



REVISTA MÉDICA DEL HOSPITAL GENERAL DE MÉXICO

Medical, Clinical and Translational Research

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ORIGINAL ARTICLE

Interaction between the cesarean section rate and the use of the Robson classification in a tertiary medical unit

Miguel A. Serrano-Berrones

Department of Gynecology and Obstetrics Coordination, Hospital Regional Lic. Adolfo López Mateos, Instituto de Seguridad y Servicios Sociales para los Trabajadores del Estado, Mexico City, Mexico

Abstract

Introduction: The Robson classification has gained recognition, and a growing number of countries are using it to understand and track cesarean section rates. **Objective:** Analyze the indication for cesarean section, using Robson's 10-group classification system considering maternal sociodemographic and medical characteristics. **Materials and methods:** Cross-sectional, descriptive, and retrospective study carried out on pregnant patients treated between January 01, 2019, and December 31, 2023, at the Hospital Regional Lic. Adolfo López Mateos of the Instituto de Seguridad y Servicios Sociales para los Trabajadores del Estado, using the Robson index. **Results:** Four thousand three hundred and fifty-six patients were obtained, of which 3060 completed their pregnancy by cesarean section and 1296 by delivery, which represents 80.20% and 19.80%, respectively. When using the Robson classification method, the groups with the highest number of cesarean sections were group 5 with 780 (25.49%), group 10 with 598 (19.54%), and group 1 with 410 (13.39%). **Conclusion:** The use of the Robson index identified three groups as those with the highest number of cesarean sections. This frequency is due to being a reference and highly complex hospital. It should be remembered that group 5 has reports of studies of vaginal birth after cesarean section, but with contributing risk factors to consider.

Keywords: Robson index. Cesarean section. Delivery.

Introduction

A cesarean section involves the removal of the fetus through an incision in the uterus. The origin of the procedure is not entirely clear and remains controversial, ranging from its attribution to the birth of the Roman Emperor Julius Caesar to the Roman law known as the "Law Regia" or "Law Caesar," which permitted the opening of the abdomen and the removal of the fetus from any deceased woman, or alternatively, to the Latin verb "caedere" (to cut).¹

The cesarean section rate has increased significantly worldwide over the past 50 years. In the early days, it was performed when vaginal delivery was impossible

and to protect the mother's life, even though the maternal mortality rate was close to 100%.¹

In 1985, based on a review of the limited data available at the time – primarily from European countries – the World Health Organization (WHO) stated that the ideal cesarean section rate should not exceed 10-15%. Based on ecological studies, the WHO reaffirmed that cesarean section rates above 10% are not associated with a reduction in maternal and neonatal mortality rates.²

In 2001, Michael Robson proposed a method that classifies the population into ten groups based on four obstetric factors, making it possible to identify the groups that contribute most to the overall cesarean

Correspondence:

Miguel A. Serrano-Berrones

E-mail: manserrb@yahoo.com.mx

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section rate, make apples-to-apples comparisons between institutions and within the same institution over time, and plan specific interventions.³

From the 1990s to the present, the cesarean section rate has been characterized by a worldwide increase in the delivery of infants, particularly in middle- and high-income countries,⁴ constituting a genuine public health problem. The WHO recommends a cesarean section rate of 10-5%, while *Norma Oficial Mexicana* 007 SSA specifies a maximum rate of between 15% and 20%.^{5,6}

The lack of international consensus on a universal system for classifying cesarean sections has made it difficult to understand the disparities in cesarean section rates across most of the world. In 2011, a systematic review concluded that the Robson classification was the most appropriate for addressing current local and international needs.⁷

In 2015, the WHO established the Robson classification system as the gold standard for assessing, monitoring, and comparing cesarean section rates, and for identifying specific groups with the aim of reducing those rates. In 2020, Mexico ranked third in cesarean section rates among member countries of the Organization for Economic Cooperation and Development, behind only Turkey and South Korea, with a cesarean section rate of 526/1,000 live births.^{6,8}

Over the past decade, the Robson classification has gained recognition, and a growing number of countries are using it to understand and track cesarean section rates.

Overuse of the procedure leads to complications for women who undergo it, not to mention the costs and surgical risks to which they are subjected. A sector-wide policy has highlighted the need for various institutions in the sector to reduce the number of cesarean sections performed.⁷ Furthermore, various forums have emphasized that widespread overuse constitutes a form of obstetric violence that violates women's reproductive rights.⁸

It is a fact that the practice of cesarean sections is a multifaceted problem, with causes that include socio-cultural, economic, and demographic factors, as well as clinical considerations, the performance of medical practice, and the organization of health services. Furthermore, health care providers' lack of familiarity with current regulations regarding humanized childbirth has led to high cesarean section rates in the country. It is therefore necessary to promote maternal care that favors vaginal delivery and to emphasize that cesarean section should be used only as a last resort to safeguard the lives of both mother and baby.^{8,9}

In recent years, various countries have expressed concern about the disproportionate increase in cesarean sections and the associated rise in the risk of maternal and perinatal complications.¹⁰ Through various studies, the WHO has reaffirmed that cesarean section rates above 10% are not associated with a reduction in maternal and neonatal mortality rates.^{11,12}

The Robson index uses obstetric variables – number of deliveries, previous cesarean section, onset of labor, number of fetuses, gestational age, and fetal position/presentation – to classify every woman in an obstetric setting into a single group.

The cesarean section rate is significant as an indicator of quality in obstetric services; therefore, using the Robson classification, it is possible to accurately identify groups of women whose characteristics make them more or less likely to undergo a surgical procedure to terminate their pregnancy.

The objective of this study was to analyze the association between cesarean section according to the Robson classification and this tertiary-care medical unit over a 5-year period at the *Hospital Regional Lic. Adolfo López Mateos* of the *Instituto de Seguridad y Servicios Sociales para los Trabajadores del Estado* (ISSSTE).

Material and methods

This is a cross-sectional, descriptive, and retrospective study that utilized the medical records of patients treated between January 01, 2019, and December 31, 2023, at the *Hospital Regional Lic. Adolfo López Mateos* of the ISSSTE, it serves as a referral hospital (third-level) for various medical units in Mexico City and throughout the country.

A review of medical records was conducted using an evaluation form that included sociodemographic variables, indications for cesarean section, and the Robson classification. The variables used included obstetric characteristics: parity, onset of labor, fetal presentation, gestational age, and number of fetuses. In addition, maternal characteristics were considered: age, age group, mode of delivery in cases with a history of cesarean section, and the indication for cesarean section. Patients were classified using the 10 Robson groups (Table 1).

The cesarean section rate was calculated as a percentage based on the obstetric population of each Robson group. The absolute frequency is the proportion of cesarean sections in each group relative to the total obstetric population, and the relative frequency is the

Table 1. Description of the groups in the Robson classification

Group	Description
1	Primiparous women with a single fetus in cephalic presentation, at 37 weeks or more of gestation, who have gone into labor spontaneously.
2	Primiparous women with a single fetus in a cephalic presentation at 37 weeks or more of gestation who have undergone induction or cesarean section before the onset of labor.
3	Multiparous women with no prior cesarean section, carrying a single fetus in a cephalic presentation at 37 weeks or more of gestation, who have gone into labor spontaneously.
4	Multiparous women with no prior cesarean section, carrying a single fetus in cephalic presentation at 37 weeks or more of gestation, who have undergone induction or cesarean section before the onset of labor.
5	Multiparous women with at least one previous cesarean section, carrying a single fetus in cephalic presentation at 37 weeks or more of gestation.
6	Primiparous women with a single fetus in a breech presentation.
7	Multiparous women with a single fetus in a breech presentation, including those with a previous cesarean section.
8	All women with multiple pregnancies, including those who have had a previous cesarean section.
9	All women with a single fetus in a transverse or oblique position, including those with a previous cesarean section.
10	All women with a single fetus in cephalic presentation at < 37 weeks of gestation, including those with a previous cesarean section.

proportion of cesarean sections in each group relative to the total number of cesarean sections (Table 2).

The data obtained were processed using Excel, as were the calculations of percentages based on the Robson classification.

Results

A total of 4,356 patients were included in the study, of whom 3,060 delivered by cesarean section and 1,296 by vaginal delivery, representing 80.20% and 19.80%, respectively. Using the Robson classification method, the groups with the highest relative rates of cesarean sections were: group 5 with 780 (25.49%), group 10 with 598 (19.54%), and group 1 with 410 (13.39%) (Table 3).

Table 2. Number of cesarean sections and percentages over the past 5 years

Year	No. cesarean sections	%
2019	1530	70.2
2020	1152	74.6
2021	859	77.7
2022	310	79.5
2023	636	80.2

The overall cesarean section rate increased gradually each year: 70.2% in 2019, 74.6% in 2020, 77.7% in 2021, 79.5% in 2022, and 80.2% in 2023 (Fig. 1).

The main indications for cesarean sections were risk of fetal distress (25.9%), preeclampsia (20.8%), repeat cesarean section (18.7%), cephalopelvic disproportion (17.6%), fetal distress (11.8%), and others (5.2%) (Fig. 2).

Decline in fetal well-being was the primary indication in groups 1, 5, and 10; pre-eclampsia was the second most common indication in groups 1, 5, 10, and 1. Repeat cesarean section was the primary indication for groups 5, 7, and 9; cephalopelvic disproportion for groups 4 and 6; fetal distress for groups 1, 3, 9, and 10; and finally, other causes for groups 1, 8, and 2.

The gestational weeks at which pregnancies were terminated were most common in Robson groups 10, 1, 5, and 4, occurring at 39.2, 38.4, 38.3, and 38.2 weeks of gestation, respectively. Likewise, the patient age groups with the highest number of cases according to the Robson classification were groups 1, 3, 4, and 8, with average ages of 34.1, 32.3, 30.4, and 29.2, respectively.

This study demonstrates that the continuous increase in the cesarean section rate was primarily driven by Robson groups 5 and 10, which accounted for the majority of the increase over the 5-year study period.

With regard to the gestational weeks at which the pregnancy was terminated, there were no significant differences, as the goal was always to allow pregnancies to reach full term (Table 4). The patients' ages were also determined, and a greater proportion was found toward the end of their reproductive years, ranging from 26 years and 3 months to 35 years and 4 months (Table 5).

Discussion

It is a fact that there has been a global increase in cesarean sections: based on epidemiological evidence,

Table 3. Distribution of childbirths and cesarean sections by Robson groups, showing their respective percentages

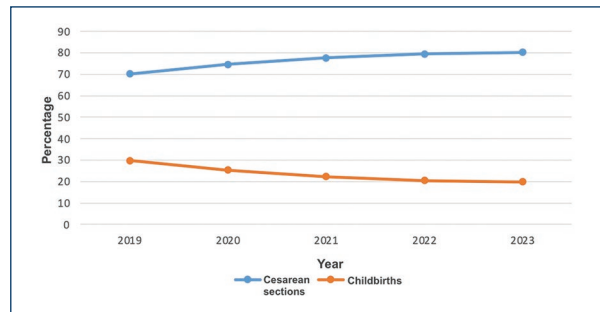
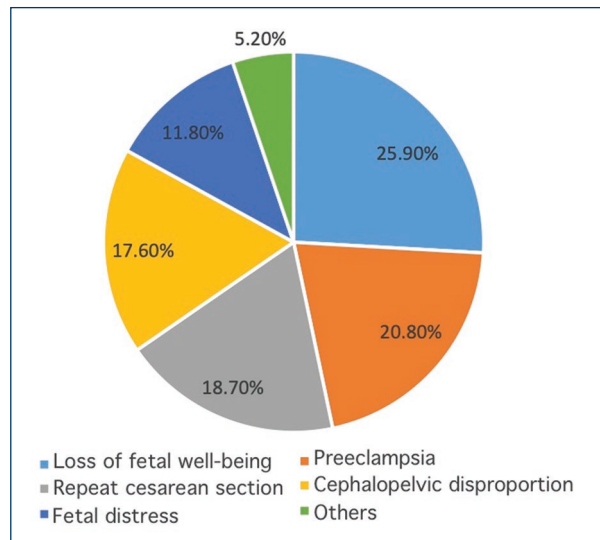
Robson group	No. cesarean sections	%	No. childbirths	%
5	780	25.49	362	27.93
10	598	19.54	36	2.77
1	410	13.39	544	41.97
2	378	12.35	16	1.23
9	272	8.88	178	13.73
3	152	4.96	6	0.46
8	146	4.77	10	0.77
7	114	3.72	2	0.15
4	106	3.46	10	0.77
6	104	3.39	132	10.18
Total	3060	99.95	1296	99.96

Table 4. Distribution of gestational weeks by Robson groups

Robson group	Weeks of gestation
1	38.4
2	37.3
3	37.4
4	38.2
5	38.3
6	35.4
7	37.6
8	38.3
9	38.1
10	39.2

numerous studies document a consistent association between advanced maternal age and a higher incidence of cesarean deliveries, which ultimately translates into an increase in pregnancy-related comorbidities.¹³

Various studies using the Robson classification have documented that the rate of cesarean sections has increased steadily. In Buenos Aires, the rate is as high as 53.5%; in Singapore, there has been a notable

**Figure 1.** Pregnancy outcomes.**Figure 2.** Indications for cesarean sections, expressed as percentages.

increase from 19.9% to 29.6%; and in Italy, the cesarean section rate rose from 12.5% to 18% over a 10-year period.¹⁴

An analysis of several studies indicates that the group contributing most to the overall cesarean section rate was group 10, at 50.9%, followed by group 5 at 14.4%, and group 1 (primiparous women with spontaneous labor), which is consistent with our findings in the present study.¹⁵ The researchers noted that, overall, 55.7% of the women were in the gestational age group of < 37 weeks' gestation, which may have accounted for more than half of the cesarean sections in group 10. Brazil has reported that, of total births, group 5 accounted for 19.2% and group 10 for 13.3%. It is also reported that 78.7% of births were classified into Robson groups 1 through 5. These figures are very similar to those reported in this study. In Vienna, the most

Table 5. Age distribution by Robson groups

Robson group	Average age
1	35.4
2	28.6
3	32.3
4	30.4
5	27.1
6	26.3
7	29.4
8	29.2
9	27.3
10	28.6

common Robson groups for cesarean births were group 5 at 20.6%, group 2 at 17.1%, and group 8 at 15%. In Lithuania, groups 1, 2, and 5 contributed the most to the cesarean section rate. In Malaysia, the group that contributed most to the cesarean section rate was Robson group 5. In Palestine, group 5 accounted for 42.6% of the overall cesarean section rate. In Austria, group 5 also made the largest contribution at 26.9%, and similarly in Sri Lanka at 29.6%.^{16,17}

In our country, the cesarean section rate varies widely depending on the healthcare facility. At the *Instituto Mexicano del Seguro Social*, at the *Unidad Médica de Alta Especialidad, Hospital de Ginecología y Obstetricia No. 4*, 10,950 births were attended to in 2019, of which 5,189 were by cesarean section, representing 47.38%.¹⁸ At the Instituto Nacional de Perinatología in 2021, 6,640 births were attended, of which 4,640 were by cesarean section, corresponding to 69.87%.¹⁹ At the *Centro Médico Naval* in Mexico City in 2019, 372 births were attended, of which 240 were by cesarean section, corresponding to 64.5%.²⁰

At the *Hospital de la Mujer de Aguascalientes* in 2016, 374 patients were treated, of whom 91 (24.3%) delivered via cesarean section.²¹

There are also studies showing that the number of cesarean sections is directly related to educational level.^{21,22} Over the past few decades, the steady increase in cesarean section rates has become a common trend across various medical facilities. The classification system proposed in 2001 by Robson defines 10 groups based on four concepts: (1) pregnancy category, (2) obstetric history, (3) course of labor, and (4) gestational age at delivery.

It is worth noting that the groups of women with a previous uterine scar, nulliparous women, as well as women with preterm pregnancies in groups 1, 2, 5, and 10, are the Robson groups that are most likely to be targeted in efforts to reduce the number of cesarean sections in each group and ultimately lower the overall cesarean section rate.

Conversely, women with a breech presentation – which includes groups 6 and 7 – and those with a twin pregnancy – which corresponds to group 8 – generally have a higher probability of cesarean delivery, as do women with a transverse presentation (group 9), all of whom have a specific obstetric indication for cesarean section.

It is important to note that women in group 5 are one of the main groups contributing to the increase in the number of cesarean sections, as preventing primary cesarean sections becomes increasingly important in the effort to significantly reduce the overall cesarean section rate. Likewise, it is advisable to seek to reduce cesarean sections among nulliparous women (groups 1 and 2), since they are the patients who will eventually make up group 5.

The Robson 10 group stands out because, as a tertiary care facility, it serves as a referral center for numerous medical units that, when faced with a risk, immediately refer patients to the hospital, where the various referred cases must be addressed. According to the results obtained regarding the most common causes of cesarean section, it was found that fetal distress contributed to 25.9% of cesarean sections. The inclusion of comorbidities or conditions associated with pregnancy is relevant, as they influence both the decision to terminate the pregnancy and the method of delivery.

The use of the Robson index identified groups 5, 10, and 1 as those with the highest patient volume and, consequently, the highest cesarean section rates. This trend – with groups 5, 10, and 1 showing high percentages – is an absolute indication for cesarean section due to presentation-related dystocia or multiple pregnancies, given that this is a referral hospital with a high level of complexity. Group 5 consists of women with reports of vaginal birth after cesarean, but with contributing risk factors to consider (Table 4). The use of the Robson classification allows us to identify the different groups of women who contribute to the increase in the number of cesarean sections.²³

Robson's classification also allows for a comparison of characteristics between cesarean delivery and vaginal delivery. Groups 1 and 3 are low-risk, and vaginal

delivery should be the first option for women in both groups; however, in that study, a significantly higher risk of neonatal death was found among women in these groups who had their pregnancies terminated by cesarean section.

An important aspect to consider is the increase in the number of cesarean sections over time, with various factors to take into account – such as financial implications, which significantly impact the budgets allocated to different medical units, not to mention infrastructure needs for neonatal care.²⁴

Various studies conducted in different regions by the WHO have shown that the specific cesarean section rate among women with a previous cesarean section (Group 5) is increasing significantly worldwide. This clearly illustrates the dichotomy: as the cesarean section rate rises, a greater number of women will ultimately be affected.²⁵ Group 10, which corresponds to preterm births, is heterogeneous, as it includes spontaneous labor, induced labor, or cesarean sections performed before term without a clear indication for the procedure. The size of this group in social security institutions is a consequence of the system's structure, as these facilities serve as referral centers for preterm delivery cases and possess the necessary infrastructure and resources to provide timely and appropriate care. It is important to emphasize that, in accordance with the current Clinical Practice Guideline: reducing the Frequency of Cesarean Sections,¹¹ patients who have had one or more cesarean sections or uterine scars should be referred to second-level care hospitals; patients with placenta previa, a previous cesarean section, or those with one or more previous cesarean sections and suspected placental accreta based on two-dimensional ultrasound or color Doppler imaging should be referred to third-level care hospitals.²⁶

The Robson index shows that groups 1, 5, and 10 account for the largest number of patients who delivered their babies via cesarean section. Group 1 includes women who should have delivered vaginally rather than by cesarean section. These are nulliparous women with a singleton, cephalic presentation pregnancy at ≥ 37 weeks' gestation, in whom labor was induced, or a scheduled cesarean section was performed (before the onset of labor).

According to internationally published studies, group I had the highest concentration of patients. This finding differs from a large number of studies reporting percentages below 16%, as a low risk of cesarean section is expected in this group.²⁷ A meta-analysis conducted by the WHO, which included²¹ countries, demonstrated

that the cesarean section rate among women with a previous cesarean section (Group 5) increased substantially across a wide range of countries. This can be understood as a ripple effect, since as the cesarean section rate increases, a greater number of women require repeat surgical procedures.²⁸ If 81.3% of women with a previous cesarean section undergo another one on a scheduled basis, and if the recommended cesarean section rate is 50 to 60% provided there is an adequate perinatal outcome, it will be necessary to prioritize this group of patients to address the increase in the rate of cesarean section. Scientific evidence shows that pregnant women who have had a previous Cesarean section face a risk of uterine rupture of up to 1% and a successful delivery rate ranging from 54 to 75%. Part of the explanation for this global trend encompasses a wide variety of reasons that are not limited to medical factors, legal proceedings in which healthcare personnel are involved due to appeals filed with various intra- and extra-institutional bodies (internal oversight bodies, medical councils, human rights commissions, etc.) when there are unsatisfactory outcomes related to childbirth; and the widespread desire among patients in labor to complete the birthing process naturally, as delays in addressing this request can have repercussions beyond the medical field.

Groups 1 and 3 are considered low-risk, and vaginal delivery should be the first choice; however, numerous studies report a significantly higher risk of neonatal death.^{27,28} It is a fact that pre-eclampsia is associated with cesarean delivery in 8 of the 10 Robson groups. Because termination of pregnancy through cesarean section is the standard treatment for preeclampsia, according to our results, patients with preeclampsia were more likely to undergo a cesarean section ($p < 0.05$). In 2013, Robson suggested that the cesarean section rate in Group 1 should be $< 10\%$, and in Group 3, the cesarean section rate should not exceed 3% ; undoubtedly, the cesarean section rates for these groups in our study are higher than recommended.²⁹ The application of the Robson classification system to our population allowed us to identify groups in which cesarean section was not medically justified; one example is patients in groups 1 and 3, who have singleton, full-term pregnancies in cephalic presentation with spontaneous labor onset. The fact that the cesarean section rate has increased over time in some groups suggests that reducing the overall rate could be achieved by performing fewer cesarean sections, as they also entail higher costs than vaginal delivery, not to mention the potential for adverse neonatal outcomes.

Mexico is one of the countries where reducing maternal and perinatal morbidity and mortality is a priority nationwide, and it is believed that the healthcare personnel throughout the country have the capacity to identify complications of pregnancy and those associated with childbirth in a timely manner, which should allow for their prompt resolution at the various medical facilities or established referral centers. We must not forget that the greatest risk of adverse outcomes associated with cesarean section may lie in the reasons for its indication rather than in the procedure itself.

It is clear that the groups of women with the highest specific cesarean section rates are those who tend to have obstetric risk factors that lead to subsequent cesarean sections.

Let's not forget that ISSSTE serves a very unique population (the civil service sector). Unlike other health care institutions – to mention just one example – it has a beneficiary population with conditions that differ from the rest, but that does not make them any less demanding. On the contrary, the demand for care and the desired level of priority are inversely proportional to the fact that patients and their families are empowered and informed by social media and fake news about their treatment. The vast majority of patients do not request a cesarean section, despite the numerous medical explanations provided to each patient and their accompanying family members at various stages of their care within the medical unit; yet the demand for the procedure remains a stark reality. The desire to avoid complaints, lawsuits, observations, recommendations, etc., before the institute's various internal and external bodies fosters this complacent medical attitude that seeks to avoid conflicts and sanctions from the authorities, and is reflected in numerous official responses and defenses of their actions. The policy pursued in recent years to unify services poses a serious problem, since each institution was established under different historical conditions and at different times, with very specific employment terms for its workers; these terms are not the focus of this paper.

Healthcare based on a healthy doctor-patient relationship that fosters this bond for the well-being of the population is the goal of efforts to unify services; the administrative aspects and equitable distribution of resources among the various institutions are not the focus of this study.

Conclusion

It is important to note that Robson's classification is a highly useful model in healthcare institutions, helping

to identify groups of women who are more likely to give birth through cesarean section. It also allows for the identification of groups of women with common obstetric characteristics who undergo cesarean sections as part of an institutional protocol, and provides guidelines for defining the behaviors that impact the overall cesarean section rate at the institution.

Reducing cesarean section rates requires the implementation of robust strategies that encompass primary health care, with an emphasis on patient education that raises awareness about the benefits of vaginal delivery and the risks of cesarean section; patient-centered care aimed at providing reassurance and support during childbirth – not merely as an established policy but as a practical reality – and the establishment of clinical monitoring based on the application and implementation of well-established protocols that serve as a tool for health care personnel and support their rational implementation.

Finally, it is necessary to train healthcare personnel in the implementation of established policies in order to optimize the environments of medical facilities and provide better care. While having adequate human resources is important, it is equally important to have all available resources at hand at all times without putting either the patient or the healthcare staff at risk.

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Ethical considerations

Protection of human subjects and animals. The author declares that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The author has obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

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ORIGINAL ARTICLE

Prognostic factors associated with poor outcomes in Código Infarto patients

Jessica M. Bazo-Medina^{1*}, Rodolfo de J. Castaño-Guerra¹, and Belinda E. González-Díaz²¹Department of Cardiology, Hospital General de México Dr. Eduardo Liceaga, Secretaría de Salud; ²Interventional Cardiology Service, Unidad Médica de Alta Especialidad, Hospital de Cardiología, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social. Mexico City, Mexico

Abstract

Introduction: In our country, ischemic heart disease remains the leading cause of death, and its incidence continues to increase rapidly. Most patients treated at our center with a diagnosis of acute coronary syndrome (ACS) have a late presentation. **Objective:** We conducted this study to identify the factors that impact patient outcomes within the Código Infarto program. **Material and methods:** A retrospective cohort study was conducted from January 2023 to January 2024, including 230 patients. Patients were classified according to time to presentation (< 12 h and ≥ 12 h). The primary outcome was in-hospital mortality. Survival was estimated using Kaplan-Meier curves and compared between groups using the log-rank test. To identify prognostic factors associated with mortality, a Cox proportional hazards regression model was used, reporting hazard ratios with 95% confidence intervals. **Results:** Late presentation occurred in 51.7% of patients, with a mean total ischemic time of 14 h. Overall mortality was 20.4%. No significant difference in survival was observed between early and late presentation groups (log-rank $p = 0.620$). In multivariable analysis, mortality was significantly associated ($p < 0.005$) with the presence of chronic kidney disease, acute heart failure, cardiogenic shock, and arrhythmias or complete atrioventricular block. **Conclusions:** In this cohort of patients with acute myocardial infarction, in-hospital mortality was high. Although late presentation was frequent, the main prognostic determinants of mortality were related to clinical severity and the presence of comorbidities, highlighting the importance of early identification of high-risk patients.

Keywords: Acute myocardial infarction. Prognosis. Mortality.

Introduction

In our country, the most recent census data from the *Instituto Nacional de Estadística y Geografía* identified heart disease as the leading cause of death, with 105,864 cases recorded through the first half of 2022.¹

Specifically, ischemic heart disease is the primary driver of economic burden among the adult population – not only due to the costs associated with patient evaluation and treatment but also because the consequences of acute coronary syndrome (ACS) – which can naturally progress to heart failure and other

complications – lead to increased morbidity within the economically active population.²

Following health policy reforms, the organization and performance of emergency systems have become more efficient; this has resulted in substantially increased access to tertiary-care facilities, significantly transforming outcomes and survival rates for patients with ACS.

At present, the treatment of acute myocardial infarction (AMI) using a primary invasive reperfusion strategy has become a reality, significantly transforming the clinical course and survival of these patients.³

*Correspondence:

Jessica M. Bazo-Medina

E-mail: jessmar_20@hotmail.com

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Código Infarto (Heart Attack Code) is an emergency care model designed to rapidly identify patients suffering from heart attacks by establishing critical pathways and strategies for immediate, comprehensive, and multidisciplinary care across the involved services—spanning from the initial medical contact to definitive management and follow-up care. Since 2015, it has been implemented at the *Instituto Mexicano del Seguro Social*, focusing on the diagnosis and reperfusion treatment of ST-elevation myocardial infarction (STEMI).^{4,5} As of 2022, thanks to the joint efforts of the healthcare staff and relevant authorities, the *Código Infarto* protocol was successfully established at our center for the first time. Consequently, the cardiology department now extends these benefits to patients without social security coverage—individuals who previously lacked access to immediate, high-quality, and humane medical care.

However, the heterogeneity of the public health system, combined with the high prevalence of adverse social determinants, limits the full impact of these strategies at the population level. In this context, 30-day mortality following AMI in Mexico has been reported at 22.6% – a figure significantly higher than the 6.5% average observed in other 6. Organization for Economic Co-operation and Development countries – highlighting persistent gaps in the timeliness and quality of cardiac care.⁶

In response, efforts have been made to improve management by optimizing quality indicators. However, factors related to patient care are just one of many elements that interact and influence the progression and outcomes of patients who undergo revascularization within this model.

Risk factors and prognostic predictors in ACS

Several studies have shown that the prognosis of ACS does not depend solely on the pathophysiological mechanisms of atherothrombosis, but is strongly influenced by the presence of traditional cardiovascular risk factors, systemic comorbidities, and clinical characteristics at the time of presentation.⁷ In young patients with ACS, although the prevalence of obstructive atherosclerotic disease is relatively low (2-10%), a high burden of modifiable risk factors has been documented, particularly smoking, dyslipidemia, and obesity, all of which are associated with an increased risk of major adverse cardiovascular events, including cardiogenic shock, arrhythmias, stroke, and stent thrombosis².

Furthermore, the type of clinical presentation influences the extent of coronary artery disease, with a higher frequency of multivessel disease observed in patients with non-STEMI (NSTEMI) compared with STEMI.⁸

Among systemic comorbidities, renal dysfunction – whether preexisting or developing during hospitalization – has emerged as one of the most significant prognostic predictors in patients with AMI. The incidence of acute kidney injury (AKI) in this context varies widely (5.2-59%) and is associated with hemodynamic instability, heart failure, advanced age, diabetes mellitus, hypertension, and higher contrast medium volume.⁹ Furthermore, it has been consistently linked to a significant increase in in-hospital and medium-term mortality, with reported risks up to 3 times higher during the first 30 days following the event.⁹ Similarly, chronic kidney disease has been identified as an independent predictor of mortality in ACS, especially when it coexists with diabetes mellitus—a condition that increases angiographic severity, multivessel disease, and 12-month mortality.¹⁰

Type 2 diabetes (T2D) mellitus is in itself a major risk factor for adverse cardiovascular events and death following an acute AMI. Diabetic patients have a greater atherosclerotic burden, more diffuse coronary artery disease, and metabolic, endothelial, and thrombotic abnormalities that account for their poorer prognosis.¹⁰ However, evidence suggests that the most unfavorable prognostic impact is observed when diabetes coexists with renal failure, underscoring the importance of evaluating both conditions together in risk models.¹⁰

Smoking, although widely recognized as a key risk factor for the development and progression of coronary artery disease, has been the subject of debate due to the so-called “smoking paradox.” Recent studies indicate that, after adjusting for age and sex, smoking does not confer a protective effect on clinical outcomes in patients with STEMI treated with percutaneous coronary intervention (PCI), and its apparent neutrality is primarily explained by presentation at younger ages and with a lower initial burden of comorbidities.¹¹ It has also been demonstrated that smoking contributes predominantly to thrombosis and coronary microvascular dysfunction, reinforcing its deleterious role in cardiovascular prognosis.¹¹

Gender-related differences also play a significant role in the course of AMI. Evidence shows that women have higher rates of in-hospital and long-term mortality, as well as a higher incidence of complications such as cardiogenic shock, atrial fibrillation, and heart failure.¹²

This increased risk can be explained largely by older age at the time of the event, a higher burden of comorbidities, and less use of invasive strategies, including PCI, highlighting the need to consider sex as an independent prognostic factor.¹²

Finally, it has been reported that even patients without traditional cardiovascular risk factors may experience an unfavorable in-hospital course, with a higher incidence of complications, likely related to a delay in early risk identification and a less timely use of invasive strategies⁷. These findings support the need for risk stratification models that incorporate not only classic factors but also comorbidities and dynamic clinical characteristics, such as in-hospital complications, to better predict prognosis in patients with AMI.¹³

Reperfusion therapy using a primary invasive strategy

Restoration of coronary blood flow is the primary therapeutic goal in patients with ACS and is associated with a lower incidence of early death, recurrent myocardial infarction, cardiogenic shock, and bleeding complications.

In this context, PCI is the procedure of choice for all patients who, following diagnosis, are in a hospital with the necessary capacity, infrastructure, and resources to perform it, or for patients who must be referred to another center with a delay of no more than 120 min.¹⁴

The use of a primary invasive strategy in accordance with the latest international diagnostic and treatment guidelines is recommended with a Class IIa recommendation for patients between 12 and 48 h after the index event and is contingent on well-established criteria indicating ongoing or persistent ischemia, including ST-T changes on the electrocardiogram, angina refractory to medical treatment, heart failure, electrical instability, and cardiogenic shock.^{14,15}

On the other hand, reperfusion ischemia is a phenomenon that can have serious clinical and hemodynamic effects, adversely affecting the patient's course and outcome. The mechanisms responsible for no-reflow and reperfusion-associated injury are highly dynamic and can persist for weeks. These mechanisms can cause both functional and structural changes that reduce the expected success following the restoration of blood flow and may even contribute to the expansion of the infarct territory.¹⁶

The pathophysiological processes involved promote oxidative stress, contribute to intracellular calcium overload and, consequently, mitochondrial dysfunction, and induce

inflammation mediated by humoral and cellular factors. In turn, microvascular occlusion and distal embolization occurring during coronary angiography are factors that contribute to perpetuating the ischemic cascade.¹⁶ Current evidence suggests that clinical effects may manifest silently yet still have significant repercussions, to the extent of promoting adverse remodeling through a maladaptive response, in which fibrosis leads to wall thinning and ventricular dilation.¹⁷

Reperfusion myocardial injury

Once the blood vessel has become permeable, ischemic processes are specifically triggered by the reintroduction of the substrates necessary for the synthesis of adenosine triphosphate. The flushing out of waste products leads to a rapid normalization of the extracellular pH and, in turn, to a massive influx of sodium (Na^+) through the sodium-hydrogen (Na^+/H^+) exchanger into the intracellular space. It takes approximately 30-60 min to restore physiological levels of calcium (Ca^{++}); however, the transient accumulation of this ion in the cytoplasm is sufficient to activate calcium-dependent lipases and proteases. The increase in intracellular Na^+ forces the sodium-calcium exchanger to operate in an unconventional manner, secreting Na^+ out of the cell to counteract its accumulation and importing Ca^{++} . The mitochondria of cardiomyocytes are sensitive to high concentrations of calcium, which facilitate the opening of the transition pore in their membrane, thereby causing them to lose their negative transmembrane potential; and despite these organelles' capacity to store large amounts of calcium, their tolerance is exceeded after prolonged conductance.^{17,18} The harmful effect of the release of mitochondrial contents into the cytoplasm causes membrane depolarization, damages lipids, nucleic acids, and proteins, and activates intrinsic necrosis/apoptosis pathways mediated by cytochrome C, calcium, and reactive oxygen species. Oxidative stress causes the uncoupling of nitric oxide synthase, leading to increased ischemia.¹⁸

Furthermore, during myocardial ischemia, cell death and hypoxemic stress trigger a cascading proinflammatory reaction that involves complement activation, increased production of free radicals, and the release of damage-associated molecular patterns, which, on binding to toll-like receptors, promote secondary signaling by activating the inflammasome.¹⁷

Similarly, the family of receptors with nucleotide-binding oligomerization domain-like structures plays a central role in myocardial infarction. The NLRP3-containing

inflammasome (composed of caspase-1, NOD-like receptors, and the ASC protein, or “apoptosis-associated speck-like protein”) is activated in both circulating inflammatory cells and cardiomyocytes, contributing to the effects of cytokines such as interleukin-1 β , tumor necrosis factor-alpha, caspase-1, and others.¹⁸

The metabolic changes that develop depend on the extent and duration of the ischemic event, and the degree of resulting damage corresponds to mitochondrial dysfunction.¹⁸

The final event resulting from cellular damage due to reperfusion following irreversible ischemia is the cytolysis of previously stunned tissue, which can occur through one or more processes – typically described as necrosis and apoptosis – or through pyroptosis, a form of cell death triggered by intense inflammasome activation caused by dysfunctional mitochondria, tumor necrosis factor receptor 1 signaling, and caspases 1, 4, and 5, as well as ferroptosis, caused by the peroxidation of membrane lipids due to the inhibition of glutathione peroxidase 4 and the simultaneous activation of Fe³⁺-mediated lipoxygenase.^{17,18}

Reperfusion in late-onset ACS

It is well known that delayed presentation of patients with AMI is associated with a higher incidence of adverse outcomes, which may include death related to revascularization therapy, as well as complications that prolong the length of hospital stay and result in a poorer short-, medium-, and long-term prognosis for survivors.¹⁹⁻²¹

The proportion of patients diagnosed with delayed-onset ACS – that is, ACS diagnosed more than 12 h after the index event – ranges from 8.5% to 40%. The characteristics most frequently observed in this group are female gender, African American ethnicity, diabetes mellitus, a history of prior coronary revascularization, low socioeconomic status, and low educational attainment. Similarly, following the recent international emergency caused by the COVID-19 pandemic, fear of infection in healthcare facilities was considered another factor contributing to delayed presentation by patients.²⁰

It is clear that delayed presentation by patients with AMI is associated with a higher incidence of adverse outcomes, which increase the length of hospital stay and result in a poorer medium- and long-term prognosis for survivors. Therefore, in cases of delayed presentation, the choice of a primary invasive strategy must be evaluated on a case-by-case basis.

In this regard, various positions and theories supporting reperfusion have emerged; for example, the

open-artery hypothesis suggests that mechanical revascularization of the infarct-related artery may limit infarct size and remodeling, reduce electrical instability, and also provide supplemental blood supply to that area through collaterals, thereby offering a survival benefit.²¹

Incidentally, studies have shown that coronary flow as low as 0.05-0.1 mL/min/g can maintain the viability of the ischemic area and that mitochondrial function and cardiomyocyte integrity can be maintained with as little as 20% of baseline coronary flow (estimated at 0.2 mL/min/g).²¹

In the same context, subtotal occlusions have been observed, as well as spontaneous resolution and recanalization of coronary lesions in up to 34% of patients who underwent post-infarction coronary angiography. It is possible that these considerations may provide a framework for evaluating revascularization in late-stage patients as a result of myocardial preservation by collateral blood vessels—a preconditioning effect induced by variations in coronary flow, which results in resistance to necrosis even during prolonged periods of ischemia.^{20,21}

In the study by Nepper et al.,²² the outcomes of an invasive reperfusion strategy in symptomatic late presenters were evaluated using CMR 3 months after the acute event, revealing that the size of the infarct territory and the left ventricular ejection fraction were lower than in patients who underwent early revascularization. However, PCI was considered equally favorable in symptomatic patients, as a myocardial rescue index of 50% or higher was found in 65% of late-presenting patients.²¹

In the BRAVE-2 study, on the other hand, asymptomatic patients with delayed presentation were studied; the primary outcome was the size of the infarcted myocardium as measured by single-photon emission computed tomography, and a significantly smaller infarct size was found in the group of patients who underwent PCI. A subsequent analysis during the 4-year follow-up – which included 88% of the patients – reported a 45% reduction in mortality for this same group.²¹

In the meta-analysis conducted by Abbate et al.,²³ of randomized trials comparing delayed PCI versus conservative medical therapy in hemodynamically stable patients, it was concluded that delayed PCI was associated with improved survival and cardiac remodeling, with symptomatic patients showing the greatest benefit—particularly those with residual ischemia, myocardial viability, and subtotal occlusions of the infarct-related artery.²¹

Results of the Código Infarto: the Mexican perspective

The outcome for patients with AMI is influenced by multiple factors that have typically been identified as associated with a higher risk of mortality and a higher incidence of major adverse cardiovascular events.

Overall, there are some differences in the prevalence of these factors; however, data from large-scale studies consistently point to the following risk factors: age over 75 years, female gender, diabetes (particularly in men under 55 years of age), hypertension, previous myocardial infarction, prior AMI, right ventricular involvement, previous heart failure, and a history of arrhythmia or previous conduction abnormalities.²⁴

Specifically with regard to treatment, patients who undergo late revascularization have a worse prognosis than those who undergo early intervention, as do those who experience failure of PCI. Short-term complications – specifically cardiogenic shock, ventricular arrhythmias, and mechanical complications – contribute to mortality following a heart attack.²⁵

In Mexico, according to the RENASICA II registry, 65% of ACS cases are considered high-risk, with STEMI showing a hospital mortality rate of 8.7%; ventricular dysfunction is also observed more frequently in 30% of cases. As of 2019, a progressive decline in mortality among *Código Infarto* patients has been reported, down to 9.4%.²⁶⁻²⁸

Patients with AMI admitted to our hospital – whether as their first point of medical contact or, more commonly, following a referral from a second- or even third-level facility, both public and private – mostly arrive with a delay that places them outside the optimal window for initiating a primary invasive strategy.

Understanding the characteristics present in our patient population – which statistically are associated with worse outcomes compared to other patients – is of the utmost importance to actively intervene in these cases.

Material and methods

A single-center, retrospective, observational cohort study was conducted at a tertiary-level public hospital.

The study included patients over 18 years of age diagnosed with ACS, with and without ST-segment elevation (NSTEMI and STEMI), who underwent PCI as part of the Code Infarction program between January 2023 and January 2024.

Demographic variables, comorbidities, clinical characteristics at admission, electrocardiographic findings, aspects related to the interventional procedure, as well as clinical course and the presence of in-hospital complications were recorded. The primary outcome was in-hospital mortality.

The data generated from the medical records were analyzed statistically using the Statistical Package for the Social Sciences (SPSS) 25.

Continuous variables were expressed as mean $\pm$ standard deviation or as median and interquartile range, depending on their distribution. Categorical variables were expressed as frequencies and percentages. Comparisons between groups were performed using Student's t-tests or analysis of variance for continuous variables, and the Chi-square test and Fisher's exact test for categorical variables.

For the univariate analysis, the association between clinical variables and in-hospital mortality was evaluated using appropriate statistical tests based on the type and distribution of the variables.

Variables with $p < 0.20$ in the univariate analysis were considered candidates for the multivariate model. A multiple logistic regression analysis was performed to identify independent predictors of in-hospital mortality, reporting adjusted odds ratios (OR) with 95% confidence intervals (CI).

Length of hospital stay was analyzed using Kaplan-Meier curves, comparing the cumulative probability of hospital stay based on time of presentation (< 12 h vs. ≥ 12 h), using the log-rank test. Statistical analysis was performed using SPSS version 25.

Results

Data were collected from patients in the *Código Infarto* program from January 2023 to January 2024 (Table 1).

As with the overall statistics, the majority of patients treated at our hospital in 2023 for AMI were men, and just over half of our patient population was 60 years of age or older.

The most prevalent cardiovascular risk factors were smoking, T2D, and systemic hypertension (SH). More than half of the patients with a myocardial infarction diagnosis were current smokers, but 39% of them had quit. In the group of diabetic patients, the duration since diagnosis of their underlying condition was more than 20 years in 24% of cases, but in 32% of cases, the duration since diagnosis was no more than 10 years. Dyslipidemia was also found in one out of every three

Table 1. Characteristics of the *Código Infarto* population

Variables	n = 230	%
Female*	55	24
Age group		
< 40 years	1	< 1
40-49 years	35	15
50-59 years	64	28
60-69 years	65	28
70-79 years*	38	17
≥ 80 years	27	12
Most common comorbidities reported in patients in the <i>Código Infarto</i> registry		
Type 2 diabetes*	100	43.5
Systemic hypertension*	133	57.8
Dyslipidemia	82	35.7
Smoking habit	148	64.3
Chronic kidney disease	21	9.1
Heart failure*	9	3.9
Atrial fibrillation*	5	2.2
Ischemic heart disease*	25	10.9
COVID-19 history	12	5.2
Global ischemia time in patients of <i>Código Infarto</i>		
Up to 12 h	111	48.3
More than 12 h*	119	51.7

*Factors associated with an increased risk of mortality in patients with acute myocardial infarction worldwide, according to the international literature.

patients; in 12% of patients, mixed disorders were found, with elevated serum levels not only of cholesterol but also of triglycerides.

Endocrine disorders, autoimmune diseases, and the use of hormone replacement therapy were reported in only one case.

Among patients already known to have a history of heart disease, a history of heart failure and ischemic heart disease was found in just under 15% of the population.

Only 5% of the patients had a previous diagnosis of severe acute respiratory syndrome coronavirus 2 infection.

Regarding hospital care and the diagnosis of patients with AMI, the following relevant data were obtained: 54% of the patients were referred from primary, secondary, and even tertiary care facilities, not only from private institutions but also from public institutions in the region.

The remaining patients presented to the Emergency Department at the *Hospital General de México* as their first point of medical contact.

In the Cox regression analysis, presentation ≥ 12 h was not significantly associated with time to hospital discharge (hazard ratio [HR] 0.87; 95% CI 0.49-1.55; $p = 0.635$).

STEMI was diagnosed in two-thirds of the cases, and in the remainder, the diagnosis of NSTEMI was established.

In 18.3% of cases, patients with AMI presented with associated complications, the most common being post-infarction angina; for this reason, they underwent PCI despite a duration of symptoms exceeding 48 h (Fig. 1).

Patients with NSTEMI had electrocardiographic presentations corresponding, in order of frequency, to inferior (57%), anterior (40%), and lateral (3%) infarcts. In this group, 85% of patients received reperfusion therapy through PCI as the primary invasive strategy (Fig. 2).

The findings reported by the Interventional Cardiology team are described in the table 2. In accordance with established recommendations regarding the strategy for coronary revascularization in the context of AMI and the expert judgment of the treating interventional cardiologist, the appropriate percutaneous procedure was performed (Table 3).

During the course of care for *Código Infarto* patients in the coronary care unit, various complications were observed (Table 4), the most common being acute heart failure in 31.3%, arrhythmias or complete atrioventricular block in 20%, and cardiogenic shock in 15.2%.

About 13.9% of patients developed AKI. In this group, contrast medium volumes greater than 200 cc were used in 55% of cases, with an average of 212.8 cc, as recorded in the procedure report.

Of the patients who experienced cardiopulmonary arrest before reperfusion therapy, 75% developed cardiogenic shock following the procedure, and 83% survived it.

Of all the variables studied that were related to death, the following were identified as statistically significant: chronic kidney disease ($p = 0.093$), heart failure ($p < 0.001$), cardiogenic shock ($p = 0.003$), atrioventricular block ($p = 0.001$), and cardiorespiratory arrest ($p < 0.001$) were identified with statistical significance; thus, these can be established as factors associated with a poor prognosis (Tables 5 and 6).

In the *Código Infarto* population between January 2023 and January 2024, a mortality rate of 20.4% was reported.

Discussion

The population served at our center represents a particularly vulnerable group within the Mexican health-care system, characterized by limited health insurance

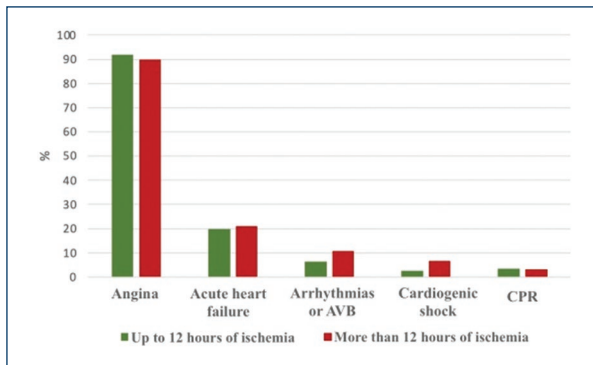


Figure 1. Complications secondary to AMI in *Código Infarto* patients at the time of presentation. We compared the presence of complications in patients with acute myocardial infarction who had periods of global ischemia of up to 12 h and those with periods longer than 12 h. Patients with delayed presentation were more likely to have acute heart failure as well as electrical and hemodynamic instability. AMI: acute myocardial infarction; AVB: atrioventricular block; CPR: cardiopulmonary resuscitation.

coverage, economic constraints, and a low sociocultural status. These conditions directly influence timely access to medical care and the prognosis of patients with AMI. The observed in-hospital mortality rate, close to 20%, is alarming not only because of its impact on individuals and families but also because of the burden it places on public health and healthcare resources.

Prevalence of a history of the condition and at-risk population

As described in other studies, women with AMI were predominantly postmenopausal, whereas among men, a significant proportion of patients were young, with 16% under the age of 50. This finding underscores the growing burden of cardiovascular disease among young and middle-aged adults, a phenomenon that is particularly relevant in middle-income countries.

Traditional risk factors, such as T2D mellitus, SH, and dyslipidemia, were highly prevalent. In addition, comorbidities associated with chronic inflammatory conditions were identified; these have been proposed as emerging cardiovascular risk factors. In the context of an aging population and increased life expectancy, it is expected that these conditions will coexist more frequently and contribute to adverse outcomes.

T2D mellitus, due to its metabolic, endocrine, and immunological effects, promotes systemic endothelial dysfunction and accelerates atherosclerosis. In our population,

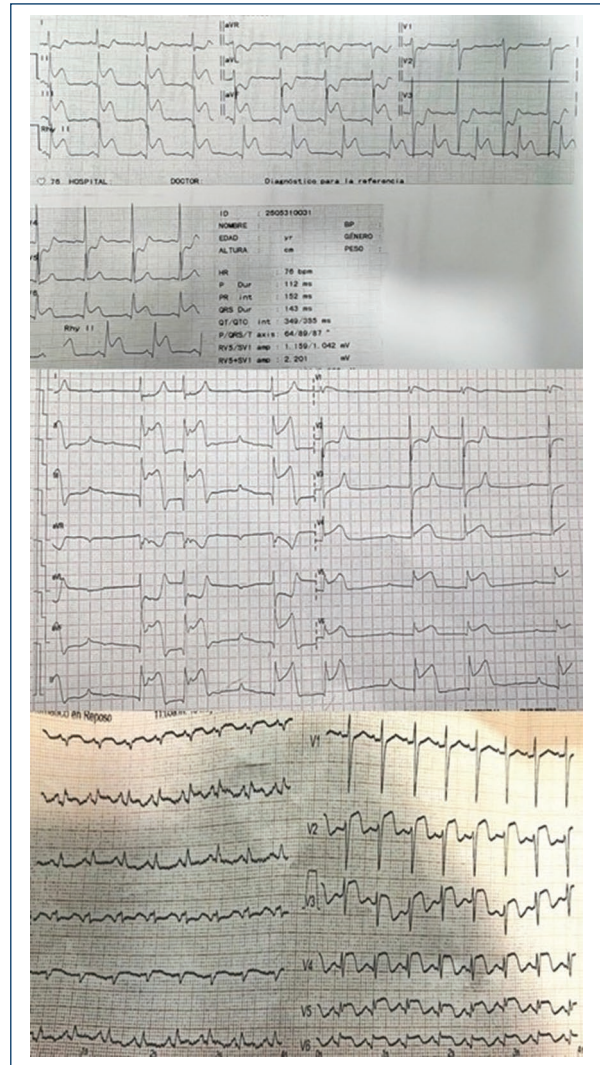


Figure 2. Diagnosis of STEMI. On the left are electrocardiograms showing STEMI in descending order, including examples of an inferolateral MI and an anteroseptal MI. STEMI: ST-elevation myocardial infarction; MI: myocardial infarction.

both patients with long-standing diabetes and those diagnosed for < 10 years experienced AMI, suggesting that a history of diabetes alone constitutes a significant risk factor, regardless of disease duration or metabolic control-variables that could not be assessed in this study.

In the multivariate analysis, chronic kidney disease was independently associated with an increased risk of in-hospital mortality (adjusted OR 6.5; 95% CI 1.2-16.2; $p = 0.017$). This finding is consistent with the known association between diabetes, hypertension, and kidney damage – conditions that are highly prevalent in our cohort and that, together, substantially increase the risk of fatal cardiovascular events.

Table 2. Angiographic characteristics of patients in the *Código Infarto*

Characteristics	(n = 230)	%
Angiographic diagnosis		
Single-vessel disease	68	29.6
Two-vessel disease	49	21.3
Three-vessel or multivessel disease	92	40
No significant angiographic lesions	21	9.1
Artery responsible for the heart attack		
Left main coronary artery	4	1.7
Anterior descending artery	29	12.6
Circumflex artery	65	28.3
Right coronary artery	39	17.0
Terminal branches of the main vessels	61	26.5
No culprit vessel identified	32	13.9
Presence of coronary ectasia	16	7.0

Table 4. Complications documented during the course of care for patients with a *Código Infarto* following PCI

Exacerbations	%
Acute heart failure	76
Arrhythmias or third-degree AV block	20
Cardiogenic shock	15.2
Acute kidney injury	13.9
Post-myocardial infarction angina	11.7
Stroke	6.1
Cardiopulmonary arrest	< 1
Death	20.4

PCI: percutaneous coronary intervention; AV: atrioventricular

Table 3. Percutaneous coronary intervention in revascularized patients in the *Código Infarto* program

PCI features	%
Treatment strategy	
PCI to the affected blood vessel	78.2
PCI to 2 or more blood vessels	17.5
Procedure performed during diagnostic catheterization	
Balloon angioplasty	16.6
DLS implant	79.6
Delayed-stenting technique	3.8
Procedural success	
TIMI 3 angiographic flow	86.2
TIMI flow < 3 or failed PCI	13.80
Patients who underwent consecutive procedures for vessels with significant lesions	34
Total length of stents (mm)	$\bar{X}$ 68.4 ($\pm$ 48.7)
Contrast agent used	$\bar{X}$ 188 ($\pm$ 99.6)

PCI: percutaneous coronary intervention; DLS: drug-eluting stent; TIMI: thrombolysis in myocardial infarction (distal flow rate).

Table 5. Univariate analysis of factors associated with mortality in patients enrolled in the *Código Infarto* study

Factors	p
Medical history and comorbidities	
Chronic kidney disease	0.093
Clinical presentation	
Heart Failure on admission	< 0.001
Cardiogenic shock on admission	0.003
Post-PCI outcomes	
Cardiogenic shock during the disease progression	< 0.001
Arrhythmia or atrioventricular block	0.001
Cardiopulmonary arrest	< 0.001
Cerebrovascular event	0.003
Acute kidney injury	0.046

PCI: percutaneous coronary intervention

Although this group is not large within the study population at first glance, it is important to remember that T2D and SH – which were also the most prevalent comorbidities – are the most common causes of nephropathy in adult patients. Therefore, as life expectancy increases, the duration of chronic degenerative diseases and the incidence of related complications will further elevate the risk of death from AMI.

Care for patients of *Código Infarto*

Poor accessibility, limited resources, and a lack of information among a population with a certain

sociocultural background, as well as problems with the algorithm for caring for patients with ACS, are factors that can collectively undermine the success of the *Código Infarto*.

Limitations in access to health care services, misinformation, and deficiencies in referral and counter-referral algorithms can work together to undermine the success of the *Código Infarto* program. Even tertiary care centers with cardiac catheterization capabilities in the metropolitan area have been overwhelmed, which has led to patients being referred to our hospital due to a lack of supplies or available space.

It is important to note that nearly half of the patients presented to our hospital as their first point of medical care and that only 48.3% had a total ischemia time of < 12 h, which indirectly reflects the structural

Table 6. Multiple logistic regression for in-hospital mortality in patients with *Código Infarto*

Variable	Adjusted OR	95% CI	p
Chronic kidney disease	4.62	1.32-16.28	0.017
Heart failure	1.05	0.17-6.29	0.953
Cardiogenic shock	4.68	1.73-12.66	0.002
Arrhythmia or atrioventricular block	2.11	0.83-5.36	0.117
Cardiopulmonary arrest	16.21	3.03-86.62	0.001
Stroke	0.22	0.02-1.92	0.174
Acute kidney injury	0.53	0.16-1.73	0.294

OR: odds ratio; 95% CI: 95% confidence interval.

deficiencies of the health care system and their impact on the timely treatment of AMI.

When analyzing the length of hospital stay using Kaplan-Meier curves, no significant differences were observed in the cumulative probability of hospital stay between patients with early presentation (< 12 h) and late presentation (≥ 12 h) (log-rank $p = 0.620$) (Fig. 3). This finding suggests that the length of hospitalization may be more closely related to clinical severity and the occurrence of complications than to the time of presentation alone.

Angiographic findings

Coronary angiography performed on patients included in the *Código Infarto* study showed that 40% had obstructive disease in all epicardial coronary arteries. Consequently, a significant proportion of these patients required procedures classified as high-risk PCI.

PCI

Although angiographic success with TIMI 3 flow was achieved in more than 80% of cases, this outcome did not necessarily translate into a better clinical prognosis. This suggests that the restoration of epicardial flow, while essential, is not sufficient to guarantee a favorable outcome, especially in patients with a high atherosclerotic burden and advanced comorbidities. The lack of information on phenomena such as no-reflow, detailed characteristics of the culprit lesion, or complications related to vascular access limits a more in-depth evaluation of the factors associated with mortality. The

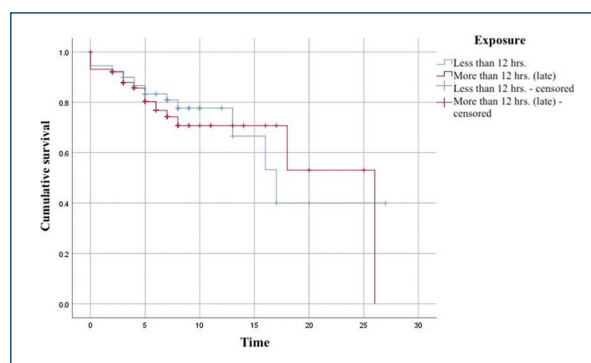


Figure 3. Kaplan-Meier curves showing the cumulative probability of hospital stay according to time of presentation (< 12 h and ≥ 12 h) in patients with a *Código Infarto* diagnosis. The comparison between groups showed no statistically significant differences (log-rank $p = 0.620$).

higher number of stents and stent length, as well as characteristics of the culprit lesion (thrombotic occlusion, size, circumference, composition, presence of ulcerated plaque, and thrombus burden in the vessel) – while they may reflect a higher ischemic risk – were not studied in relation to an increased likelihood of complications and death. Likewise, procedural complications – particularly those related to vascular access – are another set of data that, unfortunately, could not be adequately monitored but that undoubtedly have a negative impact on patient outcomes and survival.

Post-myocardial infarction complications

Of the complications observed, cardiogenic shock and arrhythmias were significantly associated with in-hospital mortality. In the multivariate analysis, both cardiogenic shock (OR 4.3; 95% CI 1.7-12.6; $p = 0.002$) and cardiorespiratory arrest (OR 15.7; 95% CI 4.0-86.6; $p = 0.001$) were identified as independent predictors of death (Table 6), underscoring the decisive impact of these complications on the prognosis of patients with AMI.

Conclusions

The patient population treated through our hospital's *Código Infarto* program is representative of the epidemiological profile of patients with AMI in Mexico, with a high prevalence of traditional risk factors and a significant proportion of young- and middle-aged patients.

In-hospital mortality was high and was independently associated with chronic kidney disease, cardiogenic shock, and cardiorespiratory arrest, highlighting the importance of clinical severity and comorbidities in prognosis, beyond the angiographic success of the procedure.

The absence of significant differences in hospital length of stay between patients with early and late presentation suggests that in-hospital outcomes are more influenced by the occurrence of complications than by the duration of ischemia *per se*, possibly as a result of standardized care protocols.

The absence of significant differences in the length of hospital stay between patients with early and late presentation may reflect the impact of standardized care protocols within the *Código Infarto* program, which allow for comparable in-hospital outcomes regardless of time of presentation. Furthermore, the length of hospital stay appears to be influenced more by clinical severity and the occurrence of complications than by the delay in presentation *per se*.

The observed mortality rate, close to 20%, underscores the urgent need to strengthen cardiovascular prevention strategies, improve timely access to medical care, and optimize the resources allocated to the comprehensive management of AMI in the Mexican public health system.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

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

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ORIGINAL ARTICLE

Factors associated with post-COVID-19 asymptomatic hypoxemia

Annier J. Fajardo-Quesada^{1*}, Ilian E. Tarife-Romero², and Luis M. Abreu-Pereira²¹School of Medical Sciences of Bayamo, Universidad de Ciencias Médicas de Granma, Granma; ²Medical Degree Program, Facultad de Ciencias Médicas Mayabeque, Mayabeque. Cuba

Abstract

Introduction: Asymptomatic hypoxemia or felonious hypoxia during and after severe acute respiratory syndrome coronavirus 2 infection posed clinical and organizational challenges: patients with dangerously low SpO₂ without dyspnea may delay seeking care, which is why home oximetry and the development of predictive models have been promoted. **Objective:** To identify factors associated with hypoxemia and asymptomatic hypoxia in patients screened after coronavirus disease 2019 (COVID-19). **Material and methods:** A prospective analytical study was conducted in 125 patients screened after COVID-19 in Matanzas in 2022. Variables included age, sex, and vaccination schedule, time since hospital discharge due to COVID-19, SpO₂, heart rate, respiratory rate, and blood pressure. Bivariate tests (Mann-Whitney, χ^2), multivariate logistic regression models (β , standard errors [SE], p, odds ratio, 95% confidence interval), and Pearson correlation analyses were performed. Model stability was assessed (pseudo R², SE, and signs of multicollinearity). **Results:** No significant associations were found between hypoxemia and sociodemographic or clinical variables; time since symptom onset showed a trend (p = 0.149). The multivariate model for hypoxemia did not identify significant predictors and had a low pseudo R² (0.1095). For festering hypoxia, the model showed a very high pseudo R² (0.999) but coefficients with large SE. The strongest correlation found was age with systolic blood pressure (r = 0.448). **Conclusions:** No robust predictors of hypoxemia or asymptomatic hypoxia were identified; the models present problems of explanatory power and instability that require interpretive caution, a larger sample size, diagnosis and correction of multicollinearity, the use of penalized techniques, and external validation before applying predictive rules in clinical practice.

Keywords: Coronavirus disease 2019. Severe acute respiratory syndrome coronavirus 2. Oximetry. Asymptomatic. Hypoxia.

Introduction

The public health emergency caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection revealed multiple atypical clinical presentations, including the so-called “asymptomatic hypoxemia” or “silent hypoxia,” a phenomenon in which patients present markedly low arterial oxygen saturation levels without the proportional dyspnea classically associated with such a degree of hypoxemia.^{1,2} This dissociation between arterial blood gas parameters and the subjective perception of respiratory distress challenges

traditional respiratory physiology and raises fundamental questions regarding the underlying neurobiological and cardiopulmonary mechanisms, as well as the organizational strategies required to ensure early detection of patients at risk of sudden clinical deterioration.^{3,4}

Asymptomatic hypoxemia is not exclusive to SARS-CoV-2 infection. In routine clinical practice, this phenomenon is observed in various respiratory and cardiovascular conditions, including lobar atelectasis, intrapulmonary shunts of different etiologies, atrial septal defects with right-to-left shunting, and neuromuscular diseases that impair respiratory mechanics.^{5,6}

*Correspondence:

Annier J. Fajardo-Quesada

E-mail: annierfq01@gmail.com

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Understanding these pathophysiological mechanisms is essential to properly contextualize the findings observed in post-coronavirus disease 2019 (COVID-19) syndrome and to avoid considering this phenomenon as a feature unique to this viral infection.⁷

From a pathophysiological perspective, asymptomatic hypoxemia emerges as a complex multifactorial phenomenon involving alterations at multiple levels of the respiratory system. Several explanatory hypotheses have been proposed, including alterations in central respiratory control mediated by dysfunction of peripheral and central chemoreceptors; ventilation-perfusion mismatch at the alveolar level, with hypoperfused but hyperventilated lung regions; endothelial injury with microthrombus formation leading to effective intrapulmonary shunting; changes in hemoglobin oxygen affinity with shifts in the oxygen dissociation curve; and central neuroplastic adaptations that modify the conscious perception of respiratory load.⁸⁻¹⁰ Recent computational models have attempted to mathematically reproduce the dissociation between SpO₂ values and the sensation of dyspnea, providing theoretical frameworks that, although requiring further clinical validation, suggest that “happy hypoxia” may be explained by a combination of moderate arterial hypoxemia, compensated hypercapnia, and central adaptation of ventilatory sensitivity.^{11,12}

In response to this clinical scenario, pulse oximetry became established as an accessible and practical tool for the outpatient monitoring of patients with COVID-19, enabling the objective detection of hypoxemia in the absence of alarming subjective symptoms. Numerous “home oximetry” programs and “virtual wards” were developed internationally to allow early identification of patients at risk of deterioration and to facilitate timely referral to emergency services.^{13,14} Recent literature documents that such programs may significantly improve the detection of silent hypoxemia and reduce mortality in specific patient subgroups, although their real-world effectiveness critically depends on appropriate patient selection, health education for the correct use of pulse oximeters, and the telephone or in-person clinical support accompanying home monitoring.^{15,16}

Nevertheless, when promoting home oximetry as a public health strategy, the growing evidence regarding the technical limitations of commercially available pulse oximeters cannot be overlooked. Rigorous multicenter studies and recent systematic reviews have consistently shown that the accuracy of many commercial oximeters decreases significantly in individuals

with darker skin pigmentation, which may lead to systematic overestimation of SpO₂ and, consequently, underestimation of true hypoxemia in vulnerable populations.¹⁷⁻¹⁹ These findings have prompted regulatory actions by agencies such as the United States Food and Drug Administration and have driven proposals to improve validation standards for medical devices by requiring more diverse populations in clinical validation trials.^{20,21}

Therefore, the interpretation of SpO₂ readings in the community is not merely a technical issue, but also an ethical and health equity concern. In large-scale population surveillance programs, systematic measurement bias may generate significant disparities in detection and timely access to specialized medical care. In addition, heterogeneity in the construction quality and calibration of available devices substantially complicates the development of reliable predictive models when input data incorporate uncontrolled systematic errors.^{22,23}

From a methodological standpoint, the development of prognostic or explanatory models to detect the risk of hypoxemia or asymptomatic hypoxemia faces multiple scientific challenges. The presence of few events of interest, that is, a low prevalence of hypoxemia in a given sample, limits the available statistical power and the stability of regression coefficients. In addition, the inherent multicollinearity among interrelated physiological variables may artificially inflate standard errors (SE) and produce coefficients that are difficult to interpret clinically.^{24,25} For these reasons, modern methodological guidelines for the development of clinical prediction models recommend robust variable selection procedures, internal validation through resampling techniques, and external validation in independent cohorts, as well as the use of regularization methods, such as ridge or lasso regression, or dimensionality reduction techniques when appropriate.^{26,27}

Within this contextual and methodological framework, the present study aimed to identify factors associated with hypoxemia and asymptomatic hypoxemia in a cohort of adult patients screened after COVID-19 infection in the province of Matanzas, Cuba, during 2022.

Material and methods

Study design and setting

An analytical prospective cohort study was conducted. The study was carried out in the province of Matanzas, Cuba, between January and December 2022.

Study population and sampling

The study population consisted of adult patients (≥ 18 years) with a confirmed history of COVID-19 infection, diagnosed by nasopharyngeal polymerase chain reaction (PCR) or antigen testing according to clinical and epidemiological records, who were undergoing post-acute follow-up after hospital discharge or outpatient surveillance. A non-probability convenience sampling strategy was used, stratified by age group (18-39, 40-59, and ≥ 60 years) and sex (female/male), with the aim of ensuring basic demographic representativeness of the sample.

The final sample size was 125 participants, determined by logistical considerations, including the availability of eligible patients, health system resources, and the follow-up capacity of the research team during the study period.

Inclusion criteria

- Adult patients of either sex, aged ≥ 18 years.
- History of SARS-CoV-2 infection confirmed by PCR or antigen testing within the 30 days before recruitment.
- Patients in the post-acute phase, defined as 7-30 days from symptom onset or hospital discharge.
- Ability to understand and sign the informed consent form.

Exclusion criteria

- Patients in critical condition requiring admission to an intensive care unit at the time of sampling.
- Patients with terminal illnesses or other conditions that prevented a complete clinical evaluation.
- Patients who did not provide written informed consent.
- Presence of conditions that irreversibly affected SpO₂ measurement, such as upper-limb amputation, non-removable nail polish, or severe peripheral hypoperfusion.
- History of chronic obstructive pulmonary disease or moderate-to-severe asthma before the diagnosis of COVID-19.

Study variables

DEMOGRAPHIC VARIABLES

- Age, measured in years as a continuous variable.
- Biological sex, classified as female or male and analyzed as a dichotomous categorical variable.
- SARS-CoV-2 vaccination schedule, classified as complete vaccination with three doses, incomplete vaccination with one or two doses, or no vaccination.

- Time elapsed from the onset of COVID-19 symptoms to evaluation, measured in days as a continuous variable.
- Time elapsed from hospital discharge to evaluation, measured in days as a continuous variable among hospitalized patients.

CLINICAL AND PHYSIOLOGICAL VARIABLES

- Arterial oxygen saturation measured by pulse oximetry (SpO₂, %), analyzed as a continuous variable.
- Heart rate, measured in beats per minute as a continuous variable.
- Respiratory rate, measured in breaths per minute as a continuous variable.
- Systolic blood pressure, measured in mmHg as a continuous variable.
- Diastolic blood pressure, measured in mmHg as a continuous variable.
- Presence of respiratory symptoms, including cough, dyspnea, dysphagia, and use of accessory respiratory muscles.

Operational definitions of outcomes

Hypoxemia was defined as arterial oxygen saturation (SpO₂) below 92%, measured by pulse oximetry at rest, with the patient seated and under standard environmental conditions, including ambient temperature of 20-25°C and sea-level altitude.

Asymptomatic hypoxemia, also referred to as silent hypoxia, was defined as the presence of hypoxemia (SpO₂ < 92%) in the absence of severe respiratory symptoms, such as severe dyspnea or use of accessory respiratory muscles, in accordance with criteria used in previous COVID-19 studies.^{1,2}

Measurement procedures

Patients were invited for evaluation through family physician offices and post-COVID-19 surveillance programs implemented by the Cuban Ministry of Public Health. Each participant underwent the following standardized measurements:

- Oxygen saturation (SpO₂): a validated clinical/commercial pulse oximeter was used (model [specify brand/model]). Measurements were obtained at rest with the patient seated, the right upper limb positioned at heart level, after a 5-min stabilization period. Three consecutive readings were recorded, and the mean value was used for analysis.

- Heart rate: recorded simultaneously using the pulse oximeter.
 - Respiratory rate: measured by direct observation for 60 s while the patient was at rest, without making the patient aware that respirations were being counted, to minimize the observer effect.
 - Blood pressure: measured using a calibrated manual aneroid sphygmomanometer with the auscultatory technique, with the patient seated and the arm supported at heart level. Two readings were obtained at a 2-min interval, and the mean value was recorded.
- Pulse oximetry devices were checked daily through quality control procedures using SpO₂ simulators, and research personnel were specifically trained in the standardized measurement technique. Conditions that could affect the readings, such as nail polish, limb temperature, and peripheral perfusion, were systematically recorded, and measurements were repeated whenever technical concerns were identified.

Statistical analysis

A descriptive analysis of demographic and clinical variables was performed. Measures of central tendency, including mean and median, and measures of dispersion, including standard deviation (SD) and interquartile range, were reported according to data distribution. Categorical variables were summarized using absolute frequencies and percentages.

For the bivariate analysis, characteristics of participants with and without hypoxemia were compared using the Mann-Whitney U test for non-parametric continuous variables and the χ^2 test or Fisher's exact test for categorical variables, as appropriate. P values were reported using a significance level of $\alpha = 0.05$.

To evaluate independently associated factors, two multivariable binary logistic regression models were constructed. The first model used hypoxemia (yes/no) as the dependent variable, while the second model used asymptomatic hypoxemia (yes/no) as the dependent variable. Independent variables included in the models were selected based on clinical-epidemiological criteria and biological plausibility: age, sex, vaccination schedule, time from symptom onset, heart rate, respiratory rate, systolic blood pressure, and diastolic blood pressure.

Regression coefficients (β), SE, p-values, adjusted odds ratios (ORs) with their 95% confidence intervals (95% CI), and Nagelkerke's pseudo-R² as a descriptive measure of model explanatory power were calculated. Indicators of model instability were examined, including

very large SE, ORs with extremely wide CIs, and unstable p values.

Multicollinearity was explored through analysis of the Pearson correlation matrix among numerical variables, and the variance inflation factor (VIF) was calculated for predictors included in the multivariable models. Problematic multicollinearity was considered present when VIF values were > 5 or when correlation coefficients of $r > 0.7$ were observed between pairs of predictor variables.

Statistical analyses were performed using R software, version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria), with the stats, epitools, and rms packages.

Ethical considerations

All participants provided written informed consent after receiving a detailed explanation of the study objectives, procedures, minimal risks, and potential benefits. Data were handled with strict confidentiality using numerical codes for participant identification and storing the information in encrypted databases.

Results

Demographic characteristics of the study population

A total of 125 adult patients with a confirmed history of COVID-19 were evaluated. The mean age of the study population was 50.17 years (SD = 18.70; range, 18-91 years). Most participants were female ($n = 85$; 68%), while 40 participants were male (32%). Regarding the SARS-CoV-2 vaccination schedule, 68 patients (54.4%) had received at least one vaccine dose, whereas 57 patients (45.6%) had not received any vaccination. The mean time elapsed from the onset of COVID-19 symptoms to evaluation was 14.57 days (SD = 3.75; range, 7-28 days). Among patients who required hospitalization ($n = 45$), the mean time from hospital discharge to evaluation was 8.33 days (SD = 2.41).

Clinical and physiological characteristics

The mean values of the physiological variables are shown in [table 1](#). The mean SpO₂ was 96.34% (SD = 4.11; range, 60-99%), with 8 patients (6.4%) presenting hypoxemia, defined as SpO₂ $< 92\%$. Of these 8 patients with hypoxemia, 5 (62.5%) met the criteria for asymptomatic hypoxemia, or silent hypoxia, whereas

Table 1. Clinical and physiological characteristics of the total sample (n = 125)

Variable	Mean	SD	Median	Range	Minimum	Maximum
Age (years)	50.17	18.70	52	73	18	91
SpO ₂ (%)	96.34	4.11	97	39	60	99
Heart rate (bpm)	75.94	12.73	76	99	19	118
Respiratory rate (breaths/min)	18.96	3.35	19	18	10	28
Systolic blood pressure (mmHg)	124.54	19.48	122	110	90	200
Diastolic blood pressure (mmHg)	77.36	10.79	76	50	50	100
Time since symptom onset (days)	14.57	3.75	14	21	7	28

SD: standard deviation; SpO₂: arterial oxygen saturation; bpm: beats per minute.

3 patients (37.5%) presented concomitant dyspnea. The mean heart rate was 75.94 beats/min (SD = 12.73; range, 19-118 bpm), the mean respiratory rate was 18.96 breaths/min (SD = 3.35; range, 10-28 breaths/min), the mean systolic blood pressure was 124.54 mmHg (SD = 19.48; range, 90-200 mmHg), and the mean diastolic blood pressure was 77.36 mmHg (SD = 10.79; range, 50-100 mmHg).

Bivariate analysis: comparison between patients with and without hypoxemia

In the bivariate analysis, no statistically significant differences were found between patients with hypoxemia (SpO₂ < 92%) and those without hypoxemia for any of the demographic or clinical variables evaluated. The mean age in the hypoxemia group was 55.25 years (SD = 16.84), compared with 49.82 years (SD = 18.93) in the non-hypoxemia group (p = 0.353). No significant differences were observed in sex (p = 0.736), complete vaccination schedule (p = 0.986), heart rate (p = 0.948), respiratory rate (p = 0.675), systolic blood pressure (p = 0.303), or diastolic blood pressure (p = 0.734). Time elapsed from symptom onset showed a trend toward statistical significance, with a longer interval in the hypoxemia group (mean = 17.13 days, SD = 4.33) compared with the non-hypoxemia group (mean = 14.39 days, SD = 3.64), although this difference did not reach statistical significance (p = 0.149) (Table 2).

Multivariable logistic regression analysis

The multivariable logistic regression model for hypoxemia did not identify any statistically significant predictors. The model showed a Nagelkerke pseudo-R² of 0.1095,

indicating low explanatory capacity. None of the variables included in the model showed a significant association with hypoxemia after multivariable adjustment. Adjusted ORs and their 95% CIs are presented in table 3.

For the asymptomatic hypoxemia model, severe instability issues were observed. The Nagelkerke pseudo-R² was 0.999, indicating an almost perfect apparent fit; however, this was accompanied by coefficients with extremely large SEs, ranging from 12.4 to 156.7, and ORs with very wide CIs. These findings indicate severe overfitting and/or extreme multicollinearity among predictors, rendering the model clinically non-interpretable.

Correlation analysis

The Pearson correlation matrix among numerical variables revealed moderate correlations mainly between physiologically related variables. The strongest correlation identified was between age and systolic blood pressure (r = 0.448; p < 0.001), followed by the correlation between age and diastolic blood pressure (r = 0.163; p = 0.072). The remaining correlations between variables were weak (r < 0.20) and did not reach statistical significance (p > 0.05), including the correlations between SpO₂ and the other physiological variables. The complete Pearson correlation matrix is shown in figure 1.

Discussion

The main observation of this prospective analysis is the absence of statistically significant associations between hypoxemia (SpO₂ < 92%) and the sociodemographic variables or resting vital signs assessed in this cohort of post-COVID-19 patients. This finding may be

Table 2. Results of the bivariate comparative analysis between groups with and without hypoxemia

Variable	Hypoxemia group (n = 8)	Non-hypoxemia group (n = 117)	Statistic	p
Continuous variables	Mean (SD)	Mean (SD)	Mann-Whitney U	
Age (years)	55.25 (16.84)	49.82 (18.93)	375.5	0.353
Heart rate (bpm)	76.13 (11.42)	75.93 (12.85)	475.0	0.948
Respiratory rate (breaths/min)	19.50 (3.89)	18.92 (3.32)	426.5	0.675
Systolic blood pressure (mmHg)	131.25 (18.64)	124.08 (19.55)	367.0	0.303
Diastolic blood pressure (mmHg)	80.00 (9.46)	77.18 (10.89)	501.0	0.734
Time since symptom onset (days)	17.13 (4.33)	14.39 (3.64)	326.0	0.149
Categorical variables	n (%)	n (%)	χ^2	
Female sex	6 (75.0)	79 (67.5)	0.114	0.736
Complete vaccination schedule	6 (75.0)	84 (71.8)	0.000	0.986

SD: standard deviation; bpm: beats per minute.

Table 3. Multivariable logistic regression model for hypoxemia ($\text{SpO}_2 < 92\%$)

Variable	β	SE	p	Adjusted OR	95% CI for OR
Age (per year)	0.042	0.035	0.234	1.04	0.97-1.12
Male sex	0.156	0.987	0.874	1.17	0.17-8.06
Complete vaccination schedule	-0.234	1.124	0.835	0.79	0.09-7.12
Time since symptom onset (days)	0.189	0.134	0.158	1.21	0.93-1.57
Heart rate (bpm)	0.012	0.045	0.789	1.01	0.93-1.10
Respiratory rate (breaths/min)	0.098	0.156	0.532	1.10	0.81-1.49
Systolic blood pressure (mmHg)	0.023	0.019	0.223	1.02	0.99-1.06
Diastolic blood pressure (mmHg)	-0.031	0.034	0.361	0.97	0.911-1.04

Nagelkerke pseudo- $R^2 = 0.1095$. β : regression coefficient; SE: standard error; OR: odds ratio; CI: confidence interval; bpm: beats per minute.

interpreted from two complementary perspectives. On the one hand, it may genuinely reflect that hypoxemia during the post-acute phase of COVID-19 is not strongly associated with routine clinical parameters available in primary care. On the other hand, the limited sample size and the small number of events, with only eight cases of hypoxemia, markedly reduced the statistical power available to detect associations with small or moderate effect sizes, thereby increasing the risk of Type II error, or false-negative findings. Previous studies in hospital and outpatient settings have shown considerable variability in the prevalence of silent hypoxemia and in its associated factors according to the timing of evaluation and the initial severity of disease.

Therefore, the absence of statistical evidence in our sample should not be interpreted as evidence of no association.^{1,2,13}

The observed trend for time elapsed since symptom onset ($p = 0.149$), although it did not reach conventional statistical significance, deserves clinical attention due to its pathophysiological plausibility. It is biologically plausible that the temporal dynamics of the disease may influence the occurrence of hypoxemia, particularly in patients who develop pulmonary involvement during late or subacute phases of infection, including organizing pneumonia, early pulmonary fibrosis, or delayed pulmonary thromboembolism. This temporal pattern supports the implementation of longitudinal

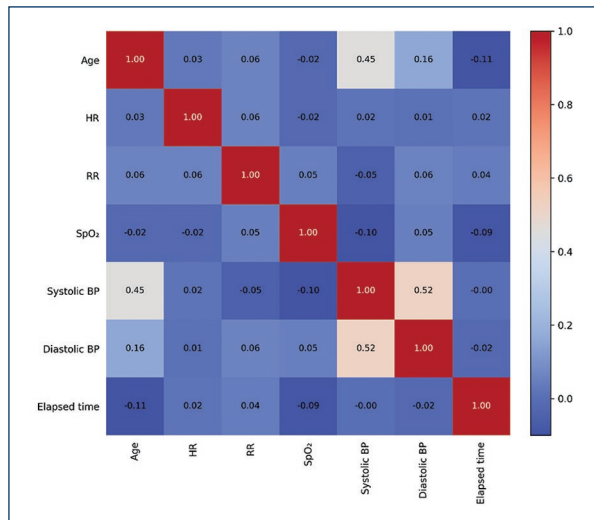


Figure 1. Pearson correlation matrix of clinical and physiological variables in the study population. HR: heart rate; RR: respiratory rate; SpO₂: peripheral oxygen saturation; BP: blood pressure; Systolic BP: systolic blood pressure; Diastolic BP: diastolic blood pressure.

designs with serial SpO₂ measurements to detect critical windows of risk and to adequately model the relationship between disease course and the probability of hypoxemia, rather than relying exclusively on single cross-sectional assessments. Home oximetry programs with repeated follow-up have shown usefulness in identifying respiratory deterioration in specific subgroups of post-COVID-19 patients, reinforcing the need to conceptualize “time” as a dynamic variable in predictive models.^{3,4,12}

The low explanatory capacity of the multivariable model for hypoxemia, reflected by a pseudo-R² of 0.1095, indicates that the variables included in the analysis captured only a small fraction of the variability of the outcome in this sample. This limitation may be attributed to the omission of relevant prognostic factors not measured in the study, such as pre-existing comorbidities, including diabetes mellitus, hypertension, and chronic kidney disease; body mass index; systemic inflammatory status, including markers such as C-reactive protein, ferritin, and interleukins; the extent of radiological lung damage, such as computed tomography involvement scores; or markers of microvascular thrombosis, including D-dimer and fibrin degradation products. Previous studies have consistently identified these variables as being associated with hypoxemia and COVID-19 severity, and their absence from our model substantially limits its explanatory capacity. In addition, the inherent noise in SpO₂ measurements due

to variability among pulse oximetry devices and potential biases related to skin pigmentation may dilute true associations. Therefore, the integration of more specific clinical variables, inflammatory biomarkers, and imaging data could significantly improve the predictive capacity of future models.^{10,17,18}

The model for asymptomatic hypoxemia showed a typical and extreme pattern of statistical instability: an almost perfect pseudo-R² of 0.999 accompanied by regression coefficients with extremely large SE and ORs with excessively wide CIs. This pattern is highly suggestive of severe overfitting, in which the model “learns” the specific peculiarities of the sample rather than generalizable patterns, or of extreme multicollinearity among physiologically interrelated predictors. In methodological practice, such a high pseudo-R² in a small sample with few events is highly suspicious and requires rigorous statistical diagnostics, including VIF calculation, principal component analysis, and influence analysis. Alternative methodological approaches, such as regularization techniques, including ridge or lasso regression, or dimensionality reduction methods such as principal component analysis, may be needed to obtain more stable estimators that are generalizable to other populations.²⁴⁻²⁶

Multicollinearity is a foreseeable methodological issue when analyzing interrelated physiological variables, such as age, blood pressure, heart rate, and respiratory rate, which may correlate with one another and create informational redundancy within the model. In the presence of severe multicollinearity, individual regression coefficients lose direct clinical interpretability, even if the overall model retains some predictive ability. However, when the variance of the estimators becomes excessively inflated, as occurred in our analysis, even the global predictive capacity of the model becomes questionable. Contemporary methodological guidelines strongly recommend that, in settings with few events per predictor variable, more parsimonious models with careful variable selection should be prioritized. Internal validation using resampling techniques, such as bootstrapping or cross-validation, should also be performed, and penalized methods should be considered to counteract excessive variance.^{10,11,14}

Another crucial element that extends beyond the statistical analysis is the metrological quality of SpO₂ measurements. A growing body of scientific evidence shows that pulse oximeters, particularly low-cost commercial models, tend to systematically overestimate SpO₂ in individuals with darker skin phototypes or higher skin pigmentation. This phenomenon may lead

to underdiagnosis of hypoxemia in individuals with higher skin pigmentation and may affect the validity of predictive models that do not account for measurement bias related to skin phototype. In response to this evidence, international regulatory agencies have proposed new recommendations for oximeter performance testing that require demographically diverse populations in pre-market validation studies. In our sample, if skin pigmentation or heterogeneity among the devices used was not adequately controlled, an unquantified differential bias may have been introduced into SpO₂ estimates and, consequently, into the prediction models.¹⁷⁻²⁰

From a comparative pathophysiological perspective, it is important to contextualize our negative findings within the broader literature on asymptomatic hypoxemia in other clinical conditions. In patients with post-operative lobar atelectasis, silent hypoxemia has been documented to persist in up to 40% of cases in the absence of apparent dyspnea, mediated predominantly by basal intrapulmonary shunts. In atrial septal defects with right-to-left shunting, hypoxemia may remain the only warning sign for years due to gradual adaptation of the chemoreceptor system. In patients with neuromuscular diseases, weakness of accessory respiratory muscles may allow prolonged asymptomatic nocturnal hypoxemia. These parallels suggest that post-COVID-19 asymptomatic hypoxemia may share common pathophysiological mechanisms with these conditions, particularly ventilation-perfusion mismatch and central adaptation of the chemoreceptor response. This opens future lines of research regarding common biomarkers and shared therapeutic strategies.⁵⁻⁸

In practical terms for the implementation of public health programs, the results of this study call for extreme caution before adopting predictive models based solely on pulse oximeter readings and conventional vital signs in small samples. The implementation of post-COVID-19 home monitoring programs should necessarily be accompanied by rigorous patient education protocols, clear warning criteria, and systems for confirming abnormal readings, such as repeating measurements under standardized conditions, in-person clinical assessment, or confirmation with arterial blood gas analysis when appropriate. In addition, the principle of health equity requires prioritizing oximetry devices validated in ethnically diverse populations or applying algorithmic corrections when interpreting readings in groups at high risk of systematic measurement error.^{3,4,6,21}

Although the present study did not identify robust predictors of hypoxemia or asymptomatic hypoxemia in

this specific cohort, it should not be ruled out that clinically useful risk determinants may be identified in larger populations, with a greater number of events, or through the incorporation of additional variables with greater pathophysiological specificity. These may include high-resolution chest imaging, serial inflammatory biomarkers, and detailed characterization of comorbidities, polysomnography data, or nocturnal oximetry. Future research in this field should prioritize longitudinal designs, diverse samples, and validated machine learning methodologies to develop truly useful prediction tools for the outpatient management of post-COVID-19 syndrome.^{10,26,27}

Conclusion

In this analytical prospective cohort from Matanzas, Cuba, conducted in 2022, no sociodemographic factors or vital signs were robustly associated with hypoxemia (SpO₂ < 92%) or happy hypoxia. The multivariable models showed either low explanatory capacity, with a pseudo-R² of 0.1095 for hypoxemia, or extreme instability, with a pseudo-R² of 0.999 for happy hypoxia accompanied by extremely large coefficients and SE. These findings suggest overfitting and/or multicollinearity.

Therefore, before proposing predictive rules based on pulse oximeter readings and vital signs, larger samples, diagnosis and correction of multicollinearity, the use of penalized methods or dimensionality reduction techniques, external validation, and rigorous control of measurement quality are required. Particular attention should be paid to potential bias related to skin pigmentation. These steps are necessary to ensure that home monitoring tools and predictive models are reliable, equitable, and clinically useful.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible

committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that ChatGPT was used only to proofread the manuscript.

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ORIGINAL ARTICLE

Detection of circulating tumor cells in liquid biopsies of post-treatment lymphoma

Rafael Cerón-Maldonado¹ , Amairani Gutiérrez-Nava^{1,2} , Luisa M. Romero-Ornelas^{1,3} ,
Christian O. Ramos-Peñafiel⁴ , Adrián De la Cruz-Rosas¹ , Anel I. García-Laguna¹ , Iveth Mendoza-Salas¹ ,
Efreem H. Montaña-Figueroa⁴ , Adolfo Martínez-Tovar¹ , and Irma Olarte-Carrillo^{1*}

¹Research Laboratory, Hematology Service, Hospital General de México Dr. Eduardo Liceaga, Secretaría de Salud; ²Department of Diagnostic Biochemistry, Facultad de Estudios Superiores Cuautitlán, Universidad Nacional Autónoma de México (UNAM), Cuautitlán, Estado de México; ³Graduate Program in Biological Sciences, Biomedicina, UNAM; ⁴Hematology Service, Hospital General de México Dr. Eduardo Liceaga, Secretaría de Salud. Mexico City. México

Abstract

Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive subtype of non-Hodgkin lymphoma. Although the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimen is the standard therapy, up to 30% of patients experience relapse or are refractory. In clinical practice, therapeutic monitoring relies on imaging studies and lacks molecular techniques. **Objective:** The objective of this study was to evaluate the expression of the molecular biomarkers BCL2, BCL6, EpCAM, VEGFR1, and TWIST1 in circulating tumor cells (CTCs) from DLBCL patients after R-CHOP treatment. **Material and methods:** The expression of these molecular biomarkers was analyzed in CTCs from 42 post-R-CHOP DLBCL patients, using CD20+ cell enrichment and quantitative reverse transcription polymerase chain reaction for CTCs detection. **Results:** Significant differences were observed in the expression of BCL2 ($p = 0.003$), BCL6 ($p = 0.001$), and VEGFR1 ($p = 0.002$) compared to healthy controls. The tumor-specific genes EpCAM and TWIST1 were not detected in healthy donors. Overexpression frequencies were as follows: BCL6 28.6% (12/42), BCL2 26.2% (11/42), VEGFR1 16.7% (7/42), TWIST1 7.2% (3/42), and EpCAM 2.4% (1/42). **Conclusions:** Overexpression of BCL2, BCL6, and VEGFR1, along with the presence of EpCAM and TWIST1 in CTCs from patients with disease progression, supports the relevance of liquid biopsies as a valuable tool to enhance the clinical management of DLBCL patients.

Keywords: Liquid biopsy. Circulating tumor cells. Diffuse large B-cell lymphoma. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Introduction

The determination of circulating biomarkers in minimally invasive liquid biopsies (LB) is one of the fastest-growing areas in cancer research.¹ The detection of circulating tumor cells (CTCs), circulating tumor DNA, and exosomes in peripheral blood (PB) and other biological fluids has gained relevance in the diagnosis, prognosis, treatment selection, and monitoring of oncological patients.²

The use of LB in clinical practice has experienced a notable increase; however, further research is still required to validate their clinical application and the methodologies employed. LB have become valuable tools in the study of oncological patients when combined with clinical examination, laboratory testing, and imaging studies.¹ Its relevance lies especially in the ability to obtain biological samples rapidly and noninvasively during chemotherapy treatment, as well as in the ease of sample collection after treatment completion. This enables

*Correspondence:

Irma Olarte-Carrillo

E-mail: irmaolartec@yahoo.com

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continuous, real-time monitoring of tumor behavior and may be crucial for the detection of minimal residual disease (MRD).^{1,2}

Although LB analysis does not replace histopathological analysis of tissue biopsies, it has become particularly relevant in tumors located in anatomically inaccessible sites and in cases where tumor burden is limited.³

Several Food and Drug Administration (FDA)-approved laboratory tests are currently available for LB analysis in cancers such as breast,⁴ prostate,⁵ and colorectal,⁶ which represent the malignancies in which CTCs research has advanced the most. However, in other cancer types, including hematological malignancies, research on circulating biomarkers is limited, even in highly disseminated cancers such as diffuse large B-cell lymphoma (DLBCL).⁷ Our research group has demonstrated the clinical impact of the detection and characterization of CTCs in *de novo* DLBCL patients, identifying that the overexpression of oncogenes associated with apoptosis resistance (*BCL2* and *BCL6*), angiogenesis induction (*VEGFR1*), and tumor dissemination (*EpCAM* and *TWIST1*) is associated with reduced overall survival (OS) and progression-free survival (PFS).⁸

In the follow-up of DLBCL patients after first-line rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy, assessment of therapeutic outcomes is based on clinical findings (resolution of lymphadenopathy), laboratory parameters (normalization of complete blood counts and lactate dehydrogenase [LDH] levels), and imaging studies (positron emission tomography/computed tomography [PET/CT] showing no metabolically active disease), without the support of a molecular tool capable of strengthening the determination of therapeutic success or failure.⁹ Therefore, the aim of this study was to determine the frequency of molecular biomarker expression in CTCs from DLBCL patients who had completed R-CHOP therapy, to confirm that LB may be used as a molecular monitoring tool in patients with this disease, a field that remains largely unexplored.

Material and methods

Study population

A total of 42 PB LB samples from patients with a histopathological diagnosis of DLBCL treated at the Hospital General de México Dr. Eduardo Liceaga were included in this study. LB samples were collected during the first follow-up visit after PET/CT evaluation. Twenty samples from clinically healthy donors were

included as normal expression controls. Clinical information and biological samples were obtained after written informed consent was provided by all participants, in accordance with the Declaration of Helsinki.

CTCs isolation

An 8 mL anticoagulated PB LB sample (Vacutainer tubes, BD Diagnostics, Franklin Lakes, New Jersey, USA) was obtained from each patient included in the study. CTCs and mononuclear cells were isolated using Lymphoprep (Axis-Shield, Oslo, Norway), according to the manufacturer's instructions. Subsequently, B cells from LB samples were isolated by positive selection using anti-CD20 MicroBeads (Miltenyi Biotec, Bergisch Gladbach, Germany), a marker expressed by DLBCL cells, following the manufacturer's recommendations and as previously described.¹⁰

RNA extraction and analysis

RNA was isolated from all samples using TRIzol reagent (Invitrogen, Life Technologies, Carlsbad, CA, USA) according to the manufacturer's instructions. RNA concentration and purity were determined using a NanoDrop 2000 spectrophotometer (Thermo Scientific, Wilmington, DE, USA).

Detection of molecular biomarkers

Relative expression levels of molecular biomarkers in CTCs were determined by "One-Step quantitative reverse transcription polymerase chain reaction (RT-qPCR)" performed in triplicate using a StepOne™ real-time polymerase chain reaction (PCR) system (Applied Biosystems). Each reaction contained 100 ng of RNA, PrimeTime™ One-Step RT-qPCR Master Mix (IDT, Coralville, Iowa, USA), and specific hydrolysis probes for *BCL2* (Hs04986394_s1), *BCL6* (Hs00153368_m1), *EpCAM* (Hs00901885_m1), *TWIST1* (Hs04989912_s1), and *VEGFR1* (Hs01052961_m1) (Thermo Scientific, Wilmington, DE, USA). *GUSB* (Hs00939627_m1) was used as endogenous control gene, and the DLBCL cell lines DS (CRL-3381™) and RC (CRL-3382™) were used as reference samples. Relative gene expression levels were calculated using the 2- $\Delta\Delta C_t$ method.

Statistical analysis

Categorical variables were expressed as frequencies and proportions. Means and standard deviations were

calculated for quantitative variables. Data normality was assessed using the Anderson-Darling test. Differences between means were evaluated using t-test. Statistical analyses were performed using the Statistical Package for the Social Sciences software version 29.0 (IBM, Armonk, NY, USA). $p < 0.05$ was considered statistically significant.

Results

Characteristics of the cohort study

The mean age at diagnosis was 57 years (range, 20-84 years), with a predominance of female patients, accounting for 54.8% (23/42) of the cohort. Laboratory findings showed that 38.1% (16/42) of patients presented with leukopenia, 4.8% (2/42) with leukocytosis, 33.3% (14/42) with anemia, 19.0% (8/42) with thrombocytopenia, and 7.2% (3/42) with thrombocytosis. Based on histopathological evaluation and immunohistochemical classification using the Hans algorithm (CD10, BCL6, and MUM1), 40.5% (17/42) of patients were classified as Germinal Center B cell-like (GCB), 45.2% (19/42) as non-GCB, and 14.3% (6/42) as not otherwise specified.

Regarding the clinical parameters included in the international prognostic index (IPI), elevated LDH levels and Eastern Cooperative Oncology Group performance status ≥ 2 were observed in 28.6% (12/42) of patients, respectively. Extranodal involvement was present in 57.1% (24/42), while 69.0% (29/42) were diagnosed with advanced-stage disease (Ann Arbor stages III-IV). In addition, 38.1% (16/42) of patients had an IPI score between 3 and 5 and were classified as having poor prognosis according to the revised IPI (Table 1).

Therapeutic outcome

Based on post-treatment clinical findings and PET/CT evaluation, 78.6% (33/42) of the analyzed samples were obtained from patients who achieved complete response (CR), whereas the remaining 21.4% (9/42) corresponded to patients with disease progression (Table 1).

Frequency of molecular biomarker expression in CTCs

Samples from 20 healthy individuals were used as normal controls for biomarker expression analysis. For *EpCAM* and *TWIST1*, whose expression is considered tumor-specific, the absence of expression was confirmed in samples from healthy donors. For *BCL2*, *BCL6*, and

Table 1. Clinicopathological characteristics of DLBCL patients (n = 42)

Parameters	Cases (%)
Age (years)	
Mean (Range)	57 (20-84)
< 60 years	24 (57)
≥ 60 years	18 (43)
Gender	
Male	19 (45.2)
Female	23 (54.8)
Leucocytes ($\times 10^3/\mu\text{L}$)	
Mean (Range)	5.5 (2.28-15.38.0)
Low	16 (38.1)
Normal	24 (57.1)
High	2 (4.8)
Hemoglobin (g/dL)	
Mean (Range)	12.7 (8.5-17.5)
Anemia	14 (33.3)
> 12 g/dL	28 (66.7)
Platelets ($\times 10^3/\mu\text{L}$)	
Mean (Range)	236 (77.5-531.1)
< 150	8 (19)
Normal	31 (73.8)
≥ 450	3 (7.2)
Cell of origin	
GCB	17 (40.5)
Non-GCB	19 (42.2)
NOS	6 (14.3)
Lactate dehydrogenase (U/L)	
Mean (Range)	313 (105-1640)
< 271	30 (71.5)
≥ 271	12 (28.5)
ECOG PS	
0-1	30 (71.5)
> 2	12 (28.5)
Extranodal sites	
No	18 (42.9)
Yes	24 (57.1)
Clinical stage	
I-II	13 (31)
III-IV	29 (69)
IPI score	
0-2	26 (61.9)
3-5	16 (38.1)
R-IPI score	
Very good	1 (2.4)
Good	25 (59.5)
Poor	16 (38.1)
Treatment response	
Complete response	33 (78.6)
Progression	9 (21.4)

DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern cooperative oncology group performance status; GCB: germinal center B-cell; Non-GCB: non-germinal center B-cell; NOS: not otherwise specified; IPI: international prognostic index; R-IPI: revised international prognostic index.

VEGFR1, the normal expression range was established based on the upper limit of the 95% confidence interval for the mean plus standard deviation. Values above this

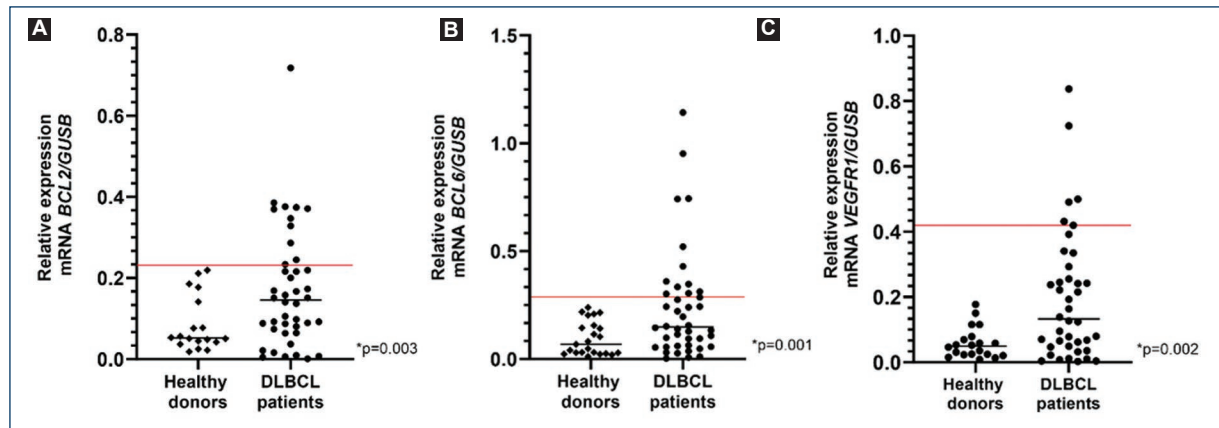


Figure 1. A-C: differential expression of *BCL2*, *BCL6*, and *VEGFR1* in healthy donors (n = 20) and diffuse large B-cell lymphoma patients (n = 42).

threshold were considered indicative of overexpression and, consequently, evidence of the presence of CTCs, as previously described.⁸ To compare biomarker expression between healthy controls and DLBCL patients, Anderson-Darling and Student's t-tests were performed. Significant differences were observed in the expression levels of *BCL2* ($p = 0.003$), *BCL6* ($p = 0.001$), and *VEGFR1* ($p = 0.002$) in post R-CHOP DLBCL patients compared with healthy donors (Fig. 1).

When molecular biomarkers were analyzed in the entire cohort of post-R-CHOP DLBCL patients, *BCL6* was the most frequently overexpressed gene, detected in 28.6% (12/42) of cases, followed by *BCL2* in 26.2% (11/42) and *VEGFR1* in 16.7% (7/42). Regarding tumor-specific markers, *EpCAM* was detected in 2.4% (1/42) of patients, while *TWIST1* expression was detected in 7.2% (3/42) (Table 2).

It was found that 8/9 (88.9%) of patients whose LB samples were obtained during active disease had over-expression/presence of at least one biomarker included in the panel.

Discussion

Over the past two decades, the study of LB has been increasingly incorporated into the management of cancer patients. Significant advances have been achieved in molecular tools for the detection of circulating biomarkers across virtually all solid tumor types, where these biomarkers have gained considerable relevance as prognostic indicators.¹¹ In DLBCL, the assessment of molecular biomarkers has contributed to patient classification, diagnosis, and prognosis, while their application in disease monitoring remains an evolving field.¹²⁻¹⁵

Table 2. Frequency of biomarker expression in CTCs from DLBCL patients after R-CHOP treatment

CTCs Biomarkers	Status	Cases n (%)
<i>BCL2</i>	Normal	31 (73.8)
	Overexpression	11 (26.2)
<i>BCL6</i>	Normal	30 (71.4)
	Overexpression	12 (28.6)
<i>VEGFR1</i>	Normal	35 (83.3)
	Overexpression	7 (16.7)
<i>EpCAM</i>	Negative	41 (97.6)
	Present	1 (2.4)
<i>TWIST1</i>	Negative	39 (92.8)
	Present	3 (7.2)

CTCs: circulating tumor cells; DLBCL: diffuse large B-cell lymphoma; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Despite the development of novel therapeutic agents, the R-CHOP regimen continues to represent the worldwide standard first-line treatment for DLBCL. International studies have reported CR rates ranging from 70% to 80% following this therapeutic regimen, although a proportion of patients either fail to respond or eventually relapse during follow-up. Nowakowski and colleagues reported a CR rate of 69% (n = 285) in 2021,¹⁶ whereas Tilly and colleagues reported a CR rate of 83.3% in 2022.¹⁷ These findings are consistent with the CR rate observed in our cohort (78.6%, 33/42). Furthermore, 21.4% (9/42) of our patients exhibited disease progression following R-CHOP therapy. The existence of

patients who do not respond to treatment or subsequently relapse highlights the need for highly sensitive and specific tools capable of identifying active disease after treatment completion. In this context, LB represents a promising approach that may be applied both at diagnosis and during patient monitoring.

Evidence of the growing relevance of LB in oncology is reflected by the approval of the CellSearch® system by the FDA for the detection of CTCs in breast, prostate, and colorectal cancers. In these malignancies, the detection of CTCs expressing epithelial markers such as EpCAM and CK8/18/19 has been associated with tumor dissemination and poor clinical outcomes, including reduced OS and PFS.⁴⁻⁶ Although its diagnostic use has been validated only for these tumor types, the underlying methodology has subsequently been applied to other malignancies, including pancreatic,¹⁸ testicular,¹⁹ lung,²⁰ hepatocellular carcinoma,²¹ and melanoma,²² among others.

At present, advances in cellular and molecular cancer analysis have demonstrated that the detection of CTCs using only epithelial markers is no longer sufficient. A deeper understanding of tumor biology requires comprehensive characterization of these cells through the evaluation of genes associated with proliferation, apoptosis resistance, angiogenesis, invasion, and dissemination. Accordingly, *BCL2* expression has been reported in CTCs from lung cancer patients,²³ while *TWIST1* expression has been described in CTCs derived from breast cancer patients.^{24,25} In hematological malignancies, particularly DLBCL, our research group has previously reported the clinical association between the expression of biomarkers such as *EpCAM*, *CK19*, *BCL2*, *BCL6*, *VEGFR1*, and *TWIST1* in CTCs and unfavorable clinical outcomes, further supporting their value as prognostic molecular biomarkers.⁸

Unfortunately, molecular testing is not routinely performed in DLBCL patients in Mexico, either at diagnosis or during disease follow-up. Consequently, patient management relies primarily on clinical findings, laboratory tests, and imaging studies. However, these approaches may fail to detect MRD due to their inherent limitations.²⁶ Unlike other hematologic malignancies, compelling evidence supporting the use of circulating molecular biomarkers for monitoring DLBCL patients after treatment remains limited. In this context, the findings of the present study reinforce the concept that molecular tools derived from LB, such as CTCs detection and characterization, may significantly complement conventional clinical and imaging-based assessments.

Examples supporting the value of post-treatment CTCs detection include the studies conducted by Rack et al. in 2014²⁷ and Matikas et al. in 2022²⁸ in breast cancer patients. In both studies, CTCs were evaluated before and after therapy. Patients with detectable CTCs both at diagnosis and after treatment completion experienced poorer clinical outcomes and lower survival rates. These findings underscore the importance of CTCs determination during disease monitoring and confirm its prognostic value after therapy. Similarly, in our study, overexpression of *BCL2* and *BCL6* was identified in CTCs from DLBCL patients with persistent disease activity following R-CHOP therapy, supporting the concept that detection and characterization of CTCs are essential for identifying ongoing tumor activity.

In hematologic malignancies, particularly leukemias, circulating molecular biomarkers already play a central role in patient monitoring. For instance, in patients with chronic myeloid leukemia, therapeutic response to tyrosine kinase inhibitors is determined through quantification of transcripts derived from the *BCR-ABL* fusion gene, establishing molecular biomarkers as the gold standard for treatment monitoring.²⁹ The growing evidence supporting circulating molecular biomarkers has substantially improved the management of leukemia patients. However, in lymphoma, particularly DLBCL, our group is among the pioneers in Mexico investigating the clinical utility of LB for disease monitoring in DLBCL.

The results of the present study highlight the importance of incorporating molecular analysis of CTCs from LB as a complementary tool for evaluating DLBCL patients after completion of first-line R-CHOP therapy. The detection of circulating biomarkers not only indicates the persistence of tumor cells but also contributes to understanding the biological mechanisms underlying treatment resistance and disease progression. Furthermore, some of the genes evaluated in CTCs, particularly *BCL2*, have been identified as potential therapeutic targets and may serve as biomarkers for targeted therapies aimed at improving outcomes in refractory or relapsed patients.^{30,31} Collectively, our findings reinforce the importance of investigating molecular biomarkers in CTCs obtained from LB in lymphoma patients, not only at diagnosis as previously reported by our group but also during treatment response monitoring in DLBCL patients.¹⁰

Conclusion

Overexpression of *BCL2*, *BCL6*, and *VEGFR1*, as well as the presence of *EpCAM* and *TWIST1*, was

identified in CTCs isolated from LB of DLBCL patients with disease progression following completion of R-CHOP chemoimmunotherapy. These findings support the clinical relevance of evaluating molecular biomarkers in CTCs obtained from LBs and reinforce their potential utility as a valuable molecular tool for disease monitoring in patients with this hematologic malignancy.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

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

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ORIGINAL ARTICLE

Correlations from sleep architecture predict nocturia in patients with sleep breathing disorders

Viridiana Mancilla-Hernández¹, Joana Miranda-Ortiz¹, Virginia Mancebo-Sosa¹, Aremy Hernández-Torres¹, Adrián Poblano^{1,2*}, Ulises Jiménez-Correa¹, and Rafael Santana-Miranda¹

¹Clinic of Sleep Disorders, Universidad Nacional Autónoma de México; ²Laboratory of Cognitive Neurophysiology, Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra, Secretaría de Salud. Mexico City, México

Abstract

Introduction: Nocturia has been reported to be a common problem in sleep breathing disorders (SBD). It is considered a multidisciplinary alteration without considering the weight of each variable involved. **Objectives:** The objective of the study was to calculate equations based on polysomnography (PSG) variables and other clinical characteristics to predict nocturia in patients with SBD. **Materials and methods:** We studied 400 patients with SBD: 100 with primary snoring, 100 with mild obstructive sleep apnea-hypopnea syndrome (OSAHS), 100 with moderate OSAHS, and 100 with severe OSAHS. We measured sleep architecture with PSG variables and calculated multiple regression models (MRM) for all SBD levels to predict subjective and objective nocturia. **Results:** We observed a progressive alteration of PSG variables in patients with SBD with nocturia as severity of the disorder increased. The MRM calculated explained one-third and a half of the variance in subjective and objective nocturia, respectively. **Conclusion:** PSG variables were altered in patients with nocturia related to SBD severity. MRM predict subjective and objective nocturia and explained a significant amount of variance. These equations could help clinicians to predict the severity of nocturia based on PSG variables.

Keywords: Nocturia. Sleeping breathing disorders. Snoring. Sleep apnea. Multiple regression models.

Introduction

Nocturia refers to the complaint of needing to awaken at least once per night to void the bladder.¹ Nocturia has been related to sleep breathing disorders (SBD), which include: obstructive sleep apnea-hypopnea syndrome (OSAHS), and primary snoring (PS), but correlation with frequency and severity is a research gap.² PS is defined as hoarse sounds caused by soft palate vibration during sleep with no other complaints. Meanwhile, OSAHS is mainly characterized by: repetitive and intermittent events of obstruction of the upper airway with events of complete (apnea) or partial (hypopnea) interruption of

airflow that last ≥ 3 s and lead to snoring, awakening and a decrease in blood oxygen saturation. The relationship is a current subject of research because it could provide a possible mechanistic explanation for the association between OSAHS and nocturia.

OSAHS alters the autonomic nervous system and increases oxidative stress, which results in endothelial injury.³ In addition, an increase of pulmonary pressure during apnea,⁴ may result in high pressure in the right heart atrium and excretion of natriuretic peptides. This increase in plasma levels of natriuretic peptides in patients with OSAHS may in turn increase salt and

*Correspondence:

Adrián Poblano

E-mail: drdislexia@yahoo.com.mx

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water excretion at night.⁵ Prevalence of nocturia in snoring, mild, moderate and severe OSASHS was 40.6%, 44.4%, 58.6%, and 57.1%, respectively, in one study.⁶

Clinicians do not currently have a way to predict nocturia based on objective patient's polysomnography (PSG) measures or with clinical subjective features. This is important because it will be more reliable because some patients could have not the appropriate required collaboration due to mental retardation, dementia, stroke, severe head trauma, or other causes. Thus, the objective of this research was to calculate multiple regression models (MRM) from the PSG to predict nocturia in patients with SBD and know how nocturia is related to SBD severity.

Material and methods

Subjects

The study subjects were four hundred patients with SBD distributed as follows: 100 with PS, 100 with mild-OSAHS (mild-), 100 with moderate (mod-) OSAHS, and 100 with severe (sev-) OSAHS. We took a complete clinical history and performed a PSG. Diagnosis of OSAHS was carried out by clinical suspicion following patient self-perception of snoring or pause in breathing or report of snoring with breathing pauses by the patient's bed partner and confirmed by means of one all-night PSG recording according to recommendations of the third classification of sleep disorders.⁷ PS was identified by self or partner-reported snoring and confirmed by PSG recording. Exclusion criteria were: urinary tract infections, chronic renal insufficiency, benign prostatic hyperplasia, prostate cancer, chronic degenerative vascular and metabolic diseases, and any neurological diseases that may affect bladder voiding (e.g. stroke, epilepsy, multiple sclerosis, dementia). These conditions were ruled out by a specialist. Clinical features of the subjects from each group are shown in table 1.

The research committee of the institution reviewed and approved the protocol (UNAM.FM.076.2022). All procedures performed in the study involving human participants were in accordance with the ethical standards. Participants were widely informed of the importance of the participation and objectives of the study and signed a consent letter for their participation in the research and publication of results in accordance with the Declaration of Helsinki.

Table 1. Clinical features of participants from each studied group

Diagnosis	n	Age (years) $\bar{x} \pm SD$	Male/ female (%)
Primary snoring	100	41.61 $\pm$ 14.86	41/59
Mild OSAHS	100	43.35 $\pm$ 14.77	50/50
Moderate OSAHS	100	49.98 $\pm$ 13.32	50/50
Severe OSAHS	100	51.25 $\pm$ 13.37	50/50
Total	400	46.54 $\pm$ 14.64	48/52

n: sample size; OSAHS: obstructive sleep apnea hypopnea syndrome; SD: standard deviation; %: percentage.

Nocturia and comorbidity assessment

Nocturia was classified in categorical fashion as follows: subjective, when the patient reported awakening to urinate at night, and objective, when one of the technicians reported that the patient voided during the all-night PSG study.

Polysomnographic recordings

PSG recordings were performed in one all-night session using digital Alice equipment with Sleepware software version 2.8.78 (Phillips Respironics Inc., Koninklijke, VA). The study session lasts approximately 8 h. We used the electroencephalographic international 10-20 simplified system for electrode placement.⁸ Gold-cup electrodes were located at F4-M1, C4-M1, and O2-M1. Electro-oculographic recordings were obtained with gold cup electrodes located on the outer corners of the left and right eye and grounded in the forehead. Electromyographic recordings were performed on the muscle of the chin and on both anterior tibial muscles. Electrocardiographic recordings were carried-out by placing electrodes at the right and left infra-clavicular spaces. Respiratory flow was measured by means of a thermistor placed in the nostrils, and respiratory movements were recorded by thoracic and abdominal sensor belts. Snoring was recorded by a microphone placed over the right lateral neck skin, and pulse oximetry was measured by an infra-red spectrography sensor on the right index finger. Recordings were scored by professionals according to international standards.⁹

We studied the following PSG variables: total sleep time (TST), sleep efficiency, latency to N1 and to rapid eye movement (REM) sleep stages; percentage of light sleep (N1 + N2 stages), percentage of deep sleep (N3

Table 2. Obesity percentage in the four studied groups

Obesity classification	Primary snoring (n %)	Mild OSAHS (n %)	Moderate OSAHS (n %)	Severe OSAHS (n %)
Adequate weight	35/35	21/21	16/16	2/2
Obesity grade I	29/29	40/40	33/33	22/22
Obesity grade II	11/11	14/14	18/18	28/28
Obesity grade III	10/10	8/8	20/20	19/19
Obesity grade IV	15/15	17/17	13/13	29/29
Total	100/100	100/100	100/100	100/100

n: sample size; OSAHS: obstructive sleep apnea hypopnea syndrome; SD: standard deviation; %: percentage.

stage), and percentage of REM sleep; apnea hypopnea index (AHI) and oxygen saturation. OSAHS severity was classified based on the AHI as follows: mild (6-15 events/h), moderate (16-30 events/h), and severe degree (≥ 31 events/h).

Statistical analysis

The sample size was calculated with 80% of beta power to observe differences between groups.¹⁰ We calculated the arithmetic mean and standard deviation (SD) of quantitative variables, and percentages of qualitative variables, respectively. The Pearson's correlation coefficient was used to provide the association measure between nocturia and several clinical and PSG components. A separately linear MRM were carried-out for subjective and objective nocturia, including a forward method with the variables with probability ≤ 0.05 to obtain equations to predict nocturia.¹¹ A value of $p \leq 0.05$ was chosen to accept calculations as significant.

Results

Overall data

Demographic characteristics for each group of the sample are presented in [table 1](#). In the whole sample, 52% of patients were women. Average patients age was 46.5 ± 14.64 (SD) years (range 18-81 years). There were no significant differences in age or gender distribution among groups. Percentage of obesity after body mass index (BMI) calculation showed that one-third of the sample was in the range of adequate weight. The SBD severity was higher as the percentage of obesity increased ($p < 0.05$) ([Table 2](#)).

Sleep architecture

Sleep architecture data in each group are presented in [table 3](#). In general, we observed that latencies N1, REM sleep, percentages of REM sleep and slow waves sleep, sleep efficiency index, and oxygen saturation differed significantly among SBD severity categories, with decreasing values in each successive category. On the contrary, time awake, percentage of nREM sleep, and the AHI increased as SBD increases in severity.

MRM

The subjective assessment of nocturia presented significant MRM scores for all OSAHS levels, but the most significant MRM score was found for the entire sample, and for moderate OSAHS, which explained nearly one-third of the variance. Correlation coefficients (r^2) and the equations are presented in [table 4](#).

The objective assessment of nocturia presented also significant values for all OSAHS levels, but the most significant MRM was for moderate OSAHS, which explained nearly half of the variance. Correlation coefficients r^2 and equations are presented in [table 5](#) ([Fig. 1](#)).

Discussion

Main findings

We observed a progressive alteration of PSG variables in patients with nocturia as SBD severity level increased, as was expected from a review of medical literature.^{6,12,13} However, the main contribution of this study was to find MRM to predict subjective and objective nocturia that explain almost one-third and one-half of the variance, respectively.

Table 3. Sleep architecture in the four studied groups

Variable	Primary snoring	Mild OSAHS	Moderate OSAHS	Severe OSAHS	F/p
Total sleep time (min)	406.12 ± 60.53	405.60 ± 56.95	403.52 ± 62.46	391.83 ± 60.03	1.25/0.29
Awake time	15.74 ± 12.34	15.83 ± 11.72	15.96 ± 11.44	18.84 ± 12.98	1.51/0.21
Sleep efficiency index	84.19 ± 12.24	84.14 ± 11.41	83.85 ± 12.74	81.06 ± 11.87	1.54/0.20
Latency to stage N1 (min)	22.45 ± 20.41	20.32 ± 19.19	19.23 ± 18.41	13.40 ± 12.49	3.41/0.01*
Latency to REM stage (min)	128.61 ± 78.64	127.80 ± 68.61	126.91 ± 74.48	114.01 ± 76.18	0.86/0.46
% light sleep	62.31 ± 10.77	63.15 ± 11.74	63.17 ± 12.73	64.02 ± 11.77	0.35/0.78
% deep sleep	19.97 ± 8.88	19.09 ± 8.87	18.62 ± 10.85	16.72 ± 8.21	2.19/0.08
% REM sleep	20.11 ± 8.04	17.96 ± 5.43	17.68 ± 6.42	16.76 ± 5.76	4.74/0.03*
Apnea/hypopnea index	2.12 ± 1.52	10.06 ± 3.20	22.66 ± 9.11	81.60 ± 35.96	39.18/< 0.001*
Oxygen saturation	91.75 ± 3.73	91.34 ± 3.00	89.95 ± 5.40	86.95 ± 7.54	21.1/0.001*

The numbers in bold mean statistically significant differences.

*Statistically significant.

F: analysis of variance score; OSAHS: obstructive sleep apnea hypopnea syndrome; p: probability; REM: rapid eye movements; %: percentage.

Table 4. Models to predict subjective nocturia in all the sample, and in patients with different severity of SBD, after a forward linear multiple regression calculations explained in methods section

SBD classification	Subjective nocturia equations
All sample	$r = 0.54, r^2 = 0.29, F = 22.67, p < 0.001$ Nocturia = $5.036 + 0.021(\text{age}) + 0.003(\text{REM latency}) + 0.010(\text{awake HR}) - 0.016(\text{SWS HR}) - 0.053(\text{SO}_2 \text{ nREM}) + 0.009(\text{AHI}) + 0.625(\text{acid-peptic disease})$
Primary snoring	$r = 0.34, r^2 = 0.11, F = 6.44, p < 0.001$ Nocturia = $-0.004 + 0.479(\text{gender}) + 0.025(\text{awake \%})$
Mild OSAHS	$r = 0.48, r^2 = 0.23, F = 9.83, p < 0.001$ Nocturia = $-0.383 + 0.023(\text{age}) + 0.003(\text{REM latency}) + 1.021(\text{acid-peptic disease})$
Moderate OSAHS	$r = 0.52, r^2 = 0.27, F = 8.84, p \leq 0.001$ Nocturia = $9.05 + 0.005(\text{REM latency}) + 0.005(\text{arousals}) - 0.218(\text{SO}_2 \text{ nREM}) + 0.121(\text{SO}_2 \text{ TST})$
Severe OSAHS	$r = 0.27, r^2 = 0.07, F = 7.92, p = 0.006$ Nocturia = $1.329 + 0.013(\text{AHI})$

SBD: sleep breathing disorders; OSAHS: obstructive sleep apnea hypopnea syndrome; AHI: apnea/hypopnea index; nREM: no rapid eye movements sleep stage; HR: heart rate; REM: rapid eye movements stage; SO₂: oxygen saturation; SWS: slow waves sleep; TST: total sleep time; r: r de Pearson; F: ANOVA value; p: probability.

Clinical implications

Clinicians could benefit from these new tools because they will be able to predict the degree of nocturia in patients with SBD of different severity, from the PSG data, for a better diagnosis and therapeutic management, since predictive PSG factors for nocturia have not been well studied previously.

Table 5. Models to predict objective nocturia in all the sample, and in patients with different severity of SBD, after a forward linear multiple regression calculations explained in methods section

SBD classification	Objective nocturia equations
All sample	$r = 0.53, r^2 = 0.28, F = 16.66, p < 0.001$ Nocturia = $-3.016 + 0.006(\text{age}) + 0.053(\text{sleep efficiency index}) + 0.060(\text{awake \%}) - 0.001(\text{REM latency}) - 0.021(\text{REM \%}) + 0.014(\text{awake HR}) - 0.011(\text{HR SWS}) - 0.025(\text{REM SO}_2) + 0.005(\text{IAH})$
Primary snoring	$r = 0.47, r^2 = 0.22, F = 8.87, p < 0.001$ Nocturia = $0.009 + 0.018(\text{awake \%}) + 0.009(\text{awake HR}) - 0.009(\text{SWS HR})$
Mild OSAHS	$r = 0.27, r^2 = 0.07, F = 8.15, p = 0.005$ Nocturia = $-0.192 + 0.009(\text{age})$
Moderate OSAHS	$r = 0.70, r^2 = 0.49, F = 14.66, p < 0.001$ Nocturia = $-14.031 + 0.187(\text{sleep efficiency index}) + 0.209(\text{awake \%}) + 0.005(\text{arousals}) - 0.030(\text{SWS HR}) + 0.029(\text{awake HR}) - 0.059(\text{REM O}_2)$
Severe OSAHS	$r = 0.43, r^2 = 0.18, F = 10.85, p < 0.001$ Nocturia = $0.120 + 0.012(\text{awake HR}) - 0.019(\text{\%REM})$

SBD: sleep breathing disorders; OSAHS: obstructive sleep apnea hypopnea syndrome; AHI: apnea/hypopnea index; HR: heart rate; REM: rapid eye movements stage; SO₂: oxygen saturation; SWS: slow waves sleep; r: r de Pearson; F: ANOVA value; p: probability.

Explanations and comparison with other studies

Clinical predictive factors for nocturnal enuresis have been described previously. For example, Guilleminault

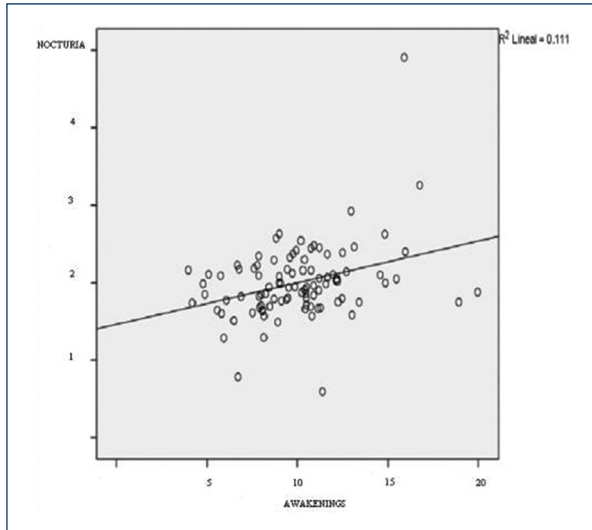


Figure 1. Typical scatterplot example showing significant correlation between averages of number of micturation (nocturia) and number of awakenings in patients with sleep breathing disorders of the study.

et al.¹⁴ found that nocturia in patients with OSAHS was related to a greater BMI and AHI in the PSG studies of elderly patients. Endeshaw et al.¹⁵ found also an increased number of voids as AHI increases in elderly adults, and Kaynak et al.¹⁶ proposed that the number of voids reflects OSAHS severity. Oztura et al.¹⁷ found significant correlations of age, BMI, hypertension, AHI, and respiratory effort index with nocturia, and Plywaczewski et al.,¹⁸ found similar results. These results are partially in line with our data, but the different methodologies used in the other studies mean that their results are not directly comparable to ours.

It was a surprising that our equations have higher prediction scores for modOSAHS than for sevOSAHS. This means that in patients with sevOSAHS, more variables participate to produce nocturia than in those with modOSAHS severity. For example, Hu et al.,¹⁹ also found that urodynamic changes in patients with nocturia were stronger in patients with modOSAHS than sevOSAHS.

Khang et al.,²⁰ found that nocturia frequency was significantly correlated with age and AHI in men < 65 years of age, and they found significant correlations between nocturia frequency and: age, AHI, Beck depression inventory and Pittsburgh sleep quality index scores. Multiple regression analysis showed that age

and benign prostatic hypertrophy were associated with nocturia, and that the presence of pathological nocturia was predicted by benign prostatic hypertrophy, age and AHI. On the other hand, in men aged > 65 years, nocturia frequency was significantly associated with Beck depression inventory and Pittsburgh sleep quality index score. However, the researchers found no relationship between nocturia frequency and OSAHS parameters.

Other authors who evaluated nocturia in patients with OSAHS found that BMI and systolic blood pressure were higher in patients with OSAHS than in a control group, and brain natriuretic peptide was also higher in patients with OSAHS than controls. In urinalysis, patients with OSAHS showed higher urinary sodium and creatinine, and higher urine osmolality than controls. However, there was no significant difference in urinary antidiuretic hormone between groups. These results indicated that patients with nocturnal polyuria and OSAHS did not compensate for the fluid imbalance presented with decreased secretion of antidiuretic hormone, but they did show increased brain natriuretic peptide level.²¹ We cannot compare our results with this report due to differences in the methods between studies.

Niimi et al.²² found no relationship between nocturnal polyuria and AHI or circadian change in extracellular fluid adjusted for body mass, while Finamore et al.²³ found that intermittent desaturations but not hypoxia length or severity (relative to TST) are associated with nocturia in subjects complaining of sleep respiratory disturbances. Chung et al.²⁴ found that hypoxia caused by OSAHS affects the incidence of nocturia, and that less desaturated patients with nocturia require complementary urological treatment for nocturia after OSAS correction. Miyauchi et al.²⁵ found an association of frequency and volume of nocturnal urination with AHI score, and prostate symptom score in young adults, but not in elderly adults. Their data suggest that OSAHS is a strong candidate factor for nocturia in young adults.

Labra et al.²⁶ compared two groups of male patients with OSAS and nocturia; the first group was treated with continuous positive airway pressure for 3 months, and the second group underwent surgical management. AHI and number of nocturia events were compared before and after treatment. Improvement of AHI and the number of nocturia events after treatment was significant. They found that AHI and the number of nocturia events were related to treatment, and the

presence of 4-5 events may be an indicator of severe OSAS and should always be clinically evaluated.

Other relevant point observed into the differential characteristics of the sample was the obesity. Although no differences in its frequency between groups were observed. It was present in significant fashion in more severe cases. The explanation is related to one study that reports results of a comparison of obese patients with sleep apnea with non-obese individuals: a bigger neck size, more prevalent hypertension, and more nocturia were present in obese patients with sleep apnea.²⁷ More research is need in future investigations to weight influence of obesity in nocturia in subjects with sleep apnea.

Proposed hypothesis

Several PSG variables are related to SBD and nocturia. Some of them are related to ageing and decreasing of water re-uptake by the nephron tubules, others factors are related to awakening and disruption of the sleep architecture, and urgency for bladder voiding, while still others are related to AHI, heart overburden, and over-production of natriuretic peptides as SBD increases in severity. Complexity of relationships in all variables needs to be discovered, as was evidenced by the equations proposed, and deserve more attention in future research.

Strengths and limitations of the study

There has been relatively little research on the topic, and thus, the findings of the study are promising. However, the r-square of the prediction equation is not high, thus the research must be continued. Moreover, the study design was cross-sectional; instead, a prospective study could have more predictive power. We did not measure other biochemical variables, such as antidiuretic hormone, brain natriuretic peptide and others that could increase the power of our MRE calculations. Functional imaging studies could be added in future research.

Conclusion

PSG variables were progressively altered in patients with nocturia as SBD level severity increase. We generated an MRM that predicts subjective and objective nocturia, which explains nearly almost one third and one-half of the total variance, respectively, which is a significant amount. These equations could benefit

clinicians in help them to predict the severity of nocturia based on PSG features in patients with SBD.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. Research committee of the institution reviewed and approved the protocol with number: UNAM.FM.076.2022.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

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

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ORIGINAL ARTICLE

Happy post-COVID-19 hypoxia

Annier J. Fajardo-Quesada^{1*}, Luis M. Abreu-Pereira², and Ilian E. Tarife-Romero²¹School of Medical Sciences of Bayamo, Universidad de Ciencias Médicas de Granma, Granma; ²Medical Degree Program, Facultad de Ciencias Médicas Mayabeque, Mayabeque. Cuba

Abstract

Introduction: Happy hypoxia, or hypoxemia with no or limited dyspnea, was a manifestation observed in patients with COVID-19 and raised interest due to its implications for outpatient follow-up and the safety of home use of pulse oximeters. **Objective:** The objective of the study was to describe the prevalence and clinical characteristics of hypoxemia and happy hypoxia in patients screened after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. **Material and methods:** A descriptive, retrospective study conducted in Matanzas in 2022. Oxygen saturations, heart rate, respiratory rate, and blood pressure were measured using a pulse oximeter in patients screened after SARS-CoV-2 infection; vaccination status, symptoms, and time since infection were recorded. **Results:** A total of 125 patients were analyzed; 68% were women; mean age 50.17 (SD 18.70). Mean saturation was 96.34% (SD 4.11); the prevalence of hypoxemia ($SpO_2 < 92\%$) was 6.4% (8 patients); and severe hypoxia was 5.6% (7 patients). Descriptive tables and figures are presented for vaccination and symptom distribution. **Conclusions:** Severe hypoxia had a low prevalence in this post-COVID cohort in Matanzas; however, outpatient detection depends on the availability and accuracy of the oximeter and clinical follow-up. These findings support the vigilant use of home oximetry integrated into clinical evaluation.

Keywords: COVID-19. Severe acute respiratory syndrome coronavirus 2. Oximetry. Asymptomatic. Hypoxia.

Introduction

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presented an unusual clinical challenge, as patients were observed to have significant hypoxemia but little or no perception of dyspnea – a phenomenon known as “happy hypoxia” or “silent hypoxemia.” This finding puzzled the medical community, as the expected correlation between decreased oxygen saturation and respiratory distress was not observed in a considerable number of cases, leading to a reevaluation of the respiratory pathophysiology in the context of COVID-19.¹

Happy hypoxia raised clinical and public health concerns because patients could remain apparently stable while developing severe hypoxemia, delaying the

pursuit of timely medical care and increasing the risk of sudden deterioration. In response, pulse oximetry was promoted as an essential tool for home monitoring and in primary care. Recent studies have confirmed its usefulness, although they have also highlighted limitations such as variability in the accuracy of readings and the need to combine its use with an appropriate clinical assessment.²

In this context, technological inequalities have been significant. Research has shown biases in the measurement of oxygen saturation in populations with darker skin tones, which can lead to delays in the diagnosis of hypoxemia among vulnerable groups. This problem has been highlighted by systematic reviews and international regulatory bodies, which call for more accurate and equitable devices.^{3,4} Therefore, the

*Correspondence:

Annier J. Fajardo-Quesada

E-mail: annierfq01@gmail.com

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interpretation of SpO₂ readings requires a critical and contextualized approach.

Various pathophysiological mechanisms have been proposed to explain happy hypoxia, including alterations in the central regulation of dyspnea, ventilation-perfusion mismatches, and hemodynamic phenomena linked to microthrombosis or changes in hemoglobin's affinity for oxygen. Recently, computational models and clinical studies have proposed new hypotheses regarding the dissociation between hypoxemia and symptomatic perception, although a definitive consensus has not yet been reached.^{5,6}

Despite advances in the global understanding of this phenomenon, there is a lack of local research characterizing the prevalence and specific characteristics of happy hypoxia in different populations. In regions such as Matanzas, where the public health response to COVID-19 included community screening and post-infection follow-up strategies, it is important to generate empirical evidence. Therefore, this study aimed to describe the prevalence and clinical characteristics of hypoxemia and happy hypoxia in patients evaluated following COVID-19 infection in 2022.

Material and methods

A descriptive, prospective observational study was conducted in Matanzas, Cuba, between March and August 2022.

Population: Adult patients (≥ 18 years) followed up after COVID-19 illness (confirmed by polymerase chain reaction or antigen test according to clinical records). Patients in critical condition in the hospital at the time of sampling and those without informed consent were excluded.

Patients were recruited through local clinics and post-infection surveillance programs; convenience sampling stratified by age and sex was used to achieve a final sample of 125 participants (a number determined by logistical considerations and availability). Each participant was measured for:

- Oxygen saturation (SpO₂) measured with a validated clinical/commercial pulse oximeter; reading taken at rest with the patient seated under standard conditions.
- Heart rate (beats per minute) recorded by the same oximeter.
- Respiratory rate (breaths per minute) measured by observation over 60 s.
- Blood pressure (systolic and diastolic) measured with a calibrated manual sphygmomanometer.

- Record of symptoms (cough, dysphagia, tachycardia, dyspnea, etc.) and vaccination status (number of doses, schedule).
- Time elapsed since discharge from the hospital due to COVID-19.
- Medical history.

Operational definitions

Hypoxemia: SpO₂ < 92%. (criterion used in the study).

Happy hypoxia: presence of hypoxemia (SpO₂ < 92%) without severe respiratory symptoms (e.g., severe dyspnea, use of accessory muscles) on clinical evaluation.

The equipment was checked daily, and staff were trained in standardized measurement techniques. Conditions that could affect readings (use of nail polish, peripheral perfusion, limb temperature) were recorded, and the measurement was repeated if there was any doubt.

Descriptive statistics were calculated: means and standard deviations for normally distributed continuous variables; interquartile range and min-max; frequencies and proportions for categorical variables. Descriptive statistics tables and graphs (bar charts, histograms, and box plots) were created to illustrate the distribution of vaccination status and symptoms. A $p < 0.05$ was considered statistically significant for exploratory comparisons.^{1,2}

The study was approved by the local institutional ethics committee, and participants provided written informed consent. Data were handled confidentially.

Results

As shown in [table 1](#), a total of 125 patients were analyzed, the majority of whom were women (68%). The average age of the participants was 50.17 years, with a standard deviation of 18.70, ranging from 18 to 91 years. The average oxygen saturation was 96.34% (SD = 4.11), the mean heart rate was 75.94 bpm (SD = 12.73), the respiratory rate was 18.96 bpm (SD = 3.35), systolic blood pressure was 124.54 mmHg (SD = 19.48), and diastolic blood pressure was 77.36 mmHg (SD = 10.79). The mean time elapsed since symptom onset was 14.57 days (SD = 3.75).

About 54.4% of the patients had received at least one dose of a COVID-19 vaccine, while 45.6% had not received any. The most common vaccination regimens were regimen EN (55 patients) and regimen A (49 patients), as shown in [figure 1](#).

Table 1. General data on the measured variables

Variables	Age	HR	RR	OS	SBP	DBP	Elapsed time (days)
Quantity	125	125	125	125	125	125	125
Media	50.168	75.936	18.96	96.336	124.536	77.36	14.568
SD	18.69653	12.73346	3.351456	4.105354	19.48388	10.78709	3.753141
Min.	18	19	10	60	90	50	4
25%	35	68	16	96	110	70	13
50%	52	75	20	97	120	80	15
75%	64	85	20	98	138	90	16
Max.	91	118	30	99	200	100	30

SD: standard deviation; HR: heart rate; RR: respiratory rate; OS: oxygen saturation; SBP: systolic blood pressure; DBP: diastolic blood pressure.

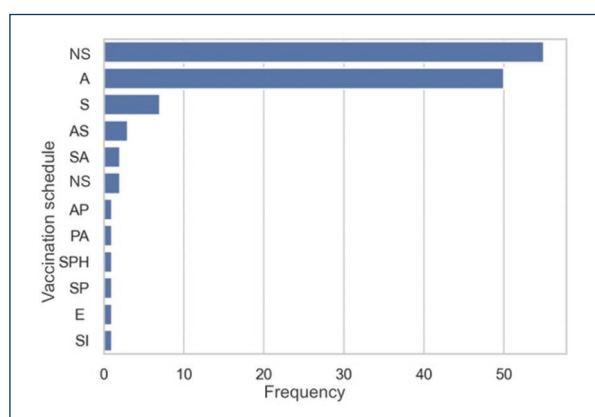


Figure 1. Distribution of vaccination schedules. NS: null schema; A: Abdala; S: Soberana 02; AS: Abdala-Soberana 02; SA: Soberana 02-Soberana Plus; AP: Abdala-Soberana Plus; PA: Pfizer-Abdala; SPH: Soberana Plus-Heberbiovac HB; SP: Soberana plus; E: EpiVacCorona; SI: Sinovac.

Regarding symptoms, cough was the most prevalent, affecting 61 patients, followed by dysphagia (50 patients) and tachycardia (49 patients), as shown in figure 2.

The prevalence of hypoxemia (oxygen saturation < 92%) was 6.4%, as shown in figure 3, corresponding to 8 patients. The prevalence of happy hypoxia (hypoxemia without severe respiratory symptoms) was 5.6%, affecting seven patients. Patients with hypoxemia had a mean oxygen saturation of 85.75%, which is considerably lower than that of the group without hypoxemia (97.06%). Patients with happy hypoxia had a mean oxygen saturation of 86.86%, a respiratory rate of 19.86 breaths/min, and a heart rate of 75.86 beats/min.

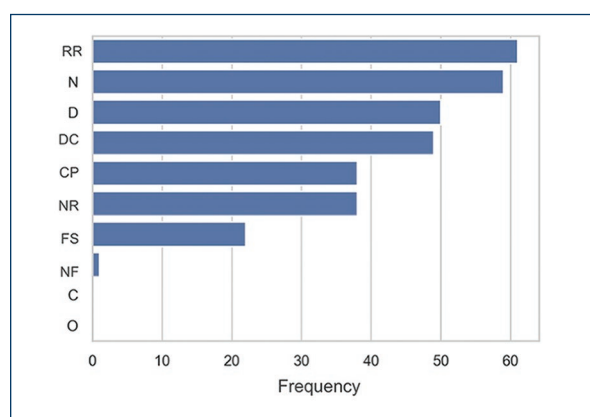


Figure 2. Distribution of respiratory symptoms. RR: respiratory rate; N: none; D: dyspnea; DC: dry cough; CP: chest pain; NR: not reported; FS: feeling of suffocation; NF: nasal flaring; C: cyanosis; O: others.

In patients with happy hypoxia, three underlying conditions were identified: hypertension (HTN), diabetes mellitus (DM), and bronchial asthma (BA), with HTN being the most common, accounting for 71.42% of cases, as shown in table 2.

Discussion

This study identified a prevalence of hypoxemia of 6.4% and of happy hypoxia of 5.6%, figures that are consistent with previous reports in outpatient and inpatient cohorts, where the proportion of cases ranges from 5% to 15% depending on the definition used and the timing of the evaluation. These findings support the notion that happy hypoxia is not an anecdotal

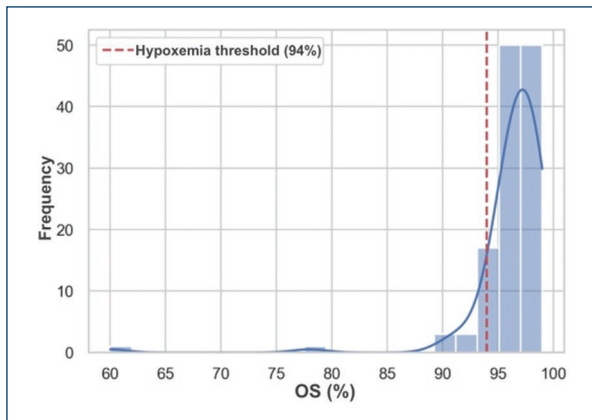


Figure 3. Distribution of oxygen saturation. OS: oxygen saturation.

Table 2. Distribución de las patologías de base presentes en los pacientes con hipoxia feliz

Pathology	Quantity	%
HTA	5	71.42
DBT	2	28.57
AB	1	14.28
No apparent pathology	1	14.28

HTA: hypertension; DBT: diabetes mellitus; BA: bronchial asthma.

phenomenon, but rather a relatively common manifestation in post-COVID patients that requires ongoing clinical attention.¹

The difference of nearly 11 percentage points in mean oxygen saturation between patients with and without hypoxemia reflects the ability of pulse oximetry to distinguish between risk subgroups. However, the identification of patients with low saturation levels but no clinical dyspnea highlights the importance of not basing assessment exclusively on subjective symptoms. This confirms observations that dyspnea is not always a reliable marker of hypoxemia in the context of COVID-19, and that the systematic use of pulse oximeters could prevent adverse outcomes.²

Experience gained during the pandemic has shown that home monitoring with pulse oximeters contributes to the early detection of clinical deterioration. Recent studies suggest that the use of these devices reduces delayed visits to emergency departments and facilitates early referral to higher levels of care. However, their effectiveness depends on patient adherence and

education on how to properly interpret the readings; therefore, monitoring programs must include educational and support components.⁶

A critical point reinforced by this study is the need to recognize the technical limitations of pulse oximeters. Recent research has indicated that these devices tend to overestimate oxygen saturation in people with darker skin, which can lead to diagnostic delays. This discrepancy in accuracy was confirmed by a systematic review and meta-analysis published in 2024 and has prompted recommendations from regulatory agencies such as the FDA to improve the accuracy of these devices.^{3,4} Consequently, the results of this study should be interpreted with these potential biases in mind.

Regarding pathophysiological mechanisms, the findings are consistent with current hypotheses suggesting a decoupling between hypoxemia and the patient's ventilatory response. Recent mathematical models suggest that an alteration in the respiratory control loops could explain the absence of dyspnea despite low oxygen levels.⁵ This interpretation is consistent with the observation that the mean respiratory rate of patients with happy hypoxia did not increase proportionally to the decrease in SpO₂, which provides empirical support for these theories.

The vaccination status observed in the sample – with just over half of the patients vaccinated – reflects the local epidemiological context in 2022 and suggests a potential modifier of the risk of developing hypoxemia. Although this study did not aim to establish causal associations, it is worth considering that vaccine protection could modulate both clinical severity and the prevalence of atypical manifestations such as happy hypoxia. Future analytical studies could explore this relationship in greater detail.

The finding that HTN is the most common condition (71.42%) in patients with “happy hypoxia” is partially at odds with the current literature on hypoxemia. Although HTN is a common comorbidity and can affect pulmonary vascular function, it is not classified among the primary causes of acute or chronic hypoxemia. The literature indicates that the conditions most commonly associated with hypoxemic respiratory failure are pulmonary diseases such as pneumonia, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), and asthma.⁷

One plausible explanation for this discrepancy is that the term “happy hypoxia” or “silent hypoxemia” gained clinical prominence during the COVID-19 pandemic, where it was observed in patients who, despite having very low arterial oxygenation, did not exhibit the

expected proportional dyspnea. In this context, HTN, diabetes mellitus (DM), and asthma are precisely the risk comorbidities frequently reported in patients with severe COVID-19. Therefore, the high prevalence of HTN may not reflect its role as a direct cause of hypoxemia, but rather its prevalence as a risk factor in the population of patients who developed COVID-19 and exhibited this paradoxical phenomenon. The pathophysiological hypothesis suggests that “happy hypoxia” in COVID-19 may be due to an initial impairment of hypoxia-sensing mechanisms rather than of pulmonary gas exchange.

This study has limitations that must be acknowledged. Convenience sampling may have introduced selection bias, and the sample size limits the precision of estimates for low prevalences. Furthermore, reliance on commercially available clinical oximeters entails an inherent margin of error, which, although controlled through standardization, cannot be completely eliminated. Nevertheless, the strength of this study lies in the fact that it is one of the first local studies to characterize post-COVID happy hypoxia, providing relevant evidence for clinical practice in Matanzas and offering a foundation for subsequent, more extensive research.

Conclusions

A prevalence of hypoxemia of 6.4% and “happy hypoxia” of 5.6% was identified in patients evaluated following COVID-19 infection, confirming that the absence of dyspnea does not rule out the presence of dangerously low oxygen saturation levels. Pulse oximetry proved to be a valuable tool for early detection, although its technical limitations and reported biases require that it be interpreted with caution and always integrated into the clinical assessment. The findings underscore the need for home monitoring protocols that include health education, clear alarm criteria, and more accurate devices, while also paving the way for longitudinal and multicenter studies that will allow for a better understanding of the pathophysiology and clinical impact of happy hypoxia in different population settings.

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Conflicts of interest

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Ethical considerations

Protection of human subjects and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution’s confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that they used ChatGPT was used to review the manuscript’s wording.

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REVIEW ARTICLE

Morphology in the diagnosis of multiple myeloma: past, present, and future

Christian O. Ramos-Peñafiel¹, Carlos Martínez-Murillo¹, Juan F. Zazueta-Pozos¹, Juan J. Navarrete-Pérez², and Adán G. Gallardo-Rodríguez^{3*}

¹Department of Hematology; ²Department of Anatomic Pathology, Hospital General de México Dr. Eduardo Liceaga, Secretaría de Salud, Mexico City; ³School of Sport Sciences, Universidad Anahuac México, Huixquilucan, State of Mexico. Mexico

Abstract

Multiple myeloma (MM) is a heterogeneous plasma cell neoplasm characterized by the overproduction of monoclonal immunoglobulins and disruption of normal hematopoiesis. Although the advent of modern diagnostic tools has transformed disease monitoring, cellular morphology continues to play a pivotal role in both initial recognition and complementary evaluation. Historically, abnormal plasma cell morphology was the cornerstone of diagnosis, with variants such as flame cells, Mott cells, Russell and Dutcher bodies providing important but sometimes subtle diagnostic clues. Bone marrow biopsies and immunohistochemistry remain essential for assessing the cellular microenvironment, establishing clonality through light chain restriction, and classifying disease extent. Flow cytometry (FC) has become a highly sensitive method to differentiate normal from clonal plasma cells, monitor measurable residual disease, and detect circulating tumor cells in peripheral blood, which may identify high-risk subgroups. Its reproducibility and rapid turnaround make it indispensable in current clinical practice, although challenges to standardization remain. Complementary molecular techniques and cytogenetic profiling further enhance risk stratification and therapeutic decision-making. Recently, artificial intelligence (AI) has emerged as an innovative tool capable of improving diagnostic accuracy, analyzing bone marrow smears with deep learning algorithms, and integrating clinical, genomic, and imaging data into advanced prognostic models. AI-based systems hold promise for reducing diagnostic times, minimizing observer variability, and increasing access to specialized evaluations through telemedicine. While technological advances have expanded the diagnostic armamentarium for MM, morphology remains a fundamental and irreplaceable element. Its integration with FC, immunohistochemistry, molecular tools, and emerging AI-based platforms defines a more comprehensive approach, ensuring accurate diagnosis, optimized monitoring, and personalized patient care.

Keywords: Multiple myeloma. Plasma cells. Flow cytometry. Immunohistochemistry. Bone marrow.

Introduction

Multiple Myeloma (MM) is a plasma cell neoplasm characterized by the excessive production of a monoclonal protein known as the M component. This disease often originates from a premalignant stage called Monoclonal Gammopathy of Undetermined Significance (MGUS) and accounts for approximately 10% of all hematologic malignancies. Plasma cells (PC) derive

from B lymphocytes after their passage through the germinal center and, upon infiltrating the bone marrow, may lead to various pathologies, including MGUS, asymptomatic MM, and plasma cell leukemia.

The first documented cases of this disease date back to the 19th century. In 1844, Samuel Solly described the case of Sarah Newbury, a 39-year-old woman who experienced pain and fatigue due to multiple bone fractures.

*Correspondence:

Adán G. Gallardo-Rodríguez

E-mail: nutriologo.agallardo8@gmail.com

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Subsequently, in 1845, Henry Bence Jones identified an abnormal protein in the urine of Thomas Alexander McBean, a 45-year-old merchant, which is now recognized as light chains (kappa or lambda), highlighting its diagnostic relevance. In 1889, Otto Kahler reported a clinical case of MM, and in his honor, the disease is also known as “Kahler’s disease.” The term “plasma cell” was coined in 1875 by Heinrich Wilhelm Gottfried von Waldeyer-Hartz, while, in 1895, Marschalko provided the most detailed description of the PC characteristic of MM.^{1,2}

The term MM was introduced in 1873 by Johann von Rustizky, who reported a case of a patient with multiple lytic bone lesions and abnormal marrow cells, later recognized as PC. In 1895, Marschalko established the morphological criteria to describe a normal plasma cell: round or oval shape, basophilic cytoplasm, a clear perinuclear halo, eccentric nucleus, and clumped chromatin.³ Although the existence of these cells was known, their functional role remained uncertain until the mid-20th century, when Astrid Fagraeus (1948) demonstrated that PC were responsible for antibody production, confirming their central role in immunoglobulin synthesis.

The main feature of MM is the expansion of PC, which, in some cases, displaces normal hematopoiesis. These cells range in size from 15 μm to 30 μm and display variable morphology, from normal PC to unusual forms. They are generally classified into four variants: mature, immature, pleomorphic, and plasmablastic. Despite morphological differences, these variants share common features such as an eccentric nucleus with a “cartwheel” chromatin pattern, high nucleus-to-cytoplasm ratio, and, in the case of plasmablasts, prominent nucleoli.^{3,4}

At present, multiple strategies are available to identify malignant PC and determine the clonality associated with malignancy. While morphology remains useful, it is insufficient to identify clonality accurately. Methods such as immunohistochemistry and, more recently, flow cytometry (FC) have proven essential tools for this purpose.

A summary of the different strategies focusing on plasma cell characteristics is described in [figure 1](#).

Methodology

Search strategy for study selection

On March 18, 2024, a comprehensive systematic historical literature search was conducted to identify retrospective and prospective studies using the PubMed, Cochrane, and EMBASE databases. The search spanned from the 1940s to the present day (2024), aiming to

provide a longitudinal perspective on the evolution of diagnostic and monitoring strategies for MM. The population of interest (P) included patients diagnosed with MM, as well as those with monoclonal gammopathies, to explore historical advancements in disease diagnosis and management. The intervention (I) focused on various diagnostic tools and techniques, including morphology, FC, artificial intelligence (AI), and other emerging methodologies. Given the historical scope of the review, no direct comparison (C) was established. Instead, the study aimed to synthesize developments across time. The primary outcome (O) was the identification and critical analysis of advancements in diagnostic and monitoring methods and their efficacy in the context of MM.

The search utilized carefully selected keywords and Boolean operators: morphology AND MM; FC AND MM; diagnosis AND MM; AI AND MM. These terms ensured comprehensive coverage of relevant studies across different eras of clinical practice. A total of 50 studies were included, encompassing historical reviews, case series, and prospective analyses that applied various diagnostic techniques to MM patients. Each article was independently reviewed by two authors. Discrepancies in study selection or data extraction were resolved through discussion and consensus, ensuring methodological rigor and minimizing selection bias.

In addition to database searches, secondary sources, such as reference lists of included articles, were screened to identify additional relevant studies. Efforts were made to include a wide range of geographical and clinical settings to enhance the generalizability of findings. A PRISMA flow diagram ([Fig. 2](#)) summarizes the selection process.

Eligibility criteria

Inclusion criteria for this review were designed to capture a wide range of studies relevant to the topic. Eligible studies met the following conditions: (1) historical reviews, case series, or contemporary reviews addressing diagnostic strategies; (2) inclusion of patients with confirmed MM; (3) use of one or more diagnostic tools or techniques relevant to MM; (4) studies focusing on adult populations; (5) follow-up and monitoring linked to clinical outcomes; and (6) publications available in English or Spanish.

Exclusion criteria were applied to maintain focus on the primary research question. Studies were excluded if they met any of the following conditions: (1) inclusion of patients with monoclonal gammopathies other than MM; (2) studies involving vulnerable or disabled

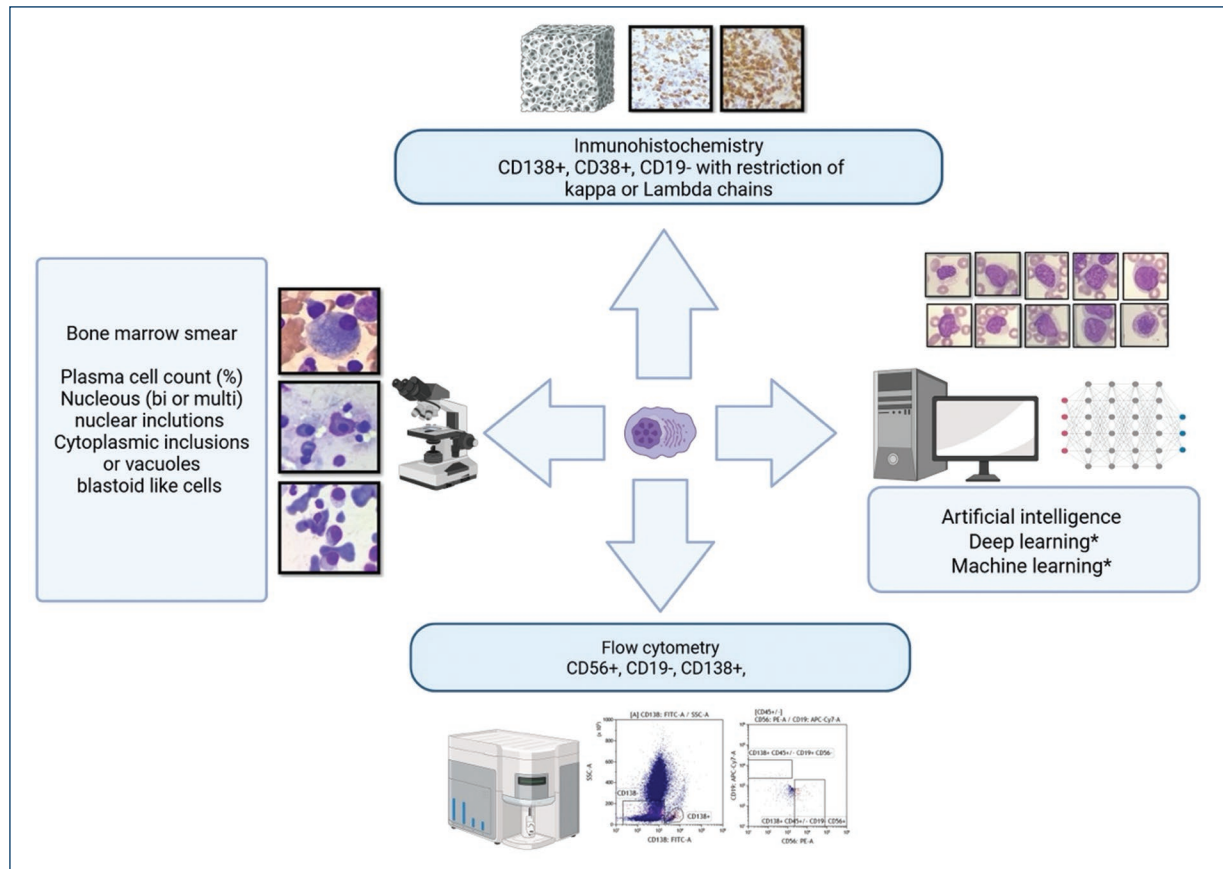


Figure 1. Schematic representation of the different strategies focused on plasma cell characteristics. *This figure was created by the authors for illustrative purposes.*

populations without explicit ethical considerations; (3) absence of a clear description of diagnostic tools or techniques employed.

All abstracts and full texts were rigorously assessed for eligibility by two independent reviewers. When disagreements arose, they were discussed and resolved by consensus. The inclusion process ensured a robust and unbiased selection of studies, with emphasis on methodological quality and relevance to the objectives of this review.

Ethical responsibilities

This article is a narrative review based on previously published literature. No experiments were conducted on humans or animals by the authors for this study. Therefore, approval from an institutional ethics committee was not required. The authors confirm that all referenced studies were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Results

Past: abnormal versus normal morphology PC, the quest for clonality

MM is currently considered a heterogeneous and multiclonal disease due to the combination of various cytogenetic alterations, particularly those involving translocations of chromosome 14, and the involvement of multiple transcription factors and signaling pathways that promote cell survival.⁵ Plasma cell infiltration varies widely, being minimal in premalignant conditions such as MGUS. For MM diagnosis, the identification of abnormal PC through bone marrow smears or histopathological studies is essential. Diagnosis is confirmed with the presence of more than 10% clonal PC in the bone marrow accompanied by at least one myeloma-defining event (anemia, renal impairment, hypercalcemia, or lytic lesions) or clonal plasmacytosis exceeding 60%.⁶

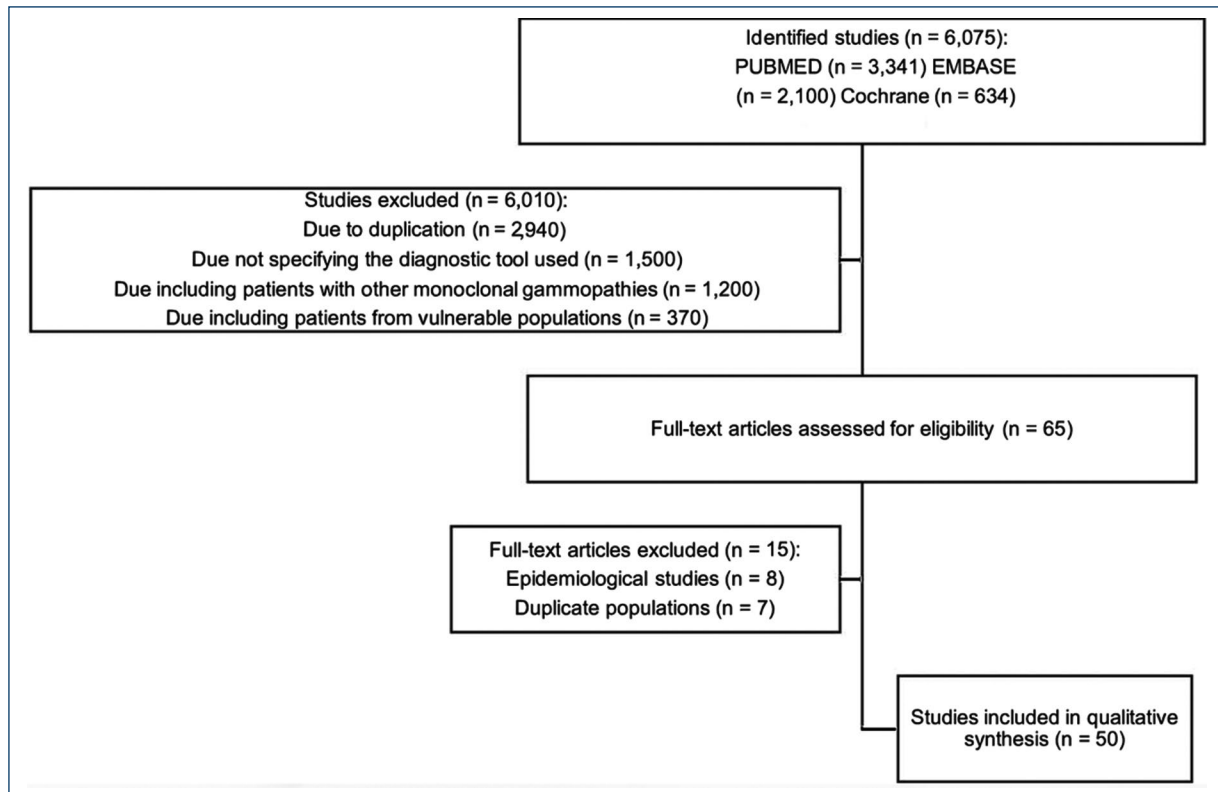


Figure 2. Flow diagram of the literature search and study selection process. *This figure was created by the authors and is based on aggregated bibliographic data.*

Clonality detection can be performed using FC or molecular techniques such as next-generation sequencing. Malignant PC exhibit a unique expression pattern characterized by markers CD38, CD138, and CD45, with profiles indicative of malignancy, such as CD45-negative, CD19-negative, and CD56-positive. In addition, an altered kappa/lambda light chain ratio (< 0.5 or > 4.0) indicates clonality. Molecular techniques also allow for the detection of mutations associated with key pathways, such as MAP-kinase/ERK, NF- κ B, and mTOR, as well as alterations in transcription factors (EGR1, MAF, and MAFB), DNA repair genes (TP53, ATM, and BRCA), and epigenetic regulation (TET2, IDH1, IDH2, and DNMT3A).⁷⁻⁹

In addition to morphological and immunophenotypic evaluation, cytogenetic and molecular studies, particularly fluorescence *in situ* hybridization, play a relevant role in the comprehensive assessment of MM. These techniques allow the identification of genetic alterations with prognostic and therapeutic implications, contributing to improved risk stratification and a better understanding of the biological heterogeneity of the disease. In this context, genetic analysis is integrated as a complementary tool to classical diagnostic methods.

Basic morphology analysis of myeloma PC

MM is a complex disease requiring a thorough analysis of bone marrow cellularity, distribution of normal and malignant cells, and their specific morphological characteristics. Malignant PC in MM are distinguished by their pleomorphism, which includes prominent nuclei, nuclear polymorphism, and, in some cases, multinucleation. These features have been associated with advanced disease stages and unfavorable prognosis. Studies, such as that by Seili-Bekafigo et al., have demonstrated that greater cellular atypia correlates with shorter survival and advanced stages according to the International Staging System (ISS).^{10,11}

Historically, morphological evaluation has been central to the diagnosis and prognosis of MM. In 1947, Bayrd classified PC as differentiated, intermediate, or poorly differentiated, associating an unfavorable prognosis with the presence of more than 50% PC in the bone marrow.¹² Subsequent classifications, such as those by Greipp et al., have provided further details regarding cellular maturity and its prognostic relevance, with plasmablasts being a distinct form associated with

worse clinical outcomes. These cells are characterized by reticular chromatin, prominent nucleoli ($> 2 \mu\text{m}$), and a clear perinuclear cytoplasm, with large nuclei ($> 10 \mu\text{m}$).^{13,14}

From a cytological perspective, PC in MM typically exhibit abundant, basophilic cytoplasm with a clear perinuclear zone corresponding to the Golgi apparatus. Some distinctive abnormalities include flame cells, characterized by reddish-purple cytoplasm due to the overproduction of IgA.¹⁵ In addition, intracellular inclusions such as Russell bodies and intranuclear inclusions (Dutcher bodies) are frequently observed. Russell bodies, first described by William Russell in 1890, are cytoplasmic accumulations of immunoglobulins, while Dutcher bodies, identified by Dutcher and Fahey, are PAS-positive intranuclear inclusions.^{16,17}

Other less common morphological forms include Mott cells, characterized by multiple cytoplasmic inclusions giving them a “grape” or “morula” appearance. Crystal-line inclusions in rod-like forms, like Auer rods, have also been described and are derived from the overproduction of light chains (kappa or lambda), first observed in 1976.^{18,19} In addition, pseudo-Gaucher cells, which mimic histiocytosis, may be found in MM, although they are more frequently observed in other hematologic disorders such as leukemias and lymphomas. The presence of these cells necessitates the exclusion of histiocytic reactions or metabolic diseases.²⁰

Usefulness of bone marrow biopsy for the diagnosis of MM

Bone marrow biopsy is a key tool for the diagnosis and classification of MM, enabling precise differentiation between MGUS, asymptomatic myeloma, and symptomatic myeloma, particularly in patients with defining events such as anemia, renal dysfunction, or lytic lesions.²¹ Histological sections reveal trabecular bone with increased cellularity due to a diffuse plasma cell infiltrate. Plasma cell morphology can be described as mature, plasmablastic, or pleomorphic.^{22,23}

Bone trabeculae frequently show thinning or osteolytic areas with irregular, punched-out margins. Osteoblastic hyperplasia may also be observed, indicating bone regeneration. In the stroma, plasma cell infiltration may be associated with reticulin deposits, the severity of which is classified using immunohistochemistry into Grades I, II, and III. These findings are corroborated with immunohistochemical markers such as CD138, CD38, and CD79A, as well as additional markers like CD30 and MUM1, reflecting an activated

lymphoid microenvironment. Malignant PC also aberrantly express CD56 and cyclin D1, with a variable proliferation index assessed using Ki67.²⁴

Solid tumoral form (plasmacytoma)

Plasmacytomas are tumors derived from PC that localize outside the bone marrow, classified as extramedullary. They can consist of mature or immature PC, typically exhibiting a diffuse distribution. Immunohistochemically, they share similar markers with those observed in the bone marrow, including adhesion molecules such as CD166.²⁵ Extramedullary localization is variable, primarily affecting the airway and gastrointestinal tract. However, cases have also been reported in less common sites such as the orbits, lymph nodes, testes, and even the central nervous system.^{26,27}

Present: relevance of FC in diagnosis and monitoring

The initial evaluation of bone marrow in patients with monoclonal gammopathies should include FC to distinguish between normal and clonal PC. Since its introduction in 2002, FC has become a standard method not only for diagnosis but also for assessing complete response, risk stratification, and monitoring measurable residual disease (MRD) in MM (MM).^{28,29} Unlike B-cell lymphoproliferative disorders, where light chain restriction is typically sufficient to determine clonality, detecting aberrant immunophenotypic profiles is crucial in MM. Normal PCs are characterized by positive expressions of CD38, CD138, CD19, and CD45, while being negative for CD20 and CD56. In addition, they exhibit polyclonal light chains in the cytoplasm and express CD27 and CD81 but predominantly lack CD117, CD28, CD52, and CD200. However, minor subsets of normal PCs may display atypical expressions, complicating the detection of clonal and aberrant populations, especially in the context of MRD.²⁹⁻³¹

In MM, markers such as CD56 and CD117 are frequently positive in malignant PC and negative in normal PC, whereas CD19 and CD45 exhibit the opposite pattern. These markers allow for the distinction between normal and malignant PC and provide critical information for diagnosis, risk stratification, and prognosis prediction.²⁹⁻³¹ For MRD monitoring, multiparametric FC can detect one abnormal cell among 10^5 to 10^6 normal cells, making it a highly sensitive technique. However, it presents limitations, such as variability in available antibodies and the potential for false negatives in cases

Table 1. Characteristics and timing of application of different diagnostic techniques for MM

Tool	Characteristics	Timing of application
Bone marrow smear. ^{3,4,15-20}	Depends on bone marrow cellularity Eccentric nucleus Bi- or trinucleated cells Variable nucleolus Vacuoles or intracytoplasmic inclusions Irregular cytoplasm in shape and color Minimal or massive infiltration	At diagnosis
Bone marrow biopsy and immunohistochemistry. ²⁴⁻²⁷	Determines cellularity and distribution of other cell compartments. Establishes clonality by light chain restriction. Application of different markers (CD138, CD38)	At diagnosis
Flow cytometry. ^{29,32}	Identification of clonality Real-time use of different fluorochromes. Cost-effective and rapid result. Reproducible outcome. Use of different markers (CD38+, CD138+++, CD19–, CD56+, CD117 –/+) to distinguish normal plasma cells from MM cells. Identifiable in bone marrow and peripheral blood.	At diagnosis Response monitoring (Measurable residual disease) Relapse Presence of circulating peripheral tumor cells
AI. ^{43,49,50}	Discerns the proportion of plasma cells in numerous images. Possibility of applying telemedicine and reducing diagnostic time.	At diagnosis

MM: multiple myeloma; AI: artificial intelligence.

with low marker expression. Despite these challenges, FC remains a valuable tool for MRD evaluation in MM, and improving its standardization and clinical validation is essential to optimize its accuracy.³²⁻³⁵

In cases where bone marrow sampling is difficult due to hypocellularity, the detection of PC in peripheral blood using FC can serve as an alternative. Similar to the concept of circulating tumor cells in solid tumors, the presence of more than 5% PCs in peripheral blood,³⁶ as described by Granell et al.,³⁷ is associated with reduced survival (relative risk 4.9; 95% confidence interval: 2.6-9.3). Detecting these cells in peripheral blood is also useful for identifying high-risk subgroups, such as patients with adverse cytogenetics, using a cutoff of 0.02%.^{37,38}

Recently, the detection of PCs in peripheral blood through FC has been combined with advanced imaging techniques, such as positron emission tomography (PET), integrating into new prognostic models. These strategies complement traditional models and expand the tools available for monitoring and managing the disease at all stages, from MGUS to symptomatic MM.^{39,40} Although these techniques have yet to be routinely implemented in clinical practice, they represent a significant advance in the personalization of MM treatment.

The future: benefits of AI

AI-based tools have significantly impacted various fields, including medicine, where they are used to solve

complex problems and improve evidence-based decision-making.^{41,42} AI employs various algorithms, with machine learning (ML) and deep learning (DL) being the most prominent. ML can be classified into three main approaches: supervised learning (SL), unsupervised learning (UL), and reinforcement learning (RL), each tailored to different types of problems and datasets.^{41,42}

In the field of hematology, AI-based models have demonstrated their utility in improving diagnostics and developing advanced prognostic models.⁴³ Although automated blood cell counts have been a standard for decades, they have limitations, particularly in identifying nucleated cells. AI-based systems overcome these issues using image libraries that enable precise differentiation between malignant and non-malignant cells.^{43,44} In addition, advanced models now analyze bone marrow smears, utilizing parameters such as cell size, distribution, and staining patterns, learning through deep neural networks.^{45,46} This approach, known as next-generation cytomorphology or Deep Heme, has achieved exceptional accuracy levels, with an area under the curve of 0.99, supporting its future integration into routine clinical practice.^{47,48}

In the context of MM, AI has primarily been used to optimize diagnosis, accelerate the interpretation of biochemical profiles, and improve the assessment of imaging studies, such as PET/CT, through radiomics techniques. These tools enable the extraction of quantitative imaging features that can correlate with the biological behavior of the disease. Furthermore, AI has

facilitated the development of innovative prognostic models that combine gene expression data with validated clinical factors, such as age, gender, and the ISS, providing a more accurate and personalized risk assessment.^{49,50} Table 1 summarizes all the concepts encompassed in the diagnosis of MM based on morphology and surface receptors.

Conclusion

Despite advancements in the understanding and management of MM, delays in diagnosis remain a significant challenge. Although modern and highly precise tools such as FC and next-generation sequencing are available, cellular morphology continues to be a cornerstone of initial diagnosis. Unlike other hematologic neoplasms, MM exhibits remarkable cellular diversity, with unusual morphological forms that, while academically intriguing, have limited clinical relevance in certain cases. Nevertheless, morphology remains a crucial complement to advanced techniques, particularly in resource-limited settings.

With the incorporation of AI-based tools, new opportunities emerge to transform the way MM is diagnosed, monitored, and managed. These technologies not only enhance diagnostic accuracy but also optimize disease monitoring and personalize prognostic models by integrating clinical, genetic, and imaging data. The future of MM management will depend on the ability to combine these innovative tools with traditional methods, ensuring that patients benefit from comprehensive, evidence-based care regardless of available resources.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

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The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

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

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CLINICAL CASE

Diagnosis and management of postural orthostatic tachycardia syndrome: an autonomic simplified assessment in Mexican style

Daniel Rebolledo-García

Clinical Research Laboratory for Autonomic Nervous System and Movement Disorders, Department of Neurology, Hospital General Dra. Matilde Petra Montoya Lafragua Tláhuac, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City, Mexico

Abstract

We present the case of an 18-year-old female patient from Tabasco, Mexico, who was diagnosed with postural orthostatic tachycardia syndrome (POTS) during a telemedicine consultation. The patient reported chronic symptoms of dizziness, tachycardia, and fatigue on standing, which improved markedly with intravenous (IV) saline infusions administered by a physician in Villahermosa. This case highlights the utility of IV saline infusions for symptomatic management in POTS, supported by evidence showing a 79-93% improvement in symptoms such as tachycardia and dizziness. In addition, we propose a modified prolonged orthostatic evaluation (15 min supine, 25 min standing, and 4 min supine) that can be performed at home, with results comparable to the tilt table test in terms of sensitivity for detecting orthostatic tachycardia, facilitating diagnosis in settings where access to specialized equipment is limited. This approach underscores the underlying autonomic dysfunction, such as baroreflex alterations, and promotes accessible strategies for general practitioners worldwide.

Keywords: Postural orthostatic tachycardia syndrome. Orthostatic intolerance. Postprandial hypotension. Home orthostatic evaluation. Autonomic dysfunction.

Introduction

Cardiovascular autonomic dysfunction – commonly termed “dysautonomia” – encompasses a heterogeneous group of disorders encountered across medical specialties, often presenting with overlapping symptoms due to impaired baroreflex signaling during orthostasis. Dysautonomia is not a singular diagnosis but a syndrome reflecting disruptions in baroreceptor input/output, leading to inadequate cerebral perfusion and hemodynamic instability during orthostasis.

Postural orthostatic tachycardia syndrome (POTS) is a common cause of chronic orthostatic intolerance symptoms that are often disabling for daily activities in young people. As the condition is usually underestimated, its prevalence in the US population is estimated at 0.1-2%, according to the clinical experience of specialized dysautonomia centers—meaning approximately 1-3 million

Americans have this diagnosis.¹ Although broad and extensive research has attempted to elucidate POTS pathophysiology, many individual and environmental factors surrounding it remain unclear. Notably, patients with POTS may simultaneously meet the diagnostic criteria for migraine, hypermobile Ehlers-Danlos syndrome, mast cell activation syndrome, or chronic fatigue syndrome.² A combination of cardiovascular deconditioning (low stroke volume), inflammatory mediators, excessive sympathetic central activation, and a possible autoimmune component targeting cardiac and vascular autonomic receptors – resulting in partial agonism and antagonism at those receptors – helps to explain and improve understanding of POTS symptoms.

No single hypothesis fully explains the pathophysiological mechanisms in POTS patients. POTS patients exhibit baroreflex dysfunction in the input and output

Correspondence:

Daniel Rebolledo-García

E-mail: neurosrc1967@gmail.com

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signal responses to stress factors. Delayed sympathetic outflow, deficient signal processing in central baroreflex pathways, or abnormal parasympathetic tone have been observed in POTS patients. Abnormal baroreflex compensatory mechanisms lead to inadequate buffering of gravitational stress: on orthostasis, blood pools in lower extremity veins, reducing venous return, left ventricular stroke volume, and cerebral perfusion.³

Syncope, a hallmark manifestation of cardiovascular dysautonomia, is a non-specific clinical symptom that can represent the debut presentation in many orthostatic intolerance syndromes. Neurocardiogenic syncope implies a transient failure of baroreflex-mediated compensation; therefore, prolonged standing triggers reflex bradycardia and vasodilation instead of the expected increase in sympathetic tone, peripheral vasoconstriction, and rising heart rate (HR) in response to the gravitational challenge. The absence of an appropriate efferent baroreflex response leads to orthostatic intolerance symptoms – which include lightheadedness, vertigo, blurred vision, facial pallor or flushing, fatigue, weakness, and palpitations – and these frequently precede a syncope episode.⁴ Therefore, syncope will be the first symptom in patients with POTS.

POTS's diagnosis is feasible in the office during clinical evaluation and can usually be identified by recording HR and blood pressure (BP) while supine and during a standard 10-min standing test (ideally without stimulation in a quiet room).⁵ More detailed autonomic function testing, including tilt table testing, can be useful, particularly when other conditions such as neurocardiogenic syncope or peripheral autonomic neuropathy are suspected, or when a patient is unable to perform a 10-min standing test. Tests that measure the integrity of the cardiovagal and peripheral vasomotor adrenergic responses will be normal in most, but not all, POTS patients.⁵ Therefore, a diagnosis of POTS can be made if the patient has an increase in HR ≥ 30 bpm within 5 to 10 min of quiet standing or upright tilt (or ≥ 40 bpm in individuals 12-19 years of age); the absence of orthostatic hypotension (> 20 mm Hg drop in systolic BP); and frequent symptoms that occur with standing, such as lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue.⁶ As the diagnosis is clinical and reproducible, it can be performed at home with a digital sphygmomanometer; we instructed our patient to do in her home.

Case presentation

An 18-year-old woman from Tabasco, Mexico, consulted through Zoom® videoconference due to symptoms of orthostatic intolerance for the past 2 years. She reported sensations of dizziness, fatigue, palpitations, blurred vision, and brain fog when standing up quickly from a chair or when remaining standing or walking for prolonged periods. She also described episodes of epigastric abdominal pain accompanied by nausea and occasional vomiting, which occurred after eating meals rich in carbohydrates. These symptoms were exacerbated by summer heat, episodes of dehydration, infections, menses, and emotional stress. She noticed improvement in her symptoms after sitting or lying down, as well as after drinking plain water.

In Villahermosa, she visited a locally recognized general practitioner who treated similar symptoms with intravenous (IV) infusions of 0.9% saline solution (1,000 mL) combined with “vitamins” (possibly B-complex vitamins or electrolytes). The patient reported significant relief post-infusion, lasting from days to weeks, allowing her to resume daily activities. For management of the orthostatic intolerance symptoms in this case, the patient was asked to undergo prolonged monitoring of BP and HR based on a protocol adapted for home use: measurement of BP and HR in the supine position for 15 min, followed by 25 min standing and 4 min returning to supine.

During the interview, she reported a history of skin, hyperflexible joints and a tendency to bruising with minimal or spontaneous trauma, and delayed healing in the knees and elbows; therefore, she underwent evaluation using the Beighton score⁷ (a nine-point scale used to assess generalized joint hypermobility).

Seated, BP was 108/56 mmHg with an HR of 52 bpm. The average supine BP was 106/58 mmHg with an HR of 67 bpm. At 3 min of standing, BP was 99/69 mmHg with an HR of 114 bpm. An intermittent increase in HR of more than 30 bpm was observed in the standing position compared with supine for more than 10 min. In addition, a few episodes of vasovagal reaction (parallel blunting in BP and HR) were noted (at minutes 5, 7, 11, and 17), which improved in the following minutes. She felt dizzy, had palpitations, fatigue, and weakness during those events, which resolved spontaneously. She returned to supine for 4 min and was asymptomatic (Fig. 1).

Furthermore, she underwent a second assessment after drinking 75 g of glucose in 100 mL of plain water. Seated, BP was 114/54 mmHg with an HR of 50 bpm. The average supine BP was 110/65 mmHg with an HR of 65 bpm.

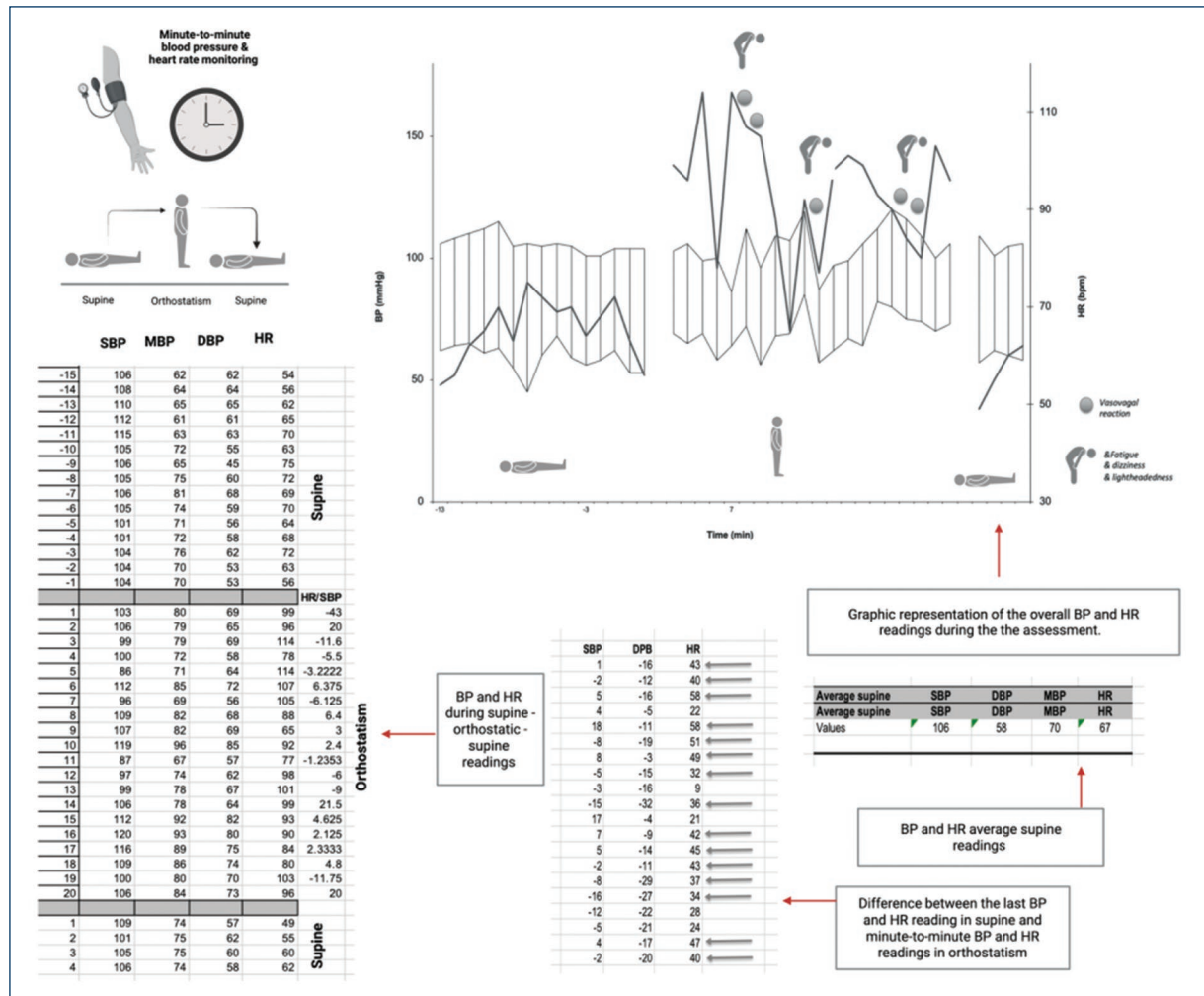


Figure 1. Summary of the initial autonomic assessment. In gray arrows, it was underscore all minutes with a rise in heart rate over 30 bpm (difference between supine and tilted HR readings).

At 3 min of standing, BP was 103/71 mmHg with an HR of 108 bpm. A continuous increase in HR of more than 30 bpm was observed in the standing position during all readings. Fewer vasovagal episodes were observed (at min 4 and 6) compared with the initial testing. At min 10, she experienced nausea, vomiting, and intolerance symptoms, which resolved spontaneously in the following minutes. The patient returned to supine for 4 min and was asymptomatic (Fig. 2).

She was diagnosed with POTS and a hypermobility syndrome (her Beighton score was 8/9 points). Given her history of anxiety and tension headaches, she started treatment with duloxetine 30 mg at bedtime. Because her intolerance symptoms worsened after the oral glucose challenge, we recommended starting acarbose 25 mg and drinking a cup of espresso before meals, along with non-pharmacologic recommendations (decrease simple

carbohydrate consumption, add extra salt to meals, fluid intake of 2,000-3,000 mL daily, use of compression stockings, periodic recumbent exercise, and avoidance of prolonged standing). A few months later, at a follow-up appointment, she had fewer orthostatic intolerance symptoms.

Discussion

This case illustrates how a POTS diagnosis can be made using accessible tools (a sphygmomanometer and sugar) in rural communities in Mexico and how such patients can receive symptomatic treatment in the office of general physicians. Improvement in orthostatic intolerance symptoms after IV saline infusions in this case underscores the importance of intravascular volume replenishment in POTS patients.

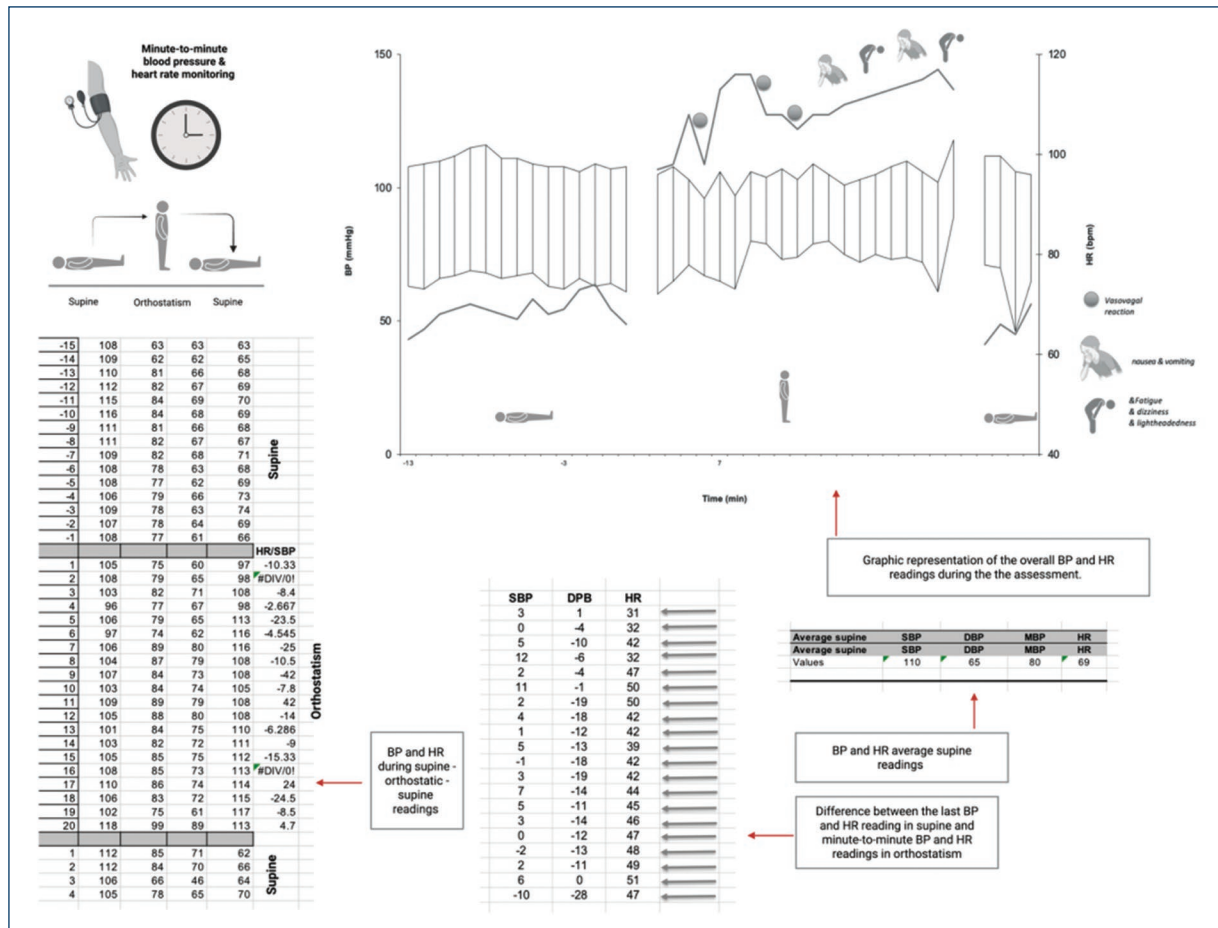


Figure 2. Summary of the second ambulatory autonomic evaluation after 75 g of glucose in 100 mL of plain water. In gray arrows, it was underscore all minutes with a rise in heart rate over 30 bpm (difference between supine and tilted HR readings).

Restoring intravascular volume increases right ventricular stroke volume and improves cerebral perfusion. A few studies have demonstrated that 1 L of IV saline reduces symptoms in up to 93% of patients, improving quality of life, although there is no robust evidence for chronic use due to risks such as volume overload.⁸ Therefore, intermittent IV infusions can be useful during POTS exacerbations, especially in ambulatory settings.

The baroreceptor response in POTS is blunted or exaggerated, resulting in inappropriate tachycardia, vasovagal reactions (parallel drops in BP and HR), or even paradoxical BP elevations due to unbuffered sympathetic activation. Other factors linked to baroreflex dysfunction in POTS patients, such as small fiber autonomic neuropathy, increased baseline sympathetic activity, relative hypovolemia, and venous pooling, collectively impair baroreflex unloading and amplify chemoreflex-driven hyperventilation.⁹ For instance, exaggerated

muscle sympathetic nerve activity (MSNA) responses to baroreflex challenges have been observed in POTS patients compared with controls, contributing to upright sympathetic overdrive and supine parasympathetic withdrawal. In addition, a phase shift between BP and HR oscillations during tilt testing in POTS patients may reflect desynchronized baroreflex-mediated cardiovascular control, further exacerbating symptoms such as dizziness, fatigue, and presyncope episodes.¹⁰

Management of orthostatic intolerance symptoms in POTS patients should emphasize lifestyle changes as non-pharmacologic strategies to support baroreflex function: volume expansion (e.g., IV saline infusions, which acutely restore preload and enhance baroreceptor sensitivity), compression garments to minimize pooling, and lifestyle modifications (e.g., counter-maneuvers like leg crossing; increased salt and fluid intake to 2-3 L/day; and avoidance of prolonged standing and

triggers like heat or simple carbohydrates). In terms of pharmacologic treatment, agents like midodrine (an α -1 agonist in peripheral arteries) or fludrocortisone (a mineralocorticoid) augment vasoconstriction and volume, indirectly aiding baroreflex buffering, though evidence for direct baroreflex sensitivity restoration is limited.¹¹

For postprandial intolerance symptoms, midodrine (5-10 mg per dose) can be used before meals to avoid a drop in BP after eating (off label). Acarbose, a drug initially used as an antidiabetic medication, inhibits the α -glucosidase enzyme in the gut's epithelial cells, delaying the breakdown of complex carbohydrates into glucose and thereby slowing glucose absorption in the gut lumen.¹² As glucose absorption decreases due to acarbose's effects, a neuroendocrine response is blunted, reducing the release of glucose-dependent insulinotropic peptide (GIP), which has vasodilatory properties that increase splanchnic blood flow and contribute to postprandial hypotension. As many patients with POTS experience nausea, vomiting, and delayed gastric emptying, acarbose can prevent this phenomenon by reducing peak levels of mesenteric blood flow and postprandial sympathetic tone withdrawal. Some studies in patients with autonomic failure have shown that low-dose acarbose (25-50 mg) attenuates postprandial BP drops and increases systolic BP by around 20 mmHg, improving orthostatic intolerance symptoms without significant side effects.¹³

In other clinical studies, premeal caffeine consumption (e.g., a cup of coffee, ~100-200 mg) can constrict splanchnic vessels and blunt postprandial hypotension in susceptible individuals, particularly in hyperadrenergic POTS subtypes, by enhancing vasoconstriction and countering insulin-mediated vasodilation—though its use should be cautious in non-hyperadrenergic cases due to potential tachycardia exacerbation.¹⁴ In our POTS patient, the combination of low-dose acarbose and premeal coffee, alongside duloxetine for comorbid anxiety and headaches, led to sustained symptom resolution, highlighting personalized, accessible pharmacotherapy for glucose-triggered postprandial exacerbations in POTS.¹⁵

Conclusion

This clinical vignette highlights the need to integrate accessible approaches for POTS in resource-limited settings, as well as the utility of IV infusions as an evidence-based symptomatic therapy and home evaluations for timely diagnosis, improving the management of these conditions—generically known as “dysautonomia”—in primary care settings worldwide.

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Conflicts of interest

The author declares no conflicts of interest.

Ethical considerations

Protection of humans and animals. The author declares that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The author has followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence. The author declares that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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CLINICAL CASE

Ischemic stroke as the initial manifestation of left atrial myxoma: case report and literature review

Viridiana Millán-Martínez*^{ID} and Gibran A. Ahued-Pozos^{ID}

Cardiology Department, Hospital General Dr. Dario Fernández Fierro, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City, Mexico

Abstract

Atrial myxomas are the most common primary cardiac tumors, and neurological manifestations from systemic embolization may represent the initial presentation. Early recognition is essential, as embolic events significantly increase morbidity and may obscure the underlying cardiac etiology. We present the case of a 62-year-old woman with hypertension and type 2 diabetes presented with sudden left-sided weakness and paresthesias. Brain computed tomography (CT) demonstrated an ischemic infarct in the middle cerebral artery territory. Transthoracic and transesophageal echocardiography revealed a heterogeneous left atrial mass attached to the interatrial septum, suggestive of myxoma; cardiac CT confirmed these findings. She underwent successful surgical excision, with histopathology confirming a benign myxoma. Post-operative recovery was favorable, with stable neurological status and preserved ventricular function. In conclusion, ischemic stroke can be the first manifestation of a left atrial myxoma. Prompt diagnosis through echocardiography and cardiac imaging, followed by early surgical resection, is crucial to prevent recurrent embolization and optimize patient outcomes.

Keywords: Atrial myxoma. Ischemic stroke. Embolism. Echocardiography. Cardiac surgery.

Introduction

Atrial myxomas are the most common primary cardiac tumors and account for approximately 50% of benign cardiac neoplasms.¹ They are predominantly located in the left atrium and, in most cases, originate in the interatrial septum at the level of the foramen ovale.^{1,2} They are usually diagnosed in adults between the fifth and sixth decades of life, with a slight predominance in women.²

The clinical presentation of atrial myxomas is variable, and a classic triad is described that includes systemic symptoms, intracardiac obstructive manifestations, and systemic embolic events.³ Among the latter, cerebral embolization represents one of the most serious complications and may be the initial presentation of the disease.⁴ Ischemic cerebrovascular events

occur primarily due to tumor fragmentation or the formation of thrombi on its surface, especially in mobile lesions with irregular contours.^{4,5} Recognizing the cardiac origin of a cerebrovascular event can be difficult, particularly in patients with coexisting vascular risk factors. In this context, transthoracic echocardiography is the most commonly used initial diagnostic method, while transesophageal echocardiography offers greater sensitivity and better morphological characterization of intracardiac masses.⁶ Other imaging modalities, such as computed tomography (CT) or cardiac magnetic resonance imaging, can provide complementary information to confirm the diagnosis and plan the surgical approach.⁷

Early surgical resection is the definitive treatment for atrial myxomas and is associated with an excellent

*Correspondence:

Viridiana Millán-Martínez

E-mail: virimillan0@gmail.com

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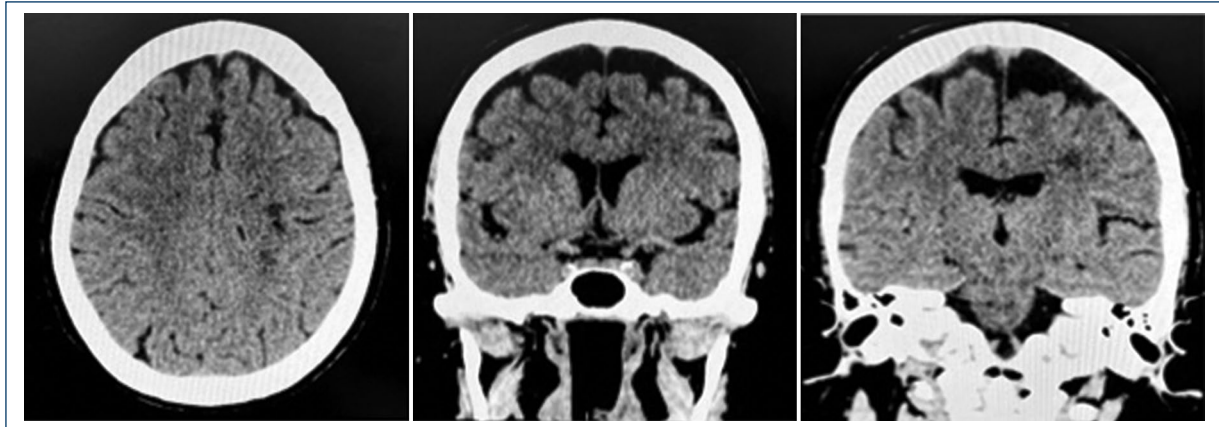


Figure 1. Plain skull CT scan. A poorly defined hypodense area is observed in the left parietal region, corresponding to the territory of the middle cerebral artery, consistent with ischemic cerebral infarction.

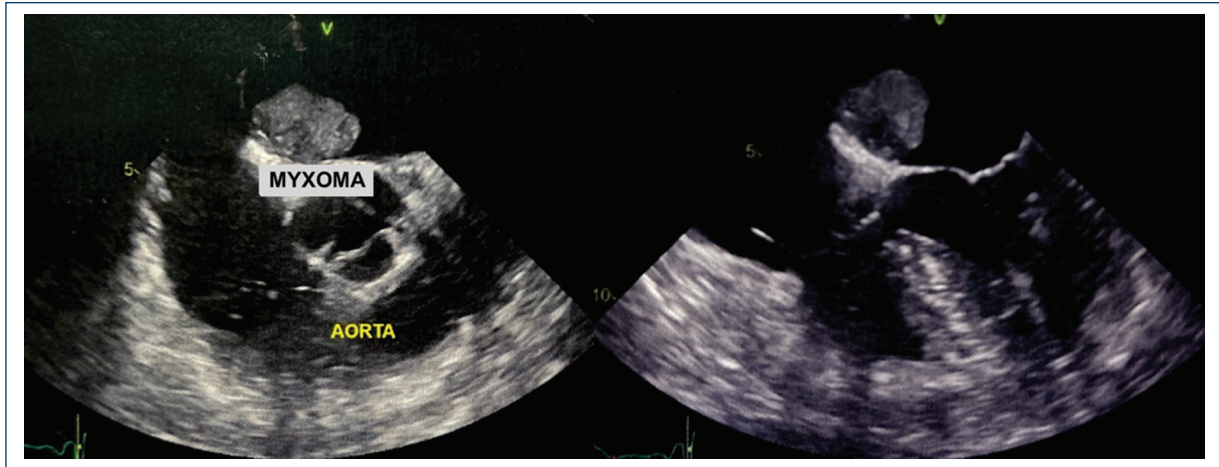


Figure 2. Transesophageal echocardiogram. Image showing an intracardiac mass located in the left atrium, attached to the interatrial septum, with features consistent with a left atrial myxoma.

prognosis and a low recurrence rate when performed in a timely manner.⁸ This report describes a case of an ischemic cerebrovascular event as the initial manifestation of a left atrial myxoma and reviews the main clinical, diagnostic, and therapeutic aspects of this condition.

Case presentation

A case report was prepared based on the clinical evaluation, imaging studies, and surgical management of a patient diagnosed with a left atrial myxoma whose initial presentation was an ischemic cerebrovascular event. Relevant clinical data, laboratory results, neuroimaging findings, and cardiological studies – including

transthoracic and transesophageal echocardiography, as well as cardiac CT – were retrospectively compiled. Surgical information and histopathological analysis were obtained from the institutional medical record. For the literature review, a narrative search of scientific articles was conducted without date restrictions; publications in English and Spanish describing case reports, case series, and narrative reviews were included. As this was a descriptive, single-patient study, no statistical analysis was performed, in accordance with methodological recommendations for case reports.

We present the case of a 62-year-old woman with type 2 diabetes and systemic hypertension who presented for evaluation due to a sudden onset of

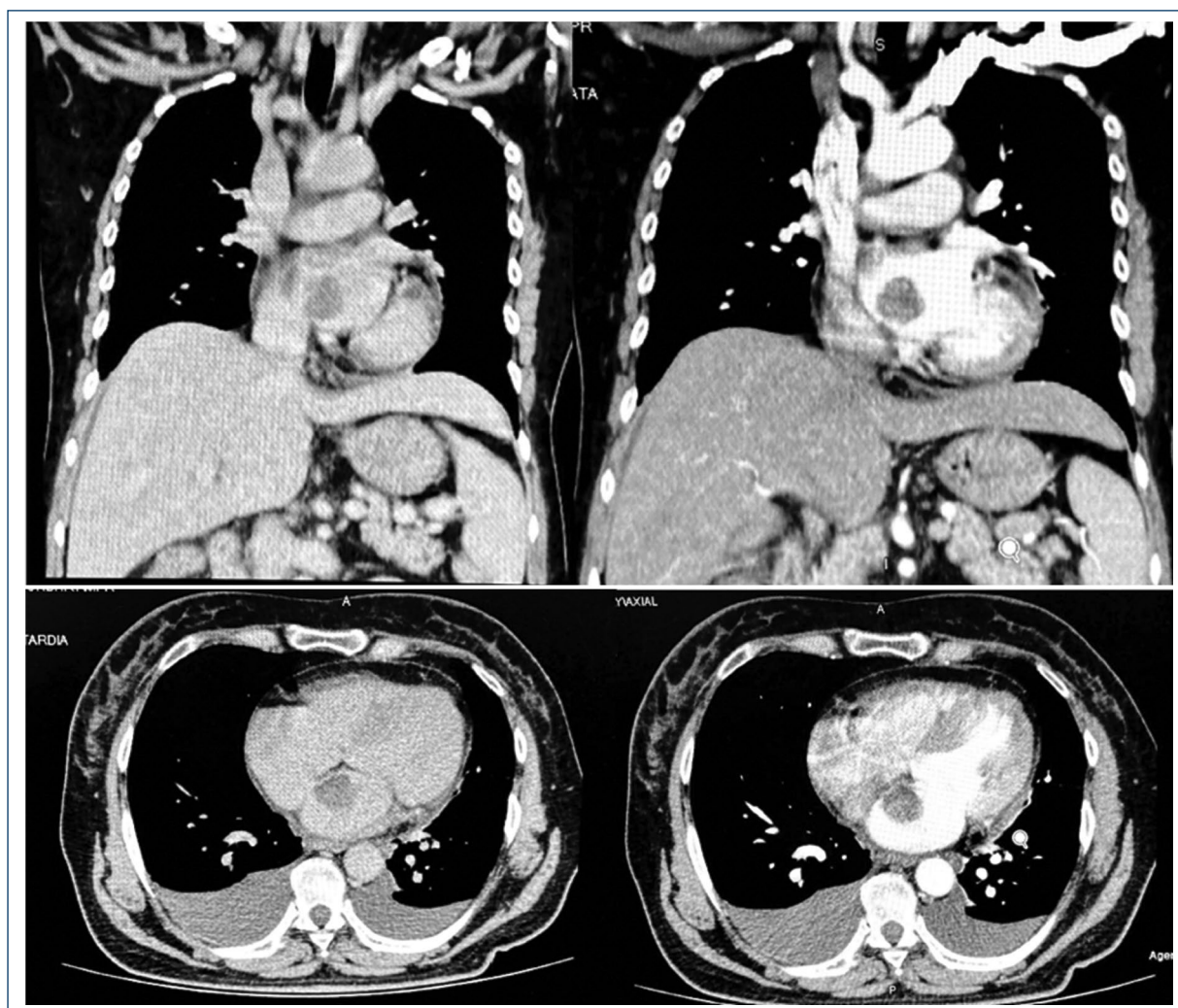


Figure 3. Contrast-enhanced cardiac angiotomography. Reconstructions in the coronal and axial planes show an intracavitary mass in the left atrium with irregular contours and heterogeneous density, adherent to the interatrial septum, consistent with a left atrial myxoma. Heterogeneous enhancement is observed following the administration of contrast medium.

weakness and paresthesias in the left half of her body. A plain cranial CT scan (Fig. 1) was performed, revealing a poorly defined hypodense area in the left parietal region, corresponding to the territory of the middle cerebral artery, consistent with ischemic cerebral infarction, with no evidence of intracranial hemorrhage or significant mass effect. During the etiological evaluation of the cerebrovascular event, transthoracic and transesophageal echocardiograms were performed (Fig. 2), revealing an intracavitary mass in the left atrium - heterogeneous, with irregular contours, a vascularized appearance, measuring approximately $28 \times 27 \times 21$ mm, and adherent to the interatrial septum - highly suggestive of a left atrial myxoma. The diagnosis was confirmed by contrast-enhanced cardiac CT angiography (Fig. 3), which

corroborated the presence of the intracavitary mass, confirming its location and morphological characteristics. Surgical resection was performed successfully, and histopathology confirmed a benign myxoma. The patient underwent complete surgical resection of the tumor; the resected specimen measured approximately 2.3 cm. Histopathological examination confirmed the diagnosis of benign atrial myxoma. The postoperative course was favorable, with no acute cardiovascular or neurological complications. Preserved left ventricular function was documented, with a left ventricular ejection fraction of 61%. The patient was neurologically stable at the time of hospital discharge and was discharged with optimal medical treatment, which included dual antiplatelet therapy, statins, and antihypertensive therapy.

Ethical considerations

This case report was conducted in accordance with the ethical principles established in the Declaration of Helsinki. Informed consent was obtained from the patient for the anonymous publication of clinical information and diagnostic images. The confidentiality of personal data was ensured at all times. In addition, institutional authorization was obtained from the Cardiology Department of the *Hospital 1° de Octubre* at the *Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado* (ISSSTE) in Mexico City to review and publish this case for strictly academic and scientific purposes. Clinical information was handled with strict confidentiality, in accordance with applicable regulations for the protection of personal health data.

Discussion

Cardiac myxoma is the most common benign primary tumor of the heart, accounting for approximately 50-60% of all primary cardiac neoplasms. It most commonly occurs in adults between their third and sixth decades of life, with a predominance in females. Most myxomas originate in the left atrium, typically at the level of the interatrial septum in the foramen ovale region. Their clinical presentation is heterogeneous and is classically described as a triad consisting of constitutional symptoms, intracardiac obstructive phenomena, and embolic events. However, in some patients, embolic manifestations may constitute the initial or sole form of clinical presentation. Neurological complications are among the most serious manifestations of cardiac myxoma and are reported in up to 20-40% of cases. Ischemic cerebrovascular events are the most common neurological complication and are usually secondary to cerebral embolization associated with atrial myxoma, which is primarily explained by two pathophysiological mechanisms: direct fragmentation of the tumor tissue and the formation of thrombi on its surface, facilitated by the tumor's irregular shape, mobility, and vascularization. Previous studies have shown that myxomas with irregular contours and high mobility present a greater risk of embolization, regardless of their size, highlighting the importance of a detailed morphological evaluation using advanced imaging techniques.

We present the case of a patient with an ischemic cerebrovascular event. During the investigation of the underlying cause, a transthoracic echocardiogram revealed an intracardiac mass, which was more precisely characterized using transesophageal

echocardiography and cardiac CT angiography, confirming the presence of a left atrial myxoma.

Early surgical resection is the definitive treatment for atrial myxoma and should be performed as soon as the diagnosis is established, due to the persistent risk of recurrent embolization and sudden death. Several surgical series have demonstrated excellent long-term outcomes, with a low recurrence rate and favorable functional recovery when resection is complete. In the present case, surgery allowed for the complete removal of the tumor, with histopathological confirmation of benignity and a satisfactory clinical course, without further neurological deterioration.

This case highlights the importance of considering cardiac tumors as an underlying cause of ischemic cerebrovascular events, particularly in patients without a clear vascular explanation. A multidisciplinary approach involving neurology, cardiology, and cardiovascular surgery is key to optimizing the prognosis for these patients.

Conclusion

Cardiac myxoma, despite its benign nature, can be associated with potentially serious clinical complications, particularly cerebral embolic events. This case highlights the importance of considering a cardioembolic etiology in patients presenting with an ischemic cerebrovascular event.

The timely use of cardiac imaging methods, particularly transesophageal echocardiography and complementary imaging techniques, allows for an accurate diagnosis and guides definitive treatment. Early surgical resection is a curative strategy and is associated with an excellent prognosis, significantly reducing the risk of embolic recurrence and improving clinical outcomes.

In patients with cryptogenic cerebrovascular events - especially in younger patients or those without traditional cardiovascular comorbidities - cardiological evaluation should be part of the diagnostic approach. A multidisciplinary management approach is key to optimizing clinical outcomes and reducing the morbidity and mortality associated with this condition.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected

and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

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

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