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Profile of proinflammatory markers in pregnant women who died of severe COVID-19

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Abstract

Introduction: *In December 2019, four cases of pneumonia of unknown origin were reported to the World Health Organization (WHO) in China, caused by SARS-CoV-2. In March 2020, the WHO declared the beginning of the COVID-19 pandemic. In COVID-19, a relevant component is vulnerable groups, such as pregnant women representing a special group due to their high mortality secondary to COVID-19.* **Objective:** *Describe the association between proinflammatory markers and survival in pregnant women with critical COVID-19, in the intensive care unit (ICU) of the General Hospital of Cholula from January 2020 to 2021.* **Materials and methods:** *This is an analytical and cross-sectional observational retrospective study conducted on pregnant women admitted to the ICU. Pregnant women, between 18 and 35 years old, at 30-40 weeks gestation diagnosed with critical COVID-19 were included.* **Results:** *It was observed that pregnant women with critical COVID-19 showed increased values of C-reactive protein, leukocytes, D-dimer, and DHL compared to surviving pregnant patients with critical COVID-19; however, no statistical significance was observed for platelet number and fibrinogen.* **Conclusion:** *In the case of pregnant women who died from critical COVID-19, there was a significant increase in inflammatory markers, in contrast to what was observed in other studies, no changes in the number of platelets or fibrinogen were observed.*

Keywords: *Critical COVID-19. Pregnant women. Proinflammatory cytokines.*

Introduction

In December 2019, four cases of pneumonia of unknown origin were reported to the World Health Organization (WHO) in Wuhan, China, later it was identified that this pneumonia was caused by a new virus, called SARS-CoV-2; which spread around the world. Consequently, on March 12, 2020, the WHO declared the beginning of the COVID-19 pandemic[1].

In the case of the COVID-19 pandemic, a relevant component of the potentially affected population was vulnerable groups, of which pregnant women represented a susceptible group because they are, especially affected by respiratory diseases, significantly increasing morbidity and mortality in this population group[2,3]. Although the spectrum of respiratory diseases is wide from mild to severe forms, the importance of COVID-19 infection is especially serious as approximately one-third of affected women died as a result of the disease[4,5].

The SARS-CoV-2 virus is an encapsulated single-stranded RNA virus, which infects the cells of the respiratory tract through its binding to the angiotensin-converting enzyme-2 receptor, this receptor is predominantly expressed in type II pneumocytes; however, various extrapulmonary cells are also located such as myocytes, endothelial cells, esophageal epithelial cells, neurons, glial cells, podocytes, and proximal renal epithelial cells[6]. SARS-CoV-2 infection is followed by

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intracellular replication and secondarily host cell pyroptosis, the products released during cell lysis, which include ATP and nucleic acids are recognized by molecular patterns associated with damage, which initiate an inflammatory response in neighboring cells. Among the proinflammatory molecules directly involved in the induction of the immune response are interleukin (IL)-6, IL-18, chemokine 10, and interferons (IFN)-1, these factors function as chemoattractants for monocytes, macrophages, and T lymphocytes, inducing the formation of a positive feedback loop enhancing the inflammatory response in the lung parenchyma and facilitating superinfection by resident microorganisms. This severe inflammation is responsible for the high morbidity and mortality rates characteristic of SARS-CoV-2 infection[7].

An important aspect in the context of SARS-CoV-2 infection is the fact that pregnant women are more susceptible to acquiring infection by this virus, related to the various physiological adaptations induced during pregnancy, among the factors involved in gestational rhinitis which is the result of estrogen-mediated hyperemia. Favoring an increase in local tissue perfusion and an increase in mucus production, these modifications would not only facilitate infection by the COVID-19 virus but could also mask the coryza present in SARS-CoV-2 infection.

In addition, it has been observed that in pregnant women there are various changes in respiratory dynamics, which are the result of the growth of the pregnant uterus, among these are: an increase in the demand for O_2 by the mother binomial, gestational anemia as a result of the plasma volume observed during the 1st 30 weeks of gestation and high fetal consumption of oxygen. These phenomena could favor the presence of dyspnea, which could mask the symptoms of respiratory distress characteristic of SARS-CoV-2 infection.

However, changes in respiratory volumes are also observed during pregnancy, such as decreased functional residual capacity, decreased end-expiratory volume, and residual volume, which together could predispose to respiratory failure in SARS-CoV-2-infected patients[8]. Together, all the factors mentioned above could favor the delay in the recognition of the signs and symptoms of COVID-19 in pregnant women, increasing morbidity and mortality in this group of patients observed during the pandemic.

One of the most important aspects of SARS-CoV-2 infection, which negatively impacts the evolution of COVID-19 infection in pregnant women, is the fact that these patients deploy an immune response dependent on the activation of Th1 lymphocytes, this type of response is associated with a significant increase in the secretion of proinflammatory cytokines, such as IFN-gamma, IL-1beta, IL-6, and IL-12, which is observed within the first 2 weeks of the onset of SARS-CoV-2 infection, generating significant damage to the lung parenchyma[9], it has been observed that the increase in IL-6 was associated with an increase in the mortality rate of patients with COVID-19[10].

Given the aforementioned background, the objective of this study is to describe the association between the concentrations of proinflammatory markers and the survival and death of pregnant patients with severe COVID-19 in the intensive care service of the General Hospital of Cholula from January 2020 to January 2021.

Materials and methods

This is a retrospective, cross-sectional study carried out in pregnant patients who were admitted to the intensive care service of the General Hospital of Cholula in the period from January 2020 to January 2021. The study period was chosen based on the complete records existing in the hospital unit. Pregnant patients diagnosed with severe COVID-19, aged between 18 and 35 years, with 30-40 weeks of gestation, without previous data of severe disease, APACHE scores were not included due to this data were only described in < 15% of the population studied.

The sample size was calculated based on the population of pregnant women who met the inclusion requirements with a complete record (total population of 39 patients) using the formula for finite samples with a confidence level of 95% and an error of 5%, obtaining a final sample of 36 patients. The proinflammatory markers that were determined in each group were: C-reactive protein (CRP), leukocytes, D-dimer, fibrinogen, and platelets, which were measured every 72 h or until the death or discharge of the patient due to improvement, at the end of the averages were made for each marker. Once the total sample was obtained, two study groups were integrated, the group of pregnant women who survived severe COVID-19 (n = 18) and the group made up of pregnant women who died from severe COVID-19 (n = 18). In all cases, the diagnosis was established by the treating physician and confirmed in the clinical file. All pregnant patients included in the study had their COVID-19 infection confirmed by a positive polymerase chain reaction (PCR) test.

The statistical analysis plan included averages, percentages, and standard deviation between the different groups.

Table 1. Clinical characteristics of pregnant women with severe COVID-19

Variable	Survival (n = 13)	Deceased (n = 25)	Relative risk (RR)
Age (years)	30	32	0.83
BMI (kg/m^2)	24	31	2.24
PAM (mm Hg)	78	80	0.65
SDG	34	37	1.04

BMI: body mass index; PAM: medial arteria pressure; SDG: week of gestation.

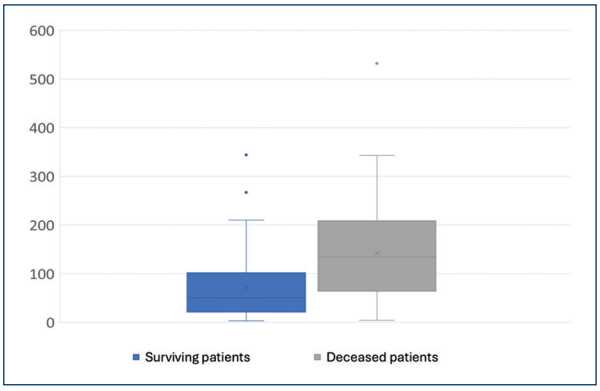

Figure 1. C-reactive protein levels in living and deceased patients due to critical COVID-19.

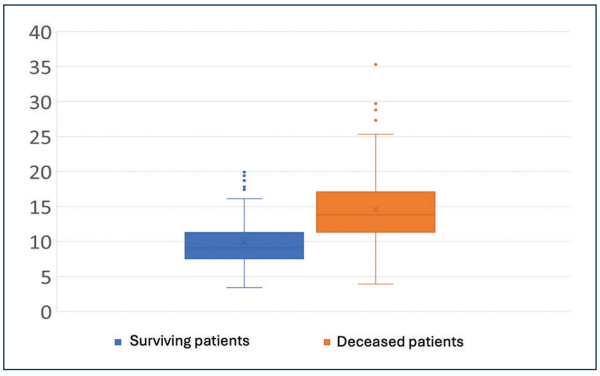

Figure 2. Leukocytes in living and deceased patients with critical COVID-19.

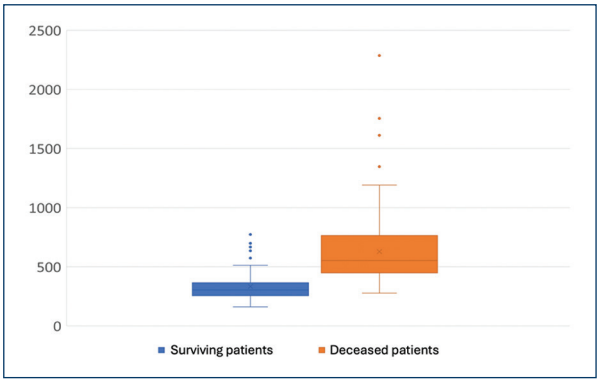

Figure 3. Lactic dehydrogenase in living and deceased patients with critical COVID-19.

The informed consent form was not used because we worked with clinical records; however, the information collected from each patient was handled confidentially, avoiding the use of the full name and social security number, replacing it with folios. It is worth mentioning that the choice of patients and the proinflammatory markers included in the study were related to the availability of complete records and the availability of reagents, respectively.

Results

The two groups involved in the study did not show significant differences in terms of age, body mass index, blood pressure, and weeks of gestation; however, overweight women showed a higher risk of death from severe COVID-19 compared to non-overweight pregnant women, which did not reach statistical significance (Table 1).

Of the total sample number (n = 36), 38% of pregnant women survived severe COVID-19 infection, whereas 62% with severe COVID-19 died. Our study showed that pregnant women who died from critical COVID-19 showed an increase in serum concentrations of CRP compared to pregnant women who survived 210 ± 12 mg/L versus 100 ± 16 mg/L (Fig. 1). In the same way, it was observed that the number of leukocytes was significantly higher among pregnant women who died from critical COVID-19 compared to survivors 14,350 ± 1200 versus 8796 ± 436 (Fig. 2). Regarding lactic dehydrogenase (LDH), it was observed that pregnant women who died from severe COVID-19 showed a significant increase in HDL concentrations compared to those of surviving pregnant women (700 ± 68 IU/L vs. 350 ± 49 IU/L) (Fig. 3).

Our results showed that the number of platelets did not show significant differences between deceased pregnant women or survivors with severe COVID-19 (278000 ± 370 mm^3 vs. 312000 ± 489 mm^3) (Fig. 4).

Our study also evaluated serum fibrinogen concentrations, observing that, such as the number of platelets, there were no significant differences in serum fibrinogen concentrations between surviving pregnant women or

those who died from severe COVID-19 (850 ± 125 versus 830 ± 75 g/L) (Fig. 5). Finally, our study quantified D-dimer concentrations, observing that non-surviving pregnant women with critical COVID-19 showed a significant increase in D-dimer compared to surviving pregnant women (4500 ± 879 ng/mL vs. 3000 ± 376 ng/mL) (Fig. 6).

Discussion

The objective of this study was to describe the relationship between various inflammatory markers, such as CRP, number of leukocytes, fibrinogen, LDH, platelets, and dimer among pregnant patients who were admitted to intensive care, who survived or died after critical COVID-19 infection.

In this sense, there are few reports in Mexico of the effect of severe COVID-19 infection on pregnant women. The present study shows that the mortality percentage of pregnant women who were admitted to the Hospital General de Cholula (HGCH) intensive care unit (ICU) was 62% and on the contrary, only 32% survived the same condition, which is in relation to the Mexican average for 2021 shown by López-Rodríguez et al.[11]. In addition, our study showed a significant increase in CRP concentrations, which was associated with higher mortality among pregnant women infected with severe COVID-19 (210 ± 12 mg/L vs. 100 ± 16 mg/L, *p < 0.05.), which is in relation to previous reports described by Tan et al.[12]. In relation to the previous point, PCR quantifications can be very useful from various points of view, on the one hand it provides valuable information regarding inflammation associated with inflammation in this particular case, after COVID-19 infection given its high sensitivity, specificity and low cost and on the other hand it has been shown that PCR could work as a potential predictor of thrombotic events, since there is recent evidence that has shown that the circulating pentameric form of PCR is capable of generating two isoforms with prothrombotic potential, which directly activate the complement system facilitating platelet aggregation, so one of the useful strategies in the future would be to evaluate the PCR-complement system relationship in patients infected with COVID-19 to establish more accurately the development of thromboembolic phenomena, which could be an important factor in the death of pregnant women with critical COVID-19 admitted to the ICU of the HGCH[13].

On the other hand, our work showed that pregnant patients who did not survive COVID-19 infection had a higher number of neutrophils compared to surviving pregnant women (14, 350 ± 1200 vs. 8796 ± 436, *p < 0.05), this finding was related to several studies in which it was observed that high concentrations of chemoattractant cytokines (IL-18) could attract a greater number of neutrophils generated during SARS-CoV-2 infection.

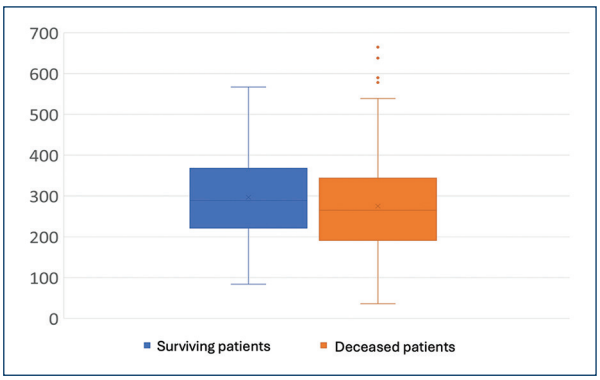

Figure 4. Platelets in living and deceased patients due to critical COVID-19.

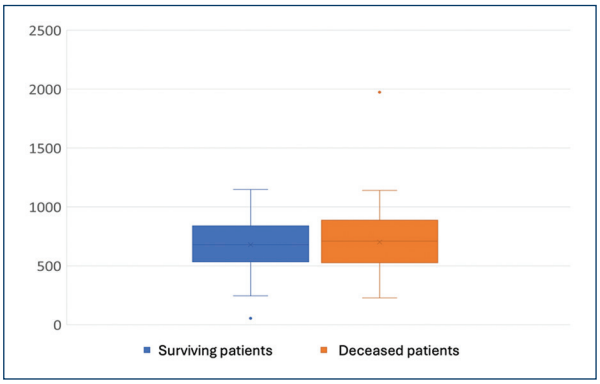

Figure 5. Fibrinogen in living and deceased patients due to critical COVID-19.

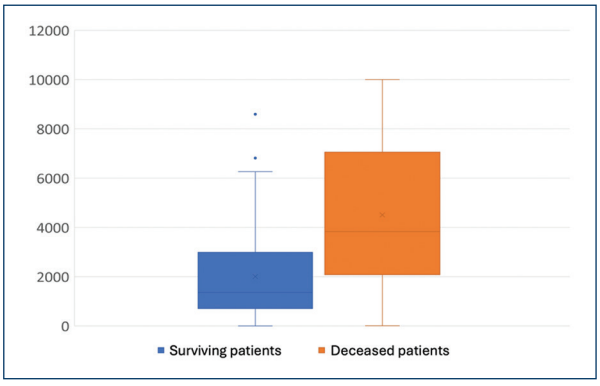

Figure 6. Dimer in living and deceased patients with critical COVID-19.

Favoring, on the one hand, the production of oxygen-free radicals and on the other favoring an exaggerated response of neutrophils after exposure to an infectious agent characterized as NETosis, this being a mechanism of "cell death" inducing the formation of extracellular traps within which the infectious agent is contained and destroyed and simultaneously due to its content (elastases, myeloperoxidase, gelatinases, and lysozyme C) secondary tissue damage[14,15]. Among the limitations of our studies regarding this point was that the hospital's protocols during the pandemic did not allow necropsies to be performed on patients who died from COVID-19, making it impossible to assess tissue damage by microscopy.

On the other hand, although LDH occupies an important place in glucose metabolism, its final product lactate is crucial in cellular metabolism when the partial pressure of oxygen is decreased, so recently LDH has been placed as a predictor marker of severity in some conditions such as acute respiratory distress syndrome and specifically in COVID-19, since the characteristic of both pathologies is the compromise tissue oxygenation secondary to lung damage. In the present study, it was observed that pregnant women who did not survive SARS-CoV-2 infection had higher serum LDH concentrations compared to survivors 700 ± 68 versus 350 ± 49 IU/L, *p < 0.05. In relation to this point, the increase in LDH in non-surviving pregnant patients infected by SARS-CoV-2 COVID-19 could mean that high lactate concentrations in the pathophysiological context of the disease would participate both as a chemical marker of disease severity, as well as a marker of severe cell damage, which could significantly modify the immune response of these patients favoring phenomena such as cytokine production proinflammatory and secondary tissue damage. However, more work is needed in experimental models of COVID-19 to determine *in vivo* the role of this enzyme in pregnancy, which is outside the scope of our study[16-18].

An important finding in our study was the fact that, unlike other studies, we did not find significant differences between platelet count and fibrinogen concentrations among pregnant women who died or survived severe SARS-CoV-2 infection (278000 ± 370 vs. 312000 ± 489 respectively *p > 0.05)[19,20]. In this regard, when studying a population in which various physiological adaptations occur during pregnancy, it is likely that platelet count and fibrinogen concentration may be modified compared with other population groups. Cines and Levine found that between 4.4% and 11.6% of pregnant women experienced gestational thrombocytopenia defined as a platelet count of < 150,000, noting that these variations in platelet count could be the result of increased plasma volume, as well as greater platelet destruction, which begins during the third trimester of pregnancy[21], in the same way, these modifications in plasma volume in pregnant women could favor fibrinogen dilution, in addition, the rapid evolution of severe COVID-19 infection in patients admitted to the HGCH ICU could be an additional factor for which no significant changes were observed in these variables. A limitation of our study could be related to the sample number, which was affected by the high number of incomplete records, as well as the availability of reagents to quantify the variables measurable in this study.

Finally, like other studies, our work showed that pregnant women who did not survive severe COVID-19 infection had significantly higher concentrations of D-dimer compared to surviving pregnant women 4500 ± 879 versus 3000 ± 376 ng/mL, *p < 0.05. Previously, D-dimer has been shown to be an important marker associated with a high risk of thromboembolic events, disease severity, and mortality risk[22].

Therefore, our findings are important, as they describe the relationship of various inflammatory markers in a population that has been little studied, but in which COVID-19 had a very important negative impact.

Conclusion

There are few reports in the literature about the characteristics of COVID-19 in pregnant women and in particular in pregnant women who died or survived severe COVID-19 infection in our country. Our work describes the characteristics of various inflammatory markers in the course of SARS-CoV-2 infection in pregnant women admitted to the HGCH ICU, which could help to typify the risk of a disease that will remain among a population with multiple comorbidities such as the Mexican population in rural areas. However, limitations of our work such as a small sample number and the changing availability of laboratory reagents for the quantification of proinflammatory markers could inaccurately reflect the results of our study.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments wereinvolving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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