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# *SAFOP* Study. Patent Foramen Ovale and SARS-CoV-2 Disease: Could They Be Considered Risk Factors for Suffering an Ischemic Vascular Accident Due to Paradoxical Embolism? Does sex matter?

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## ABSTRACT

***Objective**: To describe whether there is an increased risk of cryptogenic ischemic stroke in patients with a patent foramen ovale (PFO) and SARS-CoV-2 infection in the Gandía health department.*

***Method**: Retrospective observational study conducted in the Primary Care Team (EAP) and Hospital Emergency-Cardiology Departments in the cardiovascular problems branch of the La Safor area of Valencia, Gandía department.*

*A total of 335 selected patients were studied. These patients had to have experienced cryptogenic ischemic stroke associated with a patent foramen ovale and meet the inclusion criteria (patient >18 years, <65 years, and patient from the Gandía health department), during the years 2020, 2021, and 2022. Variables: age, sex, arterial hypertension, diabetes mellitus, cholesterol, patent foramen ovale and its structural characteristics, ischemic stroke, atrial septal aneurysm, SARS-CoV-2 infection. In terms of design, binary logistic regression models were performed, as well as a descriptive study where quantitative variables were described with the mean, standard deviation, and median; qualitative variables by frequency distribution.*

*Subsequently, a multivariate model analysis was performed including variables with statistically significant or potentially relevant effects.*

***Results**: PFO was detected more frequently among patients with COVID-19 (p<0.026) and cryptogenic stroke, with a positive result in 41.5% of PFO patients compared to 27.4% in non- PFO patients. Regarding sex, while 60% of women with PFO are positive for SARS-CoV-2, this percentage is reduced to 33.3% in men (p=0.044). In a comparative study according to PFO characteristics (PFO, medium-large PFO, ASA, PFO+ASA, medium-large PFO + ASA) we found statistical significance only in those patients with cryptogenic stroke, COVID-19 infection, and a medium-large PFO without ASA (p<0.02).*

***Conclusions**: Women with PFO and cryptogenic stroke are diagnosed more frequently with SARS-CoV-2 than men. Patients in our health area who have medium-large PFO have an increased risk of experiencing an embolic cerebral accident after SARS-CoV-2 infection. This underscores the need to identify these patients in primary care, neurology, and cardiology consultations to ensure closer monitoring and develop multidisciplinary action protocols.*

## Keywords
Cryptogenic stroke, Patent foramen ovale, SARS-CoV-2.

## Introduction

### Patent Foramen Ovale and Cryptogenic Stroke

Of the aforementioned strokes of undetermined cause or ESUS, 40% of patients have presented with patent foramen ovale (PFO), which constitutes the main cause of paradoxical embolism, increasing its percentage to 50% in patients younger than 55-60 years, making it the main cause of strokes of undetermined cause for this group [1-3], although this possibility has not been completely clarified and continues to not be considered an independent mechanism of producing paradoxical embolisms to cerebral circulation [4,5].

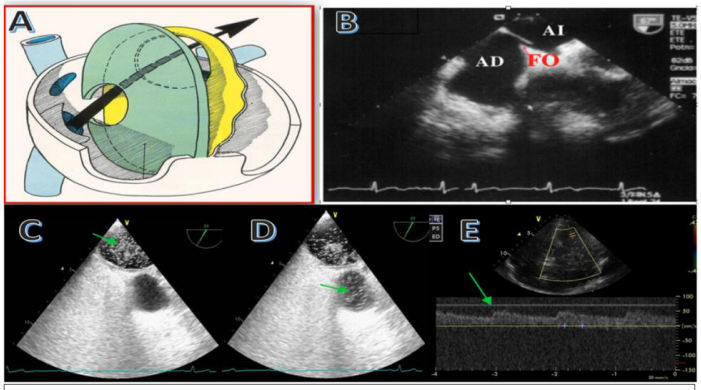
We understand the patent foramen ovale as the natural opening that allows the passage, during fetal life, of oxygenated blood from the right atrium to the left, so that oxygen and nutrients from the mother through the placenta and the umbilical vein can reach the brain and other fetal organs. With changes in circulation that occur at birth, the increase in pressure in the left atrium favors its progressive closure between 6 months to one year of life, and it should be completely closed by the completion of the first year of life. As can be seen in image 1, in some people, this closure does not occur, remaining open after birth, known as a patent foramen ovale (PFO) [3].

The frequency of PFO, according to autopsy-based research, can reach up to 25% in the general population without symptoms [1,3]. However, the most relevant aspect of this anatomical variant is its clinical impact, as it can be a cause of strokes with ischemic characteristics due to paradoxical embolisms. Clinically, there is doubt as to whether the stroke diagnosed in patients with PFO has any peculiarities regarding the rest of the strokes of atherothrombotic or embolic etiology, which could constitute a differentiating effect [5].

Let us remember that this stroke is caused by a paradoxical embolism. It has not been demonstrated that there is a typical pattern of cerebral ischemia specific to this condition, but it is true that it is usually associated with infarctions in cortical areas, strokes affecting multiple vascular areas, and the presence of infarctions of different ages in the same vascular area [1,2].

Regarding its diagnosis, the combination of transcranial Doppler (TCD), transthoracic echocardiography (TTE), and transesophageal echocardiography (TEE), complemented with bubble tests in the basal state and after Valsalva maneuver, would complete the available diagnostic tests (Figure 1). After the study, we can classify patients based on the size of the PFO:

- Small: number of micro-bubbles up to 5 in the left atrium (LA)
- Medium: from 6 to 20 micro-bubbles
- Large: more than 20 micro-bubbles




A: Schematic drawing of the cardiac chambers and the presence of PFO (black arrow).
B: Image under transthoracic echocardiogram (TTE) showing PFO (FO + red arrow).
C: Image under transesophageal echocardiography (TET) after administration of agitated saline in a patient from our study, where microbubbles are observed in the right atrium (green arrow).
D: Same patient as in image C but with passage of multiple microbubbles to the left atrium through the PFO (green arrow) diagnosed with massive SHUNT.
E: Monitoring of the D-I SHUNT with TCD in the temporal window of the MCA territory with a signal pattern compatible with mild shunt

**Figure 1:** Permanent foramen oval and its diagnose with TCD, TTE, TET.

### Other Structures Associated with PFO: Interatrial Aneurysm (ASA)

It is defined as the excursion of the septum towards the right or left atrium by 10 mm or more (Figure 2).

One of the possible pathophysiological explanations for the formation of the aneurysm he increase in right atrial pressure due to a fect in the septum primum or an associated diopathy.

The ASA is a significant emboligenic source, as it allows the formation of thrombi originating from the same vulnerability of the atrium, which generates arrhythmias at that level. It has been associated in several meta-analyses with patients who have suffered strokes of unknown origin more than those of known origin, especially those measuring more than 10 mm.

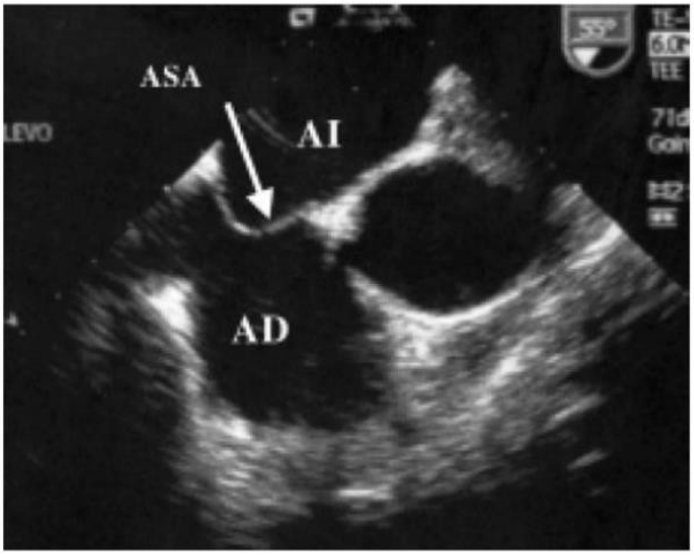



**Figure 2:** Echocardiogram showing atrial septum aneurysm (ASA) (arrow) in a patient with PFO. RA: right atrium and LA: left atrium. (Extracted from Montas de Oca[1]).

## Risk Factors for Stroke in Patients with PFO

There have been investigations regarding the signs or symptoms that may increase the risk of an embolic event in a patient [6,8], with the aim of preventing it or working towards primary prevention. Several studies have indicated that some patients are at higher risk than others of suffering a stroke due to paradoxical embolism, and these are summarized in the following table (Table 1):

**Table 1:** Factors that increase the probability that PFO is the cause of stroke.

| CLINICAL | ANATOMICAL |
|---|---|
| <55 years | ASA and atrial vulnerability that may cause:<br>• Paradoxical atrial arrhythmias<br>• Atrial fibrillation (thrombi) |
| No diagnóstico de otra causa de ictus | - Moderate to severe right-to-left shunt<br>- Greater height of the PFO measured during the Valsalva maneuver<br>- Greater septal excursion distance<br>- Septal aneurysm |
| DVT or PE | Great PFO |
| Cortical strokes. | Presence of Chiari network or Eustachian valve |
| Other factors: Valsalva maneuver at stroke onset, sleep apnea, wake-up stroke, history of migraine. | RoPe scale. |

DVT: Deep vein thrombosis; PE: pulmonary embolism; PFO: permanente foramen ovale; ASA: interauricular aneurysm.

## SARS-CoV-2 Infection as a Procoagulant Disease

COVID-19 can affect the brain and lead to a stroke through various mechanisms [7], including:

- **Vascular manifestations:** It can cause hypercoagulability, leading to a higher risk of thrombotic events such as ischemic strokes due to large vessel occlusions and cardioembolism.
- **Endothelial dysfunction:** The virus can affect the endothelial cells lining the blood vessels, contributing to vascular complications and potentially increasing the risk of stroke.
- **Neurotropism of the virus:** There is evidence suggesting that the SARS-CoV-2 virus can directly infect the central nervous system and cause neurological complications such as stroke.

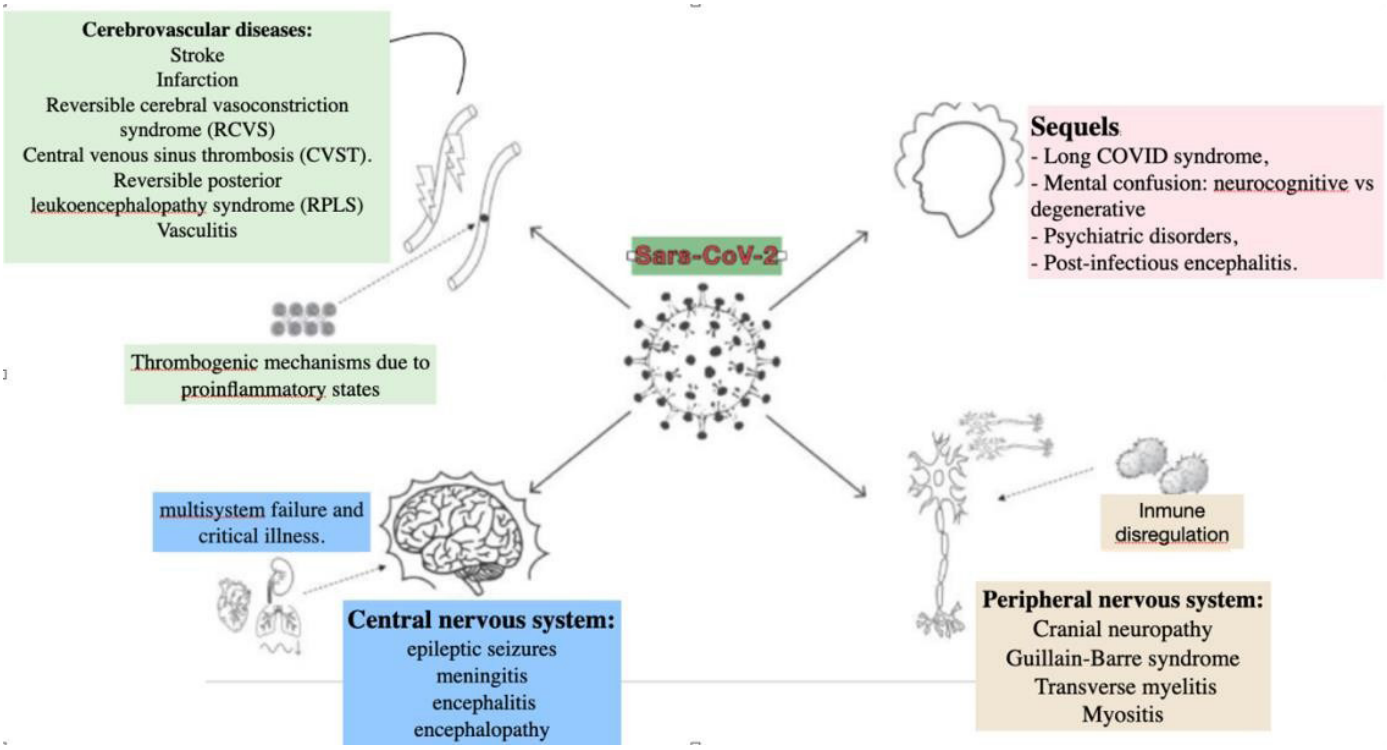



**Figure 3**. Spectrum of Neurological Complications Associated with SARS-CoV-2. Modified from Hingorani et al. [7].

- **Immune dysregulation:** The immune response triggered by COVID-19 can cause inflammation and damage to the blood vessels in the brain, increasing the risk of stroke.

Overall, the interaction of these factors may contribute to the development of strokes in patients with COVID-19, with strokes in this context often being more severe and associated with worse outcomes.
The clinical manifestations that may develop following SARS-CoV-2 infection are mention in figure 3.

Regarding COVID and PFO, studies demonstrating a direct relationship between the two have not yet been described [8,9]. However, it is understood that since COVID-19 can induce pro-inflammatory and pro-coagulant states, it would be conceivable that in the presence of a PFO, paradoxical embolism could occur due to peripheral venous thrombosis or pulmonary thromboembolism. Therefore, our objective is to determine whether patients with PFO are more prone to cerebral embolism and if this depends on the characteristics of the PFO and its association with ASA (atrial septal aneurysm).

## Material and Methods

### Design

A retrospective analytical observational study was conducted.

### Setting

The study was conducted at Francesc de Borja Hospital, located within the La Safor Health Area of Valencia. It is crucial to have joint action from primary care services (consultation and continuous care), hospital emergencies, cardiology, and neurology for a multidisciplinary approach to patients with a common protocol. The population covered by this Health Area is estimated to be around 188,500 inhabitants.

### Study Population

The study population comprises all adult patients aged >18 years and <65 years who belong to the Safor health area and who have attended the emergency department for stroke during the years 2020, 2021, and 2022.

### Inclusion criteria

- Women and men ≤ 80 years old.
- Treated at Francesc de Borja Hospital and belonging to the health department of Gandía.
- Confirmed diagnosis of ischemic stroke and/or TIA.
- In clinical history of Orion, Mizard with diagnosis of cryptogenic stroke-unknown origin stroke.

### Exclusion criteria

- Patients outside the age range.
- Patients from another community department and/or international tourists.

### Sample

A total of 1235 patients were studied after the diagnosis of ischemic stroke in the years 2020, 2021, and 2022. After selecting patients according to the inclusion criteria described in the previous section, 279 were excluded, leaving a total of 625 patients selected for the study.

### Descriptive Analysis

The collected database includes clinical variables associated with personal history, treatments prior to stroke, symptoms, and parameters measured with various tests. The descriptive analysis provides the most relevant statistics for all variables collected in the research: mean, standard deviation, minimum, maximum, median, and interquartile range (IQR) for continuous parameters, and absolute and relative frequencies for categorical variables. Due to the good sample size involved in the study, general objectives are addressed through a parametric statistical analysis approach.

### Inferential Analysis

The purpose of inferential analysis is to study the association between different study variables:

- Chi-square test of association: Measures the degree of dependence between two categorical variables. The result is considered valid as long as no more than 30% of the cells in the contingency table have an expected frequency of fewer than 5 cases, otherwise the Fisher exact test is used for 2x2 tables.
- Student's t-test: Used to determine if there is a significant difference between the means of two independent groups.
- Binary logistic regression to explain the probability of a certain variable on a binary scale (high or low probability that the cause of stroke is PFO) from an independent variable. Unadjusted OR with 95% CI and p-value of the Wald test are provided. For significant ($p<0.05$), relevant ($p<0.1$), or potentially confounding independent variables, the model is extended to a multivariate analysis, providing adjusted OR. The significance level employed in the analyses was 5% ($\alpha=0.05$).

### Studied Variables

1. Patient demographics: age, sex, ischemic stroke (defined by categories: atherothrombotic, cardioembolic, lacunar, unusual, and cryptogenic), SARS-CoV-2 infection (understood as positive Ag at the time of emergency care or positive PCR prior to or during admission).

2. We also collected data from complementary tests performed:

- For the diagnosis of ischemic stroke: brain CT scan, angio-CT, MRI, perfusion CT, chest X-ray, 24h Holter, 72h Holter, ECG.
- For the description of PFO and ASA: Transcranial Doppler: the variables were divided for stenosis (mild, moderate, severe) atheroma and/or PFO. Characteristics of PFO after TCD: the degree of SHUNT: slight (<10 microbubbles), moderate (10- 20 microbubbles), and severe (>20); and the velocity of the same (early-late). Characteristics of PFO after TTE, calculating: size, degree of SHUNT (slight (<10 microbubbles), moderate (10-20 microbubbles), and severe (>20)), and if there are associated structural alterations (ASA, atrial septal aneurysm, atrial thrombus, ASD, aortic plaque). In patients diagnosed with PFO or septal alteration after the tests, a TEE was performed to confirm the

diagnosis and the presence of other associated structures. With the TEE, agitated saline solution was used for the diagnosis of PFO, defined as the detection of microbubble passage to the left atrium within the first four cycles after opacification of the right atrium.

This was done in two phases: at rest and after the Valsalva maneuver. It was calculated:

- Degree of SHUNT (slight, moderate, severe).
- Velocity (early or late), specifying if bubble passage was positive at baseline and/or during Valsalva. If it was positive during Valsalva after being negative at baseline, it was calculated whether it was early, late, marked, or weak.
- Associated structural alterations (ASA: if there is presence of a mobile septal redundancy >10mm). All this information was collected by the researchers through review of medical records, as well as analytical and radiographic data recorded in the relevant programs.

## Ethical Considerations

This study is based on others conducted within the framework of the Doctoral Thesis entitled "Registry of the Prevalence of Patent Foramen Ovale with positive bubble test in patients from the Gandía department - RICFOPGA Study." This study was approved by the Research, Teaching and Ethics Committee (CIDE) of the Francisco de Borja Hospital for the use of personal patient data. Likewise, this study was approved by the Ethics Committee of the University of Valencia (CEIC), where the present doctoral program is being pursued, with verification number EERQV0CFZU7L7141 and registration number 209488. Each patient was asked for consent to participate in the study after appropriate information. The collection, storage, and processing of patient information were carried out in accordance with Organic Law 15/1999, of December 13, on the Protection of Personal Data.

## Results

The results reveal that within the research sample, a total of 335 patients have experienced a stroke, among whom 65 individuals (19.4%) exhibit a patent foramen ovale (PFO). Among these patients, there are 186 males (55.52%) and 149 females (44.48%), with an overall mean age of 65.8 ± 11.1 years, ranging from 31 to 75 years (Figure 4).

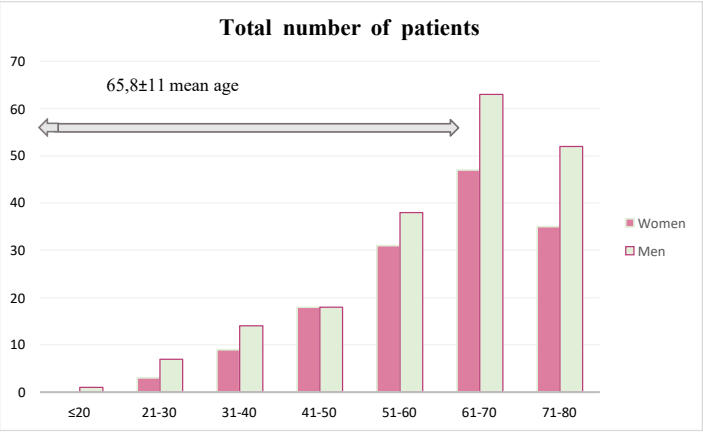


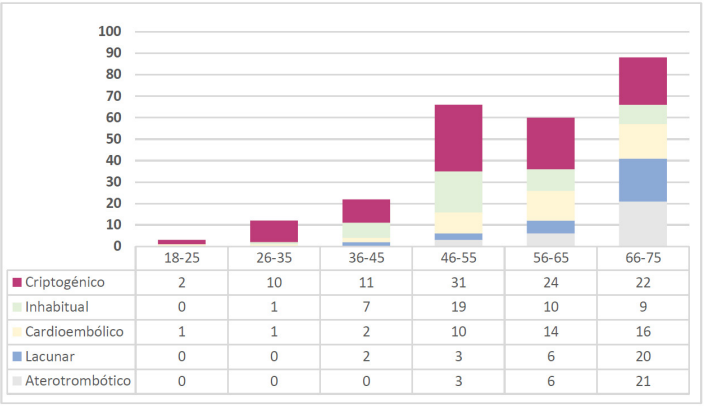

**Figure 4:** Distribution of patients by age.

Total number of patients treated for ischemic stroke or TIA in the Emergency Department and Internal Medicine Department of Francesc de Borja Hospital, under the care of Neurology and Cardiology between 2018-2021. The gray arrow indicates the overall mean age of the patients.

## Etiological subtype of stroke and study of cryptogenic stroke, as well as stroke severity

Of the initially categorized 625 patients of indeterminate origin, and after a rigorous study of possible causes, the following results were obtained according to etiology: 335 patients were diagnosed with cryptogenic stroke, 87 patients suffered from cryptogenic stroke (25.95%). There were 36 cases of lacunar stroke (10.72%); 93 cases of cardioembolic stroke (27.76%); 14 cases of unusual stroke (4.18%); and 60 cases of atherothrombotic stroke (31.34%).

In Figure 5, a comparison between the etiologies of stroke pathology and ages can be observed. A high percentage (38.4%) of atherothrombotic and cardioembolic strokes was observed among older patients (>55 years) and advanced stages. When separating the data by gender, it was found that older patients with non-cryptogenic strokes were predominantly male (61.3% vs. 38.7%, p=0.044), while the predominant group at younger ages corresponded to females (57.8% vs. 42.2%, p=0.43).




| | 18-25 | 26-35 | 36-45 | 46-55 | 56-65 | 66-75 |
|---|---|---|---|---|---|---|
| Criptogénico | 2 | 10 | 11 | 31 | 24 | 22 |
| Inhabitual | 0 | 1 | 7 | 19 | 10 | 9 |
| Cardioembólico | 1 | 1 | 2 | 10 | 14 | 16 |
| Lacunar | 0 | 0 | 2 | 3 | 6 | 20 |
| Aterotrombótico | 0 | 0 | 0 | 3 | 6 | 21 |

**Figure 5:** Comparison between the etiologies of stroke pathology and ages.

The different etiologies are presented grouped by six-year age groups (absolute value of patients in each category in the table), with a predominance of cryptogenic stroke at younger ages. The result is indicated as percentages.

## Prevalence of PFO

The prevalence of patients with PFO among those who have suffered a stroke was calculated, as well as the prevalence of stroke among the total population, and the prevalence of PFO among the total population. The prevalence of stroke in the overall population is 0.18%. In contrast, stroke with PFO has a prevalence of 0.03%. Among patients with stroke, PFO has a prevalence of 19.4%.

A total of 65 patients were diagnosed with PFO, of whom

63 suffered from cryptogenic stroke and 3 patients also had other causes, so the stroke was classified as non-cryptogenic (2 atherothrombotic and 1 cardioembolic).

## Ischemic Stroke and Sars-Cov-2

Of the 335 patients who suffered an ESUS, 107 were diagnosed with Sars-CoV-2 infection, with a prevalence of 31.94%. Separated by groups, we had 12 patients with COVID-19 and atherothrombotic stroke; 28 with COVID-19 and lacunar stroke; 9 of unusual origin; 22 cardioembolic; and 36 of cryptogenic origin.

## PFO and Sars-CoV-2

Sars-CoV-29 was detected more frequently among patients with PFO (p=0.026) and ischemic stroke, with a positive result in 41.5% of PFO patients compared to 27.4% in non-PFO patients, with these differences being statistically significant (p<0.026). Regarding gender, while 60% of women with PFO tested positive for SARS-CoV-2, this percentage decreased to 33.3% in men, showing significant differences (p=0.04).

When dividing the data of cryptogenic stroke in patients with PFO and SARS-CoV-2 infection, an increase in stroke was observed in patients with PFO and SARS-CoV-2 infection in the year 2020 compared to 2021 and 2022 (Table 1), with a gradual decrease in the number of cryptogenic strokes. As observed in Table 2, the FOP group was more prevalent in terms of stroke and SARS-CoV-2 infection (62.5% vs 27.78%, p=0.003).

**Table 2:** Cryptogenic stroke in patients with PFO and SARS-CoV-2 infection, separated by year.

| 2020- **ESUS n=42** | | | |
|---|---|---|---|
| | **PFO n=24** | **Non PFO n=18** | **p** |
| Sars-CoV-2 + | 15 (62,5) | 5 (27,78) | **0,003** |
| No Sars-CoV-2 | 9 (37,5) | 13(72,22) | 0,14 |
| 2021- **ESUS n=29** | | | |
| | **PFO n=19** | **Non PFO n=10** | **p** |
| Sars-CoV-2 + | 8 (42,11) | 3(30) | 0,07 |
| No Sars-CoV-2 | 11 (57,9) | 7 (70) | 0,66 |
| 2022- **ESUS n=16** | | | |
| | **PFO n=9** | **Non PFO n=7** | **p** |
| Sars-CoV-2 + | 2 (22,22) | 3 (42,86) | 0,25 |
| No Sars-CoV-2 | 7 (77,78) | 4 (57,14) | 0,11 |

A comparative study was conducted on patients with PFO according to their characteristics (small, medium, or large) and the presence or absence of ASA. In Figure 3, we describe the distribution of these patients according to their infection with or without SARS-CoV-2, where no statistical significance was found except in those patients with ischemic stroke and SARS-CoV-2 infection who also had a medium-large PFO without ASA (Figure 6).

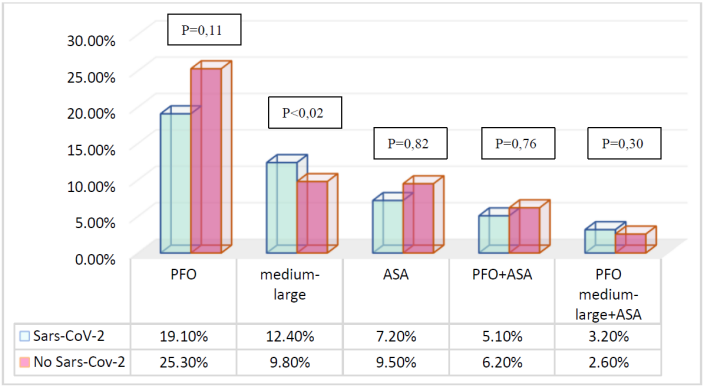



**Figure 6:** Patent foramen ovale and atrial septal aneurysm according to the diagnosis of ischemic stroke and SARS-CoV-2 infection.

## Conclusion

The most important conclusions we can draw from the results are as follows:

- Cryptogenic stroke is more prevalent in patients under the age of 55.
- Patent foramen ovale (PFO) is more frequently found in patients with an indeterminate or cryptogenic etiology of stroke, as well as in those with a positive infection for SARS- CoV-2, with women being the most affected by both conditions when experiencing an ischemic event.
- Patients infected with SARS-CoV-2 and ischemic stroke more commonly present with medium to large caliber PFO.

## Discussion

The investigation into the relationship between patent foramen ovale (PFO), ischemic stroke, and SARS-CoV-2 infection yields significant insights into the complex interplay of these factors in stroke pathology. Our study contributes to the existing body of literature by shedding light on several key aspects:

### Cryptogenic Stroke in Young Patients

Consistent with previous research [1,2], our findings underscore the predominance of cryptogenic stroke in patients under 55 years old. This highlights the importance of exploring underlying mechanisms, such as PFO, in this demographic group, as they may differ from those in older stroke populations.

### Association between PFO and SARS-CoV-2 Infection

Our study reveals a higher prevalence of SARS-CoV-2 infection among patients with PFO, particularly in women. This observation suggests a potential link between PFO and susceptibility to viral infections or the exacerbation of stroke risk factors in the presence of viral illness. Further investigation into this association is warranted to elucidate underlying mechanisms and clinical implications.

### Impact of SARS-CoV-2 on Stroke Severity

The increased prevalence of neurological sequelae in patients with SARS-CoV-2 infection in 2020 highlights the potential impact

of the pandemic on stroke outcomes [9-11]. This underscores the importance of timely recognition and management of COVID-19 in stroke patients to mitigate adverse neurological outcomes.

### Role of PFO Size in Embolic Events

Our study provides evidence of a potential association between medium to large PFO size and the development of embolic events, particularly in the context of SARS-CoV-2 infection. This finding suggests that PFO characteristics, such as size, may influence stroke pathophysiology and warrants consideration in risk stratification and management strategies.

A classification based on the size of the patent foramen ovale (PFO) according to DTC- s parameters has been proposed. Similarly to findings suggested by other authors [11,13], our study also found that medium to large-sized PFOs had a greater impact on the development of paradoxical embolism. However, further literature is needed to establish a definitive association. Overall, our study contributes valuable insights into the complex relationship between PFO, ischemic stroke, and SARS-CoV-2 infection. Further research is needed to elucidate underlying mechanisms, validate our findings, and inform clinical practice guidelines for the management of stroke patients with PFO and viral infections.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To Muñoz Navarro family and Gianmarco Nulli.


## References


1. Tesis Digital. 9.195. cited 2024 Apr 4. http://132.248.9.195/ptd2013/Presenciales/0705461/Index.html
2. Foramen Oval Permeable. Fundación Española del corazón. Contenido revisado por el Dr. Alfonso Valle Muñoz. https://www.revespcardiol.org/es-foramen-oval-permeable-situacion-actual-articulo-13123995.
3. Lamy C, Giannesini C, Zuber M, et al. Clinical and Imaging Findings in Cryptogenic Stroke Patients with and Without Patent Foramen Ovale. The PFO-ASA study. Stroke. 2002; 33: 706-711.
4. Martín Mañero C, Medina Durán P, Morales Delgado N, et al. Foramen oval permeable. Una actualización para atención primaria. Semergen. 2021; 47: 189-196. http://dx.doi.org/10.1016/j.semerg.2020.12.003.
5. Cruz-González I, Solis J, Inglessis-Azuaje I, et al. Foramen oval permeable: situación actual. Revista Espa de Cardiologia. 2018; 61: 738-751.
6. Pepi M, Evangelista A, Nihoyannopoulos P, et al. Recommendaciones for echocardiography use id the diagnosis and management of cardiac sources of embolism. Eur J Echocardiogr. 2010; 11: 461-476.
7. Hingorani KS, Bhadola S, Cervantes-Arslanian AM. COVID-19 and the brain. Trends Cardiovasc Med. 2022; 32: 323-330.
8. Nannoni S, de Groot R, Bell S, et al. Stroke in COVID-19: A systematic review and meta-analysis. Int J Stroke. 2021; 16: 137-149.
9. Tan Y-K, Goh C, Leow AST, et al. COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature. J Thromb Thrombolysis. 2020; 50: 587-595.
10. Nannoni S, de Groot R, Bell S, et al. Stroke in COVID-19: A systematic review and meta-analysis. Int J Stroke. 2021; 16: 137-149.
11. Siow I, Lee KS, Zhang JJY, et al. Stroke as a neurological complication of COVID-19: a systematic review and meta-analysis of incidence, outcomes and predictors. J Stroke Cerebrovascul Dis. 2021; 30.
12. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. Neurology. 2013; 81: 619-625.
13. Pezzini A, Grassi M, Zotto ED, et al. Do common prothrombotic mutations influence the risk of cerebral ischaemia in patients with patent foramen ovale? Systematic review and meta-analysis. Thromb Haemost. 2009; 101: 813-817.