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EDITORIAL

# Diabetes and COVID-19: Challenges for the health system

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*Take care of your body. It's the only place you have to live*
Jim Rohn

Two years ago I would not have imagined that, from one day to the next, receiving a warm hug from my family and friends would become part of a risk factor and even more, avoiding this action; since it was taken as a security measure that was called social distancing. December is a month of coexistence, parties and reflection, but in December 2019, these celebrations were held amid news coming from China, about the beginning of an outbreak of an acute respiratory disease characterized by fever, headache, cough, sneezing, myalgia, arthralgias and shortness of breath that spread throughout the world.

The appearance of a new coronavirus that was called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), caused sanitary measures, social isolation and mobility restrictions for people, that changed the lifestyle of the population. COVID-19 is a global public health problem. On June 22, 2022, 538,321,874 confirmed cases of COVID-19 and 6,320,599 deaths were reported internationally; Mexico ranks fifth in the number of deaths from COVID-19, after the United States of America, Brazil, India and Russia (table 1)[1].

Diabetes is a health problem that has reached alarming levels worldwide. It is known that today more than 500 million people live with diabetes worldwide. It is estimated that 1 in 2 adults is unaware that they are already living with diabetes, causing 240 million people worldwide to live with undiagnosed diabetes. It should be noted that Mexico is the eleventh largest population in the world and ranks seventh worldwide with the highest number of people with diabetes (14.1 million) after China (140.9), India (74.2), Pakistan (33.0), the United States United States (32.2), Indonesia (19.5), and Brazil (15.7)[2].

There is a clear need to detect diabetes early, implement non-pharmacological and pharmacological treatment early, and initiate actions to prevent complications. The key point is to create multidisciplinary groups, improve the quality of first contact care beyond diagnosis, and adequately monitor patients.

It is known that the main factors that favor the increase in the prevalence of diabetes are genetic background, unhealthy habits, including poor physical activity, sedentary lifestyle, increased consumption of foods rich in calories, sugars or saturated fats, aging population, and the growth of the urban population in marginalized areas[3]. Undoubtedly, there is evidence that changes in lifestyle have effects in controlling the disease and even more so in delaying the appearance of complications. Without forgetting that many patients have other comorbidities and risk factors that must be taken into account, such as obesity, arterial hypertension, dyslipidemia, polycystic ovary, gestational diabetes, cardiovascular diseases, etc.

Diabetes and its most common comorbidities are associated with higher mortality. This increase is usually observed in people over 60 years of age and in those who suffer from some type of diabetes, obesity

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**Table 1.** Countries with the highest number of COVID-19 deaths and their relationship to total confirmed cases and diabetes prevalence

| Country | Number of deaths* | Total per 100 000 population* | Total confirmed cases* | Total per 100 000 population* | Diabetes prevalence (%)** |
|---|---|---|---|---|---|
| United States of America | 1,003,894 | 303.29 | 85,332,271 | 25,779.94 | 10.7 |
| Brazil | 669,161 | 341.81 | 31,754,465 | 14,939.10 | 8.8 |
| India | 524,903 | 38.04 | 43,331,645 | 3,139.96 | 9.6 |
| Russia | 380,643 | 260.83 | 18,406,485 | 12,612.98 | 5.6 |
| Mexico | 325,417 | 252.39 | 5,877,837 | 4,558.84 | 16.9 |
| Peru | 231,395 | 647.2 | 3,600,993 | 10,921.42 | 4.8 |
| United Kingdom | 179,706 | 264.72 | 22,525,810 | 33,181.82 | 6.3 |
| Italy | 167,842 | 281.42 | 17,959,329 | 33,112.14 | 6.4 |
| Indonesia | 156,702 | 57.35 | 6,072,918 | 2,248.10 | 10.6 |
| France | 145,811 | 224.19 | 29,258,921 | 44,986.48 | 5.3 |
| Iran | 141,370 | 168.31 | 7,235,175 | 8,614.03 | 9.1 |
| Germany | 140,462 | 168.89 | 27,454,225 | 33,011.07 | 6.9 |

*Number of deaths, total confirmed cases, total per 100 000 data, June 2022.
**Prevalence (20–79 years) with diabetes in 2021.

and hypertension. Patients diagnosed with diabetes infected with SARS-CoV-2 have a higher rate of hospitalization, severe pneumonia, and increased mortality compared to those without diabetes infected with SARS-CoV-2. Therefore, having diabetes is a risk factor and modifies the prognosis in COVID-19, it has been shown that diabetes increases the risk of severity by 2.3 times and the risk of mortality associated with COVID-19 by 2.5 times[4].

It should be remembered that the SARS-CoV-2 virus penetrates cells through angiotensin-converting enzyme 2 (ACE2) membrane receptors, which are distributed in the heart, endothelial cells, lungs, intestines, and pancreas. When there is acute hyperglycemia, the expression of the ACE2 receptor is upregulated, favoring the entry of the virus into the cell, while in chronic hyperglycemia the cells lose their protective mechanism, becoming vulnerable to the proinflammatory effect of the virus. In this sense, it has been observed that diabetic patients with COVID-19 infection have a higher insulin requirement[5].

Pharmacological management for people with diabetes infected with COVID-19 should be governed by intensive glycemic surveillance and aggressive management against hyperglycemia. Hyperglycemia is a risk factor for the development of severe COVID-19. These patients will have significant hyperglycemia due to infection, inflammation, and stress stemming from the infection[6].

In countries where the prevalence of diabetes is very high[7] (table 1), the risk of favoring the association of diabetes and COVID-19 increases considerably and significantly complicates the evolution and prognosis of the patient. The lack of a specific treatment against COVID-19 and the medical difficulties to implement an adequate treatment in the seriously ill patient with diabetes and SARS-CoV-2 infection, The treatment of patients with diabetes and COVID-19 is essentially the same as recommended by the different health regulatory bodies; however, some clarifications should be made:

- If the patient is asymptomatic and maintains good glycemic control, the medical treatment is not modified and adequate follow-up of the patient is recommended.
- If the subject develops a mild or moderate infection, an adjustment of medical treatment is made, according to blood glucose concentrations.
- In patients with a severe infection, with dyspnea on moderate or slight exertion, low oxygenation,

pneumonia, complication of a comorbidity or requiring hospitalization, pharmacological and non-pharmacological treatment should be evaluated and the corresponding modifications made, for the best control patient's glycemic; the use of some type of insulin should always be an alternative[3].

In Mexico, the epidemiological process has followed a pattern similar to that observed in other countries, however, one of the characteristics of COVID-19 is the acceleration of contagion between people and the presence of relaxed measures that favor the spread of the coronavirus. This causes outbreaks and uncertainty in the processes of registration and estimation of the number of new cases, associated comorbidities, indicators of mortality, morbidity, direct hospitalization or associated with comorbidities. All this hinders the planning and implementation of the different health programs and has an impact on the incidence and prevalence of these diseases.

Undoubtedly, chronic diseases such as diabetes are complex and when they are associated with communicable diseases, the medical care of patients is further complicated. The challenge is to generate important changes in the health systems of the countries, considering the deficiencies in the different levels of medical care, especially in the first level. In addition, we must take into account the difficulties in acquiring health supplies, the delay in technological progress, the low level of education, poverty, geographic disparity, and economic and social risk factors.

In addition, given the great challenge of the pandemic, the participation of all those involved must be promoted: the patient, the primary caregiver, family members and health personnel. This to prevent infection in diabetic patients (hand hygiene, use of a mask, social distancing, timely vaccination), promote a healthy lifestyle (adequate food in quality and quantity, physical exercise, sleep quality, psychological support), have better control of the patient (appropriate weight for age and gender, access to medications and equipment to measure blood glucose, monitoring of blood pressure, cholesterol, triglycerides, glycosylated hemoglobin, renal, ophthalmic, and neurological function, avoiding or detecting adverse drug reactions), reduce the frequency of complications (diabetic nephropathy, neuropathy, myocardial infarction, diabetic foot), increase patient survival (timely and efficient contact with their doctors, hospitalization in specific cases and improve their quality of life such as physical, social emotional, material, and growth and development well-being). Continuing education in health, both for the patient, the primary caregiver and the health personnel is and will be an important pillar for slowing down this disease.

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## Conflicts of interest

The author declare that she have no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The author declare that no experiments on humans or animals were performed for this study.

**Confidentiality of data.** The author declare that no patient data appear in this article.

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ORIGINAL ARTICLE

# Perinatal morbidity in gestations with pathological combined first trimester screening for aneuploidies and normal karyotype

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## Abstract

**Objective:** *Positive Combined First Trimester Screening and by risk groups: 0-50, 51-100, 101-150, 151-200, 201-250, and normal karyotype relate with negative screening for adverse perinatal results.* **Method:** *Retrospective study of cases and controls in single pregnancies, with predictive analysis using multivariate logistic regression.* **Results:** *3,791 screenings were performed at our unit in 2012, with a screening/number of deliveries ratio of 89.9%. There is a greater likelihood of the newborn being underweight (AOR = 2.6, 95% CI 1.2 – 5.7), premature (OR = 2.2, 95% CI 1.03 – 4.5), admitted to the ICU (OR = 7.4, CI 95% 1.5 – 34.6) or admitted to the Neonates department (AOR = 8.1, 95% CI 1.7 – 37.7) in the case group.* **Conclusion:** *Combined first trimester screening is a predictive method for pregnant women with a higher risk of adverse perinatal outcomes.*

***Keywords:*** *PAPP-A. β-HCG. Adverse perinatal outcomes. Aneuploidies.*

## Introduction

The early diagnosis of any congenital defect in the fetus is of vital importance, as it enables the implementation of the most appropriate measures, both during pregnancy and during childbirth, as a means of preventing unnecessary risks to the mother and child and of attempting to improve the prognosis of the newborn after birth[1].

All pregnant women in the first trimester are offered prenatal aneuploidy screening, which estimates the individual risk of chromosomopathy, combining the *a priori* risk due to the mother´s age with the biochemical analysis of PAPP-A and maternal blood and free β-HCG fraction and with an ultrasound measurement of Nuchal Translucency (NT)[2,3].

Previous studies have revealed that the biochemical and ultrasound markers of first-trimester combined screening, abnormal PAPP-A, βHCG and NT in pregnancies without aneuploidy can be predictive of adverse perinatal outcomes[4-6].

Elevated NT with normal karyotype is associated with fetal structural anomalies and several genetic syndromes, including heart defects, Noonan syndrome, Smith-Lemli-Opitz syndrome and skeletal dysplasias of the achondroplastic type and thanatophoric displasia[7-12].

Low PAPP-A is associated with placental defects and has been associated with abortions, antepartum fetal death, restricted intrauterine growth, hypertensive disease of pregnancy, prematurity, and low birth weight.

Moreover, due to the association with abnormal placentation, high elevated βHCG is associated with preeclampsia, restricted intrauterine growth, antepartum fetal death and prematurity[13-16].

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The aim of our study is to find out if there are any significant differences in adverse obstetric and perinatal outcomes in pregnant women with positive combined screening and normal karyotype in the group of cases, by risk group (0-50, 51-100, 101-150, 151-200, 201-250), comparing them with the control group.

## Material and methods

Using the medical records database, we conducted a retrospective study of cases and controls in pregnant women that underwent combined screening in the first trimester in the prenatal diagnosis section of the department of obstetrics and gynecology at Miguel Servet University Hospital, Zaragoza, in the period from January to December 2012, both months included.

The following inclusion criteria were used: single pregnancies subjected to combined first-trimester screening and follow-up of pregnancy and delivery at our hospital, whereby the following were excluded from the study: twin pregnancies with aneuploidy and/or fetal malformations, and cases with an absence of data related to the mother and/or newborn.

To determine biochemical free β-HCG and PAPP-A, all the pregnant women were scheduled for blood collection between 9+0]-10+0] weeks, and for an ultrasound measurement of nuchal translucency between 11+0] -13+6 weeks and with a skull-caudal length (LCC) of between 45 and 84 mm.

The IMMULITE® 2000 automatic analyser (Siemens Healthcare Diagnostics) was used for the measurement of the biochemical parameters. The PAPP-A values in mIU/L and β-HCG values in ng/ml (with the equivalence ng/ml = IU/L), were converted into MoM, dividing the individual value of the marker by the value of the population median for the gestational age expressed in days.

The same plane as for the LCC was used to measure Nuchal Translucency (NT), with the fetus in a neutral position in accordance with the Fetal Medicine Foundation (FMF) standard https://fetalmedicine.org/education/the-11-13-weeks-scan.

A median of MoM NT of between 0.90 - 1.10 MoM, or the standard deviation of the log10 MoM NT, of between 0.08-0.13, was regarded as adequate. Prisca software version 639 – 0106 2012 was used to calculate the risk.

All the pregnant women with positive combined screening, risk >1/250 and normal karyotype were selected from the case group, who were divided into risk groups: 1-50, 51-100, 101-150, 151-200, 201-250 and the pregnant women with normal combined screening, risk < 1/14000 in the control group. Data on maternal backgrounds, delivery characteristics and neonatal morbidity was collected.

The gestational age of newborns was measured in days and was calculated through an ultrasound performed in the first trimester of pregnancy, or based on the date of the last period in which the gestational age did not changed by more than two standard deviations (< 6 days).

Preterm birth refers to births that occurred spontaneously or were induced before $36^{6}$ weeks of gestation (≤ 259 days)[17].

The weight of newborns was calculated in grams (g) at the time of delivery. The following category variables were taken into account: Low weight: Percentile (p < 10), Normal weight: Percentile: P10 – 90 and Large for gestational age (LGE): Percentile: p > 90. Weight according to gestational age was estimated using the Spanish tables of neonatal weights of the Spanish Society of Obstetrics and Gynecology (SEGO).

The SPSS programme was used for the statistical analysis of data. The description of the quantitative variables was carried out using mean and standard deviation. The chi-square test or Fisher's exact test was used to analyse the qualitative variables. Multivariate logistic regression analysis was used to assess the prediction in the case group and by risk group, in addition to the control group of the outcome variables. $p < 0.05$ was regarded as significant.

Only pregnant women that gave their consent to perform combined screening in the first trimester participated in the study, pursuant to the standards of the Society of Gynecology and Obstetrics (SEGO) and our hospital´s quality commission.

## Results

4,217 deliveries and 3,791 first-trimester combined screenings (FTCS) were performed at our hospital in 2012, with an FTCS/number of deliveries ratio of 89.9%. Of the total number of FTCS performed, 3515 FTCS were negative (92.7%) and 276 FTCS were positive (7.3%). Of the population screened in the year 2012, there were 30 true positives (TP), 246 false positives (FP), 3514 true negatives (TN) and 1 false negative (diagnosis through out-of-hospital amniocentesis). The sensitivity and specificity of FTCS in our sample were 96.8% and 93.5% respectively, with a false positive rate of 6%.

**Table 1.** Logistic regression analysis of the characteristics of the newborns, in the case and control group

| Newborn Characteristics | Cases | | | | Controls | |
|---|---|---|---|---|---|---|
| | OR | p | AOR | p | AOR | p |
| | IC 95% | | IC 95% | | IC 95% | |
| Premature ≤ 366 weeks | 2,17 | 0,041 | - | - | - | - |
| | 1,03-4,56 | | | | | |
| Weight RN < P10 | 1,9 | 0,018 | 2,6 | 0,013 | - | - |
| | 1,12-3,48 | | 1,22-5,7 | | | |
| Term gestation | - | - | - | - | 2,26 | 0,036 |
| | | | | | 1,05-4,86 | |
| | | | | | 1,06-40,36 | |

Source: Prenatal diagnosis section 2012.
OR: odds ratio; AOR: adjusted odds ratio; CI: confidence interval; NB: newborn; P: percentile; p: level of statistical significance.

There were 219 (39.9%) pregnant women with positive combined screening and normal karyotype in the study period. A control group from the same period was selected with 330 (15.7%) pregnant women with similar demographic characteristics.

Of the 549 single pregnancies included in the study, 30 (5.7%) were born prematurely and 54 (10.2%) were born with low birth weight (percentile <10). There was a greater likelihood in the case group of newborns with low birth weight (AOR = 2.642, $p$ = 0.013) and of prematurity (OR = 2.170, $p$ = 0.041) and in the full-term newborn control group (AOR = 2.265). By risk group, births with low weight were more likely in the 1-50 group (AOR = 2.269, $p$ = 0.036) and in the 100-150 group (AOR = 3.291, $p$ = 0.008) (Table 1).

52 newborns (9.8%) were admitted and observed, with 36 newborns (17.6%) in the case group and 16 newborns (4.9%) in the control group ($p$ < 0.001). Of the total admissions, 11 newborns (2.1%) were admitted to the ICU, 17 (3.2%) were admitted due to prematurity, 12 (2.3%) were admitted due to low weight and 5 (3%) were admitted due to prematurity-related complications. The prematurity-related complications observed in the newborns in question were: wet lung/lung maladaptation, hyaline membrane, bronchopulmonary dysplasia, retinopathy of prematurity and retinal hemorrhage.

We found a greater likelihood of admission to the ICU in the case group (OR = 7.4, $p$ = 0.011) and to the Neonates department (AOR = 8.120, $p$ = 0.008), the most likely causes of admission being prematurity (OR = 3.979, $p$ = 0.011), low weight (OR = 18.371, $p$ = 0.005), jaundice (OR = 4.808, $p$ = 0.002), and respiratory distress (OR = 4.808, $p$ = 0.001). Admission due to perinatal infection was more likely in the control group (AOR = 6.554) (Table 2).

The likelihood of the hospitalisation of newborns by risk group was: 1-50 group admission to the Neonates department (OR = 2.472, $p$ = 0.019), due to prematurity (OR = 4.13, $p$ = 0.01), due to prematurity-related complications (OR = 6.333, $p$ = 0.046), due to low weight (AOR = 6.322, $p$ = 0.049) and due to respiratory distress (OR = 4.8, $p$ = 0.001); in the 50-100 segment admission due to jaundice (AOR = 3.278, $p$ = 0.035), in the 100-150 group, admission to the neonates unit (OR = 2.704, $p$ = 0.028), due to low weight (OR = 2.704, $p$ = 0.015) and perinatal infection (AOR = 5.505, $p$ = 0.029); in the 150-200 group, due to respiratory distress (AOR = 5.813, $p$ = 0.01) and in the 200-250 group, admission to the ICU (AOR = 16.8, $p$ = 0.034) and due to respiratory distress (OR = 3.125, $p$ = 0.048) (Table 3).

## Discussion

The "Inversion of the antenatal control pyramid" concept is a model of prenatal care in which, gathering epidemiological, clinical, biophysical, ultrasound and analytical data between 11 and 14 weeks of gestation enables us to individualise the risk of each pregnant woman for a wide spectrum of pathological conditions (fetal death and spontaneous abortion, premature birth, preeclampsia, gestational diabetes, fetal growth restriction, macrosomia), thereby establishing preventive measures and, in some cases, therapeutic measures[18-20].

**Table 2.** Logistic regression analysis of neonatal morbidity, in the case and control group

| Neonatal morbidity | Cases | | | | Controls | |
|---|---|---|---|---|---|---|
| | OR | p | AOR | p | AOR | p |
| | IC 95% | | IC 95% | | IC 95% | |
| ICU admissions | 7,4 | 0,011 | - | - | - | - |
| | 1,58-34,67 | | | | | |
| Neonatal admissions | 4,1 | 0,001 | 8,1 | 0,008 | - | - |
| | 2,21-7,63 | | 1,74-37,73 | | | |
| Admission for Prematurity | 3,9 | 0,011 | - | - | - | - |
| | 1,38-11,46 | | | | | |
| Underweight Income | 18,3 | 0,005 | - | - | - | - |
| | 2,35-143,4 | | | | | |
| Admission for jaundice | 4,1 | 0,002 | - | - | - | - |
| | 1,67-10,08 | | | | | |
| Admission for respiratory distress | 4,8 | 0,001 | - | - | - | - |
| | 1,86-12,41 | | | | | |
| Admission for perinatal infection | - | - | - | - | 6,55 | 0,043 |
| | | | | | 1,06-40,36 | |

Source: Prenatal Diagnostic Section, HUMS, 2012.
OR: odds ratio; AOR: adjusted odds ratio; CI: confidence interval; NB: newborn; P: percentile; p: significance level.

Prematurity has major health implications due to high fetal morbidity and mortality, particularly at extreme gestational ages. Prematurity is the most frequent cause of perinatal mortality (2/3) and can cause significant long-term morbidity due to neurological, gastrointestinal and respiratory disorders[21,22].

The prevalence of prematurity in Spain is 9.5%[17,] with the rate of late prematurity (34 to 36 weeks of gestation) being far more prevalent both in Europe and in the USA, where it can vary from 50% to 75%[23,24].

*Beta* et al. conducted a predictive model of preterm delivery with the biochemical markers of the 1st trimester, maternal characteristics and obstetric history and conclude that preterm delivery could be detected with a rate of 20% in nulliparous women and 38% in women with a history of preterm delivery ≥ 16 weeks, with 10% false positives[25]. *Spencer* et al. conclude that low PAPP-A increases the risk of prematurity, but the same does not apply to βHCG. The lower the PAPP-A, the greater the risk of prematurity, even so the detection rate for low PAPP-A does not exceed 10%[26]. *Dugoff* et al, in the FASTER study, found a statistical association of PAPP-A < P5 with prematurity[5]. Prematurity was found in 6% of pregnancies in our study, with a greater probability in the case group (OR = 2).

Several studies report higher morbidity[27] and perinatal mortality in newborns with low birth weight < P10[28].

*Morris* et al. found an association between low weight < P10 and PAPP-A < P5 with a likelihood OR 2.08 (CI 1.89-2.29), with a prediction rate of 13%, for 7% of false positives[29].

*Peterson* et al. conclude that PAPP-A is positively correlated with birth weight, with a higher risk of low weight for gestational age with PAPP-A < 0.57 MoM[30].

A study conducted by *Spencer* et al. concludes that fetuses with a low weight for their gestational age are associated with lower medians of PAPP-A[26].

In our study, 2% of newborns weighing less than the 10th percentile were identified, being more likely in the case group (AOR = 2.642) and in the *1 to 50* (AOR = 2.269) and *100 to 150* (AOR = 3.291) risk groups.

With regard to morbidity in newborns, *Kirkegaard* et al. associate low levels of PAPP-A < 4 MoM and βHCG with a higher rate of admissions to neonatal

**Table 3.** Logistic regression analysis of neonatal morbidity, in the risk range of 1 to 50, 50 to 100, 100 to 150, 150 to 200, 200 to 250

| Neonatal morbidity | Segment 1-50 | | Segment 50-100 | Segment 100-150 | | Segment 150-200 | Segment 200-250 | |
|---|---|---|---|---|---|---|---|---|
| | OR | AOR | AOR | OR | AOR | AOR | OR | AOR |
| | IC 95% | IC 95% | IC 95% | IC 95% | IC 95% | IC 95% | IC 95% | IC 95% |
| ICU admissions | - | - | - | - | - | - | 5,5* | 16,87 |
| | | | | | | | 1,39-21,79 | 1,23-231,18 |
| Neonatal admissions | 2,4* | - | - | 2,7* | - | - | - | |
| | 1,15-5,27 | | | 1,11-6,57 | | | | |
| Admission for Prematurity | 4,1* | - | - | - | - | - | - | - |
| | 1,39-12,23 | | | | | | | |
| Underweight Income | 7,1* | 6,3 | - | 5,4* | 5,6* | - | - | - |
| | 2,18-23,43 | 1,009-39,6 | | 1,39-21,07 | 1,16-27,88 | | | |
| Admission for jaundice | - | - | 3,27* | - | - | - | - | - |
| | | | 1,08-9,9 | | | | | |
| Admission for respiratory distress | 4,8* | - | - | - | - | 5,8* | 3,12 | - |
| | 1,86-12,41 | | | | | 1,5-22,3 | 1,01-9,7 | |
| Admission due to prematurity complications | 6,3 | - | - | - | - | - | - | - |
| | 1,03-38,8 | | | | | | | |
| Admission for perinatal infection | - | - | - | 5,4* | 5,5* | - | - | - |
| | | | | 1,39-21,07 | 1,19-25,46 | | | |

Source: Prenatal Diagnostic Section, HUMS, 2012.
OR: odds ratio; AOR: adjusted odds ratio; CI: confidence interval; NB: newborn; P: percentile.
*Significant association.

intensive care units (ICU), regardless of gestational age and low weight[31].

In our study, there was a greater probability of hospitalisation in the neonates unit and the ICU in the case group and in the *1 to 50* and *50 to 100* risk groups, with the most likely cause of admission being prematurity (OR = 4.13), prematurity-related complications (OR = 6.333) and low birth weight (AOR = 6.322). Several studies have followed up on adverse obstetric outcomes and the relationship with biochemical and ultrasound parameters in the 1st trimester, but in general they have all been used on an isolated basis and therefore have less sensitivity and predictive value.

Our study has the major advantage of having used combined 1st trimester screening as a predictive method of adverse obstetric outcomes during pregnancy, which increases the likelihood of detecting pregnant women with a higher risk of developing pathologies, which may enable us to act from the beginning of pregnancy, modifying the risk (for example, the administration of aspirin in platelet dysfunction) or conducting a close follow-up procedure with predictable action.

One limitation of our study is that the relevance of the predictive values is limited due to the fact it is a case-control study. Nevertheless, we have been able to clearly illustrate the importance of first-trimester combined screening as a model for predicting adverse perinatal outcomes, such as prematurity, low weight and admissions to the ICU and neonates unit.

## Conclusion

Performing prenatal screening for aneuploidy, from 9+0] to 13+6 weeks of gestation, is of paramount importance, not only in screening for Down syndrome, but also for the early prediction of pregnant women at a high risk of developing adverse fetal events such as:

prematurity, low weight for gestational age and neonatal admissions.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Ethical disclosures

**Protection of people and animals.** The authors declare that no experiments have been performed on humans or animals for this research.

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REVIEW ARTICLE

# Liver biomarkers for prognosis in COVID-19

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## Abstract

*The novel coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Mortality attributable to COVID-19 remains considerably high, with case fatality rates as high as 8-11%. Early medical intervention in patients who are seriously and critically ill with COVID-19 reduces fatal outcomes. Thus, there is an urgent need to identify biomarkers that could help clinicians determine which patients with SARS-CoV-2 infection are at a higher risk of developing the most adverse outcomes, which include intensive care unit (ICU) admission, invasive ventilation, and death. In COVID-19 patients experiencing the most severe form of the disease, tests of liver function are frequently abnormal and liver enzymes are found to be elevated. For this reason, we examine the most promising liver biomarkers for COVID-19 prognosis in an effort to help clinicians predict the risk of ARDS, ICU admission, and death at hospital admission. In patients meeting hospitalization criteria for COVID-19, serum albumin < 36 g/L is an independent risk factor for ICU admission, with an AUC of 0.989, whereas lactate dehydrogenase (LDH) values > 365 U/L accurately predict death with an AUC of 0.943. The clinical scores COVID-GRAM and SOFA that include measures of liver function such as albumin, LDH, and total bilirubin are also good predictors of pneumonia development, ICU admission, and death, with AUC values ranging from 0.88 to 0.978. Thus, serum albumin and LDH, together with clinical risk scores such as COVID-GRAM and SOFA, are the most accurate biomarkers in the prognosis of COVID-19.*

***Keywords:*** *Albumin. Lactate dehydrogenase. Bilirubin. Prognosis. COVID-19. SARS-CoV-2.*

## Introduction

Since the coronavirus disease 2019 (COVID-19) outbreak began in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has quickly spread worldwide[1]. COVID-19 presentation is heterogeneous and ranges from asymptomatic disease to severe illness characterized by pneumonia, acute respiratory distress syndrome (ARDS), and sepsis that may eventually lead to death[2]. Despite the concerted efforts of health systems around the globe, mortality attributable to COVID-19 remains considerably high with case fatality rates as high as 9-11%[3]. Early medical intervention in seriously and critically ill COVID-19 patients may reduce fatal outcomes[4]. Therefore, there is an urgent need for novel biomarkers that can help clinicians identify patients with poorer prognosis. Early implementation of more aggressive drug regimens in these patients could not only increase survival rates but also optimize intensive care unit (ICU) resources.

Due to the extensive extrapulmonary manifestations of COVID-19, evaluation of patients typically includes comprehensive blood panels that allow the clinician to simultaneously estimate the effects of the disease on multiple organ systems[5]. Liver function tests (LFT) are commonly included in laboratory analyses and

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measure a variety of molecules such as transaminases, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, and albumin[6] that indicate the global function and integrity of the liver.

Large-scale descriptive studies have been conducted to examine the relationship between altered liver function and SARS-CoV-2 infection, but only a few of them describe factors that might be used to predict the most adverse outcomes of COVID-19, including ARDS development, ICU admission, and/or death[7-9]. Herein, we summarize the most promising liver biomarkers for COVID-19 prognosis in an effort to help clinicians rapidly, easily, and inexpensively predict the risk of ARDS, ICU admission, and death at hospital admission.

## Serum albumin

Serum albumin (SA) is the most abundant protein in human blood (35 to 50 g/L)[10]. SA is synthesized in hepatocytes as preproalbumin and then released to the rough endoplasmic reticulum, where an N-terminal peptide is removed to facilitate the conversion of the protein to proalbumin. Proalbumin is in turn processed in the trans-Golgi apparatus to form mature albumin that is subsequently released into circulation[11]. SA plays multiple physiological roles, including regulation of plasma colloid oncotic pressure, transportation of endogenous and exogenous molecules, anticoagulation, and antioxidation responses[10]. In clinical practice, SA level is commonly used as an indicator of mortality risk in severely ill patients such as those experiencing sepsis, trauma, or cancer[12].

Numerous studies support the use of SA as a biomarker of poor prognosis in COVID-19 patients, especially those at much higher risk of ICU admission or death. Three meta-analyses that evaluated several laboratory parameters reported decreased SA at admission in patients with severe COVID-19 (3.50 g/dL, 95% CI 3.26–3.74 g/dL) as compared to non-severe patients (4.05 g/dL 95% CI 3.82–4.27 g/dL)[13-16]. Hypoalbuminemia (SA < 30 g/L) also correlates with the severity of COVID-19 ($p$ < 0.0001) in patients from Italy[17]. Two additional meta-analyses showed that SA levels correlate with disease severity but fail to find associations among other liver parameters[9,16].

When considering these liver markers in the context of critical care, it is noteworthy that ICU patients with COVID-19 generally have lower SA values at admission than patients admitted to regular hospital floors (31.3 ± 5.2 g/L *versus* 36.5 ± 5.7 g/L; $p$ = 0.001). In fact, SA predicts ICU admission with a HR score of 1.87, 95% CI 1.05–3.32, $p$ = 0.034[18]. A study conducted in 63 COVID-19 patients from Turkey revealed that SA at admission predicts ICU admission with a cutoff point of ≤ 36 g/L, AUC of 0.989 (95% CI 0.924–1.00; $p$ < 0.001), sensitivity of 96.7%, and specificity of 93.9%[19]. On the other hand, a study of 128 COVID-19 patients from Dubai showed that SA failed to predict ICU admission (AUC 0.256, 95% CI 0.146-0.366)[20]. Thus, the use of SA as a predictor of ICU admission in seriously ill patients with COVID-19 should be performed with caution, and clinicians must take into account the genetic background and variability among the patient populations with which they work.

Regarding mortality, a meta-analysis evaluating eleven studies predominantly conducted in China indicated that SA values tend to be lower in non-survivors than survivors (-3.7 g/L, 95% CI -5.3 – -2.1; $p$ < 0.00001)[21]. A separate study conducted on 207 patients from Italy showed that hypoalbuminemia correlates with death in COVID-19 patients ($p$ = 0.003)[17]. Another study in 319 patients from Italy concluded that SA < 32 g/L is a risk factor for mortality, with HR of 2.48 (95% CI 1.44–4.26; $p$ = 0.001)[18]. Concurrently, two additional studies conducted in COVID-19 patients from China revealed that decreased SA at admission was an independent risk factor for mortality (OR = 1.929, 95% CI 1.199–3.104, $p$ = 0.007, and OR, 6.394; 95% CI 1.315-31.092, $p$ = 0.021, respectively)[22]. This evidence supports the idea that SA is an independent risk factor for ICU admission and death in patients that meet hospitalization criteria for COVID-19. As we have shown, critical consideration of SA levels may help clinicians identify patients with SARS-CoV-2 infection who are at much higher risk of developing adverse outcomes than other patients. Having a reliable and easy-to-detect biomarker at their disposal would enable clinicians to provide these high-risk patients with more aggressive medical treatments that will increase their probability of survival.

## Bilirubin

Bilirubin derives from the breakdown of the heme group in hemoglobin, which occurs in the spleen, bone marrow, and liver[23]. In these tissues, heme oxygenase, an enzyme found in macrophages, can catalyze iron release to form carbon monoxide and biliverdin. Biliverdin is in turn reduced to form unconjugated bilirubin, also referred to as indirect bilirubin, which is poorly water soluble[24]. The 200-300 mg of bilirubin produced by the human body per day is typically excreted.

Excretion of bilirubin occurs when indirect bilirubin (IBIL) is released into the plasma, where it binds albumin that is in turn transported to the liver[25]. Then, bilirubin is conjugated to uridine diphosphate sugars (UDP) via UDP-glucuronyltransferase. This increases IBIL solubility and allows its excretion through the bile. Conjugated bilirubin, also referred to as direct bilirubin (DBIL), is broken down into urobilinogens by intestinal bacteria. At this point, a small quantity of DIBIL can be deconjugated and re-absorbed by intestinal epithelial cells[23]. Any increase in the rate of release of the heme group or failure to completely excrete bilirubin leads to a concomitant elevation of total bilirubin, direct bilirubin, or indirect bilirubin depending on the step of bilirubin metabolism that is impaired[25].

Common clinical laboratory tests include measures of total bilirubin (TBIL), IBIL, and/or DBIL, which can help establish the cause of hyperbilirubinemia[24]. Elevation of bilirubin in patients with SARS-CoV-2 infection is not common. However, among COVID-19 patients who do show abnormal liver function test results during hospitalization, TBIL levels have been found to be elevated as high as 18%[8,26,27]. A large study conducted in 5771 patients from China suggested that TBIL values are independent of the severity of COVID-19[28]. Indeed, the average values of TBIL, DBIL, and IBIL fell within normal ranges of values in all patients enrolled in this study (10.4 μmol/L, IQR 7.9-14.1, 3.0 μmol/L, IQR 2.1-4.4, and 7.4 μmol/L, IQR 5.2-10.3, respectively)[28].

Conversely, emerging evidence now supports the use of bilirubin values at hospital admission to estimate a patient's risk of developing severe COVID-19. Seriously ill patients have higher TBIL and DBIL levels at admission than non-severe patients (for TBIL, 10.6 μmol/L, IQR 7.9-15.0 *versus* 10.3 μmol/L, IQR 7.9-14.0, $p = 0.053$, respectively; for DBIL, 3.3 μmol/L, IQR 2.2-5.2 0 *versus* 2.9 μmol/L, IQR 2.0-4.20, $p < 0.001$, respectively)[28]. In addition, the peak of TBIL correlates with mortality risk, where TBIL maximum values of 21-63 μmol/L confer a 3-fold increased mortality risk (HR 3.28 95% CI 2.47-4.35; $p < 0.001$), while patients with TBIL greater than 63 μmol/L show 8-fold increased mortality risk (HR 7.98 95% CI 3.88-16.41; $p < 0.001$)[28]. Higher TBIL levels also confer ~3-fold increased risk of developing severe COVID-19 (OR 2.94, 95% CI 2.18-3.97)[29]. Likewise, TBIL values are elevated in ICU patients relative to non-ICU patients (15.8 ± 6.8 μmol/L *versus* 9.1 ± 3.6 μmol/L, $p = 0.0082$, respectively)[30]. In a population of pediatric COVID-19 patients, Wang and collaborators also reported higher TBIL values in seriously ill patients than in non-severe individuals (10.13 μmol/L *versus* 6.40 μmol/L, $p = 0.05$, respectively) with OR of 1.316, 95% CI 0.575-3.014, $p = 0.516$)[4]. These studies suggest that bilirubin can be used to estimate the risk of mortality or ICU admission in adult and pediatric patients with COVID-19, especially TBIL and DBIL[31].

## Lactate dehydrogenase

Lactate dehydrogenase (LDH) is a ubiquitous enzyme in human cells. LDH consists of four polypeptide chains that constitute five different isoforms located in the cytosol and mitochondria[32]. In the cytosol, LDH catalyzes the conversion of lactate to pyruvate by transferring a hydride group from NAD+ to NADH[33]. In the mitochondria, LDH catalyzes the conversion of lactate to pyruvate by transferring a hydride group from ferricytochrome c to ferrocytochrome c. Release of LDH into cells occurs primarily as a result of necrosis[32,33]. Serum LDH is elevated in a variety of clinical scenarios including hemolysis, infection, sepsis, infarction, liver and kidney diseases, pancreatitis, bone fracture, rhabdomyolysis or myositis, hypoxia, shock, and cancer[34].

LDH elevation is one of the most commonly reported laboratory anomalies in COVID-19 patients around the world. In fact, 50-80 percent of patients with SARS-CoV-2 infection show abnormally high LDH levels[13]. Numerous studies report a strong positive correlation between LDH levels and COVID-19 severity, with higher levels present in severe or critical patients. A study conducted in 548 patients reported 250 U/L and > 445 U/L as two cutoff values for LDH that can help distinguish non-severe patients from critically ill patients who are at a much higher risk of death. Patients with LDH > 445 U/L at admission were at a 4.4-fold increased risk of developing severe COVID-19 (OR, 4.4, 95% CI 2.6-7.6) and a 2-fold increased risk of death (HR 2.0, 95% CI, 1.2-3.3; p = 0.007)[35]. In a meta-analysis of 19 papers that gathered clinical information from more than 3000 patients, LDH elevation at admission carried an 8-fold increased risk of developing severe COVID-19 (OR 8.28, 95% CI 4.75 - 14.46). LDH values were higher in patients who required ICU admission, with an OR of 5.78 (95% CI 1.65 – 20.28; $p < 0.001$)[36]. Numerous studies and meta-analyses report significantly increased LDH levels in non-survivors with respect to survivors ($p < 0.001$)[36]. This increase in LDH also associates with mortality risk, with OR values ranging from 4.09 to 10.88 depending on the study ($p < 0.001$)[37]. In line with this, a study conducted in 375 COVID-19 patients from China reported that LDH

**Table 1.** Liver biomarkers as predictors of pneumonia development, intensive care unit admission, and death in patients with COVID-19

| Liver biomarker | Cutoff point | Clinical outcome | AUC (95% IC) | Sensitivity (%), Especificity (%) | Country (Reference) |
|---|---|---|---|---|---|
| HSA | < 36 g/L | ICU admission | 0.989 (0.924-1.00) | 96.7, 93.9 | Turkey (Uyar et al.) |
| | NA | ICU admission | 0.256 (0.146-0.366) | NA | United Arab Emirates (Hachim et al.) |
| LDH | > 365 U/L | Death | 0.943 (NA) | NA | China (Yan et al.) |
| | > 303 U/L | Death | 0.829 (0.745-0.895) | NA | China (Feng et al.) |
| | > 353.5 U/L | Death | 0.949 (NA) | 94.4, 89.2 | China (Dong et al.) |
| AST/ALT ratio | > 1.38 | Death | 0.71 (0.67-0.74) | NA | China (Qin et al.) |
| | > 1.49 | Death | 0701 (0.603-0.787) | 74, 70 | Italy (Zinellu et al.) |
| | > 1.65 | Death | 0.713 (0.618-0.807) | 57.5, 82.3 | Turkey (Medetalibeyoglu et al.) |
| | > 1.26 | ICU | 0.636 (0.564-0.709) | 64.9, 60.4 | |
| | > 1.55 | Pneumonia | 0.577 (0.529-0.625) | 61.0, 55.6 | |
| Fibrinogen/ Albumin Ratio | ≤ 0.0883 | Pneumonia | 0.730 (NA) | NA | China (Bi et al.) |
| COVID-GRAM | | Pneumonia | 0.88 (0.85-0.91) | NA | China (Liang et al.) |
| LDH<br>CRP<br>Lymphocyte | > 365 U/L<br>< 41.2 mg/L<br>> 14.7% | Death | 0.978 (NA) | NA | China (Yan et al.) |
| SOFA score | ≥ 3 | Death | 0.890 (0.826-0.955) | 90.00, 83.18 | China (Liu et al.) |

Summary of the most accurate liver biomarkers for prognosis in COVID-19. Liver biomarkers are accompanied by specific cutoff value, main clinical outcome, AUC, sensitivity, specificity, and country of origin.
NA: non available; AUC: area under the curve; CI: confidence interval; ICU: intensive care unit admission; AST: aspartate aminotransferase; ALT: alanine aminotransferase; SA: serum albumin; LDH: lactate dehydrogenase; CRP: C reactive protein; SOFA: sequential organ failure assessment.

> 365 U/L predicts mortality with an AUC of 0.943. Similarly, Feng and coworkers found that LDH > 303 U/L predicts death with an AUC of 0.829. Finally, another study conducted in 119 severe-to-critical COVID-19 patients estimated that LDH > 353.5 U/L predicts mortality with an AUC of 0.949, sensitivity of 94.4%, and specificity of 89.2%[38]. As we have outlined here, LDH appears to be a reliable independent risk factor for mortality in patients who meet hospitalization criteria concurrent with severe-to-critical COVID-19.

## Ratios and clinical scores based on measures of liver function

Liang and coworkers proposed the use of the COVID-GRAM score to predict the development of critical COVID-19. The assessment takes into account such factors as lactate dehydrogenase, direct bilirubin, chest radiography, age, hemoptysis, dyspnea, unconsciousness, cancer history, neutrophil-to-lymphocyte ratio, and number of comorbidities [39]. This score has an AUC of 0.88 (95% CI 0.85-0.91) for predicting the proportion of patients at higher risk of needing critical care for COVID-19[39].

Notably, Yan and collaborators proposed a score based on LDH > 365 U/L, C reactive protein < 41.2 mg/L, and lymphocyte count > 14.7% that was shown to reliably predict mortality in COVID-19 patients, with an AUC of 0.978. In fact, use of this score permitted 100% accurate prediction of a patient's outcome ten days prior its occurrence[38].

Another score based on LDH, procalcitonin, smoking history, oxygen saturation, and lymphocyte count predicts ICU admission of COVID-19 patients with an AUC of 0.761 (95% CI 0.71–0.81; $p < 0.001$), sensitivity of 10.5%, and specificity of 99.2%. Likewise, the combined use of LDH, procalcitonin, history of chronic obstructive pulmonary disease (COPD), oxygen saturation, heart rate,

and age predicts mortality in COVID-19 patients with an AUC of 0.87 (95% CI 0.83–0.92; $p < 0.001$), sensitivity of 7.1%, and specificity of 100%[36].

Finally, the Sequential Organ Failure Assessment (SOFA) is commonly used to predict mortality in seriously ill patients with sepsis[40]. The SOFA score includes oxygenation index, mean arterial pressure, the Glasgow coma scale, creatinine or urine volume, platelets, and TBIL[40]. Liu and collaborators found that SOFA score at admission predicts mortality of COVID-19 patients with a cutoff point ≥ 3 points, AUC of 0.890 (95% CI 0.826–0.955), sensitivity of 90.00%, and specificity of 83.81%[40]. This information supports the idea that scores that take parameters of liver function into account are better predictors of pneumonia, ICU admission, and death in patients with COVID-19.

## Conclusion

As we have outlined here, liver impairment is commonly reported in COVID-19 patients, especially those with severe or critical disease who frequently experience the worst outcomes[26]. The cause of abnormal liver function in these cases remains unclear, although several hypotheses have been proposed. Firstly, hepatocytes, cholangiocytes, and endothelial cells express the angiotensin-converting enzyme 2 (ACE2) receptor that acts as the main SARS-CoV-2 entry point[41] into cells. Upon SARS-CoV-2 infection, liver cells may undergo necrosis and/or apoptosis. This can, in turn, contribute to inflammation and lead to hepatic damage. It is also believed that ARDS, hypoxia, and coagulation disorders might contribute to liver damage by increasing hepatic isquemia[42]. Further, exacerbation of the inflammatory response directly contributes to the cytokine storm often observed in severe COVID-19 cases, which in turn promotes multiple organ failure, including failure of the liver[43]. Finally, the use of hepatotoxic drugs such as acetaminophen might also alter liver function tests in patients with COVID-19[42,44].

In terms of liver function tests, serum albumin and LDH are better predictors of ICU admission and death than levels of transaminases, ALP, bilirubin, and GGT[45]. Clinical scores that include indicators of liver function such as albumin, LDH, and total bilirubin are also accurate predictors of the most adverse outcomes, including pneumonia, ICU admission, and death, in patients with SARS-CoV-2 infections. Therefore, prognosis in COVID-19 should be assessed using scores that take liver function tests such as albumin and LDH into account, together with other demographic or clinical parameters. Liver function tests greatly enhance the ability of clinicians to identify patients at higher risk of developing the most severe cases of COVID-19, which could help increase survival rates and optimize hospital resources throughout the current pandemic.

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## Conflicts of interest

The authors declare that do not exist conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

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CLINICAL CASES

# Uterine artery embolization prior to hysterectomy as a prevention of the risk of hemorrhage

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## Abstract

*Uterine leiomyomas are the most common tumors of the female genital tract, patients with uterine fibroids are usually asymptomatic. Approximately 20-50% of them experience acute symptoms such as pelvic pain, vaginal bleeding, or infertility, and will require treatment. Among the treatment options are conservative (hysteroscopy, laparoscopy or open myomectomy) and radical (hysterectomy) depending mainly on the reproductive desire of the patient. The purpose of presenting this series of clinical cases is to present a new alternative in the management of uterine leiomyomas, combining the use of uterine artery embolization and subsequent performance of total abdominal hysterectomy.*

***Keywords:*** *Embolization. Uterine arteries. Hysterectomy. Transfusion. Hemorrhage. Myomectomy.*

## Introduction

Uterine leiomyomas are the most common tumors of the female genital tract, with an estimated incidence between 40 and 60% at 35 years and between 60 and 70% at 50 years in the general population. Patients with uterine fibroids are usually asymptomatic. Despite this, 20-50% of them experience acute symptoms such as pelvic pain, vaginal bleeding or infertility, and will require treatment[1]. The standard treatment of symptomatic uterine fibroids is conservative (hysteroscopy, laparoscopy or open myomectomy) or radical (hysterectomy) depending mainly on the reproductive desire of the patient.[1] These tumors are densely vascularized. Therefore, myomectomy can often be a challenging procedure with significant risk of perioperative and postoperative bleeding, prolonged duration of the surgical procedure, postoperative complications, and need for transfusion. In the literature, it has been shown that transfusion is necessary in up to 20% of cases after abdominal myomectomy[1].

As this is an innovative technique, there is not much information regarding the benefits in terms of the need for blood transfusion. According to the study conducted by B. Mclucas in 1999, an incidence of 12.5% is reported for patients in whom only myomectomy was performed against 0% in patients who were associated with uterine artery embolization and myomectomy. As well, they report a reduction of 75% in the blood loss quantification comparing both methods. (365 ml in simple myomectomy versus 56 ml in association with embolization)[2]. As did N. Butori et al. in their publication made in 2011 and Cécile Malartic et al. 2012 publication, reporting a 0% need for blood transfusion with blood loss range of 0-800 ml[3,4]. Also, a decrease in hospital stay time of an average of 3.6 days has also been demonstrated in patients with simple myomectomy versus 3.9 days in embolization with myomectomy[2]. Reporting a range of 3-12 days[3].

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Some features of fibroids have already been identified as risk factors for such complications in open myomectomy: history of previous myomectomy, uterus volume greater than 20 centimeters, perioperative removal of more than 10 fibroids, and midline incisions[1,5-9].

The efficacy of uterine artery embolization is well documented for the treatment of uterine fibroids, alone or in combination with surgical myomectomy. Some studies on preventive embolization of uterine arteries (maximum 24 hours before surgery), have shown encouraging results with respect to blood loss, need for perioperative or postoperative transfusion, surgical revision and hemostatic hysterectomy[10]. Today, uterine artery embolization is an established procedure worldwide to treat fibroids as an alternative to surgery. However, the combination of this procedure and subsequent myomectomy is still subject to discussion.

Embolization is indicated for uterine fibroids that cause symptoms that significantly alter lifestyle, heavy menstrual bleeding, severe dysmenorrhea, anemia, pain, mass effect in the bladder or at the intestinal level[11,12]. Its contraindications would include a viable pregnancy, active infection, uterine or ovarian malignancy[13]. The following complications of this procedure are known: hematoma at the puncture site, arterial thrombosis, false aneurysm, arterial dissection, migration of atherosclerotic plaque, allergy to contrast medium, with a total incidence of 1 to 2% in all procedures[14,15]. It is extremely important to remember that uterine artery embolization can cause very significant pain after the procedure due to the ischemic changes that occur, presenting with greater intensity in the first 24 hours, with a maximum peak at 7 hours post-surgery. Therefore, joint management is recommended according to institutional protocol with the anesthesiology service for postoperative pain management, in some case series the application of epidural analgesia is even recommended in cases of uncontrollable pain[16-19].

## Case report

### *Patient 1 (Fig. 1)*

A 35-year-old female with no significant medical history. Patient who started current condition of 1 year of evolution with increased abdominal volume, added increased amount of menstrual bleeding and dysmenorrhea. Ultrasonographic findings: uterus of 34.7x24.6x12.8 cm, myometrium with heterogeneous ovoid image of hypoechoic predominance with central and peripheral vascularity of 28.3x23.2x14.2 cm, transmural myomatosis. Embolization of the uterine arteries by radiointervention service, femoral route with an 18G needle, a 5Fr vascular introducer, both internal iliac arteries and subsequently both uterine artery were catheterized using Gelfoam paste, lidocaine, 0.5% Lauromacrogol, and 1 cc lipiodol. Splinting of the ureters is performed after performing a total abdominal hysterectomy by the Urology service with double J catheters. A gynecological procedure is performed where the following findings are reported: uterus of approximately 30x14.5x6 cm with irregular edges, increased consistency, ovaries of 3 x 2 cm, weight of the piece 8900 gr, total trans-surgical bleeding of 1800 cc (1335 ml associated with extraction of surgical piece). She was admitted to the operating room with a hemoglobin of 9.8 g/dl. A transfusion of 2 trans-surgical erythrocyte concentrates was performed by the anesthesiology service due to hemodynamic instability after removal of the surgical piece, as well as vasoactive drugs and the administration of 1 gr of tranexamic acid in single dose. In recovey area we found hemoglobin of 7.8 g/dl, transfusion of 2 additional packed red blood cells is indicated, subsequently reporting a hemoglobin of 8.7 g/dl. Clinical data suggestive of pneumothorax are found, so they request support from the cabinet by means of an antero-posterior chest X-ray where pneumothorax of 40% is evident. Placement of an endopleural tube was requested from the pulmonology service. Four days later, it was decided to remove the endopleural tube. Discharge from the gynecology service with follow-up of a double J catheter by urology in an outpatient clinic, which is withdrawn by said service.

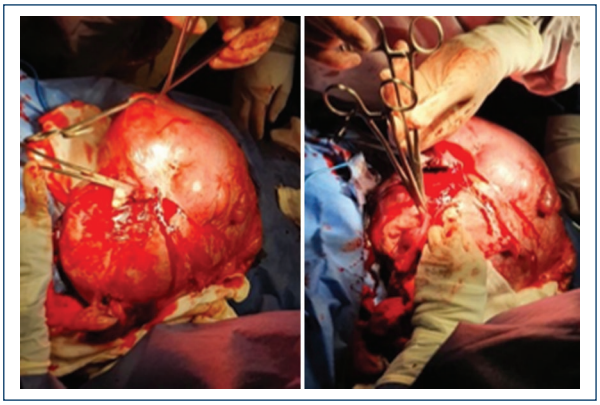

**Figure 1.** Uterus of approximately 30x14.5x6 cm with irregular edges, increased consistency. Clamps in round ligament, utero-ovarian ligament, uterine tube.

### *Patient 2 (Fig. 2)*

41-year-old female patient. Diagnosis of uterine myomatosis of large elements was made by private clinic and

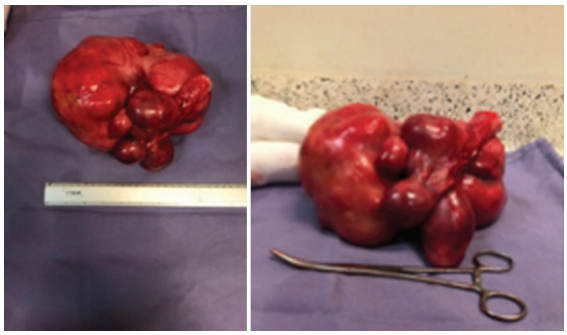

**Figure 2.** Uterus 6x5x4 cm, bilobed fibroid in the uterine fundus 25x12 cm, 3 fibroids in the posterior face of the uterus 6x5, 4x4, 3x2 cm respectively. Surgical piece removed.

they referred the patient to our unit for management. Magnetic resonance imaging cabinet study support is performed on 06.17.21: Large element Myomatosis FIGO 4, 6 y 7. Uterine artery embolization is performed on 08.10.21 by the radiointervention service: left uterine artery with 7 cc of embolizing agent consisting of Gelfoam mixture + 2 cc of sclerol + 3 cc of lipiodol; right uterine artery with 3 cc of embolizing material, a 100% decrease in tissue staining is observed. She was admitted to the gynecology operating room and the ureteral splinting was performed with a double J catheter by the urology service: laterally displaced ureteral meatus, at the expense of extrinsic compression secondary to uterine myomatosis. A total abdominal hysterectomy was performed where the following findings were reported: uterus 6x5x4 cm, bilobed fibroid in the uterine fundus 25x12 cm, 3 fibroids in the posterior face of the uterus 6x5, 4x4, 3x2 cm respectively, ovaries without alterations, total bleeding 830cc. In the recovery area, the presence of hematuria in the urine collection bag was noted, assessed by the urology service, who indicated not to remove the catheters until it was cleared. Upon admission with a hemoglobin of 14 g/dl, on the first postoperative day, a blood count was taken, where a decrease in levels up to 7.7 g/dl was noted, it was decided to transfuse an erythrocyte concentrate, with level of hemoglobin of 8.2 g/dl post-transfusion. Upon presenting adequate evolution, discharge from the service is decided and removal of double J catheters was performed post-surgical evaluation in the outpatient clinic with evidence of clear urine.

### *Patient 3 (Fig. 3)*

30-year-old female. The current condition began a year earlier with increased abdominal perimeter and

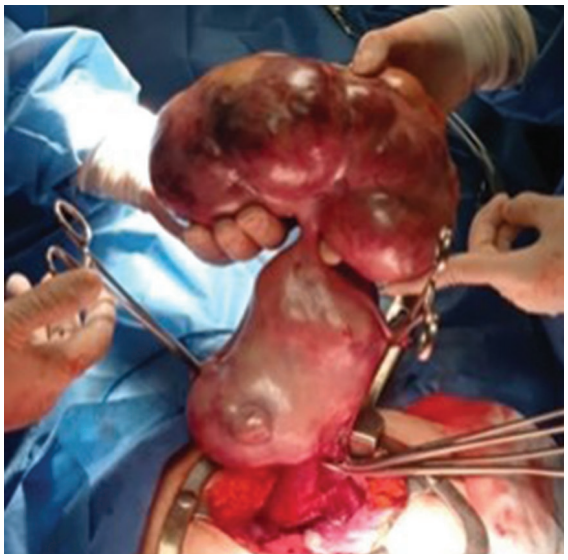

**Figure 3.** Uterus of 15x10x6 cm, irregular due to multiple fibroids, fibroid in the uterine fundus of approximately 17x12x10 cm. Surgical piece removed.

pain in the hypogastrium. On physical examination, the uterus was 25x18x15 cm, so pre-surgical tests were requested. Uterine artery embolization is performed on admission and a day later double J catheter placement is performed by the Urology service and a surgical intervention is performed where the following findings are reported: uterus of 15x10x6 cm, irregular due to multiple fibroids, fibroid in the uterine fundus of approximately 17x12x10 cm, right ovary of 3x2x2 cm, left ovary of 3x2x2 cm, weight of the piece 2,600 gr. Total bleeding 900 cc (390 ml associated with extraction of surgical piece). Patient with adequate clinical evolution, so two days after the intervention, double J catheters were removed and hospital discharge was decided. Patient who did not require transfusion of erythrocyte concentrates.

## Comment

Three cases of leiomyomatosis are presented in which, according to our literature review on the success in the use of uterine artery embolization prior to myomectomy in reducing the rate of trans-surgical bleeding, it was decided to implement in our previous case to performing a total abdominal hysterectomy in order to demonstrate the usefulness of this method. As well as the splinting of the ureters by the urology service to protect these structures. It is important to remember that this method is used as a complement to simple

myomectomy, however, there is no report in the literature regarding the success of this embolization technique together with total abdominal hysterectomy. Our three patients had loss of uterine anatomy secondary to leiomyoma-type uterine tumors. It is important to note that in our three reported cases the same pre-surgical measures were implemented and to highlight the large size of the uterine fibroids to be treated in our patients.

Despite the success shown in the literature in the implementation of this method, we must be aware of the possible complications associated with this previously discussed treatment alternative. In the case of our patients, it is worth mentioning the complications that arose after surgical management, such as the need to use an endopleural tube secondary to pneumothorax, the need for blood transfusion, the permanence of a Foley catheter and double J catheters in patients 1 and 2. It is also important to consider that performing such procedures led to an increased hospital cost. In our hospital experience, by not implementing this embolization method in patients with this type of pathology, on average they would require a transfusion of 3-4 packed red blood cells. Just as the requirement of stay in the intensive care area on average for 1-2 days has been seen derived from trans-surgical hemorrhage. It is important to remember that we must subtract from the total surgical bleeding, the bleeding derived from our surgical piece, which represents 15% of the weight of the surgical piece. With the above, we would demonstrate that on average we find in our patients an average bleeding according to the literature reports. However, with our patient 3, success was evidenced with the pre-surgical measures previously mentioned as prevention of hemorrhage, without presenting complications derived from procedures or requiring transfusion of blood products.

Therefore, it is relevant to mention that it is only a case report of three patients, in addition to the fact that, as previously mentioned, this alternative procedure has not been implemented to carry out this surgical technique, so it would be necessary to report more cases to evaluate the success or failure of this innovation. Now our patients have adequate post-surgical evolution despite the complications that have arisen.

## Conclusion

The objective of our case report is to propose a new therapeutic method for the management of uterine myomatosis of large elements in order to reduce the need for transfusion of blood products in patients who are candidates for surgical management.

Regarding our cases, it is evident that derived from underlying pathology, our patients presented complications derived from both the surgical procedure and the placement of double J catheters. However, no complications associated with performing uterine artery embolization were reported. It is important to note that our patients presented a total distortion of the uterine anatomy that compromised the correct performance of our pre-surgical steps, and this could be associated with the complications raised in our cases reports. A decrease in the requirement for blood transfusions was observed, as well as a decrease in trans-surgical bleeding estimated according to our hospital experience, in addition to a decrease in the need to stay in the intensive care area derived from complications secondary to surgical bleeding. It is worth mentioning that in our third case there were no complications associated with the surgical procedure, there was no increase in the days of hospital stay, and no transfusion of blood products was required. Such a case is the success that we would expect to find in the rest of our patients who are waiting for surgical date by our protocol.

In addition, the small number of patients in whom this new treatment method has been implemented is emphasized, so our results would not be conclusive with respect to recommending or avoiding the use of this technique.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Ethical disclosures

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# Disseminated peritoneal leiomyomatosis. A rare disease with a difficult diagnosis

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## Abstract

**Background:** *Disseminated peritoneal leiomyomatosis is a rare, benign disease characterized by the proliferation of multiple peritoneal and subperitoneal nodules consisting of smooth muscle cells. Diagnosis is difficult due to its similarity to peritoneal carcinomatosis. less There are 200 cases reported in the world literature.* **Clinical case:** *A 29-year-old female with a history of abdominal hysterectomy due to myomatosis 4 years ago, came due to abdominal pain, multiple solid images of different sizes were observed in the tomography, she underwent elective surgery, histological analysis confirmed benign smooth muscle tumors. We present a case operated on in our center.*

***Keywords:*** *Leiomyomatosis peritoneal disseminated. Leiomyoma. Surgery.*

## Introduction

Leiomyomatosis peritoneal disseminated (LPD) is a rare, benign disease characterized by the proliferation of multiple peritoneal and subperitoneal nodules consisting of smooth muscle cells[1]. The differential diagnosis of LPD is challenging due to its clinical similarity to peritoneal carcinomatosis or metastatic lesions. and its histological similarity with benign metastatic leiomyoma[2]. The first reported case in the literature was published in 1952 by Wilson and Peale[3]. There are less than 200 cases reported in the world literature, given its rarity there are no established guidelines for its treatment[4]. Some risk factors have been identified for LPD, use of oral contraceptives, metaplasia, genetics, pregnancy, iatrogenic and surgical manipulation[5]. We present a case of LPD intervened in our center.

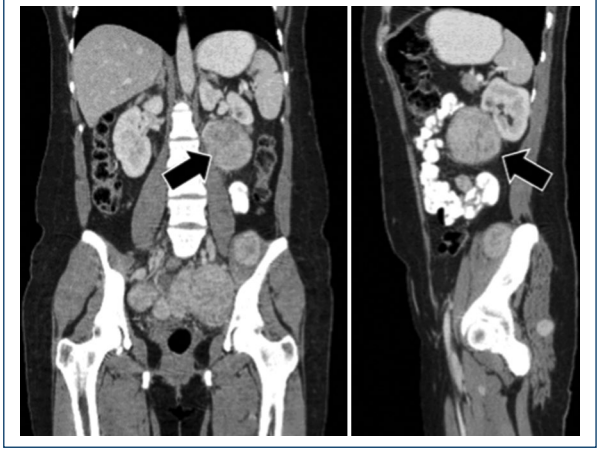

**Figure 1.** Computed tomography: heterogeneous mass with well-defined borders that displaces the left kidney.

## Clinical case

A 29-year-old female with a history of cesarean section and abdominal hysterectomy for uterine myomatosis 4 years ago. He came due to presenting abdominal pain of moderate intensity, located in the hypogastrium with irradiation towards the left pelvic limb, which increased with the passing of days. Ultrasound is performed where multiple images of solid

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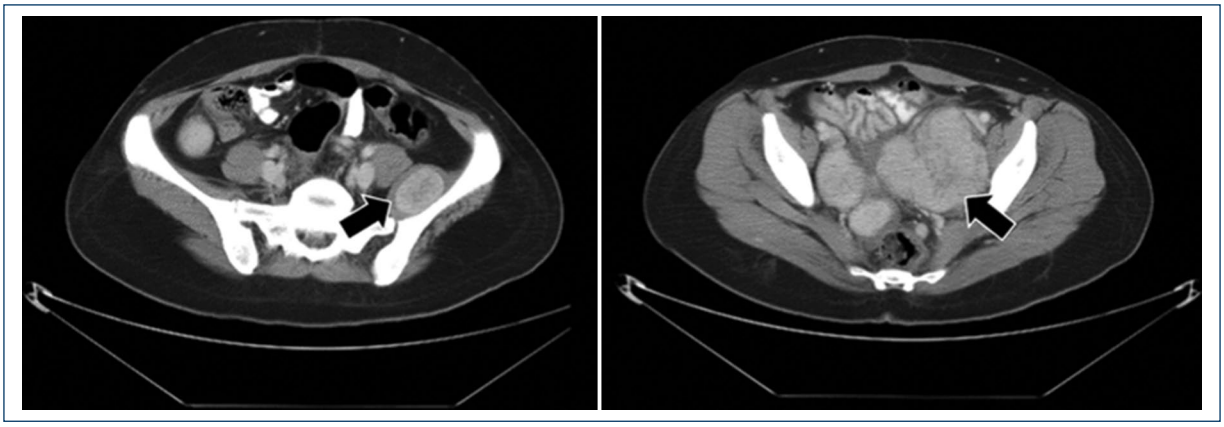

**Figure 2.** Computed tomography: multiple pelvic heterogeneous nodules.

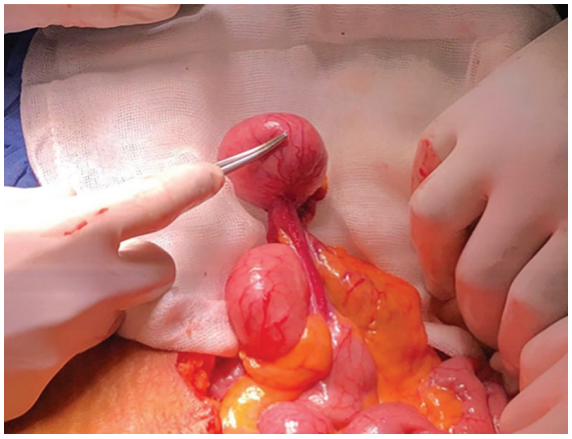

**Figure 3.** Intraoperative image showing representative pedunculated nodular formation.

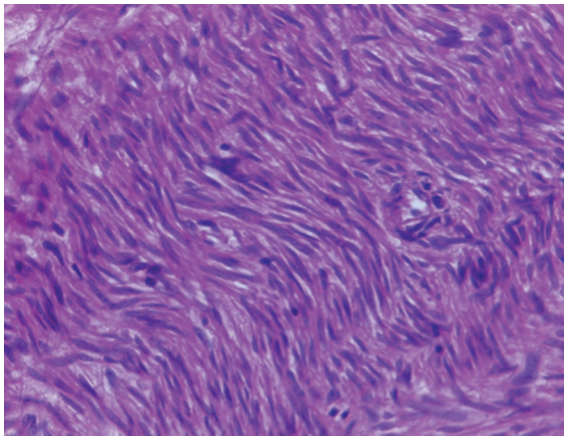

**Figure 4.** View at 40X, spindle nuclei, fine chromatin, no mitosis, no atypia.

characteristics in the pelvic cavity are identified. In the simple and contrasted abdominopelvic tomography, a left retroperitoneal image of 6.4 x 7.4 x 7.2 cm with a volume of 178.3 cc was observed. displacing the kidney on the same side (Fig. 1), multiple solid images (approximately ten) of different sizes were found in the pelvis, the largest being 7.4 x 8.0 x 7.6 cm with intense enhancement with contrast medium (Fig. 2). The patient underwent elective surgery, during surgery multiple peritoneal and retroperitoneal nodules were found in the right obturator fossa, left iliac muscle, left renal pole, pelvic cavity and right paracolic frame (Fig. 3). They were completely resected carefully by the surgeons, hemostasis was performed with electrocoagulation and sutures (Vicryl 2-0), with satisfactory postoperative evolution.

Histological analysis of the surgical specimens confirmed the diagnosis. The histological structure of the tissue consisted of benign smooth muscle cell tumors, without mitotic figures or cellular atypia, without necrosis (Fig. 4). Immunohistochemistry: overexpression of estrogen (Fig. 5) and progesterone (Fig. 6) receptors. Follow-up was continued for 1 year, being asymptomatic and without evidence of ultrasound disease.

## Discussion

LPD is an extremely rare clinical condition. Two main theories of the etiology and pathophysiology of LPD have been reported: a hormonal theory with mesenchymal stem cell metaplasia and an iatrogenic origin after surgery. According to the hormonal theory, LPD is supposed to result from the metaplastic change of mesenchymal stem cells with exposure to high levels of female

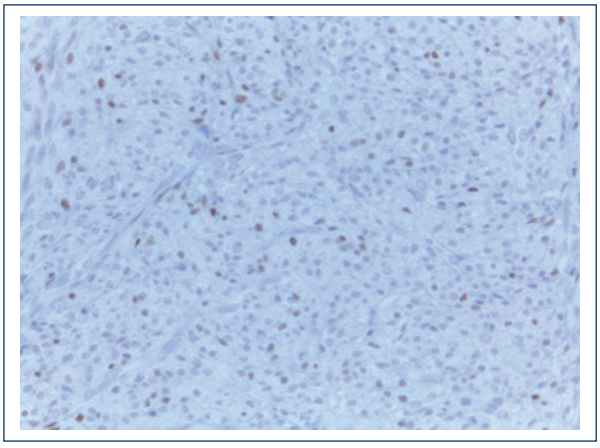

**Figure 5.** Immunohistochemistry, estrogen receptors with nuclear intensity 1.

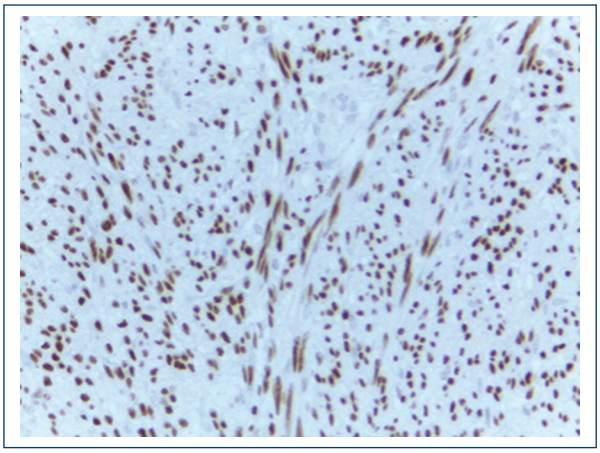

**Figure 6.** Immunohistochemistry, nuclear intensity 2 progesterone receptors.

steroids[6]. Recent publications have highlighted a link between surgical history such as hysterectomy for myomatosis or the laparoscopic uterine fibroid fragmentation technique and the development of LPD, due to the potential for tumor implantation and dissemination[7]. More specifically, LPD can present years after myomectomy or hysterectomy[8]. In our case, the history of hysterectomy due to myomatosis without adequate containment systems could have played a role in the pathogenesis of LPD.

The preoperative diagnosis of LPD can be challenging due to its clinical manifestations and nonspecific radiological features. Most patients with LPD remain asymptomatic. Symptoms, if any, are nonspecific and include abdominal pain and discomfort, bloating, or abdominal masses that may lead to intestinal obstruction[9]. In the case presented, the patient presented abdominal pain due to compression.

Ultrasound, computerized axial tomography and nuclear magnetic resonance have been described as useful elements in preoperative diagnosis. The typical images are solid nodules with regular contours and variable size scattered on the peritoneal surfaces, which can be confused with peritoneal carcinomatosis or gastrointestinal tumors due to similar image characteristics[10]. The definitive diagnosis is histological, and confirms in our case that the nodules are formed mainly by muscle fibers and fibroblasts, without atypia or necrosis. The differential diagnosis includes leiomyosarcoma, mesothelioma, tuberculosis, lymphoma and peritoneal carcinomatosis[11]. Intraoperatively, LPD presents as multiple round nodules, ranging in size from several millimeters to centimeters, and can be detected on any peritoneal surface or omentum in the abdominal cavity, small or large intestine, mesentery, and retroperitoneum[12].

There are few data on the most appropriate treatment for LPD. Recently, determining therapy according to the patient's age, symptoms, and desire to have children has been proposed. For women with reproductive desire, hormone therapy with gonadotropin-releasing hormone injection, aromatase inhibitor, or selective progesterone receptor modulator is usually the first-line treatment option. This approach is also preferred in the prevention of postoperative recurrence[13-14]. For women without reproductive desire, the best alternative may be a more extensive surgical procedure with total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, myomectomy, and excision of the nodes[15].

In this case, given the size of the nodules, the exacerbation of the symptoms and the patient's clinical worsening, it was decided to perform surgical treatment.

## Conclusion

LPD is a rare clinical condition, it is mainly associated with a history of minimally invasive uterine myomectomy or hysterectomy for myomatosis. The LPD should prefer the differential diagnoses of women with disseminated intra-abdominal or pelvic tumors, especially those with a history of gynecologic surgery. The case presented is of interest because it represents an infrequent entity that can unequivocally simulate peritoneal carcinomatosis. Surgery remains the main therapeutic weapon in symptomatic cases. Surgeons' knowledge

of this rare condition is essential to establish a correct diagnosis and ensure proper treatment.

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## Conflicts of interest

The authors declare that there are no conflicts of interest in this article.

## Ethical disclosures

**Protection of people and animals.** The authors declare that no experiments have been performed on humans or animals for this research.

**Data confidentiality.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

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# Pseudoaneurysm with risk of imminent rupture in Jehovah's Witness patient

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## Abstract

*Emergency surgery for vascular trauma is associated with a high risk of bleeding, which often requires blood transfusions. We present the case of a patient with gunshot injury with pseudoaneurysms of the giant femoral artery with skin dissection and abundant bleeding that required emergency surgery with vascular repair and discharge of the patient without complications. The Jehovah's Witness (JW) patient signed a refusal of blood transfusion in his informed consent. The need for blood transfusion was always present, some legal aspects are reviewed that can help the doctor to protect his therapeutic freedom.*

***Keywords:*** *Pseudoaneurysm. Blood transfusion. Jehovah's Witness.*

## Introduccion

The Jehovah's Witness (TJ) considers that has references in the Bible that exclude the performance of blood transfusions, red blood cells, plasma and, in the same way, the administration of platelets. On the other hand, he does not exclude the use and administration, if necessary, of albumin, preparations for hemophiliacs (coagulation factor VIII and IX), erythropoietin and immunoglobulins[1,2].

They are the fastest growing religious group in the Western Hemisphere, currently numbering more than eight million. Jehovah's Witnesses prohibit blood transfusion based on the literal interpretation of the Bible (Old Testament; Genesis 9: 3-4; Leviticus 17: 10.16 and Acts 15: 28-29). The potential seriousness of said dogma, which is accepted and maintained by the faithful to that religion with surprising uniformity and extraordinary firmness, is that it has given rise to an intense bioethical debate on the conduct that health professionals must assume when faced with a decision that It can, in some cases, lead to the inexorable death of the patient[3].

To contextualize the dimension of the problem, it is necessary to insist that Jehovah's Witnesses consider it an inadmissible offense against their dignity to be supplied with blood without their consent, to the point of assuming it as an affront that affects their own hopes, desires, expectations and particularly in his desire to live; that is, most believers prefer to die before accepting a transfusion[4].

## Case study

A 45-year-old male patient, Jehovah's Witness (JW) with a history of occasional smoking, referred a gunshot wound to the right leg 1 year ago without medical management. One month prior to admission, the patient presented bleeding at the site of the injury, for which he was sutured at the Health Sector Hospital. He was admitted to the emergency department of our hospital due to intense pain and a pulsating mass at the level of the inner

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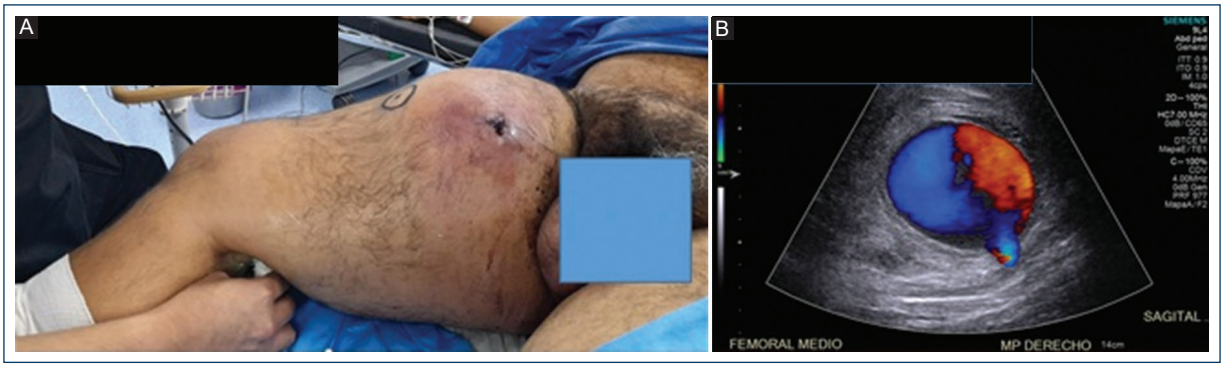


**Figure 1. A:** pseudoaneurysm of the femoral artery due to a gunshot wound. **B:** color duplex Doppler ultrasound of the femoral pseudoaneurysm.

face of the right thigh measuring 20 x 20 cm, in the course of the femoral artery, skin with erythema and an approximately 2 cm wound with sutures (Fig. 1 A). Ultrasound confirmed a giant pseudoaneurysm of the femoral artery (Fig. 1 B). The patient and relatives did not authorize the informed consent for the blood transfusion. In the operating room under general anesthesia, after applying two ampoules of tranexamic acid, proximal incisions were made on the femoral triangle and distal to a pseudoaneurysm with identification of femoral vessels. After vascular control through decreased pulsatile flow, we extended the incision in search of the wall of the pseudoaneurysm, it was found to have ruptured content, with abundant clots exiting and active venous bleeding (Fig. 2 A). At the site of the femoral artery injury, a venous fistula was observed from which the bleeding originated, so control of the proximal and distal femoral vein was verified up to the site of the injury (Fig. 2 B). After hemostasis, the femoral artery and vein were repaired end-to-end with 15 cm of the saphenous vein of the right leg; The distal pulse and venous return were restored (Fig. 3 A). Hemostasis was verified and the entire sac wall was removed with layered closure and drainage placement. There were no hemodynamic complications, total bleeding was 2000cc, so fluids with crystalloids were administered. Hemoglobin on admission was 13.70 g/dl and after surgery it was 10.70 g/dl. Despite hemodynamic stability, the patient was at imminent risk of transfusion throughout the surgery. The patient is discharged after 2 days with control by the extreme consultation without complications (Fig. 3 B and 3 C).

## Discussion

The present case does not intend to resolve such a complex dilemma between the patient's will and the professional conflict of a doctor in the face of the patient's refusal, due to his religious belief, of non-transfusion. This manuscript aims to review the medical literature and analyze the best tools in a situation of demand for transfusion in a Jehovah's Witness patient. When the patient manifestly opposes receiving transfusions of blood components for religious reasons, we are faced with one of the most relevant bioethical dilemmas of today. The dilemma of considering and ignoring life in favor of respect for the autonomy and religious freedom of the person is present[5]. In current medical practice, many problems are related to a distancing of the link between doctors and patients.

At the Clinical Hospital of the University of Chile, a Care Program was created for patients who do not wish to receive a transfusion, which has the voluntary affiliation of professionals from all medical specialties. The objective of this program is to establish strategies, techniques and procedures aimed at optimizing the care of these patients, avoiding subjecting them to unnecessary pressure and having legal support against legal actions[6]. Some hospitals have created strategies to control bleeding in TJ, one of them is based on marked prevention. All patients are treated very aggressively with iron and recombinant erythropoietin until reaching optimal concentrations (hematocrit >36%). The use of antifibrinolytics in cardiac surgery is not widespread, it is reserved for patients who are considered to be at high risk of bleeding, such as those undergoing reintervention, long surgeries and aortic surgery[7]. Preoperative hemoglobin optimization is the first step in patient management. The administration of erythropoietin at least two weeks before surgery has been shown to reduce the rate of transfusion in non-cardiac surgery. It is recognized that antifibrinolytics in cardiac surgery

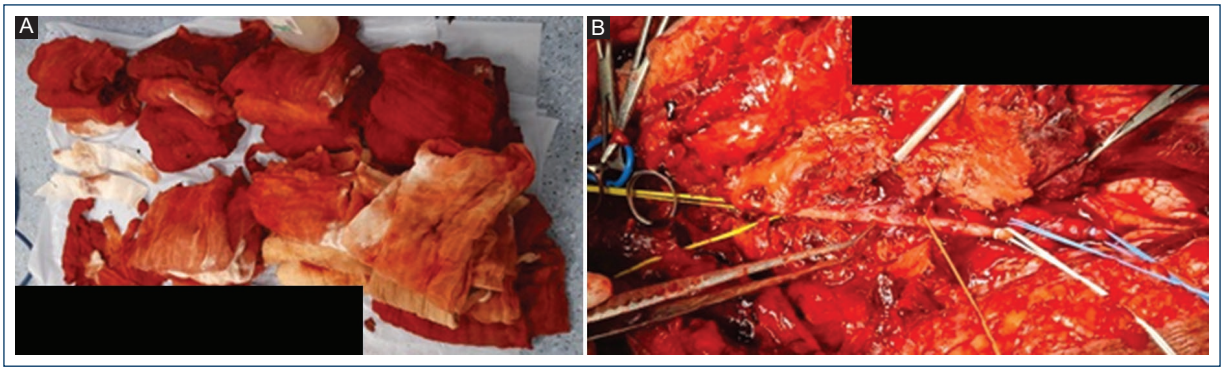


**Figure 2. A:** outpouring of copious amounts of blood from the pseudoaneurysm site. **B:** vascular control and site of the arteriovenous fistula of the pseudoaneurysm.

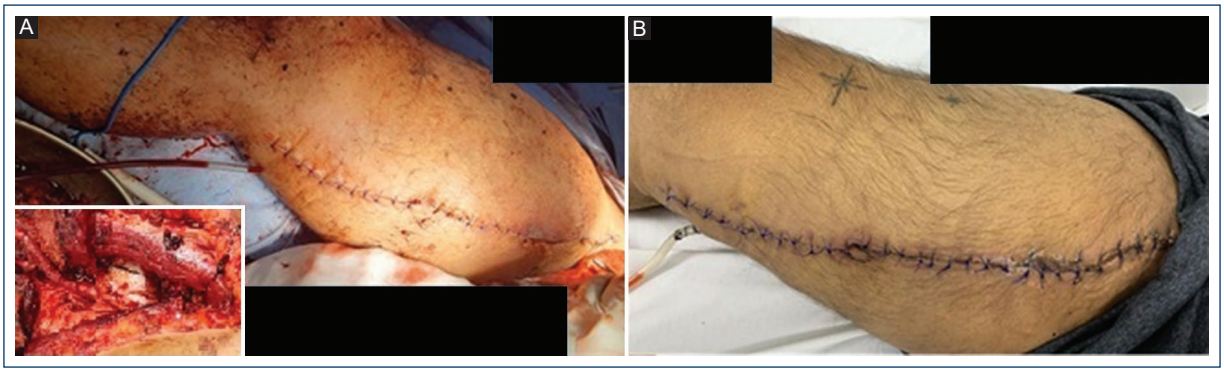


**Figure 3. A:** vascular repair with end-to-end reverse saphenous vein graft. **B:** immediate post-surgical result. **C:** surgical result one week after the repair of the pseudoaneurysm.

decrease the activity of hemostasis, bleeding and transfusions. Plasma concentrations of tranexamic acid to inhibit fibrinolysis vary from study to study. Cell salvage, normovolume hemodilution (NVH), and ultrafiltration have proven to be important techniques for blood conservation in cardiac surgery[8].

The Advance Trauma Life Support (ATLS) indicates hemorrhage as the most common cause of shock in trauma patients. Today, in its tenth edition, the updated protocol for the initial management of hemorrhage in trauma is the early use of transfusions with blood components, thus avoiding the consequent development of coagulopathy and thrombocytopenia[9]. In the management of hemorrhage, it is known that the religious rejection of blood transfusion by Jehovah's Witnesses reflects negatively on the outcome of these patients when they are victims of trauma, since morbidity and mortality is significantly higher among those with severe anemia (hemoglobin level less than or equal to 7.0 g/dl) who did not accept blood products, compared with patients receiving red blood cell replacement[10].

In stable, symptomatic, outpatient Jehovah's Witness patients with heart failure, impaired left ventricular ejection fraction, and iron deficiency, treatment with iron carboxymaltose for a period of 24 weeks improves symptoms, physical performance, and quality of life, and has acceptable results in profiles of side effects and adverse events. The benefit is seen in patients with anemia and in those with anemia[11].

The English philosopher David Ross in 1930 that the entire doctor-patient relationship must be governed by the moral principles of medical ethics[12], these being autonomy, beneficence, non-maleficence and justice. The principle of autonomy refers to the patient's freedom to accept or reject medical treatment, that is, the ability to govern himself, based on his own system of values and principles. The principles of beneficence and non-maleficence, collected from the Hippocratic Oath, indicate that the doctor must always act seeking

the good of the patient, ensuring their health and happiness. The refusal of a patient to receive a blood transfusion at a time when his life is in danger, makes the doctor face a great ethical dilemma before the duty to safeguard the life of the patient and the duty to respect his religious freedom[13].

In order to establish specific recommendations to try to prevent the aforementioned problems from continuing to occur, a working group was convened with participants from the National Medical Arbitration Commission, the Secretary of Health, the Secretary of the Interior, the Center of Human Rights, of the Mexican Academy of Surgery of the National Bioethics Commission and of the Mexican National Academy of Bioethics, who by consensus issued the following recommendations for the care of Jehovah's Witness (JW) patients. Number 5 describes what the doctor's actions are when faced with the need for blood transfusion in a seriously JW patient. The document mentions that in case of a state of necessity (real urgency), the doctor must preserve life before other legal assets and his prescriptive freedom must be respected. Despite the fact that transfusion in emergency cases in TJ does not seem to have legal implications as it goes against the religious will of the family, several forensic doctors comment that it is a serious problem, which occurs in all places where TJ patients require medical-surgical care. This must be thoroughly studied by all associations, approached by jurists and legislative authorities to find an adequate solution, given that, at least in Mexico, there still does not seem to be one and what there is seems contradictory[14]. When it is necessary to transfuse an incompetent adult patient, because he is not in a position to understand the risk to which he is subjected if he does not receive the blood transfusion (state of unconsciousness, severe hypoxic shock, dementia), and a vital emergency is documented and the transfusion does not allow delay, it must always act for the benefit of the patient. If it is not a vital emergency, it is important to know, if possible, the prior will of the patient through their relatives, prior directive or through the knowledge of the doctor who had previously treated him, respecting the patient's decision in case of refusal.[15] The patient is putting his life in danger by refusing the blood transfusion. The omission of the doctor can cause a wrongful death, concluding that if we carry out a weighting of rights based on the different criteria we could summarize that health and life are necessary for the exercise of another right, in addition to the fact that the legal framework of the associations religious, establishes that nothing that is exercised in the different religions may go against the meaning of the law in force in Mexico, in addition to the fact that the rights that are protected are not freely available to the subject[16].

In accordance with the law, the doctor, in his legal relationship, has rights and obligations with patients, the doctor must respect their autonomy and guarantee the protection of health, as established in Article 4 of the Constitution. The General Health Law obliges health professionals to protect life (articles 2, 23, 32, AE, 2003). Informed consent exempts from responsibility in case of not using a blood transfusion as long as the lack of administration of blood does not cause any harm. On the other hand, if not transfusing blood causes harm to the patient, the health professional is not excluded from civil liability, even if he did so at the express request of the patient. Respecting the autonomy of the patient is a right, but the state of necessity must also be considered by the doctor, it is better to do than not do, because according to our law, the lives of patients must be preserved. Therefore, a good justification in the clinical file will help with the legal interpretation to know if it acted according to the *lex artis*[17].

The health professional is not excluded from civil liability, even if he has done so at the express request of the patient. The doctor must offer care that protects the life of the patient, if this is not fully complied with, it can cause a possible manslaughter (articles 288 and 303 of the Federal Penal Code), even in the face of the refusal to receive the transfusion by the Jehovah's Witness stemming from their religious upbringing. Since it is a priority to protect the legally protected good such as life over the religious beliefs of the patient. In the Federal Penal Code, the state of necessity is embodied in article 15 Section V and is defined as: acting for the need to safeguard one's own or another's legal interest, from a real, current or imminent danger, not caused intentionally by the agent, injured another asset of lesser or equal value than the safeguarded, provided that the danger is not avoidable by other means and the agent does not have the legal duty to face it[18]. The protection of freedom comes shortly after life, because it is as important as life and because it defines a state of spirituality without which man would not live fully. Autonomy is nothing more than "the naked expression of freedom". It is believed that this autonomy should be exercised in its entirety, without prejudice to the rights of third parties, including authorizing the individual to refrain from receiving the medical care they need for reasons of religious belief. Doctors, upon graduation, swear to exercise the profession as a priesthood: with selflessness, with generosity, just as

Hippocrates, father of Medicine, would do. In addition, in said act they assume the duty to protect, until the last consequences, the health and life, not only of their patients but of any person with whom they have contact.

Conscientious objection can be defined, according to widespread opinion in the doctrine, as the subjective right that aims to achieve the waiver of a legal duty or the extension of responsibility when the breach of this duty has been consummated. This implies the objection, therefore, the breach of a legal duty with active or omissive conduct, against obligations of a personal or real nature, in any case for a reason of conscience. For conscientious objection, the reasons must be exclusively ethical or moral, based on the autonomy of individual conscience. In the case of blood transfusions or the need to follow a certain treatment, it would be necessary to weigh the interests at stake, although the right to life and health of people is a fundamental right, which can be valued more important than the objection of conscience[19]. The Geneva Declaration establishes that the doctor must "ensure with the utmost respect for human life from its beginning, even under threat, and not use their medical knowledge to contravene human laws", likewise, the International Code of Medical Ethics stipulates that "the doctor must, in all types of medical practice, provide a competent medical service, with full technical and moral independence, with compassion and respect for human dignity, and always with the obligation to preserve human life". Although these postulates clearly establish the doctor's right to conscientious objection, they guide him not to carry out acts against life, health and human dignity, even when requested by the patient himself, or as a result of pressure or threat[20].

Until there is a specific legal provision or express jurisprudential pronouncement on the matter, doctors in our country must adopt the following care protocol for said patients:

1. When the devotee is of legal age and is conscious, the doctors must be warned that if he does not receive the blood transfusion the chances of dying are high, that there is no effective alternative treatment and, even so, he refuses to receive a transfusion: Respect the patient's wishes and take all possible precautions and measures to save the patient's life, without transfusing them. This is due to the fact that the principles of non-maleficence and beneficence, as well as the medical values established in the Hippocratic Oath, must be applied from the priority scale of the Jehovah's Witness patient, for whom it is more burdensome to live once transfused than to die, without having received the blood transfusion, as this could truncate their life project (access to paradise), on the assumption that for the State or for the doctor their life is more important than their beliefs, since it is a personalized decision.
2. When the Jehovah's Witness is of legal age, is unconscious and, according to the doctors, needs to receive a transfusion in view of the imminent danger of death: Proceed in accordance with article 27 of the Regulations of the General Health Law on Disposal of Organs and Tissues of Human Beings. If there is no time to investigate the information referred to in said precept, it will be presumed that the patient accepts the treatment indicated by the doctors, just as if he did so expressly (ethical principle of beneficence), therefore, the treating physicians must carry out transfusions without delay and record them in the medical record.
3. When the believer is of legal age, he is unconscious, he needs to receive a blood transfusion due to the imminent risk of losing his life, but he has a blood refusal card and exoneration of legal responsibility derived from said refusal. If the card is written without ambiguity, is recent, has the signature of two witnesses, the patient's signature coincides with one of his official identifications and anticipates the hypothesis in which he prefers to lose his life than receive the transfusion, his wishes must be respected. If there is doubt on the part of the medical personnel about the authenticity or scope of the document and there is time to proceed in accordance with article 27 of the Regulations of the General Health Law on the Disposal of Organs and Tissues of Human Beings, the transfusion must be carried out and record in the medical record[21].

## Conclusion

We present the case of a TJ patient with a major vascular injury that compromised his life, who despite all the alternatives to avoid transfusion (due to the precise indication of the family not to accept the transfusion) at some point blood transfusion could become essential. Jehovah's Witness beliefs serve as the basis for a moral system, a set of ethical judgments about what to do or not do. According to this system, the rejection of the transfusion constitutes a rule of conduct to be observed, even if society ignores or underestimates it. If there is a risk of death, the border of the autonomy of the patient's will ends and the autonomy of the doctor's duty to act begins. In the care of a

Jehovah's Witness patient in hemorrhagic shock; for example, the doctor must fulfill his duty to save lives and transfuse blood, but may not fulfill the desire to save life. The will of the patient is not enough to dissipate the observance of this duty by the doctor in case of danger of death.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Ethical disclosures

**Protection of people and animals.** The authors declare that no experiments have been performed on humans or animals for this research.

**Data confidentiality.** The authors declare that no patient data appear in this article.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

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CASE STUDY

# Microbial abscesses in the posterior neck region in a decompensated diabetic patient

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## Abstract

*We present the case of deep abscesses in the posterior region of the neck in a 47-year-old man, decompensated diabetic, with a history of supracondylar amputation 3 years earlier, hypertensive and with proteinuria. The lesion consisted of an abscess that left two coalescing wounds in the fundus upon drainage: one 5 cm in diameter and 2 cm deep, the other 2.5 cm in diameter and 2 cm deep. The abscess was managed with mixed systemic antibiotic therapy (clindamycin plus clavulanic acid/amoxicillin orally and, drainage and debridement, as well as dressings with hydrogen peroxide and packaging with phenytoin suspension, non-adhesive hydro-foam with silver and a dressing with polyhexamethylene biguanide. 0.2%). The evolution was favourable with the control of the infection, granulation of the wound, adhesion of the skin to deep tissue and closure. In parallel, the metabolic and cardiovascular monitoring and control of the patient was carried out. The experience is shared for the handling of possible similar cases.*

***Keywords:*** *Deep neck abscesses. Diabetic chronic complications. Local phenytoin adjuvant. Cutaneous abscess in diabetes.*

## Introduction

The persistent imbalance of the metabolic state of diabetic patients determines different chronic complications, of which the following are the most noteworthy: angiopathies, neuropathis, retinopathies and nephropathies; these disorders lead to advanced stages of organ deterioration with consequent dysfunctioning and permanent damage[1,2]. This lack of control is directly responsible for the loss of years of healthy life (HLY)[3,4], in addition to the enormous expense incurred by health systems and family pockets[5].

The most painful aspect of this situation is the gradual evolution of patients with diabetes, who lose their capacities, health, money and the appreciation of their family: they become a major social burden. This is unfair, as although diabetes is still a disease without a cure, there are now different resources for the effective prevention and optimum control thereof.

One of the worst consequences of chronically decompensated diabetes is immune deterioration, whuich renders the patient susceptible to infections, which occur in more severe forms and for longer periods of time, in particular dermal and subdermal lesions that usually appear in extremely severe forms, severe progressions and frequent systemic complications that can lead to death (Fournier's gangrene, for example); the aggressive and resistant behaviour of infectious agents in these cases is also well-known[2,6,7].

We will now present a case that demonstrates these facts and which, fortunately, was evaluated at a time

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that enabled the patient to undergo outpatient treatment with no further complications.

## Case study

A 47-year-old single man with a somewhat relevant background: his mother and daughter are diabetics, he reports no addictions and goes to the gym 5 to 6 days a week to lift weights. He underwent a supracondylar amputation of the right pelvic limb three years ago due to a complicated neurovascular diabetic foot condition and he uses a prosthesis; he registered glucose levels of up to 500 mg/dL in that episode. He has known he has diabetes since that time (three years) when he was also diagnosed with high blood pressure, reason for which he receives treatment with insulin detemir (40 IU/day SC), captopril (25 mg/day) and a specific diet. He emphasises that he has never been a patient prone to self-care and therapeutic adherence. It proved impossible to collect more information that would have allowed for a better understanding of his metabolic status and control in the three years since he found out he was diabetic.

He attended an appointment for diabetes control with his doctor three days prior to getting in touch with us. She noticed a lesion on the back of his neck, reason for which she referred him to our Institute. The patient could not specify the time of the onset of this lesion, but he stated that "I stopped going to the gym that week" (sic) because of it. He was not given any specific treatment for the lesion, but it should be pointed out that he did not visit us immediately, but only 3 days later when he noticed that the lesion had hardened and increased in size. This lesion is located on the back of his neck; it evolved into a large bacterial abscess measuring 10 cm x 10 cm, with significant swelling and two superficial necrotic lesions, with significant perilesional inflammation. No fever, BP 130/90 mm Hg and capillary blood glucose 273 mg/dL. The result of the secretion culture was positive for coagulase *Staphylococcus aureus.*

After obtaining the patient´s informed consent for his outpatient care and consent for any future publication of his case, we proceeded to clean up and drain the purulent abscess, remove the necrotic tissue, and tunnel the abscess to the outside, washing and irrigating the sac. It was padded with non-adhesive hydrophilic silver foam (Betaplast®). His capillary blood glucose was 85 mg/dL and, in general, his laboratory tests were within normal parameters, except for blood glucose (153 mg/dL), low HDL cholesterol (28.5/dL), glycosylated hemoglobin (9.9%) and proteinuria +++. Blood pressure of 130/90 mm Hg.

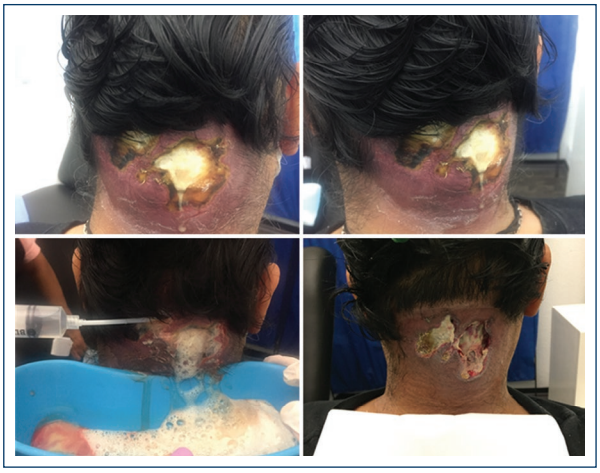

**Figure 1.** Day 1: initial appearance of the abscesses and the debridement process.

Systemic treatment consisted of clindamycin 300 mg every 8 hours plus amoxicillin (850 mg) with clavulanic acid (125 mg) every 12 hours. Diabetes management was continued, as was antihypertensive monitoring.

Day 1: The abscesses were debrided and drained, the necrotic tissue was removed (Fig. 1) and a healing strategy was established every 3 days based on hydrogen peroxide followed by padding with hydrophilic silver foam (Betaplast®), an antimicrobial dressing with polyhexamethylene biguanide (PHMB) 0.2% (Kendall Kerlix®).

Day 3: The same management of the lesion; curing it with hydrogen peroxide and applying the same compounds; the use of phenytoin suspension 125 mg/5 mL was added to the lesion).

A minimal amount of purulent secretion persisted from days 8 to 15 and the same systemic and lesion management was continued (Fig. 2). Healing sessions in the doctor´s surgery were then scheduled for every 7 days, at which the patient´s metabolic levels were within the normal limits.

Day 22: Granulation tissue was identified. A considerable reduction in the diameter of the two lesions was registered and there was no evidence of infection (Fig. 3).

Day 29: Healing with a soapy solution and use of the same padding method; antimicrobial treatment was discontinued.

The diameter of the lesions is already 50% smaller.

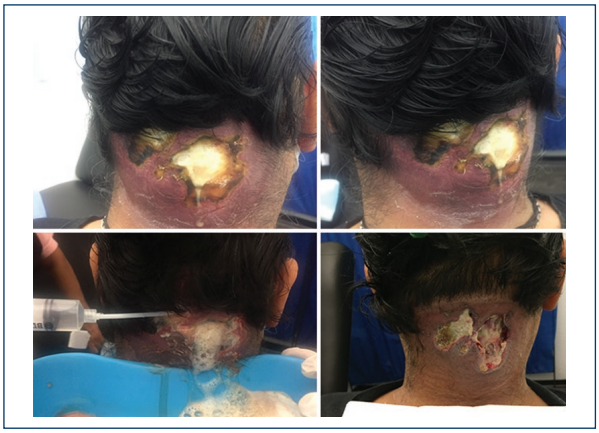

**Figure 2.** Appearance of the lesions on day 8.

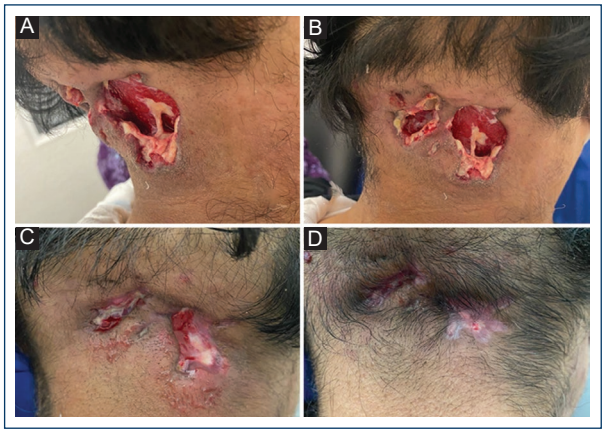


**Figure 3. A** and **B:** appearance of the lesions on day 22. **C** and **D:** on days 36 and 40.

Day 43: No signs of infection or inflammation and the skin is already attached to the deep tissues (Fig. 3). Healing with the use of a soapy solution, phenytoin, hydrogel and hydrofoam. The lesion was covered with an antimicrobial absorbent dressing with PHMB (Kendall Telfa AMD®).

Day 50: Discharge (Fig. 4).

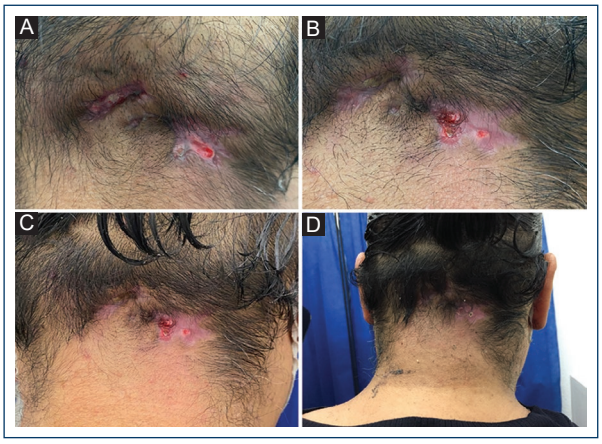


**Figure 4. A, B** and **C:** appearance of the lesions towards final evolution. **D:** day 50, the patient is discharged.

## Discussion

The type of lesion in our patient is not unusual; however, its anatomical location provided it with the potential for regional and even systemic damage. His chronically decompensated diabetic condition (glycosylated Hb 9.9% in the initial examination) surely contributed to the worsening of a lesion that might have been caused by his weight-lifting activity. Regarding the current lesion, it should be pointed out that at no time did the patient complain of pain – neither spontaneous nor due to the healing process - despite undergoing an inflammatory process and significant induration. He has obviously had diabetes for longer than he admits: 3 years; in fact, his initial diagnosis was related to the amputation of a lower limb and his subsequent insulin-based management has been inconsistent.

*Staphylococcus aureus* is the cause of frequent severe skin and subcutaneous tissue lesions in this type of patient, which are usually complicated in terms of length, depth and therapeutic difficulty. The involvement of chronic vascular and nerve damage affects.

The images illustrate the serious nature of the case. The absolute indication was his referral to the hospital for treatment, a fact the patient flatly refused. This emphatic refusal and the prevailing COVID-19 pandemic led to the decision to treat him on an outpatient basis with close monitoring of adherence, in addition to obtaining his informed and responsive consent. It is true to say that several factors contributed to the positive evolution of the condition: it was still opportune, or in other words, the local and systemic conditions remained stable, as well as the patient's adherence to the treatment prescribed and the support of his family. The therapeutic approaches – both local and systemic, were positive: drying and hydrophilic foam, as well as phenytoin, a compound that has proven to be effective on its own[8-11] and combined[12] for this indication. The local use of phenytoin dates back 60 years, and was originally used for oral lesions[9]; its topical indication is useful for speeding up the healing process due to the proliferation of low-concentration keratinocytes, which achieves the expression of dermal procollagen type I

and a reduction in the expression of the inflammatory agent JAK3[10], as well as its lipid impact, which has been illustrated in diabetic foot ulcers[9,10]. The use of phenytoin begins once there is no sign of infection in the tissue and when granulation tissue appears.

This experience has been shared as a case of absolute exception. Under no circumstances whatsoever should the outpatient management of this type of lesion and its obvious severe scope be encouraged: the indication for hospitalisation is absolute. We are sharing it in this manner, as an exception to the successful ending. The local treatment of the lesions, in addition to the adjuvant use of antimicrobials, topical phenytoin and strict follow-up procedures allowed for relief.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Ethical disclosures

**Protection of people and animals.** The authors declare that no experiments have been performed on humans or animals for this research.

**Data confidentiality.** The authors declare that no patient data appears in this article.

**Right to privacy and informed consent.** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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SHORT COMMUNICATION

# The eleventh reason to be a scientist, to be Dr. Ruy Pérez Tamayo

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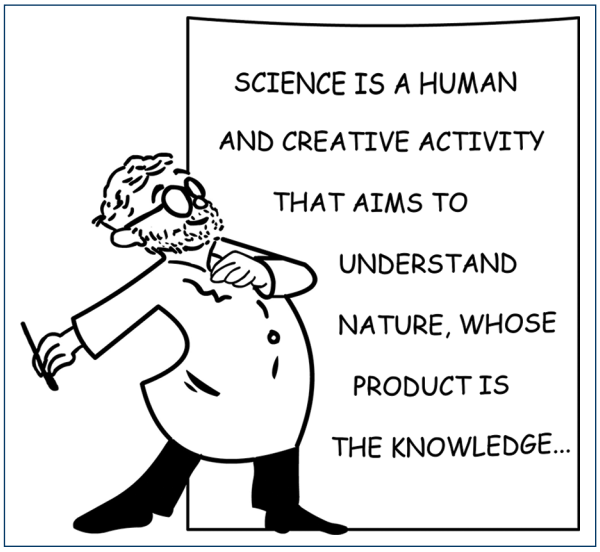


**Figure 1.** Definition of science by Dr. Ruy Pérez Tamayo.

**Figure 2.** Dr. Ruy Pérez Tamayo receiving the Luis García de Arellano Merit Medal, awarded by the H. Congress of the State of Tamaulipas 2006.

Is gone the one who will not leave, the one who lives and will live fertile every time the word "Science" is heard in Mexico. The one who does not occur in pairs, the one who became a pathologist by profession and a scientist by vocation (although he did not believe in vocations). The lover of good language, the philosopher, the professional of doubt, the music lover, the

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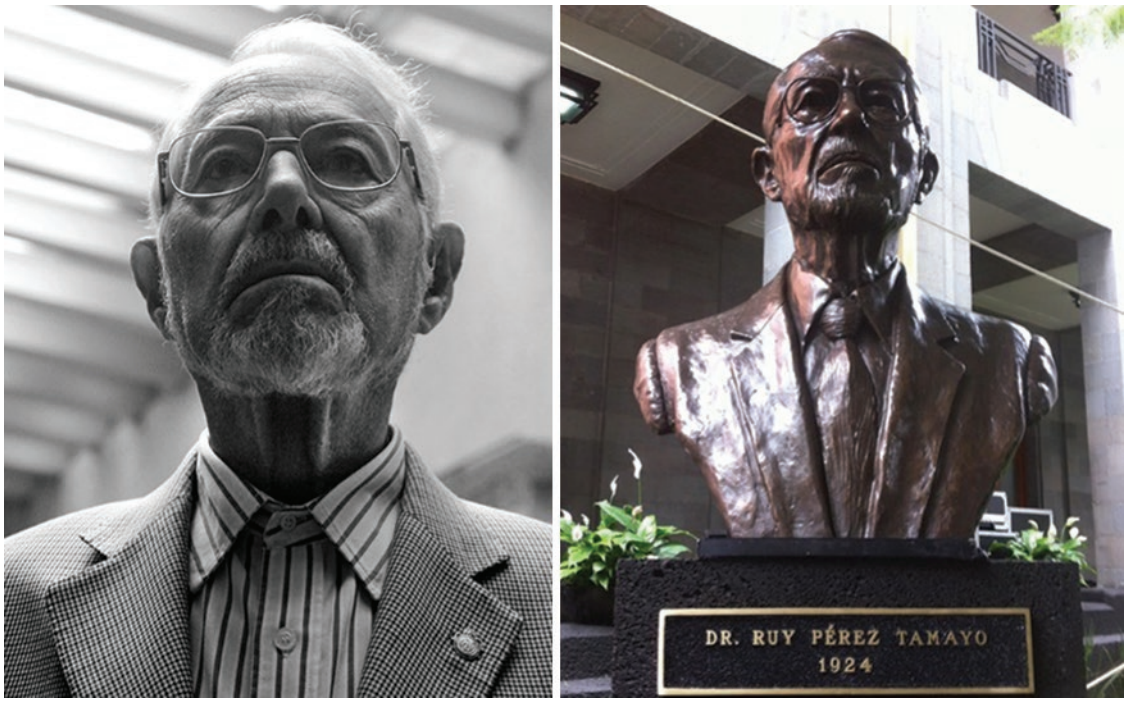


**Figure 3.** Bust of Dr. Ruy Pérez Tamayo in the Esplanade of Illustrious Doctors in the gardens of the Ministry of Health.

thinker, the school, the teacher, *El Viejo Alquimista* (1993), the one who offered us the freedom, for better or for worse, to solve and approach scientific problems, the one who taught that "science is a human and creative activity that aims to understand nature, whose product is the knowledge obtained by a scientific method organized in a deductive way and that aspires to the consensus of technically trained individuals" (Fig. 1), and that the results of an experiment are useless if no controls were made; the tough, the strong. The one who wrote 87 books and more than 160 scientific articles and other popular ones; the humanist, the writer, the disseminator, the historian, The National College (1980), the Mexican Academy of Language (1987), the Emeritus of the Faculty of Medicine of the UNAM (1994) and the National System of Researchers (1992), the Honoris Causa at various universities, the Tamaulipas decorated (2006) (Fig. 2), the professor at Harvard, the founder of the Pathology Unit of the General Hospital of Mexico (1953-1954), the Bioethics committee, the UNAM governing board (1983-1993), the bust in the Secretary of Health (2013) (Fig. 3), the science and technology counselor of the presidency, the National Science Award (1974). The one who founded, directed, protected and abounded our house, the Research Unit in Experimental Medicine (1989) (Fig. 4), which he arrived every day before seven o'clock in the morning to work. The "professor with a little face" as Dr. Raúl Cicero called him, "the swordsman", as Dr. Ruy Pérez Tamayo called him. The one who honored his teacher with his name in an auditorium "Issac Costero" (2010). The name on the street in Querétaro, in the CBT (Technological High School) of Ayapango, Edo. de México and in a Tamaulipas kindergarten. The human being, the character, the member of his family. The legacy is vast and diverse, enough to miss him, but also to motivate us to learn, to grow and honor him by following in his footsteps and his "Ten Reasons to be a Scientist" (2013) to that I dare to add the eleventh: be like him, because "At UNAM, knowledge is not only imparted, it is also generated." We had him, we learned from him, and he inspired many of us, and he will surely inspire more, through his work and his way of disseminating it "Learn from yesterday, live for today and dream for tomorrow".

Dr. Ruy Pérez Tamayo, "Don Ruy", "Dr. RPT", was born on November 11, 1924, in Tamaulipas and died on January 26, 2022, in Ensenada, Mexico. The transcendence of Dr. Ruy Pérez Tamayo imposed a time of arduous

**Figure 4.** Dr. Ruy Pérez Tamayo at the Experimental Medicine Research Unit.

preparation and work. Not only during his life, after his departure continues, and will continue, since, among other things, he laid the foundations for the current study of Anatomical Pathology in Mexico. Science in Mexico found in him, not only an intelligent human being, creative and committed to activity as a scientist, but also a great disseminator and precursor of it. He understood that science in Mexico is not underdeveloped because Mexico is an underdeveloped country, but on the contrary, Mexico is an underdeveloped country because its science is underdeveloped. He postulated science as an instrument that not only serves to understand and treat diseases, but also for the development of the country. His humanism and philosophy of science represent today a great impact on the way we do science in laboratories. He trained countless doctors and scientists in the country who profess their activities with great influence from the teacher Dr. Ruy Pérez Tamayo. This short text aims to encourage readers to seek, in his figure, knowledge, in his legacy and inspiration, in his person: The eleventh reason to be a scientist.

With perpetual gratitude, admiration and respect to Dr. Ruy Pérez Tamayo, and full empathy and solidarity with his family.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that no patient data appear in this article.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

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