratory support and pharmacological treatment, among others. We combined the chronic disease burden and the severity of illness at admission with predefined clinically relevant risk factors. Cox regression models were used to identify risk factors for in-hospital mortality.

**Results:** We enrolled 395 adult patients, their median age was 61 years; 62.8% of patients were male and 40.1% had a Modified Charlson Comorbidity Index (MCCI) ≥5. Their median Sequential Organ Failure Assessment (SOFA) score was 3; 34.9% used a high-flow nasal cannula and 17.5% required invasive mechanical ventilation. The in-hospital mortality rate was 14.7%. In the multivariate analysis, were significant risk factors for in-hospital mortality: MCCI ≥5 (HR 4.39, $P < .001$), $PaO_2/FiO_2$ ratio ≤200 (HR 1.92, $P = .037$), and advanced chronic respiratory disease (HR 3.24, $P = .001$); pre-specified combinations of these risk factors in four categories was associated with the outcome in a graded manner.

**Conclusions and clinical implications:** The relationship between multiple prognostic factors has been scarcely reported in Latin American patients with COVID-19. By combining different clinically relevant risk factors, we can identify COVID-19 patients with high-, medium- and low-risk of in-hospital mortality.

## 1 | INTRODUCTION

The epidemiological aspects, clinical characteristics, risk factors, and outcomes of COVID-19 have mostly been reported in China, Europe, and the United States.[1-4] In relation to this, most of the patients in the reports are men with a median age close to 60 years of age and suffer more than one comorbidity; mainly hypertension, obesity and diabetes.

Clinical findings most frequently observed are the respiratory features, but extrapulmonary manifestations are also documented,[5,6] such as coagulopathy, acute kidney injury (AKI), and myocardial injury, amongst others, which can be explained by the direct action of SARS-CoV2 infection on the endothelium.[5]

Older age, the severity of the disease and elevation of biomarkers such as D-dimer on admission increase the lethality rate,[1-4] especially those requiring mechanical ventilation, with a mortality rate of 40.5% (95% CI 31.2:40.6).[7]

Latin America is one of the most affected regions, presenting one of the highest mortality rate globally, being highest in South America with 9.2% case fatality ratio.[8] This excess of mortality has been associated with precarious health services, economic instability, informal jobs and a social inequity that deepened in the health crisis.[9] However, there is a severe lack of data from this region despite being more affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) than other ethnicities.[10] Chile was one of the last countries to be affected by the disease in Latin America. Nevertheless, it experienced rapid transmission and unrelenting spread, with >16 000 cases per million inhabitants, making it the most affected country in Latin America and the fourth worldwide.[11]

From a clinical viewpoint, combining different risk factors, such as disease burden, with SARS-CoV-2 severity might improve our understanding of patients' findings and facilitate clinicians' decision making to deliver the most appropriate care.

We analysed a Latin American cohort of Chilean patients with COVID-19 who were hospitalised during the first 100 days of the pandemic, focusing on their risk of in-hospital mortality, and examined the risk factors associated with SARS-CoV-2 infection upon admission.

### What's known

Clinical characteristics, pulmonary and extrapulmonary manifestations of COVID-19 as well as risk factors for adverse outcomes in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection who require hospitalisation have been reported mainly in the United States, China, and Europe. Although the Latino population is at an increased risk of adverse outcomes, and Latin America is one of the most affected regions by COVID-19, the clinical characteristics and outcomes of hospitalised patients have been scarcely reported in this population. In contrast, although several risk factors for mortality have been identified in patients with COVID-19, their role and interpretation in the clinical context are unknown.

### What's new

To our knowledge, we present one of the first prospective cohort studies in Latin America. In-hospital mortality risk was similar compared with other cohorts (14.7%), despite higher severity measured by multiple known prognostic scales, such as Acute Physiology And Chronic Health Evaluation (APACHE) II, Sequential Organ Failure Assessment (SOFA), Quick SOFA (qSOFA), and Confusion—Uremia—high Respiratory Rate—low Blood pressure—65 years or more (CURB-65) score. The use of high-flow nasal cannula (HFNC) and awake prone positioning was frequent in our cohort. We identified several risk factors and used them, in a clinical perspective, to predict in-hospital mortality. The combination of the presence of severe acute disease (defined by a $PaO_2/FiO_2$ ratio of <200) and a high burden of chronic disease (Modified Charlson Comorbidity Index (MCCI) ≥5 or chronic pulmonary disease) resulted in four groups of patients with a gradual increase in mortality risk. Even though Latinos may become more severely ill with coronavirus disease 2019, proper clinical management results in a similar survival compared with other populations. Furthermore, the combination of risk factors, based on a few acute and chronic clinical characteristics, could help physicians make a better assessment of patients with COVID-19.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and data collection

This was a prospective cohort study of adult inpatients at a University of Chile Clinical Hospital. We enrolled all patients aged >18 years who were diagnosed with COVID-19 and were admitted to the emergency department from 1 March to 11 June 2020, through prospective identification using daily admission records. COVID-19 was diagnosed when clinical findings of acute respiratory illness (fever (measured or subjective), chills, rigours, myalgia, headache, sore throat, nausea or vomiting, fatigue, congestion, cough, shortness of breath, difficulty breathing, new olfactory disorder, new taste disorder) were present with a positive result on reverse transcription-polymerase chain reaction (RT-PCR) assay of a nasopharyngeal swab and/or chest computed tomography (CT), with typical findings of COVID-19 and the absence of an alternative diagnosis. All admitted patients were included during the first 100 days since the first admission of a COVID-19 patient; therefore, no sample size calculation was performed. We excluded patients with a length of stay <24 hours, nosocomial SARS-CoV-2 infection, and

asymptomatic patients admitted for causes unrelated to SARS-CoV-2 infection, regardless of their admission RT-PCR result (Figure 1). The study protocol was conducted following the amended Declaration of Helsinki. On March 7th, 2020, the Research Ethics Committee approved the protocol (OAIC No. 1119/20) and waived the requirement for informed consent because of uncertainty regarding the risk of transmission from fomites.

The data were prospectively recorded for each patient at admission and then daily, until the end of follow-up. Using a standardised data collection form, the records were reviewed by trained physicians and then checked by a team of four physicians (FG, FM, SC and AH). Discrepancies were resolved between the same clinicians through discussions. The data included demographic characteristics, comorbidities, disease onset time, associated symptoms, vital signs at the emergency department, laboratory test results (within 24 hours of admission), characteristics of the first chest CT, medication and supportive care, and length of hospital stay.

The use of antibiotics, antiviral therapy, corticosteroids, advanced oxygen delivery techniques, need for invasive mechanical ventilation (IMV), awake and ventilated prone positioning, use of vasopressor drugs and the need for renal replacement therapy were recorded. Clinical management and the use of these therapies were based on national recommendations from scientific societies and local protocols.[12-16]

## 2.2 | Laboratory procedures and definitions

SARS-CoV-2 infection was confirmed using RT-PCR of nasopharyngeal swabs. All laboratory procedures were performed at the discretion of the treating physician, who was encouraged to follow local clinical guidelines. FilmArray of nasopharyngeal swabs, and urinary antigen (pneumococcal/*Legionella*) tests and blood cultures were performed for viral and bacterial co-infection assessment, respectively. Chest CT was performed and classified as COVID-19-unrelated, typical/atypical pattern, and unspecified, as previously suggested.[15]

Comorbidities and age were summarised using the MCCI (≥5 was considered "high comorbidity").[16] Functional dependency was defined by a Barthel score <60 in patients aged 65 years or older. Acute disease severity was classified according to the American Thoracic Society (ATS) guidelines for community-acquired pneumonia, CURB-65, SOFA, and qSOFA scores.[17-20] Cut-off values were defined by abnormal ranges or previous reports.[1,2] The ratio of arterial oxygen partial pressure to the fraction of inspired oxygen ($PaO_2/FiO_2$) was considered an indicator of the severity of the respiratory failure. If arterial blood gas analysis was unavailable (Supporting Information), $PaO_2$ was estimated by oxygen saturation, as previously validated.[21] Abnormal perfusion at admission was defined as arterial lactate ≥2 mmol/L (if available) or by clinical evaluation (capillary refill time

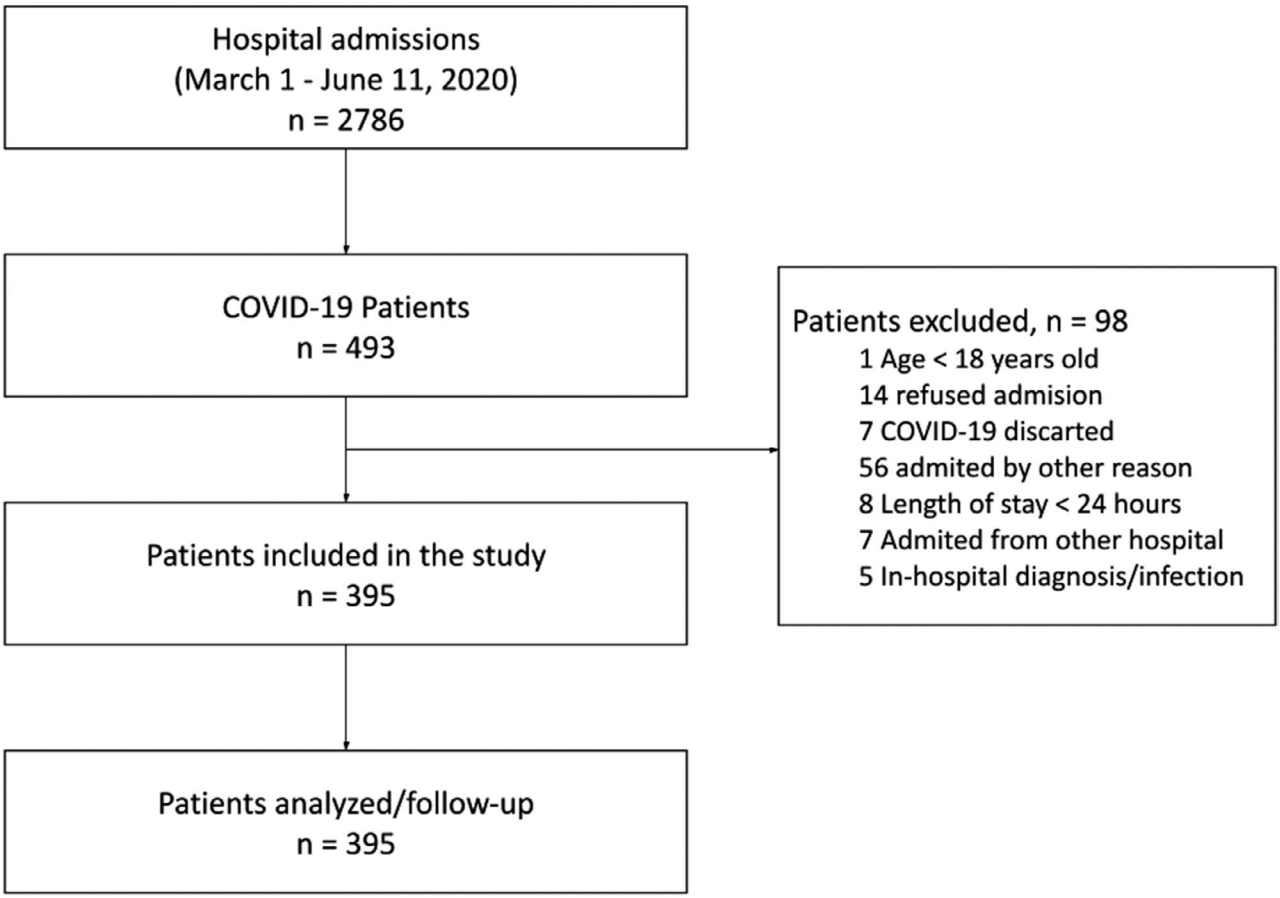


**FIGURE 1** Flowchart of the patient selection process. COVID-19, coronavirus disease 2019

>3 seconds or skin mottling score >0).[22] Definitions for AKI, deep vein thrombosis, pulmonary embolism, among others, are listed in Supporting Information.

### 2.3 | Combined risk factors and outcomes

In addition to the known scores, mortality risk was categorised based on a clinical perspective that contemplates chronic disease burden and the severity of acute illness. For these purposes, we combined specific known risk factors, such as comorbidities. MCCI is a validated prognosis tool in elder patients, which measures the burden of chronic diseases.[16] A high chronic disease burden (chronic ⊕) was defined as an MCCI score ≥5.[16] Considering that the lung parenchyma is most affected by COVID-19 and that advanced chronic lung diseases other than the chronic obstructive pulmonary disease (COPD) are not considered in the MCCI, patients with any of these diseases were also considered in the chronic (⊕) category. Similarly, the high severity of acute disease (acute ⊕) was defined as a $PaO_2/FiO_2$ ratio ≤200. Chronic ⊖or acute ⊖was considered as the absence of a chronic or acute condition, respectively. Patients were grouped into four categories: chronic ⊕, acute ⊕; chronic ⊖, acute ⊖; and intermediate categories (Supporting Information).

The primary outcome was in-hospital mortality. Secondary outcomes were the use of IMV and high-flow nasal cannula (HFNC), awake and ventilated prone positioning, septic shock, AKI, renal replacement therapy, thromboembolic disease, and co-infections. The duration and timing of IMV and HFNC were also assessed. Patients were discharged when clinical remission of respiratory symptoms, absence of fever, and suspension of supplemental oxygen for ≥24 hours was achieved. Patients were followed up until death, hospital discharge, or 10 July 2020 (to ensure ≥28 days of follow-up), whichever came first.

### 2.4 | Statistical analyses

The Mann-Whitney *U* test or Fisher's exact test was used to compare baseline characteristics and secondary outcomes between survivors and non-survivors. Cox regression models were used to identify risk factors for in-hospital mortality among baseline characteristics, excluding symptoms. Time was considered as days to the event. Hospital admission and the proportional hazard assumption for each model were tested using Schoenfeld residuals. Univariate hazard ratios (HR) and 95% confidence intervals (95% CI) were presented for variables that showed strong evidence against the null hypothesis ($P < .05$). Variables considered in the multivariate analysis were selected depending on available background and full data. In the final model, we included variables related to the chronic disease burden (MCCI and advanced chronic respiratory disease (ACRD)), and others related to acute illness ($PaO_2/FiO_2$ ratio ≤200 and abnormal perfusion), together with hypertension (a widely reported risk factor not included in the MCCI). Finally, we constructed Kaplan–Meier curves and unadjusted Cox models to explore different combined risk factors. Missing data were not imputed and available cases analysis was performed for incomplete data (Supporting Information). All statistical analyses were performed using Stata (version 12.0; StataCorp LLC) (Supporting Information).

## 3 | RESULTS

### 3.1 | Clinical characteristics and laboratory/tomographic findings

Overall, 395 patients were enrolled. Those who remained hospitalised were followed up for ≥28 days; 97.7% of whom had confirmed COVID-19 with a positive RT-PCR result. Basal characteristics of patients are presented in Table 1. The median age was 56 years (interquartile range [IQR], 49-70); 62.5% were male and 40.1% had an MCCI ≥5. In total, 58 patients died (14.7%); 313 (79.2%) were discharged. Palliative care was delivered in 37 patients (0.9%), 8 of them died at the hospital.

Symptoms that developed before hospital admission and clinical presentation at the emergency department are listed in Table 2. The most common symptoms were dyspnoea (84.6%), myalgia (77.5%), cough (76.2%), and fever (60.5%). The median time from symptom onset to emergency department consultation was 7 days (IQR, 5-10). The median SOFA, qSOFA, and CURB-65 scores were 3, 1, and 1, respectively.

Laboratory and radiological findings at hospital admission are summarised in Table 3. Over 75% of patients had an inflammatory response, hypoxia, and hypocapnia. FilmArray Respiratory Panel was performed in 84.6% of patients; seven had viral co-infections. One patient had a positive result for pneumococcal urinary antigen. Chest CT was performed in 379 patients: 344 (90.8%) had a typical pattern.

### 3.2 | Respiratory and non-respiratory support

All patients required oxygen. Two hundred and thirty-seven (60.0%) were supported using only low-flow oxygen devices. HFNC was started in 138 patients (34.9%; median duration, 5 days [IQR, 2-8]); 63.7% required awake prone positioning. Sixty-nine patients (17.5%) required IMV, 71% of whom started HFNC before orotracheal intubation (median duration, 2 days [IQR, 1-4]). The median time from hospital admission to IMV was 2 days (IQR, 1-4) (median duration, 14 days [IQR, 6-29]).

Antibiotics were indicated in 323 patients (81.8%), of whom 309 received ceftriaxone; 284, azithromycin; and 84, other antibiotics. The median treatment duration for ceftriaxone and azithromycin was 3 (IQR, 2-6) and 2.5 (IQR, 1-4) days, respectively. Heparin was indicated in 383 patients (97%). Moderate-dose steroids were used as initial therapy in 95 patients (24.1%; median duration, 5 days [IQR, 4-7]). Antivirals and antifungals were rarely administered.

**TABLE 1** Baseline demographic and comorbidities of patients

| Characteristic | Total (N = 395) | Survivors (N = 337) | Non-survivors (N = 58) | *P*-value |
|---|---|---|---|---|
| Age (y), median (IQR) | 61 (49-70) | 58 (46-67) | 75 (64-80) | <.001 |
| Male sex, n (%) | 248 (62.8) | 211 (62.6) | 37 (63.8) | >.999 |
| Current smoker, n (%) | 45 (11.4) | 39 (11.6) | 6 (10.3) | >.999 |
| Comorbidities | | | | |
| Number, median (IQR) | 1 (1-2) | 1 (0-2) | 2 (1-3) | <.001 |
| MCCI ≥5, n (%) | 158 (40.1) | 109 (32.4) | 49 (84.5) | <.001 |
| Functional dependency, n (%) | 10 (6.5) | 5 (4.6) | 5 (11.6) | .145 |
| Hypertension, n (%) | 205 (51.9) | 160 (47.5) | 45 (77.6) | <.001 |
| Type 2 diabetes, n (%) | 119 (30.1) | 96 (28.5) | 23 (39.7) | .091 |
| Obesity, n (%) | 139 (35.2) | 126 (37.4) | 13 (22.4) | .036 |
| Coronary artery disease, n (%) | 12 (3) | 9 (2.7) | 2 (3.4) | .670 |
| Heart failure, n (%) | 13 (3.3) | 9 (2.7) | 4 (6.9) | .110 |
| COPD, n (%) | 8 (2.0) | 7 (2.1) | 1 (1.7) | >.999 |
| Asthma, n (%) | 27 (6.8) | 25 (7.4) | 2 (3.4) | .400 |
| ACRD, n (%)[a] | 18 (4.6) | 8 (2.4) | 10 (17.2) | <.001 |
| Cancer, n (%) | 11 (2.8) | 6 (1.8) | 5 (8.6) | .013 |
| CKD, n (%) | 29 (7.3) | 20 (5.9) | 9 (15.5) | .024 |
| Stroke, n (%) | 11 (2.8) | 7 (2.1) | 4 (6.9) | .062 |
| Dementia, n (%) | 10 (2.5) | 3 (0.9) | 7 (12.1) | <.001 |
| Chronic liver disease, n (%) | 8 (2.0) | 5 (1.5) | 3 (5.2) | .098 |
| HIV, n (%) | 4 (1.0) | 3 (0.9) | 1 (1.7) | .470 |
| Rheumatological disease, n (%) | 11 (2.8) | 6 (1.8) | 5 (8.6) | .013 |

Abbreviations: ACRD, advanced chronic respiratory disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IQR, interquartile range; MCCI, Modified Charlson Comorbidity Index.

[a]Advanced chronic respiratory disease.

Hydroxychloroquine was used in 17 patients (4.3%). None of the patients received gamma globulin/tocilizumab or other experimental/non-validated therapies.

### 3.3 | Differences between survivors and non-survivors

The non-survivors were older, had a higher disease burden (especially advanced lung disease), were less symptomatic, and consulted the emergency department, on average, 24 hours before the survivors. They presented with greater abnormalities in vital signs and had a greater inflammatory response, hypoxemia, and alteration of gas exchange ($PaO_2/FiO_2$ ratio) than the survivors (Table 3). Additionally, the non-survivors presented with greater lymphopenia and elevated lactate dehydrogenase/D-dimer levels. There were no differences in the CT patterns between the survivors and non-survivors ($P = .09$).

The non-survivors required ventilatory support, heparin, and corticosteroids more often than the survivors. During the follow-up, 36 patients (10.7%) were diagnosed with thromboembolic disease (pulmonary embolism, N = 32), without significant differences between the survivors and non-survivors (10.7% vs 12.1%, $P = .82$). AKI and septic shock were more common in the non-survivors than in survivors (53.2% vs 14.5% and 41.4% vs 8.9%, respectively; $P < .001$) (Table 4). Differences in pharmacological therapies are shown in Supporting Information.

### 3.4 | Survival analysis and risk factors

The length of hospital stay was 9 days (IQR, 5-17) for the survivors and 11 days (IQR, 5-16) for non-survivors ($P = .523$). At the end of the study, 24 patients (6.1%) remained hospitalised with a median length of 35-day stay (IQR, 27-41).

In the multivariate analysis, an MCCI ≥5, $PaO_2/FiO_2$ ratio ≤200, abnormal perfusion, and advanced CRD were independent risk factors for in-hospital mortality ($P < .05$; Table 5). Predefined combinations of clinically relevant risk factors showed strong differences in in-hospital survival (Figure 2). Compared with chronic ⊖and acute ⊖group patients,

**TABLE 2** Clinical characteristics of patients with COVID-19 on admission

| Characteristic | Total (N = 395) | Survivors (N = 337) | Non-survivors (N = 58) | *P*-value |
|---|---|---|---|---|
| Symptoms | | | | |
| Days from onset to ER consultation, median (IQR) | 7 (5-10) | 7 (5-10) | 6 (3-10) | .021 |
| Fever, n (%) | 239 (60.5) | 221 (65.6) | 18 (31.0) | <.001 |
| Cough, n (%) | 301 (76.2) | 264 (78.3) | 37 (63.8) | .020 |
| Anorexia, n (%) | 83 (21.0) | 69 (20.5) | 14 (24.1) | .600 |
| Myalgia, n (%) | 306 (77.5) | 267 (79.2) | 39 (67.2) | .060 |
| Dyspnoea, n (%) | 334 (84.6) | 285 (84.6) | 49 (84.5) | >.999 |
| Expectoration, n (%) | 81 (20.5) | 70 (20.8) | 11 (19.0) | .860 |
| Odynophagia, n (%) | 83 (21.0) | 74 (22.0) | 9 (15.5) | .300 |
| Diarrhoea, n (%) | 63 (15.9) | 60 (17.8) | 3 (5.2) | .012 |
| Vomiting, n (%) | 22 (5.6) | 21 (6.2) | 1 (1.7) | .220 |
| Rhinorrhoea, n (%) | 42 (10.6) | 36 (10.7) | 6 (10.3) | >.999 |
| Headache, n (%) | 96 (24.3) | 89 (26.4) | 7 (12.1) | .020 |
| Haemoptysis, n (%) | 2 (0.5) | 2 (0.6) | 0 (0.0) | >.999 |
| Arthralgia, n (%) | 4 (1.0) | 4 (1.2) | 0 (0.0) | >.999 |
| Hyposmia, n (%) | 43 (10.9) | 40 (11.9) | 3 (5.2) | .170 |
| Dysgeusia, n (%) | 43 (10.9) | 42 (12.5) | 1 (1.7) | .011 |
| Clinical presentation | | | | |
| Fever, n (%) | 214 (54.45) | 186 (55.5) | 28 (48.3) | .321 |
| Oxygen saturation %, median (IQR) | 90 (84-93) | 91 (85-93) | 82 (74-88) | <.001 |
| Respiratory rate >24 bpm, n (%) | 273 (69.1) | 222 (65.9) | 51 (87.9) | <.001 |
| Heart rate >120 bpm, n (%) | 37 (9.4) | 28 (8.3) | 9 (15.5) | .090 |
| Mean BP <60 mm Hg, n (%) | 21 (5.3) | 15 (4.5) | 6 (10.3) | .100 |
| Consciousness impairment, n (%) | 47 (11.9) | 26 (7.7) | 21 (36.2) | <.001 |
| SOFA score, median (IQR) | 3 (2-4) | 3 (2-4) | 5 (4-6) | <.001 |
| qSOFA score, median (IQR) | 1 (1-2) | 1 (1-1) | 2 (1-2) | <.001 |
| CURB-65, median (IQR) | 1 (0-2) | 1 (0-2) | 3 (2-3) | <.001 |
| ATS classification (severe), n (%) | 283 (71.8) | 228 (67.9) | 55 (94.8) | <.001 |

Abbreviations: ATS, American Thoracic Society; BP, blood pressure; COVID-19, coronavirus disease 2019; ER, emergency room; HIV, human immunodeficiency virus; IQR, interquartile range; qSOFA, quick Sequential Organ Failure Assessment; SOFA, Sequential Organ Failure Assessment.

chronic ⊕and acute ⊕group patients had a higher mortality risk (HR 36.1 [95% CI: 4.9-264.0]; $P < .001$). Similarly, an increased risk of mortality was observed in the chronic ⊕and acute ⊖ (HR 20.6 [95% CI: 2.7-157.1]; $P = .003$), and the chronic ⊖and acute ⊕ (HR 6.5 [95% CI: 0.80-53.2]; $P = .079$) group patients, although with a weak statistical evidence in the latter. Compared with the other three groups, patients in the chronic ⊕and acute ⊕group required more IMV, HFNC, were admitted to intensive care units more frequently and had a higher risk of developing other secondary outcomes (Supporting Information).

## 4 | DISCUSSION

This is the first prospective Latin American cohort study on COVID-19 inpatients. Despite higher severity scores than those reported previously, the mortality rate of 14.6% was comparable to that in other studies.[1,2,23] The support measures mainly included the use of HFNC and awake prone positioning, and reduced use of experimental pharmacological therapies. Combining the chronic disease burden with the severity of acute illness at onset as risk factors resulted in four groups with markedly different prognoses, which might help stratify patients.

The baseline characteristics of the patients in our cohort, time from symptom onset to hospitalisation, frequency of symptoms, and laboratory findings were similar to those reported previously.[2] Fever was present only in 31.6% of non-survivors (Table 2), making it a poor marker of severity, as previously reported.[24] Similarly, other symptoms were less frequent in non-survivors (cough, diarrhoea, headache and dysgeusia) which clinical and prognostic significance should be explored in further studies.

Compared with previous reports on hospital experiences of COVID-19, our cohort had greater disease severity. Guan et al[1]

**TABLE 3** Laboratory and tomographic characteristics of patients with COVID-19

| Characteristic | Total (N = 395) | Survivors (N = 337) | Non-survivors (N = 58) | *P*-value |
|---|---|---|---|---|
| Laboratory characteristics, median (IQR) | | | | |
| Haemoglobin (g/dL) | 14.0 (12.7-15.0) | 14.1 (12.8-15.0) | 13.5 (11.7-14.8) | .071 |
| Leukocytes ($10^3$/mL) | 8.5 (6.1-11.4) | 8.2 (6.0-11.2) | 9.6 (6.9-13.1) | .043 |
| Neutrophils ($10^3$/mL) | 6.6 (4.5-9.7) | 6.3 (4.4-9.1) | 8.0 (5.55-10.7) | .006 |
| Lymphocytes ($10^3$/mL) | 1.2 (0.8-1.6) | 1.2 (0.8-1.6) | 1.0 (0.6-1.4) | .007 |
| Platelet count ($\times10^3$/L) | 223 (171-304) | 226 (175-303) | 207 (149-305) | .086 |
| Albumin (g/dL) | 3.6 (3.3-4.0) | 3.6 (3.4-4.0) | 3.4 (3.1-3.7) | <.001 |
| Total bilirubin (mg/dL) | 0.6 (0.4-0.8) | 0.6 (0.4-0.8) | 0.7 (0.5-1.0) | .021 |
| AST (U/L) | 54 (39-77) | 54 (38-72) | 59 (42-96) | .067 |
| ALT (U/L) | 41 (24-66) | 42 (24-66) | 38 (24-68.0) | >.999 |
| Creatinine (mg/dL) | 0.8 (0.6-1.0) | 0.7 (0.6-0.9) | 1.0 (0.8-1.8) | <.001 |
| Urine nitrogen (mg/dL) | 17 (12.0-25) | 16 (12-22) | 27 (22-43) | <.001 |
| LDH (U/L) | 385 (298-514) | 373 (287-481) | 523 (378-661) | <.001 |
| CK (U/L) | 93 (51-236) | 91 (49-220) | 146 (63-337) | .055 |
| Lactate (mmol/L) | 1.2 (1.0-1.6) | 1.2 (1.0-1.5) | 1.6 (1.1-2.7) | <.001 |
| Abnormal perfusion | 97 (24.6) | 67 (19.9) | 30 (51.7) | <.001 |
| Troponin I (ng/mL) | 0.01 (0.01-0.01) | 0.00 (0.00-0.00) | 0.00 (0.00-0.1) | <.001 |
| INR | 1.2 (1.1-1.3) | 1.2 (1.1-1.3) | 1.2 (1.1-1.3) | .400 |
| aPTT (s) | 31.0 (28.0-35.0) | 31.3 (28.3-35.3) | 32.0 (28.2-35.8) | .680 |
| D-dimer (ng/mL) | 1082 (694-1800) | 1016 (640-1542) | 1807 (1175-4480) | <.001 |
| Procalcitonin (ng/mL) | 0.1 (0.0-0.4) | 0.1 (0.0-0.3) | 0.3 (0.2-1.9) | <.001 |
| C-reactive protein (mg/L) | 160 (61-231) | 152 (57-217) | 225 (157-325) | <.001 |
| ESR (mm/h) | 55 (33-78) | 54 (33-78) | 60 (33-87) | .520 |
| $paO_2$ (mm Hg) | 76.0 (64.1-94.4) | 76.0 (65.0-91.8) | 74.3 (60.1-107.0) | .650 |
| $paO_2/FiO_2$ ratio | 208 (108-304) | 232 (118-312) | 116 (71-205) | <.001 |
| $paCO_2$ (mm Hg) | 33.3 (29.9-36.8) | 33.6 (30.3-37.0) | 31.4 (27.3-35.0) | .009 |
| Chest tomography, n (%) | | | | |
| Non-COVID-19 | 20 (5.3) | 16 (4.9) | 4 (7.4) | .090 |
| Typical pattern | 344 (90.8) | 299 (92) | 45 (83.3) | |
| Atypical pattern | 9 (2.4) | 6 (1.8) | 3 (5.6) | |
| Unspecified | 6 (1.6) | 4 (1.2) | 2 (3.7) | |

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CK, creatine kinase; COVID-19, coronavirus disease 2019; ESR, erythrocyte sedimentation rate; INR, international normalised ratio; IQR, interquartile range; LDH, lactate dehydrogenase; $paCO_2$, partial pressure of carbon dioxide; $paO_2$, partial pressure of oxygen; $paO_2/FiO_2$ ratio of arterial oxygen partial pressure to the fraction of inspired oxygen.

reported severe disease in 15.7% of their study population, whereas Zhou et al[2] reported a CURB-65 score of ≥2 in 25% participants and a median SOFA score of 2. Our cohort had ATS severe disease in 71.8% participants, a CURB-65 score of ≥2 in 39.2% participants, and a median SOFA score of 3. Specific characteristics of the Latin American population, such as chronic disease burden, genetic determinants, and social determinants, are scarcely described and need to be explored in further studies.[8]

The use of non-IMV was anecdotal and lower than that in other countries.[25] A remarkable difference in our study was the early and wide use of HFNC.[2] Overall, IMV indication among those admitted to the intensive care unit was similar to that reported previously,[2]

**TABLE 4** Advanced respiratory support

| Support | Total (N = 395) | Survivors (N = 337) | Non-survivors (N = 58) | *P*-value |
|---|---|---|---|---|
| Non-IMV, n (%) | 3 (0.8) | 1 (0.3) | 2 (3.4) | .058 |
| HFNC, n (%) | 138 (34.9) | 100 (29.7) | 38 (65.5) | <.001 |
| IMV, n (%) | 69 (17.5) | 43 (12.8) | 26 (44.8) | <.001 |
| ECMO, n (%) | 1 (0.3) | 1 (0.3) | 0 (0.0) | >.999 |
| Awake prone positioning, n (%) | 110 (27.8) | 83 (24.6) | 27 (46.6) | .001 |
| Ventilated prone positioning, n (%)[a] | 51 (73.9) | 31 (72.1) | 20 (76.9) | .780 |

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula; IMV, invasive mechanical ventilation.

[a]Among patients with IMV.

despite the higher severity. Therefore, the lower-than-expected rate of IMV and the high use of HFNC are in line with the findings of Zucman et al,[26] who suggested that HFNC might reduce the need for IMV in up to one-third of patients.[27] The role of HFNC in avoiding progression to IMV, with or without awake prone positioning and prolonged ventilated prone positioning, needs to be addressed in future research.

Few pharmacological therapies were used in this cohort. Hydroxychloroquine was infrequently indicated; prior to the RECOVERY trial,[28] corticosteroids were mainly indicated for reasons other than COVID-19. Tocilizumab, immunoglobulin, and antivirals were not used. Conversely, antibiotics and thromboprophylaxis were frequently indicated. Current evidence supports our general approach to pharmacological therapies.[27]

Regarding secondary outcomes, co-infection occurred infrequently, as reported previously.[25] AKI, experienced by 20.5% of patients, was as frequent as that reported in a study on severe COVID-19 patients.[29] Thromboembolic disease was diagnosed in 10.8% of patients. Few patients were empirically anticoagulated because of the high risk of venous thromboembolism. The latter is in agreement with the current recommendations of the American Society of Hematology, which discourages empiric anticoagulation in critically ill COVID-19 patients.[30]

We identified several risk factors related to in-hospital mortality. As described previously,[1] older age and comorbidities (hypertension, cancer, chronic kidney disease, stroke, dementia, rheumatological disease, and advanced CRD) were significant risk factors. Nevertheless, our data could be underpowered to detect an association with other important comorbidities (such as diabetes, asthma, chronic liver disease and COPD, among others). The MCCI, which groups age and several comorbidities,[31] exhibited the strongest association with mortality when analysing disease burden. Despite being clinically significant, data on COVID-19 that evaluate comorbidities based on validated indices as risk factors are limited. Advanced CRD other than COPD are not included in the MCCI, which showed a strong association with mortality.

The risk factors that accounted for illness severity on admission were similar to those described previously.[1-3] These were classified as factors related to the severity of the respiratory insult (oxygen saturation, $PaO_2/FiO_2$ ratio, $pCO_2$, and respiratory rate), systemic and non-pulmonary damage (troponin, hypoperfusion, lactate, AKI, non-respiratory SOFA score, etc), and systemic inflammatory response and coagulopathy (C-reactive protein, procalcitonin, neutrophils, lymphocytes and D-dimer). Therapies were not considered for survival analysis because of the risk of bias given our study design. In the univariate analysis, $PaO_2/FiO_2$ ratio, D-dimer, troponin, non-respiratory SOFA score, qSOFA score, lactate, altered perfusion and conscious impairment remained significant. In concordance with our exploratory hypothesis of clinical scenarios, the MCCI, advanced CRD and $PaO_2/FiO_2$ ratio were independently associated with mortality risk in the multivariate analysis.

We combined the risk factors based on a combination of chronic disease burden and the severity of illness on admission. Although other scores have been validated to classify patients with pneumonia,[32] they were not properly validated at the beginning of the pandemic. There was considerable uncertainty about the course of the illness. Grouping risk factors and effectively transforming them into distinct clinical scenarios made sense for the decision-making process in the vast majority of patients and were significantly associated with the risk of mortality. Broadly, low-risk patients had a low mortality risk, justifying a reduced need for advanced support. Conversely, identifying high-risk patients is critical for evaluating the need for advanced support or, given the circumstances, early evaluation of palliative care. Data on responses to initial therapies might be a more useful prognostic tool, especially in intermediate-risk patients. Evaluation of the usefulness of clinical scenarios needs to be addressed in further studies.

Regarding the relatively low mortality rate, we believe that the experience in other countries led to efficient, systematic management coordinated by senior intensive care physicians in close collaboration with emergency physicians, anaesthesiologists, cardiologists and internal medicine doctors, with relatively high use of HFNC and awake prone positioning, which may, in part, explain our success.

This study has several strengths. It was prospectively developed, the researchers treated most of the enrolled patients, and variables of clinical interest were reported, such as detailed information on chronic disease burden, functionality, disease severity, the use of prone positioning, HFNC and anticoagulation. Moreover, we attempted to take a more clinical approach to data analysis to help clinicians better confront this unknown disease.

**TABLE 5** Risk factors associated with in-hospital survival in patients with COVID-19

| Variable | Univariate HR (95% CI) | *P*-value | Multivariate HR (95% CI) | *P*-value |
|---|---|---|---|---|
| Age (≥65 y) | 3.629 (2.011-6.549) | <.001 | — | — |
| Male sex | 0.974 (0.568-1.669) | .923 | — | — |
| MCCI ≥5 | 6.810 (3.342-13.879) | <.001 | 4.386 (1.995-9.642) | <.001 |
| Respiratory rate ≥24 | 2.218 (1.003-4.905) | .049 | — | — |
| Conscious impairment | 3.035 (1.763-5.225) | <.001 | — | — |
| Non-respiratory SOFA score | 1.475 (1.301-1.672) | <.001 | — | — |
| qSOFA score | 2.115 (1.497-2.987) | <.001 | — | — |
| $paO_2/FiO_2$ ratio ≤200 | 3.334 (1.034-10.755) | .044 | 1.920 (1.039-3.550) | .037 |
| Lactate ≥2 mmol/L | 2.179 (1.274-3.724)[a] | .004 | — | — |
| Altered perfusion | 2.088 (1.234-3.534)[a] | .006 | 1.567 (0.908-2.705) | .107 |
| Troponin I ≥ 0.3 ng/mL | 3.812 (1.178-12.339) | .026 | — | — |
| D-dimer ≥1000 U/L | 2.877 (1.444-5.732) | .003 | — | — |
| CRP >10 mg/dL | 1.172 (0.162-8.506) | .875 | — | — |
| Hypertension | 2.749 (1.480-5.107) | .001 | 1.478 (0.753-2.898) | .560 |
| Obesity | 0.410 (0.221-0.762) | .005 | — | — |
| Cancer | 2.604 (1.011-6.706)[a] | .047 | — | — |
| CKD | 2.860 (1.394-5.871) | .004 | — | — |
| Stroke | 4.113 (1.476-11.466) | .007 | — | — |
| Dementia | 4.332 (1.953-9.610) | <.001 | — | — |
| Rheumatological disease | 3.558 (1.410-8.977) | .007 | — | — |
| Respiratory disease[a] | 4.971 (2.488-9.929) | <.001 | 3.235 (1.586-6.602) | .001 |

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; HR, hazard ratio; MCCI, Modified Charlson Comorbidity Index; $paO_2/FiO_2$ ratio of arterial oxygen partial pressure to the fraction of inspired oxygen; qSOFA, quick Sequential Organ Failure Assessment; SOFA, Sequential Organ Failure Assessment.

[a]Advanced chronic respiratory disease other than COPD/asthma.

Several limitations should also be acknowledged. First, our main limitation was the number of events, which, in turn, restricted the number of factors included in the multivariate analysis. Thus, it might be considered that other excluded and unmeasured variables had an independent effect on the outcomes. Similarly, the effect of therapies was not included, and this might have affected the reported hazard ratios (HR). Also, age was included as part of MCCI in the multivariate analysis, and its isolated effect on the outcome was

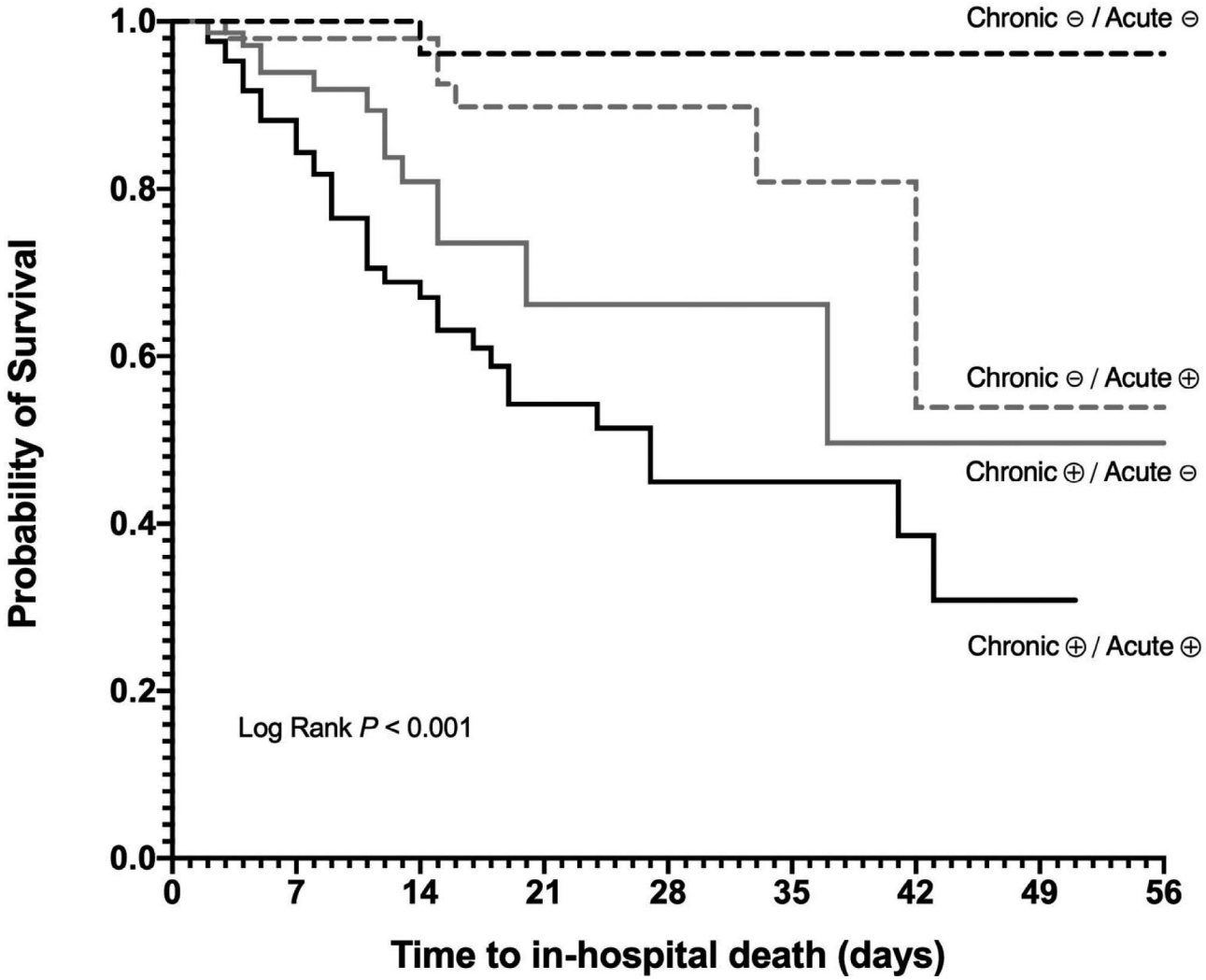


**FIGURE 2** Kaplan–Meier curves according to clinical scenarios. Survival is shown up to 56 days to ensure better visualisation and scaling. Acute ⊕, high severity of acute disease was defined as a $PaO_2/FiO_2$ ratio ≤200; Acute ⊖ absence of an acute condition; Chronic ⊕, high chronic disease burden was defined as an MCCI score ≥5; Chronic ⊖, absence of a chronic condition

not studied. Second, we observed missing values in the laboratory test results, which might have affected our statistical analysis. While performing multiple analyses may be an alternative, we preferred to exclude the variables with missing data. Third, even though our cohort was prospectively constructed, most of the information was derived from clinical registries, which are subject to bias. However, the hospital team that reviewed the clinical registries took appropriate measures to verify the clinical data and their consistency. Fourth, we reported a single-centre experience, which needs to be replicated in multicentre studies. Finally, we did not assess temporal trends in biomarkers and other clinical variables of interest that might have been prognostic factors, warranting future studies on these aspects.

## 5 | CONCLUSIONS

In this large prospective cohort of Latin American COVID-19 patients, we observed a similar mortality rate as reported in other regions, even though our patients had more severe disease. Increased use of a highly coordinated, systematic management approach and decreased use of experimental therapies could affect mortality risk. Independent risk factors associated with in-hospital mortality included the MCCI, advanced CRD, a low $PaO_2/FiO_2$ ratio and abnormal perfusion at admission. These associations were greatly enhanced when taken as groups, which, in turn, has better clinical applicability. Risk factors and the utility of combining them warrants further investigation.

## INSTITUTIONAL REVIEW BOARD STATEMENT

The study protocol was conducted following the amended Declaration of Helsinki. The Research Ethics Committee of the University of Chile Clinical Hospital (Santiago, Chile) approved the protocol (OAIC No. 1119/20) and waived the requirement for informed consent.

## INFORMED CONSENT STATEMENT

Patient consent was waived because of uncertainty of the risk of infection transmitted by fomites.

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## DISCLOSURES

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## AUTHOR CONTRIBUTIONS

All authors have read and agreed to the published version of the manuscript. Conceptualisation, Francisco Gonzalez, Fabian Miranda, Sebastián Chávez and Ariane Hernández; Data curation, Francisco Gonzalez, Fabian Miranda, Sebastián Chávez, Ariane Hernández and Dannette Guiñez; Formal analysis, Fabian Miranda and Abraham Gajardo; Methodology, Francisco Gonzalez, Fabian Miranda, Sebastián Chávez, Abraham Gajardo and Ariane Hernández; Project administration, Francisco Gonzalez; Supervision, Francisco Gonzalez and Rodrigo Cornejo; Visualisation, Abraham Gajardo; Writing – original draft, Francisco Gonzalez, Fabian Miranda, Sebastián Chávez, Abraham Gajardo and Ariane Hernández; Writing – review & editing, Francisco Gonzalez, Fabian Miranda, Sebastián Chávez, Abraham Gajardo, Ariane Hernández, Dannette Guiñez, Gonzalo Diaz, Natalia Sarmiento, Fernando Ihl, Maria Cerda, Camila Valencia and Rodrigo Cornejo.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of the article at the publisher's website.

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