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Biochemical differences based on sex and clusters of biomarkers in patients with COVID-19: analysis from the CARDIO COVID 19–20 registry

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Abstract

Background The inflammatory response associated with COVID-19 varies with sex, potentially affecting disease outcomes. Males have a higher risk of complications compared to females, requiring an evaluation of differences in inflammatory response severity based on sex.

Objective To compare clinical data, biochemical biomarkers, and outcomes among hospitalized COVID-19 patients in Latin America and the Caribbean (LA&C) based on sex and to perform a cluster analysis of biomarker profiles for both sexes.

Methods This prospective, multicenter observational registry made by the Inter-American Council of Heart Failure and Pulmonary Hypertension of the Inter-American Society of Cardiology included hospitalized COVID-19 patients from 44 hospitals in 14 countries in LA&C between May 1, 2020, and June 30, 2021.

Results Of 3,260 patients (1,201 females and 2,059 males), males had higher C-reactive protein and ferritin levels, while females had higher natriuretic peptides and d-dimer levels. Males had more cardiovascular complications (acute coronary syndrome [3.3% vs. 2.2%], decompensated heart failure [8.9% vs. 7.8%], pulmonary embolism [4.4% vs. 2.9%]), intensive care unit (ICU) admissions (56.9% vs. 47.7%), and overall mortality (27.5% vs. 22.1%). Cluster analysis identified three groups: one with normal-range biomarkers but elevated ferritin, one with coagulation abnormalities, and one with an inflammatory profile linked to renal injury and increased non-cardiovascular mortality.

Conclusions In the LA&C population hospitalized with COVID-19, males had higher inflammatory biomarker levels, correlating with increased cardiovascular complications and mortality. The cluster with an inflammatory profile showed higher non-cardiovascular mortality, while clusters with elevated ferritin levels were associated with increased ICU admissions.

Keywords Biomarkers, Cardiovascular complications, COVID-19, Latin America, Sex factors

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Introduction

Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, became a global pandemic, affecting over 200 countries worldwide. According to the World Health Organization (WHO), as of August 2, 2023, 769 million cumulative cases have been reported [1]. Latin America and the Caribbean (LA&C) have been significantly impacted, accounting for approximately 12% of total reported cases and 20% of global COVID-19 deaths, with 63% of these deaths occurring in males and 37% in females [2]. Multiple studies have investigated prognostic factors for COVID-19 [3, 4], emphasizing the important role of inflammatory and cardiovascular biomarkers in determining disease severity. Notably, variations in inflammation levels between males and females have been observed [3, 5].

Recent research indicates significant variability in COVID-19 incidence and mortality by sex, identifying male sex as a risk factor for severe COVID-19 [6–9]. Inflammatory, cardiovascular, and certain hematological biomarkers have proven useful in assessing susceptibility and a higher rate of complications in affected patients [10, 11]. Among these biomarkers, ferritin, C-reactive protein (CRP), troponin, natriuretic peptide, D-dimer, lactate dehydrogenase (LDH), lymphocyte count, and interleukin 6 (IL-6) are strongly correlated with severe disease presentations [10, 11]. However, the differentiation of these markers by sex remains debated [12].

CRP is a non-specific acute-phase protein induced by IL-6 in the liver and is a sensitive biomarker of inflammation, infection, and tissue damage [11]. COVID-19 patients with higher serum CRP levels are prone to develop severe disease, a higher rate of adverse events such as venous thromboembolism, acute kidney injury, and higher in-hospital mortality [13]. Lymphopenia, a hallmark of COVID-19, can be considered a crucial biomarker as a prognostic predictor. This hematological finding, resulting from increased circulating pro-inflammatory cytokines, has a greater impact on patients with severe COVID-19, where absolute lymphocyte counts below 1000/mm3 indicate a poorer prognosis [13, 14]. Ferritin is an intracellular protein responsible for storing and controlling iron release. During inflammation, its production increases in response to immune cells, such as cytokines and chemokines [15]. High levels of iron and ferritin during COVID-19 infection have been reported as indicators of disease severity, a higher risk of acute respiratory distress syndrome (ARDS), and prolonged periods of viral clearance and hospital stay [16].

Despite the high frequency of SARS-CoV-2 infection cases in LA&C, there is limited data providing sex-specific prognostic information for the disease. In this study, we compared clinical and cluster biochemical data of patients from the CARDIO COVID 19–20 registry (Registro Latinoamericano de Enfermedad Cardiovascular y COVID-19), evaluation outcomes during hospitalization based on sex (Fig. 1) [12].

Methods

Design and study population

CARDIO COVID 19–20 is an open prospective observational and multicenter registry coordinated and conducted by the Inter-American Council on Heart Failure and Pulmonary Hypertension (CIFACAH) of the Inter-American Society of Cardiology (IASC). It was conducted in 44 hospitals across 14 countries in LA&C, with the aim of analyze the situation of hospitalized patients with COVID-19 infection, following WHO criteria for this diagnosis. The participating countries were Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Mexico, Panama, Paraguay, Peru, Dominican Republic, and Venezuela.

Because CARDIO COVID 19–20 registry was based on data taken from medical records, individual informed consent was not required. The protocol was approved by the Scientific Committee of the IASC, and by the Clinical Research Center (CIC) and the Ethics Committee of the Fundación Valle del Lili (FVL) in Cali, Colombia (approval #1835). The FVL was responsible for coordinating and supervising the data registry—two trained physicians, acting as registry coordinators, performed continuous data quality reviews. The principal investigator or sub-investigator of every participating institution collected and stored the data in an electronic database designed in REDCap (Research Electronic Data Capture). A username and access key to the electronic data registration form were generated for each participating center. Additional information from the CARDIO COVID 19–20 registry has been previously published [12].

Participants

The study included adult subjects aged 18 years and older, with or without cardiovascular comorbidities, who presented with confirmed SARS-CoV-2 infection through polymerase chain reaction testing and that required hospitalization for more than 24 h. The subjects were included if they were hospitalized between May 1, 2020, and June 30, 2021, and they were followed 30 days after hospital discharge. The sources of information were the emergency departments, hospitalization wards, intensive care units (ICUs), or any other area designated by the participating center to treat COVID-19 patients. The primary outcome variable of this study was to compare the biochemical differences based on sex in patients with COVID-19 in this population.

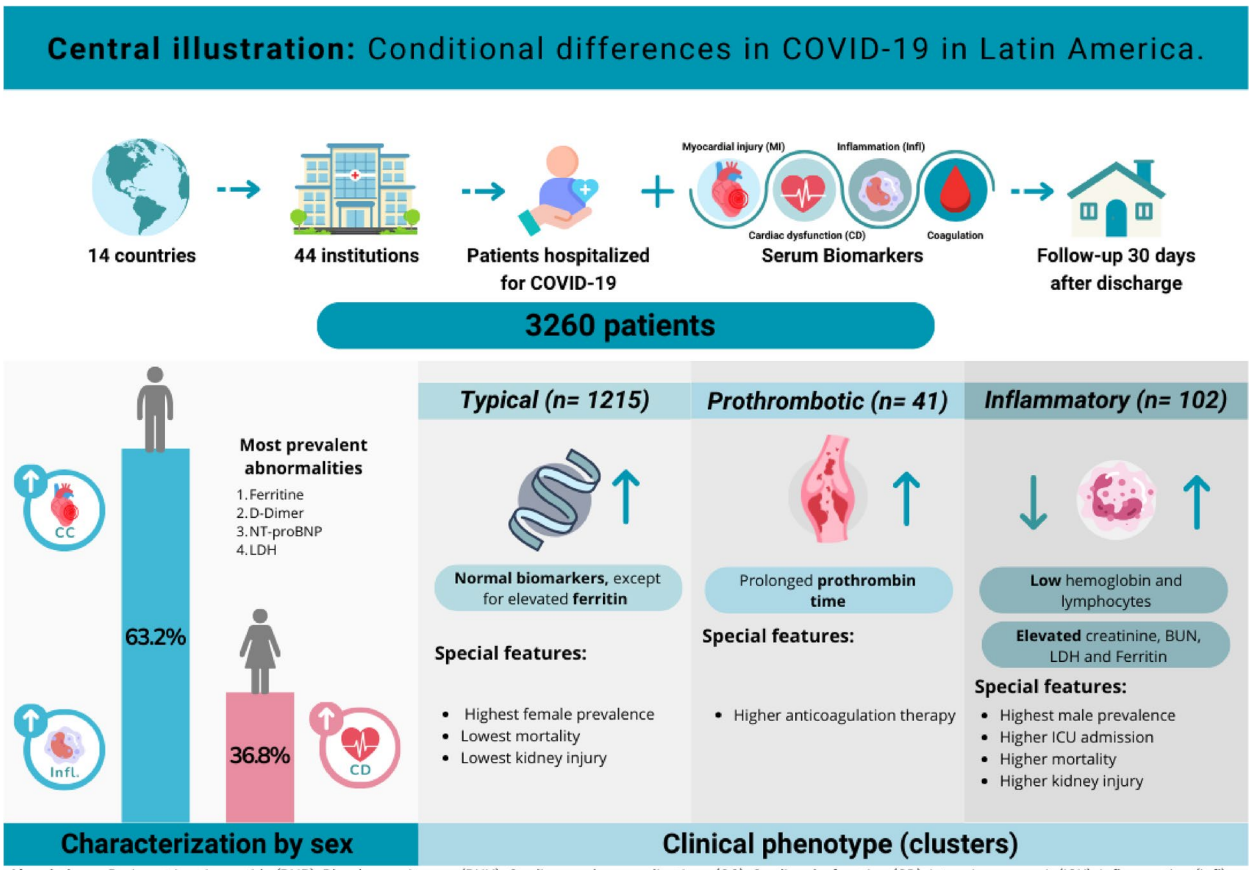

Fig. 1 Biochemical differences based on sex in patients with COVID-19

Data collection

The CARDIO COVID 19–20 registry collected information on 277 variables per recruited patient, including demographic data, cardiovascular and non-cardiovascular comorbidities, previous pharmacological treatment, management during hospitalization, laboratory results and in-hospital outcomes (cardiovascular complication and mortality). Laboratory results included cardiovascular, inflammatory, hematological, and coagulation biomarkers extracted from medical records. A specific time point was not defined for laboratory reporting during hospitalization; however, the first and last recorded laboratory parameters for each medical chart of recruited patients were entered. Patient sex was recorded as female or male, as reported in the medical records.

Biomarkers

All serological biomarkers were measured using the standard hospital assays of each country. Cardiovascular biomarkers included the measurement of highly sensitive troponin T and I as markers of myocardial injury. The B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were also considered as biomarkers of cardiac dysfunction. CPR and ferritin were used as inflammatory biomarkers. The complete blood count of the IV generation was included as a hematological biomarker. Coagulation biomarkers included the levels of D-dimer, Prothrombin Time (PT) and Partial Thromboplastin Time (PTT). The units of measurement for each biomarker were standardized according to international standards for all biomarkers registered in all participant institutions. Moreover, biomarkers were grouped by type and classified based on their results as normal or abnormal. This standardization allowed for comprehensive data analysis and ensured consistency across all measurements.

Statistical analysis

Since a non-probabilistic convenience sampling was performed, no prior sample size calculation was conducted. Descriptive analysis of the data was performed. The normality of the variables was evaluated using the Shapiro–Wilk test and boxplots. In case of rejecting the

hypothesis of normality, data were reported as median (interquartile range [IQR]). Categorical variables were presented as number and percentage. For group comparisons of continuous variables with a normal distribution, the student's t-test was used, while the Wilcoxon rank-sum test was used for non-Gaussian distributions. Proportional comparisons were made using the chi-square test or Fisher's exact test, depending on the frequency of expected values. A significance level of $p < 0.05$ was considered for all statistical tests.

Cluster analysis

The strategy proposed by Lebart et al. (1995) [17] for multivariate data exploration was used for biomarkers such as leukocytes, lymphocytes, hemoglobin, hematocrit, platelets, PT, PTT, International Normalized Ratio (INR), creatinine, serum sodium, serum potassium, blood urea nitrogen (BUN), lactate dehydrogenase (LDH), aspartate transaminase (AST), ferritin, and alanine aminotransferase (ALT). Myocardial injury and myocardial dysfunction biomarkers, as well as procoagulants, were excluded from the factorial analysis due to bias associated with their routine clinical use. Therefore, patients with low suspicion or mild severity of the disease did not undergo these tests. We chose to focus on laboratory markers that did not correlate with disease severity in their ordering process. This strategy combines factorial methods with cluster analysis, with principal component analysis (PCA) being the factorial method used in this case.

PCA was selected over alternative dimensionality reduction techniques due to its specific advantages in biomarker analysis. Unlike Factor Analysis, which assumes the presence of latent variables that may not exist in biomarker data, PCA constructs linear combinations of the original variables that maximize variance explanation. While t-distributed Stochastic Neighbor Embedding (t-SNE) and Uniform Manifold Approximation and Projection (UMAP) excel at preserving local structure through non-linear mappings, they do not permit data reconstruction, making PCA more suitable for interpreting biomarker relationships. Multiple Correspondence Analysis extends PCA for categorical variables by incorporating chi-square distances, whereas Independent Component Analysis (ICA) prioritizes the identification of independent signal sources rather than variance maximization. The linear transformation inherent to PCA facilitates direct interpretation of biomarker contributions through loading patterns.

For clustering, Ward's hierarchical method was applied to the PCA scores. While not entirely robust to outliers, this approach offers advantages over alternatives such as K-means, which assumes spherical clusters, and DBSCAN, which struggles with varying cluster densities. Ward's method iteratively merges observations by minimizing the increase in total within-cluster variance, thereby generating a hierarchical structure that enhances the understanding of patient subgroup relationships. The integration of PCA with Ward's clustering enables both dimensionality reduction and patient stratification while preserving the interpretability of original biomarker contributions [18, 19].

The objective was to obtain clusters with internally homogeneous characteristics while being heterogeneous among themselves. The determination of the number of principal components was done through scree plot analysis. Additionally, the number of groups was established using two methods: the Within Sum of Squares (WSS) method and the average silhouette method [17]. The groups are not modifiable during the statistical procedure; the researcher can only select the variables to use but cannot alter the resulting groups. All statistical analyses were performed using R version 4.2.0 (R Foundation for Statistical Computing) through RStudio 2023.06.1 + 524.

Results

Demographic characteristics

A total of 3,260 patients with confirmed COVID-19 infection were included in this study, with a notably higher proportion of males (63.2%) compared to females (36.8%). Relevant cardiovascular comorbidities were identified in both sexes, but with striking differences in prevalence. Males had a significantly higher prevalence of coronary artery disease (Male: 8.5% vs. Female: 5.6%, $p = 0.027$) and smoking (Male: 16.3% vs. Female: 8.5%, $p < 0.01$) compared to females. In contrast, the most prevalent comorbidities in females were hypertension (Female: 53% vs Male: 46.0%, $p < 0.001$), diabetes mellitus (Female: 28.6% vs Male: 25.5%, $p = 0.055$), and overweight/obesity (Female: 48.9% vs Male: 50.2%, $p = 0.5$), with only the difference in hypertension being statistically significant. Females also had higher rates of asthma/chronic obstructive pulmonary disease (COPD) (Female: 10.3% vs Male: 7.9%, $p = 0.061$) and autoimmune disease (Female: 5.8% vs Male: 2.8%, $p < 0.01$). Other comorbidities such as dyslipidemia (Male: 14.2% vs Female: 13.2, $p = 0.4$), heart failure (Male: 8.9% vs Female: 7.8%, $p = 0.3$), and atrial fibrillation (Male: 3.3% vs Female: 3.9%, $p = 0.4$) showed no significant differences between sexes. Chronic kidney disease (Female: 8.4% vs Male: 8.2%, $p = 0.6$) and cancer (Female: 5.3% vs Male: 3.6%, $p = 0.027$) had a slightly higher prevalence in females than in males, with the latter being statistically significant. Overall, these results show the distinct cardiovascular risk profiles of male and female COVID-19 patients, with

Table 1 Demographic characteristics

Characteristics		Sex		*p*-value[2]
	n = 3,260[1]	Female, *n* = 1,201[1]	Male, *n* = 2,059[1]	
Age	61.00 (48.00, 71.00)	62.00 (49.00, 72.00)	60.00 (48.00, 70.000)	**0.011**
Comorbidities				
Overweight/obesity	1,621 (49.70%)	587 (48.90%)	1,034 (50.20%)	**0.5**
Diabetes mellitus	869 (26.70%)	344 (28.60%)	525 (25.50%)	0.055
Hypertension	1,596 (49.00%)	637 (53.00%)	959 (46.00%)	**< 0.001**
Dyslipidemia	451 (13.80%)	158 (13.20%)	293 (14.20%)	0.4
Asthma / chronic obstructive pulmonary disease	287 (8.80%)	124 (10.30%)	163 (7.90%)	0.061
Autoimmune disease	127 (3.90%)	70 (5.80%)	57 (2.80%)	**< 0.001**
Chronic kidney disease	270 (8.30%)	102 (8.40%)	168 (8.20%)	0.6
Cancer	139 (4.30%)	64 (5.30%)	75 (3.60%)	**0.027**
Coronary artery disease	244 (7.50%)	68 (5,60%)	176 (8,50%)	**0.027**
Heart failure	182 (5.60%)	67 (5.60%)	115 (5.60%)	> 0.9
Atrial fibrillation	115 (3.50%)	47 (3.90%)	68 (3.30%)	0.4
Stroke	102 (3.10%)	48 (4.00%)	54 (2.60%)	**0.039**
Smoking	438 (13.40%)	102 (8.50%)	336 (16.30%)	**< 0.001**

[1] n (%)

[2] Pearson's Chi-squared test

males exhibiting more lifestyle-related risk factors and females showing higher rates of chronic metabolic and inflammatory conditions (Table 1).

Laboratory findings

Males exhibited a higher incidence of lymphopenia compared to females. Females demonstrated lower hemoglobin levels than males; however, these levels remained above the diagnostic threshold for anemia, which aligns with their hematocrit values. Neither group presented with thrombocytopenia. Statistically significant differences were noted in PT (Male: 13.0 vs Female: 13.3, $p < 0.01$), and in aPTT (Male: 32.08 vs Female: 31.0, $p < 0.01$) between sexes, though these differences lacked clinical relevance. Similarly, potassium levels displayed statistical significance without clinical implications (Male: 4.16 vs Female:4.1, $p < 0.01$). D-dimer levels were statistically significant overall, with median values for both sexes exceeding the accepted normal threshold of 0.5 µg/mL (Male: 0.71 vs Female: 0.8, $p = 0.024$). Ferritin levels were significantly elevated in males; but both sexes exhibited elevated levels with a more pronounced increase in males, yet these levels did not reach the threshold suggestive of hemophagocytic syndrome (> 500 ng/dl) (Male: 1024 vs Female: 485.35, $p < 0.001$). Additionally, CRP levels were higher in males, indicating greater inflammatory responses in this group (Male: 12.34 vs Female: 7.8, $p < 0.001$) (Table 2).

Cardiovascular complications and outcomes

Cardiovascular complications showed significant differences in the incidence of cardiac arrhythmias, pulmonary embolism, and decompensated heart failure. Arrhythmias were more frequent in males compared to females (Male: 10.0% vs Female: 7.5%, $p = 0.019$). Pulmonary embolism had a higher incidence in males compared to females (Male: 4.4% vs Female: 2.9%, $p = 0.040$). Similarly, decompensated heart failure was more prevalent in males compared to females (Male: 8.9% vs Female: 7.9%, $p = 0.007$). No statistically significant differences were found between males and females for other events such as acute coronary syndrome (Male: 3.3% vs. Female: 2.2%, $p = 0.086$), myocarditis (Male: 1.2% vs. Female: 1.3%, $p = 0.8$), deep vein thrombosis (Male: 1.5% vs. Female: 0.8%, $p = 0.2$) and arterial thrombosis (Male: 0.8% vs. Female: 0.3%, $p = 0.14$) (Table 3).

In terms of outcomes, 1,745 patients required ICU hospitalization, with a significantly higher proportion of males compared to females (Male: 56.9% vs Female: 47.7%, $p < 0.001$). The overall mortality rate was 25.5%, higher in males than in females (Male: 27.5% vs Female: 22.1%, $p = 0.003$), (Table 3).

Cluster results

Cluster analysis identified three distinct groups based on biomarker patterns, as follows:

Table 2 First laboratory test available after admission

Laboratory test			Sex		*p*-value[2]
	n = 3,260[1]	Results	Female, *n* = 1,201[1]	Male, *n* = 2,059[1]	
White blood cells cel/µL	3,235	8,710.00 (6,310.00, 12,125.00)	8,225.00 (6,000.00, 11,372.50)	9,010.00 (6500.00, 12,610.00)	< 0.001
Lymphocytes cel/µL	3,139	1,030.00 (700.00, 1,480.00)	1,152.00 (790.00, 1,590.00)	980.00 (658.00, 1,390.00)	< 0.001
Hemoglobin gr/dl	3,196	13.60 (12.10, 14.90)	12.90 (11.60, 14.00)	14.10 (12.70, 15.30)	< 0.001
Hematocrit %	3,158	40.20 (36.10, 44.00)	38.40 (34.80, 41.88)	41.60 (37.60, 45.00)	< 0.001
Platelets cel/µL	3,230	228,500.00 (176,000.00, 297,000.00)	239,000.00 (187,000.00, 307,000.00)	220,000.00 (170,000.00, 288,000.00)	< 0.001
PT seg	2,540	13.20 (12.00, 14.60)	13.00 (11.90, 14.30)	13.30 (12.20, 14.80)	< 0.001
aPTT seg	2,352	31.80 (28.00, 36.80)	31.00 (27.80, 35.90)	32.08 (28.35, 37.20)	< 0.001
INR	2,408	1.10 (1.02, 1.22)	1.09 (1.00, 1.20)	1.12 (1.03, 1.23)	< 0.001
Creatinine mg/dl	3,192	0.90 (0.72, 1.25)	0.78 (0.61, 1.03)	1.00 (0.80, 1.36)	< 0.001
Sodium mmol/L	2,906	137.00 (134.00, 140.00)	137.00 (134.00, 140.00)	137.00 (134.00, 139.22)	0.14
Potassium mmol/L	2,906	4.10 (3.79, 4.55)	4.10 (3.68, 4.50)	4.16 (3.80, 4.59)	< 0.001
BUN mg/dl	2,989	18.00 (12.50, 28.90)	15.80 (10.75, 25.30)	19.00 (13.50, 30.46)	< 0.001
LDH UI/L	2,703	369.00 (269.00, 515.25)	341.00 (251.50, 475.00)	389.00 (283.00, 539.00)	< 0.001
ASTU/L	2,659	42.00 (29.00, 65.75)	37.00 (25.00, 56.33)	46.00 (30.00, 70.00)	< 0.001
ALT U/L	2,583	37.00 (24.00, 60.00)	31.00 (20.00, 49.70)	41.54 (27.00, 67.00)	< 0.001
Glucose mg/dl	2,299	125.00 (103.00, 175.00)	123.00 (101.00, 177.40)	126.00 (104.80, 175.00)	0.3
CPK U/L	1,281	104.00 (53.00, 261.00)	80.50 (43.00, 165.75)	124.00 (60.00, 316.50)	< 0.001
D Dimer µg/ml	2,534	0.75 (0.38, 1.53)	0.80 (0.41, 1.68)	0.71 (0.36, 1.50)	0.024
Fibrinogen mg/dl	1,244	550.00 (436.00, 663.00)	510.00 (426.00, 616.00)	570.00 (448.00, 687.50)	< 0.001
Ferritine ng/ml	2,337	820.00 (396.00, 1481.50)	485.35 (215.75, 963.00)	1,024.00 (557.45, 1,724.50)	< 0.001
Sensitive CRP mg/dl	1,733	10.11 (4.54, 20.00)	7.80 (3.00, 16.00)	12.34 (5.70, 21.70)	< 0.001
Ultrasensitive CRP mg/dl	1,063	11.60 (4.49, 22.17)	8.40 (3.09, 17.04)	13.81 (6.00, 24.12)	< 0.001
Troponin I ng/ml	375	0.02 (0.00, 0.10)	0.02 (0.00, 0.10)	0.02 (0.00, 0.10)	0.6
Troponin T ng/ml	143	0.02 (0.01, 0.05)	0.02 (0.01, 0.05)	0.02 (0.01, 0.05)	0.7
Ultrasensitive Troponin I ng/ml	1216	0.01 (0.00, 0.03)	0.01 (0.00, 0.03)	0.01 (0.00, 0.03)	0.008
Ultrasensitive Troponin T ng/ml	494	0.0 (0.0058, 0.0)	0.0 (0.0049, 0.0)	0.0 (0.0062, 0.0)	0.088
BNP pg/ml	93	99.40(38.40, 424.00)	128.85 (31.92, 620.50)	99.40 (50.65, 344.00)	0.8
NT pro-BNP pg/ml	455	326.00 (81.00, 1,791.50)	426.50 (77.50, 1,724.25)	310.00 (81.50, 2,007.00)	0.9

Abbreviations: *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *aPTT* active partial thromboplastin time, *BNP* brain natriuretic peptide, *BUN* blood urea nitrogen, *cells/µL* cells per microliter, *CRP* C-reactive protein, *g/dL* grams per deciliter, *LDH* lactic dehydrogenase, *mg/dL* milligrams per deciliter, *ng/mL* nanograms per milliliter, *NT-proBNP* N-terminal Pro-B-type Natriuretic Peptide, *pg/mL* picograms per milliliter, *PT* prothrombin time, *sec* seconds, *U/L* units per liter, *µg/mL* micrograms per milliliter

[1] Median (IQR); n (%)

[2] Pearson's Chi-squared test

- Cluster 1, labeled as typical, was the largest group, including 1,219 patients. This cluster was characterized by a higher number of biomarkers within the normal range, except for elevated ferritin, reflecting the typical proinflammatory profile of COVID-19 disease.
- Cluster 2, labeled as pro-thrombotic, composed of 41 patients, mostly showed the lowest ferritin range and elevated PT (81 s).
- Cluster 3, labeled as inflammatory, consisting of 102 patients, was marked by low levels of hemoglobin and lymphocytes, elevated creatinine and BUN, a discreet rise in ALT activity, and high levels of LDH and ferritin.

The median age of patients in the three cluster groups were as follows: Cluster 1 had the youngest patients (60 years), followed by Cluster 3 (64.5 years), and Cluster 2 (68 years). Sex distribution revealed a predominance of males across all clusters, with the highest percentage in Cluster 3 (74.5%). Conversely, the most prevalent cluster for females was Cluster 1 (34.7%) (Table 4).

Table 3 Cardiovascular complications and outcomes by sex

Variable		Sex		*p*-value[2]
	n = 3,260[1]	Female, *n* = 1,201[1]	Male, *n* = 2,059[1]	
Complications				
Acute coronary syndrome	94 (2.90%)	26 (2.20%)	68 (3.30%)	0.08
Heart failure	278 (8.50%)	94 (7.80%)	184 (8.90%)	**0.3**
Cardiac arrhythmia	68 (3.30%)	90 (7.50%)	206 (10.00%)	**0.019**
Myocarditis	40 (1.20%)	16 (1.30%)	24 (1.20%)	0.8
Pulmonary embolism	126 (3.90%)	35 (2.90%)	91 (4.40%)	**0.040**
Deep vein thrombosis	40 (1.20%)	10 (0.80%)	30 (1.50%)	0.2
Arterial thrombosis	21 (0.60%)	4 (0.30%)	17 (0.80%)	0.14
Outcomes and discharge status				
Intensive Care Unit	1,745 (53.50%)	573 (47.70%)	1,172 (56.90%)	**< 0.001**
Death	831 (25.50%)	266 (22.10%)	565 (27.50%)	**0.003**

[1] n (%)

[2] Pearson's Chi-squared test

Based on the cluster classification and regarding admissions to the ICU, there was a notable variation among clusters. Cluster 3 showed the highest ICU admission rate with an interquartile range (IQR) of 68.5%, while cluster 2 had the lowest proportion, with 43.9%. Interestingly, there were no statistically significant differences in the median length of stay in the ICU between clusters. Additionally, there was a progressive increase in the proportion of deaths from cluster 1 to cluster 3. The death proportion was 22.6% in cluster 1, 31.7% in cluster 2, and 52% in cluster 3. This study found no statistically significant differences in the cause of death among the clusters, with most of the deaths (73.6%) resulting from non-cardiovascular causes, and no statistically significant differences between sexes (Table 4).

Regarding the prevalence of kidney injury during hospitalization, a linear pattern emerged: 3.8% in cluster 1, 19.5% in cluster 2, and 30.2% in cluster 3. There was a notable difference in the prevalence of anticoagulation therapy during admission for COVID-19; a higher proportion of patients in cluster 2 received this treatment, likely related to prolonged coagulation times in this group, However, no statistically significant differences were found in the sex comparison (Table 4).

Discussion

The impact of sex on COVID-19 outcomes is a significant and well-documented feature in the current clinical literature across various patient cohorts worldwide [20–22]. Generally, male population experiences worse outcomes than female population [20]. The underlying causes of this difference have been debated, with many studies attributing it to a higher burden of comorbidities, greater smoking prevalence, among other factors [15, 23]. Additionally, other studies have focused on serological biomarkers as a key area of discussion regarding sex differences [24]. For example, Lumish et al. found higher levels of high-sensitivity cardiac troponin T, ferritin, D-dimer, and creatinine associated with higher mortality in males compared to females [25].

Moreover, the cause of worse cardiovascular outcomes in males is not clear; however, a protective mechanism in females have been proposed due to a higher activation of estrogen-dependent ACE2 receptors, which favor a better anti-inflammatory response to the disease and better blood pressure control through regulation of the renin-angiotensin system. This, in turn, results in lower myocardial injury, arrhythmias, myocarditis, and pulmonary embolism, providing greater protection against COVID-19 [26, 27].

In our study, which included a sample of 3,260 hospitalized patients with COVID-19 in LA&C, we confirmed notable sex-based differences, with a higher percentage of males hospitalized compared to females. This highlights the increased risk that LA&C males face in terms of worse outcomes and mortality due to COVID-19. Interestingly, our findings are consistent with those presented by Ashktora et al. [28], who also found a higher COVID-19 incidence in males compared to females (52.60% and 47.30%, respectively). However, their study did not distinguish between in-hospital and outpatient management and was conducted in eight countries in Latin America, including Peru, Ecuador, Bolivia, Mexico, Chile, Argentina, Venezuela, and Brazil. In contrast, our study had a broader sample, including subjects from Central America and the Caribbean region, in addition to other South

Table 4 Biomarkers and outcomes analyzed by clusters

Variable	Overall, $n=1362$[1]	Cluster			*p*-value[2]
		1, $n=1219$[1]	2, $n=41$[1]	3, $n=102$[1]	
Sex					0.2
Female	463 (34.0%)	423 (34.7%)	14 (34.1%)	26 (25.5%)	
Male	899 (66.0%)	796 (65.3%)	27 (65.9%)	76 (74.5%)	
Age (median)	61.0 (49.0, 70.0)	60.0 (49.0, 70.0)	68.0 (57.0, 75.0)	64.5 (56.0, 73.8)	**<0.001**
Leukocytes /mm^3	8926.5 (6500.0, 12,445.0)	8900.0 (6545.0, 12,400.0)	7600.0 (5100.0, 9800.0)	10,380.0 (6802.5, 14,142.5)	**0.002**
Lymphocyte/ mm^3	982.0 (662.5, 1379.0)	1000.0 (680.0, 1388.0)	1120.0 (720.0, 1560.0)	800.0 (512.5, 1194.0)	**0.001**
Hemoglobin mg/dl	13.7 (12.3, 15.0)	13.9 (12.5, 15.1)	12.8 (10.3, 14.6)	11.7 (9.4, 12.9)	**<0.001**
Hematocrit mg/dl	40.4 (36.9, 44.0)	41.0 (37.5, 44.2)	37.1 (30.9, 42.2)	35.0 (28.0, 39.0)	**<0.001**
Platelet count / mm^3	233,500.0 (180,000.0, 302,750.0)	235,000.0 (181,500.0, 302,500.0)	221,000.0 (153,000.0, 276,000.0)	222,000.0 (164,500.0, 307,000.0)	0.12
PT	13.2 (12.1, 14.5)	13.1 (12.0, 14.2)	81.0 (58.7, 96.0)	13.2 (12.0, 15.1)	**<0.001**
PTT	32.0 (28.3, 36.6)	31.7 (28.0, 36.0)	37.2 (25.9, 52.8)	32.9 (30.0, 41.0)	**<0.001**
INR	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	1.1 (1.1, 3.9)	1.2 (1.0, 1.3)	**<0.001**
Creatinine mg/dl	0.9 (0.7, 1.2)	0.9 (0.7, 1.1)	1.0 (0.8, 1.3)	3.6 (2.0, 6.7)	**<0.001**
Sodium meq/l	137.0 (134.0, 139.0)	137.0 (134.0, 139.0)	136.0 (132.0, 138.1)	136.5 (133.0, 140.0)	0.3
Potasium meq/l	4.1 (3.8, 4.5)	4.1 (3.8, 4.5)	4.1 (3.8, 4.6)	4.8 (4.4, 5.3)	**<0.001**
Bun	17.8 (13.0, 27.1)	16.9 (12.5, 24.6)	22.0 (16.8, 28.0)	57.2 (38.4, 83.4)	**<0.001**
LDH UI/L	382.0 (278.2, 516.0)	376.0 (277.5, 501.5)	308.0 (238.0, 393.0)	518.5 (366.8, 806.0)	**<0.001**
AST UI/L	42.0 (29.0, 65.0)	41.9 (29.0, 63.9)	38.0 (26.0, 49.0)	62.0 (32.5, 126.3)	**<0.001**
Ferritin ng/ml	859.9 (429.4, 1509.8)	835.0 (428.0, 1461.0)	551.0 (202.0, 983.0)	1534.5 (706.1, 2697.5)	**<0.001**
ALT UI/L	37.0 (25.0, 58.0)	36.0 (25.0, 57.7)	32.0 (21.0, 46.0)	44.5 (21.6, 80.2)	0.081
Kidney injury	91 (6.7%)	46 (3.8%)	8 (19.5%)	37 (36.3%)	**<0.001**
Anticoagulant therapy	61 (4.5%)	42 (3.4%)	11 (26.8%)	8 (7.8%)	**<0.001**
ICU admission	852 (62.6%)	764 (62.7%)	18 (43.9%)	70 (68.6%)	**0.021**
Days in ICU (median)	12.0 (6.0, 20.0)	12.0 (6.0, 20.0)	15.0 (12.2, 27.2)	13.0 (7.0, 25.0)	0.055
Discharge status					**<0.001**
Deceased	341 (25.1%)	275 (22.6%)	13 (31.7%)	53 (52.0%)	
Cause of death					0.8
Cardiovascular	90 (26.4%)	71 (25.8%)	3 (23.1%)	16 (30.2%)	
Non-cardiovascular	251 (73.6%)	204 (74.2%)	10 (76.9%)	37 (69.8%)	

Abbreviations: *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *aPTT* active partial thromboplastin time, *BUN* blood urea nitrogen, *CRP* C-reactive protein, *ICU* intensive care unit, *LDH* lactic dehydrogenase, *mg/dL* milligrams per deciliter, *ng/mL* nanograms per milliliter, *pg/mL* picograms per milliliter, *PT* prothrombin time, *sec* seconds, *U/L* units per liter, *µg/mL* micrograms per milliliter

[1] Median (IQR); n (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

American countries. This geographic inclusion provides a more comprehensive perspective of the situation in LA&C, enriching the understanding of sex differences in the context of the disease.

The presence of cardiovascular comorbidities in the COVID-19 population in LA&C, as observed in our registry, was higher in men, with a greater prevalence of coronary artery disease, overweight/obesity, hyperlipidemia, and smoking. These findings play a crucial role in mortality outcomes in COVID-19, as they contribute to increased susceptibility and a more severe course of the disease. This is consistent with other studies that have described a correlation between comorbidities and poor outcomes [28]. Moreover, in our study, the mortality rate in males was 1.25 times higher than in females, following the same global trend reported by the WHO, where male mortality was 1.70 times higher [1].

Inflammatory biomarkers such as ferritin and CRP were higher in males, as previously reported in several investigations [16, 29–31]. Numerous authors have observed higher concentrations of acute-phase inflammatory biomarkers

such as ferritin and CRP in males, which are associated with disease severity and worse outcomes. These biomarkers have been suggested for monitoring the course of COVID-19 infection [16]. The elevation of CRP and ferritin levels in males was also reported by Quin. et al. in a retrospective study conducted in China, which included 548 hospitalized COVID-19 patients. Additionally, they found higher levels of interleukin-10 (IL-10), along with lower lymphocyte levels in males compared to females [10]. A recent study by Amado et al. in Rio de Janeiro, Brazil, comparing clinical data between the first and second waves of the pandemic, also found significantly higher levels of ferritin, CRP, and D-dimer in patients with severe forms of COVID-19. This finding was associated with increased mortality. However, this study did not perform sex comparisons [32]. In this context, we can highlight a notable observation regarding COVID-19. Despite the higher prevalence of autoimmune diseases (conditions that predispose individuals to a more severe inflammatory response) in the female population, male patients exhibited higher concentrations of inflammatory acute-phase reactants [33]. This observation may be attributed to more severe disease progression in males and the association of these biomarkers with poorer clinical outcomes [16, 30–32].

Regarding hematological and coagulation biomarkers, we observed greater lymphopenia in males, while D-dimer levels were higher in females (Table 2). Lymphopenia has been associated with cardiovascular risk factors, primarily hyperlipidemia. This was observed by Mathew et al. [34] in a study that found a correlation between hyperlipidemia and decreased plasmablasts and T cells in COVID-19 patients with lymphopenia. The decrease in T cells was associated with increased inflammation, manifested by higher levels of CRP, D-dimer, and ferritin, contributing to more severe disease outcomes. In our study, the percentage of dyslipidemia did not vary much (14.20% vs. 13.20% in males and females, respectively). However, this finding, combined with the higher rate of lymphopenia reported in males, could support the observed worse outcomes [14]. On the other hand, our study observed lower hemoglobin levels in the female population compared to the male population. This finding may be attributed to periodic blood loss associated with menstruation [35, 36]. However, it is important to highlight the higher prevalence of autoimmune diseases in the female population, which may contribute to this observation as part of a multifactorial phenomenon [37].

Cardiovascular biomarkers such as BNP and NT-proBNP were higher in females, while troponin levels did not show sex differences. In contrast to our study, Lumish et al. found a statistically significant difference in troponin levels, with the male population having higher concentrations of serum troponin and increased mortality [25]. On the other hand, the role of natriuretic peptides in sex differences is controversial because we did not find formal clinical studies in LA&C comparing outcomes between sexes. Although BNP and NT-proBNP levels have been described as prognostic indicators for poor outcomes in COVID-19, our results showed higher levels of these biomarkers in females but with higher male mortality [38–40].

Troponin T and troponin I have been found to be associated with severe COVID-19, worse outcomes, and a higher risk of death in some studies [41]. Higher levels of troponin have also been reported in the male population [41]. Our troponin results showed a different pattern compared to global descriptions. Troponin was measured in 65% of the population, with no difference in results based on sex. However, there was a difference in the extent of coronary artery disease, as the number of affected vessels was lower in females than in males (66.70% vs. 87.50%) [12]. Our combined data suggest that the degree of systemic inflammation and cardiovascular involvement may play an important role in the severity of the disease and mortality, particularly in males, without showing differences in the LA&C population compared to global reports. D-dimer was found to be higher in females, and this finding was not related to the degree of mortality or cardiovascular complications, suggesting the need for further investigation.

In our cluster analysis, different biomarker patterns were observed among the three groups. Cluster 1, labeled as the "typical" group and characterized by normal levels of most biomarkers except ferritin, likely represents a milder form of COVID-19, as suggested by the relatively low mortality rate and reduced frequency of ICU admissions. This aligns with the understanding that less severe cases of COVID-19 often do not exhibit pronounced laboratory abnormalities, as reported by Cao et al. in their systematic review with meta-analysis comparing laboratory results in patients with mild versus severe COVID-19 [42]. This insight could assist clinicians in determining whether continued management and monitoring in an outpatient setting is appropriate, thereby potentially reducing congestion within the healthcare system. Cluster 2, characterized as "pro-thrombotic," displays a profile with less elevated ferritin but prolonged PT values. This finding is significant as it may emphasize the role of coagulation abnormalities in COVID-19 patients, a well-documented phenomenon in the literature, associated with an increased risk of thrombotic events and disseminated intravascular coagulation (DIC) [43]. One possible explanation is that PT elevation may occur during inflammatory processes such as COVID-19 [43], and it has been used as a biomarker for disease severity [44, 45]. Additionally, 26.8% of cluster 2 patients

were receiving anticoagulant therapy at the time of hospital admission, which could prolong PT. Therefore, it is imperative that this patient profile is identified early by physicians to initiate anticoagulant therapy or adjust pre-existing treatments, given the high mortality associated with thrombotic events in COVID-19. Furthermore, this insight underscores the need to expand paraclinical investigations, including hematological tests such as chromogenic assays, to improve diagnostic accuracy and guide clinical decision-making. The most significant laboratory differences were observed in cluster 3, characterized as "inflammatory," showing substantial biomarker abnormalities, including low hemoglobin and lymphocytes, along with elevated creatinine, BUN, ALT, AST, LDH, and ferritin. These abnormalities indicate a systemic inflammatory response and multiple organ involvement, known to correlate with disease severity and poor outcomes in COVID-19 [14, 16, 42, 46]. The high ICU admission rate and mortality in this group further reinforce this association. The linear increase in mortality rates and prevalence of renal injury among the clusters may reflect the progressive impact of COVID-19 under the influence of a systemic inflammatory storm and organ dysfunction [31]. Consequently, the identification of patients with an inflammatory profile should serve as a critical alert for physicians regarding the necessity of in-patient monitoring, the heightened risk of ICU admission, and the importance of initiating treatment at an earlier stage.

In this cluster analysis, we must highlight the absence of statistical significance differences based on sex in our COVID-19 clusters ($p=0.2$). Therefore, we can interpret that sex differences in individual biomarkers do not necessarily translate into differences in the composition of groups of patients with similar profiles. The formation of clusters or subgroups by the algorithm can be influenced by multiple factors besides sex, such as age, comorbidities, or disease severity, which can mask sex differences. The complex interaction between different biomarkers and clinical factors can result in patient profiles that transcend the sex differences observed in individual biomarkers. Although sex differences in individual biomarkers may be more pronounced in the general population, they are less evident in specific subgroups of patients with severe COVID-19. The lack of significant sex differences in the clusters does not invalidate the differences observed in individual biomarkers but rather suggests a multifactorial influence on the composition of the subgroups.

Therefore, our analysis not only delineates the heterogeneity in COVID-19 presentations by sex but also highlights the potential role of specific laboratory biomarker assessments in strengthening and expediting early COVID-19 response pathways. All of this was achieved using cluster analysis as a dimensionality reduction tool, with the aim of identifying the most important features of the disease process [47, 48].

Conclusions and future perspectives

In hospitalized patients with COVID-19 in LA&C, males have elevated levels of inflammatory biomarkers related to immunity and a higher degree of lymphopenia, as well as higher mortality. Additionally, when conducting a cluster analysis, those with an 'inflammatory' profile have a higher risk of ICU admission and non-cardiovascular mortality. Moreover, based on patient cluster assignment, physicians could make earlier clinical decisions regarding patient management. Specifically, if a patient is assigned to Cluster 1, early discharge should be considered; if assigned to Cluster 2, early anticoagulation treatment may be warranted; and if assigned to Cluster 3, closer monitoring and early ICU admission should be prioritized. A sex-focused approach, a better understanding of molecular cascades and hormonal differences by sex, and profiling laboratories in clusters could enable medical and research teams to implement specific therapeutic approaches, identify higher-risk patients, assess prognosis, and impact disease outcomes. Furthermore, the implementation of these statistical models can enable the development of faster predictive models for future emergent respiratory infections, potentially allowing for a reduction in mortality.

Strenghts and limitations

The main strength of our research is that it is among the first studies to compare sex-based biomarkers in Latin America and the Caribbean (LA&C). Additional strengths include its multicentric design, which encompasses various medical centers across the continent, the considerable sample size, the standardized collection of biomarker data, and the uniformity of measurement units.

However, this study has limitations inherent to open-cohort, multicenter prospective studies based on medical records. Not all cases were consecutive, as patient inclusion may have been influenced by healthcare challenges during the COVID-19 pandemic. Additionally, the sample was non-probabilistic, as institutional participation was voluntary. While medical history and comorbidities were considered, pre-hospitalization treatments were not recorded, which may have influenced biomarker levels and clinical outcomes.

Furthermore, data collection occurred during the early stages of the COVID-19 pandemic. According to the Economic Commission for Latin America and the Caribbean, only 2.7% of the LA&C population had been vaccinated at the time of data collection, limiting the applicability of the findings to vaccinated patients. However, this also makes our findings particularly relevant for

understanding the natural history of COVID-19 infection in unvaccinated individuals [49]. Nevertheless, this aspect could be further explored in the follow-up phase.

Moreover, the study lacks long-term clinical follow-up, preventing the assessment of potential variations in mortality or cardiovascular outcomes beyond 30 days after discharge. Regarding cardiovascular biomarker measurement, some sites determined biomarker levels based on the technological resources available in each country or hospital (e.g., troponin I, high-sensitivity troponin I), potentially introducing variability in the dataset.

Finally, we emphasize the importance of conducting external validation across different temporal and geographical settings to enhance the robustness of our findings [50, 51]. Evidence from the literature highlights that evaluating clustering methods under diverse conditions helps verify the stability and reproducibility of identified patterns, thereby ensuring their reliability and practical applicability in real-world settings.

Abbreviations

COVID-19	Coronavirus Disease 2019
LA&C	Latin America and the Caribbean
ICU	Intensive Care Unit
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
WHO	World Health Organization
CRP	C-reactive protein
IL-6	Interleukin 6
LDH	Lactate dehydrogenase
ARDS	Acute Respiratory Distress Syndrome
CIFACAH	Inter-American Council on Heart Failure and Pulmonary Hypertension
IASC	Inter-American Society of Cardiology
CARDIO COVID 19–20	Registro Latinoamericano de Enfermedad Cardiovascular y COVID-19
FVL	Fundación Valle del Lili
CIC	Centro de Investigaciones Clínicas
REDCap	Research Electronic Data Capture
BNP	B-type Natriuretic Peptide
NT-proBNP	N-terminal Pro-B-type Natriuretic Peptide
IV	Intravenous
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
IQR	Interquartile Range
INR	International Normalized Ratio
BUN	Blood Urea Nitrogen
AST	Aspartate Transaminase
ALT	Alanine Aminotransferase
WSS	Within Sum of Squares
COPD	Chronic Obstructive Pulmonary Disease
ACE2	Angiotensin-Converting Enzyme 2
IL-10	Interleukin-10
DIC	Disseminated Intravascular Coagulation

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Informed consent statement
The study was conducted in accordance with the Declaration of Helsinki. Patient consent was waived by the ethics committee of the FVL (#1835) in Cali, Colombia, and by the Scientific Committee and Academic Committee of the IASC, as no interventions were intended for the participants. Additionally, the anonymization of participants´ personal information was guaranteed.

Authors' contributions
FCE, JAMO, VAR: investigation, writing original draft—review and editing. MEF: visualization, investigation, writing—review and editing. YRC, MMB, HLG: methodology, data analysis, visualization, writing—review and editing. AAAT: visualization, writing—review and editing. EP, IM, FW, JLB, MS, WA, JCO, AU, JM, DQC, PO, NAF: project administration, writing—review. AVO: methodology, data analysis. JEG: project administration, methodology, investigation, writing—review and editing. All authors contributed to the article and approved the submitted version.

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Data availability
The data presented in this study are available within the article.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the CIC, the Ethics committee of the FVL (#1835) in Cali, Colombia, and by the Scientific Committee and Academic Committee of the IASC.

Competing interests
The authors declare no competing interests.

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