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The Chemokine MIG is Associated with an Increased Risk of COVID-19 Mortality in Mexican Patients

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is an emergent viral disease in which the host inflammatory response modulates the clinical outcome. Severe outcomes are associated with an exacerbation of inflammation in which chemokines play an important role as the attractants of immune cells to the tissues.

Objective: To evaluate the relationship of the chemokines IL-8, RANTES, MIG, MCP-1, and IP-10 with COVID-19 severity and outcomes in Mexican patients.

Methods: We analyzed the serum levels of IL-8, RANTES, MIG, MCP-1 and IP-10 in 148 COVID-19 hospitalized patients classified as mild (n=20), severe (n=61), and critical (n=67), as well as in healthy individuals (n=10), by flow cytometry bead array assay.

Results: Chemokine levels were higher in patients than in the healthy individuals, but only MIG, MCP-1, and IP-10 increased according to the disease severity, showing the highest levels in the critical group. MIG, MCP-1, and IP-10 levels were also higher in COVID-19 patients with comorbidities such as renal disease, type 2 diabetes, and hypertension. Moreover, elevated MIG levels seem to be related to organic failure/shock, and an increased risk of death.

Conclusions: Our results suggest that the increased levels of MCP-1, IP-10, and especially MIG might be useful in predicting severe COVID-19 outcomes and could be promising therapeutic targets.

Keywords: Chemokine, COVID-19, IL-8, RANTES, MIG, MCP-1, IP-10

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus (SARS-CoV)-2, is an emergent pandemic disease reporting more than 250 million confirmed cases and over five million deaths globally up to November 10th, 2021 (1). Clinically, COVID-19 manifests with a mild course in most of the cases with symptoms similar to the flu, although smell/taste loss is more

frequent in COVID-19 (2,3). Moreover, unlike the flu, COVID-19 cases seem to be more likely to develop severe illness: up to 20% of COVID-19 cases develop respiratory difficulties and hypoxemia, leading to acute respiratory distress syndrome (ARDS), the leading cause of death of COVID-19, along with other complications such as shock and multiorgan failure (2-4).

Severe COVID-19 has been observed to be linked to an exacerbation of the inflammatory response, characterized by a cytokine release syndrome, which leads to a damage mainly to the respiratory tract and lung tissue but can also have systemic repercussions (4, 5). Among the upregulated molecules in COVID-19 are the chemotactic cytokines or chemokines, which mediate the recruitment of immune cells to tissue, a hallmark of inflammation (6).

In this regard, enhanced chemokine expression is a common feature of viral infections and it has been documented for diverse respiratory viral diseases, including coronaviruses (7). Particularly for SARS-CoV-2/COVID-19, increased chemokine levels have been associated with its severity, specifically, there have been recurrent reports linking the chemokines interleukin-8 (IL-8), regulated on activation, normal T cell expressed and secreted (RANTES), monokine induced by gamma interferon (MIG), monocyte chemoattractant protein-1 (MCP-1), interferon-gamma induced protein (IP-10) to COVID-19 severity, thus suggesting them as potential disease biomarkers (3, 5, 8-15). However, most of these reports have been done in Asian and European populations, leaving the need of replicating these studies in other populations as we cannot rule out the possibility of a different response to disease due to differences in genetic and/or nutritional structure in addition to putative SARS-CoV-2 viral mutations.

With the above statement in mind, the objective of the present work was to evaluate the association of IL-8, RANTES, MIG, MCP-1, and IP-10 serum levels with the disease severity and other clinical characteristics of COVID-19 Mexican patients.

MATERIALS AND METHODS

Study Subjects

The present transversal prospective study included 148 COVID-19 hospitalized patients taken from two public (Culiacan General Hospital and Culiacan Civil Hospital) and one private hospital ("Médica de la Ciudad"); recruited in the period from April to June 2020.

COVID-19 diagnostic was based on a positive result of the SARS-CoV-2 RT-PCR assay of nasal and pharyngeal swabs samples. The patients were subdivided according to the severity into mild (n=20), severe (n=61), and critical (n=67) following Yang et al.'s criteria (5). Briefly, a mild patient presents COVID-19 symptoms without respiratory compromise. Severe cases exhibit blood oxygen saturation values <94% and/or respiratory rate ≥30/min, whereas critical individuals present respiratory failure with the need for invasive ventilation (oxygen saturation <85% with high flow nasal cannula) and/or failure of other organs/shock. Patient demographic, clinical, and laboratory data were obtained from medical archives records from the corresponding institution.

Additionally, a small healthy control group was included as a means to validate chemokine measurements. It was conformed by ten healthy blood donors from Culiacan General Hospital's blood bank. Their mean age was 46.8±4.4 years. Infectious, chronic, and metabolic diseases were discarded via interview and laboratory analyses, as stated in the Official Mexican Standard NOM-253-SSA1-2012 (16).

Informed consent was obtained from all the study participants directly or indirectly from their relatives. The study was approved by the Ethics in Medical Research Committee from the Culiacan General Hospital, where it was conducted following the ethical standards

of the Helsinki Declaration of 1975, revised in 1983.

Chemokine Analysis

Blood samples were taken from patients between 2-9 days after admission, and healthy individuals on admission to the blood bank. Serum samples were separated from coagulated blood and stored at -70°C. Levels of the chemokines IL-8, RANTES, MIG, MCP-1, and IP-10 were assessed at the same time using the Human Chemokine Kit BD™ Cytometric Bead Assay (CBA, Becton Dickinson, San José, CA, USA) following the manufacturer's instructions. Briefly, 50 µl of serum samples were mixed with 50 µl of the capture-beads mix (coated with specific antibodies) and 50 µl of detection reagent (a mixture of phycoerythrin PE-conjugated antibodies) to form complexes. Samples were centrifuged and washed to remove free antibodies and resuspended on 300 µl of wash buffer for their acquisition in a BD Accuri C6 flow cytometer (Becton Dickinson, San José, CA, USA). A 200,000 threshold was established on FCS and at least 2,100 events were gating in R1 at a low speed. Also, recombinant chemokines of known concentration were prepared to generate standard curves (0 to 5,000 pg/ml). The quantification was performed with the FCAP Array v3,0 Software (Becton Dickinson, San José, CA, USA).

Statistical Analysis

The differences between the groups were analyzed by χ^2, Fisher's exact test, Mann-Whitney, or Kruskal Wallis test, as needed. Qualitative variables were expressed as frequencies and percentages while quantitative ones as median and interquartile ranges. These analyses were performed on SPSS statistics v.20 (SPSS Inc., Chicago, Ill, USA), and graphs were made in GraphPad Prism v.7 (GraphPad Software, San Diego, CA, USA). Moreover, receiver operating characteristic (ROC) curves and the area under the curves (AUC) of chemokine levels were calculated to predict invasive ventilation, organic failure/ shock, and death and to determine optimal cut-off values based on Youden's J index (17). These analyses were done with MedCalc software version 14 (MedCalc Software Ltd, Ostend, Belgium). Finally, hazard ratios were calculated with multivariate Cox proportional-hazard analysis based on chemokine cut-off points using R v.4.0.3 software (The R. Foundation, Vienna, Austria). Values of $P<0.05$ were considered statistically significant.

RESULTS

Clinical, demographical, and laboratory data of the patients can be found in Supplementary Table S1. In the chemokine level analysis, comparison with the healthy controls showed significant increases in all the analyzed chemokines in COVID-19 patient groups: IL-8 and RANTES in all the patient groups, MCP-1 and IP-10 in severe and critical patients, and MIG in critical patients (Figure 1). When comparing COVID-19 patients using the mild group as the reference, we observed increased IP-10 levels in severe and critical patients, the latter group also exhibiting increased MIG and MCP-1 levels (Figure 1). There were no differences in IL-8 and RANTES levels between the patient groups.

No differences in serum chemokine levels were observed in COVID-19 patients according to gender (Table 1). Also, we did not find an association between chemokine levels and COVID-19 symptoms (data not shown). However, the patients with hypertension (HT) showed increased IP-10 and MCP-1 levels (Figure 2). The latter also increased in the patients with type 2 diabetes (T2D), and IL-8 and MIG increased in the patients with chronic renal disease (RD) (Figure 2).

We performed ROC analysis to test if the chemokines could be predictors of disease worsening and to determine optimal cut-off points based on AUC. As shown in Table 2, MIG barely attains the category of a fair predictor of organic failure (AUC=0.7).

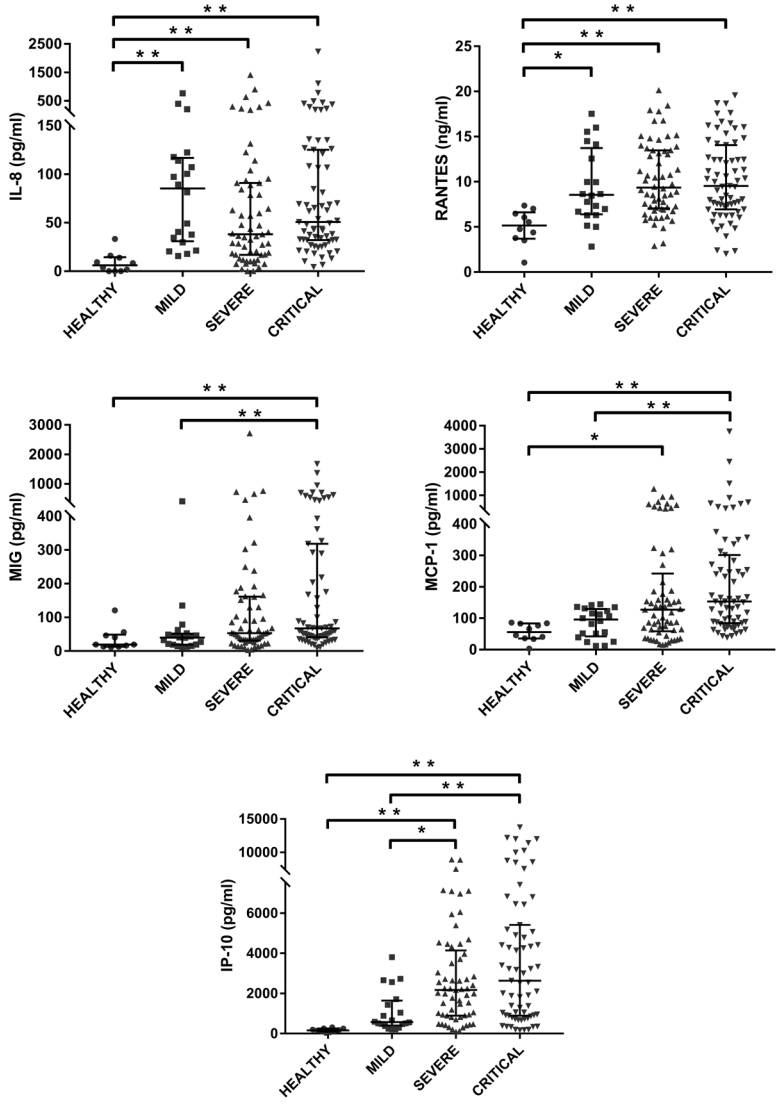

Figure 1. Serum chemokine levels of healthy individuals (n=10) and COVID-19 mild (n=20), severe (n=61), and critical patients (n=67). Values are expressed as median with interquartile ranges. *P<0.05, **P<0.01

Table 1. Chemokine levels in COVID-19 patients according to gender.

Chemokine*	Male n=93	Female n=55	P value
IL-8 (pg/ml)	43.71 (24.7-96.2)	50.73 (26.8-125.9)	0.607
RANTES (ng/ml)	9.25 (6.9-13.4)	9.44 (6.9-14.1)	0.589
MIG (pg/ml)	52.48 (31.2-176.4)	54.9 (39.2-165.9)	0.618
MCP-1 (pg/ml)	118.41 (67-227.7)	136.1 (71.9-254.1)	0.577
IP-10 (pg/ml)	1776.76 (714.5-4414.8)	2218 (885.4-4261.58)	0.527

*Values are expressed as median (interquartile ranges).

Although significant results were also observed for MIG and MCP-1 with invasive ventilation, MCP-1, and IP-10 with organic failure, and IL-8, MIG, MCP-1, and IP-10 with death; their AUC values ranged from 0.6 to 0.69, discarding their predictive utility but denoting an apparent association of high levels of these chemokines with COVID-19 clinical outcomes (Table 2).

Finally, using the cut-off points from the previous analysis, we performed a mortality predictive model which showed that high

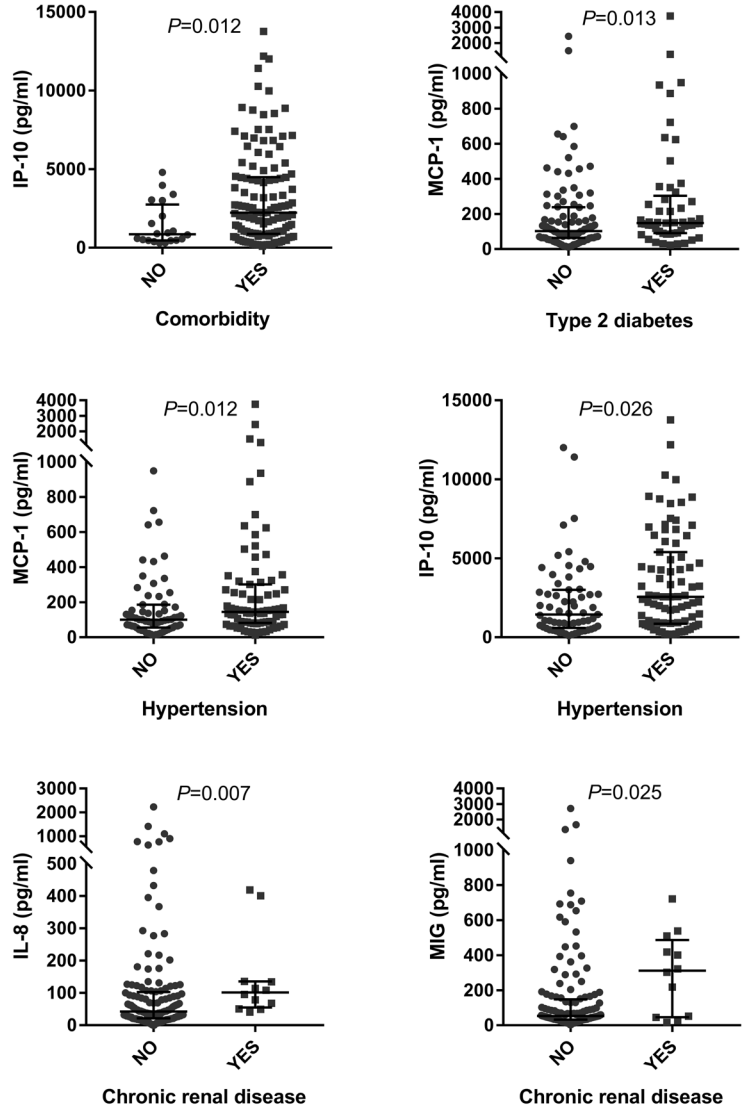

Figure 2. Association of serum chemokine levels with comorbidities (type 2 diabetes, hypertension, obesity, and/or chronic renal disease) in COVID-19 patients. Comorbidity No n=20, Yes n=126; Type 2 diabetes No n=93, Yes n=53; Hypertension No n=63, Yes n=83; Chronic renal disease No n=136, Yes n=12. Values are expressed as median with interquartile ranges. *P* values shown are the result of the Mann-Whitney U test.

serum levels of MIG (>54.12 pg/ml) seemed to correlate to an increased risk of death [Hazard ratio (HR)=1.84, 95%Confidence interval (CI)=1.07-3.2, P=0.027) (Figure 3).

DISCUSSION

In the present study, we analyzed 148 COVID-19 Mexican patient chemokine (IL-8, RANTES, MIG, MCP-1, and IP-10) serum levels in association with clinical characteristics and outcomes. The analysis showed that IL-8 and RANTES increased in all the patient groups compared with the healthy group, but there were no differences between the patients, meaning they were not associated with disease severity (Figure 1), contrasting with the previous association of high IL-8, and RANTES levels with severe, and mild disease, respectively, in the Chinese population (3, 15). Although similar results were reported in the Irish population (11), supporting the necessity of replicating these studies in other populations. On the other hand, MIG, MCP-1, and IP-10 increased in

Table 2. ROC curve analysis of serum chemokine levels for patients with unfavorable COVID-19 clinical outcomes.

	Cut-off point*	Sensitivity	Specificity	AUC**	P value
Invasive ventilation					
IL-8	21.21	87.69 (77.2−94.5)	31.33 (21.6−42.4)	0.57 (0.48−0.65)	0.146
RANTES	12.69	76.92 (64.8−86.5)	32.93 (22.9−44.2)	0.51 (0.43−0.59)	0.831
MIG	44.4	73.85 (61.5−84)	45.78 (34.8−57.1)	0.62 (0.53−0.7)	0.015
MCP-1	147.7	53.85 (41−66.3)	69.88 (58.8−79.5)	0.64 (0.56−0.72)	0.004
IP-10	2847.03	47.69 (35.1−60.5)	73.49 (62.7−82.6)	0.59 (0.5−0.67)	0.058
Organic failure/shock					
IL-8	30.45	83.33 (62.6−95.3)	34.96 (26.6−44.1)	0.56 (0.47−0.63)	0.346
RANTES	3.95	83.33 (62.6−95.4)	2.46 (0.5−7)	0.51 (0.43−0.59)	0.871
MIG	66.53	70.83 (48.9−87.4)	62.6 (53.4−71.2)	0.7 (0.63−0.71)	<0.001
MCP-1	144.4	66.67 (44.7−84.4)	61.79 (52.6−70.4)	0.63 (0.55−0.71)	0.02
IP-10	3043.62	62.5 (22.1−63.4)	71.54 (62.7−79.3)	0.65 (0.57−0.73)	0.009
Death					
IL-8	41.95	63.77 (51.3−75)	55.13 (43.4−66.4)	0.6 (0.51−0.68)	0.038
RANTES	8.45	50.72 (38.4−63)	64.94 (53.2−75.5)	0.56 (0.48−0.64)	0.202
MIG	54.12	65.22 (52.8−76.3)	65.38 (53.8−75.8)	0.69 (0.61−0.77)	<0.001
MCP-1	51.27	97.1 (89.9−99.6)	26.92 (17.5−38.2)	0.67 (0.58−0.74)	<0.001
IP-10	2730.17	49.28 (37−61.6)	75.64 (64.6−84.7)	0.64 (0.56−0.72)	0.002

Chemokine values are expressed in pg/ml except for RANTES which is in ng/ml. *Optimal cut-off point calculated according to Youden's J index. **Non-parametric estimation using exact binomial method (17).

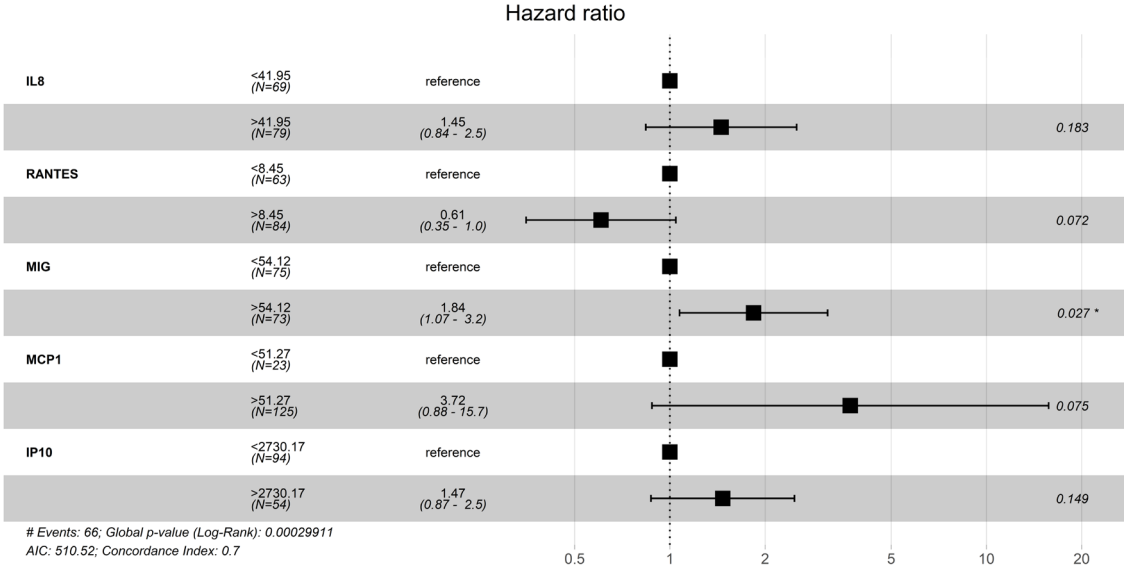

Figure 3. Forest plot and hazard ratios (HR) of the association of chemokine levels with death. Forest plots indicate the HR and 95% confidence intervals according to each chemokine cut-off point (expressed in pg/ml except for RANTES which is in ng/ml) obtained by a multivariate Cox proportional-hazards model. AIC: Akaike information criterion (AIC).

the severe and critical groups (Figure 1), corroborating previous reports that concluded that these chemokines are related to disease severity (3, 8, 11, 14, 15, 18).

Concordant with the aforementioned result, the ROC analysis showed that MIG, MCP-1, and IP-10 are associated with COVID-19 unfavorable outcomes (invasive ventilation, organic failure/shock, and death), although, according to AUC values, only MIG could

be considered a fair predictor (AUC=0.7) of organic failure (Table 2). Nevertheless, our observations corroborate the association of increased levels of MIG and IP-10 chemokines with poor prognosis as they are similar to those reported by Yang et al., Hue et al., and Sugiyama et al. (5, 10, 13). Both MIG and IP-10 are lymphocyte-targeting CXC chemokines acting on the common receptor CXCR3, a pathway previously reported to play a critical role in ARDS development (19, 20), suggesting this pathway as a putative therapeutic target for COVID-19 patient management. Regarding MCP-1, we found it to be associated with critical signs and death, similar to the observations of Xu et al. (3). These associations are plausible considering MCP-1 role in the chemotaxis of monocytes from the bloodstream which, in a pneumonia setting, cause the maintenance of inflammation and abrogation of tissue repair, extending lung damage and worsening of the disease, as described for SARS virus (21).

Limited exploration has been done regarding the prediction of mortality according to chemokine levels. A recent study observed increased inflammatory-related biomarkers associated with mortality, remarking MIG (also known as CXCL9), and MCP-1 (or CCL2), the latter showing the highest risk among the evaluated biomarkers (22). Similarly, in the present study, we showed that COVID-19 patients with elevated MIG levels (>54.12 pg/ml) had ~80% increased risk of death (HR=1.84, 95%CI=1.07-3.2, P=0.027) compared with the patients with low MIG levels. A similar trend was observed for increased MCP-1 levels (>51.27 pg/ml) although it was not significant (HR=3.72, 95%CI=0.88-15.7, P=0.075). These results could be of utility for the management of COVID-19 patients as well as for other pulmonary inflammatory diseases. In this respect, high MIG levels have been previously linked to other lung involving diseases such as sarcoidosis, and tuberculosis which is related to lung fibrosis (23, 24), and SARS which is related to adverse outcomes such as ARDS (19). Regarding the latter effect, it has been proposed that elevated MIG, and thus increased CXCR3 signaling, might enhance the recruitment of lymphocytes, neutrophils, and other inflammatory cells to target sites during infection which promotes persistence of the inflammatory response exacerbating tissue damage and ultimately leading to a fatal outcome in an ARDS scenario (19, 20).

Comorbidities such as T2D, HT, obesity, and RD have been pinpointed as risk factors for severe COVID-19 (9, 25). We analyzed the chemokine serum levels in COVID-19 patients with these comorbidities finding increased levels of MCP-1 in T2D and HT, IP-10 in HT, and IL-8 and MIG in RD (Figure 2), chemokines found related to critical signs/death (the present study, see Table 1). These associations have not been reported before in COVID-19 patients and might be helpful as further evidence of how comorbidities contribute to COVID-19 severity, given that T2D, HT, and RD are chronic low-grade inflammatory diseases and are highly prevalent among the Mexican population (25, 26).

To our knowledge, this is the first study of chemokine levels analysis in COVID-19 performed in the Latin American population. Unfortunately, it presents a few limitations such as the fact the samples were collected from patients on different days (between days 2 and 9) after hospital admission, and with a transversal rather than longitudinal approach, issues which we tried to overcome by enrolling more patients. Nevertheless, our results corroborate the findings of previous studies attributing a role to MIG, MCP-1, and IP-10 in the severity of COVID-19. Moreover, our study contributes to further understanding the risk factors for COVID-19 pathology and might aid in locating novel therapeutic targets, especially in Mexico which has been one of the most affected countries in both the number of cases and deaths (1).

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Data Availability: All data from the study is available from the corresponding author upon reasonable request.

Conflict of Interest: None declared.

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Table S1. Demographical, clinical and laboratory characteristics of Mexican COVID-19 patients.

Characteristic	TOTAL (n=148)	MILD (n=20)	SEVERE (n=61)	CRITICAL (n=67)	P value*
Gender (Male)	93/148 (62.8)	13/20 (65)	42/61 (68.8)	38/67 (56.7)	0.357
Age (years)	54 (45.7-64)	48.5 (38.7-62.7)	54 (43.5-63)	60 (46-69)	0.104
Body mass index	31.2 (27.1-35.1)	29.9 (24.2-33.1)	30.4 (24.5-33.8)	34.6 (29.8-38.7)	0.025
Presence of comorbilities	126/146 (86.3)	16/20 (80)	50/60 (83.3)	60/66 (90.9)	0.316
Type 2 diabetes	53/146 (36.3)	8/20 (40)	20/60 (33.3)	25/66 (37.9)	0.418
Hypertension	83/146 (56.8)	9/20 (45)	30/60 (50)	44/66 (66.7)	0.087
Obesity	67/146 (45.9)	9/20 (45)	26/60 (43.3)	32/66 (48.5)	0.842
Chronic renal disease	12/146 (8.2)	2/20 (10)	4/60 (6.7)	6/66 (9.1)	0.841
Symptoms					
Cough	79/113 (69.9)	16/20 (80)	34/43 (79.1)	29/50 (58)	0.048
Headache	53/113 (46.9)	12/20 (60)	21/43 (48.8)	20/50 (40)	0.301
Fever	91/113 (80.5)	18/20 (90)	36/43 (83.7)	37/50 (74)	0.249
Myalgia/althralgia	33/113 (29.2)	5/20 (25)	13/43 (30.2)	15/50 (30)	0.901
Odynophagia	15/113 (13.3)	5/20 (25)	6/43 (13.9)	4/50 (8)	0.185
Rhinorrhea	10/113 (8.8)	2/20 (10)	6/43 (13.9)	2/50 (4)	0.22
Diarrhea	14/113 (12.4)	3/20 (15)	4/43 (9.3)	7/50 (14)	0.725
Thoracic pain	20/113 (17.7)	3/20 (15)	10/43 (23.2)	7/50 (14)	0.484
Dyspnea	128/133 (96.2)	16/20 (80)	48/49 (97.9)	64/64 (100)	<0.001
Tachypnea	38/141 (26.9)	0/20 (0)	13/59 (22)	25/62 (40.3)	<0.001
Oximetry <94%	118/144 (81.9)	0/19 (0)	59/60 (98.3)	59/65 (90.8)	<0.001
Invasive ventilation	64/147 (43.5)	0/20 (0)	0/61 (0)	64/66 (97)	<0.001
Organic failure/shock	24/147 (16.3)	0/20 (0)	0/61 (0)	24/66 (36.4)	<0.001
Death	68/147 (46.2)	2/20 (10)	11/60 (18.3)	55/67 (82.1)	<0.001
Days of hospitalization	9 (5-15)	12 (7.2-15.5)	8 (5-12)	10 (4-17)	0.127
Laboratory findings					
Glucose (mg/dl)	131 (100-170)	108 (75.7-141.5)	129 (101.5-172)	142 (102-175.2)	0.084
Creatinine (mg/dl)	0.88 (0.7-1.22)	0.79 (0.69-0.96)	0.85 (72.5-1.15)	1.02 (0.7-1.59)	0.073
LDH (IU/l)	454 (316-592.5)	355.5 (250.2-467.7)	462 (264-603.7)	521 (426-634)	0.008
AST (UI/l)	33 (23-57)	43 (25-85)	28.5 (20-50.5)	40.5 (27.2-58.7)	0.064
ALT (UI/l)	42 (26.7-74)	59 (23-82)	35.5 (26-59.5)	56 (29-82)	0.404
ALP (UI/l)	87 (73-152.5)	74.5 (58.5-83.2)	97 (75-177)	93 (75-167)	0.018
Na^+ (mEq/l)	139 (136-142)	139.5 (136-142.5)	138 (135-140)	140 (138-143.5)	0.015
Total cholesterol (mg/dl)	129 (102-161)	129 (104-142)	128.5 (99.2-163.7)	131 (101-163)	0.819
Platelets (10^3/µl)	276 (205.2-378.2)	357 (220.5-522.5)	301.5 (220.7-405.7)	250 (200.5-333.5)	0.019
Leukocytes (10^3/µl)	11.66 (8.7-15.8)	12.26 (9.8-14)	10.09 (7.8-14.4)	13.1 (9.2-18.3)	0.055
Neutrophils (10^3/µl)	9.9 (6.9-14.4)	9.28 (7.5-11.6)	8.7 (6.4-12.7)	12 (8-17.2)	0.015
Lymphocytes (10^3/µl)	0.9 (0.6-1.2)	1.03 (0.8-1.6)	1 (0.7-1.4)	0.75 (0.5-0.9)	<0.001
Prothrombine time (sec)	14 (13.1-15.1)	13.2 (12.4-13.8)	13.95 (13-14.8)	14.5 (13.7-15.3)	0.009
C-reactive protein (mg/dl)	8.01 (3.8-13.8)	6.97 (2.1-13.7)	6.46 (1.1-9.4)	15 (7.4-27.7)	0.051
Procalcitonin (ng/ml)	0.13 (0.05-0.9)	0.18 (0.05-1.2)	0.05 (0.05-0.13)	0.3 (0.1-4)	0.101
CK-MB (ng/ml)	2.27 (1-3.8)	2.7 (1.2-13.9)	1.5 (1-3.3)	2.5 (1.5-4.9)	0.422
D-dimer (ng/ml)	803 (285-2820)	803 (456-2148)	402.5 (157.7-2134)	1690 (640.7-3801.7)	0.124

Quantitative variables are expressed as median (interquartile range). Frequencies show the number of individuals with the variable/total of individuals with available data. *Result of χ^2 or Fisher's exact test, and Kruskal-Wallis test comparing between mild, severe and critical. LDH: lactic deshydrogenase, AST: aspartate transaminase, ALT: alanine aminotransferase, ALP: alkaline phosphatase. Hb: hemoglobin, CK-MB: creatine kinase MB.