Original Article

Access this article online
Quick Response Code:

Website: www.jehp.net

DOI: 10.4103/jehp.jehp_1481_24

Association between SARS-CoV-2 viral load and serum biomarkers with mortality in Mexican patients

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Abstract:

BACKGROUND: The coronavirus disease 2019 (COVID-19) pandemic has resulted in high mortality among hospitalized patients; thus, identifying mortality markers in treating these patients is essential. To evaluate the association between viral load and serum biomarkers with mortality among hospitalized patients with COVID-19.

MATERIALS AND METHODS: A retrospective cohort study was conducted among 198 inpatient records from a tertiary hospital in Mexico City between January and April 2021. The association between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load and serum biomarkers with death due to COVID-19 was assessed using Cox regression models.

RESULTS: The median age was 54.9 years, and 61.6% were males. The mortality rate was 43.4%. After adjusting for potential confounders, patients with higher viral load [adjusted hazard ratio (aHR) = 1.56; 95% confidence interval (95% CI) = 1.01, 2.42; *P* value = 0.041]; and higher concentrations of BUN (aHR = 4.87;95% CI = 2.70, 8.79; *P* value = 0.001), creatinine (aHR = 1.60;95% CI = 1.01, 2.54; *P* value = 0.043), osmolality (aHR = 4.37;95% CI = 2.34, 8.14; *P* value = 0.001), and glucose (aHR = 2.41;95% CI = 1.40, 4.18; *P* value = 0.001) were more likely to have a fatal prognosis. Conversely, mortality risk was lower among patients with high concentrations of lymphocytes (aHR = 0.47;95% CI = 0.30, 0.72; *P* value = 0.001).

CONCLUSION: SARS-CoV-2 viral load and serum biomarkers such as BUN, creatinine, glucose, osmolarity, and lymphocytes could help physicians identify individuals who require closer monitoring.

Keywords:

Biomarkers, COVID-19, mortality, SARS-CoV-2, viral load

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Received: 15-08-2024
Accepted: 05-11-2024
Published: 28-03-2025

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19), affecting millions of people worldwide since its emergence in 2019. Although the severity of this disease differs from person to person, most infected cases present mild to moderate symptoms, with a good prognosis.[1,2] However, 20% of unvaccinated cases may develop pneumonia, acute respiratory distress syndrome, sepsis, and septic shock, especially if they are older or have underlying conditions such as cardiovascular disease, diabetes, cancer, or chronic respiratory diseases.[3]

COVID-19 mortality has had a significant impact on a global scale, with the Americas being one of the most affected regions.[4] During 2020, 325,415 deaths directly and indirectly associated with COVID-19 were reported in Mexico,[5] which decreased life expectancy at birth by 4.6 years.[6]

How to cite this article: Razo-Blanco-Hernández DM, Hernández-Mariano JÁ, Díaz-Cureño MA, Navarrete-Martínez L, Bravata-Alcántara JC, Rivera-Sanchez R, *et al*. Association between SARS-CoV-2 viral load and serum biomarkers with mortality in Mexican patients. J Edu Health Promot 2025;14:133.

COVID-19 is diagnosed by real-time reverse transcription polymerase chain reaction (RT-PCR) assay. These tests provide a qualitative assessment of the presence of SARS-CoV-2 (i.e., positive, negative); however, these assays also contain quantitative information on viral load.[7]

Viral load is the amount of viral RNA in a given volume expressed as infectious particles per milliliter. This is also expressed as Log10 copies/mL or Ct value.[8,9] Viral load measurements from tissue samples are indicative of active virus replication and have been routinely used to monitor severe viral respiratory tract infections, including clinical progression, response to treatment, cure, and relapse.[10-13] Nevertheless, the findings of studies that have analyzed the relationship between viral load and mortality in patients with COVID-19 are inconsistent.[14] For example, emerging evidence has shown that a higher viral load is positively associated with mortality among patients with COVID-19[15]; other data have shown that asymptomatic patients have higher SARS-CoV-2 viral loads than symptomatic patients and that, in addition, the viral load of nasopharyngeal and oropharyngeal samples was reduced as disease severity increased.[16] Also, some studies suggest that viral load is not a predictor of severity or mortality in SARS-CoV-2 infection.[17]

On the other hand, emerging evidence suggests that different serum biomarkers, such as C-reactive protein, lactic dehydrogenase, troponin T, ferritin, hematological parameters, and D-dimer could be useful for the stratification of severity and prognosis of COVID-19[18,19] since these biomarkers can be altered by the multiple organ failure produced by this virus in its most advanced stages due to the sustained hyperinflammation and secondary hypoxia suffered by the different organs.[20] Some data show that a "Cytokine storm" as a result of the extensive proinflammatory response activated by coronavirus infection could potentially damage local and systematic tissues and reduce lymphocyte count [Figure 1].[21,22] However, the evidence in this regard is scarce, with statistical significance being maintained only in some of these parameters, with variation in the results in the different studies.

Even though the WHO announced that the COVID-19 epidemic no longer constitutes a health emergency of international concern, this disease remains a topic of interest in terms of public health. To our knowledge, in the Mexican context, there are no previous studies that have examined the potential predictive role of serum biomarkers and SARS-COV-2 viral load on COVID-19 mortality. Generating evidence in this regard would help decision-making to classify early COVID-19 cases that require specific care according to their predictive risk and thereby guide early interventions aimed at their recovery. Furthermore, the data generated could help implement strategies focused on reducing risk factors that worsen the course of COVID-19. Therefore, we aimed to evaluate the association between viral load and serum biomarkers with mortality among hospitalized patients with COVID-19.

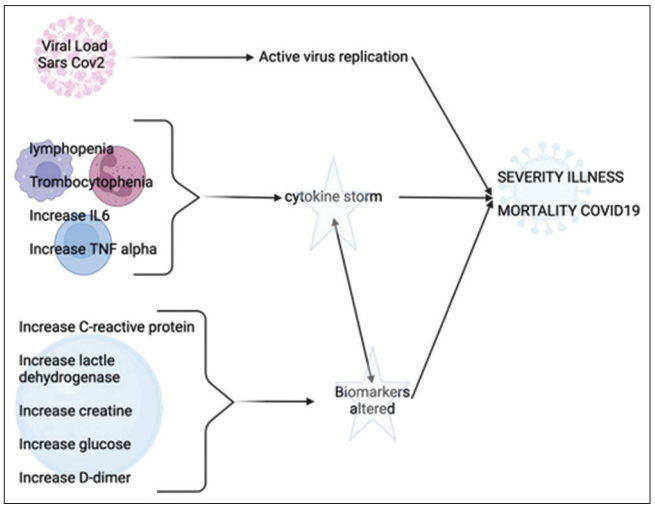

Figure 1: Cytokine storm in COVID-19

Material and Methods

Study design and settings

This is a retrospective cohort study with patients hospitalized due to COVID-19 in a tertiary hospital in Mexico City from January to February 2021.

Study participants and sampling

The sample consisted of 198 men and women (nonpregnant) aged 18 years or older, with a SARS-CoV-2-positive test [quantitative polymerase chain reaction (qRT-PCR)], who were hospitalized and did not suffer from cancer or HIV.

Data collection

Demographic (i.e., age, sex, and comorbidities) and clinical data (i.e., length of hospital stay, viral load, and serum biomarkers) as well as patient disposition (i.e., discharge or death) were extracted from the medical records. The viral load and laboratory parameters included in the study corresponded to the first results evaluated in hospitalized patients during their admission period.

Sex and comorbidities were considered as categorical covariates, while age, length of hospital stay (days), viral load (copies/milliliters), creatinine concentrations (mg/dl), blood urea nitrogen, BUN (mg/dl), gamma-glutamyl transferase, GGT (U/L), glutamic oxalacetic transaminase, TGO (U/L), glutamic pyruvic transaminase, TGP (U/L), creatinine kinase (CK-mb;

U/L), glucose (mg/dl), and osmolality (mOsm/kg) were considered as continuous variables.

Statistical analysis

Categorical covariates were described as frequencies and percentages, while continuous variables were described as mean and standard deviation (SD) or median and interquartile range (IQR) in the case of non-normal data (*P* value of the Shapiro–Wilk test <0.05). The bivariate analysis was performed using the Chi-square or Fisher's exact test for proportion differences. We used the Student *t*-test and U-Mann–Whitney test for differences in means or medians, respectively.

To estimate the survival of patients according to their viral load, we used Kaplan–Meier survival curves. Thus, we dichotomize this variable based on the median values of its distribution. The survival of the patients was also estimated by comparing the concentrations of the biomarkers according to the cutoff points suggested by the laboratory for each serum parameter. The log-rank test was calculated to determine overall differences between survival curves without crossed patterns, and the Flemington–Harrington test for crossed curves, which evaluates late differences. To evaluate the association between viral load and serum biomarkers with mortality, we build Cox regression models adjusted for potential confounders (i.e., age, sex, and comorbidities).

Ethics considerations

The study protocol received approval from the Ethics, Research, and Biosafety Committees of the hospital Juarez of Mexico (registration number HJM-803/20-I).

Results

A total of 198 patients were included. The mortality was 43.4% (95% IC 37%–50%). The mean age of the patients was 55 years, and most of them were men (61.6%). 43.4% had some underlying disease. The median hospital stay was 13 days. When we compared the general characteristics of the patients according to mortality status, we observed that those who died were older [Table 1].

The median $\log_{10}$ viral load was 4.98 copies per mL (IQR 5.77). The median $\log_{10}$ viral load at admission significantly differed between patients who were alive versus those who had died [*P* value = 0.022; Table 2].

Except for BUN, GGT, and TGO, the study population had normal median concentrations of serum biomarkers. Serum concentrations of BUN, creatinine, CK-MB, and glucose were higher among patients with a fatal outcome [Table 2]. Patients with a poor prognosis had lower albumin concentrations and hemoglobin than those who survived (*P* value < 0.004).

Table 1: General characteristics of the participants

Biochemical parameters	Total (*n*=198)	Survivors *n*=112 (56.6%)	Nonsurvivors *n*=86 (43.4%)	*P*[a]
Age (years)				
Mean (SD)	55 (14)	51 (15)	61 (12)	0.001
Sex, *f* (%)				
Female	76 (38.4)	34 (37.5)	16 (39.5)	
Male	122 (61.6)	28 (62.5)	20 (60.5)	0.770
Comorbidities				
Si	86 (43.4)	68 (60.7)	44 (51.2)	0.179
No	112 (56.6)	44 (39.3)	42 (48.8)	
Length of hospital stay				
Median (IQR)	13 (9)	12 (11)	13 (8)	0.600

DE, Standard deviation; IQR, interquartile range. [a]Bivariate analysis was performed using the Student and U-Mann–Whitney test for continuous variables with normal and non-normal distribution, respectively

Table 3 describes the proportion of patients with abnormal concentrations of serum biomarkers. Most patients present abnormal chemical parameters of BUN, albumin, GGT, glucose, and lymphocytes.

Differences in the mortality rate were observed along with survival functions for viral load and some biomarkers. The survival of patients with $\log_{10}$ viral load >4.98 copies per mL was lower than those with viral load ≤4.8 copies per mL Regarding serum biomarkers, survival was higher among patients with lower BUN, creatinine, glucose, and higher lymphocytes. The survival curves for the rest of the serum biomarkers did not show significant differences [Figure 2].

After adjusting for potential confounders, patients with higher viral load [adjusted hazard ratio (aHR) =1.56; 95% confidence interval (95% CI) =1.01, 2.4; *P* value = 0.041] and higher concentrations of BUN (aHR = 4.87;95% CI = 2.70, 8.79; *P* value = 0.001), creatinine (aHR = 1.60;95% CI = 1.01, 2.54; *P* value = 0.043), osmolality (aHR = 4.37;95% CI = 2.34, 8.14; *P* value = 0.001), and glucose (aHR = 2.41;95% CI = 1.40, 4.18; *P* value = 0.001) were more likely to have a fatal prognosis. Conversely, mortality risk was lower among patients with high concentrations of lymphocytes (aHR = 0.47;95% CI = 0.30, 0.72; *P* value = 0.001) [Table 4].

Discussion

The present study aimed to evaluate the association between load viral and serum biomarkers with COVID-19 mortality at hospital admission in Mexico in 2020. This is one of the few manuscripts to have analyzed the potential role of load viral and serum biomarkers as predictors of mortality among patients with COVID-19 in the Mexican context.

Table 2: Viral load and serum biomarkers of the study population

	Total (*n*=198) Median (IQR)	Survivors (*n*=112) Median (IQR)	Nonsurvivors (*n*=86) Median (IQR)	*P*[a]
Viral load, *copias*/mL	4.98 (5.77)	4.65 (5.61)	5.25 (6.10)	0.022
BUN (mg/dl)	24.5 (18.5)	19 (15)	28 (29)	0.001
Albumin (g/dl)	3.15 (0.90)	3.8 (0.60)	3.0 (0.70)	0.004
Creatinine (mg/dl)	0.84 (0.50)	0.80 (0.35)	0.96 (1.16)	0.021
GGT (U/L)	85 (132)	179 (147)	61 (76)	0.114
TGO (U/L)	45.5 (32.5)	45 (34)	46 (28)	0.842
TGP (U/L)	41.5 (42)	47 (56)	36 (34)	0.142
Alkaline phosphate (U/L)	106.6 (36.6)	106.2 (25.5)	106.8 (39.8)	0.963
Osmolarity (mmol/L)[b]	283 (295)	282 (293)	287 (298)	0.285
CK-MB (U/L)	11 (19)	6 (11)	16 (23)	0.001
Glucose (mg/dl)	147 (85)	126,5 (69)	147 (98)	0.001
Hemoglobin (g/dl)	15.1 (3.1)	15.4 (3.2)	14.7 (2.5)	0.017
Platelets (10^3/ul)	265 (96)	266 (116)	259 (82)	0.185
Leukocytes (10^3/ul	10.6 (5.8)	9.8 (5.4)	12.07 (7.5)	0.001
Lymphocytes (10^3/ul)	6.5 (6.8)	7.8 (2.2)	4.7 (5.2)	0.001
Neutrophils	88.9 (19)	86.1 (14)	91.1 (7.4)	0.001

IQR, interquartile range. [a]Bivariate analysis was performed using the Student and U-Mann–Whitney test for continuous variables with normal and non-normal distribution, respectively. [b]Mean±Standard deviation

Table 3: Proportion of patients with abnormal serum biomarkers in the study population

Variables	Cut-off point	Proportion of the patients
BUN (mg/dl)	>23	52.5
Albumin (g/dl)	<3.50	63.7
Creatinine (mg/dl)	>1.30	22.2
GGT (U/L)	>61	63.0
TGO (U/L)	>39	17.7
TGP (U/L)	>39	45.6
Alkaline phosphate (U/L)	>120	42.9
Osmolarity (mmol/L)	>300	29.9
CK-MB (U/L)	> 30	11.7
Glucose (mg/dl)	>110	61.3
Hemoglobin (g/dl)	<12	10.2
Platelets (10^3/ul)	<130	6,1
Leukocytes (mg/dl)	>12.4	3.,7
Lymphocytes (10^3/ul)	>5.20	60

The proportion of mortality among COVID-19 patients reported in this study was higher compared to other studies conducted in the United States[23] and European countries such as Italy, Denmark, and Spain[24-26] but consistent with the findings reported in Latin American countries such as Peru, Colombia, or Brazil.[27-29] Previous evidence suggests that social determinants of health and population density might influence mortality from COVID-19 in Latin America.[30,31]

Our results suggest that SARS-CoV-2 viral load at hospital admission is associated with the mortality of patients with COVID-19. These findings are consistent with the results reported by Dogan *et al*. (2022) and Pujadas *et al*. (2020), who have identified that higher viral load was positively associated with COVID-19 mortality.[15,32] Nevertheless, there are some studies with opposite results. For example, Hasanoglu *et al*.[16] (2021) found that asymptomatic patients had higher SARS-CoV-2 viral loads than symptomatic patients; in addition, they observed a significant decrease in the viral load of nasopharyngeal and oropharyngeal samples as the severity of the disease increased. Similarly, Le Borgne *et al*.[17] reported that respiratory viral load measurement on the first nasopharyngeal swab during initial ED management is not a predictor of mortality in SARS-CoV-2 infection.

The acute respiratory distress syndrome (ARDS) is the most serious complication of COVID-19.[33] When ARDS occurs, the virus can damage the pulmonary endothelium and trigger an inflammatory response.[34] This damage is especially significant with SARS-CoV-2 as the virus uses angiotensin-converting enzyme 2 (ACE2) receptors to enter host cells, which are predominantly found in alveolar epithelial cells, indicating that the lungs are the primary target of the virus.[35,36] The endothelium changes to allow immune cells to move to the site of infection, and the body attempts to eliminate the microbial invaders; these actions are key components of the acute inflammatory response.[37] Viral load is higher for the first within 12 days after symptoms begin,[38] but it is unclear if it stays elevated in patients with severe disease.[16] Moreover, whether the timing of the COVID-19-induced cytokine storm (which occurs around 7 to 10 days after symptoms start) overlaps with this period is not addressed in our manuscript.[39] The pathophysiology of COVID-19 ARDS is complex and involves multiple interacting mechanisms; thus, it cannot be attributed to a single pathway. Nevertheless, it is still not clear if viral load triggers a stronger immune response. Besides its direct effects, SARS-CoV-2 disrupts the immune

Table 4: Adjusted hazard ratios (HR) of the association between viral load and biochemical parameters with mortality in the study population

Variables	HR (95% CI)	*P*
Viral load (copies per mL)		
≤4.8	Ref.	
>4.8	1.56 (1.01, 2.41)	0.041
BUN (mg/dl)		
≤23	Ref.	
>23	4,87 (2.70, 8.79)	0.001
Albumin (mg/dl)		
≥3.50	Ref.	
<3.50	0.99 (0.17, 1.16)	0.100
Creatinine (mg/dl)		
≤1.30	Ref.	
>1.30	1.60 (1.01, 2.54)	0.043
GGT (U/L)		
≤61	Ref.	
>61	0.58 (0.24,1.23)	0.546
TGO (U/L)		
≤39	Ref.	
>39	0.92 (0.52, 1.60)	0.778
TGP (U/L)		
≤49	Ref.	
>49	1.02 (0.63, 1.63)	0.932
Alkaline phosphate (UI/L)		
≤120	Ref.	
>120	0.63 (0.28, 1.44)	0.280
Osmolarity (mmol/L)		
≤300	Ref.	
>300	4.37 (2,34, 8.14)	0.001
CK-MB (U/L)		
≤ 30	Ref.	
> 30	1.75 (1.00, 3.25)	0.049
Glucose (mg/dl)		
≤110	Ref.	
>110	2.41 (1.40, 4.10)	0.001
Hemoglobin (g/dl)		
≥12	Ref.	
<12	1.01 (0.54, 1.88)	0.955
Platelets (10*3/ul)		
≥130	Ref.	
<130	1.87 (0.86, 4.03)	0.109
Leukocytes (10*3/ul)		
≤12.4	Ref.	
>12.4	1.51 (0.97, 2.35)	0.066
Lymphocytes (10*3/ul)		
≤5.20	Ref.	
>5.20	0.47 (0.30, 0.72)	0.001
Neutrophils %		
	Ref.	
	4.11 (0.96, 7.45)	0.056

HR, Hazard ratio; IC, Confidence interval; Ref, reference. [a]All models were adjusted for age, sex, and comorbidities

response, triggers a cytokine storm, downregulates ACE2 receptors, and causes immunothrombosis, all of which contribute to disease progression. These complex pathways might explain why COVID-19 patients experience more severe diffuse alveolar damage, more cellular fibromyxoid exudates in the alveoli, and small airways.[40] Since all these mechanisms are induced by the virus, a higher viral load may cause more dysregulation. However, more research is still required in this regard.

In our study, we found that abnormal biomarkers of kidney function (i.e., BUN and creatinine) among SARS-CoV-2-infected patients contributed significantly to mortality. Previous studies have investigated the role of BUN and creatinine levels on COVID-19 clinical outcomes, revealing a significant association between high levels of these biomarkers with COVID-19 mortality.[41-46] The underlying mechanisms involved in the increase of renal injury levels after SARS-CoV-2 infection are not fully elucidated yet. Given that ACE2 is the primary cellular receptor of SARS-CoV-2 and is highly expressed in renal epithelial cells, the viral infection may directly lead to an interaction of SARS-CoV-2 with its receptor in the kidney to reduce ACE2 expression, resulting in abnormal activation of the renin-angiotensin-aldosterone system (RAAS).[47] The activated RAAS can significantly increase the absorption of water by kidney tubules while enhancing the resorption of urea, leading to elevated BUN levels.[48] The elevation in BUN level not only is a kidney dysfunction indicator but also can reflect inflammatory status, catabolism, nitrogen equilibrium, and renal hypoperfusion from hypovolemia, sepsis, or reduced cardiac output, many of which have been reported to be closely associated with the adverse outcomes in COVID-19 patients. The coagulation status may progress and exacerbate along with the systematic inflammatory response and multiple organ injury.[48-50]

Our findings show that patients with elevated serum glucose levels are at a higher risk of death. In our study population, 24.2% of patients had pre-existing diabetes. The association between hyperglycemia and COVID-19 mortality has been widely documented in previous studies.[51-55] Some hypotheses have been suggested to explain the link between hyperglycemia and the progression of viral respiratory infections. Hyperglycemia may negatively impact pulmonary function, suppress immune responses, and increase the production of inflammatory cytokines.[56,57] Furthermore, ACE2 is expressed in the pancreas, and it is thought that SARS-CoV-2 can directly damage pancreatic islets.[57] Nevertheless, the effect of blood glucose levels on the progression of coronavirus infection needs further investigation.

Our results suggest that serum osmolality at hospital admission is associated with the mortality of patients with COVID-19. These findings are in line with the results reported by Ramesh *et al*. (2022) and Lucijanic *et al*. (2023), who reported that hyperosmolar patients

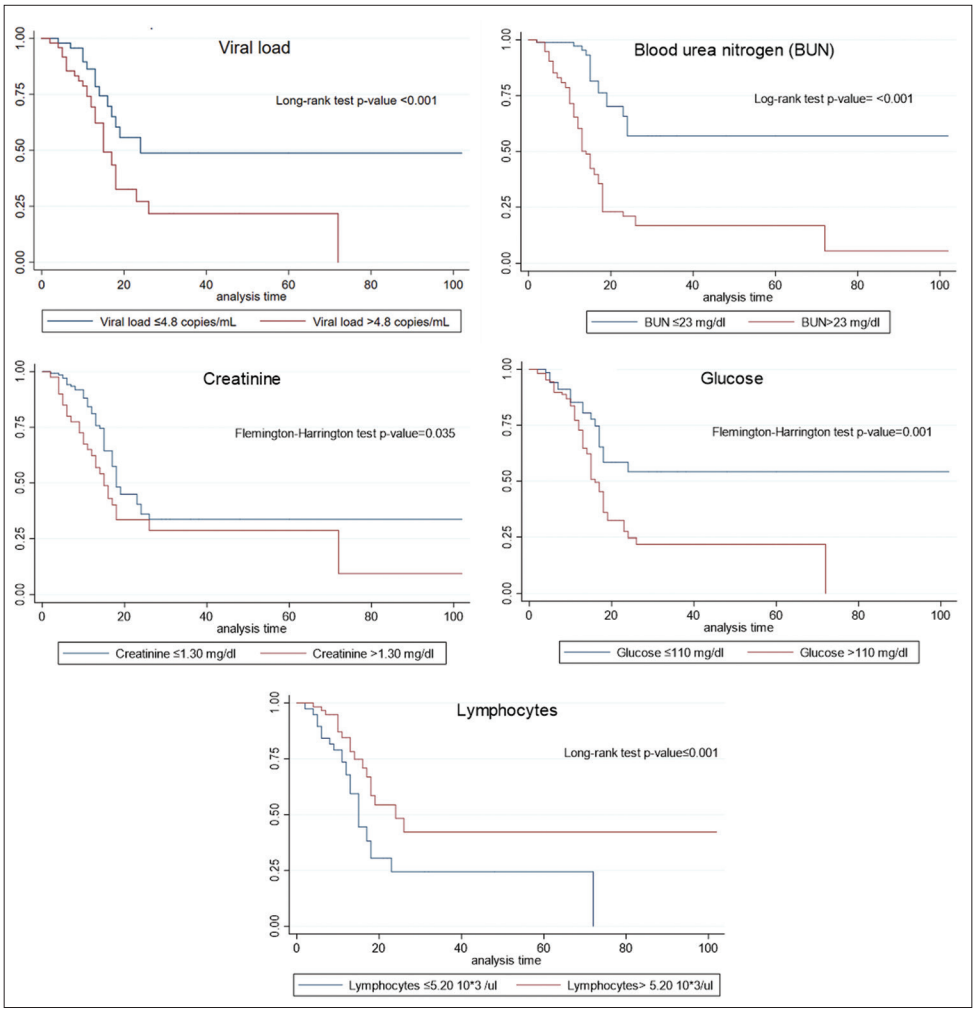

Figure 2: Kaplan–Meier survival analysis for SARS-CoV-2 viral load and serum biomarkers

presented with more severe COVID-19 symptoms, higher inflammatory status, and experienced higher mortality in comparison to normoosmolar patients.[58,59] The serum osmolality and fluid balance are determined by the concentrations of various solutes in body fluids, such as glucose, urea, sodium, potassium, and chloride, as well as the water content.[60] The use of mechanical ventilation, patient immobility, and venous stasis heighten the risk, making thromboprophylaxis necessary.[61] Moreover, the use of systemic glucocorticoids further increases this risk.[62] The rise in thrombo-inflammatory proteins reduces plasma water content, leading to increased osmolality.[63,64]

Our results suggest that serum lymphocytes at hospital admission are associated with the mortality of patients with COVID-19. These findings are consistent with different studies that have shown that lymphopenia could be a predictor of mortality.[65-69] Lymphocytes are a subtype of white blood cells and play an important role in the immune system. The major function of lymphocytes is to generate adaptive immune responses after exposure to new antigens and to retain the memory of such specific antigens.[70] The mechanisms underlying the association of lymphocyte markers with COVID‑19 infection have not been elucidated yet. Cytokine storm is characterized by an overwhelming inflammatory response and is linked to lymphopenia, where higher levels of inflammatory markers like TNF alpha and Interleukin 6 (IL-6) lead to increased lymphocyte death.[68] Elevated IL-6 levels impair the cytotoxic activity of lymphocytes, which are crucial for combating viral infections.[71] Moreover, COVID-19 may cause T-cell exhaustion through the upregulation of specific cell surface proteins.[72]

In the present study, higher CK-MB concentrations were marginally associated with mortality in COVID-19 patients. A significant link between elevated CK-MB and the mortality of COVID-19 has been widely documented in previous studies.[73,74] CK-MB is present in high concentrations in the heart muscle. It is one of three forms of creatine kinase present in the body. The CK-MB is used to diagnose heart-related conditions,

especially acute myocardial infarction. Elevated CK-MB levels indicate heart muscle damage, aiding the assessment of cardiac health.[75] The pathogenic mechanisms of SARS-CoV-2 on the cardiovascular system are not well-known. Possible causes include cytokine-mediated damage, microvascular thrombi, and/or direct cardiomyocyte injury due to viral invasion of the myocardium.[76,77]

Limitations

Our results have some limitations that need to be considered when interpreting them. This is a retrospective study on a limited number of available serum biomarkers, and other biomarkers such as D-dimer were not investigated due to data availability. The use of retrospective design could affect data quality. Nevertheless, we anticipate that any recording errors were randomly distributed. Our study design did not allow us to gather data on the onset and duration of COVID-19 symptoms, and hence, we were unable to account for disease duration before COVID-19 testing. The measurement of viral load depends on the quality and quantity of the specimen collected via nasopharyngeal swab; variations in this process could have influenced our results. However, given the lack of better, relatively noninvasive, and simpler techniques for obtaining mucus specimens from COVID-19 patients, this method remains the best available option. In addition, viral load and biomarker dynamics during infection could not be observed because the study only included a single sample of PCR testing and serum biomarkers. Levels of several biomarkers could be influenced by other factors; for example, a bacterial superinfection or dehydration caused by diarrhea may increase creatinine serum.[78] Due to the historical period of our study, our patient cohort did not include individuals who were vaccinated against SARS-CoV-2. Furthermore, our study did not consider the impact of different variants, which may affect the applicability of the findings to vaccinated patients, who now represent the majority.

Implications for health providers

SARS-CoV-2 infection can trigger a cytokine storm through hyperactivation of the immune system and the uncontrolled release of cytokines. Cytokine storms may cause ARDS and multiorgan failure. When it is detected in time (by serum biomarkers), the patient has a better chance of recovery.[22] Since elevated inflammatory cytokines are underlying processes in comorbidities (i.e., obesity, hypertension, and diabetes), healthcare providers should promote a healthy lifestyle adoption (i.e., healthy diet choices and regular physical exercise) and appropriate management of chronic diseases to reduce the risk of COVID-19-associated complications.[79,80] Moreover, it is essential to carry out actions to raise awareness about the importance of vaccination against COVID-19 and other respiratory diseases.

Conclusion

SARS-CoV-2 viral load and serum biomarkers such as BUN, creatinine, glucose, osmolarity, and lymphocytes could help medical staff identify individuals who require closer monitoring. Greater awareness of these indicators could enhance patient outcomes through more effective monitoring and treatment. Since old and comorbidities tend to have a negative impact on COVID-19, it is necessary to develop public health policies that strengthen the prevention and proper management of chronic diseases. Therefore, academics, researchers, and policymakers must work together to evaluate and improve the health systems and policy.

Acknowledgments

We are grateful to the Genetics and Molecular Diagnostics Laboratory of Hospital Juarez of Mexico for working to determine serum biomarkers and measuring the SARS-COV-2 viral load.

We thank Marco Antonio Hernández Briseño, from the Hospital Statistics Department of Hospital Juarez of Mexico, for his work in searching and collecting data for this study.

Abbreviations

aHR: Adjusted hazard ratio

BUN: Blood urea nitrogen

CI: Confidence interval

GGT: Gamma-glutamyl transferase

IQR; Interquartile range

SD: Standard deviation

TGP: Glutamic Pyruvic Transaminase

TOG: Glutamic Oxaloacetic Transaminase

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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