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**Work stress and mental health on frontline
healthcare workers during COVID-19 pandemic**

Authorities

National Institute of Health, El Salvador

Xochitl Sandoval López, MD.
Director

Carlos Hernández Ávila, MD.
Chief of Governance and Management Unit

Editorial Committee

Nadia Patricia Rodríguez Villalta, MD.
Editor in Chief and Editor, Narrative section
National Institute of Health, El Salvador
✉ nadia.rodriguez@salud.gob.sv

Edgar Quinteros Martínez, MSc.
Editor, Original Article section
National Institute of Health, El Salvador
✉ edgar.quinteros@salud.gob.sv

Fátima Larisa Chavarría Rodríguez, MD.
Editor, Case Report section
National Institute of Health, El Salvador
✉ flarisa.chavarria@salud.gob.sv

Cristian Balmore Romero Castro, MD.
Editor, Case Report section
National Institute of Health, El Salvador
✉ cristian.castro@salud.gob.sv

Susana Peña Martínez, MD.
Rosales National Hospital, El Salvador
✉ susana.pena@salud.gob.sv

Carlos Hernández Ávila, MD.
Editor, Brief Communication
National Institute of Health, El Salvador
✉ carlos.havila@salud.gob.sv

Karina Mendoza Reyes, MD.
Dr. María Isabel Rodríguez National Women's Hospital (HNM), El Salvador
✉ karina.mendoza@salud.gob.sv

Víctor David Franco, MD.
Salvadoran Social Security Institute
✉ victor.franco@issv.gob.sv

Ana María Soriano Hatch, MD.
Don Bosco University, El Salvador
✉ asoriano@udb.edu.sv

Willy Vladimir González, MD.
University of El Salvador
✉ wily.gonzalez@ues.edu.sv

MSc. Laura Chavarría de Cocar, MSc.
Gerardo Barrios University, El Salvador
✉ lchavarria@ugb.edu.sv

Emiliano Mariscal, MD.
National University of Mar Del Plata, Argentina
✉ manuelemilianomarisca@gmail.com

Delmy Virginia Granados Castro, MD.
Dr. José Antonio Saldaña National Neumology and Family Medicine Hospital, El Salvador
✉ delmy.granados@salud.gob.sv

Vicente Artola Arita, MD.
University Medical Center Groningen, Netherlands
✉ v.a.artola.arita@umcg.nl

Montserrat Amorós Gómez, MD.
International University of La Rioja, Spain
✉ montserrat.amoros@unir.net

Andrea Vallecampo, MD.
Evangelical University of El Salvador
✉ andrea.vallecampo@uees.edu.sv

Veralís Morán de Valladares, MPH.
National Institute of Health, El Salvador
✉ veralis.moran@salud.gob.sv

Style correction

Luis Trejo, BA.
Promotion of Health Department, MINSAL
✉ luis.trejo@salud.gob.sv

Desing and layout

Román Cabezas, MDes.
National Institute of Health, El Salvador
✉ roman.cabezas@salud.gob.sv

Cover photo

Adolfo Panameño
Photographer
✉ adolfopanameño@gmail.com

Editorial contribution and Spanish proofreading

Lic. Edwin López Morán
Editorial Unit, Regulation Directorate, MINSAL
✉ edwin.lmoran@salud.gob.sv

Editorial support

Daniela Flores, MD.
National Institute of Health, El Salvador
✉ danielaflloreskp@gmail.com

Josué Ramos, MD.
National Institute of Health, El Salvador
✉ jorameditins@gmail.com

Alessandra Martínez
National Institute of Health, El Salvador
✉ ralertaasistenteed2@gmail.com

Rodrigo Centeno
National Institute of Health, El Salvador
✉ ralertaasistenteed1@gmail.com

Fátima Larisa Chavarría Rodríguez, MD.
Medical-Technical correction
National Institute of Health, El Salvador
✉ flarisa.chavarria@salud.gob.sv

Morena Flores
Librarian
National Institute of Health, El Salvador
✉ morkikaflor@yahoo.com

Translation and proofreading

Jorge Llanes, Mst.
English translation
National Institute of Health, El Salvador
✉ jorge.llanes@salud.gob.sv

Fressia Cerna, Mst.
English translation, review of Inclusive topics
National Institute of Health, El Salvador
✉ fressia.cerna@salud.gob.sv

José Eduardo Oliva, MD.
Medical review of English translation
National Institute of Health, El Salvador
✉ jose.oliva@salud.gob.sv

Cristian Balmore Romero Castro, MD.
Medical review of English translation
National Institute of Health, El Salvador
✉ cristian.castro@salud.gob.sv

Josué Ramos, MD.
Medical review of English translation
National Institute of Health, El Salvador
✉ jorameditins@gmail.com

Information and technology support

Francisco Orellana, BCs.
National Institute of Health, El Salvador
✉ frnk.ore5@gmail.com

Scientific Committee

Alberto Baly Gil, PhD.
Institute of Tropical Medicine Pedro Kourí (IPK Cuba)
✉ baly@ipk.sld.cu

Ana Ruth Escoto Castillo, PhD.
The National Autonomous University of Mexico
✉ ana.escoto.1@gmail.com

Alexandre Ribó, PhD.
Independent consultant, Spain
✉ alexandre4rt@gmail.com

Dina Larios López, PhD.
Ohio University, The U.S.
✉ lopezd@ohio.edu

Carlos Alexander Ortega, PhD.
University of El Salvador
✉ carlos.ortega@ues.edu.sv

Lorena Rivas de Mendoza, MD.
José Simeón Cañas Central American University, El Salvador
✉ lirivas@uca.edu.sv

Carlos Ortez González, MD.
San Juan de Dios Hospital, Barcelona, Spain
✉ ciortez@sjdhospitalbarcelona.org

Lorena Suárez Idueta, PhD.
Oxford University, England
✉ suarezidueta@gmail.com

Carlos Vinicio Coreas, PhD.
University of El Salvador
✉ vinicio.coreas@gmail.com

Marta Castro Peraza, MD., PhD.
Institute of Tropical Medicine Pedro Kourí (IPK Cuba)
✉ martac@ipk.sld.cu

David Saúl Rodríguez, MD.
The Executive Secretariat of the Council of Ministers of Health of Central America and Dominican Republic
✉ drosdriguez@sica.int

Miriam González, MD.
St. Jude Children's Research Hospital, The U.S.
✉ miriam.gonzalez@stjude.org

Douglas Raimundo Velásquez, PhD.
University of El Salvador
✉ velasquezraim@yahoo.es

Tania Cuadra Zelaya, PhD.
University of El Salvador
✉ ethelcuadra@hotmail.com

Héctor Manuel Ramos, MD.
Epidemiology Directorate, MINSAL
✉ hramos@salud.gob.sv

Marvin J. Núñez, PhD.
University of El Salvador
✉ marvinjunuez@gmail.com

Noé Rigoberto Rivera, PhD.
University of El Salvador
✉ noerigoberto_rivera@yahoo.com.ar

Yaxsier de Armas Rodríguez, PhD.
Institute of Tropical Medicine Pedro Kourí (IPK Cuba)
✉ yaxsier@ipk.sld.cu

Jorge Pleitez Navarrete, MD.
National Institute of Health, El Salvador
✉ jorge.pleitez@salud.gob.sv

Wilfredo Belteton, MSc.
National Institute of Health, El Salvador
✉ wilfredo.belteton@salud.gob.sv

Jaime Alejandro González Rodas, MD.
Catholic University of El Salvador
✉ jaime.gonzalez@catolica.edu.sv

Guillermo Edgardo Barahona Escobar, MD.
Benjamín Bloom's Children Hospital, El Salvador
✉ guille_barahona@hotmail.com

Exchange and subscription

Nadia Patricia Rodríguez Villalta, MD.
✉ nadia.rodriguez@salud.gob.sv

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National Institute of Health, El Salvador

Urb. Lomas de Altamira, Bulevar Altamira and Ave. República del Ecuador n.º 33, San Salvador, El Salvador.

URL: <http://alerta.salud.gob.sv/>
ralerta@salud.gob.sv

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Six years paving the path for indexation

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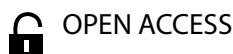
Xochitl Sandoval López

National Institute of Health, San Salvador, El Salvador.

Correspondence

✉ xochitlsandoval2005@gmail.com

ORCID: 0000-0002-0988-1313



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The *Alerta* journal of the National Institute of Health (INS) of El Salvador is more than a digital medium for scientific knowledge dissemination in health. It is now a country project that promotes research and publication culture. With this twelfth edition corresponding to volume six, number one of 2023, it begins its sixth year of life.

Since 2018, the journal has had its first steps and prepared the conditions to comply with international standards and good publishing practices through the formulation of technical standard, procedures manual and style manual, and essential documents for publication. They have been updated several times to date, as a result of the updated several times as a result of their evolution and development.

No less important are the interest and collaboration of reknown national and international researchers who were or continue to be part of the scientific committee and editorial committee. They have been gradually internationalized, seeking to broaden their vision and impact.

Alerta began its indexing process in regional databases such as Latindex, a Regional Online Information System for Scientific Journals of Latin America, the Caribbean, Spain, and Portugal. To date, *Alerta* has undoubtedly taken firm steps in the straightening of a window to the scientific world in which national and international researchers can do any publishing with the confidence that scientific rigor is a cross-cutting concept in all stages of the editorial process.

It has allowed progressive strengthening and improved the editorial quality and scien-

tific contributions for six years. It also allowed its acceptance in prestigious databases and indexes such as the Ibero-American Network of Innovation and Scientific Knowledge (Redib)¹ and the Information Matrix for the Analysis of Journals (MIAR) in Spain.

Alerta began its indexing process in regional databases. The acceptance in an index that marked the most relevant transformations of the journal was to have met the criteria for indexing in LILACS (Latin American and the Caribbean Literature in Health Sciences). Subsequently, *ALERTA* submitted to the Latin American Bibliography (BIBLAT) and PERIÓDICA (Index of Latin American Journals in Science). These are projects supported by the National Autonomous University of Mexico, which contribute relevant metrics to the journal.

The acceptance in AmelICA², a communication infrastructure for academic publishing and open science, contributed to the journal offering different products such as PDF, ePUB, XML, HTML, and viewer for different devices.

This path has been one of perseverance. Thus, we recently celebrated the indexing of *Alerta* in the Network of Scientific Journals of Latin America and the Caribbean, Spain, and Portugal (Redalyc)³. Likewise, the 100 percent translation of the journal into English is an achievement of the year 2022, which represents a relevant fact that favors the dissemination, visibility, and number of citations received per publication and authors of the journal and, therefore, its impact.

The projection for the immediate and mediate future in this project, which is a flagship of great value, is to consolidate the

indexing in Web of Science and Scopus. Complying with these criteria⁴ is our new challenge and commitment to our readers and authors to provide writing courses for reviewers to improve their skills. However, our most relevant vision at this stage is to adopt a multilingual policy that will undoubtedly be a more economical approach than translating all articles into English and offering them in electronic format. It seeks to favor even more the international citation of articles, without forgetting that despite living in the era of globalization, we must firmly maintain the richness offered by the expression of different languages and, particularly, continue to support the native language of our journal, Spanish.

In this issue, we are pleased to publish two original articles: dealing with occupational stress and mental health of front-line personnel in COVID-19 care, and clinical epidemiological characterization of patients under or equal to 40 years old with breast cancer at the Dr. María Isabel Rodríguez National Women's Hospital. Also, three striking case reports from different areas of medicine are presented such as abdominal angiostrongyliasis: a case reported in an elderly adult patient with cecal perforation, a hemophagocytic syndrome associated with varicella and a case report on erythroplasia of Queyrat, three narrative reviews entitled current applications of ultrasonography in anesthesia, physical and psychological consequences of obstetric violence in Latin American countries, and the use of cannabidiol for the control of refractory neurological symptoms in patients with convulsive syndromes and neurodegenerative diseases, a systematic review of pulmonary histopathological findings associated with COVID-19. Finally, two letters to the editor were on highly relevant topics as contributions to neonatal care from the Iberoamerican Society of Neonatology and results of the use of the Rapidec® carba NP test in El Salvador.

It is important to note that 57 % of the authors in this issue are women. It is a contribution that helps to reduce the gender gap in science, particularly in scientific publications, because throughout history, women

have been at a disadvantage to access to scientific training, the possibility of writing scientific research articles, and the recognition that this implies in societies⁵. Due to the relevant role of science, technology, and innovation play central axes in the social and economic development of peoples, we are pleased with this news on behalf of all the women who publish today. We hope the journal will be strengthened and become increasingly sustainable.

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3. Rodríguez Muñoz R, Socorro Castro AR, Formoso Mieres AA, León González JL. Términos de Redalyc y Redib para el manejo de la información en las investigaciones científicas. *Universidad y Sociedad*. 26 sep. 2022 [cited January 26, 2023];14(4):47-55. Available in: <https://rus.ucf.edu.cu/index.php/rus/article/view/3013>
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Case report

Primary surgical approach to a patient with erythroplasia of Queyrat

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Rafael Alexis Contreras Cruz¹, Elio Ausberto Martell Hernández²

1-2. Urology Department, Rosales National Hospital, San Salvador, El Salvador.

* Correspondence

✉ calexis088@gmail.com

1.  0000-0003-3222-5119

2.  0000-0003-0498-2091

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Abstract

Case presentation. A 52-year-old male patient presented to the urology office with a two-year history of noticing a bright red, pruritic, and painful lesion on the glans and foreskin with a progressive increase in size that did not improve with antibiotic and antifungal treatments. **Treatment.** Partial glandectomy with thigh skin graft was performed. **Outcome.** After one month, the graft presented a 95 % of coupling. No local recurrence of cancer was observed. The histopathological study reported invasive squamous cell carcinoma in the lesion of the foreskin and glans skin, with all surgical margins, lateral and deep limits, negative for malignancy. After eight months post-surgery, the covering of the glans was observed with an appropriate esthetic result, with a similar appearance to the natural covering.

Keywords

Penile cancer, squamous cell carcinoma, erythroplasia of Queyrat.

Resumen

Presentación del caso. Paciente masculino de 52 años que se presentó a la consulta de urología con historia de dos años de notar una lesión en el glande y el prepucio, de color rojo brillante, pruriginosa y dolorosa con aumento progresivo del tamaño que no mejoró con tratamientos antibióticos y antifúngicos. **Intervención terapéutica.** Se realizó una glandectomía parcial con injerto de piel de muslo. **Evolución clínica.** Luego de un mes, el injerto presentó un 95 % de acoplamiento. No se observó recurrencia local de cáncer. El estudio histopatológico reportó un carcinoma escamoso invasor en la lesión del prepucio y en la piel del glande, con todos los márgenes quirúrgicos, límites laterales y profundos, negativos a malignidad. Luego de ocho meses posquirúrgicos, se observó el recubrimiento del glande con un adecuado resultado estético, con apariencia similar a la cubierta natural.

Palabras clave

Cáncer de pene, carcinoma de células escamosas, eritroplasia de Queyrat.

Introduction

Erythroplasia of Queyrat (EQ) is a squamous cell carcinoma *in situ* arising from the mucosal surface of the glans and prepuce¹⁻³. It was first described in 1891 by Tarnowsky, who found a lesion on the glans, similar to the erythroplasia previously described by Paget^{4,5}. In 1893, it was named as papillary epithelioma by Fournier and Darier^{4,6}. In 1911, Queyrat coined the term, conducted a further study of the lesion and gave it the name of *érythroplasie*. Therefore, it is now known as erythroplasia of Queyrat (EQ)⁷ when referring to lesions in plate-shaped or velvety bright red patches, clearly defined raised edges, pruritic, sometimes bleeding, which require surgical treatment due to the danger of progression to invasive carcinoma^{8,9}.

EQ is one of the three most frequent variants of carcinoma *in situ* of the penis. There is not tendency to spontaneous resolution and 30 % of cases progresses to invasive carcinoma and metastasis if not adequately treated and in a timely manner¹. This disease is most frequently suffered by uncircumcised males with an average age of 68 years¹⁰.

Penile cancer can affect men of any age, although it is most commonly diagnosed between the sixth to seventh decade of life. Squamous cell carcinoma, usual type is the most frequently reported¹², followed by premalignant lesions of penile carcinoma *in situ*¹. Other less frequent correspond to sarcoma, melanoma and basal cell carcinoma¹².

It is calculated that 10 % of penile neoplasms correspond to premalignant lesions, the most frequent ones are EQ, Bowen's disease and bowenoid papulosis. The exact etiology of these premalignant lesions is not yet known; however, bowenoid papulosis is probably a virus-induced epithelial dysplasia associated mainly with human papillomavirus (HPV) 16 and 18. Patients usually consult for pruritus, pain, bleeding and difficulty in retracting the prepuce. When evaluating the characteristics of the penis, it is red, shiny and slightly pigmented, with plaques or patches on the glans in either EQ or Bowen's disease. The difference in EQ is that the prepuce mucosa is affected and presents multiple lesions similar to pigmented, keratinized, numerous and inflamed warts¹.

A low incidence of penile cancer has been described, mainly in countries with good socio-sanitary conditions and in those that practice circumcision. In the United States it represents one percent of the malignant tumors diagnosed and causes more than 400 deaths per year¹¹⁻¹³, although in coun-

tries of Asia, South America and Africa the incidence reaches 10 % and the risk of malignant degeneration increases by 30 % if treatment is not received in a timely manner¹. The 2020 Global Cancer Observatory reported an incidence of 0.28 % in El Salvador, with a mortality of 0.17 % per year¹⁴.

Multiple risk factors contributing to its development are mentioned such as not having been circumcised, phimosis, obesity, poor hygiene, lichen sclerosus, infection by HPV-16 and HPV-18, smoking, use of psoralens, immunosuppression, trauma¹ and multiple sexual partners^{2,3,15}.

Its diagnosis is usually late in most cases and seems to be associated with the low frequency of cases, patients' poor attention to their genitalia or fear of treatment¹⁶. This diagnosis is confirmed by histopathological study¹⁷. Patients who experience these conditions must be counseled and tested for HPV and other sexually transmitted diseases, including human immunodeficiency virus (HIV)¹.

Case presentation

This is a 52-year-old man, who consulted multiple times in primary care areas with a two-year history of noticing a bright red, ulcerated, painful, pruritic lesion at the level of the crown of the glans penis, with a slow and progressive increase in size and shape; there were neither lower urinary tract symptoms nor relevant past medical history. His sexual initiation was at age of 16 and referred having had multiple sexual partners; He was medicated on multiple instances with oral antibiotics and topical treatments, such as steroids, antifungals, fluoropyrimidines, chemotherapeutics, without clinical improvement. He was referred to dermatology where a tissue sample was taken from the glans and prepuce for histopathological study, which revealed the presence of invasive squamous cell carcinoma of the glans and prepuce, so he was referred to urology consultation.

Physical examination showed an abdomen with scarce adipose panniculus, soft and depressible, without inguinal nor pelvic adenopathies. There were not abnormalities at the level of the scrotum. The mucosa of the glans had an erythematous lesion of velvety appearance, indurated, bright red, with raised edges of approximately 2 × 2 cm, which did not involve the urethral meatus (Figure 1). The mucosa of the prepuce had lesions of the same characteristics, with raised edges, indurated, without bleeding, not painful and difficulty in prepuce retraction. The laboratory tests were reported within normal values (Table 1).



Figure 1. Bright red velvety lesion on the glans penis with invasion into the mucosa of the prepuce



Figure 2. After glans lining plus extended circumcision



Figure 3. Glans covering seven days after surgery, 80 % attached

Treatment

Two weeks after the outpatient evaluation, the patient was admitted to the urology department for the surgical procedure. One day before the surgical procedure, intravenous ceftriaxone prophylaxis was administered and a transurethral catheter was placed.

The surgical procedure was performed under spinal anesthesia. This consisted of local excision of the lesions of the glans and prepuce, and superficial partial glansectomy plus extended circumcision. After resection, a partial thickness skin graft was prepared from the right thigh, which created a new skin cover over the glans and was stitched with resorbable suture to the urethra and penile skin (Figure 2).

Table 1. Laboratory tests

| Laboratory test | Results |
|---------------------|-------------------------------|
| Hemoglobin | 16 g/dL |
| Leukocytes | $7.2 \times 10^3/\mu\text{L}$ |
| Neutrophils | 55 % |
| Platelets | $300 \times 10^3/\mu\text{L}$ |
| Creatinine | 0.4 mg/dL |
| Urea Nitrogen | 8 mg/dL |
| HIV test | Non-reactive |
| Rapid syphilis test | Negative to date |

Outcome

Post-surgical treatment with ketotolac was indicated for three days and ceftriaxone for five days, both intravenously. After one week the transurethral catheter was removed and he was discharged.

After a week the patient was evaluated in a follow-up consultation showing 80 % graft coupling (Figure 3), with areas of necrosis at the level of the urethral meatus. Two weeks after the surgery, the graft coupling was 90 % and scar tissue was observed in the urethral meatus. Sexual intercourses were not initiated despite having normal erections. He also had no alterations in the onset of urination and had a moderate caliber urinary stream. The histopathological study presented the invasive squamous cell carcinoma and the skin of the glans, all the lateral and deep surgical margins were negative for malignancy.

One month after the surgery, there was evidence of a 95 % coupled graft (Figure 4). Urethral meatus stenosis was identified; therefore, a urethral meatus dilation regimen was indicated for four consecutive weeks. There was not local recurrence

of disease. Eight months after the surgery, an adequate coloration of the glans lining was found with an adequate aesthetic result similar to the natural skin; the external urethral meatus had an adequate caliber (Figure 5). The patient reported resuming of sexual activity without alterations of orgasmic sensation.

Follow-up consultations will continue every three months for the next two years, then every six months for three years, then every year for five years. Finally, if recurrence does not occur during ten years of follow-up, he will be discharged from the urology service. The patient has been instructed on the need to attend for an early evaluation if recurrence in the penile skin or lymphadenopathies are detected.

Clinical diagnosis

Erythroplasia of Queyrat, defined as squamous carcinoma of the mucosa of the glans and prepuce.

Discussion

Differential diagnosis includes Zoon's balanitis, Bowen's disease, malignant melanoma of the penis, basal cell carcinoma of the penis, lichen sclerosus, bowenoid papulosis, and psoriasis¹.

In some cases, dermoscopy is considered to evaluate pigmented or non-pigmented lesions by providing information on the structures of the glans penis, finding glomerular blood vessels on a bright red background, twisted blood vessels and small red areas without structure^{3,18}. In this case, the lesion at the level of the glans and prepuce had a hard consistency and had been treated with different topical medications, so it was decided the excision and complement with histopathological studies. This study confirms the diagnosis when reporting the presence of atypical squamous cells or proliferating cells in the epidermis without invasion into the dermis in early cases. It is usually indicated in doubtful cases to conclude the clinical diagnosis. It is necessary to repeat this study if the first result is not conclusive¹.

Initiation of treatment includes cessation of smoking and risky sexual practices, sexual partner evaluation and long-term follow-up with the standard therapeutic approach including local excision, Mohs surgery and partial or complete phallectomy. Of these surgical approaches, Mohs surgery with total glans lining produces the most favorable cosmetic and functional outcome; however, these invasive procedures have the potential psychosocial effects and harm quality of

life^{1,10}. Other non-surgical modalities include the application of CO₂ laser, Nd-YAG laser, isotretinoin, 5-fluorouracil or imiquimod cream, and procedures such as cryotherapy, curettage and electrofulguration^{1,2,10,19}.

Partial glans lining has been used as a primary surgical approach for carcinoma *in situ* of the glans penis. This approach has the advantage of preserving normal appearance of the glans penis, allowing better preservation of sensitivity, erection and orgasmic sensation achieving an appearance closer to the original glans. This treatment is more suggestive for younger, sexually active men¹. It has been shown that glans penis reconstruction has better results perceived by the patient and his family, as opposed to those who underwent more aggressive procedures such as total or partial phallectomy, having profound effects on sexual function as well as on urinary function which



Figure 4. Glans lining one month after surgery, there is no local recurrence of the disease



Figure 5. Glans lining 8 months after surgery, the urethral meatus is observed with adequate functional caliber

can be drastically affected by the derivation of urinary flow through a perineal neomeatus or urethrostomy¹¹.

The tendency to delay consultation often with a long history of evolution, self-medication and failed treatment can result in progression to invasive carcinoma, requiring more extensive surgery¹.

Early diagnosis and treatment before invasion is essential to avoid the need for more aggressive treatment, thus, this avoids partial or complete amputation of the penis, improving physical, psychological and sexual well-being.

Ethical aspects

For the publication of this case, informed consent was obtained from the patient. It was for both the hospital care where the physical examination of the patient was performed and the publication of this article, with the commitment to maintain the patient's privacy, as stated in the Helsinki Declaration²⁰.

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Case report


Hemofagocytic syndrome associated with varicella

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Cesar Mateo Gavidia Leiva^{1*}, Ramón David Argueta Sales²

1. Ministry of Public Health / Directorate of Epidemiology, San Salvador, El Salvador.
2. Ministry of Public Health / Central Health Region, Santa Tecla, La Libertad, El Salvador.

* Correspondence
✉ cesarmat2015@gmail.com

1.  0000-0002-9351-9359
2.  0000-0001-8174-8114

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The authors declare there are no conflicts of interest.

Abstract

Case presentation. A 14-month-old female infant with normal psychomotor development, without comorbidities. With a one-day history of fever of 40 °C, intermittent, accompanied by diarrhea and vomiting. She was taken by her parents to a private clinic without improvement with the indicated medical treatment. Subsequently, she presented clinical deterioration and was taken to a hospital, where she was diagnosed with acute febrile syndrome, diarrhea with mild dehydration, and pharyngitis. On the fourth day of evolution, she started with macules and papules that progressed to vesicles and crusts. In addition, she presented oral intolerance, dyspnea, abdominal distension, coma, and hydroelectrolytic imbalance. **Treatment.** She started treatment with parenteral hydration, antivirals, intravenous steroids, and antihistamines; septic shock with respiratory distress was diagnosed, assisted mechanical ventilation was provided, and she was referred to a tertiary hospital for critical care medicine. Studies reported a 40 % right pleural effusion and hepatomegaly. She continued treatment with antibiotic therapy, parenteral hydration, antivirals, diuretics, antipyretics, and hemoderivatives, presented improvement, and continued therapeutic management. **Outcome.** On day 18 she presented fever and hepatosplenomegaly. Tests reported elevated ferritin, triglycerides, and cytopenia, and was diagnosed with hemophagocytic syndrome that evolved with multisystemic failure and died the following day.

Keywords

Varicella, sepsis, hemophagocytic lymph-histiocytosis, hemophagocytic syndrome.

Resumen

Presentación del caso. Lactante femenina de 14 meses de edad con desarrollo psicomotor normal, sin comórbidos. Con historia de un día de fiebre de 40 °C, intermitente, acompañada de evacuaciones diarreicas y vómitos. Fue llevada por sus padres a una clínica privada sin notar mejoría con el tratamiento médico indicado. Posteriormente, presentó deterioro clínico y fue llevada a un hospital, donde se diagnosticó un síndrome febril agudo, diarrea con deshidratación leve y faringitis. Al cuarto día de evolución inició con máculas y pápulas que progresaron a vesículas y costras. Además, presentó intolerancia a la vía oral, disnea, distensión abdominal, coma y desequilibrio hidroelectrolítico. **Intervención terapéutica.** Inició el tratamiento con hidratación parenteral, antivirales, esteroides endovenosos y antihistamínicos; se diagnosticó shock séptico con compromiso respiratorio, se proporcionó ventilación mecánica asistida y fue referida al hospital de tercer nivel para atención por medicina crítica. Los estudios reportaron un derrame pleural derecho del 40 % y hepatomegalia. Continuó el tratamiento con antibióticoterapia, hidratación parenteral, antivirales, diuréticos, antipiréticos y hemoderivados, presentó mejoría, continuó el manejo terapéutico. **Evolución clínica.** El día 18 presentó fiebre, hepatoesplenomegalia, los exámenes reportaron elevación de ferritina, triglicéridos y citopenia se diagnosticó un síndrome hemofagocítico que evolucionó con una falla multisistémica y falleció al siguiente día.

Palabras clave

Varicela, sepsis, linfocitosis hemofagocítica, síndrome hemofagocítico.

Introduction

Hemophagocytic syndrome is characterized by hyperreactivity of phagocytic cells, which attack hematopoietic cells without regulation of the immune system. It is associated with severe cytopenias due to

uncontrolled hemophagocytosis. It can be present in two forms: primary or secondary. Diagnosis is complex, but is suspected when fever, hepatosplenomegaly, cytopenia in at least two cell lines, hypertriglyceridemia or hypofibrinogenemia, and elevated ferritin levels are present¹.

The global incidence is not defined; countries such as the United States of America report an incidence of one per 100 000 inhabitants; in Latin America the incidence rate has not been recorded, but there are reports of patients in whom the syndrome is related to viral infections². Global mortality is 95 % in the absence of treatment, and 40 % with timely treatment. In Latin America, some studies describe a mortality rate of 35 %².

Varicella is caused by the varicella zoster virus whose only reservoir is the human being. It causes two diseases: varicella as primary disease and herpes zoster, when there is a reactivation of the virus. The latter is characterized by papular macules with vesicles and crusts, as well as hyporexia and fever. The lesions present in different stages of evolution, initially with a central distribution on the trunk, stomach and thorax, then spreading³. The virus is transmitted from person to person, by direct contact with skin lesions, by fomites contaminated by secretion from the lesions and by the airborne route⁴. It rarely occurs in infants because they are protected by the immunity of antibodies in breast milk⁵.

Chickenpox is highly contagious. In the United Kingdom, more than 80 % of people have been infected before the age of ten. In the United States of America, mortality in infants and children is approximately seven per 100 000 infants and 1.4 per 100 000 children⁶. The global incidence rate is 2.7 per 100 000 inhabitants, with countries such as Mexico reporting rates of 2.33 per 100 000 inhabitants⁷. The incidence rate reported by Salvadoran studies is 50.8 per 100 000 inhabitants⁸. El Salvador has a vaccination law based on the expanded program of immunization, which does not include vaccines for varicella and hepatitis A⁹.

Case presentation

This is a 14-month-old female infant, from the department of La Libertad, of low socio-economic level, living with her two parents and two siblings nine and 14 years old in a house of mixed construction with two bedrooms. There was no history of allergies, medical or surgical precedents, travel outside the country, or contact with sick people in the last 21 days. The patient was malnourished, with normal psychomotor development and with a complete vaccination schedule for her age, according to the Expanded Program of Immunization⁹.

She was initially medicated with acetaminophen 120 mg every six hours. After noticing an exacerbation of the symptoms, the parents decided to consult a private health service. She was brought for consultation with a history of one-day of fever of 40 °C, intermittent; diarrheal, liquid, fetid, yellow color, bowel movements, without glera or blood; and vomiting of gastric contents. On the second day of evolution and with no improvement with the indicated treatment the parents decided to consult a peripheral hospital, where she was diagnosed with acute febrile syndrome, diarrhea with mild dehydration, and pharyngitis; she was admitted into the hospital for study and management. The initial leukogram reported leukocytes of 12 660 and neutrophils of 85 %.

On the third day she continued to be febrile and evolved with oral lesions, a diagnosis of herpetic stomatitis was made (Figure 1). On the fourth day she presented macules in the thorax region, abdominal distension and difficulty defecating. On the sixth day, the skin lesions were in different stages of evolution; macules, papules, vesicles and

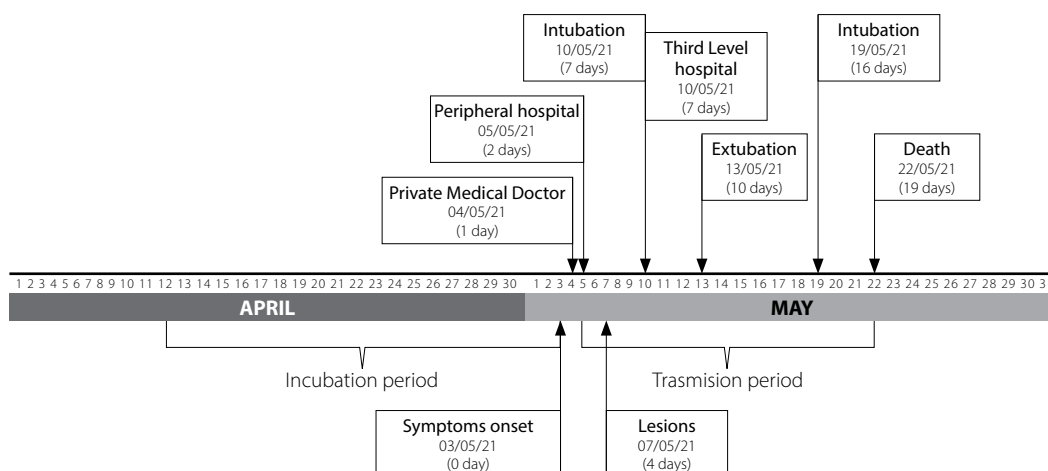


Figure 1. Timeline

Source: Authors' elaboration



Figure 2. Dermatologic lesions presented
Source: provided by the patient's mother.

crusts (Figure 2). In addition, she presented hydroelectrolyte imbalance, oral intolerance, dyspnea, 85 % oximetry, abdominal distension with Glasgow coma scale of seven points and hydroelectrolyte imbalance.

The patient was treated with 5 % dextrose solution, 20 % sodium chloride, 15 % potassium chloride, 10 % calcium gluconate, ceftriaxone 1 g every 24 hours, methylprednisolone 10 mg every six hours, chlorpheniramine 1 mg every 12 hours.

She was given mechanical ventilation and referred to a tertiary hospital being diagnosed with systemic inflammatory response syndrome, toxic shock, hydroelectrolyte imbalance and intestinal obstruction.

In the emergency unit of the tertiary hospital, the patient was critically ill, pale, under sedative analgesia with mechanical ventilation, with multiple maculopapular lesions on the skin, crusts and vesicles with clear fluid discharge. Blood pressure 102/63 mm/Hg, weak pulse 153 beats per minute, temperature 37.5 °C, weight 12 kg (at the 97th percentile), height 73 cm (at the 50th percentile), head circumference 46 cm. The thorax was hypoventilated at the right lung base with transmitted sounds. The abdomen was globose with absent peristalsis and hepatomegaly.

Anteroposterior chest X-ray and plain abdominal X-ray showed right pleural effusion of 40 %. Abdominal ultrasonography reported hepatomegaly and a splenic cephalocaudal diameter of 7.4 cm (splenomegaly).

Treatment

The patient was admitted to the tertiary hospital in the intensive care unit and was treated with 0.9 % normal saline, 5 % dextrose, 20 % sodium chloride, 25 % potas-

sium chloride, 10 % calcium gluconate, 50 % magnesium sulfate, vancomycin 180 mg every six hours, meropenem 500 mg every eight hours, clindamycin 120 mg every six hours, acyclovir 300 mg every eight hours, hydralazine 2.5 mg every six hours depending on the arterial pressure, clindamycin 120 mg every six hours, acyclovir 300 mg every eight hours, hydralazine 2.5 mg every six hours depending on arterial pressure. In addition, platelets 20 mL every eight hours, packed red blood cells 120 mL every day, dexamethasone 1.5 mg every six hours, human immunoglobulin 10 g in 24 hours, fluconazole 72 mg every day.

Tests showed hemoglobin and leukocytes within normal values, with neutrophilia, fibrinogen 117 g/L, decreased clotting times and elevated liver enzymes (Table 1).

Outcome

On the tenth day of evolution the patient presented clinical improvement, mechanical ventilation was withdrawn, with 100 % oximetry, gag reflex, response to external stimuli, respiratory frequency less than 35 breaths per minute, PaO₂/ FiO₂ greater than 150-200, PEEP less than or equal to eight cmH₂O, systolic blood pressure greater than 90 mmHg and diastolic less than 180 mmHg, temperature less than 38 °C. She started with dyspnea during the ventilator weaning process, continuous positive airway pressure was administered and then a nasal cannula was placed. When dyspnea improved, therapeutic management was continued.

After 18 days of evolution, she presented fever, dyspnea with oximetry of 87 %, hypotension, hepatosplenomegaly, adenopathy, with progressive leukopenia, coagulopathy, respiratory acidosis, cytopenia (hemoglobin 8.8 g/dL and platelets 10 000), ferritin 1500 ng/mL and triglycerides 307 mg/dL¹ (Table 1); which generated a multiorgan failure and died one day later.

Diagnosis

On the eighth day the following diagnoses were determined: acute gastroenteritis with dehydration, varicella, acute liver injury, pneumonia with right pleural effusion and septic shock, and finally, a hemophagocytic syndrome associated with an infection. The diagnosis of varicella was made by clinical and epidemiological criteria.

Discussion

Hemophagocytic syndrome or hemophagocytic lymphohistiocytosis occurs in two

ways: primary when associated with genetic mutations, and secondary when it occurs after autoimmune diseases, neoplasms or infections¹⁰. Infections related to the appearance of the syndrome are those produced by herpes viruses, human immunodeficiency virus, adenovirus, hepatitis virus, bacteria, fungi and parasites¹¹. In the pediatric population, the most common trigger is infections caused by the *herpesviridae* family, commonly known as Epstein Barr¹⁰. The patient, by clinical criteria, presented an infection by herpes virus type three or varicella zoster, and subsequently, a hemophagocytic syndrome, since she met five of the eight diagnostic criteria according to the HLH-2004 guideline¹²

(see Table 2), which gives relevance to the diagnosis. The treatment of this syndrome aims to modulate the pathological immune response it produces, with a scheme of etoposide and dexamethasone^{13,14}. If triggered by infection, aggressive therapeutic management is recommended, according to the focus of infection, the suspected or confirmed etiologic agent and the clinical status of the patient.

Multiple complications of varicella have been reported, including pneumonia, bacterial infections, hemorrhagic disorders and encephalitis; age and immunological status are described as important factors for the development of complications; the age group with the highest risk of complications

Table 1. Laboratory analysis

| Laboratory data | Unit | Reference data | Days of evolution | | | | | | | | | | | |
|----------------------------|---------------------|-----------------------------|-------------------|-----|-------|-------|-------|------|------|------|-----|------|-------|------|
| | | | 3 | 6 | 7 | 8 | 11 | 12 | 13 | 15 | 16 | 17 | 18 | 19 |
| Hematocrit | % | 33-36 % | 34.7 | | 27.0 | 25.2 | 31.0 | 22.3 | 20.6 | 38.0 | | 28.0 | 22.9 | 29.2 |
| Hemoglobin | g/dL | 10.5-12.0 g/dL | 11.3 | | 10.5 | 9.3 | 11.3 | 8.2 | 7.4 | 14.8 | | 8.8 | 10.7 | 10.7 |
| Leukocytes | 10 ³ /μL | 6-17 ×10 ³ /μL | 12.7 | | 13.9 | 9.2 | 2.9 | 2.2 | 1.9 | 1.2 | | 0.5 | | 0.2 |
| Neutrophils | % | 20-40 % | 85.0 | | 79.6 | 63.0 | | 49.0 | 78.8 | 29.5 | | 44.5 | | |
| Lymphocytes | % | 4-10.5 % | 12.2 | | 16.4 | 34.4 | | 97.0 | | | | | | 90.0 |
| Platelets | 10 ³ /mL | 150-350 10 ³ /mL | 346 | | 260 | 146 | 20 | 14 | 50 | 25 | | 4 | 10 | 20 |
| Na | mEq/L | 133-145 mEq/L | | 125 | 137 | 130 | 130 | | 128 | | 138 | | 131 | 118 |
| K | mEq/L | 3-5 mEq/L | | 3.4 | 3.22 | 4.17 | 4.3 | | 2.43 | | | | 4.71 | 5.7 |
| Ca | mg/dL | 8-10.5 mg/dL | | 8.1 | 7.85 | 8.09 | 8.0 | | | 6.8 | 6.4 | | 7.41 | 7.2 |
| Glucose | mg/dL | 60-100 mg/dL | | | 122 | 143 | | | | | | | 154 | 191 |
| UN | mg/dL | 5-18 mg/dL | | | 7.30 | 5.10 | 5.20 | | | | | | 21.0 | |
| Cr | mg/dL | 0.2-0.4 mg/dL | | | 0.18 | 0.11 | | | | | | | 0.18 | 0.41 |
| PT | s | 12.1-14.5 s | | | 11.1 | 11.8 | 11.31 | | | 12.1 | | | 16.7 | 14.6 |
| PTT | s | 33.6-43.8 s | | | 19 | 28.2 | 31 | | | 30.1 | | | 34.8 | 42.0 |
| Fibrinogen | g/L | 1.62-4.01 g/L | | | 117 | 106 | 204 | | | 411 | | | 416 | 241 |
| AST | U/L | 13-35 U/L | | | 1 054 | 1 784 | 124 | | | | | | 49.0 | 42.0 |
| ALT | U/L | 5-45 U/L | | | 416 | 775 | 156 | | | | | | 22.0 | 19.0 |
| LDH | U/L | 110-295 U/L | | | 3 847 | | | | | | | | 1 161 | |
| Albumin | g/dL | 3.6 - 5.2 g/dL | | | 2.4 | 2.0 | 2.6 | | | 1.8 | 2.5 | | | |
| Ferritin | ng/mL | 7-140 ng/mL | | | 1 000 | | | | | | | | 1 500 | |
| Dimer D | mg/L | 0-0.5 | | | | | | | | | | | 4.26 | |
| CRP | mg/L | 0-0.9 | 23.7 | | 2.13 | | 21.0 | 19.4 | | | | | 23.8 | |
| Urine culture | | | | Neg | | Neg | | | | | | | | |
| Pharyngeal exudate culture | | | | Neg | | | | | | | | | | |
| IgM for SARS-CoV-2 | | | Neg | | Neg | | | | | | | | | |
| IgG for SARS-CoV-2 | | | Neg | | Neg | | | | | | | | | |

Neg: Negative.

Source: Data obtained from clinical records.

Table 2. Criteria for the diagnosis of hemophagocytic syndrome according to the lymphohistiocytosis guideline. Hemophagocytic syndrome-2004

| Diagnostic criteria | Patient criteria |
|---|------------------|
| Fever greater or equal than 38.5 °C | Yes |
| Splenomegaly | Yes |
| Cytopenias affecting at least two of the three peripheral blood lineages | Yes |
| Hemoglobin less than 9 g/L | Yes |
| Platelets < 100 ×10 ⁹ /L | Yes |
| Neutrophils < 1 ×10 ⁹ /L | Yes |
| Hypertriglyceridemia (fasting, ≥ 265 mg/dL) and/or hypofibrinogenemia (≤ 150 mg/dL) | Yes |
| Hemophagocytosis in bone marrow, liver, spleen or lymph nodes | Not performed |
| Low or absent NK cell activity | Not performed |
| Ferritin ≥ 500 ng/mL | Yes |
| SIL-2R ≥ 2400 U/mL | Not performed |

Source: HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis.

is those over 15 years old, children under one year old, newborns and immunocompromised patients^{15,16}.

By October 18, 2021 1413 cases of chickenpox were reported in the country and two deaths due to the virus, the first, a 52-year-old female patient and the second, the patient described above, who was a female of 14 months old¹⁷. This is a significant difference with the region of Tucumán in Argentina, which reports 4777 cases of chickenpox per year. The vaccine has been implemented against this disease since 2015¹⁷.

The incubation period was possibly 20 days prior to the onset of symptoms, taking the maximum incubation period of the disease. Children with chickenpox can transmit the virus through the respiratory tract one to two days before the onset of rashes, until all lesions are crusted¹⁸. The patient started with cutaneous lesions on the fourth day of her evolution and was able to transmit it from the second day. In immunocompromised patients, the period of transmissibility may be prolonged¹⁸.

Hand washing with soap and water is important to prevent the occurrence of cases; when secretions are to be handled, the use of gloves is recommended, followed by hand washing¹⁹. If the patient is within

the period of respiratory transmission of the virus, the use of an N95 mask is recommended. In the event that it cannot be used, it is recommended that the personnel in contact be the one to protect themselves with the mask and maintain a distance of at least one meter¹⁹.

Epidemiological prevention measures are the basis for cutting the chain of transmission. They also prevent the spread of the virus. Besides, they include timely isolation, which is of utmost importance to control the disease. Moreover, it prevents the occurrence of more cases, outbreaks and deaths. Likewise, an active search for cases in the community, vaccination campaigns and timely isolation of cases should be carried out.

For the data collection, there was no availability to the clinical records of the private health center. In fact, it is considered a shortcoming affecting the integration of the continuous care.

Varicella is an endemic disease in El Salvador. Cases of this disease are more frequent in children under ten years old³, which gives relevance to this case report. The death of the female patient after 17 days of stay in two centers a consequence of complications such as pneumonia, hemorrhagic disorders and hemophagocytic syndrome, in addition to varicella.

Ethical aspects

In accordance with the principles in the Declaration of Helsinki, this case report was developed in accordance with the Belmont Report principles of non-maleficence and confidentiality, since no patient identification data are disclosed. Informed consent was requested from the patient's parents for the presentation of this case.

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Case report

Cecal perforation due to angiostrongyliasis in an elderly patient

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Rudecinda Ramírez Serrano

Salvadoran Institute of Social Security. San Salvador, El Salvador.

Correspondence

✉ rude_1709@hotmail.com

0000-0002-9775-5375

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Abstract

Abdominal angiostrongyliasis is a parasitic disease caused by the genus *Angiostrongylus costaricensis*, a nematode that infects humans through the secretions of snails or slugs, its definitive hosts. Costa Rica is considered the most endemic country, and it has been shown in different reviews that most cases occur in children and males. Case presentation. The patient was a 74-year-old woman who consulted for acute abdominal pain, with four days of evolution, accompanied by nausea, vomiting, and hyporexia. Laboratory tests reported mild leukocytosis and a negative general urine test. Abdominal ultrasonography reported a solid heterogeneous mass, poorly circumscribed in the right lateral abdomen, which led to the suspicion of acute appendicitis. **Treatment.** An exploratory laparotomy was performed, with the removal of a perforated colon tumor that spanned from the cecum to the proximal third of the ascending colon, in addition, a transverse ileum anastomosis was performed, without further complication. **Outcome.** She was managed with antibiotics and analgesics and was discharged nine days after the procedure, without complications. The biopsy showed parasite eggs consistent with *Angiostrongylus* sp.

Keywords

Angiostrongylus infections, *Angiostrongylus costaricensis*, intestinal perforation, cecum, appendicitis.

Resumen

La angiostrongiliasis abdominal es una enfermedad parasitaria causada por el género *Angiostrongylus costaricensis*, un nematodo que infecta a los humanos a través de las secreciones de caracoles o babosas; sus huéspedes definitivos. Costa Rica es el país que se considera más endémico, se ha evidenciado en distintas revisiones que la mayoría de los casos se presentan en niños y personas del sexo masculino. Presentación del caso. Se trata de una mujer de 74 años, que consultó por dolor abdominal agudo, de cuatro días de evolución, acompañado de náuseas, vómitos e hiporexia. Los exámenes de laboratorio reportaron leucocitosis leve y examen general de orina negativo. La ultrasonografía abdominal reportó una masa sólida heterogénea, mal circunscrita en flanco derecho, esto llevó a la sospecha de una apendicitis aguda. **Intervención terapéutica.** Se realizó una laparotomía exploradora, con la extirpación de una tumoración de colon perforado que abarcaba desde el ciego hasta el tercio proximal de colon ascendente, además, se realizó una anastomosis de íleo transversa, sin mayor complicación. **Evolución clínica.** Se manejó con antibióticos y analgésicos, fue dada de alta a los nueve días posteriores al procedimiento, sin complicaciones menores. La biopsia reportó huevos de parásitos consistentes con *Angiostrongylus* sp.

Palabras clave

Infecciones por *Angiostrongylus*, *Angiostrongylus costaricensis*, perforación intestinal, ciego, apendicitis.

Introduction

Abdominal angiostrongyliasis (AA) is a parasitic disease caused by the genus *Angiostrongylus* which includes at least 20 species. Two etiological types are known to affect humans: *Angiostrongylus*

cantonensis, which specifically affects the central nervous system, and *Angiostrongylus costaricensis*, which causes abdominal angiostrongyliasis. It was described in 1971 by Morera and Céspedes. *A. costaricensis* is endemic to Costa Rica and is found in areas of the tropical America¹.

Angiostrongylus costaricensis is a nematode with a complex life cycle, involving rodents as definite hosts and mollusk such as snails and slugs as intermediate hosts². Incidentally, it infects humans, in whom its life cycle is not completed³. Humans are incidental hosts, therefore, the parasite is not able to complete its life cycle and the immature stages are not expelled in the feces, but the eggs accumulate in the arterioles that irrigate the affected tissue⁴. Infection in humans is generated by consuming food contaminated with the secretions of snails or slugs, or by handling them with the hands and subsequently putting them in the mouth. Slugs have been found on ripe fruits on the ground and on vegetables eaten raw².

It was first described in 1971 in Costa Rica, then it was reported in different regions of the southern United States of America, Europe and countries of Latin America and the Caribbean⁵. The disease was first observed in Costa Rican children in 1952. According to Morera, more than 130 human cases of the disease had been discovered by 1971⁶. Subsequently, the rodent that acts as the natural definitive host and the mollusks that constitute the intermediate hosts were identified and their life cycle was clarified. The first non-Costa Rican case was found in Honduras in 1972 and the parasite has now been observed in most countries of the continent, from the United States to northern Argentina⁷.

In epidemiological terms, incidence or prevalence data are scarce; the actual prevalence of abdominal angiostrongyliasis has not been determined, and there is neither a coproparasitological test to confirm infection nor a serological "gold standard" test to ensure it⁸. Costa Rica is considered the most endemic country in the region, accounting for almost 90 % of the cases reported worldwide¹. According to Frenkel, ten to 30 cases were diagnosed each year, mostly in children⁶. It is important to mention that in some Latin American countries only isolated data have been recorded; no prevalence data are available. From the epidemiological point of view, it has been shown in different reviews that most cases occur in children and males¹.

In El Salvador between the years 2018 to 2021, 14 cases were reported, with ages ranging from two to 11 years old, mostly male, five from the central zone of the country, four from the paracentral zone, three from the western zone and two from the eastern zone. In-hospital stay was between two and eight days, with an average of two days. No data are available for adults⁹.

The incubation period varies from 14 days to several months. Humans become infected by eating contaminated food. Parasites and eggs are usually degenerated by host reaction, and eggs persist in human feces. The clinical presentation is varied and ranges from asymptomatic to severe manifestations requiring emergency surgery⁴. The clinical presentation is highly variable, making its diagnosis a challenge, symptoms such as malaise and myalgias are usually present in all cases, it can also present as an abdominal condition, which simulates acute appendicitis, associated with gastrointestinal symptoms and can be complicated with intestinal obstruction or perforation. It can also simulate a neoplasm. In laboratory studies, the most important finding is the presence of eosinophilia¹⁰.

A systematic review of cases reported that abdominal pain was present in 84 % of cases, vomiting in 50 %, diarrhea in 28 % and constipation in 14.2 %¹. Surgical intervention remains the most effective strategy for the treatment of acute AA, as no convincing data have been obtained on the use of anthelmintic drugs⁴.

Much of the physiology of the parasite that causes the disease is unknown, as well as many epidemiological aspects, and after three decades of the description of this parasitosis, confirmation is only possible through histopathological material obtained after surgery. Currently, research continues on diagnostic tests, among the most recognized are the Morera test and the most current IgG and IgG1¹¹ antibodies. The Morera test is a qualitative test, consisting of latex agglutination, which started in the 1980s and is the test currently used in Costa Rica¹².

The interest and concern that has motivated the study of *A. costaricensis* arises from the severity of the disease in humans, especially in school children and young adults, and the life cycle involving mollusks and rodents¹³.

Case presentation

This is a 74 years old female patient from the municipality of San Martín, who consulted for pain in the epigastrium of four days of evolution, which was later located in the right iliac fossa, accompanied by nausea and vomiting; she did not report having presented fever, diarrhea and other symptoms, as well as having self-medicated with oral and intravenous n-butylthioscine and oral simethicone without improvement. The patient had a history of open cholecystectomy since three years ago. In addition, she had presented with alternating episodes of

constipation and diarrhea since six months before. Blood pressure of 120/70 mm Hg, heart rate of 95 beats per minute, respiratory rate of 16 breaths per minute and temperature of 37.6 °C. She was conscious, alert and oriented in time, place and person, with no signs of dehydration, the abdomen was symmetrical and presented pain at Mc Burney's point, with positive Rovsing and Infante Diaz signs; no rebound was identified at the time of evaluation.

Abdominal ultrasonography described distended bowel loops with moderate presence of gas predominantly in the right lower abdomen with a solid heterogeneous mass, not well circumscribed in the right flank measuring 6.1 cm x 4.0 cm x 4.9 cm, with a volume of 62.1 mL. It was suggested to rule out fecal impaction.

Laboratory tests reported: leukogram: 8200 with 65.3 % neutrophils; hemoglobin: 10.8 g/dL; platelets: 431 000; prothrombin time: 11.8 seconds and thromboplastin time: 30.4 seconds. An acute abdomen is diagnosed, to rule out acute appendicitis versus cecal tumor.

Surgical intervention

Surgery was performed four hours after admission. It started with a Rocky Davis incision; according to the findings it was decided to perform an exploratory laparotomy via the midline. 200 mL of peritoneal reaction fluid were identified, the cecum with a 10 x 10 cm perforated tumor accompanied by multiple mesentery nodes, the cecal appendix with inflammatory walls being completely removed (Figure 1). Subsequently, a right hemicolectomy was performed in which the tumor was removed together with the healthy limits, from ten cm anterior to the distal ileum to ten cm posterior to the hepatic flexure of the colon (Figure 1), in addition, the nodes located in the mesentery were dissected. The surgery was completed with a lateral end anastomosis performed with manual suture with Connell and Lembert stitches, hemostasis and complete count were verified.

On the third day of intrahospital stay, histopathological studies were reported. The macroscopic findings described the ileum of 14 x 3.5 cm, the cecum and ascending colon of 9 x 5 cm, with adhesions and hyperemia in the serosa; an area of 5 x 4 cm was found in the cecum, which thickened the wall in a one-centimeter layer with perforation towards the serosa. The cecal appendix was six cm with hyperemia of the serosa, which was obliterated when the lumen was cut. Microscopic find-

ings described acute suppurative inflammation and abundant eosinophilic infiltrate involving all layers with perforation into the serosa (Figure 2). In addition, parasite eggs consistent with *Angiostrongyloides sp.* were observed (Figure 3), located in the lumen of the capillaries and also diffusely arranged, some of them were surrounded by multinucleated foreign body-like giant cells. Thrombosed blood vessels and areas with hemorrhagic infarctions were also found. No larvae were present. The borders had inflammatory changes in the serosa. The cecal appendix with lumen obliteration by collagenous and spindle cells. Four to eight lymph nodes had fibrosis, eosinophils and



Figure 1. Macroscopic anatomical specimen: distal ileum, cecum and ascending colon

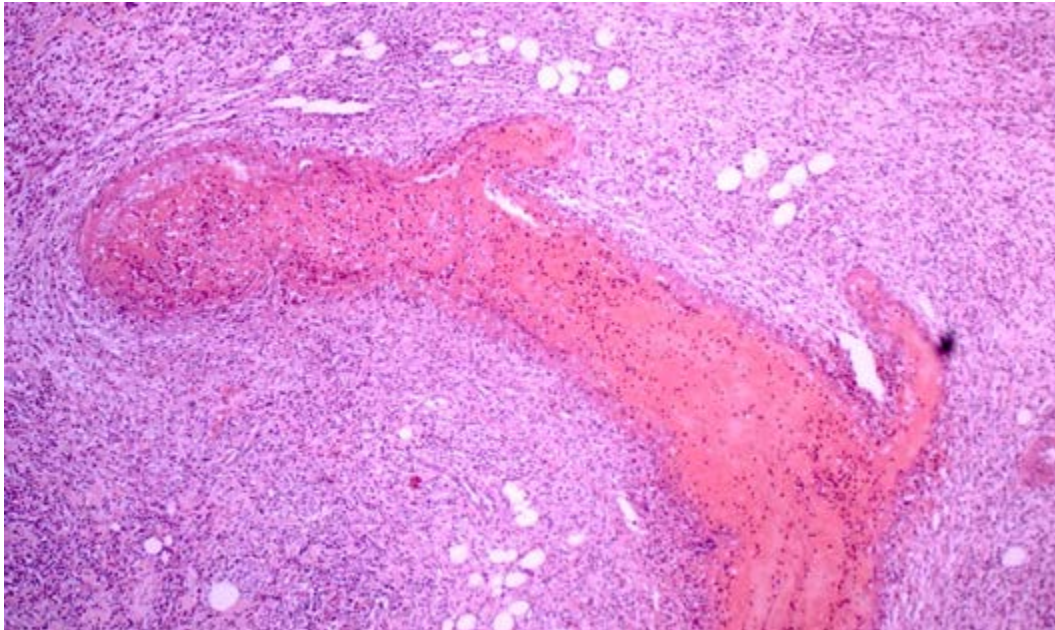


Figure 2. A thrombosed blood vessel is visualized under microscopy with hematoxylin-eosin stain (10x). The surrounding tissue shows a lymphoplasmacytic, eosinophilic and polymorphonuclear inflammatory infiltrate

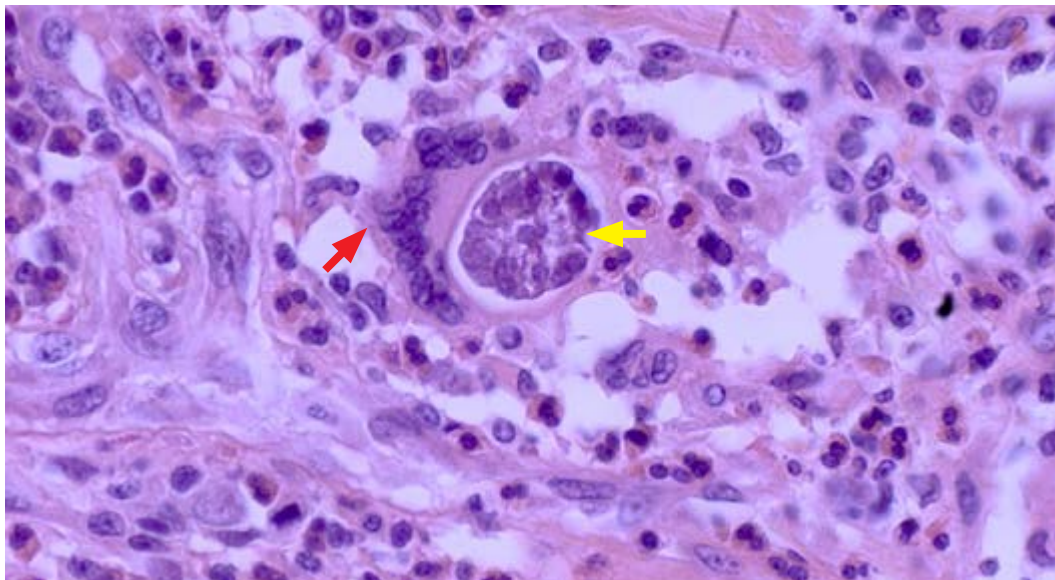


Figure 3. Hematoxylin-eosin stained microscopy (40x) shows parasite eggs (yellow arrow) consisting of angiostrongyloides sp. surrounded by multinucleated foreign body-like giant cells (red arrow)

parasite eggs. There was no evidence of malignancy. The conclusion of the report was perforated angiostrongyliasis of the cecum. Fibrous obliteration of the cecal appendix, disseminated angiostrongyliasis in four of eight pericolonar lymph nodes.

Clinical evolution

The patient remained in the hospital for nine days. Oral feeding was suspended for 48 hours, providing intravenous maintenance fluids, with double antibiotic ceftriaxone and metronidazole, and adequate analgesia; in addition to transfusion of two units

of packed red blood cells. On the fifth day, upon receiving the biopsy report, treatment was started with ivermectin six mg orally every 12 hours for two days; on the seventh day, dehiscence of the aponeurosis of 20 % was observed, which was resutured without complications. At hospital discharge, laboratory tests showed negative blood cultures, negative general stool examination, hemoglobin of 10.9 and leukogram of 11 300 with 78.5 % neutrophils. The patient was evaluated in subsequent controls without abnormalities, the operative wound healed adequately. The last control was ten months later, without unidentified sequels.

Clinical diagnosis

The clinicopathological diagnosis is established as abdominal angiostrongyliasis.

Discussion

Regarding clinical presentation, general symptoms such as malaise and myalgias are usually present in all cases. A systematic review of case reports reported that abdominal pain was present in 84 % of cases, vomiting in 50 %, diarrhea in 28 % and constipation in 14.2 %. Generally, abdominal pain is localized in the right lower quadrant. Occasionally a painful mass or plastron can also be found there, which is often interpreted as complicated appendicitis or a neoplastic lesion¹.

A case study published three years ago in Costa Rica suggests that the pathology can also be present with atypical symptoms, such as intestinal occlusions, which can lead to diagnostic but not therapeutic surgery¹⁴. In this case, a subject was reported with classic symptoms of intestinal obstruction that did not improve with medical treatment and that after 48 hours, due to the limitations of imaging studies in the health center, had to undergo diagnostic surgery, showing that there were areas of marked inflammation that led to a decrease in peristalsis, but there were no perforations or tumors that warranted a surgical procedure. Regarding the differential diagnosis it is easy to confuse the symptoms and signs of AA, because these are nonspecific, the main picture with which the confusion reported in the literature consulted is acute appendicitis, but other cases have also been reported in Europe as for example in which a patient presented with *A. cantonensis*, with abdominal pain on the fourth day of the disease. Surgical approach was discouraged by means of imaging studies and alprazolam and antihistamines (bilastin) were added to the treatment, obtaining an excellent clinical response, with disappearance of the symptoms in the following four to five days¹⁴.

In the literature reviews made in different Central American countries, eosinophilia is one of the main laboratory abnormalities in the leukogram report in AA cases, which may show more than 35 000 with eosinophilia of more than 10 % of cells. Nonetheless, eosinophilia is not specific to AA, since it can be reported in all parasitosis and other pathologies. It is defined as an absolute count of 500 eosinophils/microliter in peripheral blood. In a study carried out in Honduras, in a sample of 100 % of the entire population of selected children with an eosinophilia greater than 10 %, 45 % was associated with parasitosis¹⁵.

The Morera test which is a qualitative latex particle agglutination test. In a study conducted in Colombia in 2018, a new multiplex qPCR was analyzed for the specific, sensitive and simultaneous identification of *Angiostrongylus* species of importance in human and animal health. This test worked *in vitro*, becoming a new alternative for the diagnosis of angiostrongyliasis. However, it had yet to be validated in the field and in the clinic in patients and hosts in which parasite DNA was detected¹⁶.

Laparoscopic intervention for the acute abdomen of difficult diagnosis such as AA is a safe, feasible, and effective alternative, avoids extensive preoperative investigations or delays in surgical intervention, can help to prevent unnecessary non-therapeutic laparotomies and provide guidance in choosing the appropriate incision in patients in whom a definitive treatment cannot be completed laparoscopically.

These characteristics make laparoscopy a better option than open surgery in the management of abdominal emergencies¹⁷.

In the case presented, in which clinical findings were localized but not access to the laparoscopic approach, a less invasive approach was chosen; therefore, a Rocky Davis incision was started and decided to continue with midline exploratory laparotomy when there were findings that involved more than the base of the cecum¹⁸.

Some anatomopathological studies have revealed that the most frequently affected organs are the appendix, ileum, colon and surrounding lymph nodes. In a series of cases in which 90 patients underwent surgery, 36 had involvement of a single organ (colon, ileum, or appendix) and 25 had involvement of at least three segments (colon, appendix, and cecum). Only two cases involved the cecum and sigmoid while one case had disseminated disease⁴. Its affinity for the ileocecal region provokes a granulomatous reaction that causes abdominal pain, obstruction and even perforation; this is known as eosinophilic peritonitis, as mentioned above.

Although the ileocecal location is the most frequent, there may be independent involvement of the terminal ileum, cecum, appendix, or ascending colon. Two macroscopic presentations have been described: pseudoneoplastic, characterized by thickening of the intestinal wall, and congestive ischemia with the presence of necrotic lesions¹⁷.

Despite developments in the basic understanding of the biology and transmission of the disease, very few improvements have been made in medical treatments such as chemotherapy. Clinical attempts

lack good controls, as parasitological criteria for cure are not easy to establish, especially knowing that the infection can probably be self-limiting in most humans. Experimental chemotherapy trials with thiabendazole, albendazole, ivermectin, santonin, milbemycin D, mebendazole and with as yet undisclosed novel compounds such as PF1022A have been conducted in both *A. cantonensis* and *A. costaricensis*, with variable effects on either larval or adult stages. It is clear that chemotherapy and attempts with new drugs must be improved, since it is a disease that can be fatal¹².

Surgical intervention remains the most effective strategy for the treatment of acute AA, since no convincing data have been obtained on the use of anthelmintic drugs, it should be treated according to the surgical guidelines for appendiceal neoplasms, where masses limited to the appendix should be treated with appendectomy and masses larger than two centimeters in diameter should undergo right hemicolectomy, including appendiceal resection¹⁷.

It is extremely important to educate the general population about the correct disinfection of fruits and vegetables before consumption and to raise awareness about the potential transmission of parasites through raw foods⁴. In the case presented we can observe a broad correlation with the literature in terms of clinical presentation and anatomopathological findings, where multiple organs were involved from the cecal appendix, cecum, and ascending colon. Histologically, there was eosinophilic infiltration of the intestinal mucosa and submucosa, as well as granuloma formation with ileocecal obstruction and necrosis. The treatment indicated in the literature showed a satisfactory clinical evolution despite the patient's age being a risk factor for post-operative complications.

AA represents a diagnostic challenge for many reasons, one of them is that although it is not a new disease, at the moment there is not a specific preoperative test that can be used, thus, the diagnosis is made after treatment. Knowledge and reporting of this disease should be increased, because it causes high morbidity, and can be prevented through education to the population, strengthening the knowledge of health personnel and the population in general.

Ethical Aspects

The case presented complied with the Declaration of Helsinki and the provisions of the international ethical guidelines for research, was submitted to the hospital's

quality control department, and the confidentiality of the information will be safeguarded and protected. The consent of the patient and a family witness was requested, explaining all the beneficial aspects that the information of the clinical case will contribute to public health.

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Occupational stress and mental health on frontline healthcare workers during COVID-19 pandemic

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Mireya Yamilet Magaña Salazar^{1*}, Sonia Jeannette Méndez de Robles², Simón Martínez Díaz³

1-2. San Juan de Dios National Hospital San Miguel, San Miguel, El Salvador.

3. Ministry of Education, San Miguel, El Salvador.

* Correspondence

✉ yamaisalma@gmail.com

1. ☎ 0000-0002-8061-8796

2. ☎ 0000-0002-7850-2049

3. ☎ 0000-0003-0228-2120

Abstract

Introduction. Occupational stress posed a relevant risk for mental health disturbances in healthcare workers during the 2019 Coronavirus pandemic. **Objective.** To determine the relationship between the level of occupational stress and mental health in front-line healthcare personnel against COVID-19. **Methodology.** An analytical cross-sectional study was carried out in the emergency and hospitalization areas of the San Juan de Dios National Hospital in San Miguel, from September to December 2020. A total of 121 workers participated. The occupational stress scales of the International Labor Organization and the abbreviated Goldberg scale were used. Variable correlation analysis was performed using Spearman's coefficient. **Results.** 59.5 % were female and 44.6 % were nursing staff. 89.3 % had a low level of stress and 79.3 % had an intermediate level of alteration in mental health with a predominance of anxiety (51.2 %) over depression (8.3 %) in nurses and general services personnel between 21 and 40 years. The analysis of the Spearman correlation determined a positive correlation between occupational stress and mental health disorders (R^2 0.218; $p = 0.016$) in workers. **Conclusion.** The study showed a low and intermediate level of occupational stress in mental health; with a positive correlation, which means that the increase in stress can favor the presence of alterations in the mental health status of the worker.

Keywords


Health personnel, COVID-19, occupational stress, mental health.

Resumen

Introducción. El estrés laboral significó un riesgo importante para la presencia de alteraciones de salud mental en trabajadores de salud, durante la pandemia de Coronavirus 2019. **Objetivo.** Determinar la relación del nivel de estrés laboral y salud mental en el personal asignado en primera línea de atención contra el COVID-19. **Metodología.** Se realizó un estudio transversal analítico en las áreas de emergencias y hospitalización del Hospital Nacional San Juan de Dios de San Miguel, de septiembre a diciembre de 2020. Participaron en total 121 trabajadores. Se utilizaron las escalas de estrés laboral de la Organización Internacional del Trabajo y la escala de Goldberg abreviada. El análisis de correlación de variables se realizó por el coeficiente de Spearman. **Resultados.** El 59,5 % de los estudiados son mujeres y el 44,6 % era personal de enfermería. El 89,3 % tenía bajo nivel de estrés y 79,3 % nivel intermedio de alteración en salud mental con predominio de ansiedad (51,2 %), sobre depresión (8,3 %) en enfermeras y personal de servicios generales entre 21 a 40 años. El análisis de la correlación Spearman determinó una correlación positiva entre el estrés laboral y la presencia de alteración de salud mental (R^2 0,218; $p = 0,016$) en el personal de primera línea. **Conclusión.** El estudio demostró un nivel de estrés laboral bajo e intermedio en salud mental; con relación positiva, lo que significa que el aumento de estrés puede favorecer la presencia de alteraciones al estado de salud mental del trabajador.

Palabras clave

Personal de salud, COVID-19, estrés laboral, salud mental.

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The authors declare there are no conflicts of interest.

Introduction

Occupational stress and mental health have become more relevant issues since the emergence of COVID-19 disease and its rapid spread from China to many countries around the world¹. Healthcare workers were specially affected by the increased exposure to risk factors inherent to their professional profile, lack of sufficient protective equipment, and inadequate workplace conditions^{1,2}.

The World Health Organization (WHO) reported that 14 % of the cases of COVID-19 occurred in healthcare workers³, and the Pan American Health Organization (PAHO) revealed that more than 570 000 healthcare workers were infected in the Americas⁴.

The Ministry of Health of El Salvador reported more than 15 446 infected cases on June 2020; 45 were health care workers⁵. The Epidemiology Unit of San Juan de Dios from San Miguel National Hospital (HNSJSM) recorded 511 infected employees until December 2020.

Contingency plans at the national level began with the WHO emergency appeal, which allowed the prioritization of resource supply actions and other guidelines involving health workers⁶. HNSJSM was a national referral center for the population of the eastern region of El Salvador during the pandemic. Its infrastructure and organization of functions were modified in order to respond to the emergency situation that arose. At HNSJSM, local strategies were designed for confronting the COVID-19 pandemic according to the complexity of the areas and available resources.

Uncertainty and exhaustion due to extensive and intense work shifts increased occupational risk for health service providers and evidenced alterations in mental health⁷⁻⁹.

The evaluation and measurement of occupational stress are essential to know the type of occupation and work environments that generate a higher level of stress, and that allows to obtain a diagnosis of the problem and the opportunity to develop an intervention, thus avoiding the effects on the health of workers alter their performance¹⁰. The effects can be physiological and cognitive, the latter being behavioral and emotional disturbances¹¹.

FUNPRES (Pro-Education Foundation of El Salvador) conducted a study on the Salvadoran population during the COVID-19 pandemic, which showed the presence of alterations in mental health¹², especially in those working in areas of direct patient care, which generates the need to explore possible psychological alterations in

El Salvador. It prompted this study to determine the possible relationship between occupational stress and mental health among frontline workers against COVID-19.

Methodology

An analytical cross-sectional study was carried out which measured the level of occupational stress and mental health. It estimated the correlation of both variables in multidisciplinary personnel stationed in the frontline of care in the emergency and hospitalization areas of COVID-19 of the HNSJDSM in the second semester of 2020.

The study population was the multidisciplinary personnel who worked in COVID-19 units at that time. A total of 178 people were distributed among nursing (99), medical (23), clinical laboratory (20), radiology (19), and general services (17) personnel. The inclusion criteria were: rotation through the selected units and acceptance of participation in the study.

Workers in the selected units were contacted through their immediate supervisors and were invited to participate through the WhatsApp application, where they received the link to the questionnaire. Responses were requested anonymously. Participants answered the questionnaire between September 2 and December 19, 2020.

The virtual questionnaire was elaborated in Google Forms[®], with closed questions and divided into four parts: the first contained the informed consent form, which was adapted from the WHO/Research Ethics Review Committee (WHO/ERC) informed consent form for clinical studies¹⁸. The second part asked for the respondent's general data; the third contained the International Labor Organization/World Health Organization (ILO/WHO) occupational stress assessment scale supported by Ivancevich and Matterson in 1989¹³. The fourth part, the abbreviated Goldberg scale (GHQ-28), was developed in 1978 from a modified version of the Psychiatric Assessment Schedule, which measured mental health status. The Spanish version was from Lobo, Perez-Echaverría, 1986¹⁴.

After accepting the informed consent, the worker could continue with the next part of the questionnaire; the completion of the general data, followed by the occupational stress evaluation scale that contained 25 items related to seven segments of the work activity: organizational climate, organizational structure, leader's influence, lack of cohesion, territory, technology and group support. Item responses were according to

a Likert scale, with the following options: never, rarely, occasionally, sometimes, frequently, usually, and always. Finally, they had to answer the GHQ-28 about mental health status, which contained 28 items grouped into four subscales: subscale A (somatic symptoms), subscale B (anxiety and insomnia), subscale C (social dysfunction), and subscale D (major depression). The respondent's answer was limited to their mental situation during the previous two weeks. The questionnaire application time was approximately 25 minutes.

The results related to work stress had a minimum score of 25 and a maximum of 175. The total score was in the following ranges: low-stress level when the result is less than 90.2 points; stress between 90.3 and 117.2; intermediate level between 117.3 and 153.2 and a high-stress level greater than 153.3 points¹⁵. For this study, the construct validity was by expert opinion, and the content validity was by a pilot test. Cronbach's coefficient was 0.908.

The standardization of the results of the mental health status measurement was carried out using Likert-type scoring¹⁶. Each question had four possible answers (a, b, c, d), which indicated progressively higher levels. These were assigned values from one to four, respectively, obtaining a minimum score of seven points and a maximum of twenty-eight for each subscale. The subscales were divided into three levels of alteration to evaluate the state of mental health. The low level from seven to 14 points, the medium level from 15 to 21 points, and the high level from 22 to 28 points. To evaluate the scale in general, the low level was from 28 to 56 points, the medium level from 57 to 84, and the high level from 85 to 112. Construct validity was performed by expert opinion and content validity in a pilot test. Cronbach's coefficient was 0.932.

Data processing and analysis were performed with Excel® version 2010 and

PSPP 4.0, a free version of SPSS®. The descriptive analysis of the respondent's profile was presented in frequency tables, including arithmetic mean, minimum and maximum value, and percentage. The normal distribution of the data was verified by the Kolmogorov-Smirnov test and the value obtained for the stress scale was 1.027 ($p = 0.242$) and for the mental health scale it was 1.278 ($p = 0.07$); the correlation of variables was verified by Spearman's coefficient.

The study was approved by the Local Research Ethics Committee of San Juan de Dios National Hospital of San Miguel and the ethical considerations of the Helsinki declaration version 2000¹⁷ were applied.

Results

A total of 121 workers participated in the study with an average age of 33.5 years (minimum: 21, maximum: 60). A total of 59.5 % were female; 38.8 % were male; and 1.7 % preferred not to disclose their gender. The distribution according to profession and area was as follows: 54 nurses (44.6 %), 17 physicians (14 %), 14 clinical laboratorists (11.6 %), 27 radiology (22.3 %), and nine general services (7.4 %). 73 % of the staff had worked more than three months in the area and 91 % performed their duties in rotating shifts. Job stress and mental health disorders were found mainly among those aged 21 to 40 years (80.1 %).

81.5 % of the nursing staff presented a low level of stress, in the case of the medical staff, all presented a low level of stress, as did the clinical laboratory staff. 92.6 % of the radiology staff and 88.9 % of the general services staff presented a low stress level. Thirteen percent of the nursing staff had an intermediate stress level, and 7.4 % of the radiology staff and 11.1 % of the general service staff also had an intermediate stress level. No workers with high stress levels were found. (Figure 1).

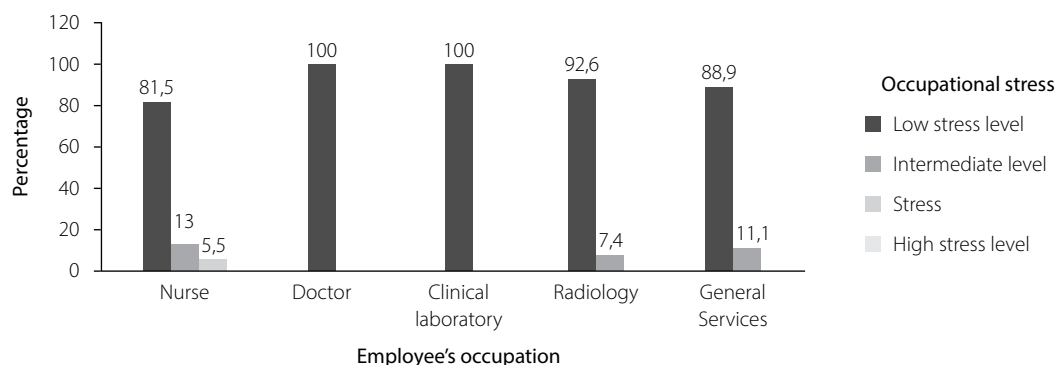


Figure 1. Occupations and their stress levels during 2020

Table 1 shows the results obtained from the occupational stress assessment. 89.3 % of the workers were at a low-stress level. There were no responses at a high level. Only 2.5 % reported stress.

On the other hand, the results according to the dimensions of the ILO-WHO scale showed that the organizational climate generates stress levels ranging from low to high (0.8 % - 81 %). The organizational struc-

ture reported low-level values of 82.6 % and 6.6 % of stress; data were not obtained for the high level. In the dimension of technology and leader's influence, the low level was 83.5 %, and the high-stress level was 1.7 % of the participants. In the lack of cohesion item, 89.3 % showed low-stress levels, and 0.8 % showed stress. In the group support item, 92.6 % showed low-stress levels and 1.7 % reached a high-stress level.

Table 1. Occupational stress scale and its dimensions

| Occupational stress scale and its dimensions (more specific evaluation of the scale) | | Level of occupational stress (general evaluation) | | | | | | | | | |
|--|--------------------|---|------|--------------|-----|--------|-----|------|-----|-------|-------|
| | | Low | | Intermediate | | Stress | | High | | Total | |
| | | n | % | n | % | n | % | n | % | n | % |
| Organizational climate level | Low-stress level | 95 | 78.5 | 3 | 2.5 | 0 | 0.0 | 0 | 0.0 | 98 | 81.0 |
| | Intermediate level | 11 | 9.1 | 5 | 4.1 | 0 | 0.0 | 0 | 0.0 | 16 | 13.2 |
| | Stress | 2 | 1.7 | 1 | 0.8 | 3 | 2.5 | 0 | 0.0 | 6 | 5.0 |
| | High-stress level | 0 | 0.0 | 1 | 0.8 | 0 | 0.0 | 0 | 0.0 | 1 | 0.8 |
| | Total | 108 | 89.3 | 10 | 8.3 | 3 | 2.5 | 0 | 0.0 | 121 | 100.0 |
| Organizational structure level | Low-stress level | 98 | 81.0 | 2 | 1.7 | 0 | 0.0 | 0 | 0.0 | 100 | 82.6 |
| | Intermediate level | 8 | 6.6 | 4 | 3.3 | 1 | 0.8 | 0 | 0.0 | 13 | 10.7 |
| | Stress | 2 | 1.7 | 4 | 3.3 | 2 | 1.7 | 0 | 0.0 | 8 | 6.6 |
| | High-stress level | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| | Total | 108 | 89.3 | 10 | 8.3 | 3 | 2.5 | 0 | 0.0 | 121 | 100.0 |
| Organizational territory level | Low-stress level | 103 | 85.1 | 5 | 4.1 | 2 | 1.7 | 0 | 0.0 | 110 | 90.9 |
| | Intermediate level | 3 | 2.5 | 5 | 4.1 | 0 | 0.0 | 0 | 0.0 | 8 | 6.6 |
| | Stress | 2 | 1.7 | 0 | 0.0 | 1 | 0.8 | 0 | 0.0 | 3 | 2.5 |
| | High-stress level | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| | Total | 108 | 89.3 | 10 | 8.3 | 3 | 2.5 | 0 | 0.0 | 121 | 100.0 |
| Group support level | Low-stress level | 106 | 87.6 | 5 | 4.1 | 1 | 0.8 | 0 | 0.0 | 112 | 92.6 |
| | Intermediate level | 2 | 1.7 | 2 | 1.7 | 2 | 1.7 | 0 | 0.0 | 6 | 5.0 |
| | Stress | 0 | 0.0 | 1 | 0.8 | 0 | 0.0 | 0 | 0.0 | 1 | 0.8 |
| | High-stress level | 0 | 0.0 | 2 | 1.7 | 0 | 0.0 | 0 | 0.0 | 2 | 1.7 |
| | Total | 108 | 89.3 | 10 | 8.3 | 3 | 2.5 | 0 | 0.0 | 121 | 100.0 |
| Lack of cohesion level | Low-stress level | 103 | 85.1 | 5 | 4.1 | 0 | 0.0 | 0 | 0.0 | 108 | 89.3 |
| | Intermediate level | 5 | 4.1 | 4 | 3.3 | 3 | 2.5 | 0 | 0.0 | 12 | 9.9 |
| | Stress | 0 | 0.0 | 1 | 0.8 | 0 | 0.0 | 0 | 0.0 | 1 | 0.8 |
| | High-stress level | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| | Total | 108 | 89.3 | 10 | 8.3 | 3 | 2.5 | 0 | 0.0 | 121 | 100.0 |
| Technology level | Low-stress level | 94 | 77.7 | 7 | 5.8 | 0 | 0.0 | 0 | 0.0 | 101 | 83.5 |
| | Intermediate level | 12 | 9.9 | 1 | 0.8 | 0 | 0.0 | 0 | 0.0 | 13 | 10.7 |
| | Stress | 2 | 1.7 | 2 | 1.7 | 2 | 1.7 | 0 | 0.0 | 6 | 5.0 |
| | High-stress level | 0 | 0.0 | 0 | 0.0 | 1 | 0.8 | 0 | 0.0 | 1 | 0.8 |
| | Total | 108 | 89.3 | 10 | 8.3 | 3 | 2.5 | 0 | 0.0 | 121 | 100.0 |
| Level of leader's influence | Low-stress level | 99 | 81.8 | 2 | 1.7 | 0 | 0.0 | 0 | 0.0 | 101 | 83.5 |
| | Intermediate level | 9 | 7.4 | 4 | 3.3 | 1 | 0.8 | 0 | 0.0 | 14 | 11.6 |
| | Stress | 0 | 0.0 | 2 | 1.7 | 2 | 1.7 | 0 | 0.0 | 4 | 3.3 |
| | High-stress level | 0 | 0.0 | 2 | 1.7 | 0 | 0.0 | 0 | 0.0 | 2 | 1.7 |
| | Total | 108 | 89.3 | 10 | 8.3 | 3 | 2.5 | 0 | 0.0 | 121 | 100.0 |

Table 2 shows the results obtained from the mental health evaluation. 79.3 % showed alterations at an intermediate level, 16.5 % at a low level, and only 4.1 % obtained alterations at a high level.

The results related to mental health status reported that 61.2 % presented a medium level of alteration in the psychosomatic symptoms subscale, 19.8 % showed a high level, and 19 % a low level. The anxiety symptoms subscale reported that 51.2 % had an intermediate level of anxiety, 35.5 % had a low level, and 13.2 % had a high level. With symptoms of social dysfunction in daily activities, 79.3 % showed impairment at intermediate level, 18.2 % at a low level, and 2.5 % at a high level. A low level of depression was found in 90.9 %, a medium level in 8.3 %, and a high level in 0.8 % (Table 2).

Figure 2 shows the level of mental health impairment according to the type of profession. On average, 77.9 % reached an intermediate level, 17.3 % a low level, and 7.93 % a high level. The intermediate level was in clinical laboratory personnel (85.7 %) and radiology (88.9 %). Only nursing, radiology, and general services had high levels of mental health disturbance (5.5 % -11.1 %).

The results of the correlation analysis through Spearman's correlation test (Rho) between occupational stress and mental health status show a positive relationship (Rho = 0.218; $p < 0.05$). It implies that the relationship before the elevation of the stress level also increases the level of alteration of the mental health status in workers (Table 3).

Discussion

During the COVID-19 pandemic, the evaluation of occupational stress and mental health of frontline workers was very relevant¹. Knowing the experience of personnel in this situation became a strategic point to improve human resource management with a focus on workplace safety.

Thus, it was found a correlation between occupational stress and mental health level in 121 interviewees, it shows how working conditions can contribute to the development of alterations in the worker's health with manifestations at the psychological level, especially in non-ordinary situations such as those experienced in the COVID-19 pandemic. Similarly, the results of studies conducted in Asian countries in a group of physicians and nurses indicate a correlation with high levels of occupational stress^{19,20}, in contrast to this study in which the levels were low.

The factors that may have influenced these results were: the period when the study

was due to a decrease in cases in El Salvador between September and December 2020. In addition, the hospital prepared a contingency plan during the pandemic (April 2020), which determined the general lines of action taken up by the head offices in their specific strategies considering some factors that affect working conditions and the state of mind of the health personnel according to the experience of other countries^{7,8,19,20}. Thus, the management oriented the improvement of the physical space, permanent supply of personal protection and biosafety supplies, and training of the personnel for the management of critical patients; Also, rest areas and schedules, improvements in food, recreational meetings for the care of emotions, continuous rotation of personnel, transfers with a prior medical evaluation, and the option of staying in the hospital for each worker.

In contrast to a study conducted in the Salvadoran population, which reported high values in anxiety and depression disorders¹², this study showed low values in health workers, similar to the findings of Kang *et al.* and Labrague *et al.* in 2020^{1,22}. However, Murat *et al.* (2021) and Magnavita *et al.* (2020), reported higher levels of stress and mental health compared to the rest of the society^{8,23}.

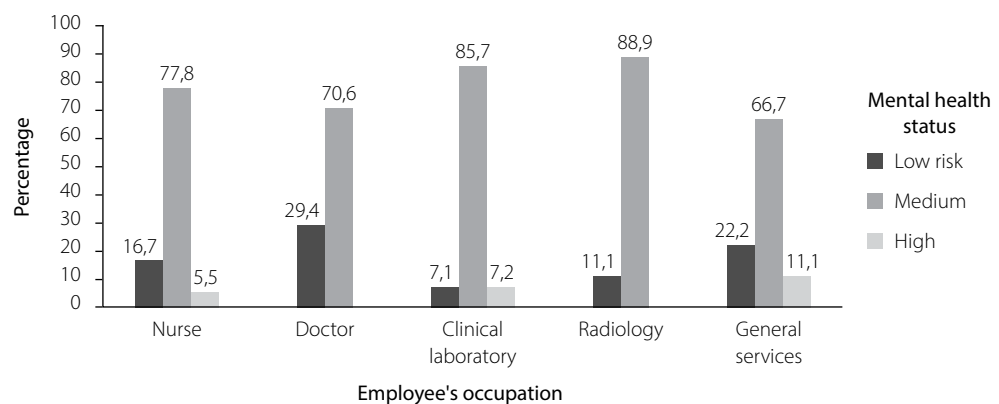
The lack of management of risk factors in the population, such as organizational support, additional disease knowledge, and preventive measures as received by health personnel, are elements that have improved worker resilience in the short term and allow them to adapt positively in stressful situations²⁴⁻²⁶. In 2020 Skalski *et al.* demonstrated the positive effect on the population when it benefits from interventions that improve mental health²⁷.

Regarding age, sex, profession, and time working in frontline areas, some differences showed that people who aged 21 to 40 years, women and nurses with more than three months in the area presented higher percentages of stress and mental health disorders. These results coincide with studies in 2020, which showed that women are more likely to have psychosocial risk than men^{28,29}. On the other hand, most nurses are female and are the closest to the patient throughout the care process^{30,31}. It increases the risk of exposure derived from care³².

Zhang *et al.* (2020) and Torrente *et al.* (2021) did not report results consistent with those previously mentioned. In their study, medical personnel were more affected by stress, anxiety, and depression^{33,34} and as for age, this research reported high levels of stress in young people and adults (21-50

Table 2. Distribution of altered mental status according to its subscales

| Mental health subscales (specific assessment by sub- scales) | | Level of alteration of mental health status (general evaluation) | | | | | | | |
|--|--------|--|------|--------|------|------|-----|-------|-------|
| | | Low | | Medium | | High | | Total | |
| | | n | % | n | % | n | % | n | % |
| Psychosomatic symptoms | Low | 14 | 11.6 | 9 | 7.4 | 0 | 0.0 | 23 | 19.0 |
| | Medium | 6 | 5.0 | 68 | 56.2 | 0 | 0.0 | 74 | 61.2 |
| | High | 0 | 0.0 | 19 | 15.7 | 5 | 4.1 | 24 | 19.8 |
| | Total | 20 | 16.5 | 96 | 79.3 | 5 | 4.1 | 121 | 100.0 |
| Anxiety | Low | 20 | 16.5 | 23 | 19.0 | 0 | 0.0 | 43 | 35.5 |
| | Medium | 0 | 0.0 | 61 | 50.4 | 1 | 0.8 | 62 | 51.2 |
| | High | 0 | 0.0 | 12 | 9.9 | 4 | 3.3 | 16 | 13.2 |
| | Total | 20 | 16.5 | 96 | 79.3 | 5 | 4.1 | 121 | 100.0 |
| Social dysfunction in daily activity | Low | 12 | 9.9 | 10 | 8.3 | 0 | 0.0 | 22 | 18.2 |
| | Medium | 8 | 6.6 | 85 | 70.2 | 3 | 2.5 | 96 | 79.3 |
| | High | 0 | 0.0 | 1 | 0.8 | 2 | 1.7 | 3 | 2.5 |
| | Total | 20 | 16.5 | 96 | 79.3 | 5 | 4.1 | 121 | 100.0 |
| Depression | Low | 20 | 16.5 | 88 | 72.7 | 2 | 1.7 | 110 | 90.9 |
| | Medium | 0 | 0.0 | 8 | 6.6 | 2 | 1.7 | 10 | 8.3 |
| | High | 0 | 0.0 | 0 | 0.0 | 1 | 0.8 | 1 | 0.8 |
| | Total | 20 | 16.5 | 96 | 79.3 | 5 | 4.1 | 121 | 100.0 |
| Social dysfunction in daily activity | Bajo | 12 | 9.9 | 10 | 8.3 | 0 | 0.0 | 22 | 18.2 |
| | Medio | 8 | 6.6 | 85 | 70.2 | 3 | 2.5 | 96 | 79.3 |
| | Alto | 0 | 0.0 | 1 | 0.8 | 2 | 1.7 | 3 | 2.5 |
| | Total | 20 | 16.5 | 96 | 79.3 | 5 | 4.1 | 121 | 100.0 |

**Figure 2.** Occupations with mental health impairment, period 2020**Table 3.** Correlation between occupational stress and mental health status, 2020

| Level of occupational stress | Level of mental health status | | | Total | χ^2 value | Significance χ^2 | Spearman's correlation | Spearman's significance |
|------------------------------|-------------------------------|--------------|------|-------|----------------|-----------------------|------------------------|-------------------------|
| | Low | Intermediate | High | | | | | |
| Low level | 20 | 85 | 3 | 108 | 10.12 | 0.038 | 0.218 | 0.016 |
| Intermediate level | 0 | 9 | 1 | 10 | | | | |
| Stress | 0 | 2 | 1 | 3 | | | | |
| Total | 20 | 96 | 5 | 121 | | | | |

years) in contrast to other studies where older adults were affected in addition to young people^{28,29}. The results in this study are likely due to the fact that the older staff did not have direct patient care functions and work teams had young adults.

This study also revealed that general service and clinical laboratory personnel presented high levels of occupational stress and mental health alterations. It is similar to what happened to nurse personnel since close contact with the patient increases work risk and stress, as showed in a study in Asia and Europe where physicians were more affected by this condition³⁵.

It is important to emphasize that the study has some limitations concerning the collection of information. It was impossible to obtain the opinion of all frontline personnel (pharmacy personnel and medical documents) even though meetings were in specific areas and individual consultations to provide explanations of all the doubts that arose. In addition, the result of the action plan, which could have changed stress levels, was not evaluated because it was not the object of the study; however, it is important to take it up in future post-pandemic follow-up research.

Finally, the study showed that it is necessary to undertake preventive and containment actions that can impact worker health and safety¹⁹⁻³⁵. Some preventive actions can lead to strength in human resource management with a focus on risk^{22,25} and work planning to identify vulnerable groups with particular needs⁸ and thus improve assignments²⁰. Despite the low-stress level identified, it is significant to consider early psychological support interventions for acute mental disorders²², as well as continuing education programs that contribute to the resilience of health personnel²⁴⁻²⁶. On the other hand, implementing new technologies, such as telemedicine, can facilitate the care process when the aim is to reduce direct contact as much as possible²⁹.

Concerning containment actions, it is necessary to prioritize the permanent provision of biosecurity measures¹⁹, detection tests³², and ensure that workers receive social security benefits for work injuries²⁰, and in turn, develop training programs that promote knowledge and skills in patient care and mental health for frontline personnel^{8,19,20}.

Conclusions

Healthcare personnel stationed on the front line of care during the COVID-19 pandemic showed occupational stress and alterations

in mental health. Even though high levels did not reach an alarming percentage to be a positive correlation between occupational stress and mental health status, they revealed personnel vulnerability before organizational and environmental conditions that can be improved not only in routine situations but also in global emergencies, these being effective strategies to reduce occupational risk and increase the quality of health care.

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Clinical-epidemiological characterization of patients under or equal to 40 years old with breast cancer

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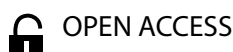
Laura Vanessa Vivas Bonilla

Dr. Maria Isabel Rodriguez National Women's Hospital (HNM). Mastology Unit, San Salvador, El Salvador.

* Correspondence

✉ lauravz90@gmail.com

ORCID 0000-0001-8354-8124



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Caracterización clínica-epidemiológica de pacientes menores o iguales a 40 años con cáncer de mama

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Abstract

Introduction. Breast cancer is among the first three cancers diagnosed in women worldwide. In women younger than 40 years old it occupies the first place in incidence. About 146 000 new cases are diagnosed globally in women under 40 years old. **Objective.** To identify the epidemiological and clinical characteristics of patients under or equal to 40 years old, diagnosed with breast cancer in a tertiary hospital specialized in women's care. **Methodology.** Descriptive cross-sectional study. Information was collected from 60 clinical records of patients diagnosed with breast cancer with an age less than or equal to 40 years old, between January 2019 and December 2020. **Results.** The highest number of cases was found in women between 39 and 40 years old (18.3 % each). Sixty percent were from the urban area; 80 % of the patients had parity between one and four children; 40 % were overweight and 58 % had no family history of breast cancer. The most frequent clinical stage was IIIA. The most common histopathological diagnosis was invasive breast carcinoma of non-special type (91.6 %), poorly differentiated with positive estrogen and progesterone receptors. **Conclusion.** Women aged less than or equal to 40 years old, with breast cancer, are patients from urban areas, overweight, with one to four children and no family history of breast cancer, with initial clinical presentation in locally advanced stages, with a diagnosis of invasive breast carcinoma of non-special type, poorly differentiated and positive estrogen and progesterone receptors.

Keywords

Breast neoplasms, female, risk factor, epidemiology.

Resumen

Introducción. El cáncer de mama se encuentra dentro de los tres primeros cánceres diagnosticados en las mujeres a nivel mundial. En las mujeres menores de 40 años ocupa el primer puesto de incidencia. Alrededor de 146 000 nuevos casos son diagnosticados en mujeres menores de 40 años a nivel global. **Objetivo.** Identificar las características epidemiológicas y clínicas de las pacientes con edad menor o igual a 40 años con diagnóstico de cáncer de mama en un hospital de tercer nivel especializado en la atención de la mujer. **Metodología.** Estudio transversal descriptivo. Se recolectó información de 60 expedientes de pacientes con diagnóstico de cáncer de mama con edad menor o igual de 40 años diagnosticados entre enero 2019 y diciembre 2020. **Resultados.** El mayor número de casos se encontró en las mujeres entre 39 y 40 años (18,3 %, cada uno). El 60 % era del área urbana; el 80 % de las pacientes tenía una paridad entre uno a cuatro hijos; el 40 % de se encontraba con sobrepeso y el 58 % no tenía antecedentes familiares de cáncer de mama. El estadio clínico más frecuente fue IIIA. El diagnóstico histopatológico más común fue carcinoma de mama invasivo de tipo no especial (91,6 %), pobremente diferenciado, con receptores para estrógeno y progesterona positivos. **Conclusión.** Las mujeres con edad menor o igual a 40 años, con cáncer de mama, son pacientes procedentes del área urbana, con sobrepeso, con uno a cuatro hijos y sin antecedentes familiares de cáncer de mama; con presentación clínica inicial en etapas localmente avanzadas, con diagnóstico de carcinoma de mama invasivo de tipo no especial, pobremente diferenciado y receptores para estrógeno y progesterona positivos.

Palabras clave

Neoplasias de la mama, mujer, factor de riesgo, epidemiología.

Introduction

Breast cancer is one of the best-known malignancies. It is among the first three cancers diagnosed in women in both developed and developing countries^{1,2}. Despite high incidence rates, the five-year survival

of women diagnosed with breast cancer is about 90 % in developed countries³. Advances in treatment and early detection, have decreased breast cancer mortality in all age groups, nevertheless for women of younger age it remains a risk factor for lower survival worldwide⁴.

According to the Global Cancer Observatory², about 247 953 new cases of breast cancer were detected in 2020 in women under 40 years old globally². The trend of breast cancer in young women is variable in different parts of the world. In women under 40 years old, breast cancer ranks first in incidence worldwide at 27.9 %, and third in women under 30^{2,4}. The age-standardized incidence in women under 40 years old is slightly higher in developed countries (8.8) than in developing countries (5, 4)⁵. The lowest rates of breast cancer in young women are from East and Southern African countries, while the highest rates are from Europe and North America^{4,5}.

In the Latin American and the Caribbean region a total of 210 100 cases of breast cancer was registered in 2020, representing 9.3 % of the total number of cases in the world. Breast cancer in women under 40 years old in this region accounts for 25.8 %, and ranks first among all cancers in this age group^{2,4}.

By the year 2020, breast cancer cases in El Salvador represented 16.4 % of all cancers, at an incidence rate of 40.5 cases per 100 000 inhabitants². From data obtained in a study conducted in the country in 2018, it was evidenced that the incidence of breast cancer in women under 40 years old amounted to 13.1 %⁶.

Early breast cancer has a low incidence compared to breast cancer in postmenopausal patients and is associated with a more aggressive clinical presentation, delayed diagnosis due to low suspicion of malignancy at the time of clinical assessment, and poorer treatment outcomes^{7,8}.

Between 2019 and 2020, the National Women's Hospital admitted 392 patients diagnosed with breast cancer. Of these, 60 patients were women under the age of 40 years, and were in advanced localized clinical stages with histologically aggressive subtypes, which can compare with international results in this age group.

This study allows to know the epidemiological and clinical characteristics of patients under 40 years old diagnosed with breast cancer in a third level hospital specialized in women's care, during the years 2019 and 2020, in order to contribute to early diagnosis, which is the basis for adequate treatment.

Methodology

A descriptive cross-sectional study was conducted at the National Women's Hospital, a tertiary health care facility specializing in women's care, in San Salvador. Sixty patients with breast cancer were identified through

the review of clinical records, in the period from January 2019 to December 2020.

Inclusion criteria were: patients aged 40 years or younger, seen for the first time in the breast or oncology service, diagnosed with breast cancer for the first time, with histopathology and immunohistochemistry report. Exclusion criteria were: patients with non-primary breast cancer and clinical records with incomplete information.

The variables included in the study were: age, marital status, schooling, area of origin, age at menarche, parity, age at first birth, lactation time, body mass index (BMI), family history, initial clinical stage, histopathologic outcome, degree of histologic differentiation and molecular classification.

With the support of the Department of Statistics and Medical Documents of the National Women's Hospital, the clinical records of the patients included in the study were reviewed. Data collection was carried out by the researcher using a digital data collection form, previously designed based on the identified variables, using the Microsoft Forms application. Each form could only be viewed by the researcher, to guarantee the confidentiality of the patients' data. The data from each document were analyzed with the Microsoft Excel program, through measures of central tendency and expressed through tables and graphs.

The research complied with the ethical principles established in the Declaration of Helsinki. The clinical records for data collection were used within the hospital facilities. With the data obtained, a database was created without identifying the patients' names, using only the file number, which was managed solely by the researcher.

Results

Epidemiological profile

71.6 % of the patients diagnosed were over 34 years old. The most frequent ages were 39 and 40 years with 18.3 % each. The youngest patient diagnosed with breast cancer was 25 years old (Figure 1).

The geographical distribution of the patients showed that 60 % were from urban areas. The marital status of free union represented the highest percentage (41.6 %), followed by married women (35.0 %) and single women (23.4 %).

The average age of menarche in the patients was 12 years in 30 %; 10.0 % at 11 years and 1.7 % at 16 years. 85 % of the patients had at least one child; one was gestational and only 13.3 % were nulliparous (Figure 2). The 3.3 % reported breastfeeding for a period

between six months and one year; 28.3 % between one and two years; 10 % for more than two years and 1.6 % did not breastfeed.

The nutritional condition of 33 % of the patients was obese: 20 % were obese grade I, 8 % were obese grade II, and 5 % were obese grade III. 40 % were overweight and 27 % were of normal weight.

Fifty-eight percent of the patients reported no family history of breast cancer; 8.3 % reported having this history in a first-degree relative; 11.6% in second-degree relatives and 1.6 % with a third-degree relative. 20 % of the women did not specify this data.

According to staging by clinical examination and TNM⁹, patients were classified as stage IA (3.3 %), IIA (11.6 %) and IIB (20 %). 30 % were stage IIIA, 26.6 % were stage IIIB, 3.3 % were stage IIIC and 5 % were stage IV (Figure 3).

The most frequent histological type of cancer was non-special type invasive breast carcinoma (91.6 %), followed by 5 % of carcinoma with apocrine differentiation; invasive lobular carcinoma with 1.7 %, and carcinoma with medullary pattern with 1.7 % (Figure 4).

According to the degree of histologic differentiation, 48 % were poorly differentiated (grade 3), 42 % moderately differentiated (grade 2) and 10 % (grade 1) well differentiated.

Regarding the molecular subtype obtained by immunohistochemistry tests, 40 % were reported as luminal B, 37 % as

triple negative, 15 % as HER2/Neu receptor positive, and 8 % as luminal A (Figure 5).

Discussion

Recent studies describe that the diagnosis of breast cancer in patients under 35 years old increases the risk of death by 5 % per year⁷, which has led to study the epidemiological and clinical characteristics of breast cancer in patients 40 years old or younger, who are considered young patients⁴⁷. The patients presented mainly locally advanced clinical stages, with histological diagnosis of non-special type invasive breast carcinoma, poorly differentiated and positive estrogen and progesterone receptors.

In a study conducted at the Cancer Institute of El Salvador in 2018, it was evidenced that breast cancer is diagnosed more frequently in women after the age of 50 years (62.5 %), with a low frequency in women between 20 and 39 years (13.1 %), but a significant increase of this disease is observed from the age of 40 years (8.1 %) and 45 years (16.3 %)²⁶.

The results of this research are related to the findings of the Cancer Institute of El Salvador, since a low incidence is reported in younger patients and an increase is presented after 35 years of age with a higher frequency in women between 39 and 40 years old, which is evidence of the exponential incidence of breast cancer.

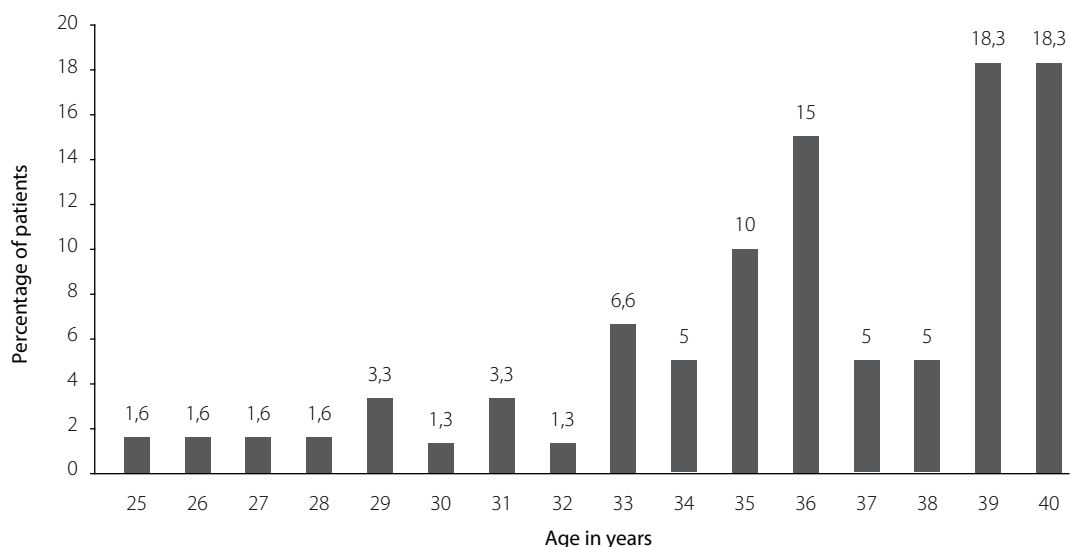


Figure 1. Age of patients at the time of the breast cancer diagnosis

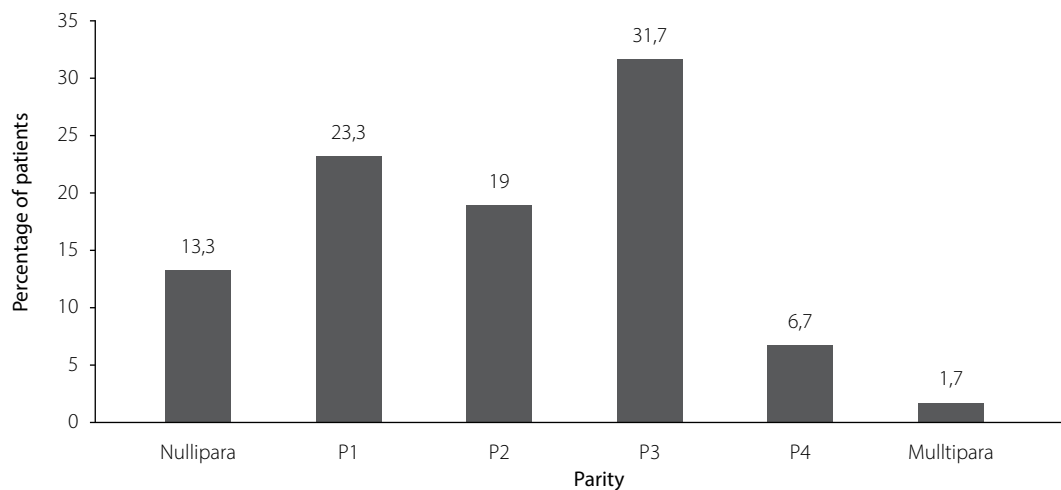


Figure 2. Population distribution according to parity

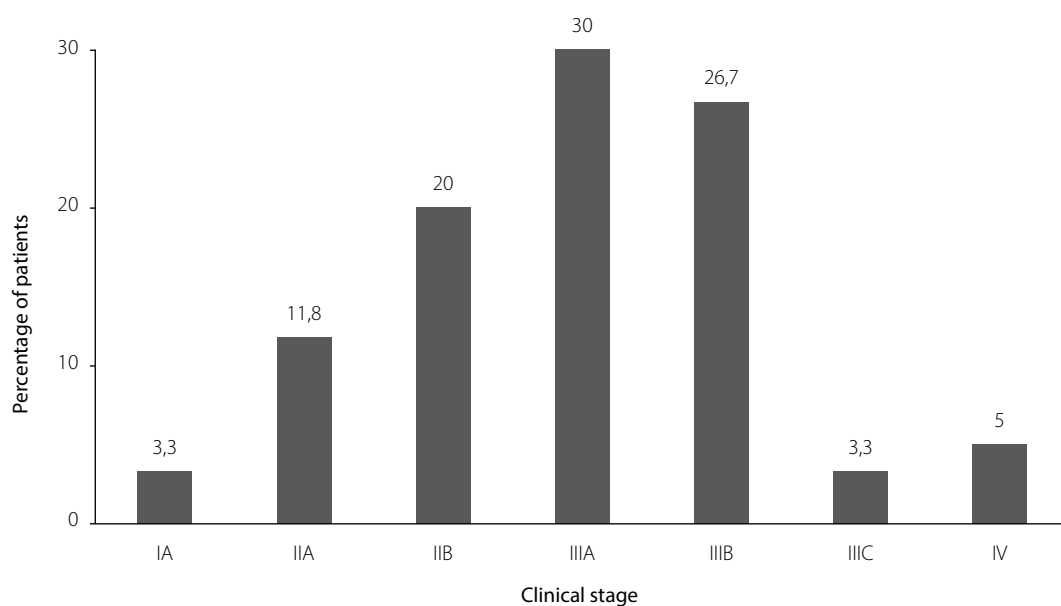


Figure 3. Population distribution according to breast cancer clinical stage at the time of diagnostic

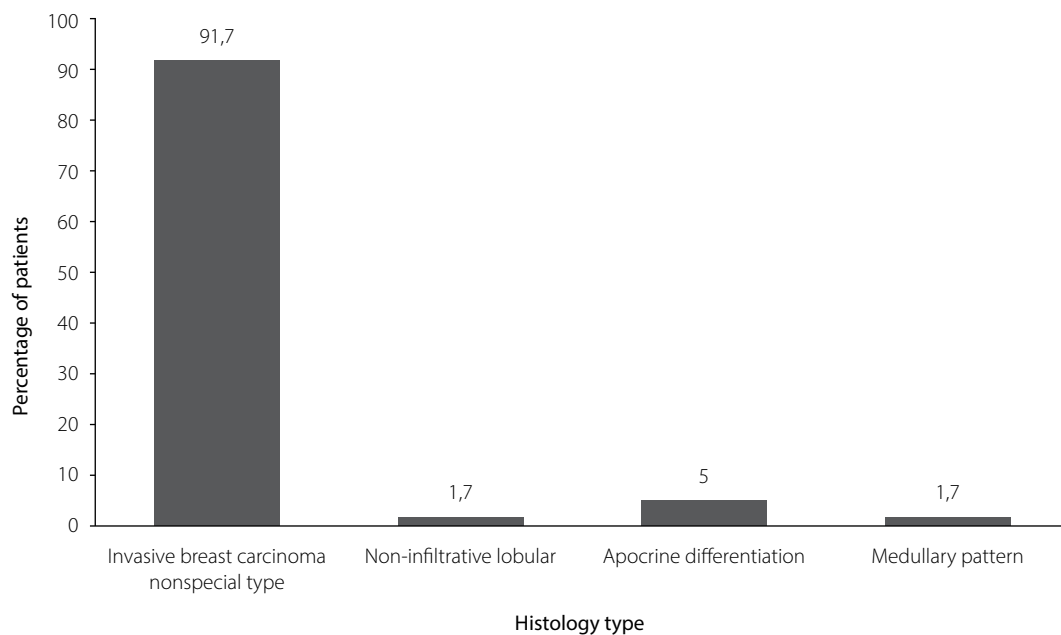


Figure 4. Distribution according to histology type of population under study

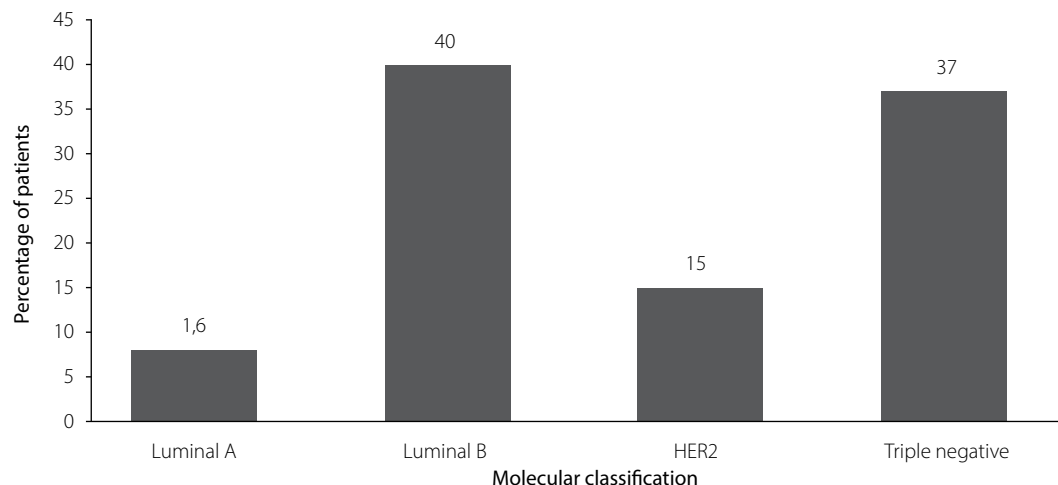


Figure 5. Frequency of determined molecular subtypes according to immunohistochemistry

Most of the patients come from urban areas. This may be related to the place where the study was conducted, given that 70.9 % of the population of San Salvador is from urban areas¹⁰. However, the delay in diagnosis may be related to the waiting time between the patient's identification of the condition and the request for medical attention¹¹, i.e., patients are diagnosed at more advanced stages and more aggressive treatments are necessary.

Among other factors related to breast cancer, hormonal stimulation has a great influence; therefore, the age of menarche is an important factor¹². It is estimated that the risk of breast cancer decreases by about 9 % for each year of delay in menarche^{12,13}; in the population studied, it was observed that the highest percentage of patients had menarche at an average age between 12 and 13 years.

The American Cancer Association has reported that having children before the age of 30 decreases the incidence of breast cancer³. In fact, there is considered to be a 3 % risk reduction for each full-term pregnancy a woman has and there is a 5 % increased risk for each year of delay in the first full-term birth^{3,12}. Similarly, for each year of cumulative breastfeeding, the risk of breast cancer is reduced by 4.3 %^{1,13}. It can be observed that, in spite of being young patients, most of them had between one and four children; more than 50 % of the patients were under 30 years old. Twenty-eight percent breastfed between one and two years. The presence of all these protective factors in the group of patients differs from the data obtained in some developed countries due to cultural differences^{7,14,15}. In Latin America, the fertility rate is higher as patients are younger¹⁶.

Family history in young patients is the main risk factor for breast cancer, especially when diagnosed in a first-degree blood

relative at an early age^{1,14}. The findings in this study differ from that premise, as 58 % of the patients had no family history of breast cancer.

Recent studies have shown that overweight is one of the main exogenous risk factors for breast cancer in both premenopausal and postmenopausal women¹⁷. A diet high in animal fat from mainly red meat and high-fat dairy shows up to a 50 % increased risk for breast cancer¹⁸.

Excess adipose tissue generates an increased risk of breast cancer through several pathways: increased sex hormone levels through increased aromatase and 17- β -hydroxysteroid dehydrogenase activity, reduced glucose uptake and, therefore, generation of a hyperinsulinemic state. Consequently, there was a reduction in sex hormone-binding hormone (SHBG) levels, increased release of IL-6, TNF- α , leptin and decreased adiponectin^{19,20}.

In premenopausal patients, physical exercise has been associated with a 23 % reduction in breast cancer risk^{12,20}. In this investigation, the highest percentage of patients were overweight and with some degree of obesity.

Based on the TNM21 staging in the initial clinical evaluation, it is evident that advanced localized stages predominate in this group of patients, which present with palpable tumor, this being the main cause of consultation^{7,22,23} and with lymph node involvement, both factors related to poor prognosis due to late diagnosis and advanced stages^{22,24,25}.

Many studies have shown that breast cancer in young patients presents in more advanced stages^{26,27}, since the low suspicion of this pathology, due to the age of the patients, is one of the main factors in the diagnostic delay^{23,28}.

The lack of a routine mammographic study in patients younger than 40 years

contributes to this, as it presents more often with a palpable mass than with a screening mammography finding^{22,25}.

Similarly, in premenopausal patients, imaging studies may be reported with probably benign findings, thus contributing to the delay in diagnosis²³, which is the reason some authors recommend the use of breast tomosynthesis as a more accurate diagnostic method^{29,30}.

A study conducted at St. Louis Hospital, Missouri, showed that patients under 40 years old had palpable tumors larger than two cm (T2/T3) in 50.4 % and nodal involvement in 44 %^{26,28}. A study at Mount Sinai Medical Center, New York, showed that patients younger than 35 years of age had larger tumors, more lymph node involvement (50 % vs. 37 %) and a higher probability of being diagnosed with stage II or III cancer (60 % vs. 43 %) than patients older than 36 years¹².

The most common histological type was invasive breast carcinoma of non-special type in 91.6 % of the studied patients. In a study conducted between 2002 and 2010 at the Central University Hospital in Osijek, Croatia, in which the characteristics of breast cancer in patients under 40 years of age and postmenopausal patients were compared, it was shown that invasive breast carcinoma of non-special type was the most frequent histological type in both groups: 70 % in young patients and 59.8 % in postmenopausal patients^{27,31}.

In terms of histologic grade, poorly differentiated or grade III tumors were the most common, occurring in 28 % of the patients. This is comparable with the results obtained in the study carried out at the University Clinical Hospital of Valencia, Spain, in which 36.4 % of patients under 35 years old with a diagnosis of breast cancer presented poorly differentiated tumors⁷.

At present it is important to classify tumors at the molecular level, since each subtype presents different behavior and aggressiveness. According to the different patterns of gene expression, so will be the impact on prognosis^{8,31,32}. Based on immunohistochemical expression according to HER2, estrogen receptor (ER), progesterone receptor (PR) and Ki67 markers, and following the criteria of the St. Gallen International Expert Consensus of 2011, the tumors were classified according to their molecular level. Following the 2011 St. Gallen International Expert Consensus criteria, tumors were classified as triple negative (ER-/PR-/HER2-), HER2 overexpressed, Luminal A (ER+/PR+/HER2-/Ki 67 < 14 %), Lu - minal B (ER+/PR+/HER2-/Ki-67 > 14 %)^{33,32}.

Molecular subtypes in patients younger than 40 years old have been shown to be variable according to the type of population studied^{24,34}. The results of the study performed in Valencia, Spain, in which the molecular subtype was compared in premenopausal versus postmenopausal patients, showed that estrogen and progesterone receptor expression was similar in both groups (70 % and 59.3 % premenopausal and 71 % and 68 % in postmenopausal). HER2 overexpression predominated in young patients (28 % vs. 22 %). In contrast, the triple-negative subtype occurred more frequently in postmenopausal patients (16.8 %) than in premenopausal patients (13.5 %)⁷.

In a study conducted in Croatia, a higher incidence of triple-negative breast cancer was found in patients younger than 40 years old compared to patients older than 60 (32 % and 10 %, respectively), HER2-positive tumors in both groups without statistical significance (20 % and 24 %). The presence of estrogen and progesterone receptors was higher in patients over 60 years old (67 % and 54 %), compared to 43 % and 44 % in patients younger than 40 years old³⁵.

In the results obtained, the most common molecular subtype (40 %) was luminal B, a subtype with positive hormone receptors and a high rate of cell proliferation, followed by triple negative, with 37 %. Triple-negative cancer correlates with a shorter survival time³⁶. Despite the obtained information on clinical presentation and histopathological report, some files lacked important information on risk, lifestyle, biological and reproductive factors, which became one of the limitations for the research.

Results achieved from this study show the heterogeneity of breast cancer, in terms of its presentation and behavior in this stage group of patients with age less than or equal to 40 years old. It is evident that most of the patients have overweight and obesity as a risk factor, therefore, strategies of food education and promotion of physical activity should be implemented, since they contribute to prevent the development of breast cancer, as these actions are associated to weight loss. This reduces the inflammatory microenvironment, improves antitumor immunity and lowers estrogen levels²⁰.

The data gathered established that the majority of patients had some conditions that are considered important for reducing the risk of breast cancer: factors such as menarche, parity, breastfeeding period and family history, which suggests studying the genetics of tumors in young women, since BRCA 1 and BRCA 237 gene mutations have

a greater association with breast cancer and occur in a higher percentage in premenopausal patients (3 %) than in postmenopausal patients (6 %) ^{31,32,36}.

Therefore, it is important to strengthen the health system with the accessibility to genetic studies that can be used for this age group of patients, to establish the origin of the disease and to be able to predict the behavior, since these factors directly influence the treatment and prognosis of this group of patients. By knowing the genetic behavior, it will be possible to individualize each case and thus improve the prognosis.

Conclusions

The characteristics of the patients with breast cancer were: patients older than 35 years old, from the urban area, with low schooling, overweight, and without family history of breast cancer; in advanced localized stages; with histological diagnosis of invasive breast carcinoma of non-special type, poorly differentiated and positive estrogen and progesterone receptors.

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Histopathological findings in lungs of COVID-19 infected subjects. A systematic review and meta-analysis

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María Virginia Rodríguez Funes^{1*}, Héctor A. Herrera Huezos², Andrea Ortiz Segura³, Cecilia Belem Osorio⁴, Dennys Molina González⁵, Verónica Reina Meléndez⁶, Juan José Vindell González⁷, Luis Ortiz-Muñoz⁸, Gabriel Rada⁹

1. Rosales National Hospital and Salvadorans for Scientific Evidence in health (SECIENSA), San Salvador, El Salvador.

2-6. SECIENSA, San Salvador, El Salvador.

7. SECIENSA y University of El Salvador, San Salvador, El Salvador.

8. UC Evidence Center, Cochrane Chile Associated Center, Pontifical Catholic University of Chile.

9. Epistemonikos Foundation, UC Evidence Center, Cochrane Chile Associated Center, Pontifical Catholic University of Chile, Department of Internal Medicine, Pontifical Catholic University of Chile Faculty of Medicine.

*Correspondence

✉ virginiarodriguezf61@gmail.com

1. 0000-0002-1398-7073

4. 0000-0002-3774-6717

7. 0000-0002-4640-4452

2. 0000-0003-4347-679X

5. 0000-0002-8034-0763

8. 0000-0001-6449-2153

3. 0000-0003-3314-9955

6. 0000-0002-1168-3594

9. 0000-0003-2435-0710

Abstract

Introduction. COVID-19 is a new disease that required prompt results from research. One approach to understanding its pathophysiology is to know the histopathological damage generated in the lungs of those affected. **Objective.** To provide a rigorous summary of the available evidence on pulmonary histopathological findings in patients with COVID-19. **Methodology.** A systematic review with a meta-analysis of proportions was developed. Primary studies of any design that had primary data on histopathologic findings of lungs in COVID-19 patients were included. Reviews and guidelines were excluded. Data sources were the Living Overview of Evidence centralized repository, PubMed/Medline, LitCovid, the World Health Organization COVID-19 database, and medRxiv until April 3, 2021. A risk of bias assessment was performed using the Joanna Briggs Institute tools for case series and case reports. Each histopathologic pulmonary finding was extracted. The frequencies found were calculated, and the data for the most frequent findings were summarized in meta-analyses using the Der Simonian-Liard random-effects method. Heterogeneity was measured. **Results.** Inclusion criteria were met by 69 articles totaling 594 subjects. Thirty-five articles were at low risk of bias. Meta-analysis of proportions showed diffuse alveolar damage in 0.62 (95 % CI 0.51-0.72), I² 59 % (p < 0.01), in its early phase (85.14 %). **Conclusion.** Early diffuse alveolar damage was the most frequent histopathological finding in lung specimens from patients with COVID-19.

Keywords

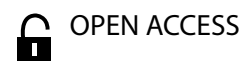
COVID-19, systematic review, autopsies, pathology, lung.

Resumen

Introducción. La COVID-19 es una nueva enfermedad que requería resultados pronto provenientes de la investigación. Un abordaje para la comprensión de su fisiopatología es conocer el daño a nivel histopatológico que genera en los pulmones de los afectados. **Objetivo.** Proveer un resumen riguroso de la evidencia disponible sobre los hallazgos histopatológicos pulmonares en pacientes con COVID-19. **Metodología.** Se desarrolló una revisión sistemática con metaanálisis de proporciones. Se incluyeron estudios primarios de cualquier diseño que tuvieran datos primarios de hallazgos histopatológicos de pulmones en pacientes COVID-19. Se excluyeron revisiones y guías. Las fuentes de información fueron el repositorio centralizado Living Overview of Evidence, PubMed/Medline, LitCovid, la base de datos COVID-19 de la Organización Mundial de la Salud, y medRxiv hasta el 3 de abril 2021. La evaluación del riesgo de sesgos se realizó utilizando las herramientas del Instituto Joanna Briggs para series de casos y reportes de casos. Se extrajo cada dato de hallazgo pulmonar histopatológico. Se calcularon las frecuencias encontradas y los datos de los hallazgos más frecuentes fueron resumidas en metaanálisis usando el método de efectos aleatorios de Der Simonian-Liard. Se midió la heterogeneidad. **Resultados.** Los criterios de inclusión fueron cumplidos por 69 artículos sumando 594 sujetos. Presentaron bajo riesgo de sesgos 35 artículos. El metaanálisis de proporciones mostro daño alveolar difuso en 0,62 (IC 95 % 0,51-0,72), I² 59 % (p < 0,01), en su fase temprana (85,14 %). **Conclusión.** El daño alveolar difuso temprano fue el hallazgo histopatológico más frecuente en muestras pulmonares de pacientes con COVID-19.

Palabras clave

COVID-19, revisión sistemática, autopsia, patología, pulmón.



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Hallazgos histopatológicos pulmonares asociados a COVID-19. Una revisión sistemática y metaanálisis

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Conflicts of interest:

The authors declare there are no conflicts of interest.

Introduction

COVID-19 is an infection caused by the SARS-CoV-2 coronavirus. It was initially identified in Wuhan, China, on December 31, 2019; three months later, nearly half a million infections had been identified across 197 countries, leading the World Health Organization to declare a COVID-19 pandemic on March 11, 2020^{1,2}.

The main source of SARS-CoV-2 transmission is the airborne route, through droplets produced in the respiratory tract and by contact. An average incubation period of 5.1 days (95 % CI, 4.5 to 5.8 days) has been reported, but variations may occur depending on the patient's immune status¹. The most frequently reported mild to moderate symptoms are fever 88.7 % (95 % CI 84.5-92.9 %), cough 57.6 % (95 % CI 40.8-74.4 %), and dyspnea 45.6 % (95 % CI 10.9-80.4 %)³, with 17.5 % of infected patients being asymptomatic¹. Complications occurred in 20.3 % (95 % CI 10-30.6 %) and the most frequent complications were: acute respiratory distress syndrome at 32.8 % (95 % CI 13.7-51.8 %); acute cardiac damage at 13 % (95 % CI 4.1-21.9 %), acute renal damage 7.9 % (95 % CI 1.8-14 %) and shock 6.2 % (95 % CI 3.1-9.3 %)³. In relation to mortality, a variation from 0.5 % to 13.9 % (95 % CI 6.2-21.5 %)^{2,4} has been described, depending on the context and age groups in which they have been reported.

Laboratory findings described for the disease are hypoalbuminemia 75.8 %, (95 % CI 30.5-100 %), high C-reactive protein 58.3 % (95 % CI 21.8-94.7 %), high lactate dehydrogenase (LDH) 57 % (95 % CI 38-76 %), lymphopenia 43.1 %, (95 % CI 18.9-67.3 %), and high erythrocyte sedimentation rate 41.8 % (95 % CI 0.0-92.8 %)⁵.

Initially, there were two theories about the pathophysiology of respiratory distress syndrome; the first dealt with direct damage to lung tissue that generates diffuse alveolar damage. It emphasizes the central role of diffuse injury to the epithelium up to the involvement of the endothelium of the distal pulmonary acini³; the second, which presumes that COVID-19 generates indirect damage resulting from a complication caused by coagulopathy and thrombosis. The endothelial injury caused by the disease breaks pulmonary vessel regulation, producing a ventilation-perfusion imbalance that promotes thrombogenesis and thrombosis⁴. Indirect clinical findings that supported this latter theory are as follows: a. High levels of D-dimer reported in several patients; b. Reports of clinical improvement of patients with heparins; c.

High incidence of thrombosis in critically ill patients; d. and some references to findings reported in autopsies^{4,5}.

Histopathological examinations of the affected lungs could show the morphological changes and guide a better understanding of the pathophysiology of respiratory failure, respiratory distress syndrome, and consequent death. Several reports on these findings have been published until April 2021, so it might be appropriate to make a systematized summary through an innovative and agile process with technological tools, which is why the present study aims to provide a systematic review with meta-analysis of the evidence available at that date, on the pulmonary histopathological findings of autopsies and biopsies of patients with COVID-19.

Methodology

This systematic review has been prepared according to the PRISMA 2020 guidelines⁶ and is part of a global project, with a general protocol established shared objectives and multiple evidence synthesis methodologies. This was conducted in parallel by working groups, which dealt with different questions related to COVID-19. This protocol was previously published⁷. The protocol for this specific systematic review was adapted to their requirements and registered in the PROSPERO platform obtaining the registration number CRD42020190598. A core team called the "COVID-19 L-OVE Working Group" coordinated the tasks supporting the self-research of all questions and provided methodological support. This question was submitted by the author team and accepted by this core team to participate in the Global Project⁷.

Eligibility criteria

The inclusion criteria for studies were: any quantitative primary study design and systematic reviews with raw data allowing calculation of frequencies for each specific histopathological finding found in the lungs of patients with COVID-19, in which any approach [autopsies (open or minimally invasive), biopsies] was used, with full text available, in any publication status and any language approachable for translation.

The excluded studies were: animal findings, findings of coronaviruses other than SARS-CoV2, cases of prolonged or convalescent period COVID, editorials, commentaries, narrative reviews/autopsy biosafety guidelines, or any other documents on autopsy procedures or biosafety protocols for specimen handlers, articles classifying

causes of death or only with photographs of histopathological findings but without textual description, as well as articles describing molecular methods of analysis or studying inflammatory markers.

Types of participants

Histopathological findings had to come from samples of confirmed COVID-19 cases, defined and accepted by the study authors (Rt-PCR reverse polymerase chain reaction, chest X-ray, chest CT scan, or any other approved diagnostic method), regardless of age, sex, outcome (alive or deceased), and in-hospital or outpatient management.

Condition Type

COVID-19 active.

Type of results

Primary outcome: Individualized pulmonary histopathologic findings. This variable was left open to introducing all possible findings and not to exclude any of them.

Secondary outcomes: Demographic characteristics of the included subjects, place of death (intra-hospital/extra-hospital) (Table 1).

Sources of Information

Electronic sources

The principal source used was the Epistemonikos Database⁸, and within this, the L-OVE platform⁹. The Epistemonikos platform maintenance team conducted the literature search using the following approach: 1. The search terms relevant to the population and results were identified as components of the search strategy, using Word2vec technology for the body of documents available in the database; 2. There was a discussion on search terms with content and method experts to identify relevant, irrelevant, or missing terms; 3. A sensitive Boolean strategy was created to track relevant terms; 4. Items not detected by Boolean were iteratively analyzed; and 5. The strategy was refined.

The artificial intelligence algorithm used in the Coronavirus/COVID-19 topic of the L-OVE platform provided instant notifications by identifying articles with a high similarity of being eligible. The authors tracked those notifications related to pulmonary histologic findings on COVID-19 from May 1, 2020, to April 3, 2021. Additional searches were performed using highly sensitive descriptors in PubMed/MEDLINE and the WHO database on Covid-19. The following electronic databases were also searched for full text:

LitCovid, BioRxiv, and medRxiv. These databases were also searched until April 3, 2021. There were no restrictions on study design, publication status, or language in any search.

Other sources

To identify articles that may have been left out of the initial electronic search, the following was as follow: 1. The reference list of other systematic references and primary studies was screened; 2. The reference list of narrative reviews and other papers was sifted; 3. A review of UN and regulatory agency websites or databases reporting on COVID-19 was conducted; 4. E-mails were sent to contact each of the authors of the included studies to request additional publications and more data on the studies that were unclear or not mentioned.

Search strategy

The following search strategy was used in Epistemonikos database and PubMed/MEDLINE (coronavir* OR coronavirus* OR "corona virus" OR "corona virus" OR "corona virus" OR "corono virus" OR "corono virus" OR hcov*OR "COVID-19" OR covid19* OR "covid 19" OR "2019- nCoV" OR cv19* OR "cv- 19" OR "cv 19" OR "n-cov" OR ncov* OR "sars-cov-2" OR "sarscov2" OR (wuhan* AND (virus OR viruses OR viruses OR viral) OR coronav*) OR (covid* AND (virus OR viruses OR viral)) OR "sars-cov" OR "sars-cov" OR "sars-cov" OR "sars- coronavirus" OR "severe acute respiratorysyndrome" OR "mers-cov" OR "mers cov" OR "middle east respiratory syndrome" OR "middle east respiratory syndrome" OR "middle east respiratory syndrome" OR "COVID- 19- related" OR "SARS-CoV-2-related" OR "SARS-CoV2-related" OR "2019-nCoV-related" OR "cv-19-related" OR "n-cov-related") AND "autopsy" OR "autopsies" OR "pathology" OR "pathology features" OR "histology" OR "biopsy" OR "thrombosis".

Selection process

The literature search results in Epistemonikos were automatically into the L-OVE Platform (automated finding), where duplicity was identified through an algorithm. It compared unique identifiers (database ID, DOI, study ID record) and citation details (e.g., authors' names, journal, year of publication, volume, number of pages, article title, and article abstract).

On the L-OVE platform, two investigators independently screened the titles and abstracts submitted by the search against the inclusion criteria. Besides, they obtained full texts for all titles that appeared to meet the inclusion criteria or additional analysis to decide inclusion. The two investigators

Table 1. Characteristics of the studies and patients included

| Author, peer-reviewed or preprint journal, DOI, and source of funding | Number of patients | Participants included | Place of death | Diagnostic method | City, country | Sample collection |
|---|--------------------|---|--|----------------------------|---------------------------|-------------------|
| Case series | | | | | | |
| Lax SF, 2020 Journal DOI: 10.7326/m20-2566. No funding ⁷⁷ . | 11 | 8 male in strata age: 1 aged 90 years; 5 aged 80years; 1 aged 70 years; 1 aged 60 years. 3 female: 2 aged 80 years and 1 aged 70 years | Intra-hospital | RT-PCR | Styria, Austria | Open autopsy |
| Bryce C, 2020 Preprint MedRxiv DOI: 10.1101/2020.05.18.20099960 No funding ⁴⁹ . | 25 | Gender distribution is no clear. Average age 67.5 years (95 % CI 34-84) | Intra-hospital | RT-PCR | New York, USA | Open autopsy |
| Wichman D, 2020 Journal DOI: 10.7326/M20-2003 Funded by U of Hamburgo ⁵⁰ | 12 | 9 M and 3 F. Average age 73 years | 2 extra-hospital and 10 Intra-hospital | RT-PCR | Hamburg, Germany | Open autopsy |
| Remmelink M, 2020 Journal DOI: 10.1186/s13054-020-03218-5 Erasmus funding for biomedical research ⁵¹ . | 17 | 12 M; 5 F. Average age 82.5 years | Intra-hospital | RT-PCR | Brussels, Belgium | Open autopsy |
| Previtalo G, 2020 Journal DOI: 10.1016/j.thromres.2020.06.042 No funding ⁵² | 35 | Adults over 18 years: 26 M; 9 F | Intra-hospital | RT-PCR | Bergamo, Italy | Open autopsy |
| Carsana L, 2020 Journal DOI: 10.1016/S1473-3099(20)30434-5 No funding ⁵ . | 38 | 33M, 5F. Average age 69 years | Intra-hospital | Nasopharyngeal swab | Milan and Bergamo, Italy | Open autopsy |
| Fox SE, 2020 Journal DOI: 10.1016/S2213-2600(20)30243-5 No funding ⁵³ | 10 | No data on gender, only African-American ethnicity. Average age 63 years. | Intra-hospital | RT-PCR | New Orleans, USA | Open autopsy |
| Prilutskiy A., 2020 Journal Boston University ⁵⁴ | 4 | 3 M, 1 F. Average age 75 years | Intra-hospital | RT-PCR | Boston, USA | Open autopsy |
| Ackermann M, 2020 Journal three fundings: INS, Botnar Research Center for Child Health and the European Research Council ⁷⁴ . | 7 | 5 M, 2 F. Average age 68 years for males and 80 years for females | It is not clear | Nasopharyngeal swab | Hanover, Germany | Open autopsy |
| Duarte-Neto AN, 2020 Journal Fundacao de Amparo a Pesquisa do Estado ⁷⁸ . | 10 | 5 M, 5 F. Average age 69 years | Intra-hospital | RT-PCR in 9 and 1 clinical | Sao Paulo, Brasil | Open autopsy |
| Menter T, 2020 Journal No mention of the funding source ⁵⁷ | 21 | 17 M, 4 F. Average age 76 years | Intra-hospital | RT-PCR | Basel, Switzerland | Open autopsy |
| Schaefer IM, 2020 Journal There are several sources of funding. Main: INS, PhAST diagnostic, Astra Zeneca and Roche/Genentech ⁶¹ | 7 | 5 M, 2 F Average age 66 years | Intra-hospital | RT-PCR | Boston, USA | Open autopsy |
| Konopka K, 2020 Journal No funding declared ³ | 8 | 5M, 3 F Average age 55 years | 4 intra-hospital, 4 extra-hospital | RT-PCR | Michigan, USA | Open autopsy |
| Deinhardt-Emmer S, 2020, Preprint Carl Zeiss Foundation ⁵⁹ | 11 | 7 M, 4 F Average age 72.3 years | Intra-hospital | RT-PCR | Greiz and Jena, Germany | Open autopsy |
| Youd E, 2020 Journal No funding ⁶⁰ | 9 | 4 M, 5 F Average age: 75 years M 69 years F | Extra-hospital | RT-PCR | Cambridge, United Kingdom | Open autopsy |
| Schaller T, 2020 Journal No funding ⁵⁸ | 10 | 7 M, 3 F Average age 79 years | Intra-hospital | RT-PCR | Augsburg, Germany | Open autopsy |

| Author, peer-reviewed or preprint journal, DOI, and source of funding | Number of patients | Participants included | Place of death | Diagnostic method | City, country | Sample collection |
|--|--------------------|---|--------------------|-----------------------|---------------------------------|---|
| Rapkiewicz AV, 2020 Journal Intramural research Program INS ⁶² | 7 | 3 M, 4 F Average age 57.4 years | Intra-hospital | RT-PCR | New York, USA | Open autopsy |
| Wu JH, 2020. Journal Funding is not clear ⁶³ | 10 | 7M, 3 F Average age 70 years | It is not clear | RT-PCR | Wuhan, China | Percutaneous ultrasonography-guided cutting bi-opsy |
| Bradley BT, 2020 Journal No funding ⁶⁴ | 14 | 6M, 8 F Average age 73.5 years | It is not clear | RT-PCR | Washington, USA | Open autopsy |
| Copin M-C, 2020 Journal No mention of the funding source ⁶⁵ | 6 | No characteristics reported | It is not reported | Hisopado nasofaringeo | Lille, France | Open autopsy |
| Skok S, 2020 Journal Open Access Funding Only ⁶⁶ | 28 | 17 M, 11 F Average age 72 years | Intra-hospital | RT-PCR | Styria, Austria | Open autopsy |
| De Michele S, 2020 Journal No mention of the funding source ⁶⁷ | 40 | 28 M, 12 F Average age 71.5 years | Intra-hospital | RT-PCR | New York, USA | Open autopsy |
| Kommos FKF, 2020 Journal 10.3238/arztebl.2020.0500 No funding ⁶⁸ | 13 | 10 M, 3 F Average age 74.61 years | Intra-hospital | RT-PCR | Heidelberg, Germany | Open autopsy |
| Valdivia-Mazeyra M, 2020 Journal No funding ⁶⁹ | 18 | 10 M, 8 F Average age 61 years | Intra-hospital | RT-PCR | Madrid, Spain | 11 open autopsies, 7 minimally invasive bi-opsies |
| Hanley B, 2020 Journal Funding Imperial Biomedical Research and Wellcome Trust ⁷⁰ | 10 | 7 M, 3 F Average age 75 years | Intra-hospital | RT-PCR | London and Oxon, United Kingdom | 9 autopsies, 1 percutaneous biopsy |
| Grosse C, 2020 Journal 10.1016/j.carpath.2020.107263 No funding ⁷¹ | 14 | 9 M, 5 F Average age 80.6 years | Intra-hospital | RT-PCR | Lintz, Austria | Open autopsy |
| Borczuk AC, 2020 Journal 10.1038/s41379-020-00661-1 No mention of the funding source ⁷² | 68 | 47 M, 21 F Average age 73 years | It is not clear | RT-PCR | New York, USA and Padua, Italy | Open autopsy |
| Roden AC, 2020 Journal 10.5858/arpa.2020-0491-SA No mention of the funding source ⁷³ | 8 | 7 M, 1 F Average age 79 years | Intra-hospital | RT-PCR | Minnesota, USA | Open autopsy |
| Nadkarni GN, 2020 Journal 10.1016/j.jacc.2020.08.041 Funded by INS ⁵⁵ | 26 | 16 M, 10 F Average age 64.61 | Intra-hospital | Nasopharyngeal swab | New York, USA | Open autopsy |
| Jiang T Journal 10.1186/s12959-020-00256-5 The National Key R&D Program of China and the National Natural Science Foundation of China ⁷⁵ | 9 | 5M, 4 F Average age 69 years | Intra-hospital | RT-PCR | Wuhan, China | Open autopsy |
| Falasca L, 2021 Journal 10.1093/infdis/jiaa578 There have been several foundation and government financings ⁷⁶ | 22 | 15 M, 7 F Average age by comorbidity: 76 years with comorbidity and 48,5 without comorbidity | Intra-hospital | RT-PCR | Rome, Italy | Open autopsy |
| Case reports | | | | | | |
| Yan L, 2020 Journal 10.5888/arpa.2020-0217-SA No funding ¹³ | 1 | 44-year-old Hispanic woman | Extra-hospital | RT-PCR | Texas, USA | Open autopsy |

| Author, peer-reviewed or preprint journal, DOI, and source of funding | Number of patients | Participants included | Place of death | Diagnostic method | City, country | Sample collection |
|--|--------------------|---|--|-----------------------|--|----------------------------|
| Sekulic M, 2020 Journal 10.1093/AJCP/AQAA091 No funding ¹⁴ | 2 | 2 M: 54 and 81 years | Intra-hospital | RT-PCR | Ohio, USA | Open autopsy |
| Lacy JM, 2020 Journal 10.1097/PAF.0000000000000567 No mention of the funding source ¹⁵ | 1 | 58-year-old female | Extra-hospital | RT-PCR | Wisconsin, USA | Open autopsy |
| Tian S, 2020 Journal 10.1016/j.jtho.2020.02.010 No mention of the funding source ¹⁷ | 2 | 1 M aged 73 years 1 F aged 84 years with lung cancer | 1 Intra-hospital Other not deceased | RT-PCR | Wuhan, China | Surgical biopsy |
| Suess C, 2020 Journal 10.1007/s00414-020-02319-8 Funded by Institute of Legal Medicine Switzerland ¹⁶ | 1 | 59-year-old man | Extra-hospital | Hisopado nasofaringeo | St Gallen, Switzerland | Autopsy |
| Tian S, 2020 Journal 10.1038/s41379-020-0536-x No mention of the funding source ³⁴ | 4 | 3 M, 1 F Average age 73 years | Intra-hospital | RT-PCR | Wuhan, China | Core biopsy |
| Yao XH, 2020 Journal 10.3760/cma.j.cn112151-20200312-00193 ¹⁸ | 3 | 2M aged 63 and 69 years 1 F aged 79 years | Intra-hospital | RT-PCR | Chongqing, China | Minimally invasive autopsy |
| Adachi T, 2020 Journal 10.3201/eid2609.201353 Funding by Japan Agency for Medical Research ¹⁹ | 1 | 1 84-year-old man | Intra-hospital | RT-PCR | Tokio, Japan | Open autopsy |
| Buja LM, 2020 Journal 10.10106/j.carpath.2020.107233 Local funding ²⁰ | 3 | 1 Hispanic male aged 62 years 1 afroamerican male aged 34 years 1 Hispanic male aged 48 years | 1 intra-hospital 2 extra-hospital | RT-PCR | Houston, USA | Open autopsy |
| Craver R, 2020 Journal 10.1080/15513815.2020.1761491 No mention of the funding source ²¹ | 1 | 1 M aged 17 years | Intra-hospital | Nasopharyngeal swab | New Orleans, USA | Open autopsy |
| Aguiar D, 2020 Journal 10.1007/s00414-020-02318-9 No mention of the funding source ²² | 1 | 1 F aged 31 years | Extra-hospital | RT-PCR | Geneva, Switzerland | Open autopsy |
| Tombolini A, 2020 Journal 10.1007/s00414-020-02354-5 No mention of the funding source ²³ | 2 | 2 F aged 64 years | Extra-hospital | RT-PCR | Macerata, Italy | Open autopsy |
| Wang C, 2020 Journal 10.1016/j.ebiom.2020.102833 Shanghai Guangci Translational Medical Research Development Foundation ²⁴ | 2 | 1 M aged 62 years 1 F aged 53 years | Intra-hospital | RT-PCR | Wuhan and Shanghai, China | Open autopsy |
| Popa MF, 2020 Journal 10.4323/rjlm.2020.1 No mention of the funding source ²⁵ | 1 | 1 M aged 88 years | Extra-hospital | RT-PCR | Constanta, Rumania | Open autopsy |
| Fitzek A, 2020 Journal 10.1007/s00194-020-00401-4. No mention of the funding source ¹² | 1 | 1 M aged 59 years | Intra-hospital | RT-PCR | German patient who died in Egypt. Autopsy in Germany | Open autopsy |
| Heinrich, 2020 Journal 10.1007/s00428-020-02872-y No mention of the funding source ¹¹ | | | | | | |

| Author, peer-reviewed or preprint journal, DOI, and source of funding | Number of patients | Participants included | Place of death | Diagnostic method | City, country | Sample collection |
|---|--------------------|---|--|-------------------------|-------------------------------------|------------------------------------|
| Bösmüller H, 2020 Journal 10.1007/s00428-020-02881-x No funding ²⁶ | 4 | 3M, 1 F Average age 72 years | Intra-hospital | RT-PCR | Tübingen, Germany | Open autopsy |
| Xu Z, 2020 Journal 10.1016/S2213-2600(20)30076-X No mention of the funding source ²⁷ | 1 | 1M aged 50 years | Intra-hospital | RT-PCR | Beijing, China | Open autopsy |
| Barton LM, 2020 Journal 10.1093/AJCP/AQAA062 ²⁸ | 2 | 1 M aged 42 years 1 M aged 77 years | Extra-hospital | RT-PCR | Oklahoma, USA | Open autopsy |
| Aiolfi A, 2020 Journal 10.1097/MD.00000000000021046 No funding ²⁹ | 2 | 1 M aged 56 years 1 M aged 70 years | 1 intra-hospital 1 no fallecido | Nasopharyngeal swab | Milan, Italy | Thoracoscopic biopsy for resection |
| Leth PM, 2020 Journal Link: https://ugeskriftet.dk/videnskab/post-mortem-ct-og-obduktion-hos-en-53-arig-mand-med-covid-19 No funding ³⁰ | 1 | 1 M aged 53 years | It is not clear | Positive test | Odense, Denmark | Open autopsy |
| Magro C, 2020 Journal 10.1016/j.trsl.2020.04.007 No funding ³¹ | 2 | 1 M aged 62 years 1M aged 73 years | Intra-hospital | RT-PCR | New York and Ohio, USA | Open autopsy limitada |
| Shao C, 2020 Journal 10.1016/j.humpath.2020.04.015 ³² | 1 | 1 M aged 65 years | Intra-hospital | RT-PCR | Beijing, China | Biopsy |
| Grimes Z, 2020 Journal 10.1016/j.humpath.2020.04.015 No mention of the funding source ³³ | 2 | 2 middle-aged M | Intra-hospital | RT-PCR | New York, USA | Open autopsy |
| Varga Z, 2020 Journal 10.1016/S0140-6736(20)30937-5 No mention of the funding source ³⁵ | 3 | 2 M and 1 F, average age 66 years | Intra-hospital | Not mentioned | Zurich, Switzerland and Boston, USA | Open autopsy |
| Okudela K, 2020 Journal 10.1111/pin.13002 No mention of the funding source ³⁶ | 1 | 1 F aged 94 years | Intra-hospital | RT-PCR | Kanagawa, Japan | Open autopsy |
| Navarro Conde P, 2020 Journal 10.1016/j.patol.2020.04.002 No mention of the funding source ³⁷ | 1 | 1 M aged 69 years | Intra-hospital | Descarte de otros virus | Valencia, Spain | Open autopsy |
| Ducloyer M, 2020 Journal 10.1007/s00414-020-02390- No mention of the funding source ³⁸ | 1 | 1 M aged 75 years | Intra-hospital | RT-PCR | Nantes and Lyon, France | Open autopsy |
| Wagner WL, 2020 Journal 10.1007/s00117-020-00743-w. No mention of the funding source ³⁹ | 2 | 1 M aged 71 years 1 M aged 76 years | Intra-hospital | RT-PCR | Heidelberg and Göttingen, Germany | Open autopsy |
| Oprinca GK, 2020 Journal 10.1007/s00414-020-02406-w No mention of the funding source ⁴⁰ | 3 | 1 F aged 79 years 1 M aged 27 years 1 M aged 70 years | 2 intra-hospital 1 extra hospitalaria | Not mentioned | Sibiu, Rumania | Open autopsy |
| Cirstea A-E, 2020 Journal 10.47162/RJME.61.1.23 No mention of the funding source ⁴¹ | 1 | 1 F aged 30 years | Extra-hospital | RT-PCR | Bucarest, Rumania | Open autopsy |
| Dettmeyer R, 2020 Journal 10.1007/s00194-020-00408-x No funding ⁴² | 3 | 3 men aged 59 to 67 years | 2 intra-hospital 1 extra-hospital | Not mentioned | Gleben, Germany | Open autopsy |

| Author, peer-reviewed or preprint journal, DOI, and source of funding | Number of patients | Participants included | Place of death | Diagnostic method | City, country | Sample collection |
|---|--------------------|---|----------------|------------------------------------|------------------------|----------------------------|
| Bidari Zerehpooch F, 2021 Journal 10.34172/aim.2021.23 No mention of the funding source ⁴³ | 5 | 1 F aged 78 years 1 F aged 75 years 1 F aged 47 years 1 M aged 48 years 1 M aged 75 | Intra-hospital | 3 by RT-PCR 1 by CT 1 by CXR | Teheran, Iran | Open autopsy |
| The COVID-19 autopsy project, 2021 Journal 10.1016/j.patol.2020.05.004 Funded by Carlos III Health Institute, CIBERONC and European Development Regional Fund ⁴⁵ | 1 | 1 M aged 54 years | Intra-hospital | RT-PCR | Madrid, Spain | Open autopsy |
| Khaba MC, 2021 Journal 10.1016/ijid.2020.09.1435 No funding ⁴⁴ | 1 | 1 M aged 19 years HIV positive | Intra-hospital | RT-PCR | Pretoria, South Africa | Open autopsy |
| Takahashi K, 2021 Journal 10.1002/rcr.2.724 No mention of the funding source ⁴⁶ | 1 | 1 M aged 82 years | Intra-hospital | RT-PCR | Okinawa, Japan | Percutaneous needle biopsy |
| Pernazza A, 2021 Journal 10.1007/s00428-020-02829-1 No mention of the funding source ⁴⁷ | 1 | 1 M aged 61 years | Not deceased | RT-PCR | Rome, Italy | Surgical biopsy |
| Zhang H, 2020 Journal 10.7326/M20-0533 Funded by National Natural Science Foundation of China ⁴⁸ | 1 | 1 M aged 72 years | Intra-hospital | RT-PCR | Wuhan, China | Percutaneous needle biopsy |

M: male, F: female, Rt-PCR: Reverse-transcription polymerase chain reaction, CXR: Chest X radiography CT: Computed tomography.

also recorded reasons for excluding some studies at any stage of the search and the selection process. They mapped out the study selection process in a flow chart adapted to the purpose of the study.

Data collection process

A standardized Excel format was used to include study data. The information to collect was as follows: primary and secondary data, study design, publication status, setting (location/country where autopsies were performed), number of subjects included, numbers of subjects with histological examination of lung tissue, the source of funding, disclosure of conflicts by investigators, a diagnostic method for COVID-19, method for retrieving specimens for histological examination; and data to assess the risk of bias for each study. Disagreements were solved by discussion and article data verification, and an author referee adjudicated unresolved ones.

Data elements

The results were presented in frequencies for each distinguishable finding, describe as a histologic morphologic findings per subject in each study. The frequencies extracted from each study from different presentations such as summary tables and detailed

descriptions with findings photographs. A pathology specialist reviewed finding descriptions and designations to summarize similar morphological ones appropriately and without error.

The articles that did not include the number of subjects in whom any morphological change occurred were assumed to be present in all of them.

Risk of bias assessment

Four reviewers made independent assessments of the risk of bias for each study. The critical evaluation tool created by the Joanna Briggs Institute (two reviewers for case series and two reviewers and case reports)¹⁰. The responses to the guiding questions and the collective supporting information led to a domain-level judgment in the form of "low risk of bias," "some doubt," "unclear," and "high risk of bias." Differences among the reviewers were solved through discussion until a reached consensus. When necessary, a third reviewer resolved discrepancies.

Measurements

Each morphologic change was at the specific lung histologic level. Moreover, it was counted and presented as a single frequency for each study.

Synthesis method

The total frequencies of findings for each study were summaries in frequencies. Then, the overall proportions were from the total number of subjects as a reference (594). Subsequently, a meta-analysis of proportions was performed for two most frequent histologic findings using the free software environment for R statistical computing with a random effects model with the DerSimonian-Liard method. The overall proportion is with its respective 95 % confidence interval. Heterogeneity was estimated using the statistic I^2 . A sensitivity analysis in which reports considered to be at "high risk of bias" was eliminated from the meta-analysis.

Results

A total of 252 references were on the L-OVE platform and 170 on PubMed and other searches. After verifying the titles, abstracts, and duplicates, 185 studies were selected for potential inclusion. Articles that reported histological findings in organs other than lungs were detached, as well as those on only biosafety measures for autopsies. Then, 116 articles were excluded, leaving 69 for inclusion, with 595 subjects. Two articles were

found that reported findings from the same subject^{11,12}. Finally, a total was 594 subjects. It is in the PRISMA flow chart (Figure 1).

Characteristics of the studies

Among 69 included studies, 38 were case reports¹¹⁻⁴⁸ and 31 were case series^{3-5,49-76}. Among included articles, 67 were in peer-reviewed journals, and two were in preprints. Peer-reviewed journals and two were in preprints. The demographic characteristics were: 381 males, 179 females, and 34 did not specify the sex of the subjects. The mean age for the case series was 87.57 years \pm SD 1.57, and for the case, the report was 61.85 years \pm SD 1.51. The studies were performed in eleven countries, mainly the United States (Table 1).

The findings reported: a total of 461 in-hospital deaths, 29 out-of-hospital, three non-deaths, 104 were unclear, and one was not reported.

Regarding diagnostic tests for confirmation of COVID-19, a nasopharyngeal swab was in 81 patients. There was mention in six of how they had confirmed the diagnosis, one by ruling out many respiratory viruses, one by computed tomography, and one by chest X-ray (Table 1).

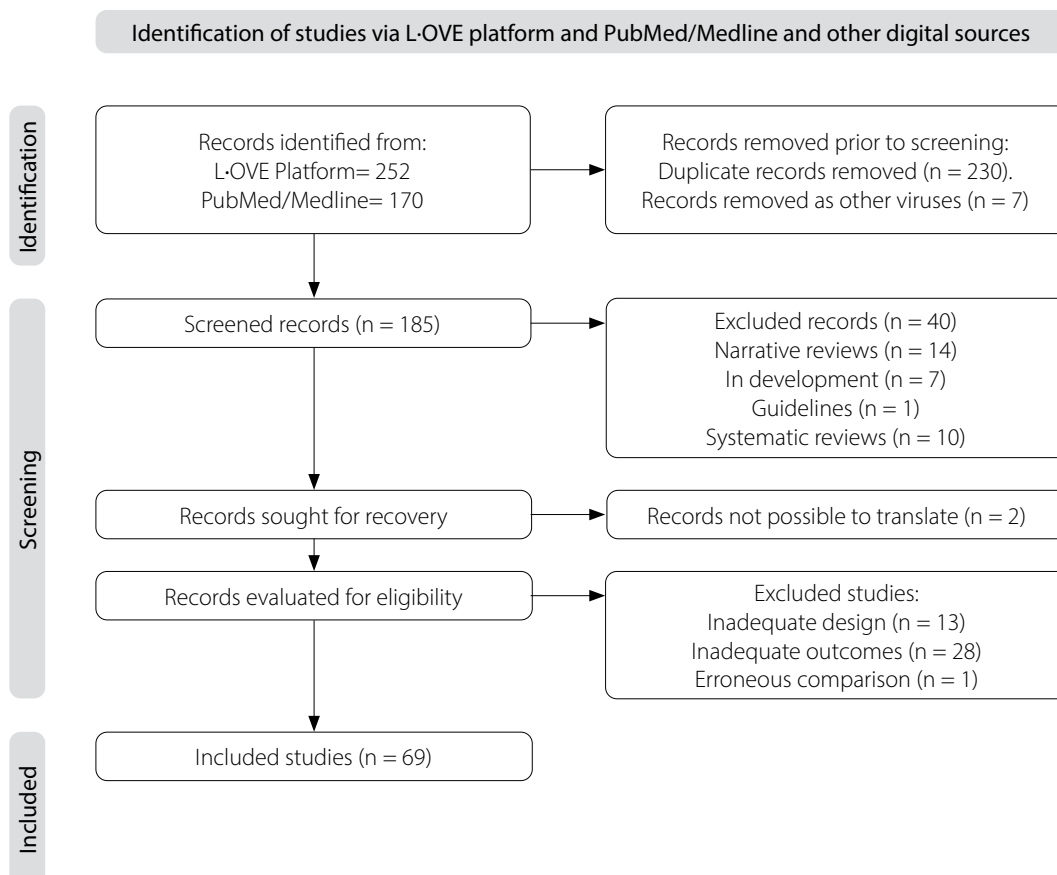


Figure 1. PRISMA flowchart of included studies

The specimens for histological examination were recovered from open autopsies, but there were open autopsies, but there were descriptions of modalities such as ten percutaneous biopsies ultrasonography-guided percutaneous biopsies, three surgical biopsies and two thorascopies (Table 1). All samples were stained with hematoxylin and eosin and examined with and eosin, examined with regular and electron microscopy and were and electron microscopy, and immunohistochemical immunohistochemistry tests.

Risk of bias in studies

Case series: 14 articles (41.36 %) were as "low risk of bias" of which six had control of the ten risks of bias required for case series assessment (19.35 %), and eight with control of nine of the risk of bias. The bias of "mention of inclusion criteria" was absent in five articles but it was unclear in ten articles. The most frequently uncontrolled bias was "adequate statistical processing of data" in 19 of the series (61.29 %). The bias that was 100 % controlled was the "clear reporting of the study outcome", followed by the bias of "clear reporting of the demographic characteristics of the subjects included in the series" and "clear reporting of the clinical information of the subjects included" in 90 % each.

Case reports: Twenty-nine articles assessed as "low risk of bias" (76.31 %), of which 20 met the seven risk of bias control requirements for case reports, and nine met six requirements. The two biases that were 100 % controlled were "clear reporting of outcome" and "the article teaches a lesson" followed by the bias "patient history was presented and used as a baseline over time" at 90 %.

Histopathological morphological findings

The most common finding by single frequency was diffuse alveolar damage (DAD) in 323 cases (55.72 %). In 275 cases, there were early components of platelet fibrin thrombi, hyaline membranes, and edema (85.14 %), followed by any arterial thrombosis (microthrombosis and macrothrombosis) in 271 cases: 252 microthrombosis and 231 macrothrombosis, of which in 19 cases of macrothrombosis identified were not in conjunction with microthrombosis. In 117 subjects presenting with any arterial thrombosis, no DAD was described equivalent to 43.17 % of all subjects with thrombosis (Table 2).

The data obtained by meta-analysis of proportions were 0.62 for DAD (95 % CI

0.51- 0.72), I^2 heterogeneity 59 % ($p < 0.01$), and 0.40 for any arterial thrombosis (95 % CI 0.31- 0.49), I^2 heterogeneity 58 % ($p < 0.01$) (Figures 2 and 3).

There was a sensitivity analysis and a removing all articles with at least one high-risk factor for bias. DAD was 0.65 (95 % CI 0.54 - 0.76), I^2 heterogeneity 59 % ($p < 0.01$), and 0.43 with any type thrombosis (95 % CI 0.33 - 0.54), I^2 heterogeneity 62 % ($p < 0.01$).

A sensitivity analysis was performed; all articles with at least one high-risk factor for bias were removed; 0.65 was for DAD (95 % CI 0.54-0.76), heterogeneity I^2 62 % ($p < 0,01$).

Discussion

This systematic review achieved to summarize histological findings retrieved from lung specimens in COVID-19 patients through a new rapid and sensitive search technology, the L-OVE platform on the Epistemonikos database. Most of the findings came from patients who had died, either in or out of hospital, and patients from whom samples were taken during their lifetime who subsequently died. At the beginning of the pandemic, results were slow because of the extreme precautions taken in pathology due to the contagious nature of the disease. However, when autopsies report could be performed safely, publications increased.

By the end of 2020, many articles that had been published in "preprint" format were later published in peer-reviewed journals, except for two that even at the time of finalizing this paper were still as preprint and therefore not peer-reviewed.

The literature currently available on lung histologic findings in COVID-19 patients is heterogeneous, as each publication responds to different objectives: To support theories for the cause of respiratory failure and cause of death^{5,54,56}; for being the first autopsy report on COVID-19 patient made in the country or region^{11,37,45}; undiagnosed home deaths but with previous suggestive symptoms or to add findings, such as being young, dying in another country or other relevant finding^{11,12}. It generated a limitation to this study since it introduces a selection bias as the cases were "chosen" by the authors. The other limitation was the definition of COVID-19. Not all included subjects were diagnosed using Rt-PCR, pre or *post mortem*. There was one case autopsied as excluded due to the presence of other viruses. But even with these limitations, this review shed light on many concerns about the cause of respiratory failure. Although some findings were described, which in many cases could

Table 2. Individualized histological findings, their frequencies and percentages

| Morphologic histological findings | Frequencies (%) |
|---|------------------------|
| Total number of cases | 594 |
| Diffuse alveolar damage | 323 (54.37) |
| Isolated morphological characteristics of DAD | |
| Acute phase Exudative | |
| Hyaline membrane | 275 (46.29) |
| Interstitial and intra-alveolar edema | 151 (25.42) |
| Capillary congestion | 125 (21.04) |
| Alveolar hemorrhage | 124 (20.87) |
| Platelet fibrin thrombi | 109 (18.35) |
| Fibrinous exudate | 63 (10.60) |
| Endothelial necrosis | 45 (7.57) |
| Loss of pneumocytes | 45 (7.57) |
| Dissociation of pneumocytes from basement membrane forming a pattern of desquamation | 40 (6.73) |
| Proliferative/Organization (subacute phase) | |
| Pneumocytic hyperplasia type 2 | 240 (40.40) |
| Diffuse interstitial lymphocytic infiltrate | 147 (24.74) |
| Deposition/proliferation of septal collagen | 101 (17.0) |
| Organized/collapsed alveoli with ductal dilatation | 86 (14.48) |
| Interstitial myofibroblastic reaction | 65 (10.94) |
| Alveolar granulocytes | 45 (7.57) |
| Enlarged megakaryocytes | 44 (7.41) |
| Intra alveolar fibrin 36 | 36 (6.06) |
| Intra alveolar macrophage | 29 (4.88) |
| Perivascular compression and lymphocytic vasculitis | 24 (4.04) |
| Interstitial proliferation | 8 (1.35) |
| Intra alveolar lymphocytic infiltrate | 5 (0.84) |
| Fibrotic (chronic phase) | |
| Fibrosis | 48 (8.08) |
| Thrombotic morphological changes | |
| Micro thrombosis in small and medium diameter arteries | 252 (42.42) |
| Pulmonary artery thrombosis | 196 (32.99) |
| Peripheral pulmonary embolism | 35 (5.89) |
| Pulmonary vessel endothelial damage | 28 (4.71) |
| Intra alveolar micro thrombosis | 11 (1.85) |
| Other morphological findings | |
| Intra-alveolar pneumocytes forming aggregates similar to giant multinucleated cells suspicious of cytopathic viral effect | 113 (19.02) |
| Suppurative pneumonia | 62 (10.44) |
| Squamous metaplasia | 17 (2.86) |
| Amyloid in pulmonary vessels | 11 (1.85) |
| Extensive <i>Corporae amylacea</i> | 7 (1.18) |
| Increased density of angiogenic intussusceptive features | 7 (1.18) |
| Pleural adhesions | 7 (1.18) |
| Mucinous secretion in bronchioles and bronchial mucus plugs | 6 (1.01) |
| Heme-phagocytic histiocytosis in the pulmonary hilum | 5 (0.84) |
| Syncytial multinucleated cells | 2 (0.34) |
| Eosinophilic infiltrate | 2 (0.34) |
| Intraalveolar mucus | 2 (0.34) |
| Acute pneumonitis | 1 (0.16) |
| Multicavitary lesions | 1 (0.16) |
| Pleural effusion | 1 (0.16) |
| Lymphocytic pleuritis | 1 (0.16) |

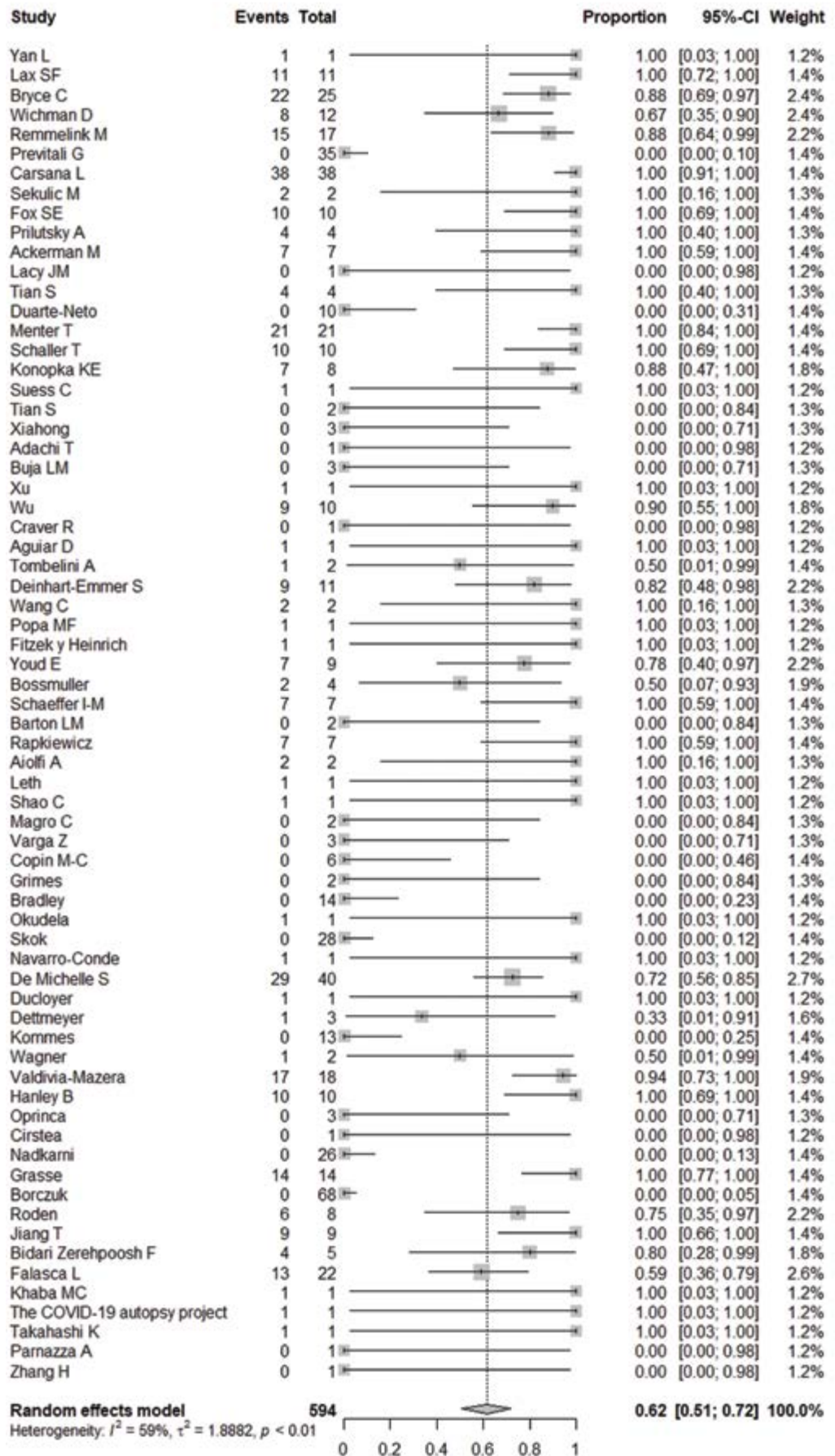


Figure 2. Meta-analysis forest plot for proportions of diffuse alveolar damage

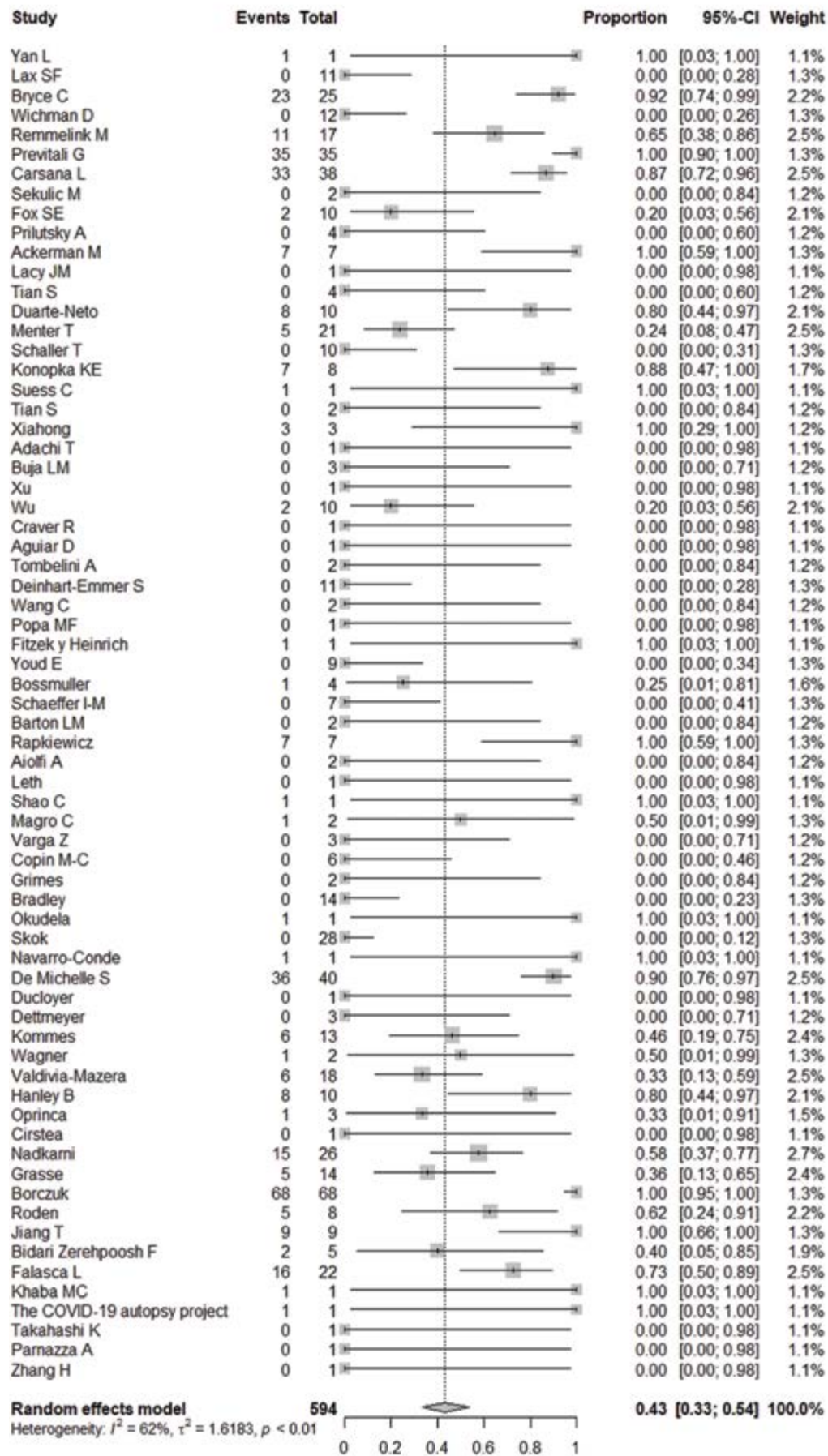


Figure 3. Meta-analysis forest plot for proportions of any arterial thrombosis

have occurred due to underlying causes of the subjects, the most frequent was DAD in all its stages. It is a morphologic feature that accompanies acute respiratory distress syndrome, regardless of its origin. However, the frequent finding of morphological alterations in early stages of DAD, with its typical hyaline membranes, intra-alveolar platelets and fibrin thrombi and edema, at the time of death and not in the stages of consolidation towards fibrosis as in acute fibrinous and organized pneumonia, reported in six autopsy cases,⁵⁴ should be emphasized. It is also important to note that there were no differences between patients who died at home and those who died of respiratory failure on mechanical ventilation. Regarding the theory of hypercoagulability that led many clinicians to use high-dose heparins and give aspirin, there is also no difference in its increased presence in critically ill patients.

These findings can guide clinical practice to the aggressive anticoagulation proposed at one time in disease management and the fact of finding few concomitant bacterial infections and thus making rational use of antibiotics in these patients. There is still much to learn about this disease, especially since new variants appear, and the clinical behavior and systemic involvement may also vary. Most of these reports are from the initial variant.

Conclusions

The most frequent histological morphological change are diffuse alveolar damage, indistinct from those produced by different viral infections. There was no finding of a specific pathognomonic characteristic that diagnoses COVID-19.

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Current applications of ultrasonography in anesthesia

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Luis Enrique Arévalo Gutiérrez

General Hospital, Salvadorean Institute of Social Security, San Salvador, El Salvador.

* Correspondence

✉ dr_arevalo82@hotmail.com

ORCID 0000-0003-3889-6810

Abstract

Ultrasound is a safe, portable, inexpensive, and easily accessible tool. Anesthesiologists can benefit from this fast and accurate diagnostic tool in their routine practice. There are multiple potential areas where ultrasound plays an important role in the guidance of blind and invasive interventions, diagnosis of critical conditions, and assessment of possible anatomical variations that may lead to modification of the anesthetic plan. This narrative review describes the main applications of ultrasound in anesthesia, ultrasound-guided techniques, and current trends in the perioperative anesthetic management of the surgical patient. A search was conducted in PubMed and Cochrane databases. Original articles, randomized and review studies in Spanish and English published between 2017-2021 were included. The use of ultrasound has entered the field of pain medicine, regional anesthesia, and interventional analgesia during the last decade and is even the standard of practice. Therefore, training and adequate learning in ultrasound should be part of the curriculum of any anesthesiology program..

Keywords

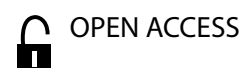
Ultrasonography, anesthesia, emergencies, Interventional ultrasonography.

Resumen

La ecografía es una herramienta segura, portátil, económica y de fácil acceso. Los médicos anestesiólogos pueden beneficiarse con esta herramienta diagnóstica rápida y precisa en su práctica habitual. Existen múltiples áreas potenciales donde la ecografía desempeña un papel importante, para la orientación de intervenciones a ciegas e invasivas, el diagnóstico de condiciones críticas y la evaluación de posibles variaciones anatómicas que pueden conducir a la modificación del plan anestésico. Esta revisión narrativa describe las principales aplicaciones de la ecografía en anestesia, las técnicas ecoguiadas y las tendencias actuales del manejo anestésico perioperatorio del paciente quirúrgico. Se realizó una búsqueda en las bases de datos PubMed y Cochrane, se incluyeron artículos originales, estudios aleatorizados y de revisión, en español y en inglés, publicados entre 2017-2021. El uso de ecografía ha entrado en el campo de la medicina del dolor, anestesia regional y del intervencionismo analgésico durante la última década, e incluso es el estándar de la práctica, por tanto, la capacitación y un adecuado aprendizaje en la ecografía deben ser parte del plan de estudios de cualquier programa de anestesiología.

Palabras clave

Ultrasonografía, anestesia, emergencias, Ultrasonografía Intervencional.



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Introduction

Although the clinical use of ultrasound was described in the 1950, it remained an experimental tool until the early 1970, when it was used to detect ascites in cadavers and splenic hematomas¹. Ultrasound units

have become more mobile and affordable routine use has expanded to the patient; in the immediate assessment of life-threatening cardiopulmonary or circulatory dysfunction in patients in operating rooms, post-anesthesia recovery units, and the perioperative setting¹.

In anesthesiology, rapid and accurate diagnostic tools are for surgical emergencies, and ultrasound has become a necessary and routine tool².

Ultrasound allows the anesthesiologist to diagnose the probable cause of hemodynamic instability, such as hypovolemia, left or right heart failure, vasodilatation, pericardial effusion, and significant cardiac disease (left ventricular hypertrophy, valvular stenosis), and usually takes only a few minutes to perform³.

The advantages of ultrasound include real-time visualization of the target structure, the distribution of the drug along and about the tissue, and the ability to control its distribution by readjusting the needle position; visualization of blood vessels, lungs, or other organs improves the success rate, speed, and safety of procedures. Compared with the fluoroscopy-guided proceedings that can only visualize bone tissue, ultrasound also allows visualization of soft tissues⁴.

The ultrasound has been in the intensive care setting, the prehospital environment. It has also been in the perioperative setting, where ultrasound is for pain medicine and regional anesthesia⁵.

Point-of-care ultrasonography (POCUS) is an easy, fast (less than four minutes), and widely available procedure. It is significantly more accurate than auscultation for discriminating between tracheal and bronchial intubation in adult patients under general anesthesia. It is possible to use with a high degree of sensitivity and specificity after training⁶.

A narrative review article was prepared by searching PubMed and Cochrane databases; moreover, original publications, randomized and review studies in Spanish and English, published in the last five years (2017-2021), were consulted. Its objective is to describe

the main applications of ultrasound in anesthesia as airway evaluation, vascular access, regional anesthesia, pulmonary ultrasound, gastric ultrasound, ultrasound neuromonitoring, and POCUS in anesthesia.

Discussion

Principles of ultrasound

Ultrasound refers to the use of sound waves (typically two to 15 MHz, but modern waves probes up to 22 MHz) being above the frequency of waves that the human ear can hear (20 to 20 000 Hz)⁷.

Its advantages include the possibility of seeing the structure in actual time, the distribution of the drug concerning the tissue (e.g., nerve tissue, blood vessels, lung, among others), and its distribution control by readjusting the position of the needle. They are capabilities that could improve the success rate and safety of the procedures^{4,8}.

The use of different transducers or ultrasound probes depends on the ultrasound frequencies. Probes can be with high frequency (10-15 MHz) and medium frequency (5-10 MHz). They provide better resolution but have less penetration. Therefore, the right choice of probes with different frequencies provides the best resolution for the required depth (Figure 1).

During probe handling, the mnemonic resource PART (Pressure, Alignment, Rotation and Tilt) is recommended. Changing the beam direction slightly, different images of the same structures can be obtained⁴.

Of the basic and advanced ultrasound imaging modes, B-mode (Brightness), M-mode (motion), and color Doppler are the most commonly used in anesthesiology. B-mode (Brightness mode) is the principal



| Type of transducer | Lineal | Curvilinear | Sectorial |
|--------------------|---|---|-----------------------------|
| | Vascular transducer | Abdominal transducer | Cardiac transducer |
| Frequency | 5-15 MHz | 2-7 MHz | 2-7 MHz |
| Penetration | Low 2-4 cm | High 20-25 cm | High 20-25 cm |
| Uses | Vascular examination, venipuncture, thyroid, breast, tendon | Abdominal pleura/lung examination, FAST* use in gynecology/obstetrics, neo-natal and pediatric settings | Cardiac, lung/pleura, FAST* |

*FAST ultrasound (Focused Abdominal Sonography for Trauma)

Figure 1. Comparative chart of the different ultrasonographic transducers

mode of any ultrasound machine. Each image obtained in B-mode is composed of pixels with brightness depending on the intensity of the echo received from the location on the body, used to assess organs in real time.

The M mode (moving mode) displays the movement of structures along a single line chosen by the operator, used for the evaluation of heart wall or valve motion, hemodynamic status (evaluation of the vena cava), and identification of lung slippage or diaphragm movement⁸.

Color Doppler helps to distinguish moving structures such as blood and determine the direction of blood flow; for example, nerves are often hypo/anechoic and can be confused with blood vessels. So the Doppler modes detect the frequency changes created by sound reflections from a moving target (called the Doppler effect). It uses the change in pitch of the sound waves to provide information about blood flow.

The four commonly used Doppler techniques are: (a) Color flow Doppler: this gives an image of the blood vessel that represents the velocity and direction of blood flow through a blood vessel. The colors (usually red and blue) denote the flow to and from the transducer, regardless of the nature of the blood vessel (artery or vein); (b) Pulsed wave Doppler (PWD) transmits short pulses of ultrasound and Doppler signals. It allows measuring the blood velocity of a small region, converting the Doppler sounds into a graph that gives information about the speed and direction of blood flow through the blood vessel; (c) Continuous wave Doppler (CWD) transmits and receives continuous waves of ultrasound. (d) Duplex Doppler system, a blood vessel is placed by ultrasonography in B-mode, and then the blood flow is measured by the Doppler technique. This combination of B-mode and Doppler allows more precise targeting of the Doppler beam to a given blood vessel⁹.

Airway assessment

Upper and lower airway management and the diagnosis of its complications are essential clinical skills to decrease morbidity and mortality. Therefore, any clinical tool that improves airway management must be helpful in the conventional clinical assessment¹⁰.

Airway ultrasound can visualize and evaluate all the structures except the posterior pharynx, posterior commissure, and posterior wall of the trachea. It is due to artifacts created by the intraluminal column of air. Thyroid and cricoid cartilage are visualized in

at least the first three tracheal cartilages (pearl necklace image) (Figure 2a and Figure 2b).

Airway applications of ultrasound are (a) prediction of difficult airway, (b) airway-related nerve blocks, (c) assessment of airway pathology that may affect the choice of airway management (e.g., subglottic hemangiomas and stenosis), or require urgent airway procurement (e.g., epiglottitis), (d) confirmation of proper endotracheal tube placement and ventilation, (e) prediction of endotracheal and endobronchial airway size (f) prediction of obstructive sleep apnea, and (g) prediction of successful extubation airway edema, assessment of diaphragm movement, and assessment of vocal cord movements.

Compared to computed tomography (CT), ultrasound is reliable in imaging all structures imaged by CT and provides nearly identical infrahyoid parameter measurements and minimal differences in suprahyoid anatomic parameters¹⁰.

Confirming the correct placement of the endotracheal tube (ETT) can be done by real-time ultrasound by placing the probe transversely in the neck at the level of the suprasternal notch during intubation to observe whether the tube is in the trachea or esophagus. It is for intubations in the emergency room outside the operating room, where capnography is not available or noise prevents auscultation¹⁰.

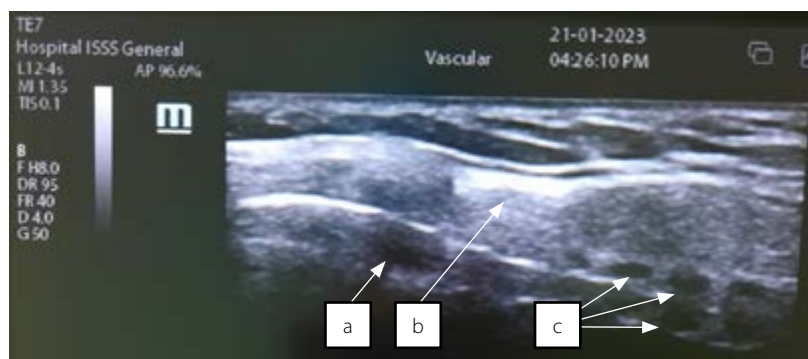


Figure 2a. Sagittal neck scan. Identification of cartilages and membranes. a. Thyroid cartilage. b. Cricoid. c. Tracheal rings



Figure 2b. Transverse section of subglottis. a. Cricoid cartilage in horseshoe shape

In addition, because the patient's lungs need ventilation several times to confirm capnography, transtracheal ultrasound is preferred. It allows faster confirmation than standard auscultation and capnography¹⁰. Confirming TTE can also be indirectly made by identifying sonographic signs of pulmonary ventilation. It includes lung sliding and diaphragmatic movement through a subcostal view^{8,10}.

Ultrasound has been successfully used to choose an appropriate endotracheal tube size, tracheostomy tube, and even double-lumen tube¹¹.

Bedside ultrasound is a safe and effective tool for diagnosing acute epiglottitis by visualizing the "P-sign" (accumulation of inflammatory fluid in the epiglottis and aryepiglottic folds) in a longitudinal view through the thyrohyoid membrane¹¹.

Ultrasound is successfully improving the yield of airway-related nerve blocks, including upper laryngeal nerve block, deep cervical plexus, alveolar nerve, and superficial trigeminal nerve¹⁰.

Prediction of successful extubation is another challenge in long-term intubated patients and those at high risk of airway edema and vocal cord injury (e.g., after thyroid surgery). The thyroid window is evaluated in the short axis by measuring the air column in the laterolateral diameter, where a value of less than 4.5 mm is considered a potential predictor for stridor compared to 6.4 mm, considered normal¹². Also, craniocaudal displacement of the liver and spleen with a cutoff value of 1.1 cm during spontaneous breathing tests, measured by ultrasound, is a good predictor of adequate extubation¹³.

Vascular access

As a "tip navigation" technique, ultrasound allows visualization of the catheter or guide-wire traveling into the cavoatrial junction along the ipsilateral brachiocephalic vein or excluding catheter misdirection in other superior vena cava tributary veins¹². Indications for vascular ultrasound include real-time needle visualization during cannulation of the internal jugular, subclavian, axillary, femoral, and arterial vascular access veins (Figure 3a).

Also, vascular ultrasound is indicated for the diagnosis of deep vein thrombosis, suspected arterial occlusion or stenosis, to measure the diameter of the inferior vena cava and variability during the respiratory cycle (right ventricular preload indicator), and for real-time monitoring of volume resuscitation and diagnosis of aortic aneurysm or aortic dissection¹⁴.

In addition, ultrasound is relevant to avoid respiratory complications since it is possible to visualize the pleura to prevent damage during puncture of the brachiocephalic vein, superior vena cava, and axillary vein. Even after difficult punctures potentially associated with pleural injury, it is possible to prevent pneumothorax and hemothorax¹⁵.

In critically ill patients, the supraclavicular area may be inadequate due to non-invasive ventilation, neck trauma, burns, tracheostomy, and others; in such patients, the axillary vein, identified by ultrasonography, could be a safe alternative, with a clean, flat, stable area and low degree of bacterial colonization^{15,16}.

Academic medical centers must consider ultrasound for challenging radial arterial catheterization (e.g., patients with morbid obesity, tissue edema, hypoxia, and vasoconstrictive therapy)¹⁷. This information is not only relevant for training in anesthesiology programs but other specialties. It includes internal medicine, intensive care, and surgery.

Although most residents gain much experience placing arterial lines, blind palpation in patients with obesity, hypotension, or pitting edema is challenging even for the most experienced residents. It can lead to repeated unsuccessful attempts and cause arterial bleeding, hematoma, spasm, or the creation of a false lumen¹⁷. Flumignan *et al.*¹⁸ found that real-time visual ultrasound guidance improved the first attempt success rate, overall success rate, and time to successful procedure up to one month, mainly in the radial artery, compared to palpation or non-visual ultrasound guidance.

Regional anesthesia

The ultrasound-guided peripheral nerve block is perhaps the most popular application used by anesthesiologists. It could be the gold standard for regional anesthesia with greater precision, expanding the ability to block smaller nerves and those in more difficult anatomical locations^{19,20}.

The use of ultrasound offers advantages such as direct observation of the nerves and surrounding structures, decreasing complications (e.g., accidental intraneural or intravascular injection), and the spread of the local anesthetic (Figure 3b).

Thus, a more precise arrangement leads to a faster onset, longer duration and improvement of the block. It allows dosing and/or reduction of local anesthetics. It has been shown when peripheral nerves are adequately reflected by ultrasound, the simultaneous use of the nerve stimulator offers no further advantages^{19,20}.

Lung ultrasound

Lung ultrasound is a quick and easy way to diagnose severe chest trauma such as pneumothorax and allows investigation of almost all causes of hypoxemia²¹.

Lung ultrasound is performed with the patient seated or supine. The sagittal and coronal planes are used in the operation room where the patients are in the supine position. Current protocol recommends to divide each hemithorax into four zones to speed up the lung ultrasound in critical cases²¹. Both lateral upper abdominal quadrants can also be examined for pleural effusions. In the operating room, Trans Esophageal Ultrasound (TEE) will be useful in detecting pleural fluid, atelectasis, or pneumonia. However, it is more limited in detecting pulmonary slippage²².

Postoperative pulmonary complications (PPCs) are associated with increased mortality, morbidity, and healthcare costs. After the non-cardiothoracic surgery, PPCs occur in up to 40 % of patients at increased risk. Lung ultrasound in the operating room detects intraoperative atelectasis and is successful for perioperative evolution.

The identification of the diaphragmatic movement also allows the exclusion of complete diaphragmatic paralysis after the procedures such as interscalene block, upper abdominal surgery, or manipulation of the internal mammary artery in coronary artery bypass surgery²².

In normal lungs, lung sliding is visualized, coast sign (M mode), A-lines, and occasional B line. In pneumothorax, lung sliding is absent, and barcode sign (M mode), B lines, and pulmonary pulse are found. In edema, three or more B lines are visualized²³. In atelectasis, the pulmonary sliding may be absent, and the pulmonary pulse will still be present. When there is consolidation, there is evidence of lung hepatization. In case of effusion, hypoechoic fluid is around the pulmonary base.

Gastric ultrasound

Aspiration remains a strange but serious anesthetic complication, contributing to 9 % of all complications related to anesthesia deaths²⁰. Gastric contents are one of the main risks for aspirations, which resulted in the development of guidelines for preoperative fasting. A stomach at risk was the presence of solid particles and/or fluid volume greater than 0.8 mL/kg. It demonstrates that assessment of antral area volume is relevant to minimize the risk of pulmonary aspiration of gastric contents^{24,20}.

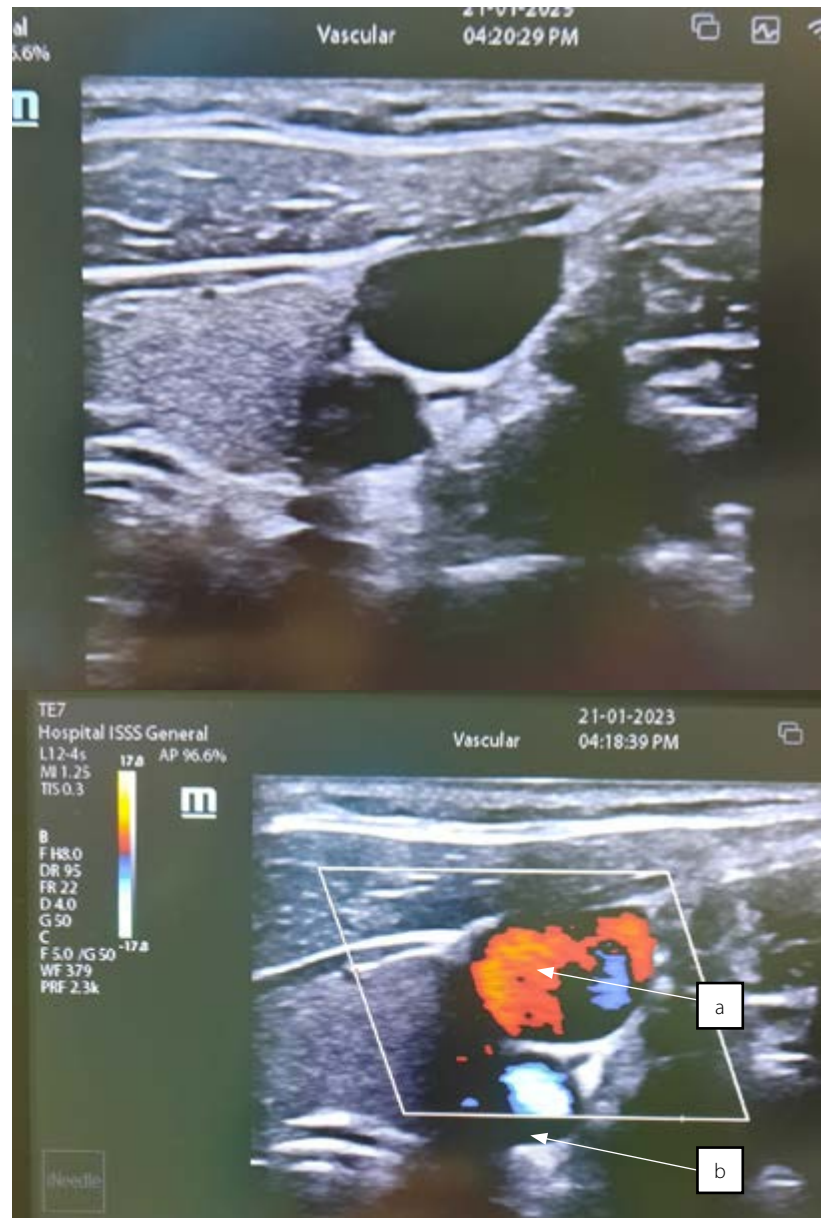


Figure 3a. Ultrasound window showing the relation of the jugular vein and neighboring structures. a. Jugular vein. b. Carotid artery



Figure 3b. Ultrasound window showing the relationship of the jugular vein and neighboring structures. a. Brachial plexus

POCUS in gastric ultrasound is a tool to assess the type and volume of gastric contents. Thus, the risk of aspiration in various settings, such as elective procedures where fasting guidelines are not followed or unknown, or in high-risk patients (recent trauma, diabetes, opioid use, active labor)^{24,20}.

The gastric antrum, located superficially (approximately 3-4 cm) is best suited for ultrasound examination and accurately reflects the contents of the entire stomach. With a sagittal scan in the epigastric region at the left subcostal margin and fanning out beyond the midline to the right subcostal region, the gastric antrum must be a hollow viscus with a prominent muscular wall located between the left lobe of the liver and the pancreas^{24,20}.

Ultrasound evaluation of gastric contents requires scanning in the right lateral and the supine positions, with limitations in certain patients such as in the case of an obstetric emergency. Therefore, it is appropriate to describe a supine scanning and data analysis that allows rapid diagnosis of a full or empty stomach^{20,24}.

Ultrasound neuromonitoring

Color-coded transcranial Doppler is an accurate, real-time, non-invasive, inexpensive tool used for the study of intracranial circulation, the diagnosis of non-thrombosed aneurysms, to monitor cerebral blood flow alterations following traumatic brain injury and in patients with sickle cell anemia, as expanded upon by Peña Martínez²⁵.

Elevated intracranial pressure (ICP) requires special precautions on the part of the anesthesiologist, such as avoiding medications, adjustment of mechanical ventilation, and neuroaxial anesthesia. Brain ultrasound is to assess elevated ICP and cerebral perfusion; current and potential applications of neuroutrasound are optic nerve sheath diameter measurement and transcranial Doppler ultrasound²⁶.

Measurement of the optic nerve sheath diameter with a value of 5.7 mm has been evaluated as a cutoff indicator for elevated ICP with the sensitivity of 74.1 % and specificity of 100 % to reflect intracranial pressure since an increase in ICP will be transmitted through the subarachnoid space surrounding the optic nerve within its sheath. It is a reliable and noninvasive means of assessing ICP in neurocritical patients. It was also in patients at risk of developing intracranial hypertension during routine surgical procedures and in healthy patients undergoing surgery requiring Trendelenburg positioning, pneumoperitoneum, or prone position¹⁴.

However, it should not replace invasive neuromonitoring techniques such as invasive intracranial pressure monitoring or substitute diagnostic techniques such as CT or magnetic resonance imaging (MRI)¹⁴. Optic nerve sheath diameter assessment and other ultrasound-based techniques represent valuable clinical tools in the ICU, emergency department, and operating room when invasive ICP measurement is undefined or even contraindicated (patients receiving anticoagulants, liver failure)¹⁴.

POCUS in anesthesia

The use of POCUS is growing worldwide, as it makes it easier for anesthesiologists to tailor patient management in the intensive care unit, before the surgery, and in the prehospital setting.

Cardiac POCUS is a low-cost, prehospital technology that is feasible and reliable for assessing whether or not a cardiac activity is present²⁷. POCUS performed by paramedics during pulse checks in cardiac arrest led to prolonged pauses in compressions but helped discriminate between acute heart disease and cardiac arrest. In patients with trauma and cardiac arrest, changes in patient management, such as the decision to suspend resuscitation, are demonstrated²⁷.

The use of POCUS for cardiac evaluation includes valvular abnormalities, biventricular function, pericardial tamponade, volume status alterations, and acute cardiac ischemia. It involves four views: parasternal long axis, parasternal short axis, apical four-chamber, and subcostal four-chamber. Volume status assessment can be obtained from an additional subcostal view of the inferior vena cava in the long axis. For cardiac views, the left lateral decubitus position is ideal, which increases the proximity of cardiac structures to the chest wall and provides clearer ultrasound images²⁸.

The use of ultrasonography, when detecting important findings, is a cost-effective way to reduce referral to echocardiograms and high-value procedures²⁸. POCUS quickly diagnoses common conditions that can cause shock, such as cardiac dysfunction and ruptured aortic aneurysm, and assesses the patient's fluid status; it has also been shown to decrease the time to surgery and CT rate in trauma patients²⁹. Likewise, Atkinson *et al.* show a diagnostic accuracy for patients with the undifferentiated shock of 60.6 % to 85 %, which improved using a structured POCUS protocol²⁹.

First-line physicians may indicate POCUS in patients with COVID-19 due to lung ultrasound being more sensitive than chest

radiographs in detecting respiratory tract involvement. These findings include pleural line abnormalities, subpleural consolidations, B-lines including the "cascade or light beam signal", consolidations and small localized pleural effusions³⁰.

In addition, it can guide fluid replacement therapy, guided catheter positioning, evaluation of alveolar recruitment candidates, measurement of ventilation efficacy, and prediction of weaning tolerance¹⁷.

Importance of ultrasonography training

In many hospitals, observation of organs with an ultrasound device has become part of a physical examination, in addition to inspection, palpation, and auscultation, which can bring benefits to the patients³¹. POCUS also complements anatomy, reinforces physical examination skills, facilitates bedside diagnosis and treatment, and is a valuable learning tool for physicians in training. For this reason, POCUS training has become an important component of undergraduate and postgraduate medical education for physicians in many specialties³².

Recently, attention has been focused on incorporating whole-body POCUS for the daily practice of anesthesiologists³³. Despite this, there is no standard ultrasound curriculum for anesthesiology residents; teaching methods include informal bedside teaching, structured expert demonstration, didactic lectures, and simulations.

Simulation model-based lectures, online learning and traditional didactics of POCUS applications such as lung ultrasound (LUS) and focused assessment with ultrasound in trauma, FAST, can be an effective way to teach ultrasound to anesthesiology residents³³.

Conclusions

Ultrasound is a portable tool that provides the anesthesiologist with the diagnostic and monitoring capabilities for the optimization of perioperative management; it has a relevant role in the management of various emergencies, being a non-invasive procedure that allows the identification of life-threatening complications. Therefore, POCUS is a cost-effective way to reduce medical referrals for high-value tests and procedures.

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Physical and psychological consequences of obstetric violence in Latin American countries

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Nancy Gisell Laínez Valiente^{1*}, Gabriela de los Ángeles Martínez Guerra², Denise Alexandra Portillo Najarro³, Andrés Fernando Alvarenga Menéndez⁴, Ana Mercedes Véliz Flores⁵

1-5. Dr. José Matías Delgado University. Dr. Luis Edmundo Vásquez Health Science School. Antigua Cuscatlán, El Salvador.

* Correspondence

✉ nancyvaliente17@gmail.com

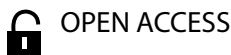
1.  0000-0001-9525-5388

4.  0000-0002-6051-4201

2.  0000-0002-4926-1194

5.  0000-0002-3652-4805

3.  0000-0003-3341-4982



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Abstract

The term obstetric violence has its origins in Latin America, it is considered an expression of gender violence and institutional violence against women. It can be exercised in two ways, physical and psychological, therefore, the aim is to define obstetric violence, its origin, divisions, and relation with women's sexual and reproductive rights, as well as to identify its physical and psychological consequences. A bibliographic search was conducted in Medigraphic, SciELO, and Google Scholar, including only publications that were found in full text, in Spanish, English, and Portuguese during the years 2014 to 2022. Obstetric violence causes the violation of women's sexual and reproductive rights, which makes it essential for all those involved in health care to be aware of the related physical and psychological repercussions that contribute to maternal and newborn morbidity and mortality, such as vaginal tears, breastfeeding problems, post-traumatic stress syndrome, and postpartum depression.

Keywords

Gender violence, obstetric violence, Latin America, women's rights, sexual and reproductive rights.

Resumen

El término violencia obstétrica tiene sus orígenes en Latinoamérica, se considera una expresión de violencia de género y de violencia institucional contra la mujer. Puede ser ejercida de dos maneras, física y psicológica, por lo que se pretende definir la violencia obstétrica, su origen, divisiones, relación con los derechos sexuales y reproductivos de la mujer, así como identificar sus consecuencias físicas y psicológicas. Se realizó una búsqueda bibliográfica en Medigraphic, SciELO y Google Académico, fueron incluidas únicamente las publicaciones que se encontraron a texto completo, en español, inglés y portugués durante los años 2014 al 2022. La violencia obstétrica provoca que los derechos sexuales y reproductivos de las mujeres sean quebrantados, lo que hace imprescindible que todos los involucrados en la atención en salud conozcan las repercusiones físicas y psicológicas relacionadas que contribuyen a la morbimortalidad de la madre y el recién nacido, tales como: desgarros vaginales, problemas en la lactancia materna, síndrome de estrés postraumático y depresión posparto.

Palabras clave

Violencia de género, violencia obstétrica, América Latina, derechos de la mujer, derechos sexuales y reproductivos.

Introduction

Obstetric violence (OV) is an expression of gender violence and institutional violence against women, characterized by the dehumanization of treatment, medicalization and pathologization during pregnancy, childbirth and puerperium carried out by health personnel^{1,2}.

In Latin America and the Caribbean, "dehumanized care" or "discrimination" are

terms used to refer to OV. References were also made to "institutional" and "structural" violence in health facilities to reflect the hegemonic model and gender inequity in health systems.

In the 2014 Geneva Declaration, "Prevention and Eradication of Disrespect and Abuse during Childbirth Care in Health Facilities," a definition of disrespectful and offensive treatment of women in childbirth had not been standardized, despite its prevalence^{3,4}.

The term "OV" has appeared in Latin America as result of the enactment of laws in countries such as Venezuela, Argentina, and Ecuador which have made it possible to define it. Since this is a multifactorial situation, not only does it consider inadequate procedures or practices that lead to the pathologization of pregnancy and childbirth, but also the patriarchal attitude exercised by health personnel during the care of pregnant women. This shows the inequality of power dynamics and which, in turn, is linked to gender-based violence in the context of gynecobstetrics, with both physical and psychological repercussions on pregnant women³.

Women who suffer obstetric violence do not easily recognize it, since it is perceived as normal². In Mexico, there is an under-reporting of OV due to the naturalization of the phenomenon by medical and obstetric personnel and even by the women themselves at the time of delivery, who are often unaware of the mistreatment received⁵. Lack of knowledge of this type of violence in routine care in health centers prevents health personnel from identifying it and patients from taking action to defend their rights⁶.

A bibliographic search was carried out in Medigraphic, SciELO, and Google Scholar, limited to full texts, published between 2014 and 2022 in Spanish, English, and Portuguese. Descriptors used were: women, violence, obstetric violence, gender violence, Latin America, origins, women's rights, reproductive rights, physical consequences, and psychological consequences.

This review aims to describe the main physical and psychological consequences of obstetric violence, as well as identifying the social repercussions in the Latin American context.

Discussion

Obstetric violence, origin y types

OV is not a recent phenomenon, and according to Ramírez *et al.*, it arises as a result of power disparities in gender relations, which undermine women's actions and worth⁷. According to the Costa Rican Association of Legal Medicine and Related Disciplines, pro-humanized childbirth organizations attribute the inequities to the patriarchal and authoritarian model that predominates in the doctor-patient relationship in the gynecobstetric area⁸. Since ancient times, women have suffered unequal treatment concerning men in all aspects of life.

Under the influence of Greek and Roman philosophy, the superiority of men over women was reinforced in rules and laws, and they were treated as the property of men. Since then, there has been inequality between men and women, favoring the former over the latter, since prejudices transferred through legal discrimination⁹. In 1960, a feminist social movement emerged to advocate for respectful childbirth and rights in perinatal care to expose OV⁹.

In 1979, the "Convention on the Elimination of All Forms of Discrimination against Women" recognized the disadvantaged conditions of women and their right to access family planning services. In 1985, the recommendations of the World Health Organization (WHO) and the Pan American Health Organization (PAHO) emerged through an interdisciplinary conference on appropriate technology for childbirth, focused on modifying the structure of health services and the attitudes of personnel who provide care to patients during childbirth¹⁰. In 2007, Venezuela was the first country worldwide to incorporate the term "obstetric violence" in its legal framework, followed by Argentina in 2009 and Mexico in 2014, with the approval of amendments to several laws that considered OV as a reprehensible practice¹¹.

OV refers to violent or perceived violent practices, behaviors, and abuses by action or omission, carried out by physicians, nurses, social workers, among other health system professionals, towards women during pregnancy, childbirth, or puerperium. This occurs in the different areas of healthcare, both in public and private services, and may result in various physical, psychological, patrimonial, economic, and sexual consequences or even lead to death^{12,13}.

For a better understanding of its consequences, OV divides into two main sections, the Physical and the Psychological¹³.

Physical obstetric violence

Physical OV is defined as any action or procedure that is not essential to care, is not clinically justified, or is performed without the consent of the pregnant woman. In addition, it includes neglecting the needs and pain of pregnant women, denial of treatment, repeated or multiple vaginal exams by more than one individual, and the execution of abrupt maneuvers, including restriction of movements and remaining in bed during labor^{14,15}.

Sometimes unnecessary procedures such as episiotomy and cesarean section are performed, without taking into account that

episiotomy should only be performed in specific cases since it has been shown that the resulting wound takes longer to heal in natural childbirth than the wound from vaginal tearing¹⁶; in addition, the cesarean section should only be performed to reduce morbidity and mortality in at-risk pregnancies¹⁷. To determine the criteria for its implementation, the ten-group or Robson's classification is recommended, which allows for the identification, analysis, and planning of the intervention.

The rise in unjustified cesarean sections is worrying because it leads to greater maternal morbimortality and increases the risk of complications such as placenta previa, placental accreta, and obstetric hemorrhage¹⁸. For instance, Latin America was the region with the highest number of cesarean births in 2018 with 44.3 %¹⁷.

Interventions not recommended by WHO, which continue to be performed without regard to specific indications, include the use of oxytocin to induce labor, enemas, and the Kristeller maneuver¹⁹.

Labor stimulation has traditionally been performed by administering intravenous oxytocin¹⁹. The application of this drug requires caution, due to its serious adverse effects. The errors related to its use are common and are related to high doses, which can cause excessive uterine activity²⁰. Furthermore, enemas are used during the dilation period, which is an uncomfortable procedure; there is no evidence of effects on the sanitary conditions of labor or on the decrease in the risk of infection for both the mother and the newborn²¹.

The Kristeller maneuver is usually indicated when there is suspicion of fetal distress, dystocia, or maternal exhaustion and consists of pressing with the hands on the uterine fundus to avoid prolonging the second stage of labor or resorting to surgery²².

Some procedures performed without prior consent include induction of labor, removal or rupture of membranes, vacuum or forceps-assisted delivery, or manual removal of the placenta²³. A study in Mexico by B. Muñoz on the medical complaints file of the National Commission for Medical Arbitration (Comisión Nacional de Arbitraje Médico) found cases in which women suffered physical OV by health personnel. In this study, it was described that, during delivery, health personnel used obstetric instruments such as forceps to extract the child, which resulted in hemorrhages and even hysterectomies caused by the maneuvers performed²⁴.

Psychological violence

On the other hand, psychological violence is a type of abuse against women, composed of different behaviors or subtle attitudes of aggression, which makes it hard to identify and demonstrate. It can be linked to physical violence, be a warning sign of it, or occur independently²⁵.

According to Jojoa-Tobar *et al.*, psychological OV has two subcategories; "1) verbal violence and the obstruction of pregnant women to express themselves freely; and 2) the omission of the right to information and autonomy in decision making of both the pregnant woman and her family in the process of childbirth"². Verbal aggression consists of mockery, humiliation, insults, dehumanizing treatment, undermining her needs, and ignoring the patient's fears or concerns²⁶.

In a study conducted in Venezuela, Araujo-Cuauro reported that, of 180 patients surveyed, 55 % responded that they had suffered some type of abuse before, during, or after delivery by health personnel, and 44.4 % perceived verbal abuse or aggression²⁷.

Verbal violence also encompasses a relationship of inequality in the framework of medical care between the patient and the health professional, called by Foucault "the power/knowledge"²⁸. It could be understood as the lack of effective communication with patients because they are considered inferior due to their lack of knowledge in the obstetric area².

Psychological OV by omission is based on the prohibition of an accompanying person in the health facility during the delivery, failure to give informed consent to the patient, or failure to report on the evolution of the delivery process and the state of health of the newborn²⁶. This type of violence includes the lack of information or the unjustified rejection of women's opinions; actions that can lead a woman to feel obliged to accept procedures and interventions that respond to the prevailing hegemonic models in some health services, in which the medical personnel holds the authority and the woman is deprived of the right to decide about her body^{29,30}.

Another occurrence is when the woman is not allowed company during the labor process. According to Andrade *et al.*, the presence of a person the patient trusts is crucial, as it helps to reduce the patient's fear, provides emotional support such as security and confidence, and reduces the risk of complications during labor³¹.

Obstetric violence and sexual and reproductive rights in Latin American countries

OV is a form of gender-based violence regarding women's human rights (WHR), specifically sexual and reproductive rights⁶. It is a multifactorial phenomenon involving institutional violence, considering that these human rights are breached in the context of pregnancy, childbirth, and postpartum in both, public and private health centers³².

According to the General Law on women's access to a life free of violence, in Mexico, women's human rights are an inalienable, fundamental and inseparable part of the Universal Human Rights included in the Convention on all Forms of Discrimination against Women (CEDAW), and other international tools that seek to guarantee a dignified treatment of women at all times, including pregnancy, childbirth, and postpartum³³.

The WHO defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"³⁴. In this sense, the right to health is the first right violated by the implementation of OV, due to the physical and psychological effects it produces. This same right enclose reproductive health, appending to the above definition "in all aspects related to the reproductive system, its functions and processes"³⁵.

The right to health is not respected if the autonomy of individuals is completely ignored³⁶. OV violates the right to personal integrity in its physical, psychological and moral dimensions; specifically, reproductive freedom and autonomy, i.e., the right to make decisions related to procreation, such as the number of children, the time interval between pregnancies, and the interventions to be performed at the time of delivery^{7,35}.

According to Soto-Toussaint, some patients are forced to wear an intrauterine device as a requirement before they discharging from hospitals, hear taunting comments, or experience delays in care because of their requirement to comply with their reproductive rights to the point of risking a perinatal death³⁷.

The mistreatment of pregnant women also occurs when the mother is labeled as ignorant, due to attitudes of superiority adopted by medical personnel³⁸.

Another of the fundamental rights violated by OV is the right to life since it represents a potential danger of death for the mother, the child, or both. This right states that everyone should enjoy their

existential cycle without interruption by extrinsic agents, with the State guaranteeing protection and respect for the lives of those under its jurisdiction³⁹.

Some countries in Latin America incorporated the defense of pregnant women in their laws. For instance, Venezuela introduced VO into the regulation of punishable conduct in 2007 in the The Organic Law on the right of women to a life free of violence. Afterwards, in 2009 Argentina published the Comprehensive Protection Law to prevent, punish and eradicate violence against women in interpersonal relationships, in which dehumanizing treatment is defined, in the context of OV, as cruel or humiliating treatment by health care personnel²⁶.

In Ecuador, article four in the Law to prevent and eradicate violence against women, published in 2018, includes the gynecobstetric harm or suffering in the concept of gender violence. In article ten of the same law, different actions considered OV are highlighted; for instance, considering pregnancy, childbirth and postpartum as diseases. It also emphasizes that such actions negatively impact women's sexual and reproductive health, as included in the above-mentioned laws⁴⁰.

El Salvador also has a legal base since 2021, mainly directed to the National Integrated Health System and aims to guarantee the right to be respected during childbirth and provide caring attention to the NB⁴¹.

Despite the existence of legislations with their respective sanctions for the different forms adopted by OV, Latin America continues reporting transgressions of rights in the gynecobstetrics context. According to the "National Survey on the Dynamics of Household Relationships" conducted in Mexico, from October 2011 to October 2015, 8.7 million births were delivered, and 33.4 % of the assisted women suffered some kind of mistreatment by health care personnel⁴².

Physical and Psychological Consequences of Obstetric Violence in Latin America

OV can present both, physical and psychological consequences. Hernández defines it as: "the product of an experience that has caused a rupture or interruption in a person's life and their immediate context, which includes their relationships with their partner, family or community. It may be visible or invisible changes, injuries or traces at the physical, emotional, psychological or health level." The damage caused by OV in women after childbirth could be perceived in the short or long

term, with varying degrees of severity, which in some cases may become irreversible²⁹.

Physical consequences

Breastfeeding

The evolution of childbirth is decisive to breastfeeding, and the problems presented in breastfeeding may be related to the interventions performed on the patient. Among the most frequent are: the use of antibiotics that could alter the microbiota and cause obstruction in the mammary duct and even mastitis; the pain caused by cesarean section could be an inconvenience for the mother when breastfeeding; an induced premature delivery may cause the newborn not to have enough suction strength; in addition, some mothers may develop post-traumatic stress syndrome and find it difficult or impossible to breastfeed⁴³.

Episiotomy

The WHO considers episiotomy a practice wrongly performed due to the complications it causes. It has been proven for 30 years that this procedure is not beneficial because it does not help expel the child or prevent vaginal tears in women but is associated with more severe tears^{44,45}. The former director of the WHO Maternal and Child Health Department, Mardsen Wagner, stated in 2000 that "performing too many episiotomies is being correctly labeled as a form of female genital mutilation."

In a study conducted in Peru by Mendoza *et al.*, it was observed that the most frequent complications in patients who had episiotomies were: hemorrhage (47.1 %), dehiscence, and grade I tear, which involves the compromise of the skin and/or vaginal mucosa (32.9 %), edema (31.8 %), grade II tear, which involved the skin, mucosa and superficial perineal muscles without the involvement of the external sphincter (29.4 %), infection (18.8 %), hematoma (17.6 %) and perineal pain (2.4 %)⁴⁶.

Incontinence

It can occur in different degrees and is caused by various reasons, among them: directed pushes, episiotomy, or the use of instrumentation. In 10 % of the cases, it is severe, and if there is no adequate treatment, the risk of complications increases. In addition, incontinence can be fecal, reducing the quality of life⁴³.

Unwarranted cesarean sections

Sadler, in his study, determined that "cesarean deliveries are associated with a two-fold

increase in the risk of severe maternal morbidity compared to vaginal deliveries." Cesarean section is associated with reproductive complications, including increased risk of newborn morbidity and mortality, preterm delivery, and increased risk of hospitalizations in the Neonatal Intensive Care Unit (NICU).

Psychological consequences

Postpartum depression (PPD)

Its worldwide incidence is 15 % and in middle-developed countries, one in five women suffers from PPD⁴⁶. During the puerperium, the risk of mood disorders increases due to the physiological changes and stress levels experienced. Women with a previous history of PPD have a risk of recurrence in the next delivery. One of the main complications of untreated or late diagnosis is suicide and filicide, the former being a significant cause of maternal mortality in the perinatal period⁴⁷.

Having experienced OV in health care services increases the probability of developing PPD by up to six times. Some risk factors consist of feelings of abandonment during labor, poor pain control, and the patient's frustration at being subjected to a cesarean section when it was not required. In the study of 432 women, de Souza *et al.* in Brazil found that physical violence by health care personnel is a crucial component of PPD, with a statistically significant association ($p < 0,01$ by Wald test)⁴⁷. On the other hand, the WHO has described that women who suffer obstetric violence have a 16 % increase in the risk of presenting alterations in the weight of the child; besides, more than 50 % present the risk of miscarriage and traumatic disorders related to childbirth⁴⁸.

Post-traumatic stress syndrome (PTSD)

One of the trigger factors for the development of PTSD is inadequate obstetric management and the perception of inappropriate care in pregnancy, childbirth, or postpartum⁴⁹. According to Vergara Arango, patients who have undergone a traumatic birth process due to a high level of stress have lower concentrations of oxytocin in their bodies and increased secretion of adrenaline, which interferes with the innate mechanisms of mother-child bonding and breastfeeding. Failure to achieve this bonding between mother and newborn can lead to the development of negative behaviors such as not knowing how to hold, breastfeed, or even rejecting the child⁴⁹.

Anxiety

It is characterized by negative thoughts, recklessness, and excitement due to constant feelings of worry. Women in the post-partum period, due to the effect of hormonal changes, are more vulnerable to the presentation or exacerbation of anxiety disorders. Silva *et al.* interviewed 209 pregnant women, 42.9 % of them presented anxiety during the third trimester of gestation; this period of time is associated with moments of vulnerability since the patient is close to her due date, which is conducive to the development of emotional disorders⁵⁰.

The consequences identified in the research reveal a clear problem in gynecobstetric services in some Latin American countries, whereas other regions have been investing years in trying to make visible the impact of this phenomenon that has affected women's maternity and lives.

A limitation of this study is that efforts to identify and eradicate OV in several Latin American countries are not evident due to the lack of publications.

Conclusions

OV is a result of gender violence in which sexual and reproductive rights are violated. The introduction of laws in several Latin American countries has contributed to preventing or reducing the number of cases of OV in different health facilities; however, despite these laws, violations of these rights continue to be reported. OV causes both, physical and psychological consequences, including difficulty in breastfeeding, urinary or fecal incontinence, tearing, hemorrhage, PPD, PTSD, and anxiety, which represent a high risk of morbidity and mortality for the mother and newborn.

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Use of cannabidiol for the control of refractory symptoms in convulsive syndromes and neurodegenerative diseases

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Laura Sofía Díaz Rodríguez^{1*}, Alejandra Elizabeth López Mirón², Alberto Armando Romero Olmedo³

1-3. Dr. José Matías Delgado University, Santa Tecla, El Salvador.

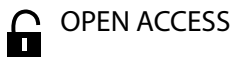
* Correspondence

✉ laura.diazr03@gmail.com

1.  0000-0002-8154-782X

2.  0000-0003-4843-6367

3.  0000-0002-9098-9945



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Abstract

As part of the alternative therapies for the control of refractory symptoms in advanced diseases, the use of cannabidiol stands out. It has been studied in pathologies such as Alzheimer's disease, Parkinson's disease, and convulsive disorders. Convulsive syndromes are present in all age groups. Within this group, epilepsy is refractory in up to 40 % of patients, who have shown a decrease in the frequency of seizures with the concomitant use of cannabidiol and conventional antiepileptics, with mild side effects such as diarrhea and drowsiness. To determine the use of cannabidiol for the control of refractory neurological symptoms in patients with seizure syndromes and neurodegenerative diseases, a literature search was performed in Pubmed, Scopus, and Embase. Meta-analyses, original articles, systematic and literature reviews, and documents from the Pan American Health Organization, published between 2017 and 2022, were included. The effects of cannabidiol make it an alternative, in addition to conventional therapeutics, for symptom control in neurological disorders, sustainably decreasing the total number of episodes with an acceptable safety profile. There is limited information regarding the use of cannabidiol in neurodegenerative diseases, the reason its effectiveness has not been demonstrated.

Keywords

Cannabidiol, refractory epilepsy, neurodegenerative diseases, neurological manifestations.

Resumen

Como parte de las terapias alternativas para el control de síntomas refractarios en enfermedades avanzadas destaca el uso de cannabidiol. Este se ha estudiado en patologías como enfermedad de Alzheimer, Parkinson y trastornos convulsivos. Los síndromes convulsivos están presentes en todos los grupos etarios. Dentro de este, la epilepsia es refractoria hasta en un 40 % de los pacientes, quienes han demostrado disminución en la frecuencia de convulsiones con el uso concomitante de cannabidiol y antiepilépticos convencionales, con efectos secundarios leves, como diarrea y somnolencia. Con el objetivo de determinar el uso del cannabidiol para el control de síntomas neurológicos refractarios en pacientes con síndromes convulsivos y enfermedades neurodegenerativas, se realizó una búsqueda bibliográfica en Pubmed, Scopus y Embase. Se incluyeron metaanálisis, artículos originales, revisiones sistemáticas y bibliográficas, y documentos de la Organización Panamericana de la Salud, publicados entre 2017 y 2022. Los efectos del cannabidiol lo convierten en una alternativa, adicional a la terapéutica convencional, para el control de síntomas en trastornos neurológicos, disminuyendo de forma sostenida el número total de episodios con un perfil de seguridad aceptable. Existe limitada información respecto al uso de cannabidiol en enfermedades neurodegenerativas, por lo que no se ha evidenciado su efectividad.

Palabras clave

Cannabidiol, epilepsia refractoria, enfermedades neurodegenerativas, manifestaciones neurológicas.

Introduction

Current therapy for advanced diseases is oriented towards symptom control rather than halting their progression. However, this usually has low efficacy, in addition to multiple adverse effects. Therefore, there is a great need for new therapies in order to improve the quality of life of these patients¹. This represents a relevant impact not only in the clinical setting but also in the psychological, social, economic, and/or spiritual spheres, contributing to the increase in total pain².

For these patients, alternatives are continuously being sought to control refractory symptoms, among which the use of cannabidiol (CBD) for the management of neurological symptoms, mainly neuropathic pain and seizures, stands out³. Pharmacological studies show that this is a promising bioactive substance effective for multiple diseases of the nervous system⁴.

CBD is one of the many derivatives of the cannabis plant, and unlike tetrahydrocannabinol (THC), it lacks psychoactive and intoxicating effects⁵. Although its mechanism of action is not well defined, since the 1990 decade it has been suggested that its effect is related to an endogenous cannabinoid system.

This system called endocannabinoid, influences different physiological processes through transmitters (anandamide and 2-arachidonylglycerol) that activate receptors, mainly CB1 and CB2; the CB1-type is located in the central nervous system and affects cognitive functions, such as memory, motor control, sensory and visceral perceptions, and pain. CB2-type receptors are located in the peripheral nervous system and mainly affect the control of neuropathic pain and the control of immune functions⁶. Although CBD has no direct action on CB1 and CB2 receptors, it can have a protective effect on endocannabinoid system alterations⁷.

The pharmacokinetics of CBD depends on the route of administration, being oral the most used, although it exists in inhaled, transdermal, and intravenous presentations⁸. Given some evidence of neuroprotective, cardioprotective, and anti-inflammatory effects, possible medicinal uses have been attributed to it⁹. In some countries, in recent years, it has been used as a complementary treatment in pathologies such as Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, neuropathic pain, and convulsive disorders that are difficult to treat¹⁰, as well as anxiety and schizophrenia⁴.

This narrative article aims to determine the use of cannabidiol for the control of refractory neurological symptoms in patients with seizure syndromes and neurodegenerative diseases. The information was searched in Pubmed, Scopus, and Embase, through the Hinari platform in Spanish and English. Metaanalyses, original articles, systematic and literature reviews, as well as information from portals of organizations such as the Pan American Health Organization (PAHO/WHO), published between 2017 and 2022, were consulted. Boolean operators OR, AND, and NOT were used with the keywords: Epilepsies, Seizure Disorder, Drug-Resistant Epilepsy, Epileptic Syndromes, Lennox Gastaut Syndromes, Dravet Syndrome, Neurodegenerative Disease, Alzheimer Disease, Parkinson Disease, Cannabidiol, CBD, Neurological Manifestations, Neurologic Symptoms, Pain, Dyskinesias, Seizures, among others.

Discussion

Refractory neurological symptoms in seizure syndromes and neurodegenerative diseases

Neurodegenerative diseases represent one of the leading causes of morbidity and mortality worldwide in older adults; although, they can begin at an earlier age¹¹; within this age group, dementia stands out, defined by the WHO as a syndrome characterized by the progressive deterioration of cognitive function, which affects 50 000 000 people per year¹².

Alzheimer's disease is the most common form of dementia, accounting for 60-70 % of cases worldwide¹², 10 % start before the age of 65¹³; It is characterized by cognitive impairment and behavioral disturbances; symptoms develop gradually and higher cortical functions deteriorate as time progresses¹⁴. These patients suffer from amnesia, behavioral changes, depression, anxiety, impaired vision, and language disorders¹⁵. As the disease progresses, symptom management becomes more complex¹⁶.

Parkinson's disease is the second most common neurodegenerative disease¹⁷ and affects 6 300 000 individuals annually¹⁸. It is detected in 1 % of people aged over 65 years, although it can be present early in patients under 40 years old¹⁹.

Parkinson's disease is characterized by motor manifestations, such as tremors, bradykinesia, altered postural reflexes and rigidity, and non-motor manifestations, such as sleep and behavioral disorders, cognitive

or autonomic dysfunction, pain, among others, which are associated to damaged structures of the nervous system²⁰. The most common symptom in this condition is tremor, which is present in more than 70 % of patients; these are unilateral, approximately between 4-6 Hz, and frequent in distal parts of the extremities²¹. Similarly, pain is common in these patients, mostly myalgia, cervicalgia, and lumbago, which worsens as the disease progresses; it is associated with stiffness and dyskinesia²².

Sleep disorders also present in these conditions; there may be difficulty in falling asleep or staying asleep, suffering nightmares, or even self-injurious behavior or aggressive behavior towards family members during sleep²³. As the disease progresses, the control of these symptoms becomes more complex, as they no longer respond to conventional therapies, being classified as refractory to treatment²⁴.

On the other hand, seizure syndromes are a group of disorders present in all age groups, epilepsy being the main one, which affects 50 000 000 people worldwide²⁵. According to the International League Against Epilepsy (ILAE) it is defined as the presence of two or more unprovoked seizures at least 24 hours apart²⁶. The ILAE defines refractory epilepsy as "epilepsy in which there has been failure of two trials of appropriately chosen and adequately tolerated antiepileptic drugs, in monotherapy or in combination, to achieve sustained seizure freedom"²⁷. It is found in 30 to 40 % of these patients²⁸.

The Lennox Gastaut syndrome is a severe form of epilepsy in childhood, affecting two to 5 % of children with epilepsy. It has been characterized by multiple daily seizures of different types, such as tonic-clonic, clonic, absence seizures, and generalized seizures, among others, which cause intellectual disability in this children²⁹.

In addition, the Dravet syndrome, also known as severe myoclonic epilepsy of infancy, is an intractable form of epileptic encephalopathy with early onset in childhood, presenting its first seizure episode between five and eight months of age, with an incidence of one in 15 000 to one in 40 000³⁰. Both syndromes are treatment-refractory epilepsies that present cognitive impairment and are associated with high mortality in these patients³¹.

Use of Cannabidiol in patients with seizure syndromes

The use of CBD for the treatment of refractory symptoms in seizure syndromes has

been studied by multiple researchers. One of the main ones is Dr. Orrin Devinsky who, since 2015, has participated in double-blind randomized clinical trials to assess the effectiveness of this molecule³². Wrede *et al.* found that CBD in concomitant therapy with anti-epileptic drugs decreased the frequency of seizure episodes in patients with treatment-refractory epilepsies³³.

Miller *et al.* identified that 68 % of patients who obtained additional therapy with another CBD drug showed improvement according to the Caregiver Global Impression of Change (CGIC) scale³⁴. This is a tool designed in 1976 to assess the severity, global improvement, and therapeutic response of a disease, which is a Likert-type scale implemented by the patient's caregiver and is used in psychiatric disorders, neurodegenerative diseases, and seizure disorders³⁵. The CGIC has been the primary instrument in multiple clinical trials on Cannabidiol in patients with seizure syndromes to assess the reduction in frequency and duration of seizures identified by caregivers³⁶.

CBD as an add-on therapy to antiepileptic drugs has been studied in the short and long term, and there is only one drug worldwide that contains highly purified cannabidiol, approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), indicated as an adjuvant in epilepsies refractory to treatment. Devinsky *et al.* evaluated patients with Dravet syndrome (DS) for 14 weeks, finding a decrease in seizure frequency from 12.4 to 5.9 episodes per month, where the adjusted median difference was -22.8 seizures with a 95 % confidence interval (95 % CI) of -41.1 to -5.4 ($p < 0.01$)³⁷. In turn, Francesco *et al.* studied for 12 weeks the use of CBD in patients with SD, where 40.2 % of them experienced a decrease greater than or equal to 50 % in seizure frequency³⁸.

On the other hand, the use of CBD added to their antiepileptic drugs was studied for 14 weeks in patients with Lennox-Gastaut Syndrome (LGS), reducing the frequency of monthly seizures by 37.2 % at a dose of 10 mg/kg/day³⁹, and 42.8 % at 20 mg/kg/day⁴⁰, compared to 21.8 % with placebo. This difference was significant from the first week of treatment⁴¹. However, according to Klotz *et al.* the treatment is shown to be more effective in patients with a higher frequency of seizures⁴².

Scheffer *et al.* studied long-term patients with SD, previously included in the Miller *et al.* clinical trial, concluding that after three years, the percentage reduction per month in total seizures was 49-55 % from

week 12. An estimated 85 % of caregivers who completed the CGIC found improvement every 12 weeks⁴³. On the other hand, Thiele *et al.* evaluated the effectiveness of cannabidiol in patients with LGS for 48 weeks. The median reduction in seizure drop frequency from baseline was 48.2 % at weeks one through 12, with a decrease from a median of 80.0 seizures per month at baseline to 37.7 per month, and was maintained for 48 weeks. In 6.3 % of the patients, no more seizure episodes were evidenced during the last 12 weeks, and 2.2 % had no more seizures during the entire study. Similarly, 72 % of their caregivers reported improvement based on the CGIC⁴⁴.

Regarding the safety of CBD, the most common adverse effects were pyrexia, somnolence, hyporexia, sedation, vomiting, and ataxia. Severe adverse effects such as seizures occurred in only five patients, one of whom was in the placebo group. In addition, six patients receiving valproate as an antiepileptic drug, presented elevation of transaminases up to three times their normal value, four of whom presented concomitant nosocomial symptoms⁴⁵.

In the same way, Szaflarski *et al.* investigated the use of CBD in patients with epilepsy refractory to treatment over a period of 48 weeks at doses between two and 50 mg/kg/day, showing that the most common adverse effects were diarrhea (29 %), somnolence (22 %) and seizure (17 %), being less frequent at doses lower than 10 mg/kg/day⁴⁶.

In a study conducted with 84 patients, tolerance was generated in 25 % in a range between three and 24 months, with an average dose of 12.6 mg/kg/day, unrelated to demographic characteristics or to their baseline treatment⁴⁷. Moreover, during the study by Szaflarski *et al.* an increase in CBD dose was needed between 12 and 48 weeks to maintain the initial response to treatment. However, no patient reported an increment in seizure episodes or the appearance of a new type of seizure^{48,45}. In turn, the percentage of adverse effects, such as drowsiness, was higher in the group of patients with CBD, thus requiring a dose adjustment in the same group³⁴.

Multiple pharmacokinetic and pharmacodynamic interactions of this molecule with the most widely used antiepileptic drugs have been identified, such as brivaracetam, clobazam, lacosamide, gabapentin, oxcarbazepine, phenobarbital, pregabalin, topiramate, among others⁴⁹. Clobazam is one of the most studied first-line drugs, since CBD increases sedation by prolonging the half-life of its metabolite N-desmethyl-

clobazam⁵⁰. Similarly, it decreases the anti-convulsant action of levetiracetam at doses of 100 mg/kg⁴⁹. In turn, it has been found that the concomitant use of cannabidiol with valproic acid can increase serum levels of liver enzymes⁴⁶⁻⁵⁰.

It is important to highlight that the effectiveness of CBD in convulsive syndromes does not only imply a reduction in the number of episodes or their length, but also reduces the need for emergency services, contributing to the wellbeing of the patient and his or her environment³¹. Thus, 40 % of parents report an improvement in the alertness of patients, as well as in social and language skills with the use of this molecule⁴⁷.

Use of Cannabidiol in patients with neurodegenerative diseases

Cannabidiol, having antioxidant and anti-inflammatory action, is considered a neuroprotective agent as an alternative complementary treatment in neurodegenerative diseases. In turn, its efficacy has been studied in the control of symptoms such as spasticity, pain⁵¹, and movement disorders such as chorea in patients with Huntington's disease⁵².

Through scales such as the Brief Psychiatric Rating Scale (BPRS) and the Parkinson Psychosis Questionnaire (PPQ), it has been possible to determine a decrease in psychotic symptoms in patients with Parkinson's disease, applying doses between 150 and 400 mg/day of oral CBD together with conventional antiparkinsonian drugs with mild side effects⁵³. Likewise, it improves mobility, emotional wellbeing, cognitive capacity and communication, in addition to achieving a reduction in general malaise with doses of 300 mg/day⁵⁴.

Among the side effects reported were somnolence, hyporexia, weight loss and diarrhea at doses of 1280 mg/day or 50 mg/kg/day. However, there are not enough clinical trials evaluating safety as well as effectiveness in patients with a history of cannabis use⁵⁵.

Leehey *et al.* describe moderate adverse effects, such as drowsiness, fatigue, diarrhea and in some cases hepatotoxicity in patients with Parkinson's disease, using doses of about 1600 mg/day. However, diarrhea has been associated more with sesame oil used as an excipient, since its frequency is independent of the dose⁵⁶.

In addition, multiple clinical trials in animals have been developed to evaluate the effectiveness of CBD combined with Tetrahydrocannabidiol (THC) for the control of anxiety, agitation and depression in

Alzheimer's disease⁵⁷. In the case of Amyotrophic Lateral Sclerosis (ALS) the effect of combined cannabidiol was studied in animals; however, low doses of THC were used to reduce the psychoactive effects; being an effective molecule for the control of refractory symptoms. More research in humans is needed to prove its effectiveness in these pathologies⁵⁸.

Conclusions

Cannabidiol's effects make it a complementary and adjuvant therapeutic alternative for symptom control in certain neurological disorders. CBD has been mainly studied in seizures refractory to conventional treatments, showing improvement in the total number of seizures in the short and long term, from the beginning of its implementation, as well as its safety in these time periods. Adverse effects are mild to moderate, such as anemia, gastrointestinal symptoms, somnolence and ataxia, and are directly proportional to the dose administered.

Additional short and long-term treatment with CBD in disorders such as Dravet syndrome and Lennox Gastaut syndrome showed a sustained reduction in total seizures. Adverse effects were more common with concomitant use of clobazam. It is important to emphasize that, though it is an alternative therapy, it does not replace conventional antiepileptic treatment, even when studies of the use of isolated and purified cannabidiol are still lacking, it alone does not control seizure episodes. There are few studies evaluating the development of tolerance with the use of CBD in refractory epilepsy, therefore more research is needed.

Furthermore, despite the fact that there is no clear evidence at the moment to support the effectiveness of cannabidiol management in patients with Parkinson's disease, there are researchers who support that cannabis derivatives, such as CBD, can alleviate motor and non-motor symptoms in the initial stages of treatment, without causing severe adverse effects. The main limitation to justify the use of cannabidiol in neurodegenerative diseases is the small number of investigations that establish the relationship between the mechanisms of action and its clinical effects.

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Contributions to neonatal care of the Ibero-American Society of Neonatology

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Sergio G. Golombek^{1*}, Susana Rodríguez², María Teresa Montes Bueno³, María de Lourdes Lemus Varela⁴, Marcelo Cardetti⁵, Lara Maksimovic⁶, Augusto Sola⁷

1-7. Iberoamerican Society of Neonatology.

* Correspondence

✉ sergio.golombek@siben.net

1.  0000-0003-0387-8989

2.  0000-0001-6015-6048

3.  0000-0002-1818-2637

4.  0000-0001-9895-7641

5.  0000-0001-6697-6389

6.  0000-0002-3018-6454

7.  0000-0002-7608-3872

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There are no conflicts of interest.

Dear Editor:

We have carefully read the article about healthcare-associated infections, which are frequent in Neonatal Intensive Care Units (NICU)¹. This makes us reflect on how neonatal teaching, training and outcomes have been widely uneven in Spanish-speaking countries² with poor and variable indicators. The figures indicate that 3100 newborn children (NB) need care in Neonatal Intensive Care Units daily in Latin America; 15 NB die every hour and 60 % of deaths occur in the first 28 days of postnatal age².

Aware of these problems, the Ibero-American Society of Neonatology (SIBEN) was founded in 2004. SIBEN is an international, non-profit, educational and academic organization founded by a group of pediatricians, neonatologists, nurses and interdisciplinary professionals and includes parents. Its legal status is registered in the United States.

The society was created with the purpose of contributing to the improvement of the quality of life of newborn children and their families in Ibero-America, promoting continuing education with a scientific and humane foundation and to support and implement educational programs for the constant advancement of the quality of neonatal care, developing guidelines for clinical practice, as well as disseminating knowledge, promoting collaborative research and developing an Ibero-American network of neonatal centers².

SIBEN has established original and participatory learning initiatives to reduce the gap between knowledge and care

received by many NB and their families. Doing more of the same is unjustified! For this reason, SIBEN provides educational incentives with awards, scholarships and grants to nursing staff and residents.

The learning objectives have been met through different modalities, virtual and in-person. In 2021, these strategies reached more than 7000 neonatal health professionals.

Regarding the implementation of continuous improvement in the quality of neonatal care, SIBEN has worked in different units, regions and countries, implementing advanced processes in the field, such as the one conducted with the National Health Service of the Dominican Republic³. This implementation of strategies and improvement actions in the country's main neonatal units succeeded in reducing neonatal mortality from 17 % to 12.1 %³ after two years of a multidimensional field program.

SIBEN has published more than 30 articles in peer-reviewed journals and several books. In addition to the annual International Congresses, local activities are developed through the "Neonatal Dialogues", an innovative face-to-face activity with interaction among teachers since 2014. Nursing staff participation has been key to the achievements. SIBEN keeps working to ensure that "one newborn at a time" gets good care and quality of life.

Its philosophy sets a precise course in promoting, stimulating, improving, and facilitating professional development of all neonatal related staff. It also reduces the gap and disparity that exists between knowledge and daily clinical practice, with openness and diversity to "do well by doing good"²⁻⁴.

At present, SIBEN is integrated by professionals who collaborate on voluntary basis, including a management team (general, operations, and scientific directors), an advisory body, and eleven councils with their corresponding chapters, as well as part-time administrative support. More than 85 % of these goes directly to its mission, with minimal administrative costs, as it has no assets.

It also has several interdisciplinary councils within its organization and more than 1000 active members in Argentina, Bolivia, Brasil, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Spain, Guatemala, Honduras, México, Nicaragua, Panamá, Paraguay, Perú, Puerto Rico, Dominican Republic, Uruguay, and Venezuela.

Participatory consensus conferences were developed to promote collaboration and unifying diagnostic and therapeutic criteria as part of the objectives in the dissemination of clinical assistance guidelines. This project began as "SIBEN Clinical Consensus" in 2007. It has an established methodology and the resulting product is a document with recommendations adapted to clinical practice. Some of them are published and available with open access.

As part of the purposes of its creation, the SIBEN network provides objective information on the magnitude of neonatal problems through the implementation of a voluntary, systematized, and confidential registry of newborns in the neonatal units of Latin America. Up to date, a total of 21 500 NB have been registered, of whom 13 500 are preterm (2500 weighing less than 1000 g and 4600 weighing between 1001 and 1500 g), and 8000 are at-term. In 2021, 42 neonatal units participated in the registry of underweight NB, of whom 2505 were less than 33 weeks old, and 3541 were older than 33. These data make it possible to identify differences between the participating units and to design strategies to collaborate in the processes of continuous improvement of the quality of neonatal care. In addition, it allows studies to establish situational diagnoses of specific pathologies.

Since SIBEN's creation, many of the proposed objectives have been met and adapted to the emerging reality in the region, maintaining presence and collaboration even during the pandemic years.

Its role during the COVID-19 pandemic was actively providing support for neonatal healthcare personnel and recognition of their efforts in situations of crisis and uncertainty, such as those that challenged the world. Since the pandemic began, SIBEN has disseminated updates on perinatal COVID-19 and issued a joint statement with the NeNe Foundation in Spain⁴.

SIBEN has fulfilled its founding mission for 18 years after its inception. It is aware that the road goes on. There are still many challenges; however, it is a work of heart to improve the health of newborn children.

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Results of the Rapidec® CARBA NP test in El Salvador

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José Eduardo Olivia Marín^{1*}, María José Luna Boza², Miguel Oscar Grande Figueroa³, Reina Esmeralda Villatoro Ventura⁴, Rene Guillermo Santos Herrera⁵, Ana Patricia Orellana de Figueroa⁶, Milagro Arenys Velásquez Escobar⁷, Zonia Elizabeth Cruz⁸, Ana Alejandra Rivera Láinez⁹, Patricia Evelyn Henríquez¹⁰, Patricia Danne Orellana Morales¹¹, Naomi Iihoshi¹², David Saúl Rodríguez Araujo¹³, Rhina Domínguez¹⁴

- 1,14. National Institute of Health, San Salvador, El Salvador.
- 2,3. National Laboratory of Public Health, San Salvador, El Salvador.
4. Executive Secretary of the Council of Ministers of Health of Central America (SE-COMISCA), San Salvador, El Salvador.
5. ECHO/SE-COMISA, San Salvador, El Salvador.
6. Ministry of Health (MINSAL), San Salvador, El Salvador.
7. National Hospital San Juan de Dios, San Miguel, El Salvador.
8. Dr. María Isabel Rodríguez National Women's Hospital, San Salvador, El Salvador.
9. National Hospital San Juan de Dios, Santa Ana, El Salvador.
10. Benjamin Bloom National Children Hospital, San Salvador, El Salvador.
11. Rosales National Hospital, San Salvador, El Salvador.
12. SE-COMISCA, New Mexico, United States of America.
13. SE-COMISCA, San Salvador, El Salvador.

* Correspondencia

✉ jose.oliva@salud.gob.sv

1.  0000-0002-6005-0558

4.  0000-0002-2412-2083

14.  0000-0001-7860-0602

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The authors declare there are no conflicts of interest.

Dear editor:

Nowadays, there are commercially available rapid carbapenemase tests that can generate results in less than two hours. One of these tests is Rapidec® CARBA NP, based on the direct detection of carbapenemase hydrolysis by carbapenemase-producing bacteria. The agility in detecting these enzymes is relevant in our country, as described in the article by Villatoro *et al.* in *Alerta* in 2018. They reported that carbapenemase-producing bacteria were isolated in 26 of 31 hospitals in El Salvador from 2014 to 2016¹.

This test analyzed the presence of carbapenemases in 122 isolated samples belonging to the *Enterobacteriaceae* family, as well as in non-fermenting bacilli, with decreased susceptibility or resistance profiles to any of the following carbapenemics: ertapenem, imipenem or meropenem. These were analyzed from five hospitals in the public health network of El Salvador between March 2020 and August 2021.

The isolated samples were obtained from both sterile and non-sterile samples (blood, urine, feces, and purulent secretions, in addition to others). Reading and interpretation of the rapid test was conducted in laboratories where it was performed following the instructions of the manufacturer. Subsequently, they were delivered to

the National Laboratory of Public Health (LNSP) for confirmation.

A total of 115 isolated samples were included in the analysis since seven of those received at the LNSP were not viable. The isolated bacteria were: *Acinetobacter baumannii* (58/50.4 %), *Klebsiella pneumoniae* (21/18.3 %), *Escherichia coli* (18/15.7 %), *Pseudomonas aeruginosa* (10/8.7 %), *Enterobacter cloacae* (7/6 %) and *Proteus mirabilis* (1/0.9 %). The above is in agreement with that reported by Villatoro *et al.* in 2018: from 2014 to 2016, *A. baumannii* was the most frequently identified carbapenemase-producing bacterium in El Salvador (85 %)¹.

Of the 115 isolated samples tested, 104 were classified as carbapenemase-positive and 11 as carbapenemase-negative using the LNSP carbapenemase detection algorithm: ethylenediamine tetraacetic acid, phenylboronic acid, Triton Hodge test, and the modified carbapenemase inactivation method. Of the 104 positive carbapenemases, 49 were categorized as metallo-beta-lactamase producing (MBL), and 55 as oxacillinase (OXA) producing. *Klebsiella pneumoniae* carbapenemase-producing isolates (KPC) were not detected. The detection of carbapenemases per isolated microorganism was distributed as follows: *Acinetobacter baumannii* (three MBL and 55 OXA), *Klebsiella pneumoniae* (18 MBL), *Escherichia coli* (17

MBL), *Pseudomonas aeruginosa* (six MBL) and *Enterobacter cloacae* (five MBL).

Some countries such as México, Panamá, Puerto Rico and Cuba, as well as Costa Rica, República Dominicana, Trinidad & Tobago, Colombia, Venezuela, Perú, Ecuador, Brasil, Paraguay, Uruguay, Argentina and Chile^{2,3} have identified variants of KPC, New Delhi metallo-beta-lactamase (NDM), Verona integron-encoded metallo-beta-lactamase (VIM) and imipenemase metallo-beta-lactamase (IMP), in *Enterobacteriaceae*, *K. pneumoniae*, *P. aeruginosa* and *A. baumannii*.

The most frequently detected carbapenemase-producing bacteria were: *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae*. These data is similar to those reported by other studies carried out in Latin America. They are as follows: *A. baumannii*, *K. pneumoniae*, *E. coli* and *E. cloacae* as KPC and NDM producing, *P. aeruginosa* as a producer of KPC, VIM and IMP, as well as *A. baumannii* producers of VIM and IMP³.

Rapidec® CARBA NP test showed a positive predictive value of 99 %. This value is consistent with that reported in other kinds of studies (92.6-100 %) ^{4,5}. The LNSP did not confirm the presence of carbapenemases in 11 of the 115 isolated samples. Of these isolated samples, ten were tested with the Rapidec® CARBA NP test and the LNSP's carbapenemase detection algorithm, and one with the algorithm alone. Of the bacteria where the presence of carbapenemases was not confirmed, four were *P. aeruginosa* with resistance to carbapenems due to membrane impermeability plus efflux pumps, as well as three *K. pneumoniae*, two *E. cloacae* and one *E. coli*, producers of extended-spectrum beta-lactamase (ESBL) and one *P. mirabilis* with no mechanism of bacterial resistance detected.

Several factors could have led to the 11 discordant results in local laboratories, which could be exogenous to the test itself: divergence in color interpretation among observers⁶, culture incubation time that may not have allowed for full enzyme expression⁷, the time interval between the reception of the clinical sample and the start of processing, the existence of hypermucoïd colonies⁸, the presence of AmpC beta-lactamase⁹, insufficient bacterial inoculum and/or the presence of isolated samples with weak carbapenemase activity¹⁰.

Rapidec® CARBA NP is a rapid test used to confirm the presence of carbapenemases in *Enterobacteriaceae* and Gram-negative bacilli such as *A. baumannii* and *P. aeruginosa*. Rapidec® CARBA NP can be

used in clinical settings to support the choice of antibiotics and infection control committees in their antimicrobial optimization programs. It also contributes to the timely detection and management of healthcare-associated infections, which are fundamental in controlling the spread of antimicrobial resistance in hospitals.

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Alerta journal

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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.

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Montserrat Amorós, MD.

Spain

✉ montserrat.amoros@unir.net

Miryam Griselda Lora Loza, MD.

Peru

✉ mlora@ucv.edu.pe

Diego Farias-Cortés, MD.

Mexico

✉ drdiegofarias@gmail.com

Julio Álvarez, MD.

Argentina

✉ julioalvarezuro@gmail.com

Neyde Madrid, MD.

El Salvador

✉ neyde.madrid@salud.gob.sv

Irina Tirado, MD.

Colombia

✉ irinasuley@gmail.com

Jessica Mireya Gutiérrez, MD.

El Salvador

✉ mireyagutierrez72@gmail.com

Mayra Lilia Chávez, MD.

Mexico

✉ courml@yahoo.com.mx

Lucía Coronel, MD.

Argentina

✉ luciacoronelsld@gmail.com

Claudio Berardi, MD.

Argentina

✉ berardiclaudio28@gmail.com

Julio Orellana, MD.

El Salvador

✉ dr.julioorellana@gmail.com

Andrea Sofía López, MD.

El Salvador

✉ 27sofialopez@gmail.com

José Adán Martínez Alvarenga, MD.

El Salvador

✉ dradanma@yahoo.com

Luis Enrique Fuentes, MD.

El Salvador

✉ lenrique.fuentes@salud.gob.sv

Giovanni Francisco Guevara, MD.

El Salvador

✉ gfguevara@gmail.com

Rhina Lissette Domínguez De Quijada, MD.

El Salvador

✉ Rhina.dominguez@salud.gob.sv

Noel Díaz Robles, MD.

El Salvador

✉ dr.diazrobles86@gmail.com

Yasmín Galván Talamantes, MD.

Mexico

✉ yazmingalvan21@gmail.com

Jorge Efraín Portillo Garay, MD.

El Salvador

✉ drportillogaray@gmail.com

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Urb. Lomas de Altamira, Bulevar Altamira y av. República de Ecuador, No.33,
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