Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Misdiagnosis rate among negative COVID-19 patients in real-life with Panbio COVID-19 antigen rapid test during 2021

Dear Editor,

We have read with interest the letter from Pilecky et al.[1] about the diagnostic performance for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of lateral flow assay (LFA) compared to quantitative reverse transcription PCR (RT-qPCR). According to available published data, the Panbio test has a sensitivity of 71.8% and a specificity of 99.6%. However, the sensitivity is usually higher when exposure to COVID-19 is suspected, or symptoms of COVID-19 are present.[2] Moreover, the probability that a positive or negative result is true varies with the prevalence and therefore influences the likelihood of misdiagnosis.[3] Focusing on the consequences of misdiagnosis is also necessary because it could help choosing the most appropriate test.

Diagnostic testing of SARS-CoV-2 is critical for the control of the pandemic. The RT-qPCR is the gold standard for diagnosing SARS-CoV-2 infection. However, this method takes a long time (several hours) and requires specialized equipment and trained personnel.[4] Besides, RT-PCR has a low detection limit but can detect SARS-CoV-2 RNA fragments that can be positive without evidence of active viral replication, overestimating the number of COVID-19 infectious patients. Rapid antigen detection tests (RADTs) are lateral flow immunoassays (LFA) that are frequently used as point of care (POC) tests for the detection of active SARS-CoV-2 infection. These tests are fast, reliable, inexpensive, and detect SARS-CoV-2 proteins in respiratory samples.[4,5]

The diagnostic performance of RADTs has been extensively evaluated,[4,6] detecting most SARS-CoV-2 positive samples among individuals at high risk for SARS-CoV-2 infection (symptomatic or direct contact with a positive case). However, despite having high specificity, RADTs can report false negatives, giving a false sense of security that often leads to relaxing preventive measures, such as wearing masks indoors or in crowded places, maintaining social distance, and ventilating closed spaces.[5] The diagnostic performance of the RADTs may change depending on symptoms and SARS-CoV-2 prevalence.[3] It may also be influenced by the variant of SARS-CoV-2 and the vaccination status.[7] Therefore, the role of RADTs needs to be re-evaluated over time according to these parameters. The Panbio COVID-19 antigen rapid test (Abbott Rapid Diagnostic Jena GmbH, Jena, Germany), from now on Panbio test, is a widely used test that detects SARS-CoV-2 viral nucleocapsid protein in biological samples (i.e., nasopharyngeal swabs).[6]

Our objective was to assess in real-life the misdiagnosis rate among negative COVID-19 patients with the Panbio test during 2021, where the prevalence of different SARS-CoV-2 variants and the proportion of vaccinated people changed substantially over time.

We conducted a cross-sectional study at the Hospital Universitario Infanta Leonor (Madrid, Spain) between January and December 2021. During that period, 23,240 individuals with a suspected COVID-19 or close contact with SARS-CoV-2 infected persons underwent a RADT to diagnose COVID-19. Of those, 19,176 patients presented negative RADTs, and only 4124 underwent a simultaneous RT-PCR test (within the next 24 h) to verify the RADT result. Of these, 3,657 people underwent the Panbio test, and 467 were assessed with other RADTs. Finally, we selected 3657 individuals who had a negative Panbio test and underwent a simultaneous RT-PCR test (within the following 24 h). All participants gave their consent before enrollment. The Ethics Committee of Hospital General Universitario Gregorio Marañón approved the study (Ref# 162/20).

The obtention of nasopharyngealswab samples was performed exclusively by trained personnel. Clinical data were collected from hospital records. Panbio test and RT-PCR results were collected as a dichotomous (positive or negative) variable. The Ethics Committee of Hospital Universitario Infanta Leonor approved the study and waived informed consent to collect clinical data.

We calculated the false omission rate (FOR) or individuals with a negative Panbio test who had a positive RT-PCR [FOR = false negatives / (false negatives + true negatives)] during the four quarters of 2021 [Q1 (January-March), Q2 (April-June), Q3 (July-September), Q4 (October-December)]. Differences between groups were evaluated by univariate analysis with the chi-square and Mann-Whitney tests. All statistical analyses were carried out using SPSS software (SPSS 26.0, IBM Corp., Armonk, NY, USA).

For the analysis, 3,657 participants were included, whose characteristics are shown in Table 1. The median age was 53.6 years, and 46.5% of them were male. Besides, 24.5% had hypertension, 9.7% had diabetes mellitus, 13.4% had cardiovascular disease, and 9% had chronic pulmonary disease. Concerning COVID-19, 80.6% had symptoms. Throughout 2021, percentages of chronic pulmonary disease and COVID-19 symptoms were significantly different among quarters ($p < 0.05$). The FOR values in all 2021 quarters were around 8%, and we did not find significant differences in FOR values among quarters by univariate analysis ($p = 0.930$; Fig. 1A). We also evaluated these differences by COVID-19 symptoms (Fig. 1B), but we did not find significant differences.

Resuming daily life requires ruling out SARS-CoV-2 infection using tests with a high negative predictive value.[5] However, mistakenly ruling out a positive individual can promote SARS-CoV-2 infection. The FOR is the probability that a RADT will give a false-negative result because the test is not sensitive enough. In our study, we found FOR values around 8% (< 10%), a similar percentage to previously published data for the Panbio test.[2,8] Besides, FOR values were constant during 2021, not being affected by changes in prevalence, SARS-CoV-2 variants, and vaccination

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Table 1
Epidemiological and clinical characteristics of participants who underwent simultaneous RADT and RT-PCR for COVID-19 diagnosis during 2021 in Hospital Infanta Leonor (Madrid).

	Total	January-March	April-June	July-September	October-December	p-value
No.	3,657	473	1,316	923	945	–
Age (years)	53.6 (34.4; 76.4)	54.8 (35.2; 80.1)	53.5 (35.2; 74.2)	51.4 (33.3; 77.2)	54.3 (33.7; 75.9)	0.427
Male (%)	1,700 (46.5%)	232 (49%)	606 (46%)	429 (46.5%)	433 (45.8%)	0.678
Comorbidity (n = 2,590)						
Hypertension (%)	635 (24.5%)	90 (24.5%)	254 (25.6%)	138 (23.2%)	153 (24.1%)	0.729
Diabetes Mellitus (%)	252 (9.7%)	44 (12%)	104 (10.5%)	55 (9.2%)	49 (7.7%)	0.118
Cardiovascular disease (%)	347 (13.4%)	57 (15.5%)	131 (13.2%)	76 (12.8%)	83 (13.1%)	0.641
Chronic pulmonary disease (%)	234 (9%)	26 (7.1%)	94 (9.5%)	40 (6.7%)	74 (11.6%)	0.011
COVID-19 symptoms (n = 3561)	2,870 (80.6%)	397 (84.8%)	1,103 (84.3%)	677 (77.9%)	693 (75.7%)	<0.001
Cough (%)	1,091 (36.3%)	131 (32.4%)	413 (36.1%)	190 (27.4%)	357 (46.8%)	<0.001
Dyspnea (%)	1,126 (37.6%)	163 (39.7%)	436 (38.3%)	229 (32.8%)	298 (40.1%)	0.027
Fever (%)	990 (33%)	152 (37%)	381 (33.4%)	248 (34.3%)	209 (28.9%)	0.930

Statistic: Differences among groups were calculated by Chi-squared and Mann-Whitney tests.
Abbreviations: COVID-19, Coronavirus disease 2019; RADT, rapid antigen detection tests; RT-PCR, reverse transcription polymerase chain reaction.

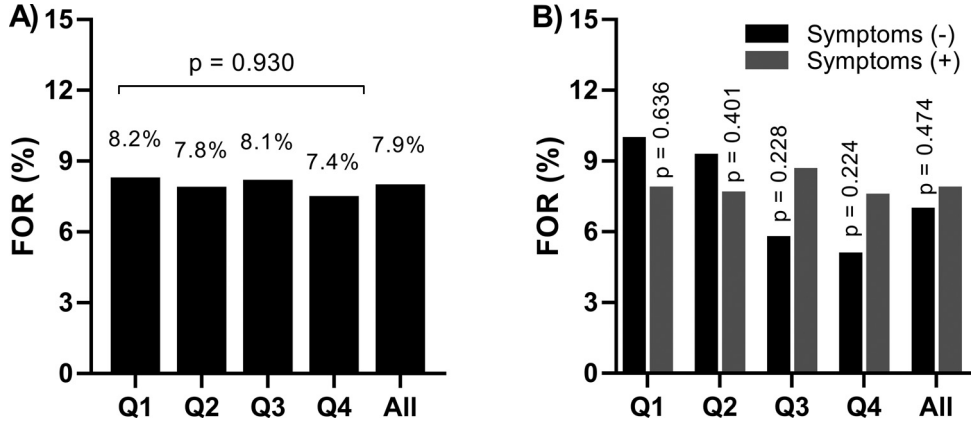

Fig. 1. Frequency of individuals with a negative result in Panbio COVID-19 antigen rapid test who had a positive RT-PCR (false omission rate) during 2021. Statistics: Differences among groups were calculated by the Chi-squared test. Abbreviations: FOR; false omission rate, RT-PCR, reverse transcription polymerase chain reaction; Q1, January-March 2021; Q2, April-June 2021; Q3, July-September 2021; Q4, October-December 2021.

rate in Spain.[9] Our data are relevant since some concerns have been raised regarding the Panbio test performance in the changing scenario of the SARS-CoV-2 pandemic.[9] In Spain, the proportion of people fully vaccinated against COVID-19 increased from 0.18% (January) to 81.9% (December). Likewise, the SARS-CoV-2 Alpha variant was dominant during the first semester of 2021 (77% in March and 45% in June). However, the SARS-CoV-2 Delta variant became dominant at the beginning of July (62%) and reached almost 100% at the end of September (99%). At the end of November, Delta was still 100% prevalent. In December, the Omicron variant emerged and became dominant (54%) at the end of the month.[9] In this regard, the appearance of SARS-CoV-2 variants could affect the diagnostic performance of the Panbio test due to changes in the altered protein, which is recognized by LFA-specific antibodies.[10]

Study limitations include lack of data for Ct ranges in RT-PCR, lack of data for COVID-19 patients with a positive result in the Panbio test, incomplete clinical information, and the number of days from symptoms onset or risk contact in asymptomatic patients. The strengths of our study are the high number of samples distributed throughout 2021 and consecutive unselected patient samples with on-site test execution in real-life conditions.

In conclusion, our study shows that the misdiagnosis rate among patients with a negative Panbio test was acceptable and remained stable throughout 2021, despite substantial changes in the COVID-19 prevalence, SARS-CoV-2 variants, and vaccination rates.

Declaration of Competing Interest

The authors declare that they have no competing interests.

CRediT authorship contribution statement

Pablo Ryan: Visualization, Conceptualization, Funding acquisition, Data curation, Writing – review & editing. **Felipe Pérez-García:** Data curation, Formal analysis, Writing – review & editing. **Juan Torres-Macho:** Data curation, Writing – review & editing. **Carlos Bibiano:** Writing – review & editing. **Juan Ignacio Lazo:** Data curation, Writing – review & editing. **Guillermo Castaño-Ochoa:** Data curation, Writing – review & editing. **Erick Joan Vidal-Alcántara:** Data curation, Writing – review & editing. **María José Muñoz-Gómez:** Data curation, Writing – review & editing. **Isidoro Martínez:** Funding acquisition, Writing – original draft, Writing – review & editing. **Salvador Resino:** Visualization, Conceptualization, Funding acquisition, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

Ethics approval and consent to participate

All participants gave their consent before enrollment. The Ethics Committee of Hospital General Universitario Gregorio Marañón approved the study (Ref# 162/20).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding authors upon reasonable request.

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Pablo Ryan
Servicio de Medicina Interna, Hospital Universitario Infanta Leonor, Madrid, Spain
Centro de Investigación Biomédica en Red en Enfermedades Infecciosas, Instituto de Salud Carlos III, Madrid, Spain

Felipe Pérez-García
Unidad de Infección Viral e Inmunidad, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Majadahonda, Spain
Servicio de Microbiología Clínica, Hospital Universitario Príncipe de Asturias, Madrid, Spain
Universidad de Alcalá, Facultad de Medicina, Departamento de Biomedicina y Biotecnología, Madrid, Spain

Juan Torres-Macho
Servicio de Medicina Interna, Hospital Universitario Infanta Leonor, Madrid, Spain

Carlos Bibiano, Juan Ignacio Lazo
Servicio de Urgencias, Hospital Universitario Infanta Leonor, Madrid, Spain

Guillermo Castaño-Ochoa
Unidad de Informatica, Hospital Universitario Infanta Leonor, Madrid, Spain

Erick Joan Vidal-Alcántara, María José Muñoz-Gómez
Unidad de Infección Viral e Inmunidad, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Majadahonda, Spain

Isidoro Martínez[1], Salvador Resino[*1]
Centro de Investigación Biomédica en Red en Enfermedades Infecciosas, Instituto de Salud Carlos III, Madrid, Spain
Unidad de Infección Viral e Inmunidad, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Majadahonda, Spain

[*]Corresponding author at: Unidad de Infección Viral e Inmunidad, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Majadahonda, Spain.
E-mail address: sresino@isciii.es (S. Resino)
[1] These authors contributed equally to this work.