Revista Española de Urgencias y Emergencias

REUE | Original Article

Respiratory rate as a predictor of severity in outpatients with SARS-CoV-2 infection

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OBJECTIVE. To evaluate the usefulness of respiratory rate (RR) as a predictor of severity in community-treated SARS-CoV-2 infection and to analyze the association of RR with course of disease.

MATERIAL AND METHODS. We included case records for 4019 patients with SARS-CoV-2 infection diagnosed in the community who were over the age of 60 years and/or were considered at high risk. The following clinical data were recorded for all patients: baseline oxygen saturation, blood pressure, temperature, heart rate, RR, and symptoms. Routine laboratory analyses and chest x-rays were also ordered for patients who were admitted to hospital.

RESULTS. Three hundred thirty-six patients (8.4%) were transferred to an emergency department, 293 (7.3%) were admitted, and 3726 were followed during treatment in the community. RR was associated with the number of days hospitalized (ρ, 0.15; *P* = .014). Tachypnea was associated with higher comorbidity, more symptoms (*P* < .001 for all symptoms evaluated), admission to an intensive care unit (46.6% *vs* 28.0%; χ^2 = 6.49; *P* = .011) with elevated markers of inflammation. None of the community-treated patients died (*vs* 28 of the hospitalized patients). Tachypnea observed during community treatment was associated with higher mortality (in 43% *vs* 2.9%; χ^2 = 133.29; *P* < .001). RR was a predictor of admission to hospital (area under the receiver operating characteristic curve, 0.789 ± 0.015; 95% CI, 0.759-0.818; *P* < .001).

CONCLUSIONS. RR is a useful as a clinical sign that predicts hospital admission and mortality.

Keywords: SARS-CoV-2 infection. COVID-19. Respiratory rate. Tachypnea. Prognostic factors.

Frecuencia respiratoria como predictor de gravedad en el paciente ambulatorio con infección por SARS-CoV-2

OBJETIVO. Evaluar la utilidad de la frecuencia respiratoria como predictor de gravedad en el paciente ambulatorio con infección por SARS-CoV-2 y analizar su relación con la evolución de la enfermedad.

MATERIAL Y MÉTODOS. Se incluyeron 4.019 pacientes diagnosticados de infección por SARS-CoV-2, con edad mayor de 60 años y/o algún factor de vulnerabilidad seguidos de forma ambulatoria. Se recogieron datos demográficos, constantes vitales (saturación basal de oxígeno, tensión arterial, temperatura, frecuencia cardiaca y respiratoria), y síntomas desarrollados, además de analítica rutinaria y radiografía de tórax en los pacientes que precisaron ingreso.

RESULTADOS. Trescientos treinta y seis pacientes necesitaron derivación a urgencias (8,4%). De ellos, precisaron ingreso 293 (87,2%). Se observó correlación entre la frecuencia respiratoria y el número de días de ingreso (rho = 0,15; p = 0,014). La taquipnea se relacionó con mayor comorbilidad, más sintomatología (p < 0,001 en todos los síntomas evaluados), más ingresos en unidad de críticos (46,6% *vs* 28,0%, X^2 = 6,49; p = 0,011) y con la elevación de marcadores inflamatorios. Ningún paciente tratado de forma ambulatoria falleció y, de los ingresados, fallecieron 28 pacientes (9,6%). La taquipnea en la valoración domiciliaria se asoció con una mayor mortalidad (43% *vs* 2,9%; X^2 = 133.29; p < 0,001). También fue un predictor de ingreso hospitalario: área bajo la curva (AUC) = 0,789 ± 0,015 (IC 95%: 0,759-0,818); p < 0,001.

CONCLUSIONES. La frecuencia respiratoria es un signo clínico útil como marcador de ingreso hospitalario y predictor de mortalidad.

Palabras clave: Infección por SARS-CoV-2. COVID-19. Frecuencia respiratoria. Taquipnea. Marcador pronóstico.

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Article Information: Received: 30-4-2024. Accepted: 20-5-2024. *Online:* 30-5-2024.
Editor in Charge: Guillermo Burillo-Putze.

Introduction

On December 31st, 2019, the Chinese government first reported an outbreak of coronavirus disease (COVID-19) in Wuhan, China. The pandemic quickly spread throughout the Chinese provinces and to the rest of the world. On January 31, 2020, the first case of COVID-19 in Spain was detected on the island of La Gomera, treated as an imported case from a transmission in Germany.[1]

From the beginning of the pandemic, it was observed that in patients who progressed to respiratory failure, the disease followed a characteristic pattern.[2] Therefore, efforts were made to identify risk factors for poor prognosis in COVID-19 patients that led to hospital admission or higher risk of death.[3,4] Understanding which patients are more likely to develop severe disease allows for objective decisions regarding admission and discharge.

However, most patients with mild or moderate COVID-19 infection did not require hospital admission but, depending on their medical history, needed medical supervision. This would not have been possible without the creation of specific surveillance programs,[5,6] which included different protocols for patient assessment. These surveillance programs were developed mainly within Primary Care[7] and aimed to identify variables that determined prognosis.[8] In our area, the EDCO program (Home COVID Care Team) was implemented, serving a reference population of approximately 950,000 inhabitants, with the goal of early evaluation of patients with risk factors for unfavorable disease progression.

The objective of this study is to assess whether respiratory rate is useful as a predictor of severity in outpatients with SARS-CoV-2 infection, and to analyze which comorbidities and clinical characteristics are associated with it.

Material and methods

We retrospectively analyzed a total of 4,019 patients (consecutively recruited from Primary Care in Tenerife, Canary Islands, Spain) in a close-monitoring program for vulnerable patients to reduce morbidity and mortality (EDCO project). Patients were recruited between February 1st, 2021, and March 30th, 2022. Inclusion criteria were confirmed COVID-19 infection by real-time reverse transcription polymerase chain reaction (RT-PCR) in patients older than 60 years, or in those older than 18 years with at least one previously recorded vulnerability factor in their medical history. Vulnerability factors were defined according to the Spanish Ministry of Health guidelines[9], including: type 1 or type 2 diabetes mellitus, arterial hypertension, severe neurological disease (Alzheimer's disease, epilepsy, stroke, Parkinson's disease, brain tumors, multiple sclerosis), chronic heart disease (including chronic ischemic heart disease, heart failure, cardiomyopathy), chronic respiratory disease (including chronic obstructive pulmonary disease —COPD—, asthma, pulmonary fibrosis, sleep apnea–hypopnea syndrome, chronic bronchitis, pulmonary emphysema, interstitial lung disease, and bronchiectasis), home oxygen therapy, active malignant neoplasm, chronic kidney disease (including hemodialysis and renal transplantation), chronic liver disease (alcoholic liver disease, non-alcoholic steatohepatitis, or autoimmune liver disease), obesity (body mass index > 30 kg/m^2), immunosuppression, and pregnancy.

Patients were evaluated by a physician at home between days 4 and 5 after diagnosis. Variables collected included demographic data, vital signs and physiological parameters (baseline oxygen saturation, blood pressure, temperature, heart and respiratory rates), and clinical symptoms such as cough, sputum, pleuritic pain, diarrhea, vomiting, and dyspnea (Table 1). According to medical indication, patients who required it received a pulse oximeter. Patients and/or family members were instructed to identify warning signs (hypotension, decreased oxygen saturation, altered consciousness, respiratory distress, or prolonged fever). If symptoms worsened, patients were advised to request referral to the emergency department. Patients were followed up daily by telephone by their primary care physician. Hospital referral criteria included tachypnea (defined as respiratory rate ≥ 22 breaths per minute [bpm]), systolic blood pressure ≤ 100 mmHg, temperature ≥ 38 °C for 3 consecutive days, baseline oxygen saturation ≤ 92%, or deterioration of general condition by medical criteria. Hospitalized patients underwent blood tests (including complete blood count, basic biochemistry, D-dimer, ferritin, LDH, and C-reactive protein) and chest radiography. Outcome variables included need for hospital admission from the emergency department, admission to the intensive care unit, and discharge or death during hospitalization. Analyzed variables corresponded to clinical data at the time of study inclusion, collected at the patient's home.

Statistical analysis

The Kolmogorov–Smirnov test was used to assess whether variables followed a normal distribution. Demographic and clinical characteristics were expressed as mean ± standard deviation (SD) or percentages for categorical variables. For continuous variables not following a normal distribution, data were presented as median and interquartile range (IQR). The Mann–Whitney U (Z) test was used for non-parametric variables, and the Student's t-test for normally distributed ones. The chi-square test was used to compare qualitative variables. Correlation analyses were performed to assess associations between quantitative variables. Receiver operating characteristic (ROC) curve analysis was employed to explore the ability of respiratory rate to predict hospital admission. All analyses were conducted using SPSS® v25.0.

Results

A total of 4,019 patients were included, 56.1% women (n = 2,253). Mean age was 56.9 ± 17.3 years (range, 18–105). Of the total, 336 patients met referral criteria for emergency care (8.4%). Of these, 43 were discharged home for continued outpatient follow-up, while 293 patients (7.3% of the total sample) required hospitalization

Table 1. Demographic variables, comorbidities, symptoms, and signs in patients with COVID-19

Characteristic	n	%	Mean ± SD / Median (IQR)
Sex			
Male	1,766	43.9	
Female	2,253	56.1	
Age (years)			
< 60	2,529	62.9	
≥ 60	1,490	37.1	
Comorbidities			
Diabetes mellitus	976	24.3	
Hypertension	2,192	54.5	
Severe neurological disease	168	4.2	
Chronic heart disease	817	20.3	
Respiratory disease	1,105	27.5	
Home oxygen use	6	0.1	
Active neoplasm	181	4.5	
Chronic liver disease	89	2.2	
Chronic kidney disease	136	3.4	
Obesity	1,333	33.2	
Immunosuppression	129	3.2	
Pregnancy	95	2.4	
Vulnerability factors			
≥ 2 factors	2,436	60.6	
≥ 3 factors	2,625	65.3	
Symptoms			
Cough	1,657	41.2	
Sputum production	567	14.1	
Pleuritic pain	104	2.62	
Diarrhea	287	7.1	
Vomiting	64	1.6	
Dyspnea	476	11.8	
Vital signs			
Temperature (°C)	4,016	99.4	36.24 ± 0.53 36.2 (36-36.5)
Systolic blood pressure (mmHg)	3,973	98.4	131.16 ± 18.1 130 (120-141)
Diastolic blood pressure (mmHg)	3,973	98.4	80.44 ± 11.43 80 (72-89)
Heart rate (bpm)	4,005	99.2	78.54 ± 13.47 78 (69-87)
Respiratory rate (bpm)	4,010	99.3	16 ± 3 15 (14-18)
Physiological data			
Oxygen saturation (%)	4,008	99.2	97.17 ± 2.76 98 (97-98)

(Figure 1). Regarding vulnerability factors, the most frequent was arterial hypertension (54.5%), followed by obesity (33.2%), diabetes mellitus (24.3%), and cardiorespiratory diseases (20.3% cardiac disease, 27.5% respiratory disease).

The predominant symptom was cough (41.2%), followed by sputum production (14.1%) and dyspnea (11.8%). Mean systolic blood pressure was 131.16 ± 18.11 mmHg, diastolic 80.44 ± 11.43 mmHg, heart rate 78.54 ± 13.47 bpm, and mean oxygen saturation 97 ± 3%. Mean respiratory rate was 16 ± 3 bpm. Twenty-five percent of patients had a respiratory rate ≥ 18 bpm.

Using the 22 bpm threshold, 126 patients (3.1%) presented tachypnea. These patients had higher prevalence of diabetes mellitus (4.6% vs 2.7%, chi-square test, 8.56; P = .003), arterial hypertension (3.7% vs 2.5%, chi-square test, 3.90; P = .048), heart disease (4.4% vs 2.8%, chi-square test, 4.92; P = .027), and active neoplasia (7.7% vs 2.9%, chi-square test, 11.60; P = .001). Patients > 60 years more frequently had tachypnea (4.2% vs 2.2%, chi-square test, 12.39; P < .001; Figure 2). Tachypnea was also associated with the presence of ≥ 2 vulnerability factors (3.9% vs 1.8%, chi-square test, 12.41; P < .001) and ≥ 3 factors (4.5% vs 2.3%, chi-square test, 14.73; P < .001). Patients with tachypnea more often reported symptoms such as cough (6.5% vs 0.01%, chi-square test, 105.99; P < .001), sputum (6.9% vs 2.5%, chi-square test, 24.35; P < .001), diarrhea (9.1% vs 2.7%, chi-square test, 24.89; P < .001), vomiting (12.5% vs 3.0%, chi-square test, 15.72; P < .001), and dyspnea (16.7% vs 1.3%, chi-square test, 317.84; P < .001).

A statistically significant direct correlation was found between respiratory rate and length of stay (rho = 0.15; P = .014). However, there was no association between tachypnea and the presence of pneumonia on chest radiography (chi-square test, 2.67; P = .10). Tachypnea was more frequent among patients admitted to the intensive care unit (46.6% vs 28.0%, chi-square test, 6.49; P = .011).

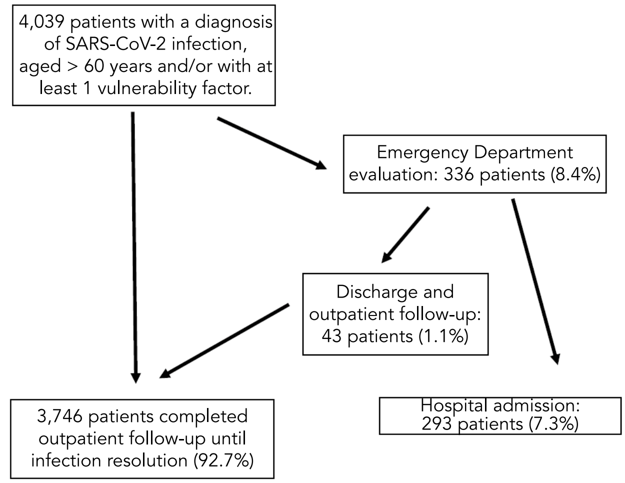

Figure 1. Patients included in the study.

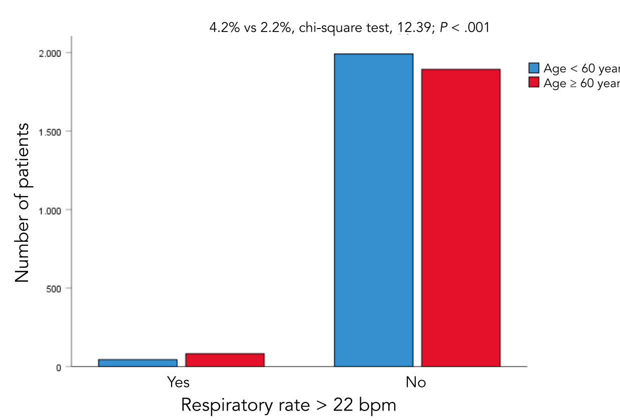

Figure 2. Presence of tachypnea in patients aged ≥ 60 years (4.2% vs 2.2%, chi-square test, 12.39; P < .001).

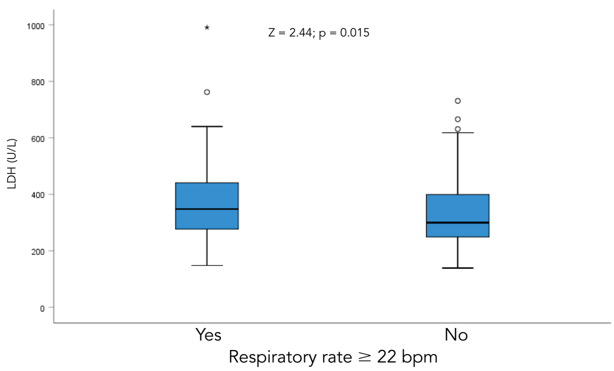

Figure 3. Relationship between LDH levels and presence of tachypnea.

Regarding laboratory parameters, tachypnea was associated with higher levels of ferritin (Z = 1.96; *P* = .049), LDH (Z = 2.44; *P* = .015; Figure 3), and C-reactive protein (Z = 2.03; *P* = .043). No outpatients died, but among hospitalized patients, 28 (9.6%) died. Considering the total sample, tachypnea was associated with higher mortality (present in 43% of deceased patients vs 2.9% of survivors; chi-square test, 133.29; *P* < .001). However, among hospitalized patients alone, tachypnea was not associated with higher mortality.

The predictive ability of respiratory rate for hospital admission is shown in Figure 4, with an area under the curve (AUC) = 0.789 ± 0.015 (95% CI, 0.759–0.818; *P* < .001), sensitivity 44.2% and specificity 94.2% at 18 bpm, while 22 bpm yielded sensitivity 31% and specificity 99%. As a predictor of mortality, respiratory rate showed AUC = 0.737 ± 0.055 (95% CI, 0.629–0.846; *P* < .001; Figure 5).

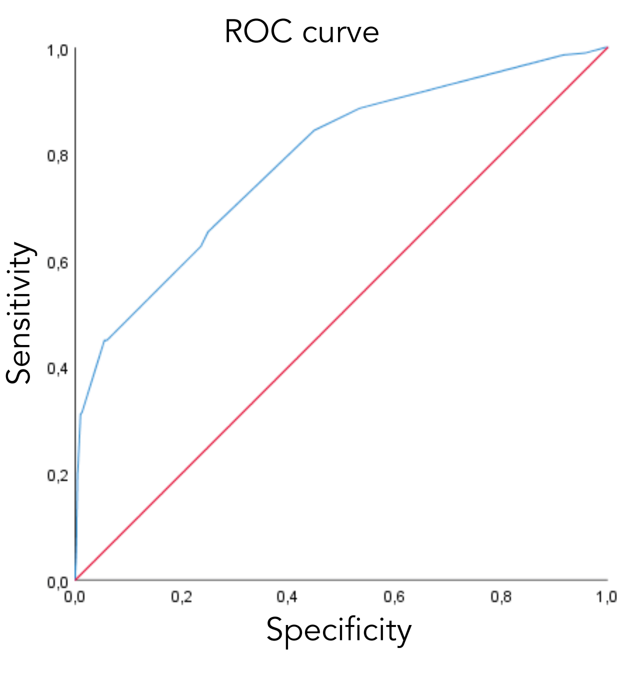

Figure 4. Relationship between respiratory rate and hospital admission. AUC, 0.789 ± 0.015 (95% CI, 0.759–0.818); *P* < .001.

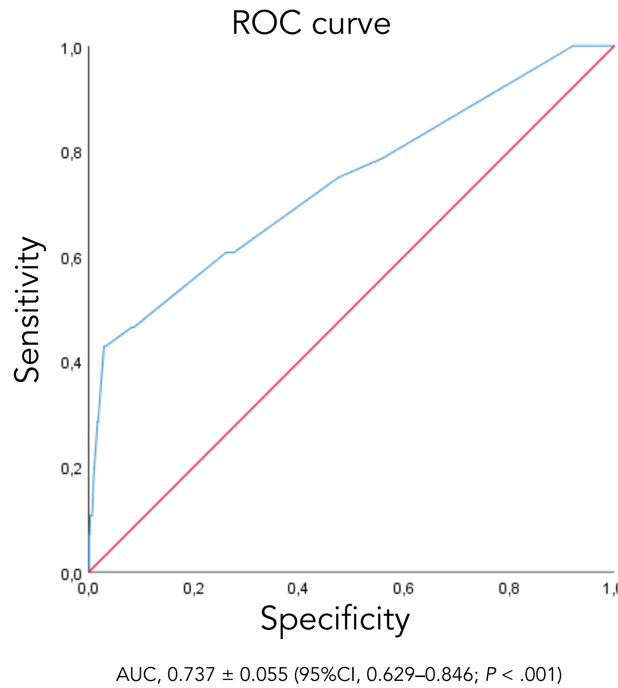

Figure 5. Relationship between respiratory rate and mortality. AUC, 0.737 ± 0.055 (95% CI, 0.629–0.846); *P* < .001.

Discussion

Respiratory rate has been described as a marker of severity in various scoring systems—both those for suspected infection, such as the quick SOFA[10] (> 22 bpm), and those assessing patients with respiratory infections, such as CURB-65,[11] the FINE scale, or the PSI scale.[12] It is also included in scales that assess other respiratory conditions, such as pulmonary embolism (PESI scale),[13] and even in polytrauma (Revised Trauma Score – RTS).[14] Therefore, its usefulness as an indicator of poor prognosis is well established. However, these scales are primarily applied in hospital settings, and their use is limited to patients with a suspected risk of poor clinical evolution. Moreover, it has been shown that traditional pneumonia severity assessment scales may have limitations in COVID-19.[15] In the outpatient setting, different referral criteria were established from Primary Care, in some cases using respiratory rate cut-off points > 25 bpm[16] or > 30 bpm.[17]

In our series, the presence of tachypnea—defined as a respiratory rate = to or > 22 bmp—was associated with a higher prevalence of vulnerability factors. This finding is consistent with the increased risk of poor outcomes previously described in elderly,[19] obese,[20] hypertensive,[21] cardiac,[22] and cancer patients with active neoplasia.[23] Among hospitalized patients, tachypnea was associated with worse clinical evolution, both in terms of longer hospital stay and higher frequency of admission to intensive care units. It was also related to higher levels of acute-phase reactants and LDH. These results are expected, since tachypnea is a parameter that reflects respiratory dysfunction[24-27] and, therefore, greater disease severity. However, literature regarding the evaluation of respiratory rate in COVID-19 patients is relatively scarce. Haimovich *et al.* defined the Quick COVID-19 Severity Index, which assigns 1 point for respiratory rates above 22 bpm and 2 points for rates > 28 bpm.[28] In Italy, the Brescia-COVID scale was developed, incorporating respiratory rate > 22 bpm to assess the severity of respiratory involvement.[29] Nonetheless, this scale was designed for hospitalized patients, where treatment intensity is determined according to the parameters met. In a recently published study, Owens *et al*. proposed a rapid triage tool to determine the need for hospitalization in patients with severe COVID-19 infection, in which respiratory rate was not considered among the evaluated variables.[30]

In our study, the presence of tachypnea was associated with higher mortality. As mentioned, tachypnea reflects respiratory dysfunction, which likely worsens prognosis due to the silent hypoxemia described in this patient profile.[31] Moreover, ROC curve analysis showed that respiratory rate is a good predictor of hospital admission [AUC, 0.789 ± 0.015 (95% CI, 0.759–0.818); $P < .001$] and of mortality [AUC, 0.737 ± 0.055 (95% CI, 0.629–0.846); $P < .001$].

Regarding poor outcome risk, numerous risk stratification models have been described as decision-support tools, most of them focused on hospitalized patients.[32,33] In Primary Care, several studies have been published describing factors associated with worse clinical evolution in outpatients with COVID-19 infection,[34,35] but most do not consider respiratory rate. In our study, the positive predictive value of tachypnea was 71%, while the negative predictive value reached 95%. The presence of tachypnea is therefore useful for screening disease severity; however, in patients presenting with tachypnea, a more comprehensive assessment of the overall clinical condition should be performed.

Identifying tachypnea may promote a faster response and earlier, more effective therapeutic interventions. Despite extensive evidence showing that altered respiratory rate is a predictor of adverse clinical events, it remains a clinical sign often unrecorded by healthcare professionals.[36,37] Conversely, training patients and relatives to measure respiratory rate could be beneficial in home surveillance programs to detect respiratory deterioration early and activate emergency services. Respiratory rate is an easy-to-obtain, immediate, and cost-free clinical parameter that, during periods of high incidence of respiratory infections, could help better identify disease severity and optimize resource use. In clinical practice, this vital sign is often not measured, having been incorrectly replaced by pulse oximetry, which presents several physiopathological, clinical, and technical limitations.[38]

This study has several limitations. First, it is a retrospective study using data from a Primary Care surveillance project for COVID-19 patients. Patient selection was performed via a computer program that screened medical records for one or more of the predefined vulnerability factors; however, these records might not have been fully updated. Therefore, it is possible that some patients with comorbidities were not selected by the EDCO program.

Among this study's strengths is its large sample size, representative of the population studied. Another strong point is the systematic measurement of respiratory rate—a clinical sign that is unfortunately seldom recorded in clinical practice—and the analysis of multiple clinical and laboratory variables in this patient profile.

Conclusions

Respiratory rate is a useful clinical sign as both a marker of hospital admission and a predictor of mortality in patients with acute SARS-CoV-2 infection. The recording of respiratory rate should be improved in both hospital and outpatient settings to more effectively screen for clinical deterioration in these patients—and, in general, in all acute or home-monitored patients—allowing for early identification of complications and prompt intervention.

ARTICLE INFORMATION

Conflict of Interest Disclosures: None reported.

Funding: The authors declare the non-existence of funding in relation to this article.

Ethical responsibilities: The authors have confirmed the maintenance of confidentiality and respect for the patient rights, agreement of publication, and transfer of rights to Revista Española de Urgencias y Emergencias.

The study protocol was approved by the Bioethics Committee of the *Hospital Universitario de Canarias* (CHUC_2022_72) and the Primary Care Management of Tenerife, ensuring the protection and confidentiality of personal data according to Organic Law 15/1999 and Royal Decree 994/1999. Verbal consent was obtained from all patients; written consent was not collected during the pandemic peak to avoid paper contamination, in accordance with prevailing health regulations at the time. The ethics committee granted a waiver of written informed consent.

Article not commissioned by the Editorial Board and with external peer review.

Note of the editors: This is a BOWMAN-generated English translation of the officially indexed Spanish-language article, which should be cited as Rev Esp Urg Emerg. 2024;3:144-149. In this translated version, the editors have supervised the process; however, it cannot be ruled out that some errors resulting from the artificial intelligence translation process may have gone unnoticed.

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