ALERTA

Scientific Journal of the National Institute of Health
San Salvador, El Salvador, Central America, July-September 2025

OPEN ACCESS
ISSN: 2617-5274
Volume 8, n.º 3

Factors influencing the consumption of tobacco, alcohol and psychoactive substances using machine learning

www.alerta.salud.gob.sv

ALERTA Scientific Journal of the National Institute of Health
Volumen 8, n.º 3, San Salvador, El Salvador, Centroamérica, July-September 2025

Exchange and subscription
Nadia Patricia Rodríguez Villalta, MD
✉ *nadia.rodriguez@salud.gob.sv*

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ISSN electronic number: 2617-5274.

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Content/Índice

Editorial

Innovations and challenges in research on nutrition, child development, mental health, and chronic diseases

DOI: 10.5377/alerta.v8i3.20768

Xochitl Sandoval López

National Institute of Health, San Salvador, El Salvador.

Correspondencia
xochitlsandoval2005@gmail.com

0000-0002-0988-1313

OPEN ACCESS

Innovaciones y desafíos de la investigación en nutrición, desarrollo infantil, salud mental y enfermedades crónicas

Suggested citation:
Sandoval López X. Innovations and challenges in research on nutrition, child development, mental health, and chronic diseases. Alerta. 2025;8(3):236-237. DOI 10.5377/alerta.v8i3.20768

Received:
July 16, 2025.

Accepted:
July 18, 2025.

Published:
July 31, 2025.

Author contribution:
XLS: preparation and revision of the manuscript.

Conflicts of interest:
The author declared there are not conflicts of interest.

Nowadays, science is advancing by leaps and bounds, enabling a deeper understanding of the factors that influence nutrition, child development, mental health, and chronic diseases. In this edition of Alerta, we highlight key issues that reflect both the advances and challenges faced in these fields.

Recent narrative reviews underscore the importance of adequate nutrition in promoting motor development, language, and anthropometric growth in malnourished children. This research consolidates evidence on how early nutritional intervention can reverse or mitigate the consequences of stunted growth, highlighting the need to create integrated public policies that prioritize food security and access to essential micronutrients.

It also explores the emerging role of glutamate in the treatment of symptoms associated with autism spectrum disorders. Although still in the preliminary stages, studies suggest that glutamatergic modulators could offer new therapeutic avenues to improve the quality of life of these individuals. However, it is essential to continue rigorous research to determine optimal dosages and minimize potential risks.

In an increasingly digitalized world, original articles that incorporate artificial intelligence (AI) to analyze large volumes of data represent a revolutionary advance. The application of intelligent algorithms allows for the identification of complex patterns and the prediction of trends with greater accuracy, facilitating more informed and personalized clinical decisions. The integration of AI into biomedical research not only accelerates discoveries but also opens up new perspectives for addressing traditional problems through innovative approaches.

Concerning the case report presented on dilated cardiomyopathy in a young patient, it is essential to highlight the importance of this type of clinical report in broadening our understanding of the manifestations and possible etiologies of this disease in young populations. The onset of dilated cardiomyopathy in young patients poses significant diagnostic and therapeutic challenges, as well as important considerations in the development of preventive and management strategies. This case underscores the need for a thorough evaluation to identify underlying causes, as well as the importance of long-term follow-up to prevent severe complications, such as heart failure or fatal arrhythmias. Furthermore, it highlights the importance of promoting research to understand better the genetic, environmental, and infectious factors involved in its etiology, thereby improving diagnostic and therapeutic approaches for this population.

Finally, it highlights the value of letters to the editor as vital spaces for scientific and social dialogue. The recent letter on the current state of scientific research in health in El Salvador reflects how the voices of the academic community can influence public policy and raise awareness in society about critical issues related to public health.

In line with this letter, it is necessary, from this important space, to emphatically highlight the significance of the entry into force of the *National Health Research Law*, promoted by the National Health Institute, with national discussion and consensus among all stakeholders involved in the issue, emphasizing that this would be a fundamental tool for strengthening the health system and promoting scientific advances that benefits the entire population. The need for specific legislation arises from the current fragmentation of efforts, the lack of timely and adequate funding, and the absence of a regulatory framework that solidly guarantees the ethics, quality, and sustainability of research. In addition, a national law would allow for the coordination of resources, promote collaboration between public and private institutions, and ensure that scientific results are translated into effective public policies.

In a context where health challenges are increasingly complex, having a robust legal framework is essential to drive innovation, improve healthcare, and reduce inequalities in access to scientific advancement. Ultimately, this editorial reinforces that such a law is not only necessary but also urgent in order to consolidate a more equitable, efficient, and well-being-oriented health research system.

In conclusion, this edition reaffirms that interdisciplinary collaboration, combining narrative reviews, technological innovation, and active participation through open communication is essential to advance toward effective solutions to global challenges in child health, mental health, cancer prevention and control, among others. At Alerta, we remain committed to promoting rigorous research that contributes to improving human lives through scientific knowledge.

Case report

Dilated cardiomyopathy associated with cocaine use: clinical case and review

DOI: 10.5377/alerta.v8i3.20731

Jocelyn Sofía Cabrera Aguilar[1]*, Oscar Aníbal Cabrera Rivas[2]

1. Department of Internal Medicine, San Juan de Dios National Hospital, Santa Ana, El Salvador.
2. Military Medical Battalion, Captain General Gerardo Barrios Military School, San Salvador, El Salvador.

*Correspondence
jsca95@gmail.com

1. 0009-0004-1357-9186
2. 0009-0006-1028-2410

OPEN ACCESS

Miocardiopatía dilatada asociada a uso de cocaína: caso clínico y revisión

Suggested citation:
Cabrera Aguilar JS, Cabrera Rivas OA. Dilated cardiomyopathy associated with cocaine use: clinical case and review. Alerta. 2025;8(3): 238-244 DOI: 10.5377/alerta.v8i3.20731

Editor:
Nadia Rodríguez.

Received:
July 3, 2024.

Accepted:
July 7, 2025.

Published:
July 31, 2025.

Author contribution:
JSCA[1]: study conception, manuscript design, data collection, data management, or software OACR[2]: data analysis JSCA[1], OACR[2]: literature search, writing, review, and editing.

Conflicts of interest:
No conflicts of interest.

Abstract
Case presentation. A 33-year-old male patient, with recently diagnosed hypertension and chronic cocaine use, presented with symptoms of congestive heart failure. He underwent an echocardiogram that reported dilatation of all four cardiac chambers and decreased left ventricular ejection fraction. The etiology of the dilated cardiomyopathy was investigated, and infectious causes were ruled out. **Treatment.** The patient was managed in the acute phase with diuretics, dobutamine drip, beta-blockers, and digitalis, in addition to vericiguat, and presented with evident clinical improvement. **Outcome.** A catheterization was recommended to rule out ischemic coronary artery disease as a differential diagnosis, in addition to magnetic resonance or endomyocardial biopsy to rule out other infiltrative pathologies; however, these were not performed due to the patient's refusal and study limitations. The patient requested voluntary discharge, and medical management was indicated, with continued outpatient study in a clinic.

Keywords
Heart Failure, Stroke Volume, Left Ventricular Dysfunction, Dilated Cardiomyopathy, Cocaine-Related Disorders.

Resumen
Presentación del caso. Se describe el caso clínico de un paciente masculino, de 33 años, con hipertensión arterial de reciente diagnóstico y consumo crónico de cocaína, que debutó con síntomas de insuficiencia cardíaca congestiva. Se le realizó un ecocardiograma que reportaba dilatación de las cuatro cavidades cardíacas y una fracción de eyección del ventrículo izquierdo disminuida. Se investigó la etiología de la cardiomiopatía dilatada, y se descartaron las causas infecciosas. **Intervención terapéutica.** Se manejó en la fase aguda con diuréticos, goteo de dobutamina, betabloqueadores, digitálicos, además de uso de vericiguat, y el paciente presentó evidente mejora clínica. **Evolución clínica.** Se recomendó realizar un cateterismo para descartar enfermedad coronaria isquémica como diagnóstico diferencial, además resonancia magnética o biopsia endomiocárdica para descartar otras patologías infiltrativas, sin embargo, no se realizaron por negativa de paciente y limitaciones de estudios. El paciente solicitó el alta voluntaria, y se indicó manejo médico y continuar estudio ambulatorio en consulta externa.

Palabras clave
Insuficiencia Cardíaca, Volumen Sistólico, Disfunción Ventricular Izquierda, Miocardiopatía Dilatada, Trastornos Relacionados con Cocaína.

Introduction

Dilated cardiomyopathy (DCM) is defined as the presence of left ventricular dilatation and global or regional systolic dysfunction not explained solely by abnormal overload conditions or coronary artery disease.[i] This is one of five types of cardiomyopathy (hypertrophic, dilated, non-dilated left ventricular, arrhythmogenic right ventricular, and restrictive).[i]

It is an important cause of cardiovascular morbidity and mortality due to congestive heart failure, and in 20 % of cases, genetic origins have been identified.[ii] Mortality due to severe congestive heart failure can reach 50 % two years after diagnosis.[iii]

The prevalence of this disease is associated with 2 % to 3 % of left ventricular systolic dysfunction and 1.5 % of congestive heart failure in the general population.[iii] Although MD is most often diagnosed in mid-life,[i] it is estimated that up to 36 % of cases occur in young patients.[iv] These patients usually present in emergency departments with symptoms of frank heart failure, and upon clinical evaluation, it is possible to identify ventricular dilatation and remodeling, the presence of myocardial fibrosis, and systolic and/or diastolic function dysfunction.[v] Therefore, a clinical case is presented as an opportunity to describe the most frequent etiologies of dilated cardiomyopathy, as well as to address possible associated risk factors and therapeutic options, based on a review of the current literature.

Presentation of the case

A 33-year-old male patient, originally from Guatemala, with a history of arterial hypertension diagnosed six months prior to consultation, has been under pharmacological treatment since diagnosis with losartan 50 mg orally, once a day. He denied the use of alcohol, tobacco, or illicit drugs; however, he reported a clinical picture of one month of evolution, characterized by bilateral edema of the lower limbs with an ascending pattern up to the infrapatellar region.

This was accompanied by dyspnea initially induced by maximal efforts, with gradual progression over two weeks, until it was limited to minimal efforts. One day prior to the consultation, he presented with intolerance to dorsal decubitus, compatible with orthopnea of recent onset. For this reason, the patient was referred to a public hospital for clinical evaluation, where signs of pulmonary congestion and vital signs were noted: blood pressure 130/80 mmHg, respiratory rate 20 breaths per minute, and oxygen saturation 99 %.

In addition, the patient verbally expressed the history of cardiomegaly, so it was decided to perform an echocardiogram, which reported: dilatation of the four cardiac cavities, akinesia of the apex, anterior, septal, and lateral walls, and severe hypokinesia of apical and middle segments of the inferior wall, in addition to severely decreased left ventricular systolic dysfunction with LVEF (left ventricular ejection fraction) of 22 %, right ventricular systolic dysfunction, mitral and tricuspid insufficiency, and mild pulmonary arterial hypertension PSAP (pulmonary artery systolic pressure) of 32.9 mmHg.

For this reason, it was classified as congetive heart failure, which was managed with intravenous furosemide at a dose of one ampoule every eight hours and oxygen therapy with a nasal cannula at five liters per minute. However, the patient was transferred due to hemodynamic instability to a hospital of higher complexity, where he was received with a blood pressure of 130/80 mmHg, a pulse of 110 bpm, a respiratory rate of 20 rpm, and an O_2 saturation of 97 %.

On physical examination, the jugular veins were found to be ingurgitated in grade II, the pulmonary semiology evaluation revealed bilateral congestive type crepitant rales. A gallop heart rhythm, systolic murmur in mitral and tricuspid foci, Levine II, and displacement of the maximum impulse point towards the sixth intercostal space were identified. At the abdominal level, moderate ascites was found, hepatojugular reflux was present, and in the extremities, lower limb edema grade II.

On admission, laboratory tests were requested (Table 1); however, troponin measurement was not included due to the hospital center's unavailability at the time of care. A posteroanterior chest X-ray showed grade IV cardiomegaly. The electrocardiogram showed sinus tachycardia, atrial enlargement, and a T-wave inversion on the lateral aspect (Figure 1).

On the third day of admission, new laboratory studies were sent (Table 2). The results included: IgG antibodies against *Trypanosoma cruzi*, with negative results, and a non-reactive rapid HIV (human immunodeficiency virus) test. Surface antigen for hepatitis B with a value of 0.3 S/CO (signal to cut-off index, reference value: 0.0-0.9), antibodies for hepatitis C with a value of 0.2 S/CO (reference: 0.0-0.9), and antistreptolysin O (ASO) of 125 IU/ml (reference value: 0.0-200). All three had negative results for these diagnostic suspicions.

Therapeutic intervention

The patient continued treatment with intravenous diuretics (furosemide) as part of the management of acute heart failure, in addition to dobutamine 6 mg/min due to its positive inotropic effect. According to what was documented in the medical evolution, the patient presented clinical improvement during his hospital stay (however, the specific criteria supporting this assessment were not detailed), so spironolactone was added to the treatment, in a dose of half a tablet orally every day, enalapril 5 mg orally every day, beta-blockers such as carvedilol 6.25 mg orally every day, clopidogrel 75 mg via orally every day. In addition, the use of dapagliflozin 5 mg daily and vericiguat 2.5 mg orally daily was indicated to improve prognosis and reduce hospitalizations.

An evaluation by a cardiologist was requested, who indicated starting digoxin via a digitalization scheme with an initial dose of 0.25 mg intravenously, followed by 0.25 mg intravenously every eight hours, and then continuing with 0.25 mg intravenously once a day as a maintenance dose.

Clinical course

Since his admission to the referral hospital, the patient was managed for acute decompensation of heart failure, and simultaneously, the etiological investigation of MD was initiated. Infectious causes such as Chagas disease, HIV, Hepatitis B and C, and a streptococcal infection, which could have triggered the indirect cardiac damage, were ruled out. In the absence of a clear etiology after initial examinations, cardiaccatheterization was recommended for further diagnostic evaluation; however, the patient declined such a procedure for personal reasons.

Table 1. Laboratory tests

Examination	Day 1	Day 3	Day 4	Units	Reference value
Leukocytes	7,5	9,7	9,2	$10^3/mm^3$	5-10
Neutrophils (%)	66,1	63,3	63,4	%	50-70
Lymphocytes (%)	24,7	25,7	24,9	%	20-40
Monocytes (%)	7,4	9,6	10,2	%	3-12
Hemoglobin	16,7	17,5	16,9	g/dL	12-16
Hematocrit (%)	52,0	52,5	49,4	%	37-54
Platelets	211	240	221	$10^3/\mu L$	150-400
Creatinine	1,2	1,1	0,9	mg/dl	0,4-1,2
Urea nitrogen	23,9	18,0	18,0	mg/dl	5-18
Sodium	137,0	141,0	139,0	mEq/l	135-150
Potassium	4,0	3,8	3,4	mEq/l	3,5-5,5
Calcium	-	9,4	9,0	mg/dl	8,5-10,5
CPK	-	52,0	-	UI/L	38-174
CPK-MB	32,2	14,2	13,9	UI/L	0-25
Albumin	-	3,9	-	g/dL	3,5-5,0
TPT	25,0	-	-	Seg	24,2-32,8
TP	15,8	-	-	Seg	8,6-11,6
INR	1,4	-	-	-	-
C Reactive Protein	-	0,2	-	mg/dl	0-8

Table 2. Complementary laboratory tests

Examination	Day 4	Day 9	Day 10	Units	Reference value
Total Cholesterol	101,0	-	-	mg/dL	140-200
HDL	33,0	-	-	mg/dL	35-65
LDL	53,0	-	-	mg/dL	75-100
Triglycerides	102,0	-	-	mg/dL	40-150
Free T3	3,4	-	-	pg/mL	2,5-3,9
Free T4	1,0	-	-	ng/dL	0,61-1,12
TSH 3rd generation	1,4	-	-	UI/mL	0,34-5,6
Rheumatoid factor	-	2,0	-	UI/mL	0-15
Uric acid	-	-	4,3	mg/L	2,3-6,1
Serum iron	-	-	177,8	µg/dL	60-180
Ferritin	-	-	262,5	µg/L	10-120

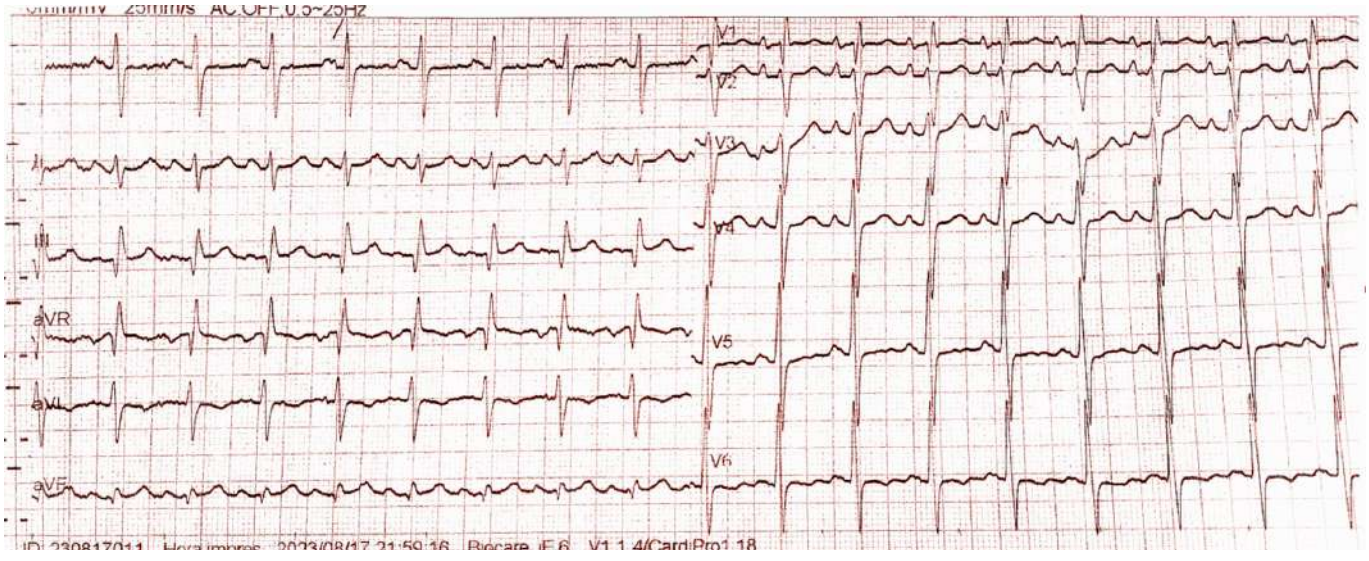

Figure 1. ECG. A 12-lead electrocardiogram is presented, velocity of 20 mm/s and voltage of 10 mm/mV. Heart rate of 110 bpm. QRS complex: 0.12 sec, P wave of 0.12 sec. T wave of 0.20 sec. Sinus tachycardia, atrial enlargement and T wave inversion on the lateral side.

Also, other etiologies could have been explored in this patient by complementary studies such as cardiac magnetic resonance imaging or an endomyocardial biopsy with Congo red staining, specific for amyloid, which could have been very useful for the differential diagnosis of infiltrative heart disease, including sarcoidosis, amyloidosis, and deposition cardiomyopathies such as hemochromatosis. These studies are essential because management and prognosis vary significantly according to etiology; however, they were not possible to perform due to limitations in the hospital center's resources.

During hospitalization, and after multiple clinical interrogations, the patient admitted a history of chronic cocaine use lasting approximately ten years. However, a confirmatory toxicological study was not performed due to a lack of resources and because the patient requested voluntary discharge. The patient was discharged with oral therapy already established, outpatient cardiology and internal medicine controls were indicated; however, after discharge, the patient did not attend his controls.

Clinical diagnosis

Congestive heart failure, cocaine-induced dilated cardiomyopathy, biventricular systolic dysfunction was diagnosed.

Discussion

DCM consists of ventricular dilatation and decreased systolic function, leading to heart failure.[vi] It has a prevalence of 36 to 40 per 100 000 inhabitants, with a predominance in men under 50 years of age.[i] Well-known causes have been described as poorly controlled high blood pressure and secondary causes such as coronary artery disease,[vii] or excessive alcohol consumptioni. In this patient, the most relevant risk factors were arterial hypertension and chronic cocaine consumption. Arterial hypertension favors ventricular pressure overload and myocardial remodeling. At the same time, cocaine, one of the most widely consumed psychoactive substances worldwide, induces coronary vasoconstriction, hypertrophy, and myocardial fibrosis, which together cause remodeling, accelerating the development of DCM.[vii,viii]

Studies have shown an increase in the left ventricular end-systolic volume mass index and a decrease in LVEF in patients with long-term cocaine use, changes that, for the most part, were found in the patient.[vii] The common pathophysiological basis is the loss of myocardial contractile capacity.[ix]

The causes can be grouped into two broad categories: genetic and non-genetic.[ix]Among the non-genetic causes, those of inflammatory-immunological origin stand out, with viral myocarditis being one of the most frequent etiologies, related to agents such as cytomegalovirus (CMV), HIV, or infiltrative diseases such as amyloidosis or sarcoidosis. In this case, pathologies such as HIV, diabetes *mellitus*, and thyroid dysfunction were ruled out. However, no specific study for CMV, amyloidosis, or sarcoidosis was performed, for reasons previously stated, and given the patient's refusal to continue with complementary studies.

Other possible causes, such as coronary artery disease, previously known, should also be considered. The main symptom that motivated the patient to consult was dyspnea, which is considered the most frequent reason for consultation.[x] The manifestations of cardiomyopathies vary according to the type of systolic, diastolic, or both dysfunction.[i] In addition, cardiac arrhythmias (especially atrial fibrillation), weakness, or fatigue may be found.[xi] Radiological findings may include cardiomegaly and evidence of pulmonary congestion.[xii]

Electrocardiographic findings are usually nonspecific, sinus tachycardia, cavity growth,[ix] left systolic overload,[ix] T-wave abnormalities, atrial fibrillationxi, and LBBB (left bundle branch block). It is worth noting that the latter finding is associated with ventricular mechanical dyssynchrony, which compromises hemodynamic efficiency by reducing cardiac output.

The gold standard, at present, is cardiac magnetic resonance imaging,[ix] since it provides information on etiology and prognostic stratification;[ix] however, in the patient described in this case report, it was not performed due to economic aspects.

Other resources that can be considered are positron emission tomography, endomyocardial biopsy, and coronary angiography (cardiac catheterization) in persons with no known history of coronary artery disease, to better define the coronary anatomy and rule out occult ischemic disease,[xi] or to measure intracardiac pressures, which are useful when evaluating the degree of evolution of the disease, response to treatment, or to establish an indication for cardiac transplantation.

For the management of acute complications, such as heart failure, the use of four drugs is indicated: beta-blockers, mineralocorticoid receptor antagonists, SGLT-2 inhibitors, and angiotensin/neprilysin receptor antagonists (ARNI), as well as other medications, including angiotensin-converting enzyme inhibitors (ACE inhibitors), diuretics, and digoxin.[xiii]

Beta-blockers can improve ventricular remodeling, function, and clinical efficacy.[xiii] Ivabradine can improve cardiac function by reducing heart rate, which decreases myocardial oxygen demand, improves coronary perfusion, and optimizes ventricular filling, thus favoring cardiac output.[xiii,xiv] It should be taken into account whether the etiology of DCM is known, in which case it will have a specific treatment.[xv] Reduced ejection fraction is associated with high morbidity and mortality.[xvi] Vericiguat, which has been shown to be effective and safe[xvi] by stimulating soluble guanylate cyclase (sGC), promotes vasodilatation and improves ventricular function, contributing to hemodynamic optimization in patients with heart failure. While ACE inhibitors have been shown to prolong survival.[xvii] Nevertheless, MD treatment aims to reduce mortality and improve quality of life.[xviii]

This clinical case highlights the importance of considering chronic cocaine consumption as a relevant etiological factor, given that in this young patient, arterial hypertension and possible coronary artery disease could be secondarily induced by such consumption. In the absence of an alternative etiology to explain the clinical picture, and considering the well-documented cardiovascular effects of this substance, the case was classified as cocaine- induced dilated cardiomyopathy.

This condition is a secondary form of DCM, due to chronic cocaine use, characterized by dilatation of ventricular cavities (mainly left ventricle), systolic dysfunction; in addition, it is secondary to catecholaminergic toxicity, fibrosis, ischemia, and myocarditis caused by this drug.

Importantly, in patients with cocaine-induced DCM, total abstinence can lead to significant recovery of ventricular function.[xix] Nevertheless, continued use increases the risk of progression to advanced heart failure, the development of life-threatening arrhythmias, and increased mortality from acute ischemic events.[xix]

Therefore, any young patient presenting with clinical findings compatible with heart failure and a history of cocaine use should be considered as a probable diagnosis and approached as heart failure with reduced LVEF. In addition, for adequate etiological characterization, it is essential to perform cardiac magnetic resonance imaging and cardiac catheterization if the exclusion of coronary artery disease is required. The recurrent challenge of dealing with cases with multiple possible etiologies is evident, in which the patient's therapeutic compliance and access to specialized studies can make the difference between clinical uncertainty and a precise therapeutic intervention.

Ethical aspects

The Helsinki Declaration and international ethical guidelines for health-related research were followed. Patient confidentiality was guaranteed, and an informed consent form was prepared, in which the patient authorized the use of their information and images for publication.

Acknowledgments

To the staff of the Internal Medicine Service at San Juan de Dios National Hospital, Santa Ana, for their contributions to the care and diagnosis of the case, and to the cardiologist specialists for their assistance in managing the case.

Funding

No external funds were received for this work.

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Original Article

Factors influencing the consumption of tobacco, alcohol, and psychoactive substances using machine learning

DOI: 10.5377/alerta.v8i3.20719

Xochitl Sandoval López[1], David A. Tejada[2*]

1. National Institute of Health, San Salvador, El Salvador.
2. National Health Observatory, National Institute of Health, San Salvador, El Salvador.

*Correspondence
david.tejada@salud.com

1. 0000-0002-0988-1313
2. 0000-0003-2502-1433

Abstract
Introduction. Addiction to psychoactive substances is a global challenge that impacts physical, mental, and emotional health, generating significant social and economic consequences influenced by individual, psychological, family, and social factors. **Objective.** Analyze the sociodemographic and mental health factors that influence dependence on alcohol, tobacco, and psychoactive substances in El Salvador. **Methodology.** A cross-sectional analytical study was conducted using data from the 2022 National Mental Health Survey. All participants were included and categorized according to their risk of tobacco, alcohol, or psychoactive substance use. Descriptive and inferential statistical analyses were performed, along with correlation, clustering, and logistic regression analyses. The programs used were RStudio 4.3.2 and QGIS 3.34.3. **Results.** The national rate of high tobacco use was 0.36%, alcohol use was 0.5 %, and moderate use of psychoactive substances was 3.2 %. There was a strong correlation between high alcohol use and moderate tobacco use (0.96), tobacco use and moderate substance use (0.93), and moderate alcohol use and moderate substance use (0.90). In the multivariate model, being female, having resilience, and having a partner are protective factors, while living in an urban area, anxiety and depression are risk factors for substance use. **Conclusion.** Geographical environment impacts substance use and is associated with mental health problems, and the use of one substance correlates with the use of additional substances.

Keywords
Substance-Related Disorders, Tobacco Use Disorder, Alcoholism, Risk Factors, Mental Health.

Resumen
Introducción. Las adicciones a sustancias psicoactivas son un desafío global que impacta la salud física, mental y emocional, generando consecuencias sociales y económicas significativas, influenciadas por factores individuales, psicológicos, familiares y sociales. **Objetivo.** analizar los factores sociodemográficos y de salud mental que influyen en la dependencia al alcohol, tabaco y sustancias psicoactivas en El Salvador. **Metodología.** Se realizó un estudio transversal analítico con datos de la Encuesta Nacional de Salud Mental, 2022. Se incluyó a todos los participantes y se categorizaron según el riesgo de consumo de tabaco, alcohol o sustancias psicoactivas. Se realizaron análisis estadísticos descriptivos e inferenciales, así como análisis de correlación, *clustering* y regresión logística. Los programas utilizados fueron RStudio 4.3.2 y QGIS 3.34.3. **Resultados.** La tasa nacional de consumo alto de tabaco fue 0,36 %, de alcohol 0,5 %, y de consumo moderado de sustancias psicoactivas 3,2 %. Hubo una fuerte correlación entre el consumo alto de alcohol y el moderado de tabaco (0,96), el consumo de tabaco y moderado de sustancias (0,93), y el moderado de alcohol y moderado de sustancias (0,90). En el modelo multivariado, ser mujer, tener resiliencia y pareja son protectores, mientras que vivir en área urbana, la ansiedad y la depresión son riesgos para el consumo de sustancias. **Conclusión.** El entorno geográfico impacta el consumo de sustancias, el consumo está asociado a problemas de salud mental y el uso de una sustancia se correlaciona con el consumo de otras adicionales.

Palabras clave
Trastornos Relacionados con Sustancias, Tabaquismo, Alcoholismo, Factores de Riesgo, Salud Mental.

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Factores que influyen en el consumo de tabaco, alcohol y sustancias psicoactivas mediante machine learning

Suggested citation:
Sandoval López X, Tejada DA. Factors influencing the consumption of tobacco, alcohol, and psychoactive substances using machine learning. 2025;8(3):245-257. DOI: 10.5377/alerta.v8i3.20719

Editor:
Hazel García.

Received:
September 19, 2024.

Accepted:
June 24, 2025.

Published:
July 31, 2025.

Author contribution:
XSL[1],DAT[2]: study conception, manuscript design, literature search, data collection,data or software management, data analysis, writing, revising and editing.

Conflicts de interest:
No conflicts of interest.

Introduction

Addiction to psychoactive substances is a global challenge that affects the physical, mental, and emotional health of millions of people around the world.[i] This phenomenon not only has individual consequences but also generates a significant social and economic impact, contributing to increased criminality, family dissolution, and overloaded health systems.[i]

According to the World Health Organization (WHO), in the year 2022, approximately 275 million people consumed some type of drug, and more than 36 million presented consumption-related disorders. In the same year, in Latin America and the Caribbean, at least 4.4 million men and 1.2 million women suffered from drug use disorders.[ii]

By 2020, 22.3 % of the world's population was using tobacco.[iii] By 2021, it was estimated that 7 % of the world's population (400 million) suffered from tobacco use disorders, while 3.7 % (209 million) had alcohol dependence.[iv]

Addiction to psychoactive substances, including alcohol and tobacco, is a multifactorial phenomenon involving genetic, biological, psychological, social, and environmental aspects.[v] These elements may vary according to the culture and context of each region. In El Salvador, scientific evidence on the causality of the phenomenon is limited, which prevents a complete understanding of the particular factors that determine the problem in this population.

In this context, the National Mental Health Survey of El Salvador (ENSM) provides important data on the prevalence of mental disorders and the use of psychoactive substances in different demographic groups. The use of advanced statistical techniques, computational methods, and machine learning models allows a deeper and more accurate analysis of these data, contributing to the identification of addressing knowledge gaps in the population of El Salvador.

Therefore, the objective of the research was to analyze the sociodemographic and mental health factors that influence dependence on alcohol, tobacco, and psychoactive substances in El Salvador using machine learning techniques. This will allow a deeper understanding of the problem and contribute to the design of more effective interventions to address this issue in El Salvador.

Methodology

An analytical cross-sectional study was conducted using secondary data from the ENSM. This survey was conducted by the Ministry of Health of El Salvador through the National Institute of Health. It was designed to obtain nationally representative information on mental health problems in the population from three years of age. For this purpose, specific questionnaires were administered to children (aged three to 12 years), adolescents (aged 13 to 17 years), adults (aged 18 years or older), and older adults (aged 60 years or older). These questionnaires were validated and reviewed by psychologists and psychiatrists. Data collection took place between August and November 2022, involving 11 269 participants.[vi]

The study To assess living conditions, the following operational definitions were constructed. Unsatisfied Basic Needs (UBN) were defined as the lack of an individual or household in at least one of the following aspects: access to housing, access to health services, access to education, and economic capacity. Access to housing was evaluated based on the criteria outlined in "The method of unsatisfied basic needs and its applications in Latin America" by the Economic Commission for Latin America and the Caribbean (ECLAC), specifically focusing on the variables of overcrowding and housing quality. Housing was considered inadequate if it had a dirt floor, dirt walls, roofs made of natural fibers such as straw or palm leaves, or was constructed from waste materials. Overcrowding was defined as three or more people sharing the same room.

Access to sanitation was assessed according to the type of excreta disposal system and the availability of basic services. Access to education was measured by the attendance of school-age children to educational institutions. Economic capacity was analyzed in terms of the probability of insufficient income, taking into account the age, educational level, household size, and employment status of household members. To classify the risk of substance use, the WHO screening test for alcohol, tobacco, and substance use (ASSIST) was used.

For continuous variables, the Anderson-Darling normality test was performed (p-value < 0.05), and the median was used, along with interquartile ranges (IQR). Additionally, frequency tables were constructed, including percentages, 95 % confidence intervals, and p-values for differences in proportions.

El Salvador is politically divided into five regions, which in turn are subdivided into 14 departments categorized by age group, sex, and place of origin. The Mann-Whitney U test was used to compare the medians between the groups based on sex and urban or rural origin. Similarly, the Kruskal-Wallis test was used to assess the differences among groups based on region, department, and educational level. To analyze differences in proportions, the Chi-square test was applied. To identify specific differences between more than two groups or measures, the Bonferroni correction was used.

To construct the logistic regression model, a correlation matrix was generated, and a cut-off point between -0.7 and 0.7 was established to include the variables in the model. The balance of the model was eva-

luated by analyzing the outcome variables and comparing the proportions of positive and negative consumption risk records using distribution plots. In addition, the Chi-square test was applied to verify whether there were significant differences in the distribution of the outcome variable.

To address the class imbalance, the oversampling method was employed using the "ROSE" package in RStudio and the "ovun. sample" function with the "over" method to increase the number of minority class samples and balance the training data.

Binomial logistic regression with machine learning was performed using a 77 % training set and a 23 % test set for smoking, as well as a 75 % training set and a 25 % test set for alcohol and psychoactive substance use.

The effect of confounding variables was controlled by stratification and covariate adjustment techniques in the model. The goodness of fit of the model was determined using likelihood ratio, Wald, ROC curve, and confusion matrix tests. For the geospatial analysis, specific rates were calculated by department and type of substance and represented in a choropleth map at the departmental level, stratified through a clustering analysis.

For data processing and analysis, RStudio version 4.3.2 was used. For geospatial analysis, QGIS version 3.34.3 was used, with the WGS 1984/EPSG: 4326 coordinate system.

The research was carried out in accordance with good clinical practice. The database was coded to maintain the confidentiality of the participants, and the study protocol was approved by the INS ethics committee under registration CEINS/2024/005.

Results

Demographics

A total of 7260 adults were analyzed, 55.4 % of whom were from rural areas, $p < 0.01$. The median age of the population was 45 years (IQR = 31-61), with a minimum age of 18 years and a maximum of 97 years, p 0.01. The median age of males was 47 years (IQR = 31-63), and of females was 44 years (IQR = 31-60), $p < 0.001$.

According to their origin, the median age of people from urban areas was 48 years (IQR = 34-64), while those from rural areas was 43 years (IQR = 30-59), $p < 1$. Regarding the regions, the metropolitan area had the highest median age at 48 years (IQR = 33-64), while the lowest was observed in the eastern region at 43 years (IQR = 30-60), $p < 0.001$. Post-hoc comparisons showed differences between the metropolitan region and the western, eastern, and paracentral regions.

The paracentral region had the highest proportion of the rural population (66.5 %), while by the department, it was La Unión (78.8 %), $p < 0.001$. In contrast, San Salvador had the highest proportion of urban population (77.8 %), $p < 0.001$. San Miguel showed no differences in the origin of the participants ($p < 0.599$).

Of the participants, 69.9 % were women ($p < 0.001$). The paracentral and western regions showed the highest proportions of women, with 71.9 % and 71.5 %, respectively ($p < 0.001$). At the departmental level, the highest proportions of women were found in Cabañas (74 %), Sonsonate (73.3 %), and La Paz (72.4 %), $p < 0.01$.

Sociodeographic, psychological, and smoking variables

94.1 % of the population presented a low level of risk of tobacco use, while 5.7 % presented a moderate risk and 0.2 % a high risk The metropolitan region had an 8 % moderate risk, and the urban area had a 6.5 % moderate risk, $p < 0.001$. In terms of age group, the group aged 20 to 29 years had the highest percentage of moderate risk (7.1 %) and was second in high risk (0.4 %). The group younger than 20 years had the highest proportion of high-risk (0.5 %). According to sex, men had the highest proportions of moderate (14.7 %) and high (0.7 %) risk compared to women (1.8 and 0 % respectively), $p < 0. 001$.

People with a mental health diagnosis showed a higher percentage of moderate (8.2 %) and high (0.4 %) risk compared to those without a diagnosis, $p < 0.01$. Anxiety and its different degrees showed a significant association with tobacco use, observing that as the degree of anxiety increases, consumption differences also increase ($p < 0.001$).

General stress status showed no significant differences ($p = 0.617$), general post-traumatic stress disorder (PTSD) ($p = 0.003$), and PTSD severity scale ($p < 0.001$) showed significant differences. Persons with suicidal ideation and behavior had higher percentages of moderate risk in tobacco use (8.7 % and 18.1 %, respectively), $p < 0.001$. People with depression and its degrees also showed differences in tobacco use ($p = 0.012$ and $p = 0.008$, respectively) (Table 1).

Sociodeographic, psychological, and alcohol variables

96.9 % of the participants had a low level of risk in alcohol consumption, while 2.9 % had a moderate risk and 0.3 % had a high risk. The metropolitan region had 3.9 % moderate risk, followed by the western and

paracentral regions with 3 % and 2.8 %, respectively, showing significant differences in moderate risk ($p < 0.001$) but not in high risk ($p = 0.334$).

The urban area registered 3.3 % moderate risk and 0.3 % high risk, with significant differences in moderate risk ($p < 0.001$) but no differences in high risk ($p = 0.627$). Male sex presented higher moderate (7.5 %) and high (0.7 %) consumption compared to the female sex, with 0.9 % and 0.1 %, respectively, $p < 0.001$.

The younger than 20 years groups and 20-29 years showed a higher moderate risk, with 4.5 % and 3.6 %, respectively, with significant differences in both moderate and high risk, $p < 0.001$. Significant differences were also found between mental health diagnosis and moderate risk of alcohol use, as well as having experienced discrimination ($p < 0.01$). In addition, PTSD, depression, and anxiety showed significant differences with moderate and high-risk levels of alcohol consumption ($p < 0.01$) (Table 2).

Sociodemographic and psychological variables of psychoactive substance use

96.8 % of the participants presented a low risk of psychoactive substance use, while 3.2 % showed a moderate risk. Only one person was classified as high risk. This was a 44-year-old woman, originally from Santa Ana, with high consumption of sedatives, negative thoughts, low resilience, stressful situations due to her illness, depression, and a violent situation. The metropolitan region had the highest percentage of moderate consumption (5.2 %), followed by the paracentral region (3.7 %) and the central region (3.5 %), with a significant difference ($p < 0.001$). Urban areas also had higher moderate consumption (3.7 %), with those under 20 years, 20-29 years, and 40-49 years showing the highest levels of moderate consumption, at 5.5 %, 3.6 %, and 3.8 %, respectively.

Men had a higher moderate risk of psychoactive substance use (5.7 %) compared to women (2.2 %), $p < 0.001$. Persons who are divorced (6.5 %) and single (4.4 %) showed higher moderate use compared to those with a partner ($p < 0.001$).

People with a mental health diagnosis had a higher risk of moderate consumption (9.0 %) compared to those without a diagnosis (3.0 %), $p < 0.001$. Likewise, those who reported negative thoughts presented a higher moderate risk (4.3 %) compared to those who did not (3.0 %), $p < 0.001$. Those with low and moderate levels of resilience showed higher rates of moderate use (3.8 % and 3.1 %, respectively) compared to those with high resilience (2.6 %), $p < 0.001$. Significant statistical differences were found between levels of depression and anxiety and psychoactive substance use ($p < 0.01$), as well as among people with suicidal ideation and behavior ($p < 0.001$) (Tabla 3).

Rates per 100 000 population of tobacco, alcohol, and psychoactive substance use

Regarding the risk of tobacco use, the national rate of moderate risk of tobacco use was 9.4 %. Cabañas had the highest rate, with 13.9 %, followed by San Vicente (13.4 %) and Santa Ana (13.3 %). For high risk, the national rate was 0.36 %, with San Vicente (2.5 %) and Cabañas (2.1 %) being the departments with the highest rates.

Regarding alcohol consumption, the national rate for moderate risk was 4.7 %. San Vicente had the highest rate, with 8.4 %, followed by Chalatenango (7.7 %) and Morazán (7.2 %). For high risk, the national rate was 5.3 %, with Cabañas (2.1 %) and Sonsonate (1.2 %) showing the highest rates per department.

Regarding the use of psychoactive substances, the national rate for moderate risk was 5.3 %. San Vicente had the highest rate, with 10.9 %, followed by Cabañas (9.6 %) and La Paz (8.6 %).

Clustering analysis

In the K-means clustering model applied to the standardized rates of smoking (high and moderate), alcohol consumption (high and moderate), and psychoactive substance use (moderate) in the different departments, three clusters were defined. The high-risk cluster included San Salvador, while the moderate-risk cluster grouped the departments of San Miguel, Santa Ana, Sonsonate, and La Libertad (Figure 1).

Correlation analysis

A strong correlation was observed between high alcohol consumption and moderate tobacco consumption (0.96). A high correlation was also found between moderate tobacco consumption and moderate consumption of psychoactive substances (0.93). In addition, there was a significant correlation between moderate alcohol consumption and moderate consumption of psychoactive substances (0.90), as well as between high tobacco consumption and moderate consumption of psychoactive substances (0.88).

Table 1. Distribution of tobacco use by psychological and mental health factors.

Variable	Category	Level of risk									Total	%	**p value
		Low	%	IC 95 %	Moderate	%	IC 95 %	High	%	IC 95 %			
Mental health diagnosis	Yes	244	91,4	(88,0-94.8)	22	8,2	(4,9-11,5)	1	0,4	(-0,4-1,1)	267	3,7	<0,01
	No	6481	94,3	(93,7-94,8)	380	5,5	(5,0-6,1)	15	0,2	(0,1-0,3)	6876	94,7	<0,01
	No data	106	90,6	(85,3-95,9)	11	9,4	(4,1-14,7)	0	0	(0,0-0,0)	117	1,6	<0,01
Negative thinking	Yes	1073	93,5	(92,1-94,9)	71	6,2	(4,8-7,6)	3	0,3	(0,0-0,6)	1147	15,8	<0,01
	No	5758	94,2	(93,5-94,9)	342	5,6	(5,0-6,2)	13	0,2	(0,1-0,3)	6113	84,2	<0,01
Discrimination	Yes	1043	93,0	(91,5-94,5)	74	6,6	(5,2-8,0)	5	0,4	(0,1-0,7)	1122	15,5	<0,01
	No	5788	94,3	(93,6-95,0)	339	5,5	(4,9-6,1)	11	0,2	(0,1-0,3)	6138	84,5	<0,01
Stress by COVID-19	Yes	6502	94,3	(93,6 , 95,0)	394	5,5	(4,9 , 6,1)	12	0,2	(0,1 , 0,3)	6908	95,2	<0,01
	No	329	19,0	(16,0 , 22,0)	19	1,0	(0,5 , 1,5)	4	1,1	(0,1-2,1)	352	4,8	<0,01
COVID-19 stress levels	No	329	93,5	(90,6-96,4)	19	5,4	(3,1-7,7)	4	1,1	(0,1-2,1)	352	4,8	<0,01
	Very low	2970	93,8	(92,9-94,7)	189	6,0	(5,2-6,8)	7	0,2	(0,1-0,3)	3166	43,6	<0,01
	Low	2971	94,3	(93,4-95,2)	173	5,5	(4,7-6,3)	5	0,2	(0,0-0,3)	3149	43,4	<0,01
	Moderate	532	94,5	(92,4-96,6)	31	5,5	(3,6-7,4)	0	0	-	563	7,8	<0,01
	High	29	96,7	(91,3-100,0)	1	3,3	(0,0-9,7)	0	0	-	30	0,4	<0,01
Resilience	Low	1436	94,6	(93,2-96,0)	76	5,0	(3,9-6,1)	6	0,4	(0,1-0,7)	1518	20,9	<0,01
	Moderate	4795	94,1	(93,3-94,9)	291	5,7	(5,1-6,3)	10	0,2	(0,1-0,3)	5096	70,2	<0,01
	High	600	92,9	(90,6-95,2)	46	7,1	(5,2-9,0)	0	0	-	646	8,9	<0,01
Stressful situation	Yes	2593	93,8	(92,8-94,8)	163	5,9	(5,0-6,8)	9	0,3	(0,1-0,5)	2765	38,1	<0,01
	No	4238	94,3	(93,5-95,1)	250	5,6	(4,9-6,3)	7	0,2	(0,1-0,3)	4495	61,9	<0,01
PTSD*	Yes	411	92,8	(90,0-95,6)	30	6,8	(4,4-9,2)	2	0,5	(0,0-1,2)	443	6,1	<0,01
	No	6420	94,2	(93,6-94,8)	383	5,6	(5,1-6,1)	14	0,2	(0,1-0,3)	6817	93,9	<0,01
PTSD* Grades	No	6420	94,2	(93,6-94,8)	383	5,6	(5,1-6,1)	14	0,2	(0,1-0,3)	6817	93,9	<0,01
	Mild-moderate	343	93,2	(90,6-95,8)	23	6,3	(3,8-8,8)	2	0,5	(0,0-1,2)	368	5,1	<0,01
	Moderate-severe	64	91,4	(84,6-98,2)	6	8,6	(2,0-15,2)	0	0	-	70	1,0	<0,01
	Severe-extreme	4	80,0	(44,9-115,1)	1	20,0	(0,0-55,1)	0	0	-	5	0,1	<0,01
Depression	Yes	4355	93,8	(93,1 , 94,5)	277	6,0	(5,3 , 6,6)	13	0,3	(0,1 , 0,4)	4645	64,0	<0,01
	No	2476	94,7	(93,8 , 95,5)	136	5,2	(4,3 , 6,1)	3	0,1	(0,0 , 0,2)	2615	36,0	<0,01
Degrees of depression	No	2476	94,7	(93,7-95,5)	136	5,2	(4,4-6,1)	3	0,1	(0,0-0,3)	2615	36,0	<0,01
	Minimum	2801	93,8	(92,7-94,7)	177	5,9	(5,2-6,8)	7	0,2	(0,1-0,5)	2985	41,1	<0,01
	Slight	1230	93,9	(92,5-95,1)	75	5,7	(4,6-7,1)	5	0,4	(0,1-0,9)	1310	18,0	<0,01
	Moderate	236	93,7	(89,8-96,3)	16	6,3	(3,7-10,2)	0	0	(0,0-1,5)	252	3,5	<0,01
	Moderately severe	59	90,8	(80,7-96,5)	5	7,7	(2,6-17,0)	1	1,5	(0,0-8,3)	65	0,9	<0,01
	Severe	29	87,9	(70,8-96,0)	4	12,1	(4,0-29,2)	0	0	(0,0-10,5)	33	0,5	<0,01
Anxiety	Yes	1318	93,3	(91,8-94,5)	90	6,4	(5,2-7,8)	5	0,4	(0,1- 0,9)	1413	19,5	<0,01
	No	5513	94,3	(93,5-94,9)	323	5,5	(5,0-6,1)	11	0,2	(0,1-0,3)	5847	80,5	<0,01
Degrees of anxiety	No	5513	94,3	(93,5-94,9)	323	5,5	(5,0-6,1)	11	0,2	(0,1-0,3)	5847	80,5	<0,01
	Slight	1081	93,3	(91,6-94,7)	74	6,4	(5,1-7,9)	4	0,3	(0,1-0,8)	1159	16,0	<0,01
	Moderate	181	94,8	(90,4-97,4)	10	5,2	(2,6-9,6)	0	0	(0,0-1,9)	191	2,6	<0,01
	Severe	56	88,9	(77,8-95,8)	6	9,5	(3,6-19,6)	1	1,6	(0,0-8,6)	63	0,9	<0,01
Suicidal ideation	Yes	451	90,9	(87,8-93,3)	43	8,7	(6,4-11,5)	2	0,4	(0,1-1,4)	496	6,8	<0,01
	No	6380	94,3	(93,6-94,9)	370	5,5	(5,0-6,0)	14	0,2	(0,1-0,4)	6764	93,2	<0,01
Suicidal behavior	yes	86	81,9	(73,0-88,4)	19	18,1	(11,6-27,0)	0	0	(0,0-3,4)	105	1,4	<0,01
	No	6745	94,3	(93,6-94,9)	394	5,5	(5,0-6,0)	16	0,2	(0,1-0,4)	7155	98,6	<0,01
Total	-	6831	94,1	(93,3-94,7)	413	5,7	(5,2-6,2)	16	0,2	(0,1-0,4)	7260	100	-

*PTSD: Post-traumatic stress disorder.

** P-value of difference of proportions of risk level.

Table 2. Distribution of alcohol consumption by psychological and mental health factors.

Variable	Category	Level of risk									Total	%	**p-value
		Low	%	IC 95 %	Moderate	%	IC 95 %	High	%	IC 95 %			
Mental health diagnosis	Yes	254	95,1	(91,6-97,2)	13	4,9	(2,8-8,4)	0	0,0	-	267	3,7	<0,001
	No	6664	96,9	(96,4-97,3)	192	2,8	(2,4-3,2)	20	0,3	(0,3-0,4)	6876	94,7	<0,001
	No data	115	98,3	(93,5-99,5)	2	1,7	(0,5-6,5)	0	0	-	117	1,6	<0,001
Negative thinking	Yes	1109	96,7	(95,4-97,6)	31	2,7	(1,9-3,8)	7	0,6	(0,3-1,3)	1147	15,8	<0,001
	No	5924	96,9	(96,4-97,3)	176	2,9	(2,5-3,3)	13	0,2	(0,2-0,4)	6113	84,2	<0,001
Discrimination	Sí	1068	95,2	(93,6-96,4)	48	4,3	(3,2-5,6)	6	0,5	(0,2-0,9)	1122	15,5	<0,001
	No	5965	97,2	(96,6-97,6)	159	2,6	(2,2-3,0)	14	0,2	(0,3-0,5)	6138	84,5	<0,001
Stress by COVID-19	Yes	6692	96,9	(96,4-97,3)	197	2,9	(2,5-3,3)	19	0,3	(0,3-0,4)	6908	95,2	<0,001
	No	341	96,9	(94,0-98,2)	10	2,8	(1,5-5,1)	1	0,3	(0,0-1,0)	352	4,8	<0,001
COVID-19 stress levels	No	341	96,9	(94,0-98,2)	10	2,8	(1,5-5,1)	1	0,3	(0,0-1,0)	352	4,8	<0,001
	Very low	3064	96,8	(96,0-97,4)	95	3,0	(2,4-3,6)	7	0,2	(0,3-0,7)	3166	43,6	<0,001
	Bajo	3055	97,0	(96,2-97,6)	84	2,7	(2,1-3,3)	10	0,3	(0,5-1,0)	3149	43,4	<0,001
	Moderate	543	96,4	(94,5-97,6)	18	3,2	(2,0-5,0)	2	0,4	(0,1-1,1)	563	7,8	<0,001
	High	30	100,0	(88,4-100)	0	0,0	-	0	0	-	30	0,4	<0,001
Resilience	Low	1471	96,9	(95,7-97,7)	43	2,8	(2,1-3,8)	4	0,3	(0,1-0,7)	1518	20,9	<0,001
	Moderate	4934	96,8	(96,1-97,3)	147	2,9	(2,5-3,3)	15	0,3	(0,2-0,5)	5096	70,2	<0,001
	High	628	97,2	(95,4-98,2)	17	2,6	(1,6-4,1)	1	0,2	(0,0-1,0)	646	8,9	<0,001
Stressful situation	Yes	2662	96,3	(95,4-97,0)	91	3,3	(2,7-4,0)	12	0,4	(0,2-0,7)	2765	38,1	<0,001
	No	4371	97,2	(96,5-97,7)	116	2,6	(2,1-3,1)	8	0,2	(0,1-0,4)	4495	61,9	<0,001
PTSD*	Yes	415	93,7	(90,7-95,6)	21	4,7	(3,1-7,1)	7	1,6	(0,7-3,3)	443	6,1	<0,001
	No	6618	97,1	(96,6-97,5)	186	2,7	(2,4-3,1)	13	0,2	(0,1-0,3)	6817	93,9	<0,001
PTSD* Grades	No	6618	97,1	(96,6-97,5)	186	2,7	(2,4-3,1)	13	0,2	(0,1-0,3)	6817	93,9	<0,001
	Mild-moderate	345	93,8	(90,6-95,9)	17	4,6	(2,8-7,3)	6	1,6	(0,6-3,5)	368	5,1	<0,001
	Moderate-severe	67	95,7	(87,8-98,5)	2	2,9	(0,7-9,9)	1	1,4	(0,2-7,7)	70	1,0	<0,001
	Severe-extreme	3	60,0	(17,1-92,7)	2	40,0	(7,3-82,9)	0	0	-	5	0,1	<0,001
Depression	Yes	4482	96,5	(95,7-97,1)	146	3,1	(2,7-3,7)	17	0,4	(0,2-0,6)	4645	64,0	<0,001
	No	2551	97,6	(96,8-98,1)	61	2,3	(1,8-3,0)	3	0,1	(0,0-0,3)	2615	36,0	<0,001
Degrees of depression	No	2551	97,6	(96,8-98,1)	61	2,3	(1,8-3,0)	3	0,1	(0,0-0,3)	2615	36,0	<0,001
	Minimum	2893	96,9	(96,1-97,5)	85	2,8	(2,3-3,5)	7	0,2	(0,1-0,5)	2985	41,1	<0,001
	Slight	1259	96,1	(94,8-97,1)	46	3,5	(2,6-4,6)	5	0,4	(0,1-0,9)	1310	18,0	<0,001
	Moderate	239	94,8	(91,2-97,0)	9	3,6	(1,8-6,6)	4	1,6	(0,5-4,0)	252	3,5	<0,001
	Moderately severe	63	96,9	(89,3-99,2)	2	3,1	(0,8-10,7)	0	0	-	65	0,9	<0,001
	Severe	28	84,8	(68,1-93,8)	4	12,1	(4,8-26,6)	1	3,0	(0,5-14,9)	33	0,5	<0,001
Anxiety	Yes	1352	95,7	(94,4-96,7)	51	3,6	(2,7-4,7)	10	0,7	(0,4-1,2)	1413	19,5	<0,001
	No	5681	97,2	(96,6-97,6)	156	2,7	(2,3-3,1)	10	0,2	(0,1-0,3)	5847	80,5	<0,001
Degrees of anxiety	No	5681	97,2	(96,6-97,6)	156	2,7	(2,3-3,1)	10	0,2	(0,1-0,3)	5847	80,5	<0,001
	Slight	1113	96,0	(94,5-97,1)	38	3,3	(2,4-4,5)	8	0,7	(0,3-1,3)	1159	16,0	<0,001
	Moderate	182	95,3	(91,0-97,7)	8	4,2	(2,0-8,2)	1	0,5	(0,1-2,8)	191	2,6	<0,001
	Severe	57	90,5	(80,0-95,9)	5	7,9	(3,3-17,6)	1	1,6	(0,3-8,4)	63	0,9	<0,001
Suicidal ideation	Yes	459	92,5	(89,7-94,5)	31	6,3	(4,4-8,8)	6	1,2	(0,5-2,6)	496	6,8	<0,001
	No	6574	97,2	(96,7-97,6)	176	2,6	(2,3-3,0)	14	0,2	(0,1-0,3)	6764	93,2	<0,001
Suicidal behavior	Yes	94	89,5	(82,0-94,1)	10	9,5	(5,2-16,8)	1	1,0	(0,2-5,4)	105	1,4	<0,001
	No	6939	97,0	(96,5-97,4)	197	2,8	(2,4-3,1)	19	0,3	(0,2-0,4)	7155	98,6	<0,001
Total	-	7033	96,9	(96,5-97,2)	207	2,9	(2,5-3,3)	20	0,3	(0,2-0,4)	7260	100	<0,001

*PTSD: Post-traumatic stress disorder.

** P-value of difference of proportions of risk level..

Tabla 3. Distribution of psychoactive substance use by psychological and mental health factors.

Variable	Category	Level of risk									Total	%	**p-value
		Low	%	IC 95 %	Moderate	%	IC 95 %	High	%	IC 95 %			
Mental health diagnosis	Sí	243	91,0	(86,9 - 93,8)	24	9,0	(6,2 - 13,1)	267	3,7	<0,001	267	3,7	<0,001
	No	6670	97,0	(96,5 - 97,4)	205	3,0	(2,6 - 3,5)	6875	94,7	<0,001	6876	94,7	<0,001
	No dato	113	96,6	(91,5 - 98,6)	4	3,4	(1,4 - 8,5)	117	1,6	<0,001	117	1,6	<0,001
Negative thinking	Sí	1098	95,7	(94,4 - 96,7)	48	4,3	(3,3 - 5,6)	1146	15,8	<0,001	1147	15,8	<0,001
	No	5928	97,0	(96,4 - 97,4)	185	3,0	(2,6 - 3,6)	6113	84,2	<0,001	6113	84,2	<0,001
Discrimination	Sí	1066	95,0	(93,5 - 96,2)	56	5,0	(3,8 - 6,5)	1122	15,5	<0,001	1122	15,5	<0,001
	No	5960	97,1	(96,5 - 97,5)	177	2,9	(2,5 - 3,5)	6137	84,5	<0,001	6138	84,5	<0,001
Stress by COVID-19	Sí	6684	96,8	(96,3 - 97,3)	223	3,2	(2,7 - 3,7)	6907	95,2	<0,001	6908	95,2	<0,001
	No	342	97,2	(94,6 - 98,6)	10	2,8	(1,4 - 5,4)	352	4,8	<0,001	352	4,8	<0,001
COVID-19 stress levels	No	342	97,2	(94,6 - 98,6)	10	2,8	(1,4 - 5,4)	352	4,8	<0,001	352	4,8	<0,001
	Very low	3059	96,6	(95,9 - 97,1)	106	3,4	(2,9 - 4,1)	3165	43,6	<0,001	3166	43,6	<0,001
	Bajo	3056	97,0	(96,4 - 97,5)	93	3,0	(2,5 - 3,6)	3149	43,4	<0,001	3149	43,4	<0,001
	Moderate	539	95,7	(93,7 - 97,1)	24	4,3	(2,9 - 6,3)	563	7,8	<0,001	563	7,8	<0,001
	High	30	100,0	(88,7 - 100,0)	0	0	-	30	0,4	<0,001	30	0,4	<0,001
Resilience	Low	1461	96,2	(95,1 - 97,0)	56	3,8	(3,0 - 4,9)	1517	20,9	<0,001	1518	20,9	<0,001
	Moderate	4936	96,9	(96,4 - 97,3)	160	3,1	(2,7 - 3,6)	5096	70,2	<0,001	5096	70,2	<0,001
	High	629	97,4	(95,7 - 98,4)	17	2,6	(1,6 - 4,3)	646	8,9	<0,001	646	8,9	<0,001
Stressful situation	Yes	2656	96,1	(95,3 - 96,8)	108	3,9	(3,2 - 4,7)	2764	38,1	<0,001	2765	38,1	<0,001
	No	4370	97,2	(96,6 - 97,6)	125	2,8	(2,4 - 3,4)	4495	61,9	<0,001	4495	61,9	<0,001
PTSD*	Yes	413	93,2	(90,4 - 95,2)	30	6,8	(4,8 - 9,6)	443	6,1	<0,001	443	6,1	<0,001
	No	6613	97,0	(96,5 - 97,4)	203	3,0	(2,6 - 3,5)	6816	93,9	<0,001	6817	93,9	<0,001
PTSD* Grades	No	6613	97,0	(96,5 - 97,4)	203	3,0	(2,6 - 3,5)	6816	93,9	<0,001	6817	93,9	<0,001
	Mild-moderate	347	94,3	(91,3 - 96,2)	21	5,7	(3,8 - 8,7)	368	5,1	<0,001	368	5,1	<0,001
	Moderate-severe	63	90,0	(80,2 - 95,3)	7	10,0	(4,7 - 19,8)	70	1,0	<0,001	70	1,0	<0,001
	Severe-extreme	3	60,0	(17,0 - 92,7)	2	40,0	(7,3 - 83,0)	5	0,1	<0,001	5	0,1	<0,001
Depression	Yes	4466	96,1	(95,4 - 96,6)	178	3,9	(3,4 - 4,6)	4644	64,0	<0,001	4645	64,0	<0,001
	No	2560	97,9	(97,2 - 98,4)	55	2,1	(1,6 - 2,8)	2615	36,0	<0,001	2615	36,0	<0,001
Degrees of depression	No	2560	97,9	(97,2 - 98,4)	55	2,1	(1,6 - 2,8)	2615	36,0	<0,001	2615	36,0	<0,001
	Minimum	2881	96,5	(95,7 - 97,1)	103	3,5	(2,9 - 4,3)	2984	41,1	<0,001	2985	41,1	<0,001
	Slight	1264	96,5	(95,3 - 97,3)	46	3,5	(2,7 - 4,7)	1310	18,0	<0,001	1310	18,0	<0,001
	Moderate	235	93,3	(89,4 - 95,8)	17	6,7	(4,2 - 10,6)	252	3,5	<0,001	252	3,5	<0,001
	Moderately severe	57	87,7	(77,0 - 93,9)	8	12,3	(6,1 - 23,0)	65	0,9	<0,001	65	0,9	<0,001
	Severe	29	87,9	(71,8 - 95,6)	4	12,1	(4,4 - 28,2)	33	0,5	<0,001	33	0,5	<0,001
Anxiety	Yes	1351	95,6	(94,3 - 96,6)	62	4,4	(3,4 - 5,7)	1413	19,5	<0,001	1413	19,5	<0,001
	No	5675	97,1	(96,5 - 97,5)	171	2,9	(2,5 - 3,5)	5846	80,5	<0,001	5847	80,5	<0,001
Degrees of anxiety	No	5675	97,1	(96,5 - 97,5)	171	2,9	(2,5 - 3,5)	5846	80,5	<0,001	5847	80,5	<0,001
	Slight	1114	96,1	(94,7 - 97,1)	45	3,9	(2,9 - 5,3)	1159	16,0	<0,001	1159	16,0	<0,001
	Moderate	176	92,1	(87,4 - 95,1)	15	7,9	(4,9 - 12,6)	191	2,6	<0,001	191	2,6	<0,001
	Severe	61	96,8	(88,8 - 99,1)	2	3,2	(0,9 - 11,2)	63	0,9	<0,001	63	0,9	<0,001
Suicidal ideation	Yes	455	91,7	(88,8 - 93,9)	41	8,3	(6,1 - 11,2)	496	6,8	<0,001	496	6,8	<0,001
	No	6571	97,1	(96,6 - 97,5)	192	2,9	(2,5 - 3,4)	6763	93,2	<0,001	6764	93,2	<0,001
Suicidal behavior	Yes	89	84,8	(76,5 - 90,4)	16	15,2	(9,6 - 23,5)	105	1,4	<0,001	105	1,4	<0,001
	No	6937	97,0	(96,5 - 97,4)	217	3,0	(2,6 - 3,5)	7154	98,6	<0,001	7155	98,6	<0,001
Total	-	7026	96,8	(96,3 - 97,2)	233	3,2	(2,8 - 3,7)	7259	100	<0,001	7260	100	<0,001

*PTSD: Post-traumatic stress disorder.

** P-value of difference of proportions of risk level.

Multivariate analysis

In tobacco use, age (OR=0.99; p < 0.01), higher educational level (OR= 0.63; p < 0.01), and female sex (OR=0.09; p < 0.01) showed a protective effect, whereas living in urban areas was associated with an increased risk of tobacco use (OR=1.46; p < 0.01). Anxiety (OR=1.81; p < 0.01), having a mental health diagnosis (OR=1.41; p < 0.01), and depression (OR=1.29; p < 0.01) were associated with an increased risk of tobacco use, while a better work environment presented a protective association (OR = 0.95; p = 0.01).

For alcohol consumption, older age (OR = 0.97; p < 0.01) and female sex (OR = 0.08; p < 0.01) showed a protective association, while living in an urban area was associated with a risk (OR = 1.79; p < 0.01). Work environment had a significant protective association (OR = 0.95; p = < 0.001), while anxiety (OR = 2.01; p < 0.01) and depression (OR =1.47; p < 0.01) were associated with risk.

In the consumption of psychoactive substances, older age (OR = 0.99; p < 0.01) and female sex (OR = 0.09; p < 0.01) showed a protective association, while urban areas represented risk (OR = 1.46; p < 0.01).

Significant protective associations were found for work environment (OR = 0.95; p = 0.013), community participation index (OR = 0.92; p = 0.009), adequate economic income (OR = 0.81; p = 0.005), having a partner (OR = 0.88; p = 0.013), higher education level (OR = 0.63; p < 0.01), with the risk factors being anxiety (OR = 1.81; p < 0.01), mental health diagnosis (OR = 1.41; p = 0.005), and depression (OR = 1.29; p < 0.01) (Tabla 4).

Discussion

This study provides an overview of the demographic and psychological characteristics of the use of tobacco, alcohol, and psychoactive substances in adults in El Salvador.

One of the most relevant findings was the strong correlation between the consumption of different substances, where individuals who consume one are highly likely to consume others. These patterns are consistent with previous research, which suggests that consumption is a gradual process that usually involves polyconsumption.[vii]

Substance use showed differentiated patterns according to origin, with higher risk levels in the metropolitan region and urban areas, similar to what has been observed in other research, which suggests that consumption is due to greater availability of drugs,[viii,ix] advertising, and social acceptance of them,[x,xi] increasing the probability of consumption and development of addictions.[xii]

Likewise, the cluster analysis confirmed the grouping of departments with similar consumption characteristics, revealing significant variations between groups. This finding coincides with previous studies that show regional and territorial differences, highlighting how the geographical context influences consumption patterns.[xiii,xiv]

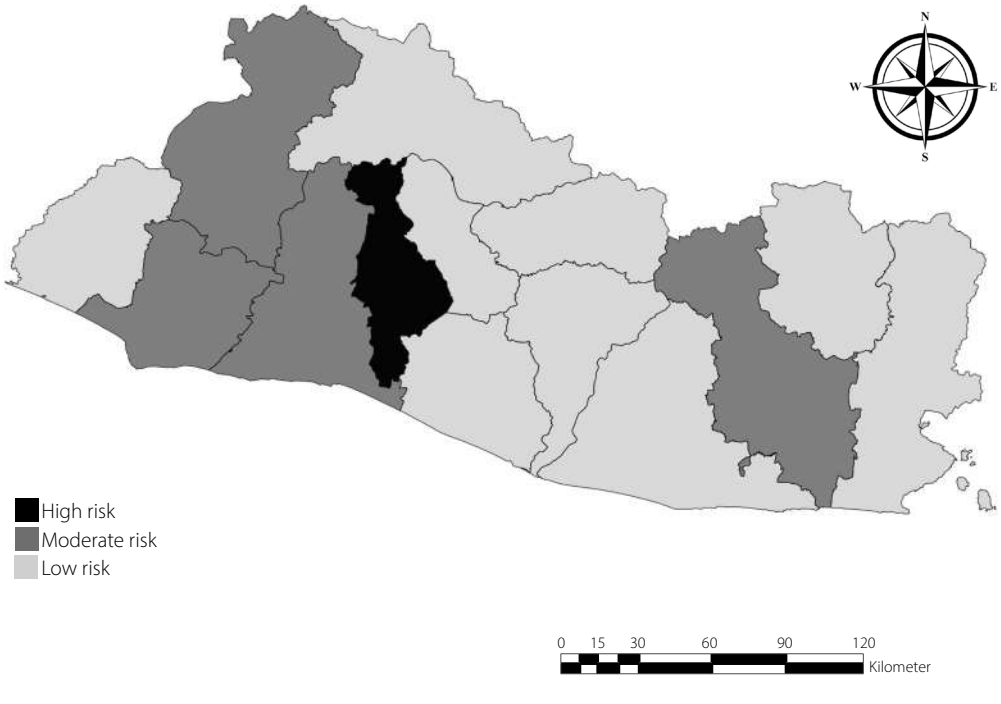

Figure 1. Geospatial analysis of substance use and risk through clusters in El Salvador, ENSM 2022

Young people showed a higher risk of consumption than older adults, consistent with previous studies indicating that the consumption of addictive substances usually begins in adolescence and young adulthood, thus explaining the observed patterns.[xiii,xv,xvi] Significant differences in substance use were identified between men and women, with the risk being higher in men, a finding widely documented in the scientific literature.[xiii] Sociocultural factors, such as masculinity norms, socialization patterns, and substance availability, could contribute to these differences.[xviii-xix]

People with lower educational levels showed a higher risk of substance use compared to those with higher educational levels, a pattern supported by previous research associating lower education with a higher prevalence of substance use.[xiv,xvii,xx] This could be related to a lower perception of risk, lack of access to information and adequate coping strategies, as well as unfavorable socioeconomic conditions that may increase vulnerability to this type of consumption.[xiv,xx,xxi]

Single people presented a higher risk of consumption, which is consistent with the literature, which indicates that the lack of a social support network and exposure to environments prone to consumption and addictions may influence this behavior.[xxii] The lack of a stable partner and family structure could increase the vulnerability of single adults to substance use. However, multiple other factors also influence this behavior.[xx]

The multivariate analysis determined that the better the working conditions, the lower the probability of consumption. This association was described by other studies that consider that unemployment or precarious working conditions can generate an environment that increases anxiety and stress and thus increases susceptibility to addictions.[iv,xviii,xx] In this sense, an adequate economic income was associated as a protective factor for tobacco consumption but as a risk factor for alcohol consumption. Economic factors play a complex role in addictions since greater economic capacity can facilitate access to substances and increase the frequency of consumption.[xvii] In contrast, adverse economic conditions can increase stress and anxiety, predisposing individuals to resort to consumption as a coping mechanism; however, multiple factors converge in the phenomenon of addictions and influence their development.[xxi,xxiii]

An association was found between various mental health problems and the use of psychoactive substances; a comprehensive approach to mental health, as well as strategies to prevent and address drug use and addictions, could contribute to solving these problems.[xxiv,xxv]

Regarding depressive or anxious symptoms, the multivariate model found that these were associated with an increased risk of substance use. The relationship between mental health problems and substance use has been widely documented, relating substance use as a coping mechanism.[xxiv,xxv]

Other studies point to the influence of neurobiological and genetic factors in the development of mental disorders and addictions.[xxv] However, other research indicates that psychological problems condition a lower capacity for control and a greater propensity to addiction.[xxvii]

PTSD also showed an association with psychoactive substance use, similar to that observed in other studies that found a relationship between PTSD and substance use as a mechanism to manage trauma. [xxviii] This association highlights the need to implement interventions that not only address substance use but also consider the psychological and social factors related to addictions.[xxix]

The COVID-19 pandemic has also contributed to the aggravation of addictions. Recent studies documented an increase in substance use as a way to cope with uncertainty and isolation.[xxx] Other studies reported a significant increase in substance use as a consequence of high levels of stress and anxiety related to COVID-19.[xxxi,xxxii]

In this study, community involvement acted as a protective factor for substance use. Some studies indicate that supportive social networks provide an environment that promotes resilience and emotional well-being, which reduces vulnerability to substance use.[xxxii,xxxiii] Social support is central to addiction prevention and treatment, highlighting its importance as an integral part of intervention strategies.[xxvii]

Resilience also acted as a protective factor, coinciding with the literature, which indicates that people with coping skills, especially those with family resilience, can face life's difficulties without resorting to the use of addictive substances.[xxxiv]

Finally, behavioral theories consider that the human being is the result of multiple interactions among biological, psychological, and social factors that condition the development and course of addictions.[vii] Similarly, addictions are also seen as developmental disorders influenced by risk factors accumulated throughout life.[xxxv]

The main limitations of the study are related to its cross-sectional design, which prevents the establishment of causal relationships and

Tabla 4. Multivariate analysis of factors associated with the use of tobacco, alcohol, and psychoactive substances in the adult population, ENSM 2022

Substance	Variables	Coefficients	OR	Standard error	z-value	95% CI	p-value
Tobacco * (Intercept)	(Intercept)	2,14	-	0,29	7,5	(4,84 - 14,89)	<0,01
	Age	-0,01	0,99	0,00	-4,7	(0,99 - 1,00)	<0,01
	Female sex	-2,36	0,09	0,05	-43,5	(0,08 - 0,11)	<0,01
	Urban area	0,38	1,46	0,06	6,8	(1,31 - 1,62)	<0,01
	Can read and write	-0,03	0,97	0,08	-0,4	(0,83 - 1,14)	0,71
	Community participation index	-0,08	0,92	0,03	-2,6	(0,87 - 0,98)	0,01
	Has a partner	-0,13	0,88	0,05	-2,5	(0,80 - 0,97)	0,01
	Higher education level	-0,47	0,63	0,09	-5,4	(0,53 - 0,74)	<0,01
	Work environment	-0,05	0,95	0,02	-2,5	(0,92 - 0,99)	0,01
	Negative thinking	0,12	1,13	0,07	1,7	(0,98 - 1,29)	0,09
	Adequate economic income	-0,21	0,81	0,08	-2,8	(0,70 - 0,94)	0,00
	Mental health diagnosis	0,34	1,41	0,12	2,8	(1,11 - 1,78)	0,00
	Depression	0,25	1,29	0,06	4,4	(1,15 - 1,44)	<0,01
	Anxiety	0,59	1,81	0,07	8,8	(1,59 - 2,07)	<0,01
	Works	-0,26	0,77	0,18	-1,4	(0,54 - 1,10)	0,15
	NBI**	-0,15	0,86	0,07	-2,0	(0,74 - 1,00)	0,06
Alcohol +	(Intercept)	1,54	-	0,31	4,95	(2,54 - 8,61)	<0,01
	Age	-0,03	0,97	0	-16,2	(0,97 - 0,97)	<0,01
	Female sex	-2,57	0,08	0,06	-44,89	(0,07 - 0,09)	<0,01
	Urban area	0,58	1,79	0,06	9,86	(1,59 - 2,01)	<0,01
	Can read and write	-0,58	0,56	0,08	-6,89	(0,48 - 0,66)	<0,01
	Community participation index	-0,24	0,78	0,03	-7,47	(0,74 - 0,84)	<0,01
	Has a partner	-0,28	0,76	0,05	-5,17	(0,68 - 0,84)	<0,01
	Higher education level	0,03	1,03	0,08	0,31	(0,87 - 1,21)	0,754
	Work environment	-0,06	0,95	0,02	-2,79	(0,91 - 0,98)	0,005
	Negative thinking	-0,07	0,93	0,07	-0,94	(0,81 - 1,08)	0,349
	Adequate economic income	0,38	1,47	0,08	4,95	(1,26 - 1,71)	<0,01
	Mental health diagnosis	-0,11	0,9	0,14	-0,74	(0,68 - 1,19)	0,461
	Depression	0,39	1,47	0,06	6,51	(1,31 - 1,65)	<0,01
	Anxiety	0,7	2,01	0,07	10	(1,75 - 2,30)	<0,01
	Works	1,65	5,18	0,22	7,41	(3,35 - 8,01)	<0,01
	NBI**	0,04	1,04	0,07	0,51	(0,90 - 1,20)	0,611
Psychoactive substances ^	(Intercept)	0,915	-	0,253	3,62	(1,52 - 4,10)	<0,001
	Age	-0,008	0,99	0,001	-6,23	(0,99 - 0,99)	<0,001
	Female sex	-1,235	0,29	0,046	-26,95	(0,27 - 0,32)	<0,001
	Urban area	0,458	1,58	0,045	10,28	(1,45 - 1,73)	<0,001
	Can read and write	-0,187	0,83	0,067	-2,79	(0,73 - 0,95)	0,005
	With partner	-0,137	0,87	0,043	-3,19	(0,80 - 0,95)	0,001
	Negative thinking	0,194	1,21	0,057	3,42	(1,09 - 1,36)	0,001
	Mental health diagnosis	0,921	2,51	0,093	9,9	(2,09 - 3,01)	<0,001
	Depression	0,872	2,39	0,052	16,73	(2,16 - 2,65)	<0,001
	Resilience	-0,635	0,53	0,228	-2,79	(0,34 - 0,83)	0,005
	PTSD symptoms*** 0.696	0,696	2,01	0,082	8,46	(1,71 - 2,36)	<0,001
	Anxiety	0,132	1,14	0,057	2,32	(1,02 - 1,28)	0,02

**UBN: Unsatisfied Basic Needs.
***PTSD: Post-traumatic stress disorder.
*AUC del 85,8 %.
+AUC del 82,4 %.
^ AUC del 70,1 %.
Likelihood ratio test and Wald test (p <0,01).

may lead to the underestimation of substance use. However, the strength of the study lies in its representativeness at the national level, which provides an overview of the situation in El Salvador and allows for a comprehensive analysis, applying precise statistical models that strengthen the findings. Additionally, the use of artificial intelligence, machine learning, and clustering techniques has been crucial in optimizing the analysis and interpretation of the data.

The results obtained from the ENSM confirm the multifactorial nature of addictions, highlighting the need for interventions that integrate mental health services and address risk factors effectively.[xxxvi]

Due to its multifaceted nature,[xxxv,xxxvi] a comprehensive approach that considers mental health problems,[xxiv,xxv] economic conditions, and access to social support networks[xxvii] is recommended to offer interventions tailored to the needs of individuals. Furthermore, considering that addictions result from multiple interactions, it is necessary to integrate various disciplines and standardize care processes in health systems and to create regulations that address specific problems such as mental health and addictions.[vii]

Conclusion

Young people presented a higher risk of substance use compared to older adults, highlighting vulnerability and the need to target prevention strategies for this group. Additionally, the geographical environment plays a key role in shaping consumption patterns, exhibiting significant variations that are closely tied to social and economic factors. A strong correlation was observed between mental health problems and the consumption of tobacco, alcohol, and psychoactive substances, suggesting that mental disorders are not only a consequence of consumption but also important predisposing factors for the development of addictions. A high correlation was observed between the consumption of different substances, where the use of one increases the probability of consuming others, which aggravates mental health problems and complicates the treatment of addictions.

These findings are important for designing prevention and intervention strategies to address the problem of addiction in El Salvador. In addition, they serve as a basis for generating new research questions and identifying areas of knowledge that require further study, thereby guiding future work on this problem.

Funding

The study was funded by researchers.

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Original Article

Effect of the LED lamp charge on the polymerization depth of a Bulk Fill resin

DOI: 10.5377/alerta.v8i3.20718

Javier Farias Vera[1]*, Susana Pilar Valdizan Cristóbal[2], Javier Guilec Mendoza Evangelista[3], Antonio Alberto Ballarte Baylon[4]

1-4. Hermilio Valdizan National University, Huanuco, Peru.

*Correspondence
jfarias@unheval.edu.pe

1. 0000-0002-3291-4224
2. 0009-0001-3110-1731
3. 0009-0000-5788-6373
4. 0000-0002-0795-9324

OPEN ACCESS

Efecto de la carga de lámparas LED en la profundidad de polimerización en resinas Bulk Fill

Suggested citation:
Farías Vera J, Valdizan Cristóbal SP, Mendoza Evangelista JG, Ballarte Baylon AA. Effect of the LED lamp charge on the polymerization depth of a Bulk Fill resin. Alerta. 2025;8(3):258-263. DOI: 0.5377/alerta.v8i3.20720

Editor:
Hazel García.

Received:
July 26, 2024.

Accepted:
July 3, 2025.

Published:
July 31, 2025.

Author contribution:
JFV[1]; SPVC[2]; JGME [3]: study conception, literature search, data collection,writing, revising, and editing. JFV[1], AABB[4]: manuscript design, data or software management, and data analysis.

Conflicts de interest:
No conflicts of interest.

Abstract
Introduction. In the field of dentistry, the use of light-curing composite resins has grown to meet this demand. **Objective.** Determine the influence of the battery charge of an LED lamp on the depth of cure of a Bulk Fill resin. **Methodology.** An experimental study in vitro used 105 samples of Bulk Fill composite resin blocks, conformed into three groups. Each group consisted of 35 samples, with the lamp loaded at 100 %, 50 %, and 10 % of its maximum capacity, respectively. A stainless steel matrix was fabricated according to the ISO standard specifications in 20 seconds. The removal of unpolymerized material was performed using the scraping test technique, resulting in polymerized (hardened) resin blocks, which were subsequently measured with a certified and calibrated digital micrometer. **Results.** The battery level significantly influenced the groups ($p < 0.01$), decreasing the polymerization depth as the load level decreased. **Conclusion.** The different battery levels of the wireless LED curing unit did influence the depth of polymerization.

Keywords
Polymerization, Composite Resins, Pressure Drop.

Resumen
Introducción. En el campo de la odontología, el uso de resinas compuestas fotopolimerizables ha crecido para satisfacer esta demanda. **Objetivo.** Determinar la influencia de la carga de la batería de una lámpara LED sobre la profundidad de polimerización de una resina *Bulk Fill*. **Metodología.** Estudio experimental in vitro, se emplearon 105 muestras de bloques de resinas compuestas *Bulk Fill* conformadas en tres grupos, cada grupo estaba formado por 35 muestras en bloques de resina cuando la lámpara está cargada al 100 %, al 50 % y al 10 % respectivamente. Se confeccionó una matriz de acero inoxidable con las especificaciones que exige la norma ISO, por 20 segundos. La remoción del material no polimerizado se empleó la técnica de *scraping test* y obteniendo bloques de resina polimerizadas (endurecidas) las cuales han sido medidas con un micrómetro digital certificado y calibrado. **Resultados.** El nivel de la batería influenció significativamente entre los grupos p <0,01 disminuyendo la profundidad de polimerización a medida que disminuye el nivel de carga. **Conclusión.** Los diferentes niveles de batería de la unidad de curado LED inalámbricas si influyeron en la profundidad de polimerización.

Palabras clave
Polimerización, Resinas Compuestas, Pérdida de Carga.

Introduction

Patients in the field of dentistry have become increasingly interested and demanding long-lasting and esthetic treatment outcomes. Consequently, to meet this demand, the use of light-curing composite resins has increased. A resin composite produces a cure when its dimethacrylate resin monomer units react chemically, which creates a rigid cross-linked polymer network[i]. Because they can be inserted into cavities and light-cured in one step in increments up to 4-5 mm thick, block-filled composite resins were developed to save time and simplify the restorative process.[ii-iv]

Professionals should use curing lights that provide the appropriate wavelengths for each resin composite to achieve an adequate amount of polymerization of the material. Due of their narrower emission spectrum, their output peak being close to the 470 nm camphorquinone absorption peak, and their ability to run on battery-operated, according to some studies, light-emitting diode (LED) photoactivation curing lamps are the best choice.[iii]

LED photoactivation devices that require an electrical connection are less common than those that are cordless. Lithium battery is present in most LED devices used in dentistry, but little is known about how it affects the performance of the material polymerization process. The battery level of some LED units may be affected as the irradiance of the units decreases as it is discharged, which deteriorates the properties of the materials used.[v-vii] The objective of this research is to determine the influence of the loading of the battery of an LED lamp on the polymerization depth of a Bulk Fill resin.

Methodology

This is an experimental *in vitro* study conducted between August and October 2023 at the laboratory's facilities, which specialize in mechanical testing of materials and calibration at HIGH LAB.TECHNOLOGY, File N.º 04661-2023, located in Jr. Nepentas 364 Urb San Silvestre, San Juan de Lurigancho - Lima- Peru.

The data collection was performed after photoactivation to initiate the polymerization of the resins. The scraping test technique, endorsed by the ISO 4049 standard, was used, which involves the removal of polymerized resin with the head of a plastic spatula.[viii-xi] The processing technique performed was necessary for both the scraping test technique and the decimal micrometer (Mitutoyo), which included a calibration certification and a radiometer to verify the required intensity of the LED. Furthermore, the responsible person knew the ISO 4049 standard and the scraping test pattern (The ISO standard for resins mentions that it is the process in which the scraping is performed, which was codified as the depth of cure measurement).[v,xi-xiv] For the preparation of composite resin samples, a cylindrical steel matrix (4 mm x 10 mm) with a fixing ring was used, which was precisely made by a turner, to which an amalgam matrix holder was added with a matrix to make a tight fit. This was done to maintain the exact measurements, precision, and characteristics in all the samples to be elaborated, thereby avoiding variations and obtaining samples with a standardized pattern for each group. The perforation depth of the steel mold is 10 mm (height), and the internal circumference is 4 mm, complying with the ISO 4049 standard, in which the Beautifil - Bulk resin (manufactured by the Japanese company Shofu) was introduced in sufficient quantity to complete the matrix (4.5 g in "Universal" shade). The glass plate was placed on the base of the steel mold, and on top of the steel mold, the acetate matrix covered the resin cylinder. The polymerization process, was carried out using a Woodpecker LED lamp (manufactured by the Chinese company Woodpecker) was used for 20 seconds; the manufacturer's recommendations were followed at a light intensity (1000 mW / cm^2 ~ 2500 mW/ cm^2 power[2]), the P2 (regular) intensity mode was used, with a light emission power of 1200 mW/cm, and the recommended time is 20 seconds for good polymerization. The photopolymerization of 35 samples was carried out with the lamp at a load of 100 %. Then, the discharge was performed with vacuum shots until reaching 50 % of the battery capacity, and then 35 resin samples were photopolymerized again. Next, vacuum shots were performed until reaching 10 % of the battery capacity, and the last 35 resin samples were photopolymerized[xiv-xvi].

With the technique of scraping, the test ISO 4049 standard is used for the polymerization process of the resin blocks. The resin cylinder is then carefully removed. The scraping is performed with a plastic spatula that has a non-sharp edge on the lower part, which was not photopolymerized and softened due to a lack of light penetration. This process was performed by only one person to avoid variations of strength when doing the scraping and also the location of the LED lamp. After obtaining the resin cylinder, a digital measuring micrometer was used to make the appropriate measurements. It was measured three times, at the ends and the center, and the average was taken. To obtain the measured value of the cylinder, the corresponding notes were made on the data collection sheet. This result was divided into three parts, and the results of the depth of cure for each sample were obtained. The 105 resin blocks were distributed in groups of 35 blocks per group. In group 1 (control) were 35 cylinders light cured at 100 % battery charge, in group 2 were 35 cylinders light cured at 50 % battery charge, and in group 3 were 35 cylinders light cured at 10 % battery charge.

The wavelength of electromagnetic radiation that determines the color is of a measure of 400 to 700 nm; it was suggested to use the light of the dental lamps with

blue color for having a wavelength that goes from 400 to 515 nm; this wavelength is necessary for the activation or initiation of the photopolymerization process.[xvii-xx] The power or irradiance of the light coming out of the tip of a LED lamp used was measured with a digital radiometer, which is expressed radiometrically as intensity and its unit of measurement according to the international system is W/m², with units of power over area.[xiv,xix-xxi] The measurement of electromagnetic radiation in all wavelengths of the electromagnetic spectrum was used. Power is defined as the amount of electromagnetic energy emitted by a focus in a unit of time. Its unit of measurement is the joule per second (J/s), also known as the watt (W).[xxii]

The discharge of the battery in the Woodpecker LED lamp was performed to determine the percentage of the lamp's charge. Vacuum discharges were made until completely discharging the shots of the lamp, in which, using the simple rule of 3, the percentage in which the shots were found was determined. The lamp completed 606 cycles of 20 seconds each cycle, being 100 % of the cycles from 606 to 572, 50 % of the cycles from 303 to 268, and finally, 10 % of the cycles from 60 to 25.

Statistical methods

The data obtained from the experiment, duly certified by the laboratory, were analyzed using SPSS version 27 statistical programs, which included measures of central tendency, Shapiro-Wilk normality tests, and inferential analysis using the ANOVA hypothesis test.

Results

Tests were performed on 105 resin blocks, divided into three groups of 35 blocks per group. Group 1 control (100 %), Group 2 (50 %), Group 3 (10 %).

Table 1 shows the polymerization depth value of the Bulk Fill resin when the LED lamp is loaded at 10 %, presenting a mean of 3.890 mm and a standard deviation of 0.174 mm; the minimum value was 3.56 mm, and the maximum value was 4.17 mm. In contrast, when the LED lamp is loaded to 50 %, it obtained a mean and standard deviation of 4.078 ± 0.147 mm. The minimum value was 3.80 mm, and the maximum value was 4.36 mm. In the end, the polymerization depth value of the Bulk Fill resin, when the LED lamp is loaded at 100 %, presented a mean of 4.253 mm and a standard deviation of 0.187 mm. The minimum value was 3.80 mm, and the maximum value was 4.61 mm.

According to the results of the Shapiro-Wilk normality test, the data are normally distributed. Table 2 shows that according to the results of the ANOVA test, there are statistically significant differences ($p < 0.05$) between the three groups studied. It was observed that the battery charge of an LED lamp influences the depth of polymerization of a Bulk Fill resin.

The differences were observed the battery charge of a LED lamp at 10 % and 50 % with a p-value < 0.001, when the battery was charged at 10 % and 100 % with p-value < 0.001, and finally, when comparing the means of battery charge at 50 % and 100 %, showed significant differences were observed with a p-value < 0.001.

Table 1. Measurement of the polymerization depth of Bulk Fill resin according to the percentage of LED lamp load.

Battery charge	Mean	Standard deviation	Minimum depth	Maximum depth
10 %	3.890 mm	0,174	3.56 mm	4.17 mm
50 %	4.078 mm	0,147	3.80 mm	4.36 mm
100 %	4.253 mm	0,187	3.80 mm	4.61 mm

Table 2. Influence of the battery charge of an LED lamp on the depth of polymerization of a Bulk Fill resin.

Battery load	Mean	Standard deviation	p-value
10 %	3.890 mm	0,174	0,000
50 %	4.078 mm	0,147	0,000
100 %	4.253 mm	0,187	0,000

Discussion

The factors involved in the polymerization process are crucial to the success of treatments based on resinous materials, such as composite resin. One of these factors is the percentage of battery power used by LED lamp to proactive the composite resins, allowing for the conversion of monomers to polymers to occur. The final result is a fully polymerized (hardened) resin.[ii]

In a study by Pereira *et al.* (2016) it is shown that the load of an LED battery influences the physical, chemical, and mechanical properties of a composite resin as in the degree of conversion, sorption, and solubility of the resin samples[vi] coinciding with the present study in which the load influenced the depth of polymerization, resin property, affecting the chemical property, where the photoactivation of the composite resins is performed by the conversion of monomers to polymers in its entirety obtained by the light intensity emitted by LED lamps.

The findings regarding the measurement of the polymerization depth showed a statistically significant difference between the control and experimental groups, as the control group E1 (high level) had a battery percentage of 100 %. In contrast, the experimental groups E1 (medium level) were charged at 50 % and E2 (low level) at 10 %. Cardozo (2019) reported that the level of irradiance from LED units altered various properties of the resins; among them, the depth of polymerization was altered, which is consistent with the findings of this research.[x]

The polymerization process can be influenced by the brand and type of lamp used for photoactivation of the resin material. Tongtaksin conducted a study to determine the effectiveness of different high-power LED lamps on the depth of polymerization of Bulk Fill composite resin where the results obtained show that there is a significant difference in the depth of polymerization of Bulk Fill composite resin after being photopolymerized with different types of LED lamps; just as the battery percentage of the LED lamp is a factor that influences the polymerization process, so are the physical protection barriers at the tip of the LED lamps as a preventive measure in the control of cross-infection control.[vii]

Concerning LED lamps, currently generation lamps usually have better technical characteristics than second-generation and first-generation lamps; however, in a study by Horna in 2019, an Elipar LED lamp with a power of 1200 mW of second-generation power of 3M brand, polymerized better in terms of depth in Bulk Fill resins concerning the Valo LED lamp (manufactured by the U.S. company Ultradent Products, Inc.) of 1400mW of power, showing that the power does not influence the depth of polymerization, in contrast to this study, in which it was found to have an influence but about the level of the load.[xxiii]

Dentistry is a profession that is constantly being updated and improved, and even more so in the different dental materials that each time present better characteristics in their uses and duration, so it is recommended to carry out studies and constant updates of materials such as resins and LED lamps, among others, in order to know the limitations that they could present.

Conclusion

The polymerization process can be influenced by the type of lamp used for the photoactivation of the resin material (composite resin) in order to determine the effectiveness of different high-power LED lamps on the depth of polymerization of composite resin Bulk Fill type. The battery percentage of a third-generation LED lamp does influence the depth of cure of a Bulk Fill composite resin. Therefore, as the battery of an LED lamp is discharges, the irradiance level decreases, which is directly proportional to the light intensity emitted from the lamp tip; consequently, the polymerization of the resin will be affected.

Funding

No external funds were received for this work.

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Original Article

Survival analysis of gastric cancer patients in El Salvador

DOI: 10.5377/alerta.v8i3.20718

Mariano Salvador Castro Mendoza[1], Hazel C. García[2], David Alexander Tejada[3]*

1. Department of Hemato-oncology, Rosales National Hospital, San Salvador, El Salvador.
2. National Institute of Health, San Salvador, El Salvador.
3. National Health Observatory, National Institute of Health, San Salvador, El Salvador.

*Correspondence
david.tejada@salud.gob.sv

1. 0009-0003-5304-8614
2. 0000-0002-8515-5532
3. 0000-0003-2502-1433

OPEN ACCESS

Análisis de supervivencia de pacientes con cáncer gástrico en El Salvador

Suggested citation:
Castro Mendoza MS, García HC, Tejada DA. Survival analysis of gastric cancer patients in El Salvador. Alerta. 2025;8(3):264-274. DOI: 10.5377/alerta.v8i3.20718

Editor:
David Rivera.

Received:
September 10, 2024.

Accepted:
June 27, 2025.

Published:
July 31, 2025.

Author contribution:
MSCM[1]: study conception, data collection, MSCM[1], HCG[2], DAT[3]: manuscript design, literature search, writing, revising and editing. HCG[2], DAT[3]: data or software management, data analysis.

Conflicts de interest:
No conflicts of interest.

Abstract

Introduction. Gastric cancer is one of the most prevalent and deadly malignancies worldwide. The survival prognosis depends on clinical presentation, diagnostic evaluation, initiation of treatment, and several other influencing factors. The objective of this research was to analyze the four-year survival of gastric cancer patients in El Salvador. **Methodology.** A retrospective cohort study was conducted with patients diagnosed with gastric cancer from a national hospital. Patient characteristics were described, and overall survival rates at one year and four years was calculated using the Kaplan-Meier method. The Tarone-Ware test was used to assess statistical significance with a p-value < 0.05 and 95% confidence intervals. A Cox regression was performed to evaluate the association between independent and dependent variables. **Results.** Seventy-nine patients were analyzed. Overall survival rates at one year and four years were 46.84% and 31.65%, respectively. Chronic kidney disease was associated with a *hazard ratio* (HR) of 4.204, smoking with HR of 3.533, age with HR of 0.98, high blood pressure with HR of 0.654, and alcoholism with HR of 0.367, all with p < 0.05. **Conclusion.** The four-year survival rate is below 40 %. Smoking, chronic kidney disease, cancer stage, and adenocarcinoma decreased four-year survival in patients with gastric cancer.

Keywords
Catheters; Umbilical Veins, Infant, Newborn.

Resumen

Introducción. El cáncer gástrico es una de las neoplasias malignas más prevalentes y mortales a nivel global. El pronóstico de supervivencia depende de la presentación clínica, del estudio de diagnóstico, el inicio del tratamiento, así como una serie de factores que influyen en esta. **Objetivo.** Analizar la supervivencia a los cuatro años de los pacientes con cáncer gástrico en El Salvador. **Metodología.** Se realizó un estudio de cohorte retrospectiva con pacientes con cáncer gástrico de un centro hospitalario. Se hizo una caracterización de los pacientes incluidos en el estudio y se calculó la tasa de supervivencia global al año y a los cuatro años, se utilizó el estimador de Kaplan-Meier y aplicó la prueba de Tarone-Ware como prueba para evaluar la significancia estadística (p < 0,05 e intervalos de confianza al 95 %). Para comprobar la asociación entre las variables independientes y la dependiente, se realizó una regresión de Cox. **Resultados.** Se analizaron 79 pacientes. La supervivencia general al año fue del 46,84 % y a los cuatro años del 31,65 %. La enfermedad renal crónica presentó un *hazard ratio* de 4,204, el tabaquismo fue de 3,533, mientras que, la edad obtuvo un *hazard ratio* de 0,98, la hipertensión arterial un 0,654 y el alcoholismo un 0,367, todas con p < 0,05. **Conclusión.** La supervivencia a los cuatro años es menor al 40 %. El tabaquismo, la enfermedad renal crónica, el estadio del cáncer y el adenocarcinoma disminuyeron la supervivencia a los cuatro años en pacientes con cáncer gástrico.

Palabras clave
Catéteres, Venas Umbilicales, Recién Nacido.

Introduction

Gastric cancer (GC) is among the most prevalent and deadly malignant neoplasms worldwide. It is currently the fifth most common cancer and the third leading cause of cancer-related death globally.[i,ii] Each year, it is estimated that approximately 980 000 new cases of GC are diagnosed and 660 000 GC-related deaths occur globally.[iii] These figures reflect the high mortality burden associated with GC, especially in regions where early diagnosis and effective treatment remain difficult to access.[iv]

Five-year overall survival in GC patients ranges from 20 % to 40 %.[v] In general, younger patients have longer survival compared to older adults, with the risk increasing with advancing age.[vi] However, these differences are determined by multiple factors, such as clinical presentation, stage at diagnosis, presence of comorbidities, substance use, and timely access to treatment.[vii-ix]

Despite advances in diagnosis and treatment, the survival of GC patients remains limited and varies significantly between individuals ten due to clinical, biological, and demographic factors that influence prognosis and treatment efficacy.[xi] Identifying and understanding of these factors is essential to improve outcomes in patients with GC and to implement effective and targeted strategies for early detection of the disease.[vi,xii]

In El Salvador, the available information on GC is limited, highlighting the importance of conducting a survival analysis of patients diagnosed in a tertiary care hospital. This analysis aims to identify the variables that influencesurvival duration in patients with GC, providing valuable information on the factors associated with prognosis. In addition, it offers a comprehensive perspective on how different factors affect clinical outcomes, contributing to a better understanding of the elements that determine the evolution of the disease.

Methodology

A retrospective analytical cohort-type analytical study was conducted with patients registered in the gastric cancer patient database of a national tertiary care hospital in El Salvador in 2019. All patients over 18 years, diagnosed for the first time, and with a confirmatory histopathological diagnosis of GC were included. Patients with incomplete records, those who died within the first 24 hours of admission, those residing abroad or identified as foreign nationals, and those with duplicate records were excluded.

Initially, the database consisted of 81 records; however, after eliminating those that did not meet criteria, the number was reduced to 79. These individuals were followed up until death or until the end of the study, at which point censoring was considered.

Survival time was measured from the date the biopsy was taken until the date of patient death or the last recorded follow-up contact.

To collect the data, a structured questionnaire was designed in digital format using KoboToolbox, a tool for creating, collecting, and managing digital forms. The questionnaire included the variables age, sex, educational level, marital status, work activity, tobacco use, alcohol consumption, diagnoses of diabetes *mellitus*, dyslipidemia, arterial hypertension, and chronic kidney disease, as well as the stage of GC, date of biopsy, presence of *Helicobacter pylori*, pathological variant of cancer, date of death, basic cause of death and the patient´s area of residence.

Statistical analysis

The normality of continuous variables was assessed using the Anderson-Darling test. When a p-value < 0.05 was obtained, the median and interquartile range were used. Statistical significance was set at $p < 0.05$, with 95 % confidence intervals. For comparison between two independent groups, the Mann-Whitney U test was used. Differences in proportions by area of origin, sex, and place of origin were analyzed using the Chi-square test.

To calculate the overall survival rate at one and four years, the Kaplan-Meier estimator was used. To test for differences among the groups, the Tarone-Ware test was used as a test of statistical significance with a p-value < 0.05 and 95 % confidence intervals.

A Cox proportional hazards model was constructed to evaluate the association between predictor variables and time to event. Prior to adjustment, the variables available in the database and the presence of missing data were identified. For variable selection, multicollinearity was assessed using the Variance Inflation Factor (VIF), and variables with a VIF ≥ 5 were excluded. Missing data were handled using multiple imputations with the predictive mean matching method, as implemented in the mice package in RStudio. The model was fitted on each imputed dataset, and the results were combined by pooling, a process that integrates the results of the different analyses to obtain a final estimate that considers the variability caused by the missing data, thereby achieving a more reliable result.

The goodness of fit of the model was evaluated using the Likelihood Ratio test and Wald test, with p-values < 0.05 to be considered statistically significant. To evaluate the predictive capacity of the model, Harrell's concordance index (C-index) was used. To verify the assumption of proportionality of risks over time, the Schoenfeld residuals analysis was used. Data processing and analysis were conducted using RStudio version 4.3.2.

This study was conducted in accordance with the Declaration of Helsinki, the Nuremberg Code, the guidelines of the Council for International Organizations of Medical

Sciences (CIOMS), and other international ethical guidelines for health research. Good clinical practice was followed, and patient identity was protected through data coding. The study protocol was approved by the Ethics Committee of the Hospital Nacional Rosales, under act number 32/2024.

Results

Seventy-nine patients corresponding to those diagnosed with GC in 2019 in a tertiary care hospital were analyzed; of these, 54 died at the end of the study (68. 3 %). Fifty-nine percent of the participants were male. The median age was 66 years (RI: 58-73), with a minimum age of 36 years and a maximum of 94 years. No significant difference was observed between the medians by sex (p = 0. 214). Fifty-six percent were from urban areas (p = 0. 779), with the highest frequency in the department of San Salvador (39 %), followed by La Paz (14 %) and Chalatenango (10 %). However, there were patients from all departments of El Salvador.

According to the sociodemographic variables analyzed, 49 % of particpants were married. In terms of educational level, 32 % had first to sixth-grade education, while 11 % had completed seventh to ninth grade. However, 29 % had no record of their education level. Regarding occupation, 34 % were farmers, followed by individuals engaged in domestic cleaning services, with 29 %.

Table 1 summarizes the clinical and pathological characteristics and comorbidities of the patients with GC. The presence of Helicobacter pylori was identified in 34 % of the cases, while in 48 %, this information could not be confirmed. Twenty-nine percent of the patients were smokers, and 26 % reported alcohol consumption. Regarding comorbidities, 10 % of the patients were diagnosed with diabetes *mellitus*, 21 % had arterial hypertension, and 6 % had chronic kidney disease.

Regarding the stage of GC at diagnosis, 34 % of patients were stage IV, followed by stages II and III, each accounting for approximately 9 % each. However, 47 % of the cases could not be staged. Regarding pathological classification, 86 % of the patients had adenocarcinoma.

Survival of patients with gastric cancer

Figure 1 shows the survival curve of GC patients. A steady decline over time is observed, with a sustained loss of patients, especially pronounced during the first two years of follow-up.

In the first year, the survival rate was 46.84 % (95 % CI: 37.03 % - 59.24 %). From the second year onwards, a stabilization of the curve is observed; however, as time goes by, the curve continues to decline, reaching a survival rate of 31.65 % (95 % CI: 22.89 % - 43.76 %) at the end of the study, equivalent to 25 of the 79 patients who made up the initial cohort.

Figure 2 shows the survival curves of GC patients at four years, classified by sex, area of origin, smoking and alcohol consumption.

Regarding sex, the survival rate at one year was 50 % (35.36 % - 70.70 %) in women and 44.68 % (32.51 % - 61.42 %) in men. At four years, survival rates were 37.5 % (23.98 %-58.65 %) in women and 27.66 % (17.42 % - 43.92 %) in men. Although women showed a higher survival rate at both one and four years compared to men, this difference was not statistically significant (p > 0.05).

Regarding the area of origin, survival at one year was 50 % (37.21 % - 67.19 %) in rural areas and 42.86 % (29.23 % - 62.83 %) in urban areas. At four years, survival rates were 34.09 % (22.61 % - 51.41 %) in rural areas and 28.57 % (16.92 % - 48.24 %) in urban areas. People living in rural areas had a higher survival rate at one year; however, this difference was reduced at four years (p> 0.05).

Regarding smoking, non-smokers had a one-year survival rate of 57.5 % (44.05 % -75.05 %), while smokers had a survival rate of 39.13 % (23.50 % - 65.14 %). At four years, survival rates are 37.5 % (25.14 % - 55.95 %) for non-smokers and 30.43 % (16.41 % - 56.46 %) for smokers; however, the difference was not statistically significant (p > 0.05).

Concerning alcohol consumption, survival at one year was 53.49 % (40.48 % - 70.68 %) for non-drinkers and 47.62 % (30.41 % - 74.58 %) for drinkers. At four years, survival was 32.56 % (21.18 % - 50.06 %) in non-drinkers and 38.1 % (22.08 % - 65.71 %) in drinkers, with no significant differences (p > 0.05).

Figura 3 shows the 4-year survival curves for GC patients classified by arterial hypertension, diabetes *mellitus*, chronic kidney disease, and pathological variant.

For arterial hypertension, the one-year survival rate is 51.02 % (38.78 % - 67.13 %) in those without the diagnosis and 52.94 % (33.82 % - 82.88 %) in those with the diagnosis. At four years, survival is 32.65 % (21.84 % - 48.82 %) in those without hypertension and 41.18 % (23.33 % - 72.68 %) in those with hypertension (p > 0.05).

For diabetes *mellitus*, the one-year survival rate was 54.39 % (95 % CI: 42.88 % - 68.98 %) in those without the diagnosis and 37.5 % (95 % CI: 15.33 % - 91.74 %) in those with the diagnosis. At four years, survival was 35.09 %

Table 1. Clinical characteristics of patients diagnosed with gastric cancer at the tertiary hospital in El Salvador in 2019

Variable		Survivors (n=25)	%	Deceased (n=54)	%	Total	%
Helicobacter pylori	Yes	11	44,0	16	29,6	27	34,2
	No	6	24,0	8	14,8	14	17,7
	No data	8	32,0	30	55,6	38	48,1
Smoker	Yes	7	28,0	16	29,6	23	29,1
	No	15	60,0	25	46,3	40	50,6
	No data	3	12,0	13	24,1	16	20,3
Alcohol	Yes	8	32,0	13	24,1	21	26,6
	No	14	56,0	29	53,7	43	54,4
	No data	3	12,0	12	22,2	15	19,0
Diabetes mellitus	Yes	3	12,0	5	9,3	8	10,1
	No	20	80,0	37	68,5	57	72,2
	No data	2	8,0	12	22,2	14	17,7
Dyslipidemia	Yes	0	0,0	1	1,9	1	1,3
	No	23	92,0	40	74,1	63	79,7
	No data	2	8,0	13	24,1	15	19,0
Arterial hypertension	Yes	7	28,0	10	18,5	17	21,5
	No	16	64,0	33	61,1	49	62,0
	No data	2	8,0	11	20,4	13	16,5
Chronic renal disease	Yes	1	4,0	4	7,4	5	6,3
	No	22	88,0	38	70,4	60	75,9
	No data	2	8,0	12	22,2	14	17,7
Cancer stage	Stage I	0	0,0	1	1,9	1	1,3
	Stage II	5	20,0	2	3,7	7	8,9
	Stage III	2	8,0	5	9,3	7	8,9
	Stage IV	9	36,0	18	33,3	27	34,2
	Not staged	9	36,0	28	51,9	37	46,8
Pathologic classification	Well-differentiated adenocarcinoma	17	68,0	47	87,0	64	81,0
	Poorly differentiated adenocarcinoma	1	4,0	3	5,6	4	5,1
	Gastric GIST* 2	2	8,0	1	1,9	3	3,8
	Non-Hodgkin's lymphoma	4	16,0	3	5,6	7	8,9
	Neuroendocrine tumor	1	4,0	0	0,0	1	1,3

***GIST:** gastrointestinal stromal tumor.

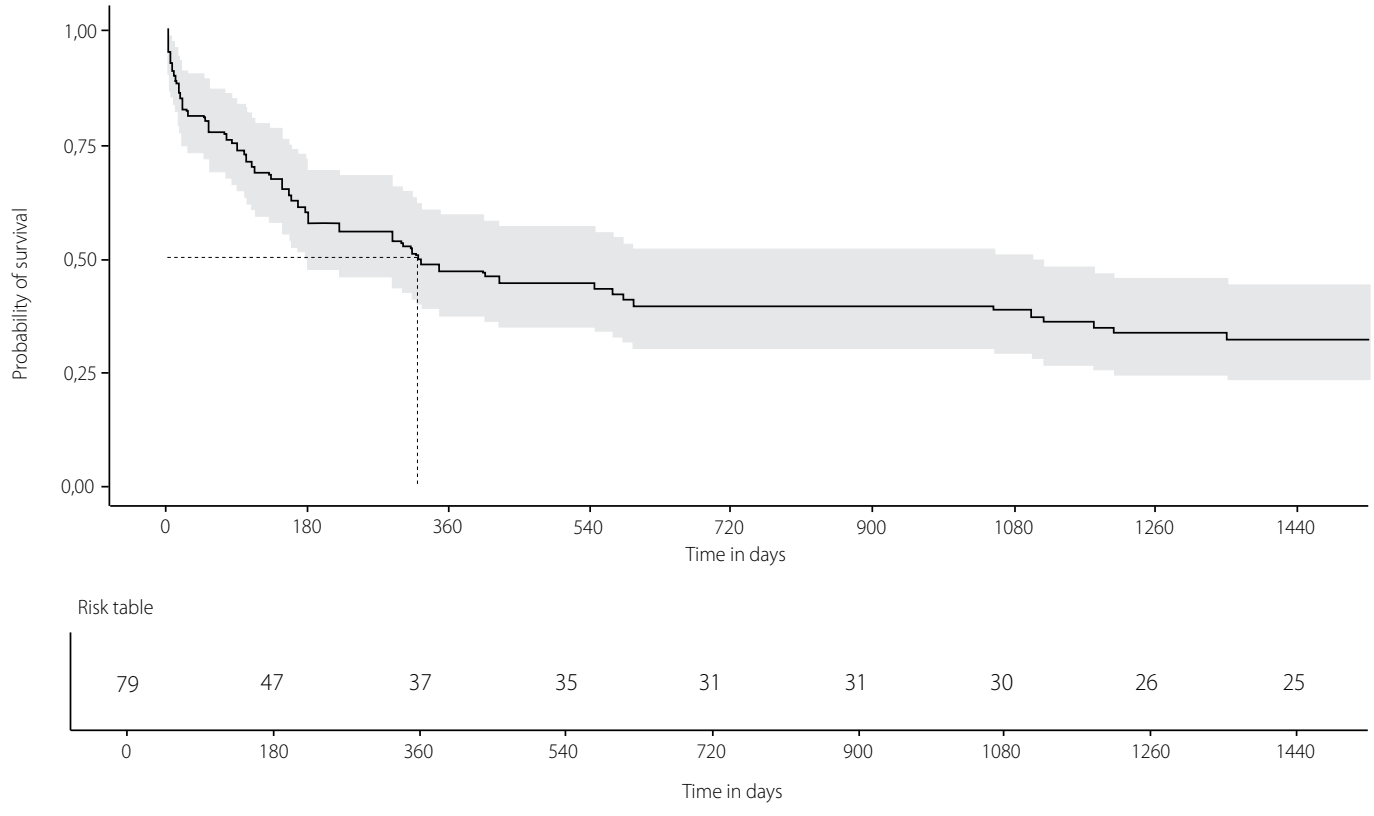

Figure 1. Cumulative survival of patients with gastric cancer at four years in a tertiary hospital in El Salvador, 2019 to 2023.

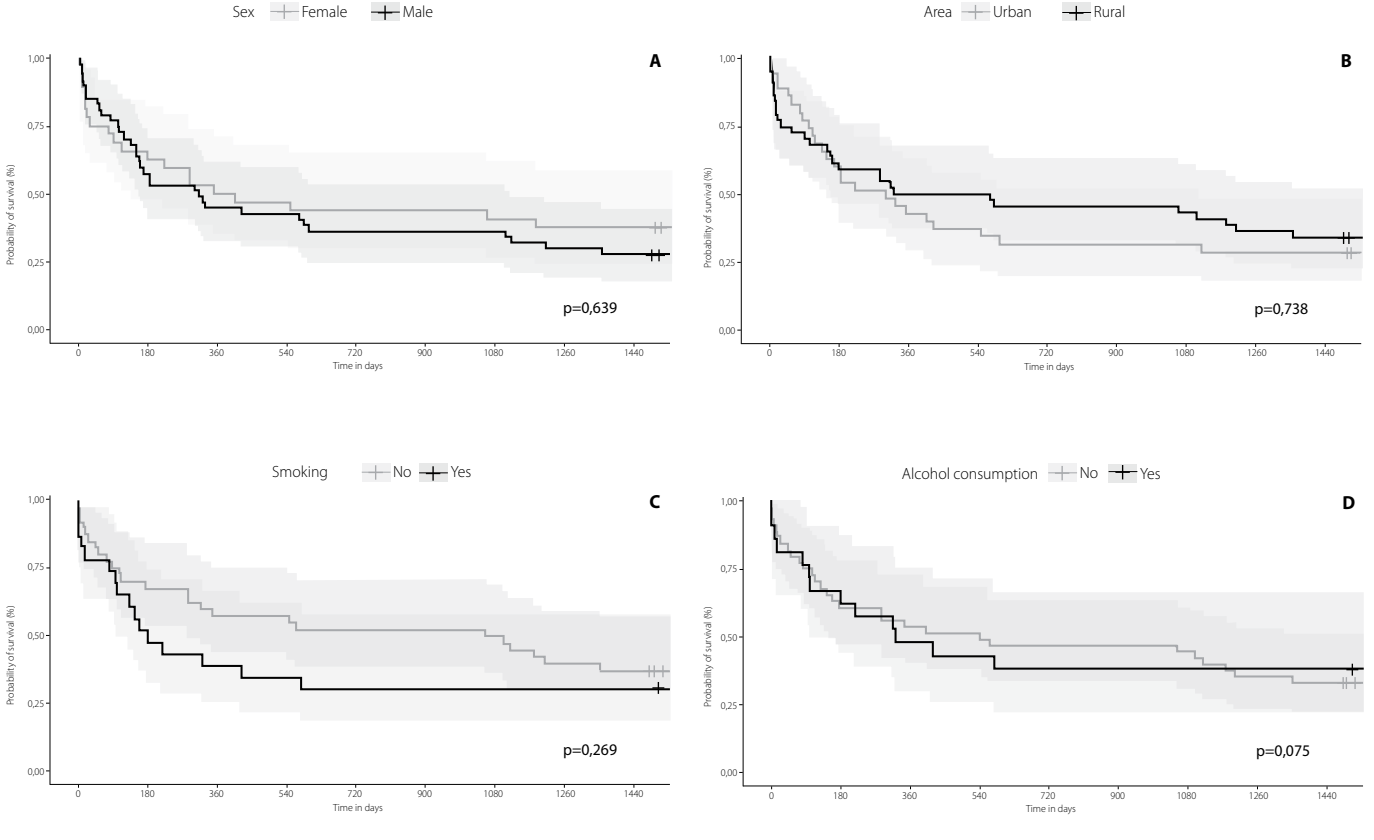

Figure 2. Four-year survival curve of gastric cancer patients by sex (Figure 2A), area of origin (Figure 2B), smoking (Figure 2C) and alcohol consumption (Figure 2D), 2019 to 2023.

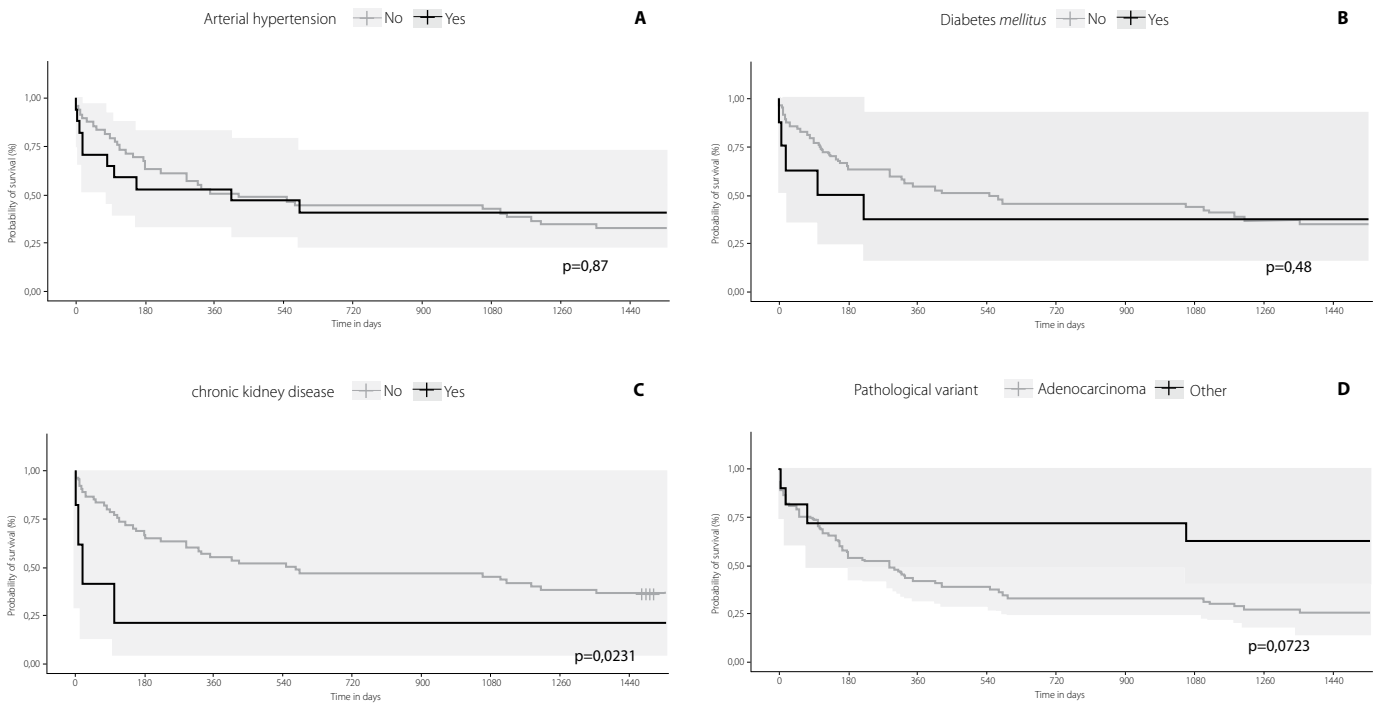

Figura 3. Four-year survival curve of patients with gastric cancer at four years of arterial hypertension (Figure 3A), diabetes *mellitus* (Figure 3B), chronic kidney disease (Figure 3C), pathological variant (Figure 3D), 2019 to 2023.

(95 % CI: 24.65 % - 49.95 %) in those without diabetes *mellitus* and 37.5 % (95 % CI: 15.33 % - 91. 74 %) in those with the diagnosis ($p > 0.05$).

As for CKD, survival at one year is 55 % (43.75 % - 69.15 %) in those without CKD and 20 % (3.46 % - 100 %) in those with CKD. At four years, survival is 36.67 % (26.29 % - 51.13 %) in those without a diagnosis of chronic kidney disease and 20 % (3.46 % - 100 %) in those with the diagnosis, with significant differences between the groups ($p < 0.05$).

When comparing survival between patients with adenocarcinoma and those with other pathological variants, it is observed that at one year, the survival rate of patients with adenocarcinoma was 42.65 % (32.37 % - 56.18 %), while those with other variants reached 72.73 % (50.64 % - 100 %). This trend was continued over four years, with survival rates of 26.47 % (17.81 % - 39.34 %) for patients with adenocarcinoma and 63.64 % (40.71 % - 99.47 %) for those with other variants; however, the differences were not significant ($p \geq 0.05$).

Table 2 summarizes the results of the multivariate Cox model analyzing the relationship between various clinical variables and the risk of death from GC. Smoking was associated with lower survival, with a hazard ratio (HR) of 3.53 (95 % CI: 1.31-9.48; p= 0.0172). Similarly, chronic kidney disease was associated with a significant increase, with an HR of 4.20 (95 % CI: 1.17-14.98; $p = 0.0329$). On the other hand, alcoholism showed a trend toward higher survival, although it did not reach statistical significance (HR = 0.37; 95 % CI: 0.12-1.04; $p = 0.0710$). Finally, neither high blood pressure nor age showed significant associations in this analysis (HR = 0.65, $p = 0.3467$ and HR = 0.99, $p = 0.3540$, respectively).

The Schoenfeld test of the proportionality of hazards tests indicate that there are no problems with the proportionality assumption for the variables included in the model ($p > 0.05$). The overall test also suggests that the model as a whole adequately meets this assumption ($p > 0.05$). In addition, the statistical tests showed that the model is significant, has a good fit, and provides an adequate explanation of the outcome from the included data ($p < 0.01$), showing moderate agreement (0.623).

Discussion

This study provides an overview of survival rates and variables associated with GC in patients diagnosed at a tertiary care hospital in El Salvador during 2019. The findings offer valuable insights into the prognosis and clinical characteristics of the disease within the Salvadoran context.

The Kaplan-Meier survival curve shows a steep decline during the first two years after diagnosis, followed by relative stabilization. The one- and four-year survival rates reflect the aggressive nature of the disease and un-

Table 2. Results of the multivariable Cox model for gastric cancer risk

Variable	Coefficient	*Hazard Ratio* (HR)	IC 95%	Standard error	z-statistic	p-value
Chronic kidney disease	1,436	4,204	1,17-14,98	0,648	2,215	0,0329
Smoking	1,262	3,533	1,31-9,48	0,504	2,504	0,0172
Age	-0,012	0,988	0,96-1,01	0,013	-0,938	0,3540
Arterial hypertension	-0,424	0,654	0,27-1,56	0,446	-0,952	0,3467
Alcoholism	-1,003	0,367	0,12-1,04	0,536	-1,871	0,0710

Harrell's average C-index: 0. 623
Standard deviation of C-index: 0. 019
Likelihood ratio test: p=0. 01
Wald test: p=0. 01
Test score (log rank): p=0. 01

derscore the importance of early diagnosis and timely treatment.[xii,xiii] These results are consistent with previous studies that have reported similar survival rates in developing countries.[xiv] The observed survival rate could be related to various factors, such as diagnosis in advanced stages, limitations in access to specialized treatment, the presence of comorbidities, and administrative aspects of the health system, as reported by other studies in the region.[xv,xvi] It is important to consider that the hospital where the research was conducted is the main referral center in El Salvador; it usually treats more complex cases and in advanced stages, which could influence the survival rates observed.

Analysis using the Cox regression model determined that smoking is a factor associated with lower survival in gastric cancer. Current literature has established smoking as an important risk factor not only for gastric cancer but for multiple types of cancers.[xiii] The mechanism by which smoking increases the risk of gastric cancer is multifactorial and includes exposure to carcinogens, induction of chronic inflammation, and alteration of the immune response.[xviii,xix] The marked difference in survival between smokers and non-smokers, mainly in the early years, shows the importance of public health interventions aimed at reducing tobacco use.[xviii]

Lower survival rates was observed in patients with chronic kidney disease, a finding consistent with previous studies reporting worse outcomes in patients with cancer and chronic kidney disease20. This condition may make cancer management more difficult, limit treatment options, and increase the risk of complications, which could explain the lower survival found in these patients.[xxi]

Regarding demographic factors, a trend toward more prolonged survival was observed in women compared to men; however, this difference did not reach statistical significance. This finding differs from some previous studies, which have documented significant differences in survival according to sex, with a slight female predominance.[xxii] The absence of statistical significance could be related to the sample size, the characteristics of the patients treated in the hospital, or to factors specific to the population of El Salvador.

Patients from rural areas had slightly longer survival compared to those from urban areas, although this difference was not statistically significant. This result contrasts with the trend observed in some studies, which have shown higher mortality rates in rural areas, mainly attributed to barriers to accessing health services.[xxiii] However, in the context of El Salvador, geographic barriers may not have a significant impact on survival. Instead, factors such as diet, exposure to environmental contaminants, the presence of comorbidities, and lifestyle differences between populations may explain this trend and have a more significant impact on survival.[xxiv]

Although no statistically significant association was found between alcohol consumption and GC survival, it is important to highlight that non-drinkers showed a more prolonged survival at 1-year follow-up. The relationship between alcohol consumption and GC is complex and has shown diverse results in different studies.[xxv,xxvi] Factors such as the type of alcoholic beverage, the

amount consumed, and the interaction with other risk factors may influence this relationship.[xxv,xxvi] However, a recent systematic review suggests that even moderate alcohol consumption carries a significantly increased risk compared to no consumption.[xxvii]

No significant difference in survival was observed between hypertensive and non-hypertensive patients, which contrasts with some studies that have suggested a possible protective effect of certain antihypertensive drugs on the development and progression of GC.[xxviii] Other studies have related the occurrence of hypertension to the use of certain drugs to treat cancer or even to increased survival associated with more effective therapies.[xxix]

Diabetic patients showed lower survival rates at one year, although this difference was not statistically significant; this trend was also maintained at four years. The relationship between diabetes and GC is complex and may be influenced by factors such as glycemic control, duration of diabetes, and antidiabetic treatment.[xxx] Recent studies indicate that new therapies and lifestyle changes have improved blood glucose control, which in turn contributes to a better quality of life and longer survival in cancer patients by reducing long-term complications.[xxxi,xxxii]

Although in this study, it was not possible to accurately assess the association between dyslipidemia and gastric cancer mortality due to the small number of cases, some studies have suggested a possible relationship between lipid disorders and GC risk, possibly mediated by inflammatory mechanisms or alterations in cellular metabolism.[xxxiii,xxxiv]

The limitation in establishing an association between dyslipidemia and gastric cancer opens new lines of research in El Salvador, which could contribute to a deeper understanding of the pathogenesis of this disease. Currently, some studies have shown that dyslipidemia is associated with an increased risk of gastric cancer, even after adjusting for age, sex, and other factors.[xxxv]Further studies are needed to explore this relationship and assess whether managing dyslipidemia could impact the prevention or prognosis of GC.

Regarding pathological characteristics, the study found evidenced that patients with adenocarcinoma presented a higher risk of mortality compared to other histological variants; however, this difference did not reach statistical significance. This contrasts with the literature, which has established adenocarcinoma as the most common and generally more aggressive histologic type of GC. The shorter survival observed in patients with adenocarcinoma highlights the importance of accurate histologic diagnosis for risk stratification and treatment planning.[xxxvi] Recent studies have identified molecular subtypes of gastric adenocarcinoma with different prognoses and responses to treatment. Future studies in this population could benefit from more detailed molecular characterization to improve risk stratification and guide personalized therapeutic decisions.[xxiii,xxxvii]

A significantly longer survival was observed in patients diagnosed at early stages of the disease. This finding highlights the importance of early diagnosis and early detection programs in the management of GC.[xiii,xxxvii]A significant proportion of cases may be diagnosed at advanced stages; this pattern of late presentation is common in many developing countries and highlights the need for improved early detection and GC awareness programs.[xxii,xxv,xxvi] On the other hand, the marked decrease in survival during the first two years after diagnosis underscores the urgency of implementing and improving GC early detection programs.[xviii,xix]

The main limitations of this study include the relatively small sample size, which may reduce the statistical power to detect significant associations, especially in subgroup analyses. As a retrospective cohort, the study is subject to inherent biases such as the presence of missing or incomplete data in the medical records. Additionally, the lack of direct interviews with patients restricted the the collection of additional clinical or contextual variables that were not routinely documented, potentially affecting the completeness and interpretability of the results.

Despite these limitations, the study presents notablestrengths. It provides specific data on GC in El Salvador, addressing a significant gap in the national and regional literature. The use of Cox proportional hazards models, along with appropriate performance metrics allowed for a robust assessment of multiple prognostic factors simultaneously. Consideration of multiple comorbidities provides a more comprehensive view of factors influencing GC survival, and follow-up of up to four years provided valuable information on survival in this population.

Finally, this study provides an overview of survival and factors associated with GC survival in Salvadoran patients. The findings underscore the critical importance of early detection, management of comorbidities, and consideration of modifiable risk factors such as smoking.

The identification of smoking and chronic kidney disease as factors associated with survival opens up new lines of research that could have important implications for the prevention and comprehensive manage-

ment of CG. Further studies, preferably multicenter and prospective, are needed to confirm and extend these findings, as well as to evaluate specific interventions aimed at improving clinical outcomes in this population.

Conclusion

Survival of less than 40% at four years for GC patients reflects the severity of the disease and the complexity of its management from diagnosis onwards, highlighting the persistent challenge this condition poses particularly in achieving favorable long-term prognosis and ensuring adequate management.

The profile of patients diagnosed with GC, characterized by a predominance of older men, urban residency and a high rate of Helicobacter pylori infection, suggests deficiencies in the early detection of the disease, highlighting the need to strengthen prevention and improve early diagnosis strategies and the implementation of intervention programs on the risk factors identified in the study.

The factors most strongly associated with reduced survival of patients with gastric cancer were smoking, chronic kidney disease, and, more decisively, the clinical stage and histological type of tumor.

Acknowledgments

To Yanira Burgos for being part of the research advisory, who at the time of this publication has passed away and enjoys eternal life.

Funding

No external funds were received for this work.

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Original Article

Detection of vacA and cagA genes in *Helicobacter pylori* strains in Salvadoran patients

DOI:10.5377/alerta.v8i3.20761

Ruth Elizabeth Salinas[1]*, Liliam Herrera[2], Angélica María Salgado[3], Emerson Pocasangre[4]

1,4. Evangelical University of El Salvador, San Salvador, El Salvador.
2. Solidarity Fund for Health/ Evangelical University of El Salvador, San Salvador, El Salvador.
3. Salvadoran Social Security Institute, San Salvador, El Salvador.

*Correspondence
ruthsalinas1705@gmail.com

1. 0000-0003-2548-8965
2. 0000-0002-7998-9311
3. 0009-0000-1228-0765
4. 0000-0002-7488-6241

Abstract
Introduction. *Helicobacter pylori* infection has become an prevalent disease and an economic and public health problem. The main concern is that some strains are associated with gastric cancer, especially the vacA and cagA genes. **Objective.** Determine the prevalent *Helicobacter pylori* genotypes in patients who attended the Specialty Clinic of the Salvadoran Social Security Institute. **Methodology.** A quantitative, descriptive, cross-sectional study was conducted. The unit of analysis was endoscopic gastric samples. A consecutive non-probabilistic sampling was performed. The selection of patients was carried out by a gastroenterologist. The real-time polymerase chain reaction technique was applied to identify the virulence genes, cagA and vacA of cultures positive for *Helicobacter pylori*, using standardized methods. **Results.** Ninety-seven participants were obtained, from whom a biopsy sample was acquired and cultured; however, the recovery rate of *Helicobacter pylori* in culture was 26 %. All samples were positive for the 16S rRNA ribosomal virulence genes and the cagA and vacA oncogenes. The infection was predominant in females, with 76 %, and the average age was 55 years. It was found that 64 % of positive participants had a previous diagnosis of infection with *Helicobacter pylori*. **Conclusion.** The virulence genes cagA and vacA were found in all samples positive for *Helicobacter pylori.*

Keywords
Helicobacter pylori, Polymerase Chain Reaction, Oncogenes, Stomach Neoplasms, Virulence.

Resumen
Introducción. La infección por *Helicobacter pylori* se ha vuelto un problema económico y de salud pública, convirtiéndose en una enfermedad prevalente. La principal preocupación es que algunas cepas están asociadas con el cáncer gástrico, especialmente los genes vacA y cagA. **Objetivo.** Identificar la presencia de los genes vacA y cagA en cepas de *Helicobacter pylori* aisladas a partir de muestras de biopsias gástricas. **Metodología.** Se realizó un estudio transversal descriptivo. La unidad de análisis fueron las muestras gástricas endoscópicas. La selección de los pacientes la realizó un gastroenterólogo. Se aplicó la técnica de Reacción en Cadena de la Polimerasa en tiempo real para la identificación de los genes de virulencia, cagA y vacA de los cultivos positivos al *Helicobacter pylori*. **Resultados.** Se obtuvieron 97 participantes; sin embargo, se obtuvo un porcentaje de recuperación de *Helicobacter pylori* en cultivo de 26 %. Todas las muestras fueron positivas para el gen ribosomal rRNA16s y los genes de virulencia cagA y vacA. La infección predominó en el sexo femenino con un 76 %, la edad promedio fue de 55 años. Se encontró que el 64 % de participantes positivos tenían diagnóstico previo de infección por *Helicobacter pylori*. **Conclusión.** Los genes de virulencia cagA y vacA, se encontraron todas las muestras positivas a *Helicobacter pylori.*

Palabras clave
Helicobacter pylori, Reacción en Cadena de la Polimerasa, Oncogenes, Neoplasias Gástricas, Virulencia.

Introduction

The high incidence of *Helicobacter pylori* (*Hp*) infection probably contributes to the fact that gastric cancer mortality ranks second among cancer deaths, worldwide.[i-iii] Due to the causal relationship between *Hp* and gastric tumors, the International Agency for Research on Cancer (IARC) recognized *Hp* as a Group 1 carcinogen, indicating that it is a definite carcinogen.[i-iii] Currently, *Hp* is the only bacterium that has achieved this distinction, classified as dangerous in terms of oncogenicity. According to this information, gastric colonization by this bacterium increases up to six times the risk of gastric cancer up to six times, compared to people who do not present colonization, so it has been the only bacterium with a significant association with gastric adenocarcinoma; in addition, it has been related to one of the main causes of cancer deaths worldwide.[i-iii]

OPEN ACCESS

Detección de genes vacA y cagA en cepas de *Helicobacter pylori* en pacientes salvadoreños

Suggested citation:
Salinas RE, Herrera L, Salgado AM, Pocasangre E. Detection of vacA and cagA genes in *Helicobacter pylori* strains in Salvadoran patients. Alerta. 2025;8(3):275-281. DOI: 10.5377/alerta.v8i3.20761

Editor:
Edgar Quinteros.

Received:
December 22, 2023.

Accepted:
July 10, 2025.

Published:
July 31, 2025.

Author contribution:
RES[1], LH[2], AMS[3]: study design, literature search. RES[1]: data or software management. RES[1], AMS[2], EP[3]: data collection and execution of laboratory test. RES[1], LH[2], AMS[3], EP[4]: writing, revising, and editing.

Conflicts de interest:
No conflicts of interest.

This disease has become a public health problem due to its high prevalence; in addition, prevention measures have not been clearly identified, which makes it necessary to have local data on the pathogenicity of *Hp* strains, through the detection of cagA and vacA genes, due to the consequences that this infection and, specifically, these oncogenes entail.[iv,v]

Real-time polymerase chain reaction (RT-PCR) allows the identification of genes relevant to the diagnosis of various diseases, including the detection of *Hp* virulence factors. Endoscopic tests in patients with *Hp* infection and dyspepsia often reveal diagnoses such as chronic antral gastritis, erosive antral gastritis, and nodular antral gastritis, which have been associated with the presence of the *Hp* virulence genes cagA and vacA. In addition, the most common premalignant gastric lesions, such as gastric atrophy, intestinal metaplasia, and low-grade dysplasia, are also associated with these same *Hp* virulence factors.[vi]

The most common endoscopic diagnoses in patients with dyspepsia are chronic antral gastritis, erosive antral gastritis, and nodular antral gastritis, as well as the presence of the cagA and vacA genes in isolated strains. The most frequent premalignant gastric lesions are gastric atrophy, intestinal metaplasia, and low-grade dysplasia.[vii]

The prevalence of the cagA oncogene is 50 %, while that of the vacA oncogene is 87.5 %.[viii] These data are essential for the development of public health strategies aimed at detecting and effectively managing the infection.

The cagA and vacA proteins are considered important virulence markers in *Hp*. These markers can be identified more easily through the genes that encode them, called virulence-associated genes. Furthermore, the simultaneous presence of *Hp* has been detected in the oral cavity and gastric mucosa, with variations in prevalence depending on the population analyzed, the sampling method, and the techniques used for detecting the bacterium.[ix]

The presence of *Hp* in the oral mucosa of patients with dyspepsia leads to dissemination, with the potential for reinfection after treatment for *Hp* eradication, so ideally, treatment for the oral cavity should be applied.[x]

It is essential to identify strains with carcinogenic potential in the general population, especially those with histopathological features that increase their risk for *Hp* infection. In cases of gastric cancer, these strains are usually highly virulent, and it has been documented that, in some individuals, multiple oncogenic strains can coexist in the gastric mucosa. Therefore, it is essential to further study the virulence genes associated with oncogenicity in Hp, as well as to strengthen strategies for eradicating the bacterium.[xi, xii]

In El Salvador, there is no study on the genetics of *Hp*, and the country lacks a diagnostic service for the general population; therefore, this research is relevant. The objective of the study was to identify the presence of the vacA and cagA genes in *Helicobacter pylori* strains isolated from gastric biopsy samples.

Methodology

The research was of a descriptive cross-sectional type. It was conducted at the Santa Ana Regional Hospital and the Specialty office of the Salvadoran Social Security Institute (ISSS), from October 2021 to March 2022.

The unit of analysis was endoscopic samples from patients diagnosed with gastric disease. All samples from patients who attended in the period stipulated for data collection were included, and those who met the inclusion criteria, which were: patients over 18 years of age and who consulted in the gastroenterology department at Santa Ana Regional Hospital or Specialty Office in the department of San Salvador. Likewise, patients with or without previous treatments for *Hp* eradication or patients who had received treatment with amoxicillin, clarithromycin, or metronidazole in the last month for another reason, even if not for *Hp* eradication, were considered; and the last criterion was patients who agreed to participate in the study.

The selection of patients was made by a gastroenterologist, based on the aforementioned inclusion criteria, who indicated to the researchers the patient who was a candidate for inclusion in the study.

Regarding the variables and indicators investigated, general information was obtained from the participants, such as: age, sex, history of infection, endoscopic diagnosis, and the detection of *Hp* genotypes, specifically VacA and CagA.

The data collection instrument was a physical form. The information on the variables of interest was collected in two moments, the first was when the endoscopic sample was taken from the patient's file and the second when the results of the sample processing were obtained at the microbiology laboratory of the Evangelical University of El Salvador (UEES); The samples were transported in test tubes with distilled water and in a cooler to perform the bacterial culture and subsequent PCR-RT tech-

nique to identify the VacA, cagA and 16s rRNA genotypes of the *Hp*-positive cultures.

Each of the samples were double seeded (sample 30 was used to improve the percentage of bacterial recovery) on Columbia agar enriched with 5 % horse defibrinated blood and bacterial growth enzyme inhibitors and placed in a CO_2 incubator with the following conditions: 5-10 % O_2, 5-10 % CO_2, 80-90 % N_2, 35 - 37º C, 95 % humidity, until seven days before the culture was considered negative.[xiii,xiv] For colonies suggestive of *Hp*, Gram staining was performed to search for curved Gram-negative bacilli before performing RT-PCR, which was carried out using standardized methods.[xiii,xiv] Nucleic acid extraction was performed from gastric biopsies using the NucleoSpin® Tissue kit (Macherey-Nagel, Germany), following the manufacturer's recommendations. Each kit allowed the purification of up to 50 samples. Each extraction yielded approximately 60 µL of genomic DNA, sufficient to perform the reactions in duplicate and ensure the reproducibility of the results.

For the amplification of the vacA and cagA genes, the iTaq™ Universal SYBR® Green Supermix enzyme was used, preparing the master mix according to the manufacturer's instructions. The reactions were performed in a final volume of 20 µL, including specific primers for the vacA and cagA genes. The primer sequences were taken from the study by Ranjbar *et al.*,[xv] which demonstrated high sensitivity and specificity for these molecular targets.

Real-time PCR amplifications were performed on the MiniOpticon Real-Time PCR System MiniMyGo S® under previously validated thermocycling conditions for the detection of *Hp* genes. All procedures were performed in a sterile and controlled environment to avoid cross-contamination.[xvi]

The data obtained were processed using Excel 2010 and presented in tabular form. Qualitative variables were represented in frequencies and proportions; quantitative variables were presented using measures of central tendency. The information was stored by the researchers and subsequently delivered to UEES for final storage. Averages, frequencies, and percentages were calculated to obtain the results.

Each of the participants was asked for informed consent upon verifying that they met the inclusion criteria, in which the importance of the study was explained to them, as well as the respect for ethical principles and confidentiality, that there was no remuneration, and that the data would be used in a group manner and for scientific research purposes. The research protocol was submitted for evaluation by the UEES ethics committee and approved in minute 187, dated August 9, 2019. It was also submitted for evaluation by the ISSS ethics committee and was approved on June 29, 2020. It had the approval of the ISSS gastroenterologists, as well as the directors of the health centers where the research was carried out (Santa Ana Regional Hospital, Specialty Clinic of the ISSS).

Results

Information was collected from 97 participants, from whom a biopsy sample was obtained and submitted for culture. However, *Hp* recovery was achieved in 26 % of the cases, i.e. 25 samples were positive. The results obtained from the *Hp*-positive samples are presented below. According to the general data collected, the infection predominantly affected females, with a prevalence of 76 %. The average age was 55 years (standard deviation, 16.3), with a range from a minimum of 25 years to a maximum of 85 years. Regarding the history of *Hp* infection, it was found that 64 % of the positive participants had a previous diagnosis of infection, which indicates that they were probably reinfected patients or those in whom the bacteria could not be eradicated.

Within the endoscopic data collected (Table 1), the diagnosis of gastropathy/acute gastritis was the one that predominated in 60 % of the cases, followed by erosive gastropathy, with 20 %, in a smaller proportion, with 8 %, nodular gastritis, esophagitis, and gastric and duodenal ulcers in 4 %.

Table 2, shows that the two oncogenes, vacA, cagA, were detected in all the samples positive for *Hp* (n=25).

Discussion

The purpose of the study was to identify the genotypes of *Hp* strains, for which endoscopic gastric samples were collected to be cultured; however, a lower percentage of recovery was obtained compared to the number of samples collected. In a study conducted in Costa Rica, the viability of *Hp* bacteria culture was determined by obtaining gastric biopsies from 44 participants. *Hp* was recovered in 27 biopsies, with a recovery percentage of 61.4 %,[xvii] indicating that the percentage of recovery in culture was lower than the number of samples taken. This may be because the conditions of transport and growth of *Hp* are demanding; in addition, it requires a medium reduced in O_2 and loaded

with CO_2, contrary to the great majority of bacteria. In addition, as mentioned by Molina-Castro *et al.*, among some of the reasons that can influence a false negative result in the culture are excessive contamination, because it does not allow successful isolation of *Hp* colonies, an altered physiological state of the bacteria and a low bacterial load in the sample, since they produce an alteration in their environment and reduce their viability, hindering growth in culture media.[xvii]

Table 1. Endoscopic diagnosis

Diagnosis	Frequency	Percentage
Acute gastropathy/ gastritis	15	60 %
Nodular gastritis	2	8 %
Gastric and duodenal ulcer	1	4 %
Erosive gastropathy	5	20 %
Esophagitis	2	8 %
Total	25	100 %

Table 2. Positive samples for *Helicobacter pylori* genes using PCR-RT

Genotype	Frequency (n=25)	Percentage
VacA	25	100 %
CagA	25	100 %

Among the study participants, the female group was the predominant one; unlike a study about the prevalence of *Hp* in asymptomatic patients in Ecuador, where, it was found that *Hp* infection predominated in the male sex with 51.5 %; in addition, it is exposed that hygiene habits influence the significant increase of cases in the male sex.[xviii]However, it should be noted that women are more likely to consult than men, which may increase the proportion of infected women.[i]

Some studies show an increase in the prevalence of *Hp* infection according to sex,[xix-xx], others report that infection predominates in the female sex;[xix-xxi] however, this difference is not so significant, therefore, it is said that the distribution of the disease is homogeneous, according to sex.[xix-xxi] Models have even been created to predict the prevalence of *Hp* infection as a function of climatic conditions. In the end, it is concluded that in developing countries, the prevalence of this infection remains high, apparently regardless of climatic conditions or the sex of the patients.[xix]

Regarding the age most affected by *Hp* infection, a study from Cuba reported an average age of 69 years for infected patients, with the maximum age being between 60 and 69 years (57.1 % infected);[xx] however, the average age varies according to the region,[xxi] i.e., the prevalence will behave differently in each age group and region of the world. In developing countries, the prevalence rates are highest, ranging from 60 % to 80 % in the adult population. In contrast, countries with high socioeconomic development have an infection rate reduced to 30-50 % in the adult population.[xxi] The highest prevalence has been found in Africa (79.1 %), followed by South America and the Caribbean (63.4 %), and finally North America (37.1 %) and Oceania (24.4 %).[xxi] Variations in the region are due to differences in hygiene conditions, access to drinking water, overcrowding, food availability and climate; additionally, they depend on each country's guidelines for diagnosis and treatment.[xviii-xxi]

The average age of this study is within the range reported by other researchers.[xix-xxi] The recognition of the most affected age group is important because surveillance, detection, and treatment measures should be intensified in these groups.[xix-xxi]

Regarding the participants who had a previous diagnosis of *Hp* infection, it can be observed that most patients already had this history. According to a study conducted in Mexico, the annual recurrence of *Hp* infection was 9.3 %, with an annual reinfection of 7 %. This data was lower compared to data reported for developing countries with a higher prevalence of *Hp*.[xxii] It is also mentioned that developed countries tend to have a low prevalence of *Hp* infection.[xxii] Regarding the type of strains found, cagA and vacA were isolated in reinfection. The reinfection rate for cagA was 10 % and 5.3 % for vacA.[xxii] The high prevalence of *Hp* infection could explain why the patients in this study had a history of diagnosis of *Hp* infection and probable reinfection or recurrence.

The endoscopic diagnoses found in this study were gastropathy, acute gastritis, erosive gastropathy, gastric and duodenal ulcer, nodular gastritis, and esophagitis in patients reporting *Hp* infection. A study was carried out in Panama,[xxiii] where endoscopic diagnoses of erosive gastritis (33.5 %), nodular gastritis (3.5 %), non-erosive gastropathy (48.6 %), gastric intestinal metaplasia (5.14 %), duodenal ulcer (5.14 %), duodenal ulcer and esophagitis were found, duodenal and gastric ulcer (4.2 %), in which an association was found between nodular gastritis, intestinal

metaplasia, duodenal ulcer, and gastric ulcer with *Hp* infection. Likewise, Duarte-Chang mentions that there are studies reporting the association between nodular gastritis, peptic ulcer disease, and *Hp* infection.[xxiii]

According to a Guatemalan study on premalignant lesions, the found that among the cases studied, 83 % presented some premalignant lesion such as atrophy, metaplasia, or dysplasia, among which the most frequent was gastric atrophy (70 %), followed by gastric intestinal metaplasia (11 %) and dysplasia (2 %). When reviewing the presence of *Hp* in these endoscopic findings, it was found that in atrophy, 62 % had *Hp* infection, in intestinal metaplasia, 66 % and in gastric epithelial dysplasia, 67 %.[xxiv]

Endoscopic findings are important in *Hp* infection, since they allow the detection of premalignant lesions; due to this, the Kyoto classification criteria have been created, which evaluate atrophy, intestinal metaplasia, thickened folds and nodularity; however, ideally, these patterns must have histological confirmation, which at the moment is still the gold standard for histopathological diagnosis. Nevertheless, optical endoscopic diagnosis is important, since it saves unnecessary biopsies in certain cases; there is even talk that the application of artificial intelligence in endoscopic diagnosis could improve the effectiveness of the diagnosis.[xxv]

Regarding genotyping, it was found that the two oncogenes of interest for the study, cagA, vacA, and the rRNA 16s ribosomal gene, were detected in all *Hp*-positive participants. The prevalence of cagA and vacA strains is said to be variable, with data reported in Ghana of 74.8 %, Nigeria 90 %, South Africa 95 %, Japan 100 %, Brazil 47.8 %, in Colombia from 43 % to 90.5 %, among others,[vii] data in the range of the proportions found in this study.

In a 2021 study conducted in El Salvador, the presence of *Hp* was detected by PCR in 20 % of the irrigation water used for food crops. Of these, 100 % of the isolated strains carried the vacA and cagA genes;[xxvi] these findings coincide with the data found in the present study.

Amplification of the 16S rRNA gene was performed to confirm the identification of *Hp*. This ribosomal gene is widely used for the identification of *Hp* in stool, blood, and biopsy samples using different techniques (qRT-PCR, antibodies, antigens); in addition, although it is not directly involved in antibiotic resistance, it is used in studies together with other genes to track resistant strains.[xxvii]

The Maastricht V/Florence Consensus Report takes up the topic of the importance of *Hp* eradication and mentions that it can be successful in preventing progression to gastric cancer, because people who have strains with one of the "gastric cancer phenotypes" have an increased risk of cancer.[v]

It also mentions that, in the case of infected patients with active chronic gastritis, eradication of *Hp* is the cure for this disease, improving the symptomatology and quality of life of affected individuals. Several meta-analyses show that the premalignant gastric atrophy lesion can be reversed to a certain extent, both in the antrum and in the gastric body.[v]

Likewise, it takes up the clinical and economic benefits of *Hp* eradication. It refers that there are studies that have evaluated the cost-effectiveness of *Hp* screening and treatment policies for the prevention of gastric cancer, concluding that *Hp* screening and treatment is cost-effective and that effects can be seen in the short and medium term, and that the reduction of infection and complication costs are seen in the long term. This benefit may be most significant in communities with a high risk of gastric cancer, decreasing the severe burden of morbidity and mortality from this disease.[v]

According to Maastricht V, countries with a significantly increased risk of gastric cancer, mainly due to the high prevalence of oncogenic strains, should offer endoscopic and/or serological screening and surveillance, targeting mainly people between 50-65 or 70 years of age.[v]

One of the most important limitations of this study was its interruption due to the COVID-19 epidemic, from the purchase of supplies to the suspension of endoscopies. This caused a delay in the research execution, but the results were not affected.

According to the results of this research, the importance of the implementation of molecular techniques is notorious, for the detection of oncogenes that are available to the general population, in addition, the expansion of the search should not only be limited to oncogenes, but also to genes related to antimicrobial resistance in order to perform epidemiological surveillance for *Hp*.[v,xxviii]

Conclusions

Most participants had a previous diagnosis of *Hp* infection, which is important because it implies the existence of reinfection, failure to eradicate, or recurrence of the bacterium.

The main endoscopic diagnoses were acute gastropathy/gastritis, followed by erosive gastropathy, nodular gastropathy, esophagitis, and gastric ulcer. Such findings could be produced by the presence of bacteria, and some of these endoscopic

diagnoses are recognized as premalignant lesions in other investigations.

In this study, the two virulence genes, cagA and vacA, were found to be present in all samples in which *Hp* was isolated; this data is relevant due to the risk of gastric cancer produced by these strains.

Acknoledgments

To the Evangelical University of El Salvador, especially the FACMED, for their support of the research team. To the gastroenterologists of ISSS: Yánez, Arias, and Salazar, for their support in carrying out this research.

Funding

The research was funded by the Evangelical University of El Salvador.

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Narrative review

Relationship between lipid-based nutritional supplements and psychomotor and anthropometric development in malnutrition

DOI: 10.5377/alerta.v8i3.18442

Luis Alonso Alvarado Cerritos[1]*, Faviola Estefani Valle Martínez[2], Odalys Melany Martínez Argueta[3], Pablo Ernesto Salazar[4]

1-4. Dr. Luis Edmundo Vásquez School of Health Sciences, Dr. José Matías Delgado University, Antiguo Custatlán, El Salvador.

*Correspondence
luisalvarado5002@gmail.com

1. 0009-0008-9860-1977
2. 0009-0004-4363-8108
3. 0009-0005-8834-9163
4. 0000-0002-8265-5603

Relación entre suplementos nutricionales basados en lípidos y el desarrollo psicomotor y antropométrico en desnutrición

Suggested citation:
Alvarado Cerritos LA, Valle Martínez FE, Martínez Argueta OM, Salazar PE. Relationship between lipid-based nutritional supplements and psychomotor and anthropometric development in malnutrition. Alerta. 2025;8(3):282-289. DOI: 10.5377/ alerta.v8i3.18442

Editor:
Veralís Morán.

Received:
July 22, 2024.

Accepted:
June 27, 2025.

Published:
July 31, 2025.

Author contribution:
LAAC[1], FEVM[2], OMMA[3], PES[4]: study conception, manuscript design,data collection, data analysis,writing, revising and editing. LAAC[1], FEVM[2], OMMA[3]: literature search. PESC[4]: data or software management.

Conflicts of interest:
The authors declared there are not conflicts of interest.

Abstract
Malnutrition affects a significant proportion of children aged six to 24 months, causing low weight and shorter height for their age, as well as a predisposition to multiple diseases. It is important because it is during these ages that the greatest changes in children's early brain development occur. When this occurs, delays in motor and language development may result, hindering children from achieving their optimal developmental outcomes. This literature review provides a summary of the evidence on the effect of lipid-based nutritional supplements. The objective was to analyze the effect of lipid-based nutritional supplements on anthropometric, motor, and language development in malnourished children between six and 24 months of age. Original articles and literature reviews in Spanish and English, published from 2019 to August 2024, were included. Databases such as Google Scholar, SciELO, HINARI, and PubMed were consulted. This review demonstrates that lipid-based nutritional supplements improve length and weight for age, as well as motor and language development scores, making them a valuable tool for addressing the described problem.

Keywords
Dietary Supplements, Child Development, Malnutrition.

Resumen
La desnutrición afecta una importante proporción de los niños en edades de seis a 24 meses, ocasiona bajo peso y menor longitud para la edad, así como predisposición a múltiples enfermedades. Presenta importancia ya que es en estas edades donde se produce el mayor cambio en el desarrollo cerebral temprano de los niños. Cuando este se afecta, se enlentece el desarrollo motor y de lenguaje, evitando que los niños alcancen su máximo potencial. Esta revisión bibliográfica ofrece un resumen sobre la evidencia del efecto de los suplementos nutricionales basados en lípidos. El objetivo fue analizar el efecto de suplementos nutricionales basados en lípidos en el desarrollo antropométrico, motor y lenguaje en niños desnutridos, entre seis a 24 meses de edad. Se incluyeron artículos originales y revisiones bibliográficas en idioma español e inglés, publicadas de 2019 hasta agosto de 2024. Se consultaron bases de datos como Google Académico, SciELO, HINARI y PubMed. Esta revisión evidencia que los suplementos nutricionales basados en lípidos incrementan la longitud y el peso para la edad, como también los puntajes del desarrollo motor y de lenguaje, esto los convierte en una herramienta útil para afrontar la problemática descrita.

Palabras clave
Suplementos Nutricionales, Desarrollo Infantil, Desnutrición.

Introduction

Child malnutrition encompasses clinical, biochemical, and anthropometric alterations of multifactorial origin, among which the following stand out: inadequate diet, presence of infections, poverty, poor sanitary conditions, and food insecurity.[i]

It manifests as low weight for height and low weight for age, affecting more than 50 million and 149 million children, respectively, which makes it a public health problem that remains prevalent because, in the long term, it can impact the development of children's learning skills and their productivity as productive adults.[ii,iii]

Malnutrition predisposes to acute diseases, mainly of respiratory and gastrointestinal origin, by compromising the immune system. In addition, there is evidence of a lack of adequate growth, as indicated by anthropometric measurements, a deficit in cognitive development, and impairment in motor and language development, primarily during the first two years of life. This is because proper functioning depends on obtaining macromolecules in the diet, such as proteins, lipids, and carbohydrates.[iv,v]

For this reason, in recent years, lipid-based nutrient supplements (LNS) have been studied, which are a fortified and individually packaged paste, generally made with a base of peanuts, cereals, vegetable oils and powdered milk, intended to supplement the diet of children from six months of age, depending on their needs and nutritional status.[vi] In addition, their formulation also includes foods based on wheat or corn, water fortified with vitamins and minerals. There are also prepared foods intended for children from six to 59 months, which are consumed in small quantities and prepared with a lipid base that provides proteins and micronutrients.[vii]

Regarding their effects, an increase in the concentration of essential fatty acids has been observed in children with malnutrition who received LNS. These acids are involved in multiple processes in the body, such as protection of the gastric mucosa, hemostasis, maintenance of endothelial function, reduction of the risk of developing allergies, and improvement of the immune system.[viii]

Furthermore, LNS also increases high-density lipoprotein (HDL) levels and their ability to scavenge excess cholesterol from tissues;[ix] in addition, LNS has been shown to decrease the prevalence of anemia and iron deficiency.[x] Additionally, improvements in growth and reduction of underweight have been observed in children aged six to 24 months.[xi]

The previously described effects enable us to highlight the role of LNS in preventing infant malnutrition, positioning it as a potential therapeutic and preventive approach to mitigate short- and long-term alterations related to infant malnutrition.[xii-xvi]

This work consists of a narrative review of original and review articles dated from January 2017 to August 2024. Google Scholar, SciELO, HINARI, and PubMed databases were consulted in Spanish and English language, the Boolean operators AND, OR, and NOT were used, and the descriptors: Child Nutrition Disorders, Child Developmental Deviations, Childhood Malnutrition, Growth Disorders, Lipid-based Nutritional Supplements were used and combined in different ways together with the Boolean operators. This review aimed to analyze the effect of lipid-based nutritional supplements on the development of anthropometry, motor skills, and language in malnourished children aged six to 24 months.

Discussion

Composition and generalities of lipid-based nutritional supplements

LNS is formulated with basic foods such as skim milk powder, peanut, soy, vitamin and mineral premix, and carbohydrates such as lactose, maltodextrin, and sucrose. Among the main energy sources are lipids, such as essential fatty acids, obtained from vegetable sources.[xv]

They are nutritional support strategies for home use aimed at populations at nutritional risk in low- and middle-income countries. They are targeted as a supplement to the daily diet to increase caloric and protein intake.[xvi]

There are currently three LNS formulations, each with a different daily portion, nutritional value, and energy content. These include: Small Quantity LNS (SQ), designed to supplement the regular diet, which provides 3 g of protein and 10 g of fat in 20 g of product; Medium Quantity LNS (LNS-MQ), traditionally used to treat moderate acute malnutrition in children, which provide 6 g of protein and 16 g of fat in 45-90 g of supplement; while Large Quantity LNS (LNS-LQ), used in the treatment of severe acute malnutrition in children, provide 15 g of protein and 28 g of fat in 180-280 g of product.[xvii]

Okronipa *et al.* reported in Mexico that even sugar-free LNS are well accepted by caregivers and children, thanks to their pleasant taste and the possibility of being consumed directly from the packaging or mixed with water or other foods.[xviii]

In other parts of the world, their acceptability is limited; however, Merrill *et al.* evidenced in Bangladesh that designing and manufacturing an LNS with locally and culturally appropriate products improves its acceptability compared to imported nutritional products.[xix]

Lipid-based nutritional supplements and anthropometric development

Anthropometry is the study of measuring the human body in terms of its dimensions, including bone, muscle, and adipose tissue[xx,xxi]. For children under two years of

age, the Ministry of Health of El Salvador recommends assessing nutritional status by weight and length for age.[xxii]

Mbabazi *et al.*, conducted a randomized, double-blind trial in children aged 12 to 59 months with growth retardation, using four formulations of LNS enriched with milk protein, permeated whey, soy protein, or maltodextrin, compared to a reference group that did not receive any supplementation. In the children who did not receive the intervention, there was no growth, and they gained body fat, unlike those who received an LNS, regardless of their formulation, who presented an increase of 0.56 cm in height, which reflects a recovery of 0.17 of the Z value of height and an increase in fat-free mass deposits.[xxiii]

In a study by Griswold *et al.*, in Sierra Leone, 2691 children aged 6-59 months with moderate acute malnutrition, defined by a Mid-upper arm circumference (MUAC) of ≥ 11.5 cm and < 12.5 cm, were studied. They were divided into four study arms: the first, a soybean blend; the second, a soybean blend with oil; the third, Super cereal Plus amylase; and the fourth arm, LNS. Anthropometric measurements were taken every 14 days. During their development, the participants gained an average of 13.1 ± 17.5 g/kg/day and an average MUAC of 0.4 ± 0.03 cm/day. Recovery, defined in the study as a MUAC ≥ 12.5 cm in 12 weeks, was achieved by 63 % of the children, with no significant difference between interventions.[xxiv]

In a longitudinal study conducted by Fazid *et al.*, in Pakistan in children aged 6-23 months, participants were divided into two arms: a treatment arm that received Ready-to-Use Supplementary Food (RUSF) and health counseling and a control arm that received counseling only. Of the 1680 children included in the study, 810 were assigned to the treatment arm, of whom 256 had low height-for-age, 72 had low weight-for-age; 870 were assigned to the control group, of whom 362 had low height-for-age, and 80 had low weight-for-age. They performed monthly follow-ups for one year, during which anthropometric measurements were taken, and counseling was provided. It was observed that in the intervened arm, the participants presented an increase in average height, from 73.4 cm to 82.1 cm (a total of 8.52 cm difference), an increase in height-for-age from -1.13 to -0.93 standard deviations (SD), and a total of 0.19 SD compared to the control arm, in which no statistically significant increase in height-for-age was observed.[xxv]

Huybregts *et al.*, conducted a longitudinal, cluster-randomized, controlled trial in 1132 children aged six to 23 months who were free of acute malnutrition at enrollment and were divided into two arms. One received the Innovative Approaches for the Prevention of Childhood Malnutrition (PROMIS) intervention plus SQ-LNS supplementation, while the other received no intervention. The intervention arm showed a 29 % reduction in the incidence of acute malnutrition, mainly between six to ten months of age, attributing the preventive effect to the consumption of SQ-LNS.[xxvi]

In 2019, Das *et al.*, conducted a systematic review of the effect of LNS in children aged six to 23 months, including 17 studies with a sample of 23 200 previously healthy or at-risk children for prevalent diseases such as malaria, diarrhea, and malnutrition at baseline. In the groups using LNS, there was evidence of a 7 % reduction in the prevalence of moderate stunting and a 15 % reduction in the prevalence of severely stunted children. In addition to improving measures such as mean arm circumference and serum hemoglobin, greater effectiveness was achieved using LNS for a longer period, recommending a minimum use of 12 months of LNS to obtain a more significant recovery of anthropometric measures.[xxvii]

A meta-analysis by Dewey *et al.*, included 14 randomized clinical trials of children between six and 24 months at risk of malnutrition from countries with low or medium economic income, where LNS was used. In the groups that used the SQ-LNS, there was evidence of a reduction in the prevalence of stunting, ranging from 9 % to 16 %, compared to children who did not receive the intervention. Additionally, a greater benefit was observed in children with a higher degree of malnutrition.[xxviii]

Khan *et al.*, evaluated the impact of LNS-MQ in 870 children aged 6-23 months at risk of stunting in Thatta and Sujawal districts of Sindh, Pakistan, divided into two groups: one receiving the intervention and the other serving as the control. The initial rates of stunting and wasting were comparable in the two groups studied. There was evidence of a reduction in the risk of stunting, especially in children under 12 months of age, by approximately 9 % and in wasted children by 22 %. This supports the recommendations of a greater benefit at ages of nutritional vulnerability.[xxix]

Dewey *et al.*, conducted a two-stage meta-analysis in 2022 that included 14 studies, which were conducted on 37 066 children aged six to 24 months at risk of undernutrition in low- and middle-income countries. In which the same participants were measured at baseline and the end of the study; in some cases, longitudinal post-intervention follow-up was performed, ranging from six to 18 months. Those who received SQ-LNS showed reductions in the prevalence of severe wasting and stunting of 31 % and 17 %, respectively.[xxx]

According to the document "The Double Burden of Malnutrition," RUTF (Ready-to-Use Therapeutic Food) is an effective strategy for treating severe acute malnutrition, which has been shown to reduce mortality. In food-insecure contexts, LNS with lower energy density, fat, and sugar content are used to improve nutritional status, promote growth in young children, and treat moderate acute malnutrition.[xxxi]

Lipid-based nutritional supplementation and motor and language development

The brain is a heterogeneous organ composed of multiple processes, neuronal connections, neurotransmitters, and specific anatomical areas that each have different functions. Due to its high functional and structural complexity, brain development extends from birth through the first years of life, a period during which it undergoes the most significant number of changes, culminating in adulthood, when its development is considered complete.[xxxii] During the first years of life, a critical stage for neuronal plasticity, the brain requires a constant supply of nutrients to facilitate its proper development.[xxxiiii] That is why malnutrition has been associated with multiple cognitive, social, and motor deficiencies during childhood development.[xxxiv]

LNS has been used in several studies conducted in low- to middle-income countries as a measure to improve motor and language development. In a study conducted in the Democratic Republic of Congo, children aged six to 18 months with malnutrition and at risk of malnutrition belonged to two geographic areas of interest to the researchers. Participants were divided into two arms according to area; one arm received intervention with the government's infant and young child feeding (IYCF) program plus an LNS, while the control arm received only the government's IYCF program without LNS. Motor and language development were assessed using the ASQ-3 tool in the Communication and Gross Motor Development modules (Ages and Stages Questionnaire, 3rd edition). The results showed that children in the treatment group scored higher in communication and motor response compared to those in the control group. In addition, LNS decreased the likelihood of motor developmental delay by 18 % and the likelihood of language developmental delay by 19 %, highlighting its preventive role in language development.[xxxv]

Not only have LNS been observed to prevent developmental delay in children at risk of malnutrition, but studies have also been conducted looking at the efficacy of LNS in acutely malnourished children. In a study by Olsen *et al.*, conducted in five hospitals in Burkina Faso, 1613 malnourished children were divided into 12 groups. Six groups received a soybean-based supplement, and six groups received an LNS. Using the Malawi development assessment tool (MDAT), which assesses four developmental domains (fine motor, gross motor, language, and social skills), it was found that at the end of the 12 weeks of intervention, children who received LNS increased their scores assessed with the tool in the language and fine motor domains.[xxxvi]

In another study conducted by Mbabazi *et al.*, in Uganda, 1950 children with low weight for height were divided into four groups, depending on the composition of the LNS administered to them, comparing those containing milk protein, soy protein, both or none of the above; it was found, through an evaluation with the MDAT tool, that all children who received the LNS, after 12 months of intervention, increased their scores in the four domains of the evaluation, with a greater increase observed in children who consumed LNS with milk protein.[xxxvii]

In addition, in a meta-analysis conducted by Prado *et al.*, in which 14 studies were evaluated from nine countries, with a total population of more than 30 000 children between six and 24 months of age, with different nutritional status (incorporating both healthy and malnourished children) who received LNS, their results in language, motor, and socio-emotional development were compared mainly using tools such as Extended Ages and Stages Questionnaire (EASQ), Developmental milestones checklist (DMC), MDAT and Kilifi Development Inventory (KDI). Increases in scores in the areas of language, social-emotional, and motor development were reported in all the studies reviewed, corresponding to each of the tests used. In addition, these increases were found to be greater in children with low height-for-age at the beginning of the interventions. Individually, the increases were more significant in those with acute malnutrition.[xxxviii]

In a 6-month follow-up study by Cornelius M *et al.*, in a northern province of South Africa in undernourished children aged 6-12 months,

a population of 750 children was divided into three study groups, one with LNS-SQ, one with LNS-SQ plus four additional nutrients (phosphorus, magnesium, potassium, and manganese) and a control group that received no intervention. Each group underwent anthropometric and psychomotor development measurements at six and 12 months of age, using the "Kilifi Developmental Inventory (KDI)" tool, which includes the assessment of skills such as movement in space, motor coordination, dynamic balance, and static balance. It was observed that, when measured at 12 months of age, children who received LNS-SQ plus four additional nutrients scored 25 % higher on the KDI than children in the control group.[xxxix]

Currently, LNS is now considered one of the most promising interventions to improve language and motor development in children with malnutrition due to its ease of administration, which leads to good adherence to indicated treatment. More research is needed to support this intervention as a primary tool to benefit children affected by this condition, exploring possible health effects.

Conclusion

The effectiveness of LNS in improving anthropometric measures such as weight-for-age and length-for-age in malnourished children has been clearly demonstrated. Regarding motor and language development, the studies reviewed indicate that children who receive LNS achieve better results on standardized tests assessing these developmental areas. Likewise, LNS is attributed with having a preventive effect against delays in motor and language development.

It is important to note that more significant improvements were observed when LNS administration was combined with interventions that promote good feeding practices—such as the IYCF program and the PROMIS strategy—along with food security and proper handwashing.

Therefore, it should be emphasized that using LNS as a standalone intervention may not produce the same benefits in development and anthropometric measures as when it is combined with the aforementioned strategies. Additionally, the formulations of lipid-based nutritional supplements can differ depending on the region where they are produced. This review considers the results of studies that used various types of lipid-based nutritional supplements, recognizing that outcomes may vary depending on the specific formulation.

Funding

No external funds were received for this work.

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Narrative review

Physical and mental effects in older adults due to prolonged use of benzodiazepines

DOI: 10.5377/alerta.v8i3.18116

Consuelo Cubero Alpízar[1]*, Kattia Medina Arias[2], Beatriz Villalobos Núñez[3]

1-3. University of Costa Rica, San Jose, Costa Rica.

*Correspondence
consuelo.cubero@ucr.ac.cr

1. 0000-0003-2073-0839
2. 0000-0001-9322-836X
3. 0000-0003-3902-9487

Abstract
The potential effects and risks of benzodiazepine use have been documented for several decades, with older adults being particularly affected due to the significant changes in pharmacokinetics and pharmacodynamics associated with aging. The objective of this narrative review was to provide answers regarding the effects of benzodiazepine use on the physical and mental health of older adults. A search was conducted in PubMed, Cochrane, Scielo, and LILACS, as well as in the repository of the Library, Documentation, and Information System of the University of Costa Rica. The effects on physical health identified were an increased risk of falls and fractures, while in mental health, an increased risk of dementia and decreased cognitive processing speed were reported. The results emphasize the importance of limiting the prolonged use of benzodiazepines in older adults and promoting non-pharmacological therapeutic alternatives, such as cognitive-behavioral therapy, especially for the management of insomnia and anxiety. Raising awareness among those who prescribe this type of medication is essential so that they seek alternative ways to address conditions such as insomnia and anxiety in this population.

Keywords
Substance-Related Disorders, Aging, Benzodiazepines, Metabolic Side Effects of Drugs and Substances, Quality of Life.

Resumen
Los efectos y riesgos potenciales por el consumo de benzodiazepinas han sido documentados durante varias décadas. Las personas adultas mayores tienen un efecto particularmente importante por los cambios relevantes en la farmacocinética y farmacodinamia propios del envejecimiento. El objetivo de esta revisión narrativa fue dar respuesta sobre los efectos por el consumo de benzodiazepinas en la salud física y mental de las personas adultas mayores. Se realizó una búsqueda en PubMed, Cochrane, Scielo y LILACS y en el repositorio del Sistema de Bibliotecas Documentación e Información de la Universidad de Costa Rica. Los efectos en la salud física identificados fueron mayor riesgo de caídas y fracturas; mientras que, en salud mental se reportó mayor riesgo de demencia y disminución de la velocidad del procesamiento cognitivo. Los resultados recalcan la importancia de limitar el uso prolongado de benzodiazepinas en personas adultas mayores, promoviendo alternativas terapéuticas no farmacológicas, como la terapia cognitivo-conductual, especialmente para el manejo del insomnio y ansiedad. La sensibilización dirigida a quienes prescriben este tipo de medicamentos es fundamental, de manera que busquen formas alternativas de abordar los padecimientos de esta población como el insomnio y la ansiedad.

Palabras clave
Trastornos Relacionados con Sustancias; Envejecimiento; Benzodiazepinas; Efectos Metabólicos Secundarios de Drogas y Sustancias; Calidad de vida.

OPEN ACCESS

Efectos físicos y mentales en adultos mayores por consumo prolongado de benzodiazepinas

Suggested citation:
Alpízar CC, Medina Arias K, Villalobos Núñez B. Physical and mental effects in older adults due to prolonged use of benzodiazepines. Alerta. 2025;8(3):290-296. DOI: 10.5377/alerta.v8i3.18116

Editor:
David Rivera.

Received:
June 25, 2024.

Accepted:
May 27, 2025.

Published:
July 31, 2025.

Author contribution:
CCA[1]: study conception, CCA[1] KMA[2], BVN[3] manuscript design, literature search, data collection, data or software management, data analysis, writing, revising and editing.

Conflicts of interest:
The author declared there are not conflicts of interest.

Introduction

The effects and potential risks of benzodiazepine use have been documented for several decades[i] and have been identified for different age groups. However, in the elderly, this effect is particularly important, as there are relevant changes in pharmacokinetics and pharmacodynamics that are typical of the physiology of this life cycle.[ii]

The uses of these drugs are broad. However, the literature indicates that in older adults, they are mainly used for anxiety and insomnia.[iii,iv] In addition, prolonged use has been documented, which contravenes the stipulations of the management guide, which indicates that they should not be prescribed for more than four weeks.[v] The aim is to prevent dependence and avoid the development of potentially harmful effects.

On the other hand, improvements in healthcare technologies and overall living conditions have contributed to the increase in life expectancy. This also translates into a challenge for society and health systems as a whole since the population is reaching old age with a series of health problems or multiple pathologies and consequently consumes a large number of drugs, which leads to a decrease in the quality of life.[vi]

In line with the above, an increased consumption of benzodiazepines has been documented in the older adult population, together with adverse effects such as dependence, cognitive impairment, gait disturbances, and increased risk of falls, among others.[vii,viii] All these effects are directly related to basic activities of daily living such as personal hygiene, independence at home, and moving from one room to another within their own home or outside it, affecting, to some extent, the socialization of older adults. In addition, they require a great deal of assistance, which causes dependence on third parties for their care.

Consistent concerns have been documented in the international literature regarding the prolonged use of benzodiazepines in older adults. Studies conducted in countries such as Finland, the United States, France, and the Netherlands have reported adverse cognitive effects associated with their use, which has led to calls for attention to their use in this population.[viii] Nonetheless, its prescription remains a frequent practice. At the same time, it has been shown that a significant proportion of users -particularly older adults- are not fully aware of the potential risks associated with the use of these drugs.[i] On the other hand, recent reviews have addressed relevant pharmacokinetic aspects, as well as the limitations in detecting consumption due to the fact that, in some cases, people do not report their use voluntarily.[ix]

Similarly, some authors[i,x] propose a change in the approach to caring for various health problems, with the aim of improving the conditions of older adults and, consequently, their quality of life. In addition to the above, the World Health Organization has declared the current decade as the "Decade of Healthy Aging," which increases the need to influence modifiable factors that contribute to favoring this initiative, one of which involves polypharmacy and specifically the prescription of benzodiazepines.[xi,xii]

In this same line, important variables are determined on which actions should be generated to favor healthy aging, among which are independence, autonomy, and informed consent in health matters. All the aspects mentioned are linked to medications that have effects on these components, such as benzodiazepines.[xi,xii]

This research design responds to a narrative review of the literature. A search was conducted in PubMed, as well as in the Cochrane, Scielo, and LILACS databases and the repository of the Library Documentation and Information System from the University of Costa Rica. Studies on the effects on physical and mental health of benzodiazepine use in older adults (over 60 years of age) were included. The search strategy included the following keywords: benzodiazepines, aging, adverse effects, adverse effects, long-term adverse effects, mental health, physical health, benzodiazepines, physical and human conditioning, long-term adverse effects, benzodiazepines, and long-term adverse effects, health status and aging. The identified citations were collated and loaded into EndNote 20, a bibliographic software or citation management system (Clarivate Analytics, PA, USA).

This review aimed to provide answers about the effects of benzodiazepine use on the physical and mental health of older adults. Thus, the importance of this research is highlighted, as it adds valuable information to the growing literature and helps to understand better the impact of this type of medication on older adults. Consequently, it provides input for developing better strategies in a comprehensive approach to this issue.

Discussion

This study aimed to map the physical and mental effects associated with long-term consumption of benzodiazepines in older adults, a particularly vulnerable population due to the physiological and cognitive changes associated with aging. The findings identify specific adverse effects in two major areas: physical health and cognitive health. This also revealed an interrelationship between the two "dimensions" since the effects in one dimension tend to exacerbate those in the other, enhancing the overall negative impact. Given the above, the information obtained from the review provides a comprehensive overview of the potential risks associated with these substances, detailing their documented effects and potential implications for clinical practice and public health.

Given the aforementioned and to contextualize, it should be noted that drugs belonging to the benzodiazepine family comprise a group of substances widely used

in medicine to treat different conditions, some of which are anxiety disorders, insomnia, seizures, and withdrawal syndrome, among others.[xiii] In addition to the above indications, they are being used for all population groups according to their particular condition and need.[vii,viii,xiv] Despite the above, there are various studies indicating that the population stratum that uses it most or has the greatest number of indications is the elderly.[xiii]

In view of the above, it should be noted that the normal aging process involves natural physical and mental changes, but certain drugs can promote an acceleration in the manifestation of these changes or induce greater deterioration. In addition, it is particularly important to clarify that aging, itself, does not always result in a severe reduction of physical and mental capacities. Nevertheless, it is a stage of life in which some bodily and cognitive functions may gradually diminish and this makes them especially vulnerable or sensitive to the effect of different substances.[ix]

As mentioned above, in older adulthood, the body undergoes physiological changes, some of which can manifest themselves as a decrease in muscle mass, loss of bone density and a decrease in cardiovascular capacity.[xv] Similarly, the brain undergoes modifications, such as a slight decrease in information processing speed and memory, which are considered to be part of normality in this phase.

However, the use of certain medications, especially in inappropriate doses or for prolonged periods, can exacerbate these changes, such as BZDs, commonly used to treat anxiety or insomnia in older adults,[xvi] which can intensify drowsiness, confusion, and affect motor coordination, increasing the risk of falls and fractures.[xiv,xvi-xviii] In addition to the above, age-related changes in liver and kidney function or the distribution of drugs in the body will alter the normal or expected response of the body during older adulthood;[xix] this may result in some drugs interacting with the aging process and generating more pronounced side effects at this stage of life. This is associated with an increased risk of falls and fractures among those who consume these substances as a result of the effects of benzodiazepines, in addition to the changes expected at this stage of life.

In the review conducted by Zhong *et al.*, in addition to the results observed in Table 1, it was found that patients, recent users of BZD, defined according to most of the studies included in the review as less than two years of use, also had an increased risk of dementia (RR 1.55; 95 % CI 1.33 - 1.83; p 0.32; I^2=15.0)20. An increased risk was also found (RR 1.55; 95 % CI 1.17-2.03; p < 0.01; I^2 = 72.6) when evaluating patients with a history of BZD use, with the last dose administered between two and 12 years prior to the start of the studies.[xx]

In the review published by Gómez *et al.*, in addition to the adverse effects described (Table 1), there was also evidence of high BZD consumption in the population > 60 years of age and that the use of BZDs was more frequent in women. However, the limited number of studies in the region does not allow for the generalization of results, which suggests that the exploration of BZD use in MA is in its initial stages and has denoted a need for further and more in-depth study.[xx]

Although the study by Young *et al.* did not find an increased risk of angle-closure glaucoma in BZD users (Table 1), it was reported that new users (without exposure to BZD 30 days prior to the index date) did present an increased risk (Adjusted OR 1.62; 95 % CI 1.09 - 2.37) of this disease.[xxi]

Now, in response to the objective of this review, it is important to distinguish between the effects of the physical and mental components. However, the fact that they are linked is emphasized, as the effects on the mental component enhance the effects on the physical component, and vice versa.[xxii]

Effects on physical health

This population group faces changes in muscle mass and strength,[i,viii-xvi] due to conditions such as sarcopenia;[xxiii] the consumption of BZD aggravates this age-related effect, and, as a result, there are more cases of falls and fractures among users of these drugs.[xvi]

The above reinforces what is reported in the literature when it expresses concern about the indiscriminate prescription and consumption of benzodiazepines among the elderly.

In this same line of argumentation, another group of effects is also found, such as an increase in the risk of acute closed glaucoma and an increased risk of cancer (although it should be clarified that this study included people who were not older adults since age was not a selection criterion), decreased sexual desire, anorgasmia and erectile dysfunction, regarding these the literature mentions that some may be dose-response and others require more research. However, it is worth mentioning, as they should be addressed in greater depth in future research.[xxiv-xxvii] In addition, it is noteworthy to understand that new studies are associating the consumption of these with inflammation processes, which, in turn, are related to the appearance of certain types of cancer and with the serious and complex behavior of conditions such as asthma or pneumonia; however, more research is required in this regard.[xxviii]

The aforementioned is particularly important in a society with an increasing number of older adults, and the trends of the main health organizations (PAHO and WHO) indicate a decade of healthy aging and improved quality of life for older adults. The regularization of benzodiazepines, which are used in this age group to treat insomnia and anxiety,[xxvi] is fundamental. There are other alternatives for these conditions, including some non pharmacological ones. BDZ consumption is among the modifiable factors that contribute to achieving optimal aging.

Table 1. Effects on physical and mental health of long-term benzodiazepine use in the elderly population

Author and year	Description of the study	Time of use	Health effects identified
Zhong, Wang, Zhang, Zhao, 2015[xx]	**Study Type:** systematic review and meta-analysis. **Objective:** quantify the relationship between long-term benzodiazepine use and dementia. **Population:** six studies were included for a total of 45 391 participants.	Ever use: whether they used BZD during the follow-up time of the studies, maximum follow-up ranged from eight to 25 years.	For the risk of dementia in patients who have ever used BZD compared to those who never used them, significant pooled RRs were obtained (RR 1.49, 95 % CI 1.30- 1.72) with low heterogeneity (p 0.19, I^2 35.1).
Poly TN, Islam MM, Yang HC, Li YJ 2019[xvi]	**Study type:** systematic review and meta-analysis. **Objective:** assess the magnitude of hip fracture risk with benzodiazepines. **Population:** 30 studies were included in the review.	Studies in which patients had at least 14 days of exposure to benzodiazepines were included.	In studies that included participants ≥ 60 years, a pooled RR for hip fracture risk of 1.35 (95 % CI 1.24 - 1.47; p < 0.0001) was obtained with a moderate risk of heterogeneity between studies ($I^2$73.37; Q 90.12; r^2 0.02).
Díaz, Martínez-Cengotitabengoa, Sáez, Cano, Martínez-Cengotitabengoa, *et al.*, 2017[xvii]	**Type of study:** systematic review **Objective:** collect updated data on the relationship between benzodiazepine use and the risk of falls in older adults. **Population:** 12 articles were included.	The follow-up period of the included studies ranged from five days to ten years.	BZD exposure is associated with the risk of falls in older adults; among the drugs evaluated were lorazepam, alprazolam, clonazepam, and flurazepam.
Goméz, León, Macuer, Alves, Ruiz, 2017[viii]	**Type of study**: systematic review **Objective:** conduct a review of the available information on the use of benzodiazepines in older adults in Latin America. **Population:** 21 articles were included.	Not specified	The most frequent adverse effect identified in studies included in this review was the risk of falls and fractures due to falls. Other adverse events identified were chronic headache, insomnia, and dependency.
Young *et al.*, 2019[xxi]	**Type of study:** case-control **Objective:** investigate whether BZDs increase the risk of acute angle-closure glaucoma in a geriatric population. **Population:** 1117 cases and 4468 controls.	One to 30 days	BZD use did not significantly increase the risk of acute angle-closure glaucoma (adjusted OR, 1.14; 95% CI, 0.94-1.37).
Liu, Jia, Jian, Zhou, Zhou,Wu, Tang, 2020[viii]	**Type of study:** systematic review and meta-analysis. **Objective** explore the following two questions in the elderly: is benzodiazepine use associated with impaired cognitive functions in the elderly? And, which cognitive domains have decreased functionality associated with benzodiazepine use and abuse? **Population:** 13 articles were included in the review, but only eight could be included in the meta-analysis.	Not specified	Impairment in processing speed was found in BZD users (N 253; SMD -0.61; 95 % CI -0.91 - 0.31; I^2 0; p < 0.0001). There was no significant cognitive deficit in BZD users (N 9262; SMD -0.18; 95 % CI -0.36 - 0.00; I^2 87; p 0.05), but there was in those who abused (N 7726 SMD -0.23; 95 % CI -0.44 - -0.03; I^2 86 p 0.02).

SMD: Standardized Mean Difference.

DOI: 10.5377/alerta.v8i3.18116

Effects on cognitive health

Older adults frequently present alterations in their cognitive functions as part of the aging process. Among these changes are difficulties in memory, especially in the short term, and in processing speed, which means that tasks are performed more slowly.[xxiii] Additionally, they experience difficulties with concentration and certain executive functions, including problem-solving and decision-making.

This frames what are considered some of the main psychological changes of aging, which should be considered and confronted with the common effects of benzodiazepines. In this regard, the literature refers to disorientation, confusion, mood changes, and sleep disturbances, among others. This reinforces the evidence found, which details how they affect cognitive processes and slow down learning and memory,[xxix] increasing the risk of dementia, cognitive impairment, and the speed at which information is processed.[viii,xiv,xv]

From the mapping of the evidence compiled in this review, it is observed that, in the context of various national and international policies aimed at promoting active, healthy, and functional aging, with the full participation of older adults in society, the use of benzodiazepines requires special attention. The literature suggests that their prescription should be careful and, preferably, carried out by specialists such as geriatricians, who can assess the changes inherent to aging and adequately weigh the risk-benefit ratio when prescribing these drugs to treat common conditions such as insomnia or anxiety.[xxx]

It is important for health professionals to be aware that cognitive deterioration can lead to long-term physical deterioration and vice versa and to take into account the importance of restrictions in the prescription of this group of drugs.

Limitations and recommendations of the review

Among the main limitations identified were the time required for the search process and the scarcity of studies with large samples, long follow-up periods, and direct comparisons between benzodiazepine users and non-users. Nevertheless, the information gathered is relevant, especially when considering the projected growth of the older adult population. In addition, it highlights the need for research to investigate the causes of prolonged prescription of these drugs and to explore therapeutic alternatives to address common problems such as insomnia or anxiety. This allows to identify priority areas for future research.

The similarities between the studies are explained by the nature of the documented adverse effects, such as falls and cognitive impairment. On the other hand, differences in specific findings, such as oncologic risks, can be attributed to variations in methodological designs, population characteristics, and prescribing practices in different geographic regions.

These results underscore the importance of limiting the prolonged use of benzodiazepines in older adults and promoting non-pharmacological therapeutic alternatives, such as cognitive-behavioral therapy, especially for the management of insomnia and anxiety.[xxx]

On the other hand, it is important to recommend the importance of continuing medical education to sensitize prescribers of the risks associated with the use of benzodiazepines, as well as strict prescription and follow-up protocols, prioritizing the intervention of specialists such as geriatricians.

All of the above cannot be overlooked; however, it is recommended that longitudinal research be conducted to compare consumers and non-consumers, evaluating the long-term effects on various health dimensions.

Conclusion

The main side effects on physical and mental health identified were increased risk of falls, dementia, as well as loss of cognitive abilities. According to the available evidence, it has been found that there is a reduction in the quality of life and the possibility of self-care of older adults associated with the side effects of benzodiazepines. The literature emphasizes the importance of adopting alternative measures to improve the quality of life for the older adult population. Therefore, it is essential to raise awareness among those who prescribe this type of medication so that they seek alternative ways of dealing with the ailments of this population, such as insomnia and anxiety.

Funding

No external funds were received for this work.

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Narrative review

Glutamate's role in symptom control of autism spectrum disorder

DOI: 10.5377/alerta.v8i3.20715

Valeria María Mendoza Rodríguez[1], Daniela Marisol Rodríguez Olivares[2], Francisco Javier Villatoro Rubio[3*], Pablo Ernesto Salazar Colocho[4]

1-4. Dr. Luis Edmundo Vásquez School of Health Sciences, Dr. José Matías Delgado University, Antiguo Cuscatlan, El Salvador.

*Correspondence
frankciss8th@gmail.com.

1. 0009-0000-6180-6778
2. 0009-0005-1102-8791
3. 0009-0008-8917-8775
4. 0000-0002-8265-5603

Abstract
Autism spectrum disorder is a complex and persistent condition that has received increasing attention through the recent decades. Numerous research studies have highlighted the role of the neurotransmitter glutamate in this disorder, suggesting that alterations in its function could be significant in the development of the disorder's symptoms. Literature research was conducted in the PubMed, MEDLINE, Google Scholar, Scielo, and PsycARTICLES databases from 2019 to 2024, original and review articles in English and Spanish were selected to evidence the influence of neurochemical imbalance on the development of autism symptoms. The findings proved a relationship between the neurochemical imbalance of glutamate and some symptoms of ASD, suggesting that the receptors of this neurotransmitter could be involved as therapeutic targets, positive developments were observed in verbal intellectual quotient and improvement in social responsiveness after treatment with allosteric modulators of glutamate receptors.

Keywords
Autism Spectrum Disorder, Glutamate Receptors, Neurodevelopmental Disorders.

Resumen
El trastorno del espectro autista es una condición compleja y persistente que ha recibido cada vez más atención en las últimas décadas. Diversas investigaciones han resaltado el papel del neurotransmisor glutamato en este trastorno, sugiriendo que las alteraciones en su funcionamiento podrían desempeñar un papel clave en el desarrollo de sus síntomas. Para la elaboración de esta revisión narrativa, se realizó una búsqueda bibliográfica en las bases de datos PubMed, MEDLINE, Google Académico, SciELO y PsycARTICLES de los años 2019 a 2024, se seleccionaron artículos originales y de revisión en inglés y español, con el objetivo de evidenciar la influencia del desequilibrio neuroquímico en el desarrollo del trastorno del espectro autista. Se demuestra la existencia de una relación entre el desequilibrio neuroquímico del glutamato y algunos síntomas del trastorno del espectro autista, que permite involucrar los receptores de dicho neurotransmisor como objetivos terapéuticos; se ha observado un desarrollo positivo en el coeficiente intelectual verbal y una mejora en la capacidad de respuesta social después del tratamiento con moduladores alostéricos de los receptores de glutamato.

Palabras clave
Trastorno del Espectro Autista, Receptores de Glutamato, Trastornos del Neurodesarrollo.

Introduction

Autism spectrum disorder (ASD) is a set of complex and persistent neurodevelopmental disorders characterized by two main domains: social interaction and communication and restrictive and repetitive behaviors. It is important to mention that symptoms must be present from the early stages of development and cause clinically significant social and occupational impairments.[i]

OPEN ACCESS

Rol del glutamato en el control de síntomas del trastorno del espectro autista

Suggested citation:
Glutamate's role in symptom control of autism spectrum disorder. Alerta. 2025;8(3):297-304. DOI: 10.5377/alerta.v8i3.20715

Editor:
Veralís Morán.

Received:
July 31, 2024.

Accepted:
July 1, 2025.

Published:
July 31, 2025.

Author contribution:
VMMR[1], DMRO[2], FJVR[3], PESC[4]: data analysis, writing, revising, and editing. VMMR[1], DMRO[2], FJVR[3]: study conception, literature search. FJVR[3]: manuscript design. PESC[4]: data or software management.

Conflicts of interest:
No conflicts of interest.

This spectrum encompasses a diversity of disorders that share characteristics such as difficulties in social communication, restricted behaviors and the display of repetitive behaviors.[ii] In recent decades, the incidence of ASD has increased globally, affecting both boys and girls, and this could be due to the increase in diagnostic tools for this disorder. The World Health Organization (WHO) estimates that one in every 100 children is diagnosed with ASD in the United States; by 2016, one in every 36 children was diagnosed with this disorder.[iii] ASD poses economic and social challenges to the patients, with maintenance and subsistence costs exceeding $60 000 per year in the United States. In addition, only 15-20 % of adults with ASD are employed.[iv]

Currently, the origin of ASD is not fully understood. However, it is recognized as a complex condition in which genetic, neurobiological, and environmental factors interact.[v] An example of this is mutations in genes responsible for encoding receptors for various neurotransmitters, which are compromised in ASD and thus contribute to some of its distinctive features, such as glutamate, a crucial neurotransmitter with inhibitory effects that are involved in ASD.[vi] There are several studies, such as those by Hardan *et al.*, Schiller *et al.*, or Soorya *et al.*, which have demonstrated the efficacy of drugs acting on the regulation of glutamate concentrations at the brain level to provide a new therapeutic tool for symptom control in ASD patients, which is of utmost importance due to the limited number of treatments available.[vii-ix] Preclinical and clinical studies have corroborated the efficacy of glutamate receptor allosteric modulators in regulating neuronal excitability and synaptic conduction, which decreases the behavioral and cognitive effects of ASD.[x]

A literature search of databases was conducted for this narrative review, including PubMed, MEDLINE, Google Scholar, Scielo, and PsycARTICLES. Keywords such as autism, "intervention", "glutamate", "receptors" and "therapies", both in Spanish and English, were used to broaden the search results. Fifty scientific articles were selected according to the inclusion and exclusion criteria selected from the publications obtained using the search filters. One of the inclusion criteria for selecting studies was that they had to be published between 2019 and 2024. Additionally, only experimental and descriptive studies, available in Spanish or English, were considered. Those with a lack of adequate documentation for diagnostic confirmation by standardized tools were excluded in order to evidence the influence of neurochemical imbalance with the development of symptoms of autism spectrum disorder.

Discussion

General aspects of autism spectrum disorder and glutamate receptors

ASD is a pervasive neurodevelopmental disorder that can hinder skill acquisition. The WHO defines it as difficulties in social skills and communication with the environment, as well as inflexible or repetitive behaviors, unusual interests, and variations in the perception of sensory stimuli. Its development is influenced by a variety of factors, including environmental, genetic, and prenatal aspects.[xi]

It is characterized by a multifactorial etiology, although a precise cause triggering the associated neurological changes has not yet been identified. However, an alteration in brain connectivity, both in function and structure, has been observed.[xii] This phenomenon can occur in individuals of various races, ethnicities, socioeconomic backgrounds, and gender. However, it is more prevalent in boys than in girls, with a ratio of approximately two to one.[xiii]

Clinical symptoms are typically identified during the second year of life, although they may appear earlier in some cases. They can manifest in different ways: in some cases, a child follows a typical development and then experiences stagnation; in other cases, the opposite may occur, where children who have followed a normal pattern experience regression in language, communication, and loss of previously acquired skills.[xiv]

The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) categorizes ASD into three levels of severity, which include symptoms associated with social communication, repetitive and restricted behaviors. The first level implies a need for support, the second level a substantial need for support, and the third level denotes a very substantial need for support.[i,xv]

Several factors influence the biological origin of ASD at the brain level. Among them, alterations in the neuronal pathways stand out, particularly the imbalance between the glutamatergic (excitatory) and GABAergic (inhibitory) pathways, as well as dysfunctions in the cholinergic pathway, synaptic plasticity, and oxidative stress processes. Similarly, several comorbid disorders have been reported in ASD, such as anxiety disorder, sensory processing,

sleep, attention deficit, oppositional defiant disorder, intellectual disability, obsessive-compulsive disorder, etc.[xvi]

Glutamate, a key neurotransmitter in the central nervous system (CNS), plays a crucial role in the normal transmission between neurons, thereby facilitating communication between them. It also plays a crucial role in the plastic changes of the CNS during development, as well as in learning and memory processes. Its dysfunction has been associated with several diseases, including Alzheimer's disease, Parkinson's disease, and certain forms of epilepsy, and is involved in the treatment of ASD.[xvii]

Advances in genetic technology and diagnostic testing have made it possible to identify specific causes of ASD in approximately 40 % of patients with access to specialized genetic services. These studies focus on the detection of genetic syndromes, molecular and cytogenetic alterations, as well as metabolic disorders. For example, mitochondrial disorders may affect up to 20 % of people with ASD, along with the possible involvement of other metabolic disorders.[xviii]

Glutamate and its receptors in the development of autism

Brain development is a highly complex process involving numerous events such as synaptogenesis, axonal and dendritic arborization, neuronal migration, and synaptic plasticity, among others. These processes aim to establish the full functionality of the brain.[xix] However, sometimes, alterations at the cellular, biochemical, and structural levels may occur during neonatal development. Among the possible neurobiological causes of autism, the presence of abnormalities in the formation and function of synapses has been suggested.[xx]

Glutamate, which is a substance used as a substrate in protein synthesis, is the most prevalent excitatory neurotransmitter in the brain, used in approximately two-thirds of synapses. Glutamatergic transmission plays a crucial role in regulating motor, sensory, and cognitive systems and is involved in fundamental processes such as synaptic plasticity, adult neurogenesis, and neurodegeneration.[xxi]

During brain development, glutamate receptors change their distribution and molecular characteristics, rendering the brain more susceptible to variations in glutamate neurotransmission during growth. For this reason, the role of neurotransmitters and their receptors during the early stages of development is of paramount importance.[xxii]

During the 1990s, early studies focusing on plasma glutamate levels revealed a significant increase in these levels in children with ASD compared to controls. Similarly, more recent research has demonstrated a decrease in plasma glutamine levels, which are directly related to glutamate levels.[xxiii]This same glutamate-glutamine relationship has been observed in relatives of patients with ASD, as well as when comparing patients with autism with healthy individuals. These investigations clearly underline the implication of glutamate concentration in the development of this disorder.[xxiv]

The imbalance between GABA, the main inhibitory neurotransmitter, and glutamate, the main excitatory neurotransmitter, is an area of interest in autism spectrum disorder research because it has been suggested that this imbalance may contribute to the symptoms observed in autism spectrum disorder.[xxv] On the other hand, it has been proposed that there may be hyperactivity of the glutamatergic system or under activity of the GABAergic system in certain areas of the brain of individuals with ASD, which may contribute to increased neuronal excitability, problems in the modulation of sensory processing, and difficulties in the integration of sensory information, which are common features of autism.[xxvi]

In a study by Ajram *et al.*, a reduced GABA/glutamate ratio was found in the frontal lobe of children with autism, in the occipital lobe of adolescents with high-functioning ASD, and the prefrontal cortex of adults with this disorder.[xxvii] On the other hand, a 2020 investigation in New Jersey by Bhandari *et al.*, observed increased GABA levels in the visual cortex, decreased GABA levels in the sensory-motor cortex, and a decreased GABA/creatinine ratio in the anterior cingulate cortex in children with ASD compared to control individuals. These findings underscore the importance of maintaining a balance between excitatory and inhibitory stimuli in the development of autism.[xxviii]

It is worth mentioning that excitatory neurotransmitter signaling, mediated by glutamate receptors, regulates cognitive functions such as memory and learning, which are often compromised in autism.[xxix] Furthermore, being found throughout the central nervous system, glutamate plays a key role in brain development by influencing processes such as neuronal migration, differentiation, survival, and synapse formation.[xxx] However, at high concentrations, glutamate can act as a potent neurotoxin that causes cell death, which could be part of the pathophysiology of certain neurological disorders, including ASD. Although glutamate has

difficulty crossing the blood-brain barrier, its plasma and CNS levels are closely related.[xxxi]

Children with ASD have been found to have significantly higher plasma glutamate concentrations compared to healthy controls and controls with intellectual disability, which has been corroborated in post-mortem studies revealing anatomical changes in regions such as the cerebellum and hippocampus.[xxxii] These findings support the idea that alterations in glutamate signaling may play an important role in the pathophysiology of autism. However, more research is needed to understand from a mechanistic perspective the basis of the origin of ASD.

It is critical to recognize that autism is a complex and multifactorial disorder and that the relationship between imbalance in GABA and glutamate neurotransmission with ASD symptoms is not yet fully understood. Nevertheless, this area of research remains highly relevant and may offer new insights into the underlying biology of ASD and possible therapeutic approaches.[xxxiii]

Moreover, it is important to mention that metabotropic glutamate receptors (mGluRs) are a type of G-protein-coupled receptors that are activated by glutamate action in the CNS. In general, they are responsible for modulating synaptic efficiency and regulating the precision of neurotransmission. Among the eight subtypes, mGluR1 and mGluR5 belong to the group 1 (Gp1) family and are associated with various neurological disorders, including Alzheimer's disease, autism, and Parkinson's disease.[xxiv] Group1 mGluRs are distributed differently throughout the CNS. While mGluR1 is mainly found in the hippocampus, cerebellum, and substantia nigra, mGluR5 is expressed in the hippocampus, amygdala, olfactory bulb, striatum, nucleus accumbens, septum, and dorsal horn.[xxxv]

In addition, Gp1 mGluRs can also be affected by the allosteric binding of certain modulators, such as positive allosteric modulators (PAMs) and negative allosteric modulators (NAMs), which cause sensitization or desensitization of these receptors. PAMs and NAMs indirectly regulate glutamate transmission and are therefore used in clinical trials targeting related CNS disorders.[xxxvi]

While the exact pathogenic mechanism of ASD remains elusive, studies in mouse models of ASD and patients suggest the involvement of Gp1 mGluRs in the disorder[xxxvii] CFMTI, a selective mGluR1 antagonist, ameliorates MK-801-induced social interaction deficits in rodents, suggesting the therapeutic potential of mGluR1 antagonists in addressing pathological social interactions.[xxxviii] However, research on mGluR1 has focused primarily on cognitive rather than emotional and behavioral dysfunctions in rodent models of ASD. Although mGluR1 antagonists have shown efficacy in schizophrenia models, their application in ASD has not been as extensively studied. Research in this area is limited, and further studies are required to determine the efficacy and safety of these treatments in the management of ASD.[xxxix]

ASD is influenced by genetic and environmental factors, suggesting that treatment with Gp1 mGluRs antagonists may address individual symptoms rather than the disorder as a whole. Therefore, a combination treatment of multiple therapies may be necessary to intervene in the progression of ASD effectively.

Glutamate receptor antagonists and symptom control in patients with autism

Treatment for ASD is carried out in several areas, including a set of cognitive-behavioral interventions with speech, occupational, and physical therapies, as well as, in some cases, pharmacological treatments. From the cognitive perspective, the aim is to provide a systematic and regular approach, which encourages the application of the child's self-regulatory skills in a variety of social situations.[xl,xli]

Although there are currently no approved medications for the management of the core symptoms of ASD, psychopharmacological treatment is used to address other common symptoms in patients with autism.[xviii] This includes the use of stimulants, alpha-2 agonists, anticonvulsants, and antidepressants for the intervention of symptoms such as hyperactivity, inattention, impulsivity, irritability, aggression, self-injurious behavior, repetitive behaviors, and insomnia. In addition, antipsychotics such as risperidone and aripiprazole are licensed for the management of irritability associated with the disorder.[xlii]

Given the extensive role of glutamate in neurotransmission and its connection to the development of various pathologies, clinical trials have been conducted using several drugs that block NMDA receptors, a ionotropic subtype of glutamate receptors.[xliii] This has made it possible to establish links between these receptors and central nervous system disorders such as epilepsy, pain, ischemia, addictions, neurodegenerative diseases, and social deficits.[xliv-xlvi]

Recognition of the involvement of glutamate in various neurological conditions has prompted the search and investigation of

drugs that specifically modulate the glutamatergic pathway, with a focus on metabotropic glutamate (mGlu) receptors. Special attention has been given to memantine, which acts on NMDA receptors.[xlvii] Memantine is a non-competitive antagonist with a remarkable selectivity for NMDA receptors in the brain. This action allows it to restore physiological glutamatergic neuronal transmission and ameliorate the pathological effects associated with elevated synaptic glutamate concentrations.[xlviii]

Hardan *et al.*, in their double-blind study, compared memantine treatment of children with ASD; half of the participants received memantine as an adjuvant, while the other half received only a placebo. The study focused on evaluating the efficacy and safety of memantine in children with autism. In terms of safety, the study found that 64 % of individuals experienced mild adverse effects, such as dizziness, headache, fatigue, nausea, constipation, or diarrhea. In comparison, only 0.7 % experienced serious effects that resulted in treatment discontinuation.[vii]

An improvement in social responsiveness was observed in all study groups (memantine and placebo). However, after the end of treatment, participants who received a placebo or a reduced dose showed a worsening on the Social Responsiveness Scale (SRS), with increases of ten to 20 points over their scores during treatment. In addition, a higher percentage of placebo patients (73 %) had a significant increase in SRS score compared to those treated with reduced-dose (66.7 %) and full-dose memantine (64.3 %), suggesting that memantine may offer more sustained improvement in ASD symptoms.[vii]

In the clinical trial conducted by Soorya *et al.*, the use of memantine as an adjuvant compared to placebo in adolescents with autism was investigated to assess its impact on social skills. The results revealed a significant improvement in verbal recognition memory among participants treated with memantine. Furthermore, when analyzing the IQ of individuals who received memantine, a positive development in verbal IQ was observed after treatment.[viii]

This is consistent with the clinical trial conducted by Schiller, *et al.*, in 2023, in which the effect of memantine was examined in patients with epileptic encephalopathy, including ten patients who had previously been diagnosed with attention deficit hyperactivity disorder and eight patients previously diagnosed with autism spectrum disorder. During the study, significant improvements were identified in the electroencephalograms (EEGs) of the memantine-treated participants, including a reduction in the amplitude and frequency of epileptiform discharges, fewer nocturnal awakenings, and the absence of seizures on follow-up EEGs in two patients who initially had seizures. Less functional impairment was also observed in these participants, although no significant differences were found with respect to placebo.[ix]

In neuropsychological assessment, participants with ADHD and ASD treated with memantine showed lower scores on scales such as the Conners-3 ($p = 0.039$) compared to their baseline values. In contrast, the placebo group showed no significant changes ($p > 0.05$). In addition, those treated with memantine showed a reduction in global indices of impulsivity and emotional lability, suggesting an improvement in social and cognitive skills.[ix]

Due to this new research, therapies involving mGluR allosteric modulatory drugs can be extended to regulate neuronal excitability and synaptic conduction selectively. This allows for reduced behavioral and cognitive effects characteristic of many brain disorders such as ASD and improves the social responsiveness of patients.[x] Although a direct relationship between the reduction of ASD symptoms and the use of glutamate receptor allosteric drugs has not been demonstrated, some research has concluded that there is an improvement in certain social abilities, which is an important precedent for future studies.

Conclusion

Autism spectrum disorder is a complex condition that encompasses a variety of disorders that share characteristics such as difficulties in social communication, restricted behaviors, and the display of repetitive behaviors. Research has highlighted the role of glutamate in this disorder, demonstrating that alterations in its function are significant in the development of the disorder. These alterations affect communication between neurons and, consequently, contribute to the symptoms of autism, including difficulties in social interaction and repetitive behavior patterns. Due to experimental studies, both at the preclinical and clinical level, it is possible to verify that therapies with allosteric modulator drugs of metabotropic receptors manage to selectively regulate neuronal excitability and synaptic conduction, which allows less behavioral and cognitive effects typical of autism spectrum disorder and helps its social responsiveness, especially at a verbal level.

Acknowledgments:

To the Research Committee of the School of Medicine at Dr. José Matías Delgado University

Funding

No external funds were received for this work.

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Narrative review

Fundamentals and applications of survival analysis for health research

DOI: 10.5377/alerta.v8i3.20675

David Daniel Rivera Rosales[1]*, David A. Tejada[2]

1-2 Ministry of Health, National Institute of Health, San Salvador, El Salvador.

Correspondence
ddaniel.rivera@salud.gob.sv*

1. 0000-0002-8744-9403
2. 0000-0003-2502-1433

Abstract
Survival analysis is a statistical method that focuses on the time it takes for an event of interest to occur. It combines time, which is a continuous variable, with the occurrence of the event, a dichotomous variable; in addition, its distinctive feature is the presence of censored data. The Kaplan-Meier method is a nonparametric test that estimates the probability of survival over time, which is calculated each time an event occurs. The *log-rank* test is used to compare survival patterns between independent groups. Cox proportional hazards regression is the most widely used multivariate model in survival analysis; it evaluates predictive factors and estimates the *Hazard Ratio* as a measure of association. The use of traditional models requires assumptions such as proportional hazards and non-informative censoring, and when this criteria is not met, researchers must choose appropriate techniques according to their objectives, population and resources. Options include Bayesian models, stratified, time-dependent covariates or artificial intelligence techniques; the latter offers an alternative for modeling complex scenarios, handling large volumes of data and overcoming the limitations of conventional methods.
Keywords
Survival Analysis, Investigative Techniques, Biostatistics, Kaplan-Meier Estimate, Cox Model.

Resumen
El análisis de supervivencia es un método estadístico que se centra en el tiempo que tarda en ocurrir un evento de interés. Esta combina el tiempo, que es una variable continua, con la ocurrencia del evento, una variable dicotómica; además, su característica distintiva es la presencia de datos censurados. Se realizó una búsqueda de publicaciones del 2019 al 2024, con el objetivo de describir los principales métodos para realizar análisis de supervivencia y las diferentes opciones cuando no es posible usar los modelos tradicionales. Se elaboró una revisión narrativa de las técnicas más utilizadas, limitaciones y sesgos encontrados con mayor frecuencia en las investigaciones publicadas. El método Kaplan-Meier estima la probabilidad de supervivencia a lo largo del tiempo, el test de *log-rank* compara patrones de supervivencia entre dos grupos independientes. La regresión de riesgos proporcionales de Cox es el modelo multivariado usado con mayor frecuencia y estima la influencia de las variables predictoras en la probabilidad de supervivencia en un tiempo determinado usando el *Hazard Ratio* como medida de asociación. Para la utilización de estas pruebas se requiere cumplir supuestos como proporcionalidad de riesgos y censura no informativa, cuando esto no es posible, los investigadores deben elegir técnicas adecuadas según sus objetivos, población y recursos. Las opciones incluyen modelos bayesianos, estratificados, covariables dependientes del tiempo o técnicas de inteligencia artificial; esta última ofrece una alternativa para modelar escenarios complejos, manejando grandes volúmenes de datos y superando las limitaciones de los métodos convencionales.

Palabras clave
Análisis de Supervivencia, Técnicas de Investigación, Bioestadística, Estimación de Kaplan-Meier, Modelo de Cox.

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Fundamentos y aplicaciones del análisis de supervivencia para la investigación en salud

Suggested citation:
Rivera Rosales DD, Tejada DA. Fundamentals and applications of survival analysis for health research. Alerta. 2025;8(3):305-314. DOI: 10.5377/alerta.v8i3.20675

Editor:
Nadia Rodríguez.

Received:
November 27, 2024.

Accepted:
June 26, 2025.

Published:
July 31, 2025.

Author contribution:
DDRR[1], DAT[2]: study conception, manuscript design, literature search, data collection, data or software management, data analysis, writing, revising and editing.

Conflicts of interest:
The authors declared there are not conflicts of interest.

Introduction

Survival analysis is a statistical method in which the variable of interest is the time it takes for an event to occur.[i,ii] This variable comprises two components: time, which is continuous, and the occurrence or non-occurrence of the event, which is dichotomous.[iii,iv] The method was originally used to analyze the time until death of patients, hence its name.[v,vi] While this remains one of its most common applications, the event of interest does not have to be death; it can also refer to the occurrence of a complication, such as acute myocardial infarction, or a patient's recovery from illness.[i,vii]

A distinctive feature of survival analysis is the presence of incomplete information, or "censored data".[v] This occurs when the event of interest does not happen during the patient's follow-up period.[viii] The most frequent form of censoring in this type of study is right-censoring, which occurs when the outcome happens after the end of the observation period.[iii,v]

Two other, less common types of censoring are left-censoring, which occurs when the event happens before observation begins.[v] For instance, a study examining the prevalence of dementia in Germany between 2004 and 2012 revealed how incorporating left-censored data (cases diagnosed prior to 2004) could impact the outcome of the analysis.[ix] The second type is interval censoring, where only the time interval during which the event occurred is known, not the exact time.[iii,v] This is common in school-based oral health programmes that rely on fixed-interval assessments, such as annual or biannual examinations, where the exact moment when a tooth cavity develops is unknown.[x] Censoring can be classified as either informative or non-informative. Non-informative censoring, also known as independent censoring, is not related to the risk of experiencing the event of interest.[v] Since failure to meet this assumption could bias the results, survival analysis assumes non-informative censoring.[vii] The presence of censored data requires the use of statistical methods that go beyond simple linear regression.[v]

Additionally, survival curves are non-negative, meaning they always show positive progression. This is because the events studied are cumulative, with their incidence accumulating over a defined period of time. Typically, survival time distributions are skewed, which limits the applicability of parametric models that assume a normal distribution. This requires either non-parametric models or logarithmic transformations for proper analysis.[i,viii,v]

Nowadays, survival analysis is frequently employed in cohort studies and clinical trials. It has proven useful in fields such as epidemiology, oncology and cardiology for comparing the efficacy and safety of medical and surgical treatments, and for estimating recovery time, time to recurrence as well as disease-free and complication-free periods[ii,vi] Given how useful and frequent survival analysis is in health research and publications, it is crucial for health professionals to familiarize themselves with the methods used in these analyses.[xii] However, certain elements and methods are often overlooked in existing reviews, such as non-proportional hazard models, Bayesian approaches, artificial intelligence applications, and the common limitations and biases found in these types of studies.

A search was conducted in the PubMed, Virtual Health Library, Google Scholar and Scielo databases for articles published between 2019 and 2024, using the following keywords: "Survival Analysis", "Kaplan Meier", "Cox proportional hazards", "Non proportional hazard","Proportional hazards assumption", "Análisis de supervivencia", "Riesgos proporcionales de Cox" and "Modelos de riesgos no proporcionales". Figures were generated in RStudio version 9.4.19 1370 using simulated data. The objective of the narrative review was to describe the main methods used in survival analysis in health research and outline alternative options when traditional models are not applicable.

Discussion

General considerations

The methodology of survival analysis can be summarized in three key steps. The first step involves estimating the survival function, also known as the survival curve. The second step involves comparing survival curves. The third step involves estimating the effects of explanatory variables on survival time.[v]

The "survival function" refers to the probability that a patient will survive for a given period of time.[xiii,xiv] A related concept is the "hazard function", which represents the probability of an event occurring within a specific time period.[v] "Median survival" is defined as the time at which the event has occurred in 50 % of observed subjects.[ii] A key assumption relating to the hazard function is the "proportional hazards assumption" (PHA), which posits that the risk of experiencing an event remains constant throughout the follow-up period.[xv]

In survival studies, two timepoints must be clearly defined: the start and end of follow-up, based on the study objectives. The follow-up period must be long enough to allow for the observation of a reasonable number of events.[iii]Each patient has a different starting date for follow-up, known as "calendar time" or "secular time".[xiv] These dates are standardized to a common reference point in time, known as "time zero".[i,xvi] A patient's follow-up period spans from time zero until the event occurs or they are censored.[i,xvi] Regardless of the variable under analysis, the time it takes for the event to occur is commonly referred to as "survival time".[vii] In clinical trials, time zero is usually the moment of randomization, or when the patient begins the intervention.

In observational studies, however, it can vary, potentially corresponding to study entry, the start of exposure to a risk factor, or the occurrence of an index event.[xvii]

Sample size calculation in survival analysis

Unlike other types of study, the reliability and power of survival analysis depend not on the total number of individuals in the sample, but on the number of observed events.[xviii]

A practical rule for determining the appropriate sample size is to ensure there are at least ten events per covariate for reliable Cox regression analysis. For example, if five covariates are to be analyzed, then 50 events would be required.[iii,xix] However, this approach may not reflect the complexity of the relationships between predictors and outcomes.[xx]

There are, statistical methods available for determining the appropriate sample size in such studies, including the Freedman, Schoenfeld and Lakatos methods.[xviii] First, the number of events required for the analysis must be calculated, and then the number of patients needed to observe that number of events must be estimated. [xxi] Thorough analysis of the population characteristics and study objectives is essential to select the appropriate sampling method and avoid methodological errors.[xxii,xxiii]

The actuarial life table

The study duration is divided into fixed-length time intervals, during which each patient is observed.[i,vi,xii] The length of these intervals is determined by the frequency of the event.[vi] Follow-up time is expressed as the number of intervals until the event or censoring occurs, based on the assumption that censoring occurs at the midpoint of each interval.[i]

Kaplan Meier

This is the most widely used method of survival analysis in health science.[vii,xxiv] It is a non-parametric test which estimates the probability of survival over time by updating this probability each time an event occurs. Therefore, there will be as many estimates as there are events, unless multiple events occur simultaneously.[vii,viii] For the model to be valid, censoring must be non-informative.[vii] The model is typically represented in graphs, with the X-axis denoting time and the Y-axis representing survival probability. Marks (*e.g.* "+" signs) are added to indicate censored data[xi,xiii] (Figure 1).

The software used for these analyses usually provides confidence intervals (CIs) for each survival probability point. Many researchers then connect these points to illustrate the confidence band of the curve. While these CIs are valid for each point, additional statistical adjustments are needed to depict the full confidence bands appropriately.[xxiii] Other options to Kaplan-Meier include the Breslow estimator or the Breslow-Aalen method.[iii]

Log-rank test

This is a non-parametric test based on the chi-squared distribution, which is the most commonly used method for comparing survival curves.[ii,viii,xiii] Rather than comparing final or median survival, it compares overall survival patterns.[viii] The null hypothesis is that there is no difference between the survival curves of two or more independent groups[ii,v] (Figure 2). The survival curves must not cross; if they do, the test may fail to detect differences.[v,vii,viii] In such cases, weighted log-rank tests,[v,vii] or the Lin and Wang modified log-rank test[v] are recommended. The test's power increases if the PHA is met.[iii,vii] Other alternatives to Kaplan-Meier test include the Tarone-Ware, Peto-Peto-Prentice or Fleming-Harrington tests.[iii]

Cox proportional hazards regression model

Cox Proportional Hazards Regression Model (CPR) is the most widely utilised multivariable model in the field of survival analysis.[iii,xiii] It is used to analyze predictive factors (covariates) that influence survival. [ii] It yields a measure of association known as the Hazard Ratio (HR), which is defined as the hazard function of the exposed or treated group divided by the hazard function of the unexposed or control group. [xvi] The HR is analogous to the Odds Ratio (OR) from logistic regression and is interpreted similarly. HR > 1 indicates increased risk, HR = 1 indicates no difference, and HR < 1 indicates reduced risk.[iv,xv]

As with any statistical model, the Cox model is predicated on several assumptions: proportional hazards, non-informative censoring and independence of survival between individuals. The latter indicates that the survival of one participant does not impact the survival of another.[xiv] In addition, the log-linear assumption is referenced, which stipulates that the relationship between the natural logarithm of the instantaneous hazard rate of the covariates or predictor variables must be linear.[xxvii] Testing

the Proportional Hazards Assumption Prior to the formulation of inferences from the model, it is essential to verify the PHA; otherwise, the analysis may be biased.[iii] A number of methodologies are at researchers' disposal for the purpose of testing this assumption.[v,xxvi] The most common of these is the Schoenfeld residuals test, which compares observed versus expected events. The null hypothesis posits that the residuals are independent of time. In the event of its rejection, it is assumed that risks vary over time and the assumption is broken[xxvi](Figure 3).

Another useful method is the *log-minus-log* plot. The survival function is changed using a double logarithmic transformation for the covariates. If the PHA holds, the resulting lines will be parallel and non-crossing.[v,xxvi] It is recommended to use more than one method in order to verify this assumption. [xxvi]Non-Proportional Hazard Models

A wide range of tests for analysing non-proportional hazards is available, and no clear consensus exists on the optimal approach. [xxviii] One preliminary strategy is to partition the follow-up period into intervals where the

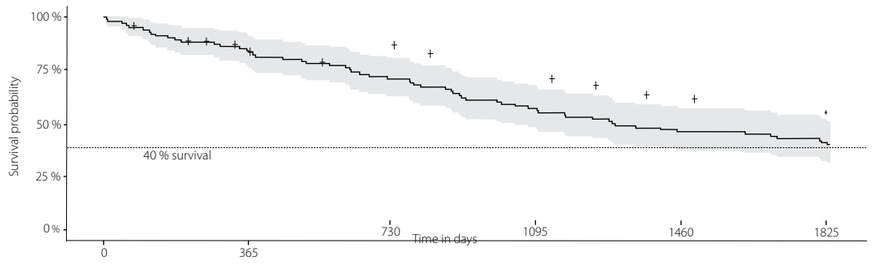

Figure 1. Kaplan-Meier Graph. Five-year survival of a group of patients with a given health condition. The curve starts at 100 % and decreases with each event. Crosses (+) represent censored data. In this example, the five-year survival rate is 40 %.

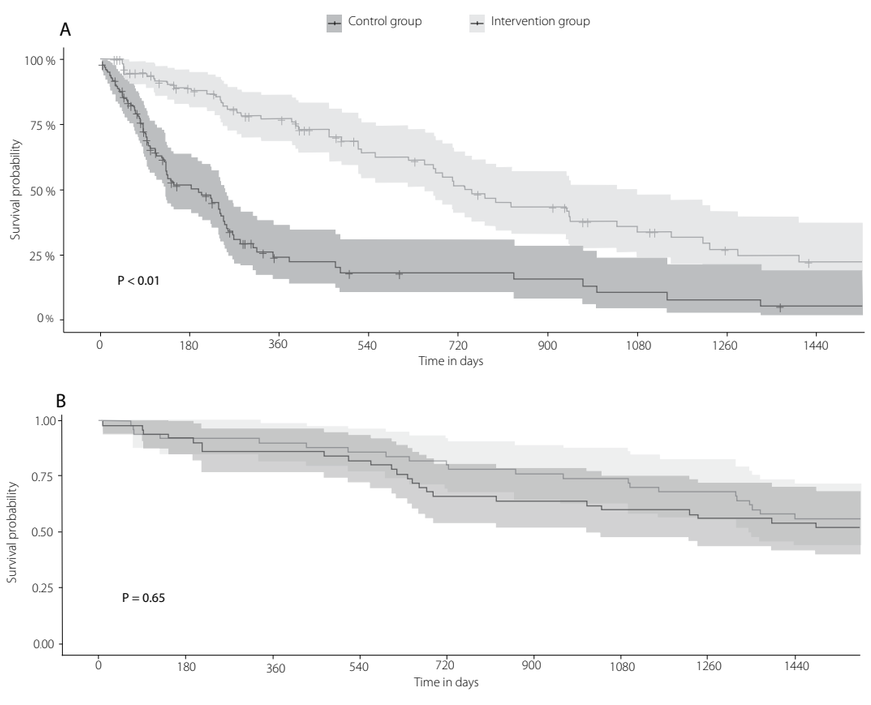

Figure 2. Log-Rank Test. This compares an intervention group with a control group. Figure 2A shows that $p < 0.01$, so the null hypothesis is rejected and a statistically significant difference between the groups is indicated. Figure 2B shows that $p = 0.65$, which means the null hypothesis is not rejected and suggests no significant difference between the groups.

PHA holds and to construct separate models for each interval.[xxix]For instance, in a study that made a comparison between endovascular repair and open surgery for abdominal aortic aneurysms, since the PHA was not met, the analysis was divided into four time periods: six-month survival, four-year survival among those who survived the first period, eight-year survival, and survival beyond eight years.[xxx]Further possibilities for exploration include the stratification of the model based on variables that contravene the PHA, and the extension of the model through the incorporation of time-dependent covariates. [xxix,xxxi] The latter approach is most frequently employed in the context of clinical trials.[xxviii] For example, a study analyzed the relationship between CA19-9 levels and survival in pancreatic cancer patients receiving chemotherapy. Following the discovery that the PHA had not been met, the researchers proceeded to implement a Cox model with time-dependent covariates. This entailed the introduction of periodic CA19-9 measurements into the model. The baseline HR was established at 1.56, with a maximum recorded of 2.0 HR attained two months following the commencement of chemotherapy treatment.[xxxii]Additional techniques that may be employed include frailty or random effects models,[xxviii,xxxiii] parametric models such as piecewise exponential and accelerated failure time models, and machine learning (ML) approaches.[xxviii]

Bayesian Survival Models

Bayesian survival analysis is a flexible tool that allows for the modelling of the time to an event, such as death or recovery. This is achieved by integrating prior information through a priori distributions and enabling dynamic decision-making. In contrast to conventional methods, Bayesian approaches do not necessitate the PHA.Techniques such as the Integrated Nested Laplace Approximation have been proven to be especially useful due to their capacity to process large datasets with great expediency and accuracy. Bayesian models provide credibility intervals, which offer a more intuitive analysis in complex clinical and epidemiological settings by better reflecting uncertainty[xxxiv]

They are also useful when the sample size or number of events is small in relation to the number of variables. For example, in a survival analysis of 299 heart failure patients, of whom 96 died, 11 variables were analyzed. According to traditional rules, at least 110 events would have been needed (ten per variable), so a Bayesian Cox regression provided a more reliable analysis in this context.[xxxvi]

Use of Artificial Intelligence in Survival Analysis

Artificial intelligence (AI), along with its branches of ML and deep learning (DL), has become a valuable tool in survival analysis. These technologies facilitate the processing and analysis of large volumes of data, enabling the identification of complex patterns and relationships that are difficult to discern using traditional statistical methods.[xxvi]

ML and DL methods have transformed survival analysis by overcoming the limitations of traditional models. Prominent ML models include multitask logistic regression networks, DeepSurv and survival random forests. These methods can handle complex and non-linear relationships, identify patterns in high-dimensional data and provide more accurate predictions. Their flexibility allows the integration of clinical, biomarker, and genomic data, thereby enhancing treatment personalization and informed decision-making.[xxviii] DL models are particularly effective at analyzing high-dimensional datasets where the number of features exceeds the number of observations, which is a challenge for traditional methods.[xxxviii] Deep neural networks can model complex nonlinear relationships between variables and outcomes, such as disease progression or death, thereby improving prediction accuracy. Their capacity to learn from large datasets enables them to identify significant patterns that traditional methods may overlook.[xxxviii,xxxix]

One example of the utility of machine learning (ML) in survival analysis is a study that analyzed 100 544 pathological images from 78 patients, successfully predicting one-year progression-free survival following immunotherapy in patients with small-cell lung cancer.[xl]

Limitations of Survival Analysis

If the probability of the event of interest is low, a large sample size is required to ensure a sufficient number of events for reliable analysis. When the event takes a long time to occur, extended follow-up periods are necessary, which can lead to an increased number of censored cases due to patients dropping out of the study.[xli] Furthermore, the risk of the event occurring may vary over long timeframes, which breaks the PHA.[xxix]

Models recommended for long-term survival analysis, such as in cancer studies, include milestone survival analysis, restricted mean survival time analysis, area under the survival curve model, nomograms, and the previously mentioned accelerated failure time models and ML techniques.[xxix,xli]

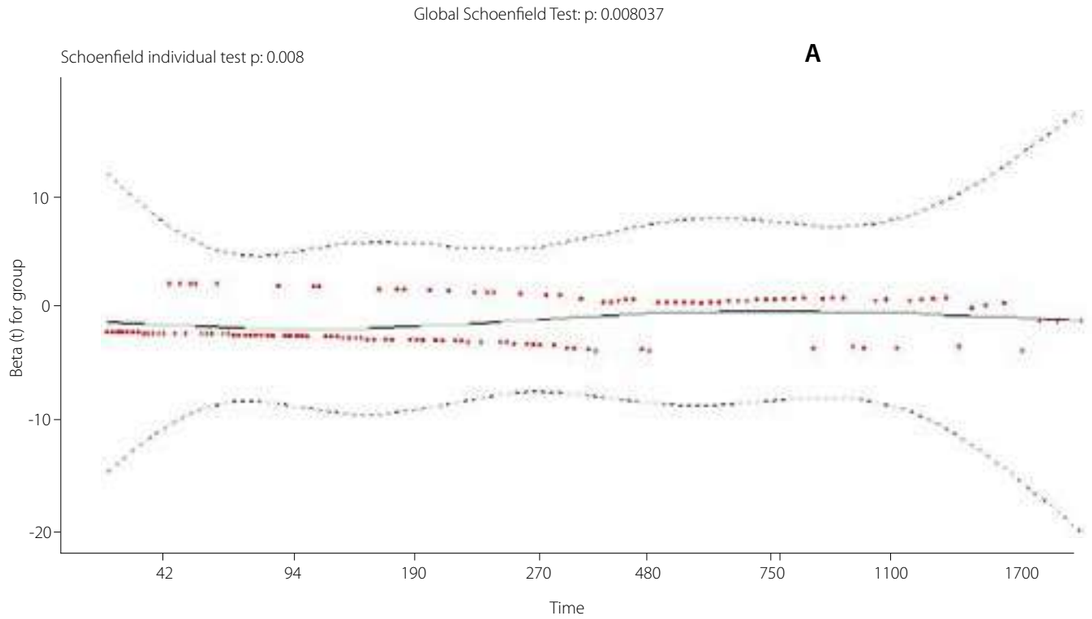

Figure 3. Schoenfield test. The objective of this study is to ascertain the factors that influence the probability of complications in patients undergoing surgical treatment one year after the intervention. It is necessary to determine whether the Cox proportional hazards model is adequate for the analysis. To this end, a Schoenfeld test will be performed to ascertain whether the variables included meet the assumption of proportionality of risks. Figure 3A rejects the null hypothesis ($p < 0.05$), thus indicating that the proportional hazards are not met. This implies that the risk of complications is not constant throughout the follow-up period, necessitating the use of an alternative model for the comparison of treatments. As depicted in Figure 3B, the null hypothesis is not rejected, thereby validating the proportionality of risks and affirming the efficacy of the Cox regression model.

Biases in Survival Analysis

Informative censoring is regarded as a form of selection bias, arising when censored subjects exhibit a higher or lower risk of the event in comparison to those who remain in the study.[ii,v]

An illustration of this phenomenon can be found in the context of a clinical trial, in which a patient was excluded from further participation due to the emergence of an adverse effect related to the study medication or the necessity to modify the therapeutic regimen.[v]

In instances where the occurrence of informative censoring is suspected, researchers may decide to exclude these patients from the analysis or utilize adjusted models such as stratified models, standard regression adjustments, joint modelling, or inverse probability of censoring weighting estimation.[v,vii]

Lead-time bias occurs when a disease is detected at an early stage, prior to the onset of symptoms, through screening,[v] which may lead to an overestimation of survival time and intervention effectiveness.[xliii,xlvi] To exemplify this, consider the scenario in which two patients develop cancer at the age of 15 and both succumb at the age of 60. In this case, it can be deduced that the actual survival time for both patients is equivalent. However, if an individual is diagnosed at the age of 40 and another at 50, it may give the erroneous impression that the latter has a longer survival time. To circumvent this issue, it is imperative to initiate follow-up evaluations at the commencement of the intervention or exposure under scrutiny.[xlv]

The phenomenon of stage migration bias occurs when patients with cancer who are at the threshold between stages are more likely to be assigned to the more advanced stage. This approach has been shown to enhance survival outcomes in both stages of the disease. In the initial stage, it functions by excluding more aggressive cancers, while in the subsequent stage, it encompasses a relatively lower proportion of cases that are less severe. This phenomenon is referred to as the Will Rogers effect.[v] A competing risk is defined as an event that either prevents or modifies the occurrence of the event of interest.[xlvi]To cite an example, in a study where the outcome is kidney failure, if a patient dies before developing this condition, death becomes a competing risk. In a similar vein, if the outcome is cardiovascular death and a patient dies from another cause, that other cause is also considered a competing risk.[xlvii]

The employment of classical methods, such as the Kaplan-Meier or Cox regression, in the context of competing risks may result in the introduction of bias and an overestimation of the effect of the treatment or exposure under investigation.[xlvi,xlvii] The most common methods for conducting these analyses are cause-specific hazard models and the Fine and Gray model.[xlvii]

It is imperative to exercise caution when conducting a comparative analysis of surgical interventions and conservative management strategies. Surgical complications are more likely to occur in the perioperative period, violating the PHA. Furthermore, the benefits of surgery often manifest over an extended timeframe, which may not be captured if the follow-up period is too brief.[xlviii] In such cases, it is advised that the efficacy and safety of the treatments be evaluated independently. In order to evaluate the effectiveness of preventive surgeries, it is advised that the follow-up process commence in the post-operative period.[xlviii]

Limitations of the Review and Recommendations

A broad spectrum of survival analysis methods and adjusted models exists for a variety of applications, rendering it impractical to describe all variations and statistical foundations in this review. Nevertheless, the objective of this study was to highlight the most commonly used methods, with a view to assisting researchers in selecting the most appropriate techniques for their research objectives and identifying common biases in such studies.

It is recommended that the event(s) of interest and the start and end points of follow-up be clearly defined; that potential biases be assessed before data collection; and that an appropriate sample size calculation method tailored to survival analysis be applied. Following the selection of the statistical model in accordance with the study's objectives, it is imperative to undertake a thorough verification of the underlying assumptions and ensure their validity.

Conclusion

The most frequently employed methods for survival analysis are the Kaplan-Meier method and the CPR model. However, it is imperative to verify that the necessary assumptions for the application of these statistical techniques, such as PHA and non-informative censoring, are met prior to their implementation.

In instances where the implementation of conventional methodologies is unfeasible, researchers are required to select

appropriate analytical techniques in accordance with their research objectives, the characteristics of their population, and the availability of resources.

The advent of technological advancements has enabled the integration of AI into survival analysis, thereby facilitating the modelling of complex scenarios, the management of voluminous data, and the identification of intricate patterns. This development has served to overcome the limitations of conventional approaches, consequently generating novel prospects in the domain of medical research.

Funding

No external funds were received for this work.

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Narrative review

Oral diseases and their relationship with nutrition in older adults

DOI: 10.5377/alerta.v8i3.19197

Manuel Antonio Espinoza Molina

School of Dentistry, Evangelical University of El Salvador, San Salvador, El Salvador.

*Correspondence
manaesp@hotmail.com

0009-0004-4259-8650

Abstract
Population aging is one of the most relevant demographic phenomena of the 21st century. The relationship between oral health and overall health is complex and multifaceted, especially among older adults. Some general health conditions that are prevalent in this age group may act as predisposing factors for oral health deterioration, such as diabetes, which can lead to xerostomia or reduced salivary flow. Moreover, due to the aging process, this population is more lilkely to experience nutritional problems, caused by decreased regulation of food intake, assimilation, and metabolism, as well as by physical, psychological, and social changes, and the coexistence of age-related diseases. A literature search was conducted in scientific databases such as PubMed, LILACS, and the Virtual Health Library The review included open access articles published in Spanish and English, between August 2019 and August 2024. This review aimed to describe the main oral diseases in older adults and how they influencenutritional status. Preventing and treating oral diseases is essential to preservingoral health and proper nutrition in this population.
Keywords
Oral Health, Nutritional Status, Older Adult, Dental Caries, Periodontitis.

Resumen
El envejecimiento poblacional es uno de los fenómenos demográficos más relevantes del siglo XXI. La relación entre la salud bucodental y la salud general es compleja y multifacética, especialmente entre las personas mayores. Algunas condiciones de salud general prevalentes en este grupo de edad pueden actuar como factores predisponentes para el deterioro de la salud bucal, como la diabetes, que puede inducir a xerostomía o reducción del flujo saliva. Además, por el proceso de envejecimiento, esta población presenta mayor probabilidad de problemas nutricionales, debido a una disminución en la regulación de la ingesta, asimilación y metabolismo de los alimentos, como también cambios físicos, psicológicos y sociales y coexistencia de enfermedades propias a esta edad. Se realizó una búsqueda bibliográfica en bases científicas como PubMed, Lilacs, Biblioteca Virtual en Salud, se incluyeron artículos de libre acceso publicados en español e inglés, entre agosto de 2019 hasta agosto de 2024, con el objetivo de describir las principales enfermedades bucodentales en el adulto mayor y cómo influyen con el estado nutricional. La prevención y el tratamiento de las enfermedades bucales, son fundamentales para mantener la salud bucal y la nutrición en esta población.

Palabras clave
Salud Bucal, Estado Nutricional, Adulto Mayor, Caries Dental, Periodontitis.

OPEN ACCESS

Enfermedades bucodentales y su relación con la nutrición en el adulto mayor

Suggested citation:
Espinoza Molina MA. Oral diseases and their relationship with nutrition in older adults. Alerta. 2025;8(3):315-322. DOI: 10.5377/alerta.v8i3.19197

Editor:
Veralís Morán.

Received:
November 14, 2024.

Accepted:
July 1, 2025.

Published:
July 31, 2025.

Author contribution:
MAEM: study conception, manuscript design, literature search, data collection, data or software management, data analysis, writing, revising and editing.

Conflicts of interest:
The author declared there are not conflicts of interest.

Introduction

The aging of the population is a global phenomenon that has gained particular relevance in recent decades. According to data from the World Health Organization (WHO), the number of individuals aged 60 years or older is expected to double by 2050.[i] This demographic shift presents significant public health challenges, particulary in addressing the specific needs of older adults. The demographics profile of El Salvador reflects aging trends, influenced by country-specific factors such as birth, mortality, and migration rates. According to the most recent national population censusconducted in 2024, the population aged 60 years or older was 894 433, representing 14.83 % of the total population. Of these 381 668 (42.7 %) were men and 512 765 (57.3 %) were women.[ii] Older adults face unique health challenges, including declining functional capacity, the onset of chronic diseases, and loss of independence.

Oral health is a fundamental component of overall health, yet its impact on nutritional status remains underdocumented.

According to the WHO, nearly 3.5 billion people are affected by oral diseases, with three out of four residing in middle-income countries.[iii] Oral diseases are among the most prevalent human conditions. It is estimated that over 1 billion cases of oral diseases occur globally, surpassing the combined total of the five major noncommunicable diseases, mental disorders, cardiovascular diseases, diabetes *mellitus*, chronic respiratory diseases, and several types of cancer.

Oral problems such as dental caries, periodontal disease, tooth loss, and the presence of inadequate dentures can limit the ability to chew and swallow, thereby affecting nutrient intake and absorption. In older adults, this interrelationship is even more pronounced due to the higher prevalence of oral diseases and physiological decline in functional capacity.[iii] A literature search was conducted for articles published in PubMed, LILACS, the Virtual Health Library, in both Spanish and English, between August 2019 and August 2024. Boolean operators and the following search terms were used: Oral Health AND Nutritional Status AND Aged; Oral Health AND Aged AND Periodontitis; Oral Health AND aged AND Dental Caries. A total of 225 articles were obtained. Of these only documents from the United Nations, narrative reviews, systematic reviews, randomized clinical trials and epidemiological surveys were considered, resulting in 46 articles. Of those, studies that did not include data on the nutrition status of the study population were excluded. As a result, 35 articles were included in this review. The objective of this review was to describe the main oral diseases in older adults and how they influence nutritional status.

Discussion

Most oral disorders can be prevented and treated in their early stages. However, he global prevalence of these oral conditions continues to increase, driven by rising urbanization and changes in living conditions.[iv] In addition, the marketing and consumption of sugar-rich foods and beverages, as well as tobacco products and alcoholic beverages, has intensified, contributing to the development of oral disorders and other noncommunicable diseases.[iv]

The association of oral health with general health, morbidity, and mortality in older adults underscores its relevance healthy aging.[v]

Oral health is a key component of well-being in the general population, especially amoung older adults, and is directly influenced bys ocioeconomic conditions and access to health services. Poor oral health is not an inherent of aging. Early detection of common diseases increases the likelihood of maintaining good oral health in later life.

Oral diseases and many chronic systemic diseases share common risk factors, including unhealthy diets, tobacco and alcohol use, which can be improved with health counseling. A growing body of evidence has documented a bidirectional association between oral health and chronic systemic diseases, highlighting the importance to incorporateoral health into chronic disease management strategies. WHO recommends a multidisciplinary approach to oral health, do to the inseparable links between oral and systemic health. However, it is essential to promote awareness of the importance amoung all the healthcare personnel in order to optimize prevention and care.[vi,vii] Regarding epidemiological data from El Salvador, some articles were identified that address oral health problems in older adults, however, these do not establish a relationship with nutritional status.

Escobar *et al.*, reported important findings from a population in El Salvador: 100 % (n= 553) of respondents aged 60 years or older had some type of edentulism, of which 90.6 % (n= 501) presented partial edentulism and 9.4 % (n = 52) complete edentulism. The same study found that 52.98 % (n= 293) of this population reported no changes in their quality of life, while 34.18 % (n= 189) reported moderate changes, and 12.84 % (n= 71) reported severe or very severe changes in their quality of life.[viii]

Vizcaino K *et al.*, noted that the older adult population in Latin America is the most affected by adverse oral health conditions, such as dental caries, periodontal disease, tooth loss, and oral cancer, in addition to having more limited access to and less effective use of dental services.[ix]

Impact of nutrition on oral health

Nutrition refers to the intake of macronutrients: proteins, carbohydrates, and fats, as well as micronutrients, including vitamins and minerals, that are essential for the proper functioning of the body.[x] Eating habits, food choices, culinary preparations, portion sizes and frequency of intake may all influence oral health,[xi] as there is a bidirectional relationship between oral health, diet, and nutrition. Food and nutrients influence the condition of oral tissues; and compromised oral health can reduce the body's ability to adequately utilize the nutrients consumed.[x]

Oral diseases that affect nutrition in older adults

There are several oral diseases that can directly affect nutrition in older adult, including:

A. Dental caries

Dental caries is the most common oral health problem worldwide.[xii] It is a dental condition characterized by the demineralization of the tooth structure, caused by cariogenic bacteria that metabolize sugars to produce, primarily, lactic acid.[xiii]

The main contributing factors to the development of dental caries are largely related to inadequate oral hygiene practices. Key risk factors include the presence of cariogenic bacteria, frequent consumption of sugary drinks, and a diet high in carbohydrates.[xiv]

Due to age-related changes in salivary function and immune response, along with the presence of multiple comorbidities and drug-induced xerostomia, caries becomes the most prevalent dental disease among older adults.[xv] In addition, gingival recession, which is common in this stage of life, increasesthe risk of root caries.

The relationship between systemic diseases and dental caries is significant, as several medical conditions, such as diabetes, polypharmacy, and xerostomia substantially increasing the risk of caries development.[xvi]

B. Periodontal disease

Periodontal disease includes gingivitis and periodontitis. It is characterized by bacterial infection that leads to gingival inflammation, tooth loss, bone resorption, and gingival recession.[xvii] Gingivitis is the earliest stage of periodontal disease and refers to inflammation between the gumline and the tooth. Gingivitis is often reversible with improved oral hygiene practices.[xviii] Periodontitis occurs when inflammation, triggered by microorganisms and mediated by the host response, progresses into a chronic, destructive, and irreversible condition that damages the tooth attachment and supporting bone. Tooth loss and edentulism, defined as the partial or total loss of teeth, represent the final stages of untreated periodontitis.[xix]

Genco *et al.*, report that with increasingage, there is a greater loss of periodontal support, and by the age of 65, aproximately 70 % of individuals are affected by periodontitis.[xx] O'Connor J *et al.*, emphasize that age-related changes, including immune system alterations, cellular aging, inflammation, and altered wound healing play key roles in the pathogenesis of periodontal disease. Risk factors for periodontitis in older adults are similar to those in younger age groups and include inadequate brushing and flossing, limited financial resources, lower levels of education, lack of medical follow-up, and cigarette smoking.[xxi]

Among the aging population, systemic diseases have been identified as accelerators of periodontal disease progression. Diabetes *mellitus*, respiratory disease, cardiovascular disease, stroke, osteoporosis, osteoporosis, arthritis and Alzheimer's disease have all been linked to an increased risk of periodontal disease. A bidirectional relationship exists between periodontitis and systemic disease, with well-established associations between periodontitis and a higher risk of several chronic diseases, including cardiovascular disease, diabetes, rheumatoid arthritis, cancer, and chronic obstructive pulmonary disease (Figure 1).[xix,xxi]

C. Xerostomia (hyposalivation)

Xerostomia is the sensation of dry mouth, characterized by reduction in salivary flow and alterations in saliva composition. Itaffects approximately one-third of the older adult population.[xxii] Age-related changes, chronic diseases, and medication use contribute to xerostomia in older adults. A decrease in saliva production is common among older adults with who experience polypharmacy.[xxiii] Chan *et al.*, reported that the risk of caries increases by 60 % in older adults with low resting salivary pH and reduced stimulated salivary flow.[xxiii] Dry mouth and xerostomia are sometimes used interchangeably; however, true xerostomia results from acute or chronic salivary gland hypofunction and is associated with inadequate salivary secretion. Typically, patients report dry mouth when salivary output is reduced by more than 50 %.[xxiv] Nonetheless, the sensation of dry mouth can also occur despite normal secretory function of the salivary glands, this condition is referred to as pseudoxerostomia or false xerostomia. The causes of this subjective symptom include changes in saliva composition, mouth breathing, atypical oral and facial symptoms, burning mouth syndrome, oral dysesthesia, and mental, psychological, and psychiatric disorders. In more than half of the cases of pseudoxerostomia, a 50 % reduction oral fluids intake was observed.[xxiv]Age-related factors, including structural and functional changes in the salivary glands, medication use, systemic diseases, and psychosocial factors, contribute to xerostomia in older adults.[xxiv] Adolfsson *et al.*, found that one in two older adults in a primary care setting experienced some degree of dry mouth,

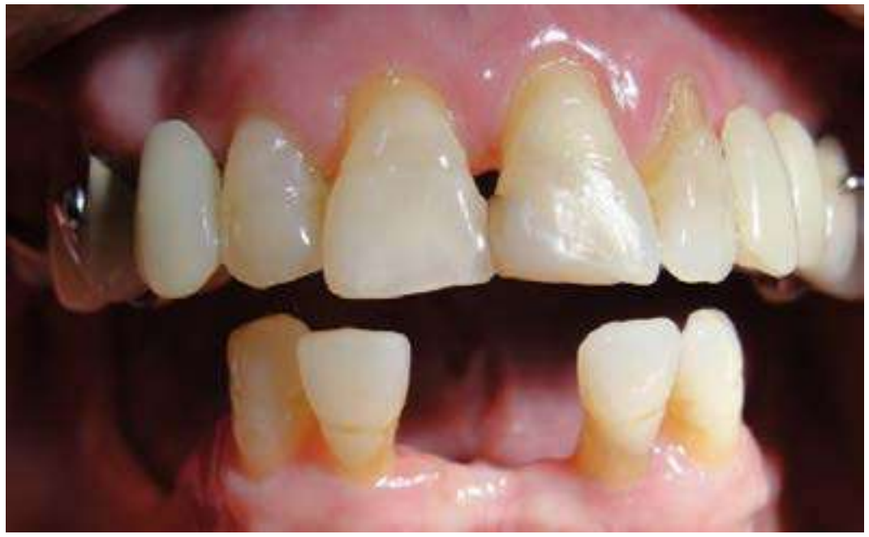

Figure 1. Periodontal disease conditioned to diabetes *mellitus*. Female patient, 67 years old, with periodontal disease conditioned to diabetes mellitus, with loss of support in the existing teeth, inadequately adjusted upper prosthesis, and multiple missing teeth in the lower jaw.

with a prevalence of 43.6 %, and higher rates observed amoung women 61.2 %.[xxv]

The diagnosis of xerostomia is primarily based on a thorough anamnesis, clinical evaluation, and physical examination. Clinical findings may include absence of pooled saliva, sticky mucosal membranes, reddened mucosa, and loss of tongue fissures and papillae. When necessary, sialometry can be used a diagnostic tool to objectively measure salivary flow rates and assess salivary gland function.[xxv] Xerostomia can impair the retention of removable dentures and reduce their comfort during chewning in older adults.[xxvii] Pain while chewing do to ill-fitting dentures has been identifiedas a risk factor for nutritional deficiency in this population.[xxvi] However, the evidence linking hyposalivation and malnutrition remains limited.[xvii,xxvi]

D. Oral cancer

Oral cancer (OC) is the most common type of head and neck cancer and includes cancers of the lips, tongue, palate, oropharynx, tonsils, and other oral structures. The most frequent type is squamous cell carcinoma.[xxvii] OC is considered a high-risk disease amoung older adults, with its prevalence increasing with age, typically appearing after 64 years of age. Each year, more than 54 000 new cases and 11 000 deaths from OC are reported.[xxvii] OC ranks 13th among the most common cancers worldwide, and alcohol consumption is one of the main causes.[iv] The risk of oral cancer increases with age and is therefore significantly higher in adults aged 65 years and older.[xxiii]

Alcohol consumption, especially heavy drinking, also increases the risk of oral cancer. Smoking and alcohol act synergistically, and individuals who both smoke and drink have up to 30 times greater risk of OC compared to non-smokers and non-drinkers.[xxiii]

OC is also associated with human papillomavirus (HPV) infection. Although the HPV vaccine protects against several HPV types associated with oral cancer, the vaccine first became available in 2006.[xxviii]

Early diagnosis improves outcomes. The primary method for early diagnosis is a physical examination, consisting of systematic inspection and palpation. The five- year survival rate for early-stage oral cancer exceeds 80 %, only about a one-quarter of cases are diagnosed at thisstage.[xxviii] Once cancer spreads to adjacent tissues or regional lymph nodes, the five-year survival rate declines. For individuals with with distant metastases, the five-year survival rate drops to 40 %.[xxix] Recognizing common presenting symptoms, such as non-healing lesion, red or white patches, and hoarseness, is key to early diagnosis. For thorough visual inspection of the entire oral cavity, tools such as the VelScope (a tissue autofluorescence method), digital palpation, and lymph node evaluation can detect the majority of OC (Figure 2).[xxx]

E. Cervical non-carious lesions

Non-carious dental lesions in older adults constitute an oral health problem, due to factors that are difficult to control and that can have a significant impact on quality of life. This group of lesions includes: attrition, defined as physiological wear caused by the contact of opposing teeth with each other in the absence of an abrasive substance; the amount of load applied and the duration of load application contribute to this form of wear. Non-axial (lateral) loads associated with chronic clenching (parafunction) cause surface bending in the cervical region that exceeds established enamel failure stresses.[xxxi] In older adults, attrition may be more severe due to loss of tooth structure over the years.

Abrasion is the loss of tooth structure caused by external abrasive substances, such as excessive brushing or the use of abrasive toothpastes. Older adults may be more prone to abrasion due to changes in brushing technique or decreased manual dexterity.[xxxii]

Tooth erosion or corrosion is a loss of tooth structure caused by exposure to acids of non-bacterial origin, such as gastric acids, reflux or vomiting, consumption of acidic beverages and foods. Older adults may be more susceptible to erosion due to dietary changes, medications, or medical conditions.[xxxii]

Abfraction is the loss of tooth structure at the cervical crown-root junction area due to excessive occlusal forces. Older adults may experience abfraction due to periodontal support loss and changes in occlusion.[xxxii]

However, there are combined lesions, which, in many cases, older adults may present a combination of non-carious lesions, making diagnosis and treatment difficult (Figure 3).

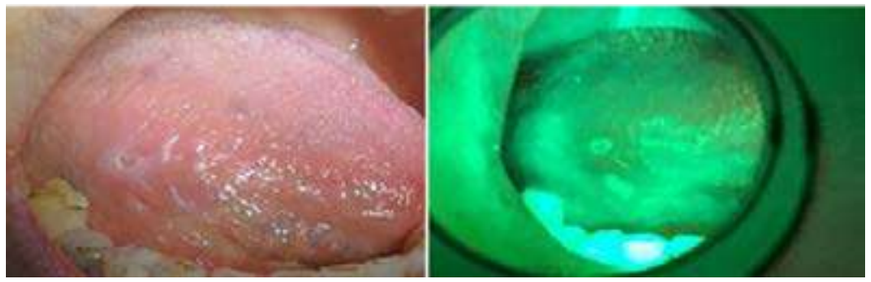

Figure 2. Autofluorescence examination. The non-vascular lesion, the area of inflammation of approximately two centimeters in diameter, can be observed. The lesion coincides with a fracture of obturation in pieces 4-6. Diagnosis: traumatic ulcer.

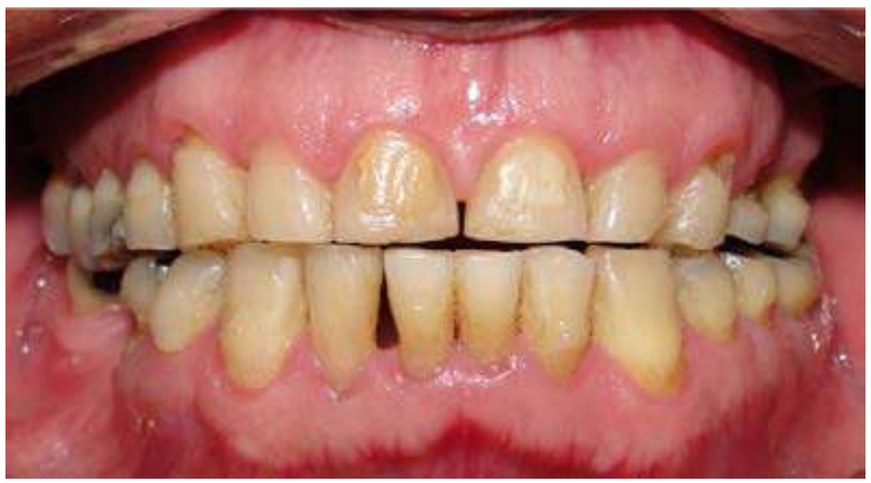

Figure 3. A 62-year-old female patient presents with periodontal disease conditioned to diabetes *mellitus* in the lower incisors and non-carious cervical lesions (abfractions and attrition) in canines, premolars, and molars.

F. Impact of oral health on nutrition

The oral cavity is located in the first part of the digestive tract and is responsible for chewing, salivation, and swallowing, allowingthe food bolus to reach the stomach for nutrition. In older adults, several common dental problems, such as dental caries, periodontal disease, tooth wear, and OC, can lead to pain, infection, and tooth loss and jeopardize the normal digestive process, for nutritional intake along with the risk of spread of oral infections to the gastrointestinal tract and other parts of the body.[xxiii]

Salivation is important for taste sensation, bolus formation and swallowing. There are drugs and systemic diseases that cause a decrease in salivary flow, which in turn can affect nutritional intake and favor the development of nutritional deficiencies, as well as increase the risk of frailty, morbidity and mortality in older adults.[xxiii,xxiv]

G. Implications for improving oral health and nutrition in older adults

Diet, nutrition, and oral health are interrelated. Older adults are at increased risk for nutritional deficiencies and oral disease. Tooth loss is associated with the type of diet and with the nutritional status of older adults.[xxxii] Patano *et al.*, have mentioned the importance of the integrating oral health care into general health care services for older adults.[xxxiii]

A multidisciplinary team including oral and health care professionals should collaborate to carry out a comprehensive geriatric assessment that includes the oral, nutritional, and medical status of older adults to formulate an integrated, coordinated, and patient-oriented treatment plan to improve their oral and general health.[xxiv] This integration includes policymakers, academics, educators, and organizations.[xxxiv,xxxv] The available evidence suggests aa knowledge gap regarding the relationship between oral diseases and nutrition in older adults. The current body of literature is limited; therefore further research is recommended to deepen and substantiate this relationship.

Ethical aspects

The photographs are securely stored in the author's archive. The principles established in the Declaration of Helsinki and the international ethical guidelines for health-related research were upheld. Informed consent was obtained from the patients for the publication of the photographs, ensuring respect for autonomy, confidentiality, and privacy.

Conclusion

The relationship between oral diseases and nutrition in older adult is complex and bidirectional. Oral diseases may negatively affect nutrition, as difficulties in chewing and swallowing can lead to insufficient intake of essential nutrients. In addition, inadequate nutrition can increase the risk of developing oral diseases, such as dental caries, periodontal disease, and oral cancer.

Oral diseases, along with their consequences such as tooth loss and oral pain, can impair the ability to eat and digest food. Malnutrition is very common amoung older adults with oral diseases. Early prevention and timely treatment of oral diseases, particulary dental caries and periodontal disease, are essential to maintaining both oral health and nutrition in older adult. Epidemiological studies should be conducted on the oral health situation in adult and older adult populations in El Salvador, ensuring the inclusion of representative samples. Collaboration amoung dentists, nutritionists, and other health professionals is essential to address the oral and nutritional needs of the older adults.

Funding

No external funds were received for this work.

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Letter to the editor

Current situation of scientific research in health in El Salvador

DOI: 10.5377/alerta.v8i3.20760

Javier Isaac Molina Velásquez

San Miguel Regional Hospital, Salvadoran Social Security Institute, San Miguel, El Salvador.

Correspondence
javier_molina100@hotmail.com

0000-0002-0520-2707

Dear Editor:

Regarding the article on research in health sciences, published in Alerta, volume 1, number 1,[i] it mentions that health research should play a crucial role in identifying and solving health problems that affect the communities of our country. Therefore, it is important to know the current panorama of health research in El Salvador, and its evolution through time, in order to promote new regulations and projects that allow fostering the research culture for the benefit of the Salvadoran society.

It is important to reflect on the fact that strengthening the infrastructure and promotion of health research in El Salvador would allow: obtaining data, information, and scientific evidence for decision making, improving public health policies, creating new health strategies, developing more accurate disease prevention actions, and finally, improving the health of the population in general.

Although there is no consolidated research culture in El Salvador, it is possible to advance through the regulation, strengthening, and effective application of policies that promote it.[ii] Legislation is still being developed; however, it is important to approach the existing regulatory framework. Therefore, some ideas are developed below.

In the Constitution of the Republic of El Salvador, the importance of scientific development is generally recognized through Article 53, which states: "The right to education and culture is inherent to the human person. The State will promote research and scientific work", so it has always been necessary to create more laws to promote and regulate scientific activity. As a result of what was described above, in 2016 the Law for Scientific and Technological Development in El Salvador was published, which is the product of many consultations and workshops with the different universities and institutions linked to research, science and technology in the country, as part of the actions embodied in the National Policy for Science, Technology and Innovation, which was aimed at solving the problems of professional training in research.[iii]

Another important regulation is the Law of Higher Education of El Salvador, which, in its article three, establishes that higher education integrates three functions: "Teaching, scientific research and social projection"; furthermore, this same law authorizes universities to choose the best way to execute these functions, as specified in article 25, paragraph three, which states that "State and private universities are empowered to: a) Determine how they will fulfill their teaching, research, and social projection functions, and the pro-

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Situación actual de la investigación científica en salud en El Salvador

Suggested citation:
Molina Velásquez, JI. Current situation of scientific research in health in El Salvador. Alerta. 2025;8(3):323-324. DOI: 10.5377/alerta.v8i3.20760

Editor:
Hazel García.

Received:
January 13, 2025.

Accepted:
July 11, 2025.

Published:
July 31, 2025.

Author contribution:
JIMV: study conception, manuscript design, literature search, writing, revising, and editing.

Conflicts of interest:
No conflicts of interest.

portion of their study plans and programs, their Statutes, and Regulations"; Article 23 of the Regulations of the Higher Education Law states that "for the development of research, Higher Education Institutions (HEI) must have an organizational structure, policies and necessary regulations, personnel in charge of administering and executing projects, budget, infrastructure and other necessary resources"; however, in practice there are still significant structural, economic and professional limitations that make it difficult to promote research in El Salvador.

An important point to take into account in this journey towards scientific development is the Organic Law of the University of El Salvador, which establishes in article three, that one of the purposes of the university is: "To carry out philosophical, scientific, artistic and technological research of universal character, mainly on the Salvadoran and Central American reality". Moreover, in El Salvador, with the creation of the Secretariat of Scientific Research of the University of El Salvador and the restructuring of the Scientific Research Council, CIC-UES, at the beginning of 2015, it was sought to modernize the Research Policy that would govern scientific research at the University of El Salvador, for the five years 2016 - 2020; however, these efforts had a limited impact in the field of health research, mainly due to a lack of resources and poor linkage with the needs of the national health system.

In recent years, important steps have been taken. The members of Parliament of the Health, Agriculture, and Environment Commission issued a favorable opinion for the creation of the Law on Clinical Trials with Products Regulated by the Superintendence of Health Regulation, which seeks to regulate clinical trials carried out with drugs, nutritional supplements, pharmaceuticals, medical devices, and equipment, as well as new health technologies. Also, in February 2025, a draft bill for a Health Research Law was presented to the legislative assembly, aimed at promoting, developing, and regulating scientific research projects in this field.

Moreover, the National Institute of Health is promoting two normative documents that are in the process of being made official by the Ministry of Health this year: the Manual of Health Processes and Procedures and the Technical Guidelines for Health Research, which will contribute to the legal strengthening of research. However, it is essential to ensure that all these initiatives have clear mechanisms for financing, monitoring and effective application.

Although progress in legislation is recognized, there are still structural, economic and linkage limitations with the needs of the health system. It is indisputable that there is much to be done in strengthening the training of researchers, in consolidating the infrastructure for research, in guaranteeing its financial sustainability, and in orienting research towards the country's health priorities, but this is the challenge that in the medium term will allow the creation of public health policy bases, contributing to improving the care of the population and allowing the country to position itself at the international level in this field.

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Alerta

Types of articles and preparation

Alerta offers authors the opportunity to publish different types of articles. The types of manuscripts allowed are below. Please read the instructions carefully prior to submitting your article.

Original article

Research works that have not been published or proposed for revision in other journals and provide information to understand or propose solutions to the main health problems. Case series studies, descriptive and analytical cross-sectional studies, case-control studies, cohort studies, and randomized controlled trials are considered for publication. Results must be original.

The article must have the following structure: abstract, keywords, introduction, methodology, results, discussion, conclusion and references. The text must have a maximum of 4000 words and a minimum of 3000, not including references, abstract and text of figures and tables. The abstract must have a maximum of 250 words and must be structured in introduction, objective, methodology, results and conclusion. Use of acronyms, abbreviations and bibliographic citations in the abstract is not allowed. A maximum of 35 references and a minimum of 25 are allowed. 65 % of references must not be older than five years since their publication date. Only 10 % of grey literature is allowed as part of references. Tables and figures must not be more than five in total.

For observational studies, it is recommended the format according to STROBE guidelines. For randomized controlled trials, it is recommended the format according to the CONSORT statement.

Review article

Review articles that present the result of an analysis of recent information or a thematic update of interest in public health, following any of the accepted methodologies for this purpose. It is required to indicate that it is a narrative or systematic review.

Systematic review and meta-analysis

Systematic reviews representing a synthesis of evidence, original, quantitative or qualitative studies, that use a rigorous process to minimize biases and that identify, evaluate and synthesize studies to answer a specific clinical question are accepted. The search process for the original studies, the criteria used for the selection of those that were included in the review and the procedures used in the synthesis of the results obtained by the reviewed studies must be described in detail.

The article must have the following sections: abstract, keywords, introduction, methodology, results, discussion, conclusion and references. The text must have a maximum of 4000 words and a minimum of 3000, not including references, abstract and text of figures and tables. The abstract must have a maximum of 250 words and must be structured in introduction, objective, methodology, results and conclusion. Use of acronyms, abbreviations and references in the abstract is not allowed. There is no limit to the number of references. 75 % of them must not be older than five years since their publication date. The use of grey literature as part of references is not permitted. Tables and figures cannot be more than five in total.

Recommended format: PRISMA guide.

Narrative or critical review

Narrative or critical review must have descriptive writing and make a comprehensive presentation and discussion of topics of scientific interest in the field of public health. A clear formulation of a scientific object of interest with logical argumentation must be presented.

The article must have the following sections: abstract, keywords, introduction, discussion, conclusion and references. The text must have a maximum of 3500 words and a minimum of 2500, not including references, abstract and text of figures and tables. The abstract must have a maximum of 200 words. Use of acronyms, abbreviations and references in the abstract is not allowed. A maximum of 50 references and a minimum of 30 are allowed. 70 % of them must not be older than five years since their publication date. Only 15 % of grey literature is allowed as part of references. Tables and figures cannot be more than three in total.

Brief communication

This type of scientific paper is shorter than an original article. They are works that aim to publish data of interest in the health situation on a report of a research in development and innovative techniques or methodologies, among others.

The article must have the following sections: abstract, keywords, introduction, methodology, results, discussion, conclusion and references. The text must have a maximum of 2000 words and a minimum of 1500, not including references, abstract and text of figures and tables. The abstract must have a maximum of 200 words and must be structured in introduction, objective, methodology, results and conclusion. Use of acronyms, abbreviations and bibliographic citations in the abstract is not allowed. A maximum of 20 references and a minimum of 15 are allowed. 65 % of them must not be older than five years since their publication date. Only 5 % of grey literature is allowed as part of references. Tables and figures cannot be more than three in total.

Case report

This type of text refers to the presentation of clinical cases that meet established criteria and whose diagnostic and treatment aspects make a considerable contribution to scientific knowledge on the subject. It must respect the provisions of the Declaration of Helsinki and international ethics guidelines ffor health-related research involving human beings.

The text must have the following sections: abstract, keywords, introduction, case presentation, treatment, outcome, clinical diagnosis, discussion, ethical aspects and references. The text must have a maximum of 2000 words and a minimum of 1500, not including references, abstract and text of figures and tables. The abstract must have a maximum of 200 words and must be structured in case presentation, treatment and outcome. Use of acronyms, abbreviations and bibliographic citations in the abstract is not allowed. A maximum of 20 references and a minimum of 15 is allowed. 70 % of them must not be older than five years since their publication date. Only 5 % of grey literature is allowed as part of references. Tables and figures cannot be more than five in total.

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Letter to the editor

Letter to the editor or the editorial committee clarifying, discussing or commenting on the content presented in previous issues of this journal. Comment letters on specific public health issues may also be accepted. Letters must have the following sections: title and object of correspondence. It can have a maximum of 1000 words and a minimum of 700. Tables and figures are not accepted. A maximum of five references and a minimum of three are accepted.

Summary of the characteristics of the different articles

General format for the presentation of articles					
Type of manuscript		Word count	References	Abstract	Tables or figures
Original articles		3000 – 4000	25 – 35	250 words (structured)	Up to 5
Review articles	Systematic	3000 – 4000	As appropiate	250 words (structured)	Up to 5
	Narrative	2500 – 3500	30 – 50	200 words	Up to 3
Brief communications		1500 – 2000	15 – 20	200 words (structured)	Up to 3
Case report		1500 – 2000	15 – 20	200 words (structured)	Up to 5
Letter to editor		700 – 1000	3 – 5	No	No

For further information, please refer to the instructions to authors on our website at: www.alerta.salud.gob.sv

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